EXHIBIT 49

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

IN RE: ROUNDUP PRODUCTS LIABILITY LITIGATION	MDL No. 2741 Case No. 16-md-02741-VC
This document relates to: ALL ACTIONS	

VIDEOTAPED DEPOSITION OF
ALFRED NEUGUT, M.D., Ph.D.
New York, New York
August 7, 2017

Reported by: BONNIE PRUSZYNSKI, RMR, RPR, CLR
JOB NO. 127893

August 7, 2017
9:01 A.M.

DEPOSITION OF ALFRED NEUGUT, M.D., Ph.D., held at the offices of Weitz & Luxenberg, P.C., 700 Broadway, New York, New York, before Bonnie Pruszynski, a Registered Professional Reporter, Registered Merit Reporter, Certified Livenote Reporter, and Notary Public of the State of New York.

A P P E A R A N C E S:

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GRANT HOLLINGSWORTH, ESQ.

Also Present: Lem Lattimer, CLVS

I N D E X

E X H I B I T S

THE VIDEOGRAPHER: This is the start of media labeled number one of the video recorded deposition of Dr. Alfred Neugut in the matter of In re: Roundup Products Litigation on August 7th, 2017, at approximately 9:01 a.m.

My name is Lem Lattimer. I'm the legal video specialist from TSG Reporting. The court reporter is Bonnie Pruszynski from TSG Reporting.

Counsels, please introduce yourselves.

MR. LASKER: Eric Lasker from Hollingsworth LLP for Monsanto.

MR. HOLLINGSWORTH: Grant Hollingsworth from Hollingsworth LLP for Monsanto.

MR. TRAVERS: Jeff Travers from the Miller Firm LLC for Dr. Neugut.

MS. ROBERTSON: Pearl Robertson with Weitz & Luxenberg for Dr. Neugut.

THE VIDEOGRAPHER: Will the court reporter please swear the witness in.

THE WITNESS: I will affirm.

ALFRED NEUGUT, M.D., Ph.D.,
called as a witness, having been first duly sworn, was examined and testified as follows:

EXAMINATION

BY MR. LASKER:

Q. Good morning, Dr. Neugut. Let's just jump right in. I know you have been through this process before, so I assume you understand the deposition process and what we will be doing for the next seven or eight hours today. Correct? You are familiar with that process?

A. Yes.

MR. LASKER: Let's mark as the first exhibit the deposition notice and document request. This will be Exhibit 14-1.

A. Could I ask that you speak a little louder? It's actually --

Q. Yeah, I will speak louder. Thank you. And anytime, obviously -- anytime, if you don't hear me, definitely let me know. We want to make sure you understand the questions that I am asking.

(Exhibit 14-1, Deposition Notice and Document Request marked for identification, as of this date.)

Q. For the record, Exhibit 14-1 is a deposition notice for your deposition here today. And there is a list at the end, request for production of certain types of documents.

We have been provided by your counsel with a copy of your CV and a copy of some billing records. But if you can review the request for production and confirm that you do not have any other documents that would be responsive to these requests.

A. No. Everything that I had I sent to Mr. Travers to forward to you.

Q. And that would be your billing records and your CV; correct?

A. I sent him a copy of a lecture that I gave to the Court on Science Day a few months ago, so that also, I think.

Q. Anything else?

A. Off the top of my head, I'm not recalling anything else that was responsive to this.

Q. Okay.

MR. LASKER: I am not sure if we received those slides from you, although I believe we have them.

MR. TRAVERS: Yeah. I sent Heather an e-mail asking if she needed us to resend them.

Q. Dr. Neugut, just so I can be clear starting off, am I correct in my understanding that prior to being retained by plaintiffs' counsel for purposes of this litigation, you had not conducted any review of the epidemiological literature with regard to glyphosate and cancer?

A. I don't believe so, not specifically, no.

Q. So, you had not looked at the literature of NHL and glyphosate or cancer and glyphosate?

A. No.

Q. So, it would be fair to say then that you had not formed any opinion with respect to any potential association between glyphosate and NHL or cancer; correct?

A. I didn't know anything about it.

Q. Let's mark as Exhibit 14-2 a declaration that you had submitted early on in this litigation.

(Exhibit 14-2, Declaration of Alfred Neugut marked for identification, as of this date.)

Q. Dr. Neugut, first of all, can you confirm that this is your signature on this document?

A. Yes.

Q. And this is dated April 28, is that 2015 or 2016?

A. It looks like 2016.

Q. '16.

And this is a declaration that you submitted setting forth your opinions as of April 28, 2016, with respect to glyphosate and cancer; correct?

A. Yes.

Q. I'm going to mark as Exhibit 14-3 one of the invoices that you provided for your time as of February 17, 2017.

(Exhibit 14-3, February 17. 2017 Invoice, Neugut to Miller Firm marked for identification, as of this date.)

Q. Dr. Neugut, can you identify Exhibit 14-3 as an invoice that you submitted with your time for services rendered in this litigation as of February 17, 2017?

A. Yes.

Q. As of February 17, 2017, you had spent ten hours of work in reviewing documents and literature and having various meetings with and preparing some documents with plaintiffs' counsel; correct?

A. I don't recall. It is my first bill.

Q. As of this bill, if this bill is accurate, as of February 2017, you had spent ten hours of work on this litigation; correct?

A. As I say, I would have to see all my bills to know how they are laid out. I don't have them in my head in terms of the history of this litigation and my billing, but if this is the first bill, then this would sort of compile, although I might have put time in previously unbilled prior to taking the case.

Q. Do you have any reason to believe,

first of all, that your invoice for -- that you have submitted to plaintiffs' counsel for your time as of February 2017 would be inaccurate?

MR. TRAVERS: Objection, asked and answered.

A. Not inaccurate in the sense of what I billed for my time working on the case on behalf of plaintiffs. But as I say, I wouldn't have taken the case without previously reviewing -- if I were asked to take the case, I would have spent some time on my own reviewing the literature, which I would not have billed for. So, I might have -- I'm sure that I put some time into reviewing the literature on glyphosate and lymphoma before agreeing to act as a witness.

Q. Do you recall, sitting here today, how much time you spent reviewing literature before you agreed to work with plaintiffs' counsel in this case?

A. I wouldn't have kept a record of that, and this is a while ago, but it would have been certainly on the order of a couple or a few hours.

Q. Do you recall how much time you had spent reviewing the literature as of the date of your April 2016 declaration, which would be approximately ten months, nine to ten months before your first bill here?

A. No.

Q. Would it have been more than five hours?

A. It would have been -- again, I'm reconstructing, going back to that time, but my -- my assumption is that at the time, I would not have taken -- my taking the case was heavily based on the IARC review, and if I had, I had read the IARC review, then -- I don't know if I am a fast or a slow reader, but it would have taken me a few hours to read, and I would have based my opinion heavily on that document, and I am assuming that would have been a few hours.

But I don't know if I particularly billed -- if my ten hours subsequently included that review, those hours, or if that was, as I say, part of my initial review prior to even taking the case, for which I didn't necessarily bill plaintiffs.

Q. Okay. I think I understand then. So, as of the time of this April 2016 declaration, you had reviewed the IARC monograph; correct?

A. I wouldn't have taken the case, I think, absent that.

Q. And it was subsequent to this declaration that you then started reviewing the underlying epidemiological literature in preparing the report.

A. I don't know the timing of that. That would have been probably more in line with -- well, what report are we talking about now?

Q. Your expert report in the MDL that you submitted.

A. That would be more in conjunction with the timing for that, yes.

Q. Okay. So, the actual review of the underlying studies, epidemiological studies, would have taken place after your April 2016 declaration.

A. Yes.

Q. You state -- well, let me ask it this way: Is it your opinion, Dr. Neugut,

that the IARC monograph classifying glyphosate as a probable carcinogen in and of itself provides a reliable scientific basis for you to opine that glyphosate causes NHL in humans?

A. I think that the IARC reviews are the most authoritative reviews in the field, and I think as a starting point, yes, it's a fair starting point, and unless there is a strong reason to disbelieve them for some reason, the answer is yes.

Q. Just to be clear, in your April 2016 declaration, at paragraph 16, you state in the second paragraph that IARC's assessment -- or second sentence of paragraph 16 --

MR. TRAVERS: Do you mean paragraph --

MR. LASKER: Let me start that again. I had the wrong number here.

Q. In your April 2016 declaration, paragraph six, the second sentence, you state quote, "IARC's assessment on glyphosate provides a reliable scientific basis for an opinion that glyphosate does cause

non-Hodgkin's lymphoma in humans; correct?
A. And we're talking about paragraph six?
Q. Yes.
A. Yes.
Q. And to be clear, in reaching your opinion that is expressed in your expert declaration in April 2016 that glyphosate causes non-Hodgkin's lymphoma in humans, you relied solely on the IARC monograph; correct?
A. I would not say solely, but I would say heavily.
Q. You had not reviewed any of the underlying literature at that time, though?
A. I cannot recall. My guess is, I may have looked up one or two of the papers, but heavily -- but predominantly, it was the monograph itself.
Q. Now, as a basis for your reliance on the IARC monograph, you also state in paragraph two of your April 2016 declaration, the last sentence, that you would -- and I am quoting from your declaration, "equate the term 'probable' as used in the IARC monograph as corresponding to my understanding of the

legal term 'within a reasonable degree of medical certainty'"; correct?
A. Yes, that's-- there I -- yes, that's what I wrote. Um-hum.
Q. Now, IARC in its preamble states that the term "probable" has no quantitative significance.
MR. TRAVERS: Objection.
Q. Correct?
MR. TRAVERS: Calls for a legal conclusion.
A. I don't know.
Q. Have you ever reviewed the preamble to the IARC monographs?
A. Yes, but I don't recall offhand that sentence, but --
Q. Okay.
MR. LASKER: Let's mark that as Exhibit 14-4.
(Exhibit 14-4, World Health Organization IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Myon, France, 2006 marked for identification, as of this date.)
Q. And Dr. Neugut, if I could direct

you -- and for the record, this is, Exhibit 14-4 is the preamble to the IARC monographs dated 2006, that had been marked previously in this litigation, both by plaintiffs' counsel and by Monsanto in various depositions.
If I could direct you to page 22 of the preamble. And at this place in the preamble, IARC is setting forth it various classification schemes for -- for substances that they analyze; correct?
A. Yes.
Q. And for group two -- we are going to go through this. Group one would be if an agent is carcinogenic to humans according to IARC; correct?
A. Yes.
Q. And for IARC, that category is used when there is sufficient evidence of carcinogenicity in humans; correct?
A. Yes.
Q. So, group two is a category for substances that IARC defines as being either probably carcinogenic or possibly carcinogenic to humans; correct?

A. Yes.
Q. And in its preamble, IARC states, and it's at lines 29 and 30 on page 22, that the terms "probably carcinogenic" and "possibly carcinogenic" have no quantitive significance; correct?
A. Correct.
Q. And IARC also states in its monograph that IARC may ident- -- let me start that again.
IARC also states in its monograph that IARC may identify cancer hazards even when risks are very low with known patterns of use or exposure; correct?
A. I don't know where you are reading.
Q. Do you know that? You have reviewed the monograph, haven't you? You said that you have.
A. Yes.
Q. And does that sound familiar to you?
A. Yes.
Q. And just so we are clear, on page two of the monograph, lines 22 through 24, in the preamble, IARC states exactly that, makes

exactly that point; correct?
A. Yes.
Q. You also state in your April 2016 report, and this is in paragraph six, the first sentence, "In reviewing Monograph 112, it is my opinion that IARC continued its tradition of rigorous transparent analysis and used a sound methodological approach when reviewing the evidence on glyphosate." Correct?
A. Yes.
Q. What investigation did you conduct prior to signing this declaration to confirm for yourself that the Working Group 112 in its analysis of glyphosate had followed a rigorous transparent analysis and followed a sound methodological approach?
A. Because I read through the report carefully.
Q. Did you do anything other than reading the report in reaching this opinion?
A. No.
Q. What is your understanding of the amount of time that the working group spent in conducting its analysis of glyphosate

prior to issuing its classification?
MR. TRAVERS: Objection, calls for speculation.
THE WITNESS: Am I supposed to answer?
Q. Yes.
MR. TRAVERS: If you can.
Q. Unless he tells you not to answer, you should answer the question.
A. Well, the meetings run about a week or more, but I mean, the preparation for the meetings run weeks.
Q. And so, it's your understanding that the -- how much time then would you understand the working group spent in analyzing and evaluating glyphosate to reach its classification?
A. Weeks.
MR. TRAVERS: Objection, calls for speculation.
Q. Now, you know an individual named Dr. Aaron Blair?
A. I don't think -- I cannot -- I probably have met him at least once, like years ago, but I don't know him. We don't

play stickball together. But I mean, I certainly know him by reputation.
Q. Okay. Dr. Blair has -- what is your understanding of Dr. Blair's reputation?
A. It's outstanding.
Q. And Dr. Blair was the chairperson of Working Group 112 that conducted this analysis and evaluation of glyphosate; correct?
A. Yes.
Q. And Dr. Blair was deposed in this litigation about the IARC working group's analysis; correct?
A. Yes.
Q. And you have read that deposition; correct?
A. Yes.
Q. Dr. Blair testified specifically with respect to the Working Group 112 and glyphosate, that the working group only spent one or two days total in analyzing whether glyphosate can cause cancer; correct?
MR. TRAVERS: Objection, misstates his testimony.
A. I don't recall offhand, but I do

recall that it was only a couple of -- they were evaluating several carcinogens at the same time, so it was a limited amount of time on glyphosate specifically.
MR. LASKER: Just so we are clear, because of the objection, let's mark as Exhibit 14-4 -- I'm sorry, 14-5. I didn't mean to mess that up. I don't think we have to mark the declaration. Let's just use this as an exhibit.
MR. TRAVERS: Yeah. Do you have a copy?
MR. LASKER: Yes. We are not going to mark this as an exhibit. We will just use this for the witness' reference.
Q. So, if I could ask you to turn to pages 115, or page 115, and this in the minuscript version, so there is four pages per page, but page 115, line 12 to line 16, there was a question of Dr. Blair:
"So, you would have maybe a day or two of analysis and evaluation that went into the IARC working group classification of glyphosate; correct?"
"Answer: Roughly correct."

Do you see that?
A. Yes.
MR. TRAVERS: Objection. This takes it out of context.
Q. You have no reason to doubt Dr. Blair's testimony?
A. No.
Q. And to provide context, if I could ask you to look to page 114, lines 13 through 21, here Dr. Blair is being asked about that time period prior to the working group meeting; correct?
A. So, it's -- it will take me a minute to orient, if I can have that.
Q. That's fine.
A. Okay. Your question?
Q. And Dr. Blair on page 114 states that while there was some assembling of data tables prior to the working group meeting during that one-week period, the evaluation processes didn't start until the actual working group meeting; correct?
A. Yes.
Q. And in fact, Dr. Blair resists the suggestion that any analysis was done prior

to that one-week meeting, doesn't he?
A. I wouldn't know.
Q. Well, he states at line eight, in describing what happened beforehand, "Some of the time it's just putting things in a table. That's hardly an analysis, it's an assembly of the data." Correct?
MR. TRAVERS: Objection. I think your previous question misstates his testimony.
Q. That's what Dr. Blair testifies; correct?
A. That's what he says.
Q. And do you consider a one- to two-day review of all of the scientific evidence regarding glyphosate and cancer, and that would be not only the epidemiology but the animal studies and the genotox, to be a rigorous analysis?
MR. TRAVERS: Objection, misstates his testimony.
A. I would have no way of knowing.
Q. Now, the IARC working group also did not consider all of the glyphosate animal carcinogenicity data during that one-week

session because it did not have sufficient time; correct?
MR. TRAVERS: Objection, misstates the evidence.
A. I don't know.
Q. Do you know Dr. Charles Jameson?
A. No.
Q. Dr. Jameson chaired the animal cancer bioassay subcommittee on glyphosate for the IARC working group. Were you aware of that?
A. No.
Q. Do you know that Dr. Jameson was deposed in this litigation about his subgroup's work in analyzing the animal data for the IARC monograph?
A. Do I know that he was deposed?
Q. Yes.
A. I don't think I have a specific knowledge of that, no.
Q. Let me show you Dr. Jameson's deposition testimony. We will be going back to Dr. Blair's deposition testimony at some point. You can put that to the side for the moment.

MR. TRAVERS: I'm just going to object, because Dr. Neugut didn't review or rely upon this deposition, so --
MR. LASKER: I understand that, but Dr. --
MR. TRAVERS: He's not going to have sufficient time to fully analyze Dr. Jameson's testimony to accurately answer questions.
MR. LASKER: That -- I understand that, but Dr. Neugut is the one who offered an expert opinion that the IARC working group had put in a -- what was his words? -- rigorous analysis of the glyphosate data, and to that extent, his lack of knowledge of that process is relevant.
Q. Dr. Neugut, if I could direct you to Dr. Jameson's testimony on page 191, lines 12 to 24. And -- whoops, I'm sorry.
Lines 12 to 24 on page 191, Dr. Jameson is referring to the fact that some data tables were provided to him at some point at the meeting; correct? And just to be -- just to put this in context for you, on

line 190 -- on page 190, line nine, these were data tables with respect to underlying study data for tumor counts of 14 cancer bioassays on glyphosate.

And then we continue on to page 191, where he is asked whether he had access to those materials during the IARC working group meeting.

Do you see that?

A. Yes.

Q. And on -- further down, starting at line 25 on page 191, and then continuing on to 192, line six, question:

"You did not then proceed to actually review and look at the data that was provided in those supplemental tables; correct?"

And there is an objection, and then the answer:

"There was -- the amount of data in the tables was overwhelming, and it would not have been possible to review those, that data during the meeting."

Correct?

A. Yes.

Q. Do you believe that having insufficient time to consider all of the data on the animal cancer bioassays for glyphosate reflects a rigorous evaluation process?

MR. TRAVERS: Objection, misstates the testimony.

A. I would have no way of being able to characterize what he was able or not able to evaluate at the meeting. I mean, I think the data that was described in the monograph was consistent with, with the report of carcinogenicity that came out of the report.

Q. But just to be clear, in offering your opinion in April 2016 that glyphosate can cause NHL, in which you relied upon the rigorous process that the working group engaged in, you were not aware of the fact that there was animal data tables that the IARC working group did not review because they didn't have time; correct?

MR. TRAVERS: Objection, misstates the testimony, and it's inconsistent with IARC monographs.

A. Certainly, I'm not aware of whether they had or did not have data that wasn't

available, and relied on what they did report in their monograph and what they voted on as part of their process, as part of their normal process.

Q. Now, Dr. Jameson, you talked about the animal studies that IARC did discuss, and there were four animal studies that are discussed in the monograph as providing the data upon which the working group relied in reaching its conclusion or its classification that glyphosate was a probable carcinogen; correct?

MR. TRAVERS: Wait. Objection. Wait. You say "Dr. Jameson, you talked about." Do you mean, "Dr. Neugut, you talked about the animal studies"?

MR. LASKER: I'm sorry. I will start that again. Thank you.

Q. Dr. Neugut, you had previously in one of your previous answers -- you can keep that.

In one of your previous answers, you said you relied upon what IARC described in its monograph, what the working group described in its monograph with respect to

the animal studies; correct?

A. Yes.

Q. And the monograph relies upon four animal studies as providing the data that they used in reaching their classification; correct?

A. Yes.

Q. Now, Dr. Jameson testified that the IARC working group did not actually have the study documents for those four animal studies.

MR. TRAVERS: Objection.

Q. Are you aware of that?

A. No.

MR. TRAVERS: Misstates his testimony.

Q. Okay. Let's have you look to Dr. Jameson's deposition at page 279, lines six to 16. And here Dr. Jameson testifies that IARC relied on summaries of the studies provided by either EPA or JMPR as opposed to the actual studies themselves; correct?

A. I don't have the ability to absorb this at this point, but it looks like that.

Q. And Dr. Jameson also acknowledges,

continuing on, on page 279, lines 17 through 24, that the scientists who prepared those summaries at EPA or at the JMPR, which is part of the World Health Organization, they were the ones who had actually looked at the underlying study documents; correct?

A. I don't know where you are referencing.

Q. Lines -- page 279, line 17 through 24.

A. Yes.

Q. And those EPA and World Health Organization scientists, in the very same summaries upon which IARC relied, concluded that the four studies at issue did not provide evidence that glyphosate causes cancer; correct?

MR. TRAVERS: Objection, misstates the evidence.

Q. And if you want, I can direct you to page 284, lines eight through 17, and why don't we read that -- I will read that into the record. Question to Dr. Jameson:

"And with respect to all four of these studies, the findings that IARC

cited to as evidence in support of a sufficient evidence of carcinogenicity in animals, in all of those students, the EPA or the JMPR had concluded that those findings were not related to glyphosate; correct?"

There is an objection.

"Answer: That's what their document indicated."

Correct.

MR. TRAVERS: I'm going to object. We don't know which EPA document this is talking about. There are several EPA documents.

MR. LASKER: Okay. We are going to just note for the record the speaking objections and the sort of misinformed objections --

MR. TRAVERS: It's not misinformed. It's just unclear what document.

MR. LASKER: It may be unclear to you. It's very clear that there was some testimony. If you are going to continue to make those sort of objections to every question, we will have to seek relief

from that.

MR. TRAVERS: I mean, he just says that -- he references a document. We were just -- we don't know what document it is.

MR. LASKER: Well, maybe you should review the deposition testimony of Dr. Jameson, but the testimony is very clear.

MR. TRAVERS: Well --

MR. LASKER: Let me ask --

MR. TRAVERS: Can you offer the document so the witness knows which one it refers to?

BY MR. LASKER:

Q. If you're -- if -- Dr. Neugut, starting on 283, line 14, directly before the testimony I just read, Dr. Jameson is confirming that this is, the discussion is with respect to the four animal data -- four animal studies that IARC relied upon in its monograph; correct?

A. By now I have forgotten the question. I'm sorry. So --

Q. From page 283, line 14, through

284, line 17.

A. Um-hum.

Q. Dr. Jameson states that IARC's conclusion was based upon a summary or review document prepared, one by EPA and the other by JMPR, and that is the question starting line 283 on line 21, answering on 284, line seven; correct?

A. Yes.

MR. TRAVERS: I have got the same objection.

Q. And from line eight -- page 284, line eight to line 17, Dr. Jameson confirms that in that review document that IARC relied upon for those four studies, the EPA or the JMPR concluded that the findings were not related to glyphosate; correct?

MR. TRAVERS: I have got the same objection.

A. Correct.

Q. Dr. Neugut, is it your opinion that for a scientist, relying upon a summary document rather than the underlying study itself reflects a rigorous review process?

A. I don't know what Dr. Jameson

relied upon, so I don't know, but I would say it's better of course to rely on the original data.

Q. Do you agree, sitting here today, with the IARC working group's assessment of the epidemiological literature regarding formulated glyphosate products and non-Hodgkin's lymphoma?

A. Specifically with regard only to the epidemiologic data?

Q. Yes.

A. Yes.

Q. The IARC working group on the monograph concluded that the epidemiological evidence associating glyphosate with non-Hodgkin's lymphoma was limited; correct?

A. Was limited, it's probably even a little stronger than that, but it's on -- let's say it's on the stronger side of limited, but I think limited is fair.

Q. As defined by IARC again in that preamble, the term "limited" means, quote, a positive association has been observed between exposure here to glyphosate and non-Hodgkin's lymphoma, for which a causal

interpretation is credible, but chance, bias or confounding could not be ruled out with reasonable confidence; correct?

A. Purely on the basis of the epidemiologic studies, without taking into account, say, biology, toxicology, et cetera, et cetera.

Q. You agree with that assessment; correct?

A. Yes.

Q. Now, the IARC working group had the option and chose not to -- well, strike that.

The IARC working group concluded that the epidemiological evidence did not reach the level of being sufficient to establish a causal relationship between glyphosate and NHL; correct?

A. I'm sorry.

Q. The IARC working group determined that the epidemiological evidence did not reach the level where they could find it was sufficient to show a causal relationship between glyphosate and non-Hodgkin's --

A. Purely on the basis of the epidemiologic studies, without taking into

account biology, et cetera, yes.

Q. You agree that the epidemiology alone is not sufficient to show a causal relationship between glyphosate and non-Hodgkin's lymphoma; is that correct?

A. For -- for the purposes for which they were evaluating it, I would say that's correct.

Q. The IARC working group also concluded that there was not even limited epidemiological evidence to associate glyphosate with any other type of cancer; correct?

A. That adds to the causal relationship.

Q. I'm not sure I understood your answer. Maybe my question wasn't clear.

The IARC working group in considering cancers other than non-Hodgkin's lymphoma concluded that there was not even limited evidence --

A. Correct.

Q. -- to support an association; correct?

A. Yes.

Q. And you agree with that; correct?

A. Yes.

Q. So, let's break down the three qualifiers in the IARC -- in the definition of "limited" that we have spoken about with respect to the epidemiology.

So, when you talk about the fact that chance could not be ruled out, with respect to any epidemiological association between glyphosate and non-Hodgkin's lymphoma, that is addressing an issue that epidemiologists deal with, with tests for things like statistical significance; correct?

A. Part of it is statistical significance, yes.

Q. And the way that epidemiologists try to rule out chance is, they look to see whether the -- either the odds ratios or the relative risks are above 1.0 and are statistically significant; correct?

A. Yes.

Q. You would agree that for an epidemiological study to be considered a positive study with respect to a potential

exposure and an outcome, that study must report an odds ratio or relative risk that is above 1.0 and is statistically significant; correct?

A. Statistical significance nowadays is not really as much of a requirement as it might have been in the past, so I would not agree that it's totally mandated.

Q. Okay. Let me ask you, if I could -- and let's mark -- we will mark this, a deposition transcript, but this is deposition testimony that you gave in the Actos litigation in January of 2013. Just to set the -- to establish the precedent, you served as an expert for the Miller firm, the same plaintiffs' counsel here today, in connection with the Actos litigation; correct?

A. Yes.

Q. And you were deposed a number of times in that litigation, just like you are being deposed here today; correct?

A. Yes.

Q. So, I'm going to ask you about some of your testimony in that litigation at

various points today.

But if we could start just on your January 7, 2013 deposition testimony, and in particular, on page one -- I'm sorry, 233 of your testimony. And in particular, line nine through line 13. I think I asked this question the exact same way here today, but the question was asked of you, "When you say a positive study, are you saying a study that has an odds ratio relative risk of greater than one and is statistically significant?" And your answer is "yes"; correct?

A. Yes.

Q. And that is your -- you agree with that testimony; correct?

A. Yes.

Q. Now, when a study does not show a positive finding, it is considered -- well, strike that.

There is also the possibility of a negative study in which you have an odds ratio or relative risk below 1.0 that is not -- that is also statistically significant; correct?

A. Yes.

Q. So, when a study does not show a positive or a negative finding, it is considered a null study that has no finding; correct?

A. Or it's in a direction and not quite statistically significant.

Q. Let me ask you again. We will be switching from various testimony you have offered in the past, but let's take the October 22, 2014 testimony. And I'm sorry, I will be referring back and forth to some of these, so we will just have to work our way through that.

Here you go.

This is again testimony that you provided in that other Actos litigation, on October 22, 2014, and if I could turn you to page, or refer you to page 117 -- I'm sorry, page 113, lines 15 to 21, and just to give you a reference point, this is a fairly long answer that you are providing that starts on page 111, but it continues to be your testimony through to page 113.

And there you state that, on line 17 through 19, "When a study does not show a

positive finding, it is actually null. It has no finding." Correct?

MR. TRAVERS: Sorry, which page is this on again?

MR. LASKER: On page 113, from lines 17 through 19.

Q. Dr. Neugut, you testified that "when a study does not show a positive finding, it is actually null. It has no finding." Correct?

A. Yes.

Q. And you agree with that; correct?

A. Yes.

Q. And you would not label an exposure as being associated with an outcome unless there is a finding of an increased risk that is statistically significant; correct?

A. That's correct.

Q. Epidemiologists determine whether a finding is statistically significant -- they can do that in different ways. One is based upon a 95 percent confidence interval; is that correct?

A. Yes.

Q. And a finding would be then

statistically significant in the positive direction if the lower bound for the 95 percent confidence interval is greater than 1.0; correct?

A. Yes.

Q. Epidemiologists can also measure statistical significance with something called a P value; correct?

A. Yes.

Q. And a study is statistically significant if a P value is less than 0.05; correct?

A. Yes.

Q. The size of a study can also impact the ability, or can impact the ability of a study to find a statistically significant result; correct?

A. Yes.

Q. So, this is measured by what epidemiologists refer to as power, the power of a study; correct?

A. Yes.

Q. A study that has more power will be better able to identify statistically significant associations if they exist;

correct?

A. Yes.

Q. Epidemiologists generally give less weight to studies that have lower power; correct?

A. I'm sorry, that didn't --

Q. Say it again? I will do it again.

A. Yeah.

Q. Epidemiologists, in evaluating a study, would give it less weight if it has low power; correct?

A. Because you don't have the ability to assess significance.

Q. So yes --

A. Yes.

Q. -- low power means --

A. Um-hum.

Q. One way to measure, sort of a shorthand way of measuring the power of a study is to look at the width of the confidence intervals; correct?

A. Yes.

Q. So, the narrower the confidence interval, the greater the power of the study; correct?

A. Yes, but that's-- okay. Yes, that is -- that's sort of an a posteriori way of looking at it, but yes.

Q. You would agree that it's not proper epidemiological methodology to measure power based on the total number of individuals who are in the study; correct?

A. Can you rephrase that or give me a better -- tell me what you mean exactly.

Q. For example, if you have a case-control study, and in that case-control study there is a certain number of individuals whose data is reviewed who had the outcome of -- had the, let's say, non-Hodgkin's lymphoma. So, you have a case-control study, and there is a certain number of people who have non-Hodgkin's lymphoma in the study.

With respect to any one exposure measure --

A. Yes.

Q. -- it would not be appropriate to determine the power of the study based upon the number of individuals who were in the study; correct?

A. The power of the study is going to be determined by both -- by -- really by the number of endpoints, by the number of people with the disease, but also by the number of people who are likely to be exposed.

Q. Right.

So, with respect to a study, if you had 10,000 people in a study but only three of them were exposed to the substance at issue, the fact that there is 10,000 people in the study wouldn't make it a powerful study; correct?

A. That's correct.

Q. And it wouldn't be reasonable to call a case-control study a big study and say that it has more weight just because there is a large number of individuals who start out as potential cases in the study; correct?

MR. TRAVERS: Objection, calls for speculation.

A. So, you would have to look at each study and kind of assess it on a -- on its own merits with regard to those parameters.

Q. Okay. But as a general matter, you would want to look at the number of

individuals who are -- have the outcome and have the exposure you are looking at to determine power; correct?
A. Yes.
Q. It would not be a reasonable methodology just to look at the number of individuals in a case-control study that had the outcome of interest; correct?
MR. TRAVERS: Objection, asked and answered.
A. Yes.
Q. Let me show you a table listing some of the glyphosate epidemiological studies.
(Exhibit 14-5, Table of Studies marked for identification, as of this date.)
MR. TRAVERS: Who prepared this table?
MR. LASKER: We will address that shortly, but I have some questions first.
MR. TRAVERS: Can we --
Q. Dr. Neugut --
MR. TRAVERS: I object.
MR. LASKER: You can object. Your

objection is noted.
MR. TRAVERS: I think it's important to know who prepared the table before answering questions about it.
MR. LASKER: That's fine.
Q. Dr. Neugut, there is a table, and these are a listing of some of the studies, I take it you are familiar with as well, with respect to glyphosate and non-Hodgkin's lymphoma; correct?
A. Yes.
Q. And this has a listing of various studies with the number of cases in the study identified; correct?
MR. TRAVERS: I'm going to still object. We don't know where this table comes from or the accuracy of the members.
Q. Dr. Neugut?
A. Yes.
Q. Now, the table lists at the very top, the study that is listed at the very top of this table is the Cocco 2013 study; correct?
A. Yes.

Q. And the table indicates that this study included 1,869 individuals with non-Hodgkin's lymphoma; correct?
MR. TRAVERS: Same objection as to the source of this table.
A. Yes.
Q. Now, it would not be fair, though, to suggest from this table presentation that Cocco is the most powerful study looking at glyphosate and non-Hodgkin's lymphoma; correct?
MR. TRAVERS: Same objection to the source of the table.
A. Again, you would need to know the likelihood of exposure.
Q. Well, you know, in fact, that Cocco was the least powerful of all of the studies looking at glyphosate and non-Hodgkin's lymphoma; correct?
A. I don't have a good memory, and I don't know -- I can't relate to each paper without seeing it.
Q. Okay. Let's mark your expert report, because this is in your expert report.

MR. LASKER: And we can make this, I'm sorry, 14-6.
(Exhibit 14-6, Expert Report of Albert Neugut, M.D., Ph.D. marked for identification, as of this date.)
Q. And you discuss the Cocco paper, I believe it is on pages 16 and 17 of your report.
A. Um-hum, yes.
Q. And you can refresh your recollection, but specifically on page 17, you talk about the -- the numbers of exposed cases and controls and the power of the study; correct?
A. Yes.
Q. And does this refresh your recollection that this study that is listed in the table 14-5 as the largest of the studies in fact was the least powerful of all the epidemiological studies looking at glyphosate in non-Hodgkin's lymphoma?
A. It didn't have much exposure, correct.
Q. The table listing of Exhibit 14-5, which is based upon a total number of study

subjects, by itself does not provide any meaningful information regarding the relative power of these glyphosate studies, does it?

MR. TRAVERS: Objection, form.

A. Well, you can judge the power by the width of the 95 percent confidence interval.

Q. I understand. But if you could look to 14-5 in specific, the prior exhibit that we had.

A. 14-5?

Q. The table, I'm sorry. Not your report, the prior exhibit, which has this table listed.

So, this table 14-5 does not provide any meaningful information with respect to the relative power of the glyphosate epidemiological studies regarding non-Hodgkin's lymphoma; correct?

MR. TRAVERS: Objection to form.

A. I suppose not. It doesn't say anything about it.

Q. And you would not consider this to be a methodologically sound approach for an epidemiologist to take in analyzing the

relative power of these studies; correct?

A. I guess a priori it might have been a good try, but if in fact the exposures are rare, then it's -- you don't get a lot of power from -- even from a large study.

Q. So, for an epidemiologist who had actually looked at the underlying studies and understood the actual data, this would not be a methodologically sound way to present the data on these tables -- on these studies; correct?

MR. TRAVERS: Objection to form.

A. The question doesn't make sense to me, but -- so I can't answer the question.

Q. Okay. Let me restate the question then.

An expert who had reviewed the -- an expert epidemiologist who reviewed the underlying glyphosate literature would not present data in this fashion to compare the relative power of these studies; correct?

MR. TRAVERS: Objection, calls for speculation.

A. I mean, it would be a -- it might be one way to start, but it wouldn't

necessarily be totally informative.

Q. This table does not provide you with any information as it's presented on the relative power of these studies at all; correct?

A. It's not complete.

Q. And an epidemiologist who presented this table as an illustration of the relative power of these studies would not be following a reliable epidemiological methodology; correct?

MR. TRAVERS: Objection, calls for speculation, and takes the document out of context.

A. I'm -- I don't know what an epidemiologist would do. I wouldn't be able to assess power directly from this. Power is based on a number of factors that go beyond the sample size.

Q. Okay. You said you wouldn't know what an epidemiologist would -- you know, you are an epidemiologist; correct? You have been trained in epidemiology?

A. So, sample -- so power is not based solely on the sample size.

Q. So, this table does not follow standard epidemiological methodology of looking at questions like power; correct?

MR. TRAVERS: Objection, it takes it out of context.

A. It's not complete, I would say.

Q. You would not present the data in this way yourself; correct?

A. It depends on what I wanted to show to someone.

Q. If you wanted to talk about the relative power of a study, you would not present the data this way; correct?

A. It would be a beginning of showing it, but it wouldn't be a totality.

Q. But you would present other data if you were trying to present the power of studies; correct?

A. That's correct.

MR. TRAVERS: It's been about an hour, if you want to take a break.

MR. LASKER: Let's just put this into context.

Q. Dr. Neugut, you are aware that plaintiffs retained another epidemiology

expert in this litigation; correct?
A. You mean someone against me?
Q. No. Someone on the same side, plaintiffs' counsel.
A. Oh, plaintiffs.
Q. Yes.
A. I'm sorry. Yes.
Q. Dr. Ritz?
A. Yes.
Q. And I have shown --
MR. LASKER: Let's mark this as 14-6? 7, sorry.
(Exhibit 14-7, Expert Report of Dr. Beate Ritz, M.D., Ph.D. marked for identification, as of this date.)
Q. So, just to confirm, now, this is Dr. Ritz's expert report that she submitted in this litigation, and just to confirm, if you could turn to page 15.
A. Fifteen?
Q. Of Dr. Ritz's expert report. And on the top of page 15, Dr. Ritz states, "In reviewing the literature, the sample sizes, and especially the number of cases, should be noted because of their bearing on statistical

significance and the width of confidence intervals." Correct?
A. Yes.
Q. And she states, "Because many of the smaller studies had suggestive findings but wide confidence intervals, it is particularly important to instead consider pools and meta-analysis that summarize across these smaller studies and not only provide a much larger sample size but may allow us to assess NHL subtypes with sufficient precision." Correct?
A. Yes.
Q. And then it states, "Here I show the sample sizes of each human study of glyphosate in non-Hodgkin's lymphoma"; correct?
A. Yes.
Q. And the table that Dr. Ritz then presents in her expert report is the exact same table that has been marked as Exhibit 14-5; correct?
A. Yes.
MR. LASKER: We can take a break.
THE VIDEOGRAPHER: The time is

10:06 a.m. We are off the record.
(Recess taken.)
THE VIDEOGRAPHER: The time is 10:15 a.m. We are on the record.
BY MR. LASKER:
Q. So, Dr. Neugut, let's go back to the limited epidemiological evidence --
THE VIDEOGRAPHER: Sir, is your mike on?
MR. LASKER: Oh, I'm sorry. Let's not go back. Go back in a second. Thank you.
Q. We were discussing -- I'm sorry.
MR. LASKER: Is this good?
Q. Dr. Neugut, we were discussing the limited epidemiological evidence with respect to glyphosate and non-Hodgkin's lymphoma, and one of the other factors that you mentioned is that bias and confounding could not be excluded as an explanation for the findings in those studies; correct?
A. I don't believe I mentioned that, but --
Q. That is the definition of "limited"; correct? That bias and

confounding could not be ruled out as an explanation for the findings; correct?
A. So, again, we are now going along with the IARC definition of -- you know, with the IARC definition of "limited," yes.
Q. And we talked about your -- your testimony regarding the limited definition of --
A. Um-hum.
Q. -- the glyphosate epidemiology; correct?
A. Purely on the basis of the epidemiologic data.
Q. Right.
A. Correct, um-hum.
Q. So, looking just at the epidemiological data, bias and confounding cannot be excluded as an explanation for the findings in those studies; correct?
A. Yes.
Q. And these are additional and separate concerns that are not addressed by measures of statistical significance; correct?
A. I -- I would say that they are all

intertwined and bound together. It's hard to --

Q. Okay.

A. To say -- it's hard to separate one from the other.

Q. Okay. Let me restate --

A. This is all a -- I think in epidemiologic thinking, you can't so easily take one thread and separate it from the other threads.

Q. Let me restate the question.

A calculation of statistical significance does not answer the question about whether the underlying study has issues with bias or confounding; correct?

A. Correct.

Q. And a finding of a statistically significant association by itself does not mean that there is a cause and effect between an exposure and the outcome of interest; correct?

A. Correct.

Q. And that's because although a statistical -- a statistically significant association may exist, there is always the

concern that the finding may reflect bias in the way that the study was conducted or the presence of confounding factors; correct?

A. If we are talking about a single study, yes, um-hum.

Q. Confounding factors are factors that are associated with both exposure and the outcome, and therefore could lead to a reported association that is not truly a relationship between the two, exposure and outcome; right?

A. Yes.

Q. When an epidemiological study is conducted, it's therefore mandatory that the study collect information on potential confounders, so that the analysis can be controlled to measure the -- to properly measure the effect of the exposure of interest; correct?

A. "Mandatory" is a strong word. "Desirable" I think would be a better word.

Q. Okay. Let's mark -- this may be taking you back a ways, a little ways.

MR. LASKER: Let's mark this as 14-8.

(Exhibit 14-8, ASCO-SEP Medical Oncology Self-Evaluation Program, Third Edition Excerpt marked for identification, as of this date.)

A. That's going back to -- to --

Q. Not too far. I think this is 2014 or so.

A. You could be reading the -- I'm up to the sixth edition now. You guys are out of date.

Q. It's hard to get these.

But in any event, just for the record, chapter -- this is a book produced by ASCO-SEP Medical Oncology Self-Evaluation Program. And this is, as you note, the third edition, and I have copied here chapter one, which is the chapter that you prepared on epidemiology and prevention; correct?

A. Yes.

Q. And in this chapter, you discuss a number of issues, including how to properly evaluate epidemiological data; correct?

A. Yes.

Q. And on page five, you were discussing the issue of confounding in

connection with smoking and asbestos and lung cancer, I believe. In the middle of that first column, the first full paragraph that starts, "In analytical epidemiology, observational studies are carried out."

Do you see that?

A. Yes.

Q. And at the end of that paragraph, you state, last sentence, "It is mandatory in a study that looks at this exposure and outcome to collect smoking information so that it can be statistically controlled and the individual effects of asbestos exposure can be appropriately measured." Correct?

A. Yes.

Q. And so, there are circumstances in which you agree that it is mandatory to collect data on potential confounders; correct?

A. I think that that is true. So, again, are you asking me a question?

Q. I just did. I think that was a question, and you are answering, yeah.

A. So again, I mean, I think the answer is contextual. You know, let's say

that the -- how mandatory it is, is a contextual issue, and I would say if we are talking about asbestos, smoking and lung cancer, then where you have a risk factor which has a relative risk of ten, then yes, doing an asbestos study with lung cancer and not taking into account cigarette smoking is a very -- would be -- would be difficult -- or would be mandatory there or -- but that doesn't mean that in every instance, you can take into account every confounding factor. That would be almost impossible in real life.

And so, that's why I say it's desirable in many instances to take into account confounders, and it's done to varying degrees under different circumstances. But sure, one wants to take into account confounders to the degree that it's possible.

Q. Do you agree -- and we can go back to his deposition testimony if you want, but do you agree with Dr. Blair that there is evidence of an increased risk of non-Hodgkin's lymphoma in farmers that existed prior to the introduction of glyphosate?

A. Yes.

Q. So, there is something going on with farmers and their exposures that is leading to an increased risk of non-Hodgkin's lymphoma that we know for a fact is not glyphosate; correct?

A. Yes.

Q. So, farming, to the extent that glyphosate exposure is associated with farming, which is a fair assumption; correct? Farmers use glyphosate; correct?

A. Yes.

Q. So, farming or at last some other farming exposures would be confounders of any epidemiological analysis of glyphosate in non-Hodgkin's lymphoma; correct?

A. Yes.

Q. For -- strike that.

So, you agree that it would be mandatory or at least extremely desirable in trying to reach an epidemiological finding with respect to glyphosate and non-Hodgkin's lymphoma to control for these potentially confounding other farming exposures; correct?

MR. TRAVERS: Objection, misstates

his prior testimony.

A. Well, to some degree by -- if it's possible, yes.

Q. So, for example, any epidemiological analysis that is trying to properly measure a potential association between glyphosate and non-Hodgkin's lymphoma should be adjusted to control for potential confounding effects of exposures to other pesticides; correct?

MR. TRAVERS: Objection, calls for speculation.

A. Well, other pesticides that are known to cause lymphoma.

Q. And you, in fact, make that point a number of places in your expert report, that an epidemiological analysis of glyphosate and non-Hodgkin's lymphoma should control for exposures to these other pesticides; correct?

A. To the degree that it's possible, yes.

Q. Now, there are standard epidemiological methods that are used to try and adjust for confounding; correct?

A. Yes.

Q. So, there is -- one method is to do some statistical analyses or regression analyses to be able to adjust for exposures to other risk factors; correct?

MR. TRAVERS: Objection, compound question.

A. Yes.

Q. Another method is to conduct a stratified analysis; right?

A. Define that.

Q. Okay. So, in a stratified analysis, you compare -- you look at the odds ratios of individuals with exposure to the substance you are looking at, but not a confounding exposure, and you also have a measure that has it where they are exposed to that substance and the other factor. You have one that doesn't have the confounding and the other that does. Correct?

A. That could be done.

Q. So, the -- we talked about statistical significance. We talked about confounding. The third issue that is raised with respect to limited epidemiological evidence is bias; correct?

A. I don't know.
Q. Okay. Let me go back. The definition of "limited" that we have talked about for the epidemiological evidence in this case, for glyphosate and non-Hodgkin's lymphoma, cannot exclude the possibility of bias; correct?
A. Yes.
Q. How would you define the concept of bias in an epidemiological study?
A. Every study has bias.
Q. What is bias, just sort of the lay perspective?
A. Bias is a directional error. There are errors in every study. We are human beings, so every study, particularly in humans, that is conducted, has errors inherent in it. Every study, observational studies in particular.
So, the errors can be random or the errors can be directional. So, bias are directional errors where there is -- where the -- because of the nature of the error, it gives a tilt to the estimate that you get for the odds ratio, for the risk ratio, at the

end. It tends to give it a -- either a positive or a negative result because of the nature of the responses that the subjects give.
I mean, the truth is error is bad, but whether it's directional -- well, you can smile, but error -- nondirectional error is bad also, but biased error is worse than -- than non-biased error.
Q. And biased error is what you defined as a directional error.
A. Right.
Q. And a directional error means that you have a reported odds ratio, a risk ratio that is actually not reflective of the true association, because it has been artificially shifted in a certain direction, either higher or lower; correct?
A. Yes.
Q. Now, in your expert report, you discuss two study designs for observational epidemiology, cohort and case-control studies, that can be subject to different types of biases; correct?
A. Yes.

Q. Given the choice between these two study designs, most people prefer cohort studies, because the individuals in the study are unbiased at the beginning of the study when you get your data; correct?
MR. TRAVERS: Objection, calls for speculation.
A. I would say that in general, one prefers cohort studies to case-control studies, for the reason you give, but the reality is that the truth is, it's the quality with which the studies are conducted that in the end determine which one is really the better one.
Q. But just to confirm, as a general matter, most people prefer a cohort study, given the choice between the two, because people are unbiased at the beginning of the study when you get your data; correct?
MR. TRAVERS: Objection, asked and answered, calls for speculation.
A. I would say that -- let's say that cohort studies are preferred. I'm not sure I would agree with -- precisely with the reason that you are giving, but the answer is that

the cohort studies are generally preferred.
Q. Okay. Let's go back to your January 7, 2013 deposition. That should still be in front of you. It's going to be one of these transcripts. I think it's the top one there. Yeah.
A. Did I misquote myself?
Q. You disagreed with yourself a little bit, but --
MR. TRAVERS: Objection, move to strike.
Q. Let's look at page 174 in your deposition.
A. Is it -- is this the document?
Q. The January 7 one, yeah. It should have January.
Page 174, lines seven through ten, and I believe I quoted you correctly. "Most people prefer a cohort study, given the choice between the two, mainly because the people are unbiased at the beginning of the study when you get your data." Correct?
MR. TRAVERS: Objection. You didn't read the full answer.
A. So, yes. No, I'm not disagreeing

with what I said four years ago, but if you are asking me as I sit here now why people prefer a cohort to a case-control study, there are other reasons.

Q. What other reasons are there that people prefer a cohort study to a case-control study?

A. I think it's a more naturalistic -- it's more naturalistic.

Q. That is because you are actually following people over time to see outcomes?

A. Just it's prospective. I think it's prospective as opposed to retrospective.

Q. And given the choice between the two study designs, a prospective study design is --

A. It's more natural. It's the natural order of life.

Q. And as an epidemiologist, that is preferable in the study design?

A. Again, we are talking sort of do you prefer apples or do you prefer pears, but again, whether you like apples or pears, the truth is, when you look at the fruit, the one that has the bruises on it is the one you are

not going to eat. So, the quality of how you carry out the study is ultimately -- a bad cohort study is not as good as a good case-control study, and vice-versa, you know.

Q. We are going to look at the quality of the studies.

A. No, I understand, I'm sure we are. But I'm saying that --

Q. I want to make sure I got your full answer, though, because you had stated that there is testimony about cohort studies, the individuals are unbiased at the beginning of the study.

A. Um-hum.

Q. That was one. And two, you mentioned that cohort studies are more naturalistic than case-control studies. Are there --

A. Again, this brings up the issue of temporality, but again, temporality is not usually a major issue.

Q. Okay. So, with temporality, if I understand correctly, a cohort study allows you to make sure you have temporality, and a case-control study, you can't be as certain.

Is that correct?

A. Temporality is very rarely -- I would have to say uncommonly a major -- a major concern.

Q. Let's -- we will circle back to that. Let me just continue from your report.

In your report you mentioned that the main difficulty with cohort design is that they are expensive and time-consuming, particularly with outcomes like cancer; correct?

A. Yes.

Q. But as compared to a cohort study, a case-control study is more susceptible to bias; correct?

A. They are both susceptible to bias, just different biases.

Q. Let's look at your expert report.

A. I will say they are both susceptible to error, just different error.

Q. Your expert report, which I think was 14-6. It should be still in front of you, Dr. Neugut.

MR. LASKER: If you can give him his expert report.

Q. It's 14-6. They should be in order.

No, you can keep it. I have my own copy.

A. Sorry.

Q. And just on page eight of your expert report -- well, pages seven through nine, you are comparing the cohort study design to the case-control study design; correct?

A. Yes.

Q. And at the bottom of page eight, with respect to case-control studies, you state that a disadvantage of case-control studies, as compared to cohort studies, is that they have an increased susceptibility to bias; correct?

A. Yes.

Q. For example, one disadvantage of a case-control study that you don't have with cohort studies generally is the possibility of recall bias; correct?

A. Have less concern for recall bias, yes.

Q. So, recall bias occurs when cases,

for example, of NHL, people with NHL, are more likely to recall prior exposures than healthy controls that don't have the disease; correct?

A. Yes.

Q. Recall bias is not an issue in cohort studies because the study population is followed prospectively and the investigators gather the exposure information prior to any cancer diagnosis. I'll do it again.

Recall bias is not an issue in cohort studies because the study population is followed prospectively and the investigators gather exposure information prior to any cancer diagnosis; correct?

A. Recall bias is much less or not an issue, yes.

Q. It's not an issue at all; correct?

A. Not in the way it is in a case-control study, that's correct.

Q. Case-control studies are also more prone to selection bias than cohort studies; correct?

A. Yes.

Q. Selection bias can occur when a selection of individuals into a study is based both on the disease status and their exposure status; correct?

A. I'm sorry, say that again.

Q. Selection bias can occur when selection of individuals into a study is related both to their disease status and to their exposure status.

A. It's possible.

Q. And with a case-control study, you are specifically selecting subjects based upon their disease status. That's how you choose the cases; correct?

A. Yes.

Q. So, that takes you halfway to where you could have a selection bias problem; right? You have one of the --

A. You have to talk louder.

Q. That would take you halfway to where you could have a selection bias problem. You are already selecting based upon disease, so if there is anything in the methodology that creates selection based upon exposure, you have a selection bias issue;

correct?

MR. TRAVERS: Objection, compound question.

A. I don't understand the point.

Q. Okay. If there is, in a case-control study, some difference in the selection of cases or controls that impact the likelihood of exposure, that can introduce a bias into the study; correct?

MR. TRAVERS: Objection, calls for speculation.

A. Again, I'm not following the question easily.

Q. In a case-control study --

A. Um-hum.

Q. -- if there is some difference in the selection method or the selection of cases and controls that is associated with the exposure of interest, that would create a selection bias; correct?

MR. TRAVERS: Objection, calls for speculation.

A. That would be -- that would be extraordinarily uncommon, if I'm understanding correctly what you are asking,

and I don't think it would be applicable in this particular -- I don't think it would be applicable in -- at least in the context of what we are talking about.

Q. Okay. But if there was some difference in the selection of cases or controls in a cohort study that was associated with the likelihood of exposure, that would create a selection bias; correct?

MR. TRAVERS: Objection, asked and answered.

A. Yes, it could, but as I say, I don't think it would be relevant in the context. There might be exposures and outcomes where that might play a role in a case-control study -- we're talking now of case-control studies or --

Q. Um-hum.

A. But I don't think that would be applicable here.

Q. If there was a difference in the response rate for inclusion in the study between cases and controls, in other words, cases participate in a study at a higher likelihood than controls, that can raise a

concern about selection bias; correct?
MR. TRAVERS: Objection, calls for speculation.
A. Yes, but then you might not know which way the -- again, the direction of the arrow could go either way.
Q. A cohort study -- strike that.
In your expert report, you talk about two types of biases with -- that can occur in a cohort study, and the first is loss to follow-up; correct?
A. Yes.
Q. And one method -- and loss to follow-up is, you are following them prospectively and you want to know what happens to them prospectively, and if ten years from now you lose track of that person, you can't track what happened to them, you have a loss to follow-up; correct?
A. Yes.
Q. So, one method that epidemiologists can use to reduce the problem of loss to follow-up, is if they have another source of information for outcomes, like a hospital database or a Medicare database, to be able

to track the outcome of those individuals prospectively; correct?
A. In a large cohort study, you hope you have such a database, but that is often difficult with free living individuals.
Q. But when you do have such a database, and in particular the AHS study had that, that addresses this concern of loss to follow-up; correct?
A. As long as the people stay in the area where the registry is.
Q. And with respect to the Agricultural Health Study, that was the case, in fact; they were able to continue to track those individuals through the database?
A. Yes.
Q. You also state --
MR. TRAVERS: I just want to -- just an objection. When you say "AHS," are you referring to De Roos 2005 or --
MR. LASKER: The Agricultural Health study. That would be De Roos 2005 as well, yes. The study is the study.
MR. TRAVERS: Well, it's two different -- there are different phases

to the study. I just want to -- just for clarity, I just want to make sure which --
MR. LASKER: There is an overall study, and there is lots and lots of publications --
MR. TRAVERS: Okay.
MR. LASKER: -- which by design is a study design.
A. I'm referring to the --
Q. De Roos 2005?
A. Yes.
Q. Okay. You also state that cohort studies may be subject to detection observer bias.
A. I'm sorry?
Q. In your expert report, you say that cohort studies may be subject to detection observer bias. What is that?
A. I knew you were going to ask me that.
Q. If you don't know, that's fine. This is mentioned in your expert report on page eight; right?
A. That -- it's basically the -- it's

the complement to what you -- we talked about earlier with regard to the case-control study, which is that the knowledge of the -- of the exposure affects the -- affects the diagnosis subsequently. So, it's sort of the prospective equivalent of what you were calling earlier -- what we were calling earlier selection or diagnostic bias, that knowing, for example, that someone was exposed to -- to an exposure, might influence how they are diagnosed subsequently.
Q. That issue, detection observer bias, is not a concern in the Agricultural Health Study; correct?
A. So, I was listing, you know, potential biases. To what degree it plays a role in this particular -- this was a theoretical, if you will, or general discussion of cohort versus case-control studies, and I wasn't specifically speaking with regard to the Agricultural Health Study. It was a general discussion of cohort versus case-control studies.
Q. Yeah, I understand that.
A. Right. So --

Q. I'm just trying to clarify that that issue, detection --
A. Right. So --
Q. Sorry. Detection observer bias is not a concern with the Agricultural Health Study; correct?
A. I would probably not rate it as a major bias in the analysis of the outcomes.
Q. It's not any bias. I mean, there is no issue of people being diagnosed with non-Hodgkin's lymphoma based upon their exposure; correct?
MR. TRAVERS: Objection to form.
A. I would doubt it.
Q. Now, in its conclusion that the epidemiological literature for glyphosate and non-Hodgkin's lymphoma is limited, IARC also considered an IARC meta-analysis of the epidemiological studies; correct?
A. Yes.
Q. Now, you have never conducted or published a meta-analysis yourself; correct?
MR. TRAVERS: Objection, compound question.
A. Personally, I have not. I think

one of our fellows has done one now that is sort of winding its way through the literature, but for all intents and purposes, the answer is no.
Q. You do agree, though, that meta-analyses usually do not substantially alter one's understanding of the underlying studies; correct?
MR. TRAVERS: Objection, calls for speculation.
A. I don't know what that means.
Q. Okay. Let's mark as 14-9 an article that you have published that I think states exactly that. Let's see if I am right.
(Exhibit 14-9, Etiology article, Meta-analysis: Use of combined oral contraceptive in the past ten years is associated with an increased risk for breast cancer, 1996 Nov-Dec marked for identification, as of this date.)
Q. And Dr. Neugut, I'm handing you a -- I think it was maybe a letter or an editorial, I'm not sure how you describe this -- that you prepared for the American

College of Physicians entitled "Meta-Analysis: Use of combined oral contraceptives in the past 10 years is associated with an increased risk for breast cancer."
MR. TRAVERS: I just have one question. Is this just the abstract or is there a full study?
MR. LASKER: This is the full document. It's a commentary.
MR. TRAVERS: Okay.
Q. And on page three of your commentary, or three of four, the first -- the second paragraph, I'm sorry, you state: "As is usual for meta-analysis -- for meta-analyses, the overall results do not substantially alter one's understanding of the previous studies."
And by "previous," you mean the underlying studies, I take it; correct?
A. Yes.
Q. And you agree with that; correct?
A. Yes.
Q. And in particular, when observational studies report small relative

risks, less than 2.0, it's your view that meta-analyses are probably as good as can be done and suggest that there is not a greater concern, or greater cause for concern; correct?
MR. TRAVERS: Objection, misstates his commentary.
A. Yes.
Q. Just to be clear, my question was, correct, you do believe that when observational studies report small relative risks, meta-analyses are probably as good as can be done and suggest that there is not a greater cause for concern; correct?
A. Yes.
Q. You have also cautioned, and cautioned in this commentary, about reaching causation opinions based upon statistically significant findings below 2.0 in meta-analyses; correct?
A. Yes.
Q. And in your opinion, we should refer to such findings -- or strike that.
We should not refer to such findings as small but statistically

significant, but instead should state that such findings are statistically significant but small; correct?

A. I would point out that this was written 20 years ago.

Q. That's why I am asking you today.

A. And this is --

Q. You agree --

A. And this is an old -- you know, I had hair then.

Q. That's good to know.

A. So --

Q. I'm asking if you agree with that statement today.

A. I think -- so, I agree that with smaller risk ratios, one has to exhibit more caution, but I think that the field has moved in that direction. And by "the field," I am referring to epidemiology in general. And that back in the 1990s, that there was more caution with going below risk ratios of two, and even legally, the Daubert -- if we are talking about a Daubert hearing, the legal field would have been more cautious below a risk ratio of two.

But now, risk ratios of 1.3 and 1.4 are taken seriously. Many risk factors that we take very seriously in public health are really at that level of 1.3 and 1.4, and even 1.2, and we consider them significant carcinogens and act on them in the public health sphere.

So, I would say that -- that while it is true that it's more difficult, it makes it more difficult methodologically to establish a risk in that range, and that's why we are for the most part sitting here talking about this risk ratio, but that doesn't mean it's unimportant. I would disagree with my statement to the degree that it's -- when I say statistically significant but small, "small" doesn't mean unimportant. "Small" means small and difficult to establish with -- to the degree that we would like to be comfortable and confident that it's a true causal association.

It makes it more difficult methodologically for us an epidemiologists and scientists to be -- to establish it as a probable carcinogen or a true or an absolute

carcinogen, which is why -- why we are -- why we are sitting here.

Q. Just so I understand your prior testimony, one of the factors that you mentioned in your consideration of these types of findings in meta-analysis is your understanding of the changes in the Daubert standard with respect to what courts are looking for?

A. No, I'm not making a legal -- I was not trying to make a legal conclusion for you guys. That's your job. I'm simply saying, I recognize that -- I'm simply saying that even in the legal field, the standard of what is big and small, if I am understanding the legal ramifications, has changed also in the last 20 years.

Q. There are certain guidelines that have been set forth on how to conduct meta-analyses; correct?

A. Yes.

Q. And you cite to such guidelines in your expert report; correct?

MR. TRAVERS: What page is that?

MR. LASKER: Page nine.

A. Yes.

Q. And in particular, you cite to an article, and this is the third full paragraph in the meta-analysis, in discussing how to perform a meta-analysis, you cite to a -- guidelines prepared by Walker, Hernandez and Kattan in 2008; correct?

A. 2008?

Q. Yes.

A. Um-hum.

Q. Is that correct?

A. Yes.

Q. This is an article that you rely upon as authoritative in providing guidelines on proper approaches for meta-analyses; correct?

A. Yes. Again, I don't do them personally, but as a reference.

MR. LASKER: Let's mark this paper as 14-10.

(Exhibit 14-10, Cleveland Clinic Journal of Medicine, June 2008, Meta-analysis: Its strengths and limitations marked for identification, as of this date.)

Q. Dr. Neugut, this is the guideline article that you cite in your expert report for meta-analyses; correct?
A. Yes.
Q. So, as one of the key points at the beginning on this first page of the Walker guidelines, one of the key points that is stated right under the abstract, is that there are many caveats in performing a valid meta-analysis, and in some cases a meta-analysis is not appropriate and the results can be misleading. Correct?
A. Yes.
Q. And you agree with that; correct?
A. I suppose, yes.
Q. And on page 436, there is a section on randomized control trials versus observational trials.
A. I'm sorry, page?
Q. 436. Do you see that?
A. Yes.
Q. And the Walker guidelines state that some researchers believe that meta-analysis -- meta-analyses should be conducted only on randomized control trials;

correct?
A. Yes.
Q. And that is because -- let's take a step back and define, a randomized control style -- a randomized control trial is a different type of epidemiological study where, for instance, in drug studies, where they will have a placebo group and a control group, and the investigators will provide the medication to the subjects and actually have a controlled study going forward; correct?
MR. TRAVERS: I object to the testimony of counsel.
A. A randomized control trial is a cohort study where the -- where the investigators provide the exposure to the subjects.
Q. Okay. So, let me make sure I understand your testimony then. Is it your testimony that a randomized control trial is a -- is a type of cohort study?
A. Yes. I mean it's a specialized form. It falls under -- there are only two kinds of studies in epidemiology, cohort studies and case-control studies. A

randomized trial is a specialized -- falls under the rubric of cohort studies. I mean --
Q. Okay. Fair enough.
A. But, I mean, it's an easy -- it's an easier form of study to analyze, because you have -- you are giving the exposure to the individual or not giving the exposure to the individual, rather than having it be decided upon by subject choice or by, you know, random -- by -- not random, but by -- well, by subject decision.
Q. The concern that the Walker guidelines are noting here with meta-analyses outside of randomized control trials is that observational trials are more prone to confounding and bias errors than randomized control trials; correct?
A. I think they are saying that to meta-analyze observational studies, there is going to be heterogeneity between the studies, so it makes it a little more difficult or makes it more difficult to combine them in a way where you can be confident that the result that you get is not

due to some -- something other than purely the exposure and outcome relationship.
Q. And there -- the meta-analysis methodology does not allow for the investigators to address problems of confounding or bias in the underlying studies; correct?
A. In the usual meta-analysis, the answer is, for the most part, no. For the most part, no. Again, I'm not an expert in meta -- I mean, I can read them, I can analyze them, but for the most part, the answer is no.
Q. Okay. Just to be clear for my question, so the answer is no, in a meta-analysis, you cannot fix problems of bias or confounding in the underlying studies.
MR. TRAVERS: Objection, misstates.
A. I don't want to misstate it. I mean, the truth is that generally speaking, if you put together several studies, the biases are going to dilute out presumably over the -- over the several studies, and it's probably not going to be as big a

problem as -- you know, as people think or as one might presume.

You can't -- bias is omnipresent. So, if you are going to start just throwing around the word "bias," and say, "Bias, bias, bias, the study sucks," then you can throw out 90 percent of the epidemiology studies, and then we know nothing about anything.

But you have to look at studies and use judgment and common sense, and assess how big the bias is, how important is the bias, how well does the study address the bias, and then put them together, and that's part of the methodology of putting -- of doing a meta-analysis, is to qualitatively assess them as well.

Q. Okay. So, just so the record is clear, if an underlying study has an issue with recall bias --

A. Every study has an issue with recall bias.

Q. I understand. Let me ask the question.

If an underlying study has a problem with recall bias, the meta-analysis

methodology will not change that; correct?

MR. TRAVERS: Objection, asked and answered.

A. Not necessarily, no, but then again, you have to ask yourself how big is the recall bias. You have to ask yourself why is it only in non-Hodgkin's lymphoma. You have to ask yourself why -- you know, how -- it's not enough to say recall bias, the study can't be looked at.

Q. I'm not -- that wasn't my question. Mine is a methodological question, and we will be discussing individual studies. But methodologically, a meta-analysis does not provide any -- does not fix an underlying recall bias in one of the underlying studies; correct?

MR. TRAVERS: Objection, asked and answered.

A. No, it does not.

Q. And the meta-analysis would not fix an underlying selection bias in any of the studies, underlying studies; correct?

A. No, it would not.

Q. And a meta-analysis would not fix a

problem with confounding in any of the underlying studies; correct?

A. Not if the study itself did not address it, no.

Q. Now, another concern raised about meta-analysis in these Walker guidelines, and you mention it as well in your expert report, is the issue of publication bias; correct?

A. Yes.

Q. And publication bias occurs where investigators will not submit findings where there is no showing of a statistically significant result because those data are, for whatever reason, perceived as being less interesting; correct?

MR. TRAVERS: Objection, misstates the evidence.

A. That is a little simplistic. I would say publication bias is more complicated than that.

Q. But the concern about publication bias is that statistically significant associations are published and findings that are null are not published. That would be a publication bias; correct?

MR. TRAVERS: Objection, asked and answered.

A. So, the entire epidemiology methodologic system is set up to be conservative, so that null findings are the norm. We don't want to find positive findings. The system is set up not to find positive findings. It's biased, for lack of a better word, to avoid finding positive findings. Sort of like the legal system, you don't want to find someone guilty, you want everyone to be innocent unless they are really guilty.

So, on some level that's how epidemiology is constructed. So, when you have a positive finding, it's taken more seriously than when you have a null finding. So, on a certain level, publication follows that -- that track or that scenario, so that when you do have a positive finding, an editor, a publisher, a reviewer takes a positive finding as something that is more significant than several negative findings or null findings. I don't mean negative, that may have been null.

And so, so it's more important to report positive findings. So yes, there is some bias towards publishing positive findings, but that is how the system -- that is not necessarily a, let's say a, a criticism. That is not necessarily a, a bad thing in the literature. That may be the way it should be, that -- I mean, it wasn't intended that everything should come out 50/50, you know, that 50 percent of the studies should be null and 50 percent of the studies should be positive.

But then again, some of the publication bias is also that some studies never reach -- there's publication bias in other ways, that some studies, if you started off and you wanted to recruit 200 patients into your sample, and you ended up running out of money after 100 people, so you never finished your study, so those studies don't get published either, because you only reached 100, and so a half study -- half studies don't get published either. So, that is part of publication bias also.

What happened to all those, you

know, incomplete -- there are incomplete studies that are part of publication bias, too. There are all sorts of -- if you want to call them biases that -- you know.

Q. Well, just to be clear, because "publication bias" is the term in your expert report, and it's also in the Walker guidelines that you cite to, just so I am understanding the term correctly, publication bias refers to the situation where positive findings are published but null findings in another study may not be published; correct?

A. Publication bias refers to where anything isn't published that could have been, should have been, might have been published. Could be positive findings. As I say, if you didn't finish a positive study and it never got published, or you dropped dead before your successor could -- and so no one ever picked up the study to submit it to a journal, that is also publication bias. It goes both ways.

I suspect, as you say, more null findings are not published than positive findings, but it's also true that there

are -- I'm sure there are positive findings. I have many papers that are sitting in my computer on my hard drive that I thought were the greatest studies ever done, and that have been rejected by ten or 12 journals and that are not published, and they are sitting there gathering dust in my computer that, you know, I think the world is waiting to see, and no journal will publish them, and who knows? You know, so, there is that bias, too.

Q. Okay. But specifically with respect to this, the guidelines for meta-analysis, the concern that you raise and that Dr. Walker raises in his guidelines is that positive findings may be published and null findings may not be published; correct?

MR. TRAVERS: Objection, misstates.

A. That tends to be the way it goes. Yes.

Q. And the meta-analysis guidelines you cite in your expert report state that, quote, to ameliorate the effects of publication bias on the results of meta-analysis --

A. I'm sorry. Are you quoting me now

or you're quoting this?

Q. I'm quoting your guidelines, and if you want, it's on page 432.

MR. TRAVERS: Objection. They are not his guidelines.

A. You are quoting this.

Q. Okay. The Walker guidelines cited in your expert report. The meta-analysis guidelines you cite in your expert report state on page 432, and it's in the second column, the third full paragraph, "to ameliorate the effect of publication bias on the results of meta-analysis, a serious effort should be made to identify unpublished studies." Right?

A. Yes.

Q. And the same guidelines that you cite in your expert report, on page 433, state, in the border, "Exclusion of non-published studies increases selection bias." Correct?

A. Yes.

Q. How can the exclusion of non-published studies from meta-analysis increase selection bias?

A. I'm sorry, say it again.
Q. How can the exclusion of non-published studies from a meta-analysis increase selection bias?
A. I suppose if you haven't included every study, then you are -- you have to be concerned that you are biasing the results upward.
Q. And these recommendations in the Walker guidelines that you cite in your expert report, they are consistent with lots of other meta-analyses guidelines on how to treat unpublished studies, aren't they?
A. I don't know.
Q. So, you have also written about the use of time trends for the incidence of specific cancers to provide some clues as to potential causes of cancer; correct?
A. I have?
Q. Yes.
A. I guess.
Q. Well, let's go back to your chapter on epidemiology and prevention in the ASCO-SEP, and I didn't write the number on this one. Which is this? 14-8.

A. That is the ASCO-SEP?
Q. Yes.
MR. TRAVERS: And this is a 1996 article?
MR. LASKER: No. This is 2014, maybe. I don't know when this -- the copyright is 2013.
Q. That's it. And on pages, I think two and three, you are discussing some sort of time trends that you -- to compare against exposures to sort of get some clues as to causation; correct?
A. Yes, um-hum.
Q. So, for example, you show how time trends in lung cancer incidence can be traced to increases and decreases in smoking; correct?
A. Yes.
Q. And when you do a time trend analysis for cancer, you need to account for latency; correct?
A. Oh, it depends, but depending on the context, yes.
Q. And generally, just so the record is clear, the issue for latency is that for

cancer, there is usually a period of years after an exposure before cancer would be developed and diagnosable; correct?
A. Depends on what the exposure and the outcome is.
Q. But the concept of latency is that there is some time period that elapses from exposure until a cancer; correct?
A. Yes.
Q. And you would then be looking -- for time trend, you would be looking for impacts on the cancer rate some years after changes in the exposure incidence; correct?
A. Again, it would depend on the specific context that we are talking about. It varies from -- every exposure and every outcome has its own unique idiosyncratic relationship.
Q. Plaintiffs' expert Dr. Weisenburger has, and he's an expert in this litigation for plaintiffs, has opined that the latency created for non-Hodgkin's lymphoma caused by pesticide exposure would be on the order of ten years or more. Does that sound right to you?

MR. TRAVERS: Objection. Do you have his report, if you are going to ask about it?
Q. First off, while we are getting the report, out, let me ask you, does ten years sound like a reasonable estimate of the latency for non-Hodgkin's lymphoma following pesticide exposure?
A. I wouldn't have any basis on which to make a judgment.
Q. You have not looked at that question?
A. No.
Q. You do agree that the issue of latency is a significant factor in analyzing epidemiological findings; correct? For cancer.
A. Say the question again.
Q. You do agree that this concept of latency is an important issue to be aware of in reviewing findings from epidemiological studies of an exposure and an cancer outcome.
A. I think if one has a specific epidemiologic association and mechanism, then the answer is yes.

Q. And Dr. Weisenburger's report --
MR. LASKER: Let's mark as -- what did I say it was? 14-11.
(Exhibit 14-11, Expert Report of Dr. Dennis Weisenburger, M.D. marked for identification, as of this date.)
Q. It's Dr. Weisenburger's report, and we are marking pages one through six, because that's the section in which he discusses the issue of latency.
MR. TRAVERS: I will object, that it's not the full report.
MR. LASKER: That's fine.
Q. And on page five of his expert report, Dr. Weisenburger is talking about the issue of latency; correct?
A. I'm on page five. Can you point out --
Q. The whole paragraph on page five.
A. The one that begins, "Only one large cohort study"?
Q. That's it.
A. Can I have a moment to look at it?
Q. You can.
A. Okay. What is the question?

Q. So, Dr. Weisenburger in this paragraph is talking about the issue of latency for pesticide exposure and non-Hodgkin's lymphoma; correct?
A. Yes.
Q. And Dr. Weisenburger talks about 6.7 years as perhaps being too short of a time period to account for latency between pesticide exposure and non-Hodgkin's lymphoma; correct?
A. In terms of latency?
Q. Yes.
A. Yes.
Q. And he talks about various studies and suggests a cutoff of ten years as being the, you know, reasonable estimate of the latency period for exposure to pesticide and non-Hodgkin's lymphoma; correct?
A. Yes.
MR. TRAVERS: Objection, misstates his opinion.
Q. And do you have any reason to disagree with Dr. Weisenburger's analysis of this issue of latency?
A. Do I have any reason to --

Q. Disagree with Dr. Weisenburger's analysis of latency.
MR. TRAVERS: Objection, calls for speculation.
A. I have no basis on which to agree or disagree. It would depend on what -- whether one thinks that glyphosate is a tumor initiator or a tumor promoter. You know, latency periods can be as short as one or two years, depending on the exposure and the outcome.
And I am not sure, even as I sit here, what the actual mechanism is by which -- that is not my expertise per se, what the precise mechanism is by which glyphosate causes non-Hodgkin's lymphoma biologically, so I would have difficulty characterizing the latency period, but I have no reason to doubt his expertise.
Q. So, just to be clear, you do not have an expert opinion on the latency period for glyphosate exposure and non-Hodgkin's lymphoma?
A. Correct.
Q. And you do not have an expert

opinion that glyphosate is a tumor promoter; correct?
A. As opposed to an initiator?
Q. Yes.
A. Well, it wasn't shown to be a mutagen, so I guess once it's not a mutagen or -- I don't know -- as I said, I don't know specifically its exact mechanism of how it's causing -- how it is precisely causing cancer.
Q. So for a -- if we are doing a time trend analysis of non-Hodgkin's lymphoma, if Dr. Weisenburger is correct with a ten-year latency period, we would want to look and see how incidence of non-Hodgkin's lymphoma changed ten years after exposures to glyphosate? Is that a correct understanding of how the time trend analysis would work?
MR. TRAVERS: Objection, compound and misstates Dr. Weisenburger's testimony.
A. Are you talking now on a population scale?
Q. Yes. Like the way you presented in your chapter.

A. So, when I talk about it in my chapter, we are talking about lifestyle factors that are prevalent across an entire population, like cigarette smoking or postmenopausal women taking hormonal -- you know, menopausal hormones, which is a very widespread phenomenon.

If you are talking about exposures where only a small fraction of the population is actually exposed, and where the relative risk is 1.2 or 1.3 or 1.4 -- let's say 1.3 or 1.4, then to see that impact on the -- you know, on the population prevalence of non-Hodgkin's lymphoma would require quite a -- that would be rather -- rather profound. I don't know if you would see it on a population scale.

Q. So, is it your understanding that exposures to glyphosate in the population are rare?

A. No. It's fairly common, but in a -- in a selective portion of the population.

Q. And those would be sort of agricultural populations?

A. Agricultural, gardeners, you know, my wife, I don't know, but she's got tomato plants now, but -- so, it may be profound. I don't know. It's not my -- again, I am not going to put myself up as an expert in that regard, in how much the attributable risk is going to be across the population.

I'm simply saying that if you want to see a population effect, it has to be a fairly prevalent -- it's not just -- it's both the risk and the prevalence of exposure that is significant in order to see a -- to see a population-based time trend change, you know.

Q. Fair enough.

A. In addition to the latency. You know, I mean then first latency will play a role and you might have to wait -- again, if he says ten years, you might have to wait ten years to first see it show up.

Q. Dr. Neugut, in your report, you -- your expert report, you note that epidemiological studies use a multistep process to establish causal inferences; correct?

A. Yeah.

MR. TRAVERS: What page?

Q. Well, if you need to refer to your expert report for this, it's at page six.

But first, principles of causal inference are used to construct theories which help us formulate testable hypotheses; correct?

A. Yes.

Q. Epidemiologists then design studies to test those causal hypotheses; correct?

A. Yes.

Q. And that is the definition of a scientific method; right? The formulation of hypotheses and the testing of those hypotheses to determine whether they can be validated; correct?

A. Yes.

Q. And you also agree that a hypothesis generally cannot be validated based upon the results of any one epidemiological study; correct?

MR. TRAVERS: Objection, calls for speculation.

A. Any one single -- well, I'm sorry,

say that question again.

Q. You would agree that a hypothesis generally cannot be validated based upon the results of any one epidemiologic study.

MR. TRAVERS: Same objection.

A. You mean could there be one single epidemiologic study which is so terrific or so profoundly good that I could reach a conclusion based solely on that? The answer is, there probably could be.

Q. But as a general matter?

A. But -- and there have been, so the answer is, I don't agree with that statement, but I think with -- with risk ratios like this, and prevalences like this, this isn't one of the contexts where that is probably going to be true.

Q. Okay. So, in the context particularly that we are dealing with here, a scientist following the scientific method would be formulating hypotheses, testing those hypotheses to see if they could be validated, and then testing those hypotheses again to determine whether those findings are replicated; correct?

A. Yes.
Q. Epidemiologist studies also -- strike that.
Epidemiological studies sometimes will report out results that are not linked to any preset hypothesis; correct?
A. So, could you just define that a little better for me?
Q. So you -- epidemiological studies, they can have a hypothesis that they are designed to test.
A. Right.
Q. But they can also report out other results that are not part of the original hypothesis, but they have the data; correct?
A. Yes.
Q. And those types of studies are often studies that report out a large number of different potential associations relating to different exposures; correct?
MR. TRAVERS: Objection, calls for speculation.
A. Yes.
Q. Those are often referred to as exploratory studies; correct?

A. Sometimes, yes.
Q. And in those studies, the results can generate future hypotheses that then must be tested through studies that are designed to test those hypotheses; correct?
MR. TRAVERS: Objection, calls for speculation.
A. So, again, how much weight you put on them really is again a contextual question, but in general, I would probably agree with what you are saying.
MR. LASKER: And just in -- objection, calls for speculation, with an expert witness I have never heard before. All of his testimony is his opinion, none of it is speculation, so I'm going to object to your objection.
MR. TRAVERS: Well, you are asking for speculation.
MR. LASKER: I'm asking for his opinions.
Q. So, just so I understand, when an epidemiologist reviews the findings of an epidemiological study, one question that must be considered is whether the study was

designed -- let me state that again.
When an epidemiologist is analyzing the finding of an epidemiological study, one question that must be considered is whether that study was designed to test the hypothesis that is the subject of that epidemiologist's inquiry; correct?
MR. TRAVERS: Objections, calls for speculation.
A. Whether it was the primary hypothesis?
Q. Correct.
A. Yes.
Q. Okay. Let's talk about the -- some of the specific epidemiological studies you mentioned in your expert report. And let's start with the De Roos study, 2005 De Roos study. There is two of them.
MR. LASKER: We will mark that as Exhibit 14-12.
(Exhibit 14-12, Environmental Health Perspectives, January 2005, Cancer Incidence among Glyphosate-Exposed Pesticide Applicators in the Agricultural Health Study marked for identification,

as of this date.)
Q. And Dr. Neugut, we have already had some brief mention of this study. The De Roos 2005 is part of a larger initiative called the Agricultural Health Study; correct?
A. Yes.
Q. And the Agricultural Health Study is funded by the National Cancer Institute and the National Institute of Environmental Health Sciences in collaboration with EPA and the National Institution of Occupational Safety and Health; correct?
A. Yes.
Q. The AHS study is not funded by private companies; correct?
A. Not to my knowledge.
Q. Monsanto does not fund the Agricultural Health Study; correct?
A. I don't think so.
MR. TRAVERS: Objection, which -- I think we have to be specific, because there is one AHS study funded by Monsanto.
MR. LASKER: That's not correct.

MR. TRAVERS: It's from the AHS cohort.
Q. Dr. Neugut, specifically, De Roos 2005 was not funded by Monsanto; correct?
A. I would have no idea, but not to my knowledge.
Q. The Agricultural Health Study, and specifically De Roos -- well, the Agricultural Health Study is the only prospective cohort study that has looked for a possible association between glyphosate and cancer; correct?
A. The only cohort study, yes.
Q. Yes.
The Agricultural Health Study was initiated to address some of the limitations of case-control studies that had looked at potential associations between farming exposure and cancer; correct?
MR. TRAVERS: Objection, calls for speculation.
A. I don't know, but I assume.
Q. Okay. Can you pull out Dr. Blair's deposition testimony again. It should still be in front of you. I think it's probably

over there.
Dr. Blair is one of the initiators, one of the original investigators for the Agricultural Health Study; correct?
A. He's a coworker.
Q. And if I can refer you to Dr. Blair's deposition testimony at page 94, specifically, line -- page 94, lines six to 16, Dr. Blair testifies that the Agricultural Health Study was initiated to address some of the limitations of case-control studies that had looked at potential associations between farming exposures and cancers; correct?
A. And his answer was, "It was initiated and formed to provide a different design to look at the same issue."
Q. And then the next question:
"It was initiated at least in part to address some of the limitations of case controlled studies; correct?
"Answer: Yes."
A. Yes.
Q. You have no reason to doubt that, do you?
A. No.

Q. The AHS study was initiated to avoid the problem of recall bias in case-control studies; correct?
A. Yes.
Q. The Agricultural Health Study also was designed to avoid misclassification bias; correct?
A. Misclassification bias of what type?
Q. Misclassification of exposures.
A. How did it do that?
Q. By going to farmers that had better recall and also periodic follow-up.
MR. TRAVERS: Objection, move to strike.
A. So, you are saying it did not have misclassification bias? Misclassification error?
Q. I direct you to Dr. Blair's deposition testimony at page 96, line two through seven.
A. To try and deal with issues of misclassification.
Q. Yes.
"The Agricultural Health Study was

also designed to try and deal with issues of misclassification of exposures by going to farmers, who you testified earlier had better recall, and also periodic follow-up; correct?
Answer by Dr. Blair: "Yes."
A. I emphasize the word "tried."
Q. You have no reason to believe that that was part of the effort in the design of the Agricultural Health Study; correct?
A. That was part of the --
Q. Effort in the design of the Agricultural Health Study.
A. Effort?
Q. You have no reason to doubt Dr. Blair's testimony that --
A. That was part of the effort?
Q. Yes.
A. Okay. Fair enough.
Q. Now, the Agricultural Health Study, I think as you note in your report, includes some 57,311 private and commercial applicators who are licensed to apply restricted-use pesticide at the time of

enrollment into the study; correct?
A. Yes.
Q. And Dr. Neugut, I think it's going to be easier for the videographer if you could remove your hand --
A. I apologize.
Q. No problem. I think the court reporter is getting it, but --
MR. TRAVERS: We have been going over an hour.
MR. LASKER: Do you want to take a break?
MR. TRAVERS: Yeah, before you get into it.
MR. LASKER: That's fine.
THE VIDEOGRAPHER: The time is 11:35 a.m. We are off the record.
(Recess taken.)
THE VIDEOGRAPHER: The time is 11:41 a.m. We are on the record.
THE WITNESS: Thank you.
BY MR. LASKER:
Q. Dr. Neugut, before the break, we were talking about the Agricultural Health Study. The Agricultural Health Study focused

on private and commercial applicators of pesticide because they were likely to have the highest levels of exposures to pesticides; correct?
A. Yes.
Q. The hypothesis being tested in De Roos 2005 was whether glyphosate exposure was associated with cancer or cancer subtypes; correct?
A. Oh. Yes.
Q. And we will -- I'm going to turn to some of the comments you have in your expert report in a minute, but you would agree, I take it, that De Roos 2005 does not provide evidence that would validate the hypothesis that glyphosate exposure causes non-Hodgkin's lymphoma; correct?
A. Yes.
Q. And De Roos 2005 did not find an association between glyphosate exposure and non-Hodgkin's lymphoma either in its analysis adjusted solely for age or in its analysis controlling for other pesticides or other potential confounders; correct?
A. Correct.

Q. De Roos 2005 also does not find any increased association with non-Hodgkin's lymphoma with higher exposure levels to glyphosate either measured by duration or measured by duration and intensity of exposure; correct?
A. Correct.
Q. The days of exposure to glyphosate-based herbicides in the exposed members in the Agricultural Health Study cohort in De Roos 2005 was significantly higher than any reported days of exposure in the glyphosate case-control studies; correct?
A. In the glyphosate --
Q. Case-control studies.
A. Yes.
Q. The lowest exposure group in De Roos 2005 had between one and 20 total days of glyphosate exposure; correct?
A. Yes.
Q. The lowest exposure group in De Roos 2005 includes individuals who would be categorized in the highest exposure groups in both McDuffie and the Eriksson 2008 studies; correct?

A. Yes.
Q. The highest exposure group in the Eriksson study was ten days or more; correct?
MR. TRAVERS: Objection. If we are going to ask about specific studies, I think we need the --
A. I don't recall offhand.
MR. LASKER: Okay. Well, if you want to refer to the study, we can do that.
Mark this as 14-13.
(Exhibit 14-13, Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis marked for identification, as of this date.)
Q. So, this is the Eriksson study and -- a 2008 study, and at page 1659 in that study --
MR. TRAVERS: Sorry, do you have a copy?
MR. LASKER: I'm sorry, I didn't include you?
MR. TRAVERS: Or did you?
MR. LASKER: Is that what's in your

hand?
MR. TRAVERS: No. This is De Roos.
MR. LASKER: I'm sorry.
Q. So table two of Eriksson shows that their breakout for the low exposure group and the high exposure group is ten days; correct?
A. Yes.
Q. So, the lowest exposure group in -- or the highest exposure group in the Eriksson study included -- would be within the lowest exposure group in De Roos 2005; correct?
A. Well, maybe yes or maybe no. It could have been --
Q. Partially.
A. Overlapped it.
Q. The highest exposure group in the McDuffie study, and if you need to, I will show you that study, was greater than two days per year; correct?
A. Yes.
MR. TRAVERS: I'm going to object. If we are going to ask about the specific figures in a study, I think we need to --
Q. If at any time, you need to refer to a study, let me know.

A. That one I remember.
Q. Okay. So, the middle exposure group and the dose response analysis in De Roos 2005, and this is the De Roos 2005 paper at 52, table three, that middle exposure group had between 21 and 56 days of exposure; correct?
A. Yes.
Q. And compared to this lowest dose group, individuals with this higher duration of glyphosate exposure had a non-statistically significant 30 percent lower risk of non-Hodgkin's lymphoma; correct?
A. Yes.
Q. The highest exposure group in De Roos 2005, in the dose-response analysis, had between 57 and 2,678 days of glyphosate exposure; correct?
A. Yes.
Q. So, there was at least one individual in the De Roos 2005 study that had the equivalent of more than seven years' worth of daily glyphosate exposure; correct?
A. Yes.

Q. And compared to the lowest dose group, the risk of non-Hodgkin's lymphoma in this highest dose group, up to as much as seven years of daily glyphosate exposure, was also reduced; correct?
A. Yes.
Q. De Roos 2005 also analyzed dose-response for glyphosate based upon the intensity of glyphosate exposure; correct?
A. Yes.
Q. And De Roos 2005 calculated intensity of exposure based upon factors like how glyphosate was used and whether the applicator used protective gear; correct?
A. Yes.
Q. None of the case-control studies in the glyphosate literature included any measure of the intensity of exposure to glyphosate.
MR. TRAVERS: Objection, misstates evidence.
A. None of the --
Q. None of the case-control studies in the glyphosate epidemiological literature include any measure of the intensity of

exposure to glyphosate; correct?
MR. TRAVERS: Same objection.
A. I don't believe they do.
Q. De Roos 2005 also reported that there were lower risks of non-Hodgkin's lymphoma with increased duration and intensity of glyphosate exposure; correct?
A. Yes.
Q. There is no data anywhere in the epidemiologic literature reporting a higher risk of non-Hodgkin's lymphoma with greater intensity exposures to glyphosate; correct?
MR. TRAVERS: Objection, misstates evidence.
A. I'm sorry.
Q. There is no data anywhere in the epidemiologic literature reporting a higher risk of non-Hodgkin's lymphoma with greater intensity exposure to glyphosate; correct?
A. Not to my knowledge.
Q. So, there is no such data; correct?
MR. TRAVERS: Objection, asked and answered.
A. Again, to my knowledge, no.
Q. Now, in your expert report, you

identify four criticisms of De Roos 2005; correct? And we can go -- it's on your report at pages 12 to 13.

A. Yeah, I mean --

Q. If you want to pull your report out, we can walk through this. And in your report on page 12, you identify four limitations in the De Roos 2005 paper; correct?

A. Yes.

Q. I would like to talk with you a bit about those criticisms.

First, I believe I am correct that three of these criticisms relate in some way to the length of follow-up in the study, and when exposures to glyphosate would have occurred in comparison to the development of non-Hodgkin's lymphoma. Correct? Criticisms one, two, and four?

A. Yes, but -- well, four is more complicated, but the one and two, you are correct.

Q. Okay. Well, we will get to four in a minute, and we will also get to one and two in a minute.

Let's start with number three. I want to understand that one first. I'm putting those into one category and three in the other.

A. Okay.

Q. So, with respect to your third criticism, and this is set forth on page 13, in this criticism you are, if I understand correctly, raising the concern that there may be an elevated risk of non-Hodgkin's lymphoma in the control group due to exposure to another pesticide; correct?

A. As you stated earlier, farmers are at elevated risk -- forget about why, whether it's because of other pesticides, herbicides, et cetera, farmers are at elevated risk of lymphoma. I mean, I think it's a good study design to use farmers as the overall sample population, mainly because it's a population in which you are going to get a large number of people exposed. That's why it's a good sample, you know, sample universe, but then when you are looking for a risk ratio, you are already starting off with a higher risk in the unexposed group.

Q. Well, correct, but there is no differential with farmers. There is farmers in the numerator and there's farmers in the denominator; correct?

MR. TRAVERS: Objection. I think that misstates the study design.

A. Yes, but it's harder to see a -- to see an elevation when you are starting off with a higher -- from a higher platform, or it may be -- it may be harder to see an elevation when you are starting off from a higher platform.

Q. Well, I'm a little bit confused about that. If you were, for example, to do a study of -- an epidemiological study of asbestos and smoking, to be able to do that study, you might want to start off with a full cohort of smokers and then look at asbestos in the differential; right?

A. You are right.

Q. Having smokers be your entire population doesn't undercut the study. It actually allows you to look at the exposure you are interested in; right?

A. It --

Q. Dr. Neugut, is that correct?

A. I'm thinking.

Q. Okay. No, continue. I'm sorry. I didn't know if your mind was turning to something else.

A. So, even in the context of multicausal phenomena, which is essentially what we are in a sense talking about, it is still a little harder to see elevated risk ratios in that. While yes, you can still account for an elevated risk in the context of other causes, like other herbicides or other risk factors that farmers may have for lymphoma, but it's still harder to see it on top of that elevated risk than if you were in a population where there was no elevated risk of non-Hodgkin's lymphoma.

Q. Well, all populations have different risk factors that could impact an outcome. What you are trying to do in an epidemiological study is -- and specifically with glyphosate, is to tease out the glyphosate impact; correct?

A. Correct.

Q. And in that context, you don't want

to have different -- you know, where you have more farmers in the numerator and less farmers in the denominator.

A. No, that is true, but it's a tradeoff of sorts. You know, you also have -- you're comparing high exposed to low exposed, which is different than comparing high exposed to unexposed.

Q. Yes, I understand. That is a different issue, but not the issue we are talking about on page 13 of your report. Correct?

A. No.

Q. Okay. So, specifically on page 13 of your report, this third criticism, though, the concern you are mentioning is that the control group, the individuals not exposed to glyphosate, would have had exposures to other pesticides, and specifically you mentioned 2,4-D; correct?

A. Um-hum, yes.

Q. And the point you are making there is that 2,4-D might be associated with non-Hodgkin's lymphoma.

A. Yes.

Q. And therefore, the cases, the denominators that are in the -- in the risk ratio, would have a higher incidence of non-Hodgkin's lymphoma that is not attributable to glyphosate; correct?

A. Yes.

Q. And the reason that would occur is, as you hypothesize in your expert report, if individuals -- individuals who use glyphosate are less likely to use 2,4-D; correct?

A. Okay. Yes.

Q. And that is because you would have fewer 2,4-D exposure, less 2,4-D exposure in the glyphosate-exposed individuals that could push their risk up; correct? As compared to the cases. Strike that.

A. I don't know.

Q. I will restate that.

The concern that you are raising in your report is that if there are -- if there is a difference in the incidence of exposure to 2,4-D between the glyphosate exposed and the glyphosate non-exposed, that would potentially bias your outcome for the glyphosate -- reported glyphosate risk ratio;

correct?

A. Well, more if they are misclassified between the two of them, but yes.

Q. And your concern here is that because there are 2,4-D exposure -- 53 percent of the control group has exposure to 2,4-D, that can result in De Roos reporting an underestimation of the true NHL risk with respect to glyphosate; correct? That's what you state in your report.

A. Yes.

Q. Now, you were able to determine that 53.3 percent data point for the use of 2,4-D in controls from De Roos 2005; correct? That's data you got from the De Roos study?

A. I believe so.

Q. Let's pull out the De Roos study again. That is page -- Exhibit 14-12, and it's on page 50, table one, I believe. And the data point for never exposed to glyphosate and exposure to 2,4-D is in that first column of table one, towards the bottom; correct?

A. Yes.

Q. And there it reports that individuals never exposed to glyphosate, 53.3 percent of them were exposed to 2,4-D; correct?

A. Yes.

Q. Now, directly to the right of that, the second column reports the prevalence of exposure to 2,4-D among individuals with the lowest exposure level of glyphosate; correct?

A. Yes.

Q. And they actually had a higher exposure rate to 2,4-D than those who were never exposed; correct?

A. Yes.

Q. And in the highest exposure group for glyphosate, the third column, those individuals had an even higher exposure rate to 2,4-D; correct? 85 percent?

A. Um-hum, yes.

Q. So, based upon the analysis in your expert report, if 2,4-D was associated with an increased risk in non-Hodgkin's lymphoma, then that means that the effect reported by De Roos for glyphosate would actually be an overestimation of the NHL risk, not an

underestimation; correct?
A. If 2,4-D is associated with non-Hodgkin's lymphoma, correct.
Q. So, your expert report analysis here, your criticism number three was incorrect; right?
A. It's probably not a problem.
Q. If I could ask you to turn back to table one for De Roos 2005. There is also data on -- one, two, three, four, five, six, seven, eight -- I think nine other pesticides; correct?
A. Yes.
Q. And in every instance, with each one of these pesticides, individuals who have exposure to glyphosate also have higher exposures to those other pesticides; correct?
A. Yes.
Q. And in every instance, individuals with the highest level of exposure to glyphosate have the highest level of exposure to each of those other pesticides; correct?
A. Yes.
Q. And based upon your -- the analysis you presented in your expert report, that

would also create a bias that could artificially suggest a dose-response analysis with glyphosate exposure; correct?
A. Yes.
Q. So, the results in the study, to be clear, because exposure to glyphosate is associated with higher exposures to other pesticides, if you were to look simply at exposure to glyphosate and not adjust for exposures to other pesticides, you could find an apparent dose-response that in fact was due to confounding; correct?
A. If they were associated with NHL, yes.
Q. Now, I want to move to some of your other criticisms of the AHS study. On page 12 of your report, you talk about the follow-up period for the De Roos study, a median follow-up period of 6.7 years; correct?
A. Yes.
Q. And just so I am clear, you weren't stating here that De Roos 2005 only considered exposures that took place a median of 6.7 years prior to NHL diagnosis, are you?

A. No.
Q. The follow-up time is just the number of years after AHS had gathered information on prior exposures; correct?
A. Had gathered --
Q. Information on prior exposures.
A. Yes.
Q. At the time of -- that the AHS gathered information on prior exposures, the cohort on average had 15 years of prior exposure; correct?
A. I don't know, but I -- I believe they certainly had exposure prior to the time of entry.
Q. You read Dr. -- again, Dr. Blair's deposition.
A. Yes.
Q. Do you recall him testifying about this?
A. Yes.
Q. And Dr. Blair testified that at the time AHS gathered information at the inception, the cohort on average had 15 years of prior exposure; correct?
A. I don't recall that it was on

average. I know some had that much exposure. I don't know the distribution.
Q. Okay. Why don't we look at Dr. Blair's deposition testimony again. And this is at pages 96 -- page 96, lines 11 to 15. If you can read that and see if that refreshes your recollection.
A. I'm sorry, the page?
Q. Ninety-six. And lines 11 through 15.
Does that refresh your recollection that at the time that the AHS started gathering information --
A. Yes.
Q. -- there is an average of 15 years of prior exposure; correct?
A. Yes.
Q. And at the time that the Agricultural Health Study gathered information on the cohort's prior exposures, which was over the mid 1990s, glyphosate had been on the market for about 20 years or more; correct?
A. Yes.
Q. So, the AHS study allows for a

sufficient latency period between exposure to glyphosate and potential NHL; correct?
A. Yes.
Q. And the potential latency period in the De Roos 2005 study is up to 27 years; correct?
A. Yes, I think -- yeah, I don't think latency period is a major problem.
Q. Now, your concern, if I understand correctly, regarding the follow-up period in the AHS study is that longer follow-up would have resulted in more cases of non-Hodgkin's lymphoma; correct?
A. Yes.
Q. And that relates back to this issue about power; correct? More cases of NHL would give the study more power.
A. Yes.
Q. And that's also your point with respect to the age of the cohort. If the cohort was older, then would have more cases of NHL; correct?
A. Yes.
Q. Now, also, just to be clear, when you state in your expert report the age of

the cohort, that is data that is based upon the age at enrollment; correct?
A. At study entry, yes.
Q. So, the age of the cohort at the time of the actual De Roos analysis would be a median of 6.7 years older; correct?
A. Sure.
Q. So, the population at the time of the 2005 De Roos paper, for purposes of the analysis, would have been within that 50- to 55-year age range that you state in your report is where you see that exponential increase in cancer incidence; correct?
A. Well, "exponential" is a strong word, but let's say where you see an increase.
Q. Okay. I thought "exponential" was your word.
A. Oh.
Q. On page 12, you state in your report, "Ages" -- it's sort of towards the bottom on page 12. "Ages of 50 to 55 years, when we see an exponential increase in cancer incidence," about five or six lines from the bottom.

A. Then I guess it's a good word.
Q. So, the age of the cohort at the time of De Roos 2005 is right in that spot where we are seeing that exponential increase.
A. But it's just starting at -- it's still a young group.
Q. But again, the issue is, you want to get enough cases of NHL; correct?
A. And there are too few to really have enough power.
Q. So, now the -- now, the NHL -- I'm sorry. The De Roos study 2005 has 92 cases of non-Hodgkin's lymphoma; correct?
A. Yes.
Q. And the De Roos study in fact is one of the most powerful epidemiologic studies of glyphosate and non-Hodgkin's lymphoma, isn't it?
A. I don't know offhand, but does it have the tightest confidence limits?
Q. Well, let's look at your expert report. You have that information there, don't you?
Have you -- let me ask this

question. Have you looked to determine the relative power of the De Roos 2005 study as compared to the case-control studies for glyphosate in non-Hodgkin's lymphoma?
A. I haven't done power analyses on them, but in the -- you know, the --
Q. Can you state, sitting here today, whether there is any case-control study that is more powerful in answering the question whether glyphosate is associated with non-Hodgkin's lymphoma?
A. We don't talk about statistical power after a study is completed a posteriori. If you have a positive finding, then that is a more powerful study.
Q. Well, let me take a step back.
First of all, it's your criticism here that the Agricultural Health Study does not have sufficient power because of the years of the follow-up and the age of the cohort; correct? That is your criticism.
MR. TRAVERS: In.
A. And that in part because the -- yes.
Q. And in offering that criticism, you

do not know whether in fact the Agricultural Health Study, De Roos 2005, is the most powerful of all the epidemiologic studies to answer the question of whether glyphosate causes non-Hodgkin's lymphoma.

A. I did not do a power analysis.

Q. Let's look at -- you mentioned that one way you can determine the power of a study is by looking at the confidence intervals and the range of the confidence intervals. We talked about that earlier; right?

A. Yes.

Q. And in your expert report, you actually provide information on that on page 43, particularly where there is these forest plots of the different studies; correct?

A. Yes.

Q. And those forest plots, both the forest plot from Schinasi and Leon and the forest plot in Chang and Delzell, would allow you to look and see the relative weight of these different epidemiological studies and the different power -- relative power;

correct?

A. Yes.

Q. And of the case-control studies, the only case-control study that has -- is reported in these forest plots as having higher power than De Roos 2005 is the McDuffie study; correct?

A. Is what?

Q. Is McDuffie.

A. I'm sorry, is?

Q. McDuffie.

A. You are talking about in Chang and Delzell?

Q. Either one.

A. Yes.

Q. And the McDuffie study, the risk ratio there is not adjusted for other pesticides; correct?

A. I don't know offhand.

Q. Okay. Should we go to McDuffie and check that out?

MR. LASKER: And this is 14-14.

(Exhibit 14-14, Cancer Epidemiology, Biomarkers & Prevention by McDuffie, et al marked for

identification, as of this date.)

Q. And in particular, if you can look at table three on page 1159 of McDuffie. I'm sorry, table three. No, it's table two. Sorry, table two.

And they have the odds ratio for glyphosate of 1.2, which is the odds ratio you report on in your expert report and on page 43; correct? About midway through the table, the farthest to the right column.

A. Okay.

Q. And you can see that odds radio adjusted footnote B; correct?

A. Yes.

Q. And the footnote on the bottom explains what the odds ratio is adjusted for; correct?

A. Yes.

Q. It's not adjusted for exposure to other pesticides; correct?

A. Yes.

Q. So, of the odds ratios adjusted for other pesticide exposure, De Roos 2005 is the most powerful study that exists for glyphosate and non-Hodgkin's lymphoma;

correct?

A. I may or -- I don't know. Perhaps.

Q. Not perhaps. You have the numbers right here. De Roos 2005 is the most powerful study with respect to non-Hodgkin's lymphoma and glyphosate adjusted for exposure to other pesticides; correct?

MR. TRAVERS: Objection, asked and answered.

A. Okay. That may be.

Q. It is; correct?

MR. TRAVERS: Objection to the testimony of counsel.

A. Again, it's a little hard for me to be definitive as I sit here now and trying to make a decision in 30 seconds, in a minute, but okay, I will agree. But --

Q. This is not something that you considered in preparing your expert report and your criticism of the Agricultural Health Study.

A. That doesn't mean -- whether it has the most or the least, it doesn't have adequate power.

Q. And so then I take it your

testimony would be that none of the case-control studies have adequate power.

MR. TRAVERS: Objection.

Q. Correct?

MR. TRAVERS: Misstates the testimony.

A. Having power, having a positive finding is -- a posteriori is really enough. If you have a positive finding, the question of whether you had statistic power up front is really -- sort of begs the question.

Q. So, is it your testimony then that an epidemiologist would only consider the power of a study if the finding of a study is null?

A. I would say that in designing a study, you would be concerned about the statistical power in designing the study, but once you have a positive finding, the question of how much power you had up front is much less of a concern.

Q. So, if a study has --

A. Statistical power is -- statistical power is a concern in the context of the null find.

Q. So, if you have a study with very low power, very wide confidence intervals, but it's a positive finding, it's your testimony that you would not be concerned about the power of the study in weighing the importance of that study?

A. I'm sorry, can you repeat the question?

Q. Sure.

If you have a study that reports a positive finding with very, very wide confidence intervals, a very low power study, is it your testimony as an epidemiologist that you are no longer concerned about the power of that study?

A. Of course you are. Then you don't have a positive finding.

Q. No, no, let me strike that. Let me repeat it to make sure I am clear.

If you have a study that reports a statistically significant result with very wide confidence intervals, so it's a study with very low power but a statistically significant result, is it your testimony that as an epidemiologist, you are no longer

concerned with the power of that study?

MR. TRAVERS: Objection, asked and answered.

A. So, of course, if you are talking about a sample size where you get down to the level of six cases versus one, then you can consider it, and an epidemiologist would use his logic and his common sense, his or her logic or common sense to evaluate the study and all of that.

But the answer is, if you have a positive finding and it's statistically significant, then the consideration of statistical power in the context of a positive finding is less of a concern than it is in the context of a null finding.

And the issue of statistical power is an issue in the design of a study up front and whether you should be doing the study in the first place or whether you have enough power to do the study and whether it's going to give you the ability to define an outcome with enough confidence that you are going to get an answer.

If you end up with a null finding

and wide confidence limits, then you haven't answered the question that you started out with, which is basically what happened at least in the first report, in this report from 2005 with glyphosate.

Q. Dr. Neugut, there is no epidemiological study anywhere in the literature which reports in its most fully adjusted model a statistically significant increased risk of non-Hodgkin's lymphoma with glyphosate, is there?

MR. TRAVERS: Objection, misstates the evidence.

A. I'm unaware when you go up to the higher levels, maybe not with the ever/never analyses, but I think in some of the dose-responses, there are. What about De Roos 2003?

Q. De Roos 2003 did not have a dose-response -- the fully adjusted model, which is set forth on page 43 of your report, is not statistically significant.

MR. TRAVERS: Move to strike testimony of counsel.

Q. That's correct; right?

A. Yes.
Q. So, again, and you're talking about dose-response analyses, the only dose-response analysis anywhere in the epidemiological literature for glyphosate and non-Hodgkin's lymphoma adjusted for other exposures is De Roos 2005; right?
A. Yes.
MR. TRAVERS: Objection, misstates the evidence.
Q. So it is correct to state --
A. I'm sorry. Say the last point again before I say yes to that one.
Q. The only dose-response analysis adjusted for exposures to other pesticides anywhere in the literature --
A. Um-hum.
Q. -- in the epidemiological literature, is De Roos 2005; correct?
MR. TRAVERS: Objection, misstates evidence.
A. I don't know, but it sounds right.
Q. There is no odds ratio anywhere in the epidemiological literature that reports for glyphosate and non-Hodgkin's lymphoma an

adjusted odds ratio positive association statistically significant; correct?
MR. TRAVERS: Objection, misstates the evidence.
A. Not that -- correct, for the herbicides, for the -- um-hum.
Q. So, going back now to the issue of power, to the extent that you have a criticism of power with respect to the Agricultural Health Study, that same criticism in your mind applies to all of the case-control studies for glyphosate and non-Hodgkin's lymphoma; correct?
A. All of them have difficulties with power, yes. Non-Hodgkin's lymphoma is a rare outcome, and glyphosate is -- in many of them is an uncommon exposure, too.
Q. So, let's look now at the -- I think it's your -- I think it's your final criticism, maybe your second. Go back to page 12 of your expert report.
So, your second criticism is talking about the inability to determine disease latency for NHL in the AHS cohort; correct?

A. Yes.
Q. And this is that concept that we were talking about earlier, you want to have some period of time that has passed between the exposure and the outcome to account for this latency period for the development of the cancer; correct?
A. Yes.
Q. Okay. And your criticism here is that there might not be sufficient latency, or there is not -- there is not a way to tell whether there is latency between exposure and diagnosis; correct?
A. Yes.
Q. Now, the De Roos 2005 study, though, takes exposure data from that period of 1993 to 1997; correct? It considers exposures back in that 1990s time period; correct?
A. Yes.
Q. And so, there is in effect a lag time in that study, because you are looking at cancers that developed later in time than the exposures, than the latest possible exposure that you are looking at; correct?

A. I don't follow the question.
Q. So, at the time of enrollment, we had data for De Roos 2005 of exposures from the mid '90s back; correct?
A. Back?
Q. Into history. It could be as early as whenever they first were exposed.
A. I see.
Q. So, your exposure period is mid 1970s to the mid 1990s.
A. Yeah.
Q. Correct?
And then you are looking at non-Hodgkin's lymphomas that can develop as late as December 31, 2001; correct?
A. Yes.
Q. And to deal with the issue of latency, studies often will have this sort of lag period where they are looking for development of cancer at some period of time after the period of exposure; correct?
A. Yes.
Q. That is what De Roos 2005 in effect did; correct?
A. How did they do it?

Q. By having exposures that were up to the mid 1990s and having cancer development --
A. I see.
Q. -- at that later date; correct?
A. Yes. I don't think the latency thing is necessarily a problem here.
Q. Okay. So, criticism two in your report is not really as much of an issues as it might be otherwise.
A. So, it will vary from -- depending on the -- if you say -- if everyone truly had 15 years of exposure on average beforehand, then latency is probably not going to be a major problem.
Q. Okay. So, again, this is -- for your criticism two, I just want to make sure we are clear on your testimony. The second criticism you have of the AHS De Roos 2005 study in your report at 12, pages 12 to 13, it's probably not a major concern; is that fair?
A. I won't speak for the Weisenburger, but again, I will be -- you know, to my knowledge, I will say I am agnostic on the

subject.
Q. Okay. Let's talk about your final criticism then, your fourth criticism of the AHS study. And this is -- you are dealing here with non-differential exposure misclassification, and I think your point, your point here -- let me make sure I understand your -- your criticism.
You state that intensity of exposure to glyphosate was collected only for enrollment from 1993 to 1997; correct?
A. Yes.
Q. And your concern here is that there would have been a dramatic increase in the intensity of exposure potentially after that time period; correct?
A. Well, I really have two concerns, and I may not have stated it correctly here. I think we have been talking primarily about biases, but in a cohort study, you also have -- in every study, you also have the problem, as we said earlier, of non-differential misclassification, and I think there is probably enough non-differential misclassification that it

would have -- again, in the context of a null study -- if a null study, again, because epidemiologic analyses are conservative, they mitigate against positive findings, so non-differential misclassification attenuates risk ratios, so, having a null finding could easily arise from having significant misclassification of exposure.
Q. I have a few follow-ups on that. First of all, let me make sure, you said there are two issues here. One is non-differential misclassification.
A. That's in the first place, from the time of enrollment.
Q. And the second one is intensity of exposure.
A. Well, but --
Q. I'm just trying to understand if those are the two.
A. Those two. One is that, in the first place, when they filled out the questionnaires at enrollment, that they incorrectly stated their exposure.
Q. Okay. So that let me make sure I understand this. I just want to break out

the two opinions, so I understand them. The first opinion is that there would have been more intensity of exposure if they had subsequent measure --
A. More or less, or if they weren't exposed to glyphosate and confused it with a different --
Q. Well --
A. -- herbicide, or vice versa.
MR. TRAVERS: You have to let him finish answering.
Q. Okay. I just want to break it out. You said there is two.
A. So one is that -- so, when you fill out -- when you are asked about were you exposed to glyphosate, some people are going to say no when it's a yes; some people are going to say yes when it's a no. That's not recall bias, but just fill out the questionnaire wrong.
Q. I understand.
A. So, in general on questionnaires like that, there is a 10, 20 percent kind of error. If I ask you how much broccoli do you eat, you know, you are not going to --

Q. Well, I eat a lot of broccoli, but I get your point.
A. So, you are not going to fill it out -- you are not going to be right about -- and that degree of misclassification, when we are talking about a risk ratio of 1.3 or something of that sort, is enough to -- to nullify a -- a risk ratio in the realm of 1.3 or 1.4, again. So, when you get -- again, as I said, epidemiologic analysis is conservative. It -- errors generally attenuate -- generally are biased towards giving you a null finding. So that kind of an error or random misclassification -- again, this is not biased error, this is just people are just making innocent errors in filling out a form, that are random -- will bias the error toward -- will bias the estimate towards one.
Q. So, I understand that point, and I want to ask you questions about that, but I want to make sure I am clear. Is there any other criticism that you were trying to address in this paragraph four?
A. If you filled out -- if you entered

the study in 1993 or 1994, something like that, that your use of the -- of the herbicide may have changed subsequently, and that may have a change -- that may affect your subsequent risk of developing the disease. I realize that there were -- I think there were subsequent attempts to fill out follow-up questionnaires to kind of re- -- reestimate the -- to requantify the, the -- I don't know, call it the true exposure or the -- certainly if we are talking about the intensity of exposure, we are not talking now about never-ever, but say the quantity, but that wasn't reflected, at least in the De Roos 2005 paper. If there are subsequent analyses, then that may play a role.
But again, if someone changed their exposure pattern over time, that would be -- that would be something significant and may be important in terms of their risk.
Q. So let me just -- I'm going to take each one of those in turn.
First of all, with respect to the intensity of exposure of the 2005 cohort, we

do have the actual intensity data for that cohort. Whether they had other intense exposures in the future after the enrollment period, we do know the intensity of exposure at the time of enrollment; correct?
A. Yes.
Q. So, we are able to, and in fact De Roos 2005 does do an assessment of actual intensities of exposure to determine whether more intense exposures give rise to a greater risk of non-Hodgkin's lymphoma; correct?
A. Yes, but I believe there was some -- as I mentioned here, I believe there was some change in 1996 that actually, there was some secular change that actually caused a change in the overall use of Roundup, in 1996, in the middle of this study, that may have made a more dramatic or may have occasioned a more dramatic impact.
And how much it may or may not have affected risk, I don't know. I'm just raising it as a potential issue.
Q. Okay. But just so I am clear, the -- first of all, the fact that there was a change in the use pattern in '96, '97 would

not alter the findings in De Roos 2005 with respect to the analysis that they had and the data they had that more intense exposures did not increase the risk of non-Hodgkin's lymphoma; correct?
MR. TRAVERS: Objection, compound.
A. I don't know. I mean, it wouldn't have -- I guess it depends on how much change there was in the farmers, in the pesticide applicators' use of the agents, you know, of Roundup, and in the 6.7 years, it depends how many cases you are getting subsequently and what the latency period is.
It's a complicated issue. We are not talking about a lot of cases here either. You know, change of a few subjects is going to change -- change of a few cases, one way or another, exposure and outcome, is going to change the risk ratio fairly substantially.
Q. And with respect to this latency issue, the time period you are talking about of -- after 1996, of a potential change in the pattern of use of glyphosate, if Dr. Weisenburger is correct with respect to latency, that would be irrelevant to the

findings for De Roos 2005; correct?
A. If Dr. Weisenburger is correct, you mean with regard to a ten-year latency --
Q. Yes.
A. -- then yes, it would be irrelevant to what I am saying.
Q. And we will get to --
A. It would be irrelevant for the De Roos 2005 analysis.
Q. We have also talked about, there is a subsequent analysis, and we will get to that in a moment.
With respect to the first point about exposure and misclassification, that's, if I understand correctly, an issue that arises in every study that obtains exposure data through questionnaire; correct? There is nothing unusual about --
A. You mean like recall bias?
Q. Well, no. Here you are talking about exposure misclassification. Maybe I misunderstood. You not talking about recall bias in --
A. No. But I'm saying that it arises in every cohort study, like recall bias

arises in every case-control study?
Q. No. As in -- let's start that again. I will restate the question.
The issue that you talked about with respect to exposure misclassification would be an issue not only with De Roos 2005, but every case-control study for glyphosate; correct? They are all based on questionnaires.
A. So, I am saying that if you are going to start to throw around recall bias for every case-control study, then you have to throw around non-differential misclassification for every cohort study. But it's been assessed, and there is a paper on it by Blair which assessed it and shows that the degree of misclassification would have been sufficient -- they estimated it to some degree, and it suggests that it would have been -- even a reasonable amount, reasonable meaning even a, shall we say a -- what one would expect under normal circumstances of everyone doing it correctly, and doing even a decent quality, recruitment of subjects, and everyone doing their best

filling out the questionnaires, that the degree of misclassification was sufficient to have attenuated a risk ratio in the -- in the realm that we are talking about, to null.
That's why I was saying earlier, when you get null findings, you have to be very suspicious, that there -- that they're not meaningful in a sense, that they're-- that they're-- that they arise out of errors or out of -- that's why there's publication bias and things like that.
Q. Let me just make sure I understand this concept of bias towards the null. Now, in the AHS study, when they looked at the dose-response analysis, they were finding risk ratios below 1.0 for the higher exposure groups; correct?
A. Yes.
Q. So, a bias towards the null then would mean that those risk ratios were actually increased as compared to what they would have been; correct?
A. Yes.
Q. So, the issue of differential exposure misclassification for the

Agricultural Health Study would not have lowered those odds ratios, it would have increased them; correct?
A. I'm -- I can't follow that logic. That is too complicated for me to --
Q. Okay. Let me step back. Maybe it's the way I asked the question. I will frame it correctly.
In the De Roos 2005 paper, if there was this non-differential exposure misclassification, that would mean that the odds ratios reported for that dose-response below one were actually lower than the reported numbers; correct?
A. It would not solely be from exposure misclassification.
Q. Right. But any differential -- non-differential error, including the exposure misclassification error you identify as your concern for the Agricultural Health Study, would have increased those odds ratios as reported in the De Roos 2005 dose-response; correct?
A. Yes.
Q. So, that is not a concern, then,

that the De Roos study is missing a positive association. It's that the De Roos study might be missing a negative association; correct?

A. That's getting too complicated for me to -- again, to work out sitting here.

Q. Okay. But it is correct then, though, that in the AHS study, if there was non-differential misclassification, including non-differential exposure misclassification, the risks of glyphosate in association with non-Hodgkin's lymphoma would have been overestimated; correct?

MR. TRAVERS: Objection, asked and answered.

A. Would have been overestimated? No, it would have been -- it would have been attenuated. It would have been --

Q. Or not?

A. Why would it have been --

Q. You're biasing towards the null; correct? It's going closer to 1.0; correct?

A. Yes.

Q. The reported odds ratios were below 1.0; correct?

A. Now we are getting into it, but -- so I -- it's getting too complicated to, like, tease out now what that means in real terms, so you are going to tell me that glyphosate has a protective effect on -- we should all be taking glyphosate so we don't get lymphoma?

Q. I'm trying to understand your criticism, Dr. Neugut.

A. It's really -- it's getting too complex to -- you know, there are too many variables involved in this and too many assumptions to really make a -- to, as we sit here, make a -- make a meaningful statement about what a -- what a 0.9 means as opposed to a 1.0, or whether it's just, you know, within the bounds of statistical analysis.

Q. Dr. Neugut, this is your criticism number four on page 13 of your expert report. And in your expert report, you state that because of this non-differential exposure misclassification, there could be a bias towards the null, and that the reported association between glyphosate and NHL would be underestimated.

A. Yes.

Q. That's what you state in your report.

A. Absolutely.

Q. If there is -- and in fact, we know for a fact that there is, that the AHS study in its dose-response analysis reports risk ratios for the higher exposure groups below 1.0, a bias towards the null would be pushing those numbers up, not down; correct?

MR. TRAVERS: Objection, asked and answered.

A. The glyphosate analysis, as I recall it, is still above 1.0 in the AHS study for ever/never, and for most of the exposure categories. I don't think it really comes out that --

Q. Let's look back at 2005 De Roos.

MR. TRAVERS: Eric, just whenever you get a break in a subject, we have got -- lunch is here.

MR. LASKER: Yes. Once we get through this.

Q. I just want to make sure we are clear, because I thought we had discussed

this previously. The -- on page 52 --

A. I'm sorry.

Q. -- of the De Roos study, 2005 study.

A. Fifty-two?

Q. Page 52. The odds ratios for glyphosate and non-Hodgkin's lymphoma, for the two -- for the increased dose groups, as you increase cumulative exposure, and as you increase intensity-weighted exposure, those odds ratios are below 1.0; correct?

A. Yes, but --

Q. If there is non-differential misclassification, those numbers have been biased upwards toward the null of 1.0; correct?

A. Yes.

Q. Which means that the true relationship between glyphosate and non-Hodgkin's lymphoma as you increase dose is an even lower odds ratio, a greater reduced risk than is reported; correct?

MR. TRAVERS: Objection, asked and answered.

A. So, I was referring to

misclassification in terms of being exposed at all, not talking about the misclassification, or classification of how much intensity or how long people were exposed. I don't know -- I didn't think through or analyze the exposure intensity part of it, and I don't know how that would affect the attenuation here.

Q. Dr. Neugut, if there was non-differential misclassification biasing these numbers towards the null, as you suggest would occur in your expert report, for AHS -- for the De Roos 2005 paper, that would have resulted in an overstatement or overestimate of the odds ratio that increased dose of exposure, not an underestimation; correct?

MR. TRAVERS: Objection, asked and answered.

A. Could you say the question again.

Q. Sure.

If your -- again, we are talking about your criticism of AHS, the De Roos 2005, your fourth criticism. If there is this non-differential exposure

misclassification, then --

A. It's not my criticism. It's Aaron Blair's. I'm just quoting a paper. But go ahead.

Q. Okay. Well, okay. But is it not your opinion in here?

A. No, no, no. The paper is good.

Q. Okay. So, your criticism then of the AHS paper, of the De Roos 2005, is there could be this non-differential exposure misclassification, and if that in fact occurred, the dose-response analysis that is reported in the 2005 De Roos paper is actually overestimating the risk of glyphosate exposure for non-Hodgkin's lymphoma, and not underestimating it; correct?

MR. TRAVERS: Objection, mischaracterizes his testimony. It's asked and answered.

A. It's overestimating?

Q. You state in your expert report that if there is a bias towards the null, the association of exposure to glyphosate and association with non-Hodgkin's lymphoma would

be underestimated, because there is a bias towards the null, meaning the numbers have been artificially pushed towards one.

A. I'm looking at table two, not at table three.

Q. I know, but I am asking you about table three.

A. Well, I can't answer with regard to the exposure. That's not -- that's a different categorization.

Q. So, sitting here today, if there is non-differential exposure misclassification, you cannot state what biasing towards the null would mean with respect to the numbers reported in the 2005 De Roos paper?

MR. TRAVERS: Objection, asked and answered.

A. That's correct.

Q. So, with respect to the dose-response analysis then in De Roos 2005, am I correct in my understanding that you do not have a criticism of that finding based upon non-differential exposure misclassification?

A. Specifically, no.

MR. LASKER: Why don't we take a break here.

MR. TRAVERS: Okay.

THE VIDEOGRAPHER: The time is 12:47 p.m. We are off the record.

(Luncheon recess taken.)

AFTERNOON SESSION
THE VIDEOGRAPHER: The time is 1:50 p.m. We are on the record.
BY MR. LASKER:
Q. Dr. Neugut, good afternoon.
We talked previously about Dr. Blair's deposition that you have read. And you are aware from that deposition, I take it, that there is a 2013 update of the Agricultural Health Study data that contains additional data for glyphosate and non-Hodgkin's lymphoma; correct?
A. Yes.
Q. You have not offered any expert opinion regarding that study in your expert report; correct?
A. Yes.
Q. You are aware, though, that the 2013 AHS analysis included five years of additional exposure data beyond the data in De Roos 2005; correct?
MR. TRAVERS: Objection, mischaracterizes the study.
A. I am aware that it exists. Is that what you are asking me?

Q. No. My question is, are you aware that the 2013 analysis included five years of additional exposure data beyond the data in De Roos 2005?
MR. TRAVERS: Same objection.
A. What is -- am I aware of it?
Q. I will ask the question again.
A. I'm sorry.
Q. You are aware that the 2013 analysis of the Agricultural Health Study data includes five years of additional exposure data beyond the data in De Roos 2005; correct?
A. Yes.
Q. You are also aware that the 2013 analysis had an additional seven years of follow-up for non-Hodgkin's lymphoma; correct?
MR. TRAVERS: Objection, mischaracterizes the study.
A. I don't know the details, but I know that it has additional follow-up. I don't know -- I couldn't quote you the numbers, but --
Q. Okay. Let's take a look at

Dr. Blair's deposition testimony on this. And if you have Dr. Blair's deposition before you, pages -- on page 168.
A. What page?
Q. 168. And specifically lines six to line 16.
And having reviewed Dr. Blair's deposition testimony, does that refresh your recollection that the 2013 AHS analysis had an additional seven years of follow-up for NHL beyond De Roos 2005?
A. Yes.
Q. The 2013 analysis of the AHS data was three to four times larger than the De Roos 2005 study; correct?
MR. TRAVERS: Objection, mischaracterizes the study.
A. Can -- I don't know. If it's in Dr. Blair's testimony, then I read it at some point, but --
Q. Let me refer you to page 171, specifically lines 21 through 24. Dr. Blair testifies here that the 2013 cohort study, with results for glyphosate and non-Hodgkin's lymphoma, is more than four times larger than

the De Roos 2005 study; correct?
A. Yes.
Q. The answer is yes. You have no reason to disagree with Dr. Blair on that; correct?
A. No.
Q. The 2013 study, with even longer follow-up, also analyzes applicators that had even higher levels of cumulative exposure to glyphosate than in De Roos 2005; correct?
A. I believe so.
Q. That goes to one of the issues you had talked about in your report, about additional years and different uses of glyphosate and more intense exposures; correct?
A. I don't recall offhand, but yes, I -- I don't recall.
Q. And according -- Dr. Blair was one of the listed investigators that prepared that 2013 analysis; correct?
A. I wouldn't know.
Q. Dr. Blair testified -- well, let me just state -- let me just ask this. The ever/never risk ratio for glyphosate and NHL

in this larger 2013 AHS analysis was below 1.0. It was around 0.9; correct?
A. I don't know.
Q. Let's look at Dr. Blair's testimony on page 172, line 16 to line 24.
A. Okay.
Q. Dr. Blair reports that this 2013 analysis of the AHS data reported an ever/never odds ratio or risk ratio for glyphosate and non-Hodgkin's lymphoma of approximately 0.9; correct?
MR. TRAVERS: Objection, that misstates his testimony.
A. "Reports" means what?
Q. Dr. Blair states --
MR. LASKER: And if we are going to have speaking objections, we can switch you and you can be the witness, but otherwise, please do not provide speaking objections, counsel.
MR. TRAVERS: Well, you can't misrepresent --
MR. LASKER: Dr. Neugut can respond to the questions. You cannot.
MR. TRAVERS: I'm just giving

reasonable objections. You are misstating the testimony.
MR. LASKER: Well, if you continue, we'll have a whole record of this --
MR. TRAVERS: Okay, it's on the record.
MR. LASKER: And we can bring this to the judge if you want, but your objections have been ridiculous all day.
Q. Dr. Neugut, once again, Dr. Blair testifies that the ever/never ratio for glyphosate and non-Hodgkin's lymphoma in this larger 2013 AHS analysis was below 1.0, approximately 0.9; correct?
MR. TRAVERS: Objection, misstates his testimony. You can just read the transcript.
A. Yes, but obviously it's unpublished and all of that, but -- yes.
Q. But this 2013 study, just so the record is clear, this 2013 AHS study reports a risk ratio for glyphosate and non-Hodgkin's lymphoma for ever/never use of below 1.0 at around 0.9; correct?
A. Yes.

Q. And Dr. Blair also reports that there was in fact, in one of the dose-response analyses, a statistically significant negative finding for diffuse large B-cell lymphoma; correct?
MR. TRAVERS: What page is that?
A. I don't recall.
Q. I will refer you to page 195.
A. 195?
Q. Yes. And particularly lines nine through 21.
The 2013 AHS data finds a statistically significant negative association between increased glyphosate exposure and diffuse large B-cell lymphoma; correct?
A. Yes.
Q. Now, the 2013 AHS analysis that Dr. Blair testified to, that was attached as an exhibit to Dr. Blair's deposition; correct?
A. I don't know.
Q. You have reviewed Dr. Blair's deposition; correct?
A. Yes.

Q. Did you, in reading his deposition, note that that study was marked as an exhibit to the deposition?
A. I don't notice things like that when I read depositions. I don't look at the index. I don't look at the supplements.
Q. Well, in the testimony, as we are going into the questions that you are reading, it was marked as an exhibit. You saw that; correct?
MR. TRAVERS: Objection, asked and answered.
A. As I said, I don't know that I did.
Q. Have you ever looked at the 2013 AHS analysis?
A. No.
Q. Now, you have -- well, strike that.
I take it then you have no opinions with regard to the methodology or the findings in that 2013 AHS analysis.
A. No.
Q. Now, you previously -- well, let me make sure the record is clear there.
Am I correct in my understanding then that you don't have any opinions with

regard to the 2013 AHS analysis?
A. It didn't play a role in my opinions.
Q. Now, you have previously, I think we have discussed, been retained as an expert witness by the same attorneys who are representing the plaintiffs in this case; correct? In other litigation?
A. Only for the Actos, I believe for the Actos litigation.
Q. And in that litigation, like in this one, you were retained to provide an opinion based upon epidemiologic evidence that a substance, there it was a drug, caused cancer; correct?
A. Yes.
Q. And in that litigation, you relied upon a non-published, non-peer-reviewed epidemiological study in support of your opinion, didn't you?
A. I don't recall.
Q. Okay. Let's go back to your January 7, 2013 deposition, and it should be in front of you. Dr. Neugut, it looks like this.

If I could direct you to page 157, 158, and you can, I think -- it starts on page 157, line 20, to 158, line six. You may recall this -- well, you will recall this better than I would. I wasn't there.
But does this testimony refresh your recollection --
A. Which line, which page?
Q. From page 157, line 20, through 158, line six.
A. Yes.
Q. Does that refresh your recollection, Dr. Neugut, that in the Actos litigation, where you were represented by the same plaintiffs' counsel that you are represented here today, in offering your opinion as to whether exposure can cause cancer, you relied upon a non-published, non-peer-reviewed study?
A. I wasn't aware at the time that it wasn't published, I think, or I was in error at the time, or I had some confusion about it, as I say here. This was a series. It was in the same context of a cohort study, where this was the fourth, if I recall --

again, it's a while ago. But if I recall, it was the fourth follow-up from the same study, and it was not -- I did not rely upon it in actual litigation subsequently in any of the testimony that I gave in any of the trials.
Q. Just to be clear, Dr. Neugut, in this deposition testimony we just reviewed, you stated that you were going to be relying upon the non-published, non-peer-reviewed results of a nested case control, and your answer was yes; correct?
A. So I -- yes, it is, but I do not recall in what way I did rely on it and how I did or did not.
Q. But just for the record, in other litigation in which you were represented by this same plaintiffs' counsel who represents you here today, in which you were asked to assess the epidemiology for exposure causing cancer, you relied upon a non-published, non-peer-reviewed study, and in this case, you chose not even to look at the 2013 AHS data; correct?
A. Yes.
Q. Let's take a look at some of the

case-control studies for the glyphosate and non-Hodgkin's lymphoma. One of those was a study by Cantor in 1992; correct?
A. I'm sorry, I am -- I was -- my mind was wandering.
Q. That's all right. 1992 Cantor study.
A. What about it?
Q. That was one of the studies you looked at in your analysis; correct?
A. Yes.
MR. LASKER: And let's mark the Cantor study as Exhibit 14-15.
(Exhibit 14-15, Cancer Bulletin, May 1, 1992, Pesticides and Other Agricultural Risk Factors for Non-Hodgkin's Lymphoma among Men in Iowa and Minnesota marked for identification, as of this date.)
Q. And for the record, this is the Cantor 1992 study that you discussed in your report; correct?
A. Yes.
Q. What was the testable hypothesis for this study?

A. I'm sorry, ask your question again.
Q. What was the testable hypothesis in the Cantor 1992 study?
A. What does "testable hypothesis" mean?
Q. Well, I was, I thought, taking that from you. You had described your methodology for reviewing epidemiological studies, and you talked about the fact that you first formulated a hypothesis.
A. You mean the primary hypothesis?
Q. If that's what you meant. Just to make sure we are talking on the same page here, in your expert report on -- let's see, where was it? Page six. You talk about this multistep process to establish causal inferences; correct?
A. Um-hum.
Q. And so you -- you first formulate a testable hypothesis, and then you design studies to test the hypothesis; correct?
A. Yes.
Q. So, my question for you with respect to Cantor 1992 is, what was the testable hypothesis of that study?

A. I guess it was being a farmer, or being a -- having a farming occupation, or however you want to phrase the -- however you want to phrase that.
Q. Okay. Would it be fair to say that Cantor 1992 was not designed to test the hypothesis whether glyphosate can cause non-Hodgkin's lymphoma?
A. Yes. That was a secondary -- secondary aim, analysis, however you want to phrase it.
Q. Now, the Cantor study looks at individuals who are diagnosed with non-Hodgkin's lymphoma between 1980 and 1983; correct? And if you look at the methods section for case selection on the first page.
A. Yes. Um-hum, yes.
Q. So, the cases of NHL in this study were diagnosed somewhere between -- well, certainly less than ten years after glyphosate first became available for use in the market; correct?
A. Something less than that, yes.
Q. Now, we talked earlier about Dr. Ritz, and I believe her expert report is

still in front of you. Can you just pull out Dr. Ritz's expert report.
It's thicker than that, about this thick.
A. Is this it?
Q. No. Maybe on the bottom.
A. The very bottom. I'm sorry.
Q. Always the way.
So, Dr. Ritz, she is another expert witness epidemiologist on behalf of plaintiffs in this litigation; correct?
A. Yes.
Q. And if you could turn to page 18 and 19 of her report. Dr. Ritz states that "the findings of Cantor are less informative because there was not sufficient time to account for the latency of non-Hodgkin's lymphoma."
Do you see that?
A. Yes.
Q. And she states that "one would like to see a medium potential latency period of at least ten years for an epidemiologic study of glyphosate and non-Hodgkin's lymphoma to be informative." Correct?

A. Yes.
Q. Do you agree with Dr. Ritz on that?
A. I stated earlier that I am agnostic with regard to the question of latency period. We have spoken earlier about Weisenburger's opinion. I don't know what the latency period is, so I don't know the answer.
Q. Do you agree that this question of latency period is important in analyzing what one can glean from the Cantor 1992 study with respect to glyphosate?
A. If one knew what the latency period -- if one knew what the mechanism is of how glyphosate -- if one was -- one knew definitively how glyphosate causes lymphoma, so that one could definitively establish the latency period, then yes, it would be very important. But otherwise, it's difficult to be able to know how to apply it in this instance.
Q. If Dr. Weisenburger is correct that the latency period is ten years for glyphosate and non-Hodgkin's lymphoma, do you agree with Dr. Ritz that that would mean that

the Cantor study is not informative with respect to glyphosate and non-Hodgkin's lymphoma?
A. I would say that it would be difficult to say how it would have enough cases to be able -- how it would be informative.
Q. That's because the individuals in the study would have been exposed too close in time to their diagnosis for latency to have occurred and for the exposure to have been related to non-Hodgkin's lymphoma; correct?
A. It wouldn't have been impossible for a few of them to have been, but for at least for some -- for a large number of them, it would have been probably not possible.
Q. And in your expert report, you state that Cantor had again low power because there were only 26 cases of NHL with exposure to glyphosate; correct?
A. Yes.
Q. And this goes back to our earlier discussion. The key number for power is the number of individuals who were both exposed

and had the outcome of interest; correct?
A. Yes.
Q. And you believe that a study that has only 26 individuals with exposure to glyphosate and NHL does not have sufficient power to provide reliable information regarding any potential causal relationship between glyphosate and non-Hodgkin's lymphoma; right?
MR. TRAVERS: Objection, misstates his testimony.
A. I didn't say that.
Q. Let me make sure I understand your testimony then. Okay. So let me -- let me rephrase the question.
Do you believe that a study with only 26 individuals with exposure to glyphosate and NHL is severely limited in its ability to provide information regarding any potential causal relationship between glyphosate and NHL?
A. If you have a -- if you have a null finding, then you have to -- then I think you have to be limited in terms of how you interpret a null finding in that context,

because you didn't have enough statistical power to be able to find the positive association.
Q. With respect to power, is it your opinion then that power only matters for a finding of a positive association and doesn't matter with respect to reaching an opinion about a causal relationship?
MR. TRAVERS: Objection, asked and answered.
A. That question doesn't make sense.
Q. Okay. Let me restate.
If a study is insufficiently powered, in your opinion does that severely limit your ability to reach a causal opinion based upon that study?
A. If a power is insufficiently -- if a study is insufficiently powered, then you have to interpret a null finding with extreme caution or with -- or -- or not be able to draw a -- not be able to draw a definitive conclusion from it. In other words, if there was insufficient power to start with, and you have a null finding, then you certainly are limited in being able to conclude that there

is no positive association.
Q. Okay. I understand that, but I'm asking the other direction as well. Is it fair to say that if a power -- if a study is insufficiently powered, it is severely limited in providing you with the type of evidence that you would want to have as an epidemiologist to reach a causation opinion?
MR. TRAVERS: Objection, asked and answered.
A. I'm not sure that isn't saying the same thing. How is that question different?
Q. The answer may be yes, but let me just make sure I understand in my own mind.
A. If I -- if I had an insufficiently -- if I had a study that a priori was -- had poor -- was small, so it didn't have sufficient power in the first place that I was happy doing it, but having then conducted the study, I had a positive association, I would still take the positive -- I would still have to take the positive association at least -- seriously, and take it -- because, as I said in our morning discussion, I think positive

associations always have to be at least seriously entertained and analyzed, because -- because the system, the structure of epidemiologic and statistical analysis militates against positive findings.

Of course, if the numbers are really tiny, then you can take that into consideration and say it's really so small, that even though it's statistically significant, that the numbers are so small, I'm not going to really give it that much credit, or maybe it's a statistical artifact or maybe it's bias.

But that's why we are given brains, and we are supposed to use our logic and our judgment and our common sense, and that is what epidemiology is all about. Epidemiology is the ultimate in judgment, causal considerations, the application of logic, common sense, and intelligence to taking data and trying to analyze it, and to be able to interpret what you find, because you will never have pure, unadorned, perfect data to -- well, you will almost never have pure, absolute data that you can interpret without

having to use your brain to, to analyze.

So you have -- as with everything else, you have to apply your, your logic and thinking to what you see, and to come up with the best interpretation you can. Reasonable people may reasonably disagree, as in every other -- as in many other walks of life, but in epidemiology, that is particularly a -- more so than in most other scientific endeavors, that is a particularly crucial part of what we do in our daily endeavors.

Q. Dr. Neugut, let me ask the question again, because I still don't understand the answer.

Do you believe, if a study has insufficient power, that that is a significant limitation in your ability to use that study to reach a causation opinion?

MR. TRAVERS: Objection, asked and answered.

A. I think it certainly limits the ability of the study to be able to give you a correct answer.

Q. Now, many of the other case-control studies of glyphosate and non-Hodgkin's

lymphoma discussed in your report had even less power than the Cantor study; correct?

A. I would think so, yes.

Q. The Hardell study in 2002, that has less power than the Cantor study; correct?

A. Yes.

Q. The Cocco study, the Cocco, C-O-C-C-O, study we looked at earlier, that has less power than the Cantor study; correct?

A. Yes.

Q. The Orsi study, that has less power than the Cantor study; correct?

A. Yes.

Q. And the Eriksson study, that one, let's look at that one, because that is a little bit more involved. I think I marked that Exhibit 14-13, so you should have that in front of you. Exhibit 14-13.

A. That's -- oh, I see. That's Eriksson?

Q. Yes. 14-13. Eriksson 2008, and the information is -- can be determined from table two for all exposures with glyphosate, table two on page 1659. That study involved

29 individuals with exposure to glyphosate who had non-Hodgkin's lymphoma; correct?

A. Yes.

Q. And the Eriksson -- so that's -- I think there is three more cases in Eriksson than there was in Cantor 1992; correct?

A. Yes.

Q. The Eriksson study had only 18 controls, though; correct?

A. Yes. Exposed controls, you mean. Or am I mischaracterizing it?

Q. You're looking at the study.

A. Am I looking at table two?

Q. Yes. 18 exposed controls -- 18 controls for 29 cases; correct?

A. This is the number of exposed cases and number of exposed controls.

Q. And in Cantor 1992, they actually had, I believe, 49 controls. Correct? And you can look back to that, if you need to. Do you need to look back at the Cantor study to confirm if they had 49 controls for glyphosate? It's on table six.

A. Table six?

Okay.

Q. And the power of a case-control study is determined both by the number of cases and the number of controls; right?
A. Yes.
Q. And so from this data, it appears that Eriksson also had lower power than Cantor with respect to glyphosate and non-Hodgkin's lymphoma; correct?
A. Which one has lower power?
Q. Eriksson.
A. A priori, yes.
Q. Now, to put these numbers into context, we have been talking about 26 exposed cases or 29 exposed cases, the updated 2013 Agricultural Health Study analysis, depending on which definition of non-Hodgkin's lymphoma you used, was studying between 250 and 350 individuals with exposure to glyphosate and non-Hodgkin's lymphoma; correct?
A. Yes.
Q. So, that is somewhere between ten to maybe 13 times larger than any of these case-control studies; correct?
A. Well, the statistical power doesn't

exactly go by multiplication, but it's larger, certainly.
Q. Mathematically, it's ten to 13 times larger, the AHS 2013 study, than any of these case-control studies --
A. Yeah.
Q. -- we talked about.
A. Um-hum.
Q. And the earlier De Roos 2005 study, the published study that we talked about that you have looked at, that had 92 individuals with exposure to glyphosate and who had been diagnosed with non-Hodgkin's lymphoma; correct?
A. Yes.
Q. So, again, numerically, much larger than these case-control studies; correct?
A. Yes.
Q. Now, the other comment you make in your expert report about the Cantor study is that it is also limited by the lack of adjustment for other herbicides used in the cohort. And that's page 14 of your expert report; correct?
A. Yes.

Q. And that's your opinion; correct?
A. It's limited by that, yes.
Q. And you have -- I think you testified earlier that this lack of adjustment for other exposures to pesticides limits a study's ability to tell us anything about the true association between glyphosate and non-Hodgkin's lymphoma; correct?
A. I didn't say "anything about." I said it limits our ability to tell us precisely what's going on.
Q. And as you already discussed -- strike that.
Well, as you already discussed, the McDuffie study does not adjust for exposures to other pesticides; correct?
A. No.
Q. It's correct that it doesn't; right? Let me restate that question, because I gave you a double negative.
The McDuffie study does not adjust for exposures to other herbicides or other pesticides; correct?
A. No, it does not.
Q. And the Lee study, which you also

address in your expert report, it does not adjust for exposures to other pesticides; correct?
A. Correct.
Q. And the Eriksson study, except for -- well, the Eriksson study in its analysis of latency and its analysis of dose-response and its analysis of NHL subtypes, it does not adjust for exposures to other pesticides; correct?
A. Correct.
Q. Now, let me just make sure I understand the bases for your testimony that the Cantor study -- and first of all, the Cantor study reports an odds ratio for glyphosate of 1.1 with confidence intervals of 0.7 to 1.9; correct?
I'm not sure you are looking at the right study, Dr. Neugut. The Cantor study.
A. Oh, I'm sorry. Getting out of hand here. Cantor study.
What was the question, please?
Q. The Cantor study reported an odds ratio of 1.1 with confidence intervals of 0.7 to 1.9.

A. Yes.
Q. That is a null finding for glyphosate and non-Hodgkin's lymphoma; correct?
A. Not an elevated finding, yes.
Q. It's a null finding.
A. Essentially.
Q. And now you state here that -- in your expert report, that this finding was not adjusted for other pesticide exposures, but Cantor adjusted for other high-risk exposures; correct?
And if you could look at the Cantor study at page 2448, at the top of the second column.
A. He adjusted for other risk factors, if that's what you are asking.
Q. Well, for other exposures that he looked at in the study; correct?
A. Yes.
Q. And to the extent that any of -- and he looked at a number of different pesticides and herbicides and insecticides in this study; correct? You can look to table three and table four and table five and table

six. And table seven, table eight.
A. Yes.
Q. And by a high-risk exposure, Dr. Cantor means that he adjusted for any exposure with an odds ratio above 1.5 when it was adjusted solely for age and state of residence; correct?
A. Yes.
Q. So, to the extent that the -- any of these other pesticide exposures met that criteria, Dr. Cantor did control for those pesticide exposures; correct?
A. Yes.
Q. So, that limitation that you noted in your expert report is actually -- for the Cantor study, is actually incorrect; right?
A. What limitation?
Q. You state that there was a lack of adjustments for other herbicides used by the cohort, is the word you used in your expert report.
A. Did I make an error?
Q. That is my question of you. It's on page 14 of your expert report. I think your expert report is up there. And on the

top, page 13 to 14, you are talking about the Cantor 1992 study. At the very top of 14, the last line in your discussion of Cantor, you state that "interpretation of the results is also limited by lack of adjustments for other herbicides used by the cohort." Correct?
A. I guess I was referring specifically to the one where he was using the 26 versus -- that that specific analysis, but perhaps in the other analyses --
Q. Well, table -- we look at the analysis on table six; correct? In Cantor.
A. I may have made an error.
Q. Just so we are clear, the criticism in your expert report of the Cantor study, that it was limited by lack of adjustment for other herbicides, that is incorrect.
A. I missed that.
Q. Let's turn to the McDuffie study. And I think -- have we already marked this? Yeah. This was 14-14, so you have that already in front of you.
And Dr. Neugut, the McDuffie study also was not designed to test the hypothesis

that glyphosate might be associated with non-Hodgkin's lymphoma; correct?
A. Not specifically.
Q. That would be a secondary finding in the study; correct?
A. I'm not sure that that is accurate. I mean, it was to look at pesticides and non-Hodgkin's lymphoma. I mean, and if you say that glyphosate was one of them -- I don't think glyphosate was particularly the one that they were targeting, but they were looking at pesticides in general.
Q. Well, McDuffie in their study actually specifically discusses -- and I will refer you to page 1161.
A. 11 --
Q. 1161.
A. 61, um-hum.
Q. And this is in the second column of the text on that page, the full bottom paragraph on the right side, full complete paragraph that starts, "We reported results," on the right-hand column.
A. Um-hum.
Q. And the authors of the McDuffie

paper themselves describe their analyses in this study as exploratory; correct?
A. And so?
Q. I'm just asking if it's correct that this was an exploratory study. We talked about that before.
A. That's -- that may or may not be true, but that may -- their aim may have been to do a study to look at exploratory -- to do an exploratory study.
Q. Right. No, I'm not -- I just want to make sure I understand. The McDuffie study with respect to glyphosate was an exploratory study.
A. That's -- yes. I mean, they may not have had a specific villain in mind when they were looking -- when they were setting up the study, to say this particular agent is what we are primarily focused on. We are looking in general at pesticides and lymphoma, and here is a list, and we will look at all of them and see what pops up associated or not associated with lymphoma.
Q. Right. That's what we were talking about earlier this morning, that there are

epidemiological studies that are exploratory studies, and then there are -- that are not actually testing hypotheses, but they are generating additional hypotheses. Correct?
A. Yes.
Q. Now, in the -- in your expert report discussing McDuffie, you state, on page 14, that the McDuffie odds ratio of 1.2 was adjusted for high-risk exposures. That is on page 14 of your report.
A. Yes.
Q. And so, this is the type of adjustment we were just discussing about with -- in the Cantor study; correct?
A. Yes.
Q. Now, in fact, the McDuffie study did not adjust for high-risk exposures, did it?
A. No.
Q. So that's another mistake in your report?
A. Okay.
Q. Yes?
A. Yes.
Q. In its most adjusted odds ratio,

McDuffie adjusted for medical variables, age and study area; correct?
A. Family history, but -- is that what you mean by "medical variables"?
Q. Yes. Yes.
A. Um-hum.
Q. And that is set forth on table two in the odds ratio of 1.2 that you mentioned in your expert report for glyphosate; correct?
A. Yes.
Q. Why would an epidemiologist, in this case Dr. McDuffie, adjust for medical variables like family history of cancer or specific medical conditions?
A. Well, family history may or may not be related to risk of lymphoma. I mean, conditions tend to run in families, so, if you had a family history of lymphoma, you may be at increased risk of getting a lymphoma, so that is a fair variable to adjust for.
Q. You agree with Dr. McDuffie then that to try and zero in on whether there is a true association for pesticide exposure and non-Hodgkin's lymphoma, you would want to

adjust for medical variables like family history and these medical conditions?
A. Certain medical conditions that may or may not be related to risk of -- of getting lymphoma, yes.
Q. So, just so I am clear then, do you believe that Dr. McDuffie's adjustment of her findings for medical variables like family history of cancer, and the specific conditions she lays out, improves the reliability of the findings in her study?
A. At worst, it doesn't hurt it. At best, maybe it improves it.
Q. Now, in your report, you point to an analysis of odds ratios for, I think less than or equal to two days per year and greater than two days per year. Do you recall that?
A. We are talking now still about McDuffie?
Q. Yes.
A. Yes, I believe so.
Q. And you rely on these findings from McDuffie in your expert report as evidence of a dose-response in support of your Bradford

Hill analysis; correct?
A. Yes.
Q. Now, this analysis of less than or equal to two days versus greater than two days exposure for glyphosate, in McDuffie, that was not adjusted for exposures to other pesticides; correct?
A. Correct.
Q. And as we were talking about this morning, in the De Roos 2005 study, if that finding in De Roos 2005 is correct that there is greater exposures to other pesticides at greater levels of glyphosate exposure, then the failure to adjust for other pesticide exposures could confound and create an artificial appearing dose-response that doesn't exist; correct?
A. Could or could not. I don't know.
Q. So, it's certainly possible that confounding could artificially increase the reported odds ratios for high exposure to glyphosate in the McDuffie study; correct?
A. I would really not be able to say.
Q. The -- now, the analysis in McDuffie that you cite as evidence for

dose-response was not even adjusted for those other medical variables and family history that we just discussed; correct?
A. Yes.
Q. The analysis in McDuffie for dose-response also does not take into account duration of exposure; correct?
A. Correct.
Q. So, if there was an individual who used glyphosate twice a year, let's say, for each of ten years, they would be categorized in the low exposure group with 20 cumulative days of exposure; correct?
A. I'm sorry, I missed -- I didn't follow the last question.
Q. If there is an individual in McDuffie who had used glyphosate every year for ten years two times a year, they would be in the low exposure group; correct?
A. Yes.
Q. And they would have 20 days of cumulative exposure; correct?
A. Yes.
Q. If there was another individual who used glyphosate for only one year but used it

on three different occasions, they would be characterized in McDuffie as high exposure; correct?
A. Yes.
Q. So under McDuffie, you could have in your dose-response analysis someone with three days of exposure being classified as high exposure and someone with 20 days of cumulative exposure being classified as low exposure; correct?
A. Yes.
Q. And in your own epidemiological research, when you have looked at pesticides and you've looked at dose-response, you have actually -- you looked at cumulative exposure, not per time period exposure; correct?
A. Have I done pesticide exposure?
Q. In your -- in your research, in your epidemiological research, when you do a study like this and you are doing a dose-response analysis, you look at cumulative exposure; correct?
A. Sometimes you do, sometimes -- I mean, you know, you never know what is the

right -- what is the right way to analyze dose and dose-response. Sometimes you do cumulative, sometimes you do it other ways.
MR. LASKER: Let's mark as Exhibit 14-16...
(Exhibit 14-16, American Journal of Epidemiology, Reported Residential Pesticide use and Breast Cancer Risk on Long Island, New York marked for identification, as of this date.)
Q. And Dr. Neugut, Exhibit 14-16 is one of the epidemiological studies that you conducted; correct?
A. Jesus Christ. Don't put that in the record.
Q. She can't do that, unfortunately. She has to take everything down.
Dr. Neugut, Exhibit 14-16 is one of the studies that you were an investigator on; correct?
A. Yes.
Q. Looking at pesticide exposure and the potential risk of breast cancer; correct?
A. Yes. Yes.
Q. And in this study, you conducted a

dose-response analysis; correct?
A. Yes.
Q. And you used cumulative exposure as your measure for dose-response; correct?
A. Yes.
Q. And we in fact know, going back to the glyphosate findings in McDuffie, that if one were to look at cumulative exposure, there is no increased risks in the high exposure group; correct?
MR. TRAVERS: Objection, misclassifies, or mischaracterizes the study.
A. I'm sorry, can you repeat the question?
Q. We know in fact that for the McDuffie data, because the McDuffie data has now been analyzed further by the North American Pooled Project, that when you look at cumulative exposure, there is no evidence of increased risk of non-Hodgkin's lymphoma with glyphosate; correct?
MR. TRAVERS: Objection, mischaracterizes the studies.
A. I don't know that study.

Q. You don't know the North American Pooled Project study?
A. No. I haven't looked at it.
Q. Well, we will talk about that in a moment.
Now, in your expert report, you also note that McDuffie had a low response rate; correct?
A. Yes.
Q. And McDuffie had a 67 percent response rate among cases and only a 48 percent response rate among controls; correct?
A. Yes.
Q. And that is -- that differential goes back to one of the potential concerns we discussed this morning about potential selection bias; correct?
A. Yes.
Q. So that's an issue with the De Roos study as well; correct?
A. It's an issue, but I would say --
Q. I'm sorry, let me go back.
This issue of selection bias is an issue of concern for McDuffie, the McDuffie

study; correct?
A. Yeah, although I would say that in the studies of that type, it's not as big a differential as it may sound. I mean, you get differentials like that in case-control studies. But yes, it's an issue.
Q. And the goal of the case-control study is not to have this sort of a differential in your response rates between cases and controls; correct?
A. Correct.
Q. Let's talk about the Hardell study. So this is a study -- Exhibit 14-17.
(Exhibit 14-17, Exposure to Pesticides as Risk Factor for Non-Hodgkin's Lymphoma and Hair Cell Leukemia: Pooled Analysis of Two Swedish Case-control Studies marked for identification, as of this date.)
Q. And Dr. Neugut, this is, I think, one of the studies that we spoke about earlier that had very low power to analyze a question of an association between glyphosate and non-Hodgkin's lymphoma; correct?
A. Yes.

Q. And that is because there were only eight cases and eight controls, I think, in this study.
A. I don't remember the exact number, but it was a very small number.
Q. Now, when Hardell -- Hardell has in his analysis, he has a multivariate analysis that he presents in this study; correct?
A. Yes.
Q. What confounders did Hardell adjust for in his multivariate analysis?
A. I think he adjusted for exposure to other herbicides or pesticides.
Q. Where do you see that in Dr. Hardell's study?
A. "When risk estimates for different pesticides are analyzed" --
Q. What page are you on?
A. 1045. The first paragraph.
Q. In 1045?
A. Top paragraph.
Q. Okay.
A. "When risk estimates for different pesticides were analyzed, only subjects with no pesticide exposure were taken as unexposed

whereas subjects exposed to other pesticides were disregarded."

I'm assuming that means they were excluded from analysis.

Q. They were excluded from the definition of "unexposed."

A. I am not exactly sure what he means, but --

Q. What Dr. Hardell is stating here, and this is a methodology that carries through in all the Swedish studies, is that their definition of "unexposed" excluded not only individuals unexposed to glyphosate, but individuals unexposed to any pesticide; correct?

A. Correct. That's a different way of -- that's a different way of adjusting for herbicide exposure.

Q. Well, if you are taking out information from the controls so that the cases have exposures to glyphosate and exposures to other herbicides, but the controls don't have exposure to any pesticides --

A. No. I would assume then, you have

to take them out of both groups.

Q. But it's not -- there is -- is there anywhere where it's stated that they take that out of both groups?

A. Kind of ambiguous.

Q. If in fact the Swedish case-control studies defined unexposed so that there was no exposure to any pesticide and allowed other exposures, exposures to other pesticides to occur with the glyphosate exposed cases, that would be a methodological flaw in the study; correct?

A. Probably, yes.

Q. That would make it impossible to actually adjust for the potential impact of other exposures; correct?

A. Yes.

Q. Now, the Hardell study pools the findings from two other case-control studies, an earlier study by Hardell and a study by -- I don't know if I am getting this correctly. Is it Nordstrom? Is that correct? Dr. Neugut?

A. I'm sorry?

Q. The Hardell study 2002 pools the

findings from two earlier case control studies, one by Hardell and Eriksson and one by Nordstrom; correct?

A. I'm sorry, I was still -- I was still in the middle of this one.

Q. No, we're still with Hardell.

A. Yeah.

Q. The Hardell study, Exhibit 14-17, pools the data from two earlier case-control studies, one by Hardell and Eriksson and one by Nordstrom; correct?

A. Yes, um-hum.

Q. And you do not discuss those earlier case-control studies in your expert report; correct?

A. Right.

Q. Is it fair to say once you pool those studies into a larger study, it's the later pooled study that provides all the data relevant to a causation theme?

A. Yes.

Q. Let's turn to De Roos 2003, which is the De Roos case-control study. And this would be Exhibit 14-18.

(Exhibit 14-18, Integrative

assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men, Occup Environ Med 2003 marked for identification, as of this date.)

Q. And the De Roos paper pools all of the -- all of the prior North American -- I'm sorry, U.S.-based case-control studies that looked at glyphosate and non-Hodgkin's lymphoma; correct?

A. Yes.

Q. And this De Roos study has -- 2003 case-control study, has the same latency issue or problem that Dr. Ritz identified with respect to the Cantor study; correct?

A. You mean that the cases were diagnosed between '83 and '86?

Q. Well, if we look at the data from the De Roos study, and it's on page -- table two, page four of nine, and you will have to actually look back to the study population, because there are three different studies that are pooled there.

A. Um-hum.

Q. But if you look at page one and two, you will see the three different

populations, and when they were diagnosed. Correct?
A. Yes.
Q. And so for Iowa and Minnesota and Kansas, those exposures were between 1979 and 1983; correct?
A. Yes.
Q. And if you look at table two in the -- and that is -- just to step back, that is the problem that Dr. Ritz was highlighting in the Cantor study; correct? Those dates of exposure?
A. I don't recall what she was highlighting, but that is an issue, yes.
Q. And if you look at table two in De Roos 2003, the case control study, and you look at the data that was included in the analysis for the pesticides, roughly 82.6 percent of the cases would have been diagnosed with non-Hodgkin's lymphoma between 1979 and 1983; correct?
A. Yes.
Q. And so, those exposures, those cases, again, at the very earliest, the very earliest, still could not have been exposed

to glyphosate more than nine years prior to their diagnosis; correct?
A. Yes.
Q. And so that did not come close to the median ten-year latency period that Dr. Ritz opined would be necessary to look for a potential association between glyphosate and non-Hodgkin's lymphoma; correct?
A. Yes.
MR. TRAVERS: Objection, misstates Dr. Ritz's testimony.
Q. And the remaining 17.4 percent of the cases were diagnosed between June 1983 and June 1986; correct?
A. Are you talking about the Kansas cases or --
Q. Yes. I'm sorry, the Nebraska cases.
A. The Nebraska cases.
Q. Let me just confirm, so that the record is clear, you can go back and look at the study populations. And once you look at that, am I correct in my understanding that the remaining 17.4 percent of cases were

diagnosed between June 1983 and June 1986?
A. Yes.
Q. So, even for these Nebraska cases, they would not have had a median ten-year latency period to examine with respect to glyphosate and non-Hodgkin's lymphoma; correct?
A. They would have had just barely ten years.
Q. That would have been the maximum, not the median; correct?
A. It's hard for me to figure out, but if it was starting in '74 -- right? '75, '74?
Q. Let's say -- we can talk about '74 or '75. I don't think it matters for this question.
A. Um-hum.
Q. If the question is whether or not there would be a median of ten years --
A. Oh, I see.
Q. -- of latency, which Dr. Ritz identified --
A. So, I guess it would be about eight years, seven or eight years.

Q. Eight years would be maximum.
A. Okay.
Q. Correct?
A. Yes.
Q. It wouldn't be a ten-year median latency, even for that smaller --
A. Yes.
Q. -- population; correct?
A. Yes.
Q. Now, de Roos 2003 --
A. And again, I'm not subscribing to the ten-year -- I told you, I'm personally not --
Q. You're agnostic.
A. I'm agnostic on the latency period.
Q. I understand.
A. But I respect my colleagues.
Q. Now, De Roos in the 2003 study presents results for a logistic and a hierarchal regression analysis; correct?
A. Yes.
Q. And those analyses are described on page two of the De Roos 2003 study; correct? The left-hand column, middle of the page talks about statistical analyses?

A. Yes.
Q. And as explained in that statistical analysis section, De Roos controlled for other pesticide exposures in the hierarchal regression analysis; correct?
A. Yes.
Q. Did not -- De Roos did not control for these other pesticide exposures in the logistic regression analysis; correct?
A. No.
Q. Again, the answer is unclear from my question. Is it correct that Dr. De Roos did not control for the other pesticide exposures in the logistic analysis?
A. That's correct.
Q. Let's move on to the Lee study.
MR. LASKER: And this will be Exhibit 14-19.
(Exhibit 14-19, Non-Hodgkin's Lymphoma Among Asthmatics exposed to Pesticides marked for identification, as of this date.)
Q. So, Lee, the Lee study likewise uses pooled data from the same case-control studies in the United States; correct?

A. Yes.
Q. So, Lee would have the same latency issue as Cantor and De Roos 2003; correct?
A. Yes.
Q. The odds ratio I think you have already noted for Lee for glyphosate was not adjusted for exposure to other pesticides; correct?
A. Yes.
Q. Now, in your report, you discuss the fact that there was odds ratios provided for glyphosate for non-asthmatics and then for asthmatics; correct? Page 15 of your expert report.
A. Yes.
Q. And there are different point estimates of 1.4 and 1.2 that were found in that study, but you state that there was no evidence or no indication of an effect modification in that study; correct?
A. Yes.
Q. So, the fact that you have point estimates of odds ratios that are different, that in and of itself, just a different number, doesn't provide you with an

indication of a true difference; correct?
A. Yes.
Q. What sort of analysis would you need to see to determine whether there has been an actual meaningful difference between two different groups in a study?
A. Well, there is an analysis called effect modification, which is some kind of -- I'm not a statistician, but that analyzes for whether the two analyses are statistically different from each other. It's basically looking at whether subgroups differ from each other, and whether the fact that being asthmatic would somehow make you more or less, or being not asthmatic would somehow make you somehow respond differently, let's say, to an herbicide than being not -- than -- whether having asthma somehow plays a role in your susceptibility to the exposure vis-a-vis the outcome.
Q. So, if I understand correctly, as an epidemiologist, when you see different point estimates for different groups that are being studied, to determine whether that is a meaningful difference, you would like to see

some sort of statistical analysis to see if they are -- those two groups are statistically significantly different; correct?
A. Correct.
Q. Okay. I would like to refer you back again to Dr. Ritz's report, at pages 15 to 16.
A. Dr. Ritz's report?
Q. Yes.
A. Which page?
Q. Pages 15 and 16. And at these pages in Dr. Ritz's report, she is discussing the findings of, as I call it, the North American Pooled Project; correct?
A. You mean on the bottom of 15?
Q. And over to -- and continuing on to page 16.
A. Okay.
Q. Now, the North American Pooled Project was also discussed in Dr. Blair's deposition, which you read; correct?
A. Yes.
Q. And the North American Pooled Project pooled the data from all of the

case-control studies in the United States and Canada; correct?
A. I believe so, yes.
Q. So, the North American Pooled Project contains all the data that is in De Roos 2003 and then also the data in McDuffie 2000; correct?
A. McDuffie --
Q. 2001.
A. Yes.
Q. So, just like we talked about earlier with Hardell, the NAPP analysis now is a later study that pools all the data from the earlier case-control studies, and that's the study that you can look to for the most up-to-date data from all those studies. Correct?
A. I wouldn't know.
Q. As a general matter, if it is in -- strike that.
If it is correct that the North American Pooled Project has pooled the data from the De Roos 2003 and McDuffie 2001 study, then that study would provide the most fulsome information and would be the study

that you would look to for any conclusions from all of those case-control studies; correct?
A. Again, I -- since I haven't looked at it and I don't know what it exactly did, I wouldn't know.
Q. Okay. Well I'm not talking about -- let me just back up.
So, we already talked about the Hardell study and the fact that that pooled two earlier studies, and so in your analysis, you looked at the later pooled analysis from Hardell 2002; correct?
A. Yes.
Q. And if in fact, and I will ask you to assume, but you have read Dr. Blair's deposition as well, the NAPP pooled the data in De Roos 2003 and McDuffie 2001, then you would look to that NAPP data for the -- to analyze the full set of case-control information from the North American case-control studies; correct?
A. I'm sorry, say that last question again.
Q. Okay. So, if it is correct, as

Dr. Blair testified, that the North American Pooled Project pooled all the data from McDuffie 2001 and De Roos 2003, then you would no longer look at those earlier studies, you would look at the pooled analysis in the North American Pooled Project, to determine whether that data provides evidence of an association between glyphosate and NHL; correct?
A. Since you are telling me this out of a context that I don't know, I -- I -- it's difficult for me to answer the question with any degree of confidence.
Q. As a methodological question, though, just so I am clear, when you have a case-control study that pools data from earlier case-control studies, you look at that later pooled analysis; correct? That's what you did in your report; correct?
A. That's what I did for those particular studies. Whether I would do it for this other study, I don't know.
Q. Do you agree with Dr. Ritz, and maybe you just don't have an opinion, that the findings in the North American Pooled

Project are relevant to the causation analysis for glyphosate and non-Hodgkin's lymphoma?
A. I have no way of knowing, since I haven't looked at it, evaluated it or assessed it. Aside from what I read in the transcript from Dr. Blair, I think, I really don't have any knowledge or information about it.
Q. You are aware that the findings from the North American Pooled Project have been presented at a number of scientific conferences; correct?
A. I know they were presented at the one meeting. I don't know that they keep repeating the same data at different meetings. That is not usually considered kosher.
Q. And why is it not considered kosher to keep --
A. To keep presenting the same data over and over again?
Q. Yes.
A. It's like, you know -- I guess that's like repeat publications, you know. I

mean, I'm not criticizing them. I'm simply saying, you know, you don't usually publish the same thing over and over again. Repeat publications.

There may be different meetings where, you know, under different circumstances, where, with modifications, you know, and updates, different analyses are included, updated, variations.

I'm not criticizing other scientists. I'm simply saying you wouldn't just repeat -- you wouldn't do the same thing several times at different places. That would be -- you know, it would be like -- I don't know what word to use. It would be -- it would be like publishing the same thing two different places. You would get two publications out of one, you know.

Q. So, in her expert report, Dr. Ritz only discusses the odds ratios found by the NAPP before it adjusted for the use of other pesticides; correct?

A. Shall I read her paragraph? Is that --

Q. You don't know one way or the

other?

A. The question is, what does she say?

Q. The question is what she reported, whether she reported adjusted odds ratios or unadjusted odds ratios for other pesticide exposures.

MR. ADLER: You mean Dr. Ritz?

MR. LASKER: Dr. Ritz.

A. So, I can't tell. She doesn't say. She doesn't say what it's adjusted for.

Q. Let's -- I'm going to have you take a look at the next exhibit in line, and this was --

MR. LASKER: We will mark this as Exhibit 14-20.

(Exhibit 14-20, An Evaluation of Glyphosate Use and the Risk of Non-Hodgkin Lymphoma Major Histological Sub-Types in the North American Pooled Project marked for identification, as of this date.)

Q. And Dr. Neugut, this is a slide presentation that was marked as an exhibit in Dr. Blair's deposition, and I believe you read his testimony about the data presented

with respect to this study. Correct?

A. A while ago, but yes.

Q. And if I could ask you to turn to -- and I will represent to you that this slide deck is for the same conference, the ISEE conference in Brazil, that Dr. Ritz is discussing in her expert report. On page 15, she talks about the presentation of ISEE.

Do you see that?

A. Yes.

Q. So, the -- on the ninth -- unfortunately, they are not numbered. If you could count nine pages into the slide presentation, there is a data table of glyphosate use and NHL risks.

Do you see that?

A. It's two-sided.

Q. It's open, pointing up. Right there?

A. This one?

Q. Yeah.

MR. TRAVERS: Eric, just to clarify, do you recall which exhibit this was from the Blair deposition?

MR. LASKER: I do not, I'm sorry.

Q. This table presents an ever/never overall odds ratio for glyphosate and NHL; correct? Both for NHL in total and for various subtypes; correct?

MR. TRAVERS: I'm just going to object. He hasn't relied on this for his expert opinion and hasn't previously reviewed any of this data.

A. What he said.

Q. Okay. Just so I am clear, I know you haven't looked at this before, but I'm asking you, the data presented there --

A. Yes.

Q. -- is from the North American Pooled Project for glyphosate use and NHL risks overall and for various subtypes; correct?

A. Yes.

Q. And for the overall odds ratio, they present one odds ratio that is not adjusted for other pesticide exposures; correct? That is ORA.

A. Yes.

Q. And then another odds ratio, or ORB, that is adjusted for the use of 2,4-D,

dicamba and malathion; correct?
A. Yes.
Q. For ever/never use, the odds ratio for glyphosate and non-Hodgkin's lymphoma, after adjusting for exposure to 2,4-D, dicamba and malathion, is 1.13 and it is not statistically significant; correct?
A. Yes.
Q. So, the NAPP, for its adjusted odds ratio, pooling all the case-control data from North America, had a null finding for ever/never glyphosate use and non-Hodgkin's lymphoma; correct?
A. Had a positive but null finding, yes.
Q. We talked earlier about your definition of "positive." Under your definition we talked about this morning, the North American Pooled Project, pooling all of the data from the De Roos 2003 and the McDuffie 2001 study, adjusted for use of other pesticides, had a null finding for glyphosate and non-Hodgkin's lymphoma; correct?
MR. TRAVERS: Objection, misstates

his prior testimony.
Q. That's correct?
A. Yes.
Q. If you could turn to -- and this is the slide that is the third slide from the end of the entire deck, so go to the end of the slide deck and count sort of three from the end. You will see another table. It says "Proxies versus Self-Respondents." It looks, Dr. Neugut, like this. Just go to very end of the study, and then count back. There you go. Do you see that?
So, here we see the results of the North American Pooled Project for this dose-response analysis, and they have duration, they have frequency, and they have lifetime days; correct?
A. Yes.
Q. So, the frequency is the measure that McDuffie reported just for Canada, and now we have the full pooled dataset. McDuffie reported frequency in her study; correct?
A. McDuffie reported --
Q. Frequency, days per year.

A. Yes.
Q. We now have, with the North American Pooled Project pooling all of that data together, we have information on cumulative exposures, which multiplies frequency by duration; correct?
A. Yes.
Q. So, that doesn't have the potential misclassification issue for dose-response that we talked about in McDuffie; correct?
A. Correct.
Q. And when you look at the complete pooled data from McDuffie and from De Roos 2003, for this cumulative exposure measurement, glyphosate does not show evidence of a dose-response; correct?
A. Which line are you looking at?
Q. The bottom line, lifetime days. That would be cumulative exposure; correct? Duration times frequency.
A. Yes. It doesn't show, um-hum.
Q. So, just to be clear, the complete data pooled from McDuffie and from De Roos 2003 for cumulative exposure to glyphosate, does not provide evidence of a dose-response;

correct?
A. I wouldn't go that far. I mean, you have the frequency showing -- showing a relationship.
Q. Again, let me -- let me state the question again.
You have -- you have duration, you have frequency, and you have lifetime days; correct?
A. Yes.
Q. And lifetime days, that is a cumulative exposure measure of the type that you used in that study in Long Island; correct?
A. So, you know, you don't know what is the right association or the right -- the variable to use in any given analysis. To say because you did it in that study in 2006, that's what you should be doing in this study in 2017, or that they should be doing with a different outcome, that's-- that's foolish.
Q. Let me ask this question, and let's see if I can get a clear answer.
For cumulative exposure --
A. Hmm?

Q. For cumulative exposure --
A. Right.
Q. -- the complete pool of data from McDuffie and from De Roos 2003 does not show evidence of a dose-response for glyphosate and non-Hodgkin's lymphoma; correct?
A. So, cumulative exposure as measured this way, and as they analyzed it here, and as I am not seeing in a fully published report that is peer reviewed in a journal, and as I am not having the ability to analyze it carefully, then yes, as you are showing it to me in this table, you are correct. But to say that this is the be all and end all of everything is not -- not fair.
Q. Just to be clear, the North American Pooled Project pooled together all the data from McDuffie and from De Roos 2003; correct?
A. I don't know. I told you I haven't had a chance to look at it, and you are giving it to me now for the first time to look at in a slide like this. I didn't even get to hear the speaker say it out loud or go to Brazil. So, to -- you know.

Q. Dr. Neugut, you did have the opportunity to read Dr. Blair's deposition testimony when he talked about these findings; correct?
A. But they weren't published, and I didn't consider them in my report.
Q. You had the opportunity to review these findings, if you wanted to. They were exhibits to Dr. Blair's deposition.
A. They weren't published.
Q. You considered unpublished data for these plaintiffs' attorneys, as an expert witness --
A. I told you that was under other circumstances and a different context. To bring it now into this is a different issue. Here we are considering a different question under different circumstances.
Q. And you made a decision not to consider the data in the North American Pooled Project or in the 2013 AHS analysis after reading Dr. Blair's deposition, but without actually yourself looking at the data; correct?
A. Yes.

Q. So, after reviewing Dr. Blair's deposition and his testimony of the findings of those -- of the North American Pooled Project and the 2013 AHS data --
A. Wait. I'm sorry. You are mischaracterizing my statement. I didn't look at the answers and then say I'm not going to include it. A priori, I didn't include anything that wasn't published.
The fact that he then happened to then -- I happened to then read his transcript, and in his transcript there was a characterization or description of unpublished data didn't then come into -- didn't then -- I didn't then say, oh, look at that, I'm now not going to include that because it either bears on or doesn't bear on. The decision up front was not to include unpublished data, up front.
Q. Were you aware prior to reading Dr. Blair's deposition that there was additional data from the Agricultural Health Study?
A. No.
Q. Were you aware prior to reading

Dr. Blair's deposition that there was additional data that had been presented in scientific --
A. No, I wasn't aware of the NAPP study.
Q. -- conferences from the North American Pooled Project?
A. No, I was not, but as I said in my report, my takeoff for this entire evaluation was from the original IARC study, and I have tried to follow the -- take that as my --
Q. I understand.
A. My, shall we say takeout point, and to follow the guidelines of IARC and to stick more or less closely or reasonably to, to whatever their characterization has been, and I have -- and -- and if things have been published subsequent to that, that's been fair to include, and I have reviewed whatever publications, et cetera, have emanated subsequent to that, peer-reviewed, et cetera.
But I have followed the IARC guidelines, and I state that in my -- I believe somewhere in my report, or say something to that effect, and I have stuck to

that, and --
Q. That wasn't clear to me, so let me --
A. And I have been -- I believe I have tried to be consistent with that. If subsequently there were other unpublished things, and I -- it is stated specifically in my report, and I -- I believe, and I have tried to adhere to that, and if you want to say that in a different litigation, that wasn't the rules or that I in one particular unpublished thing -- again, as I say, I believe that was an error on my part, because I misunderstood that particular follow-up study, but that's a different issue.
But -- but in general, I think peer-reviewed published things should be, you know, the name of the game.
Q. Let me just make sure I understand your testimony then, because I didn't appreciate this.
Am I correct then in my -- let me just ask the question. Am I correct then in my understanding, Dr. Neugut, that in assessing the epidemiological evidence for

this case, for glyphosate and non-Hodgkin's lymphoma, you followed the methodology that is used by IARC?
A. I don't want to say I got 17 people together and put them in a room and, you know, talked to them that way.
Q. Fair enough.
A. But I tried to adhere -- since I -- I believe that they are the most authoritative and reasonable way to do this, they were certainly the takeoff point. They were what initially, shall I say, convinced me or persuaded me that glyphosate and NHL had an association, and I have tried -- at least insofar as trying to subsequently form opinions in this case, since IARC was the original platform from which this all emanated, I have tried to adhere to their criteria and methodologies for establishing, I guess what I would consider to be public policy, as well as judgments with regard to this issue.
Q. Okay. So just -- that's fair. So, I understand then that for your expert opinion in this case, you have, in analyzing

the epidemiological literature, sought to adhere to the preamble and the guidelines as to how that data would be considered by IARC; correct?
A. Yes. I mean, if I may have deviated or made a few mistakes along the way, a couple of mistakes, you know, in interpreting a couple of the papers, that is on my head, but -- and if I -- I may make errors. I'm human, too. But then, that's on me, but -- but I have tried to follow that methodology, because I think it is a reasonable one, and I think it's a correct one for public policy.
Q. Okay. And for other cases, where you were not starting off with an IARC monograph, you employed a different methodology for reaching a causation opinion from epidemiological studies. Is that fair?
A. Not necessarily. I mean, as I say, I am not sure in the Actos case that I didn't make an error with regard to the particular instance where you pointed it out. I think I misread -- I think I may have mischaracterized the follow-up data there. I

think I thought -- there was a fourth follow-up, and I think I thought, given how it was presented to me, I thought it was actually a publication.
If you would have seen -- I mean, this is a couple of years ago. I believe that the way the fourth -- that was the fourth follow-up to a large cohort study, and I believe the way it was presented to me, it looked to me like a publication, and I believe at the time I thought it was actually a publication.
But putting that aside, I don't know that I was -- that I actually had a different attitude at the time, but it may well be that under other circumstances, I might use a different approach, depending on the context or the circumstances and whatever it might demand in a certain case.
Q. And let's just take it outside of litigation altogether. When you are doing an epidemiological analysis as part of your independent scientific research, do you follow the IARC methodology then, or do you have other methodologies that you use for

your independent assessments?
A. It depends on the context. Again, for the purposes of public policy, and where you are making true public health or issues that affect standard of care, public people, public health, et cetera, then I think you have to adhere strictly to peer -- the IARC rules and public policy, peer-reviewed things.
If I am sitting around trying to decide how to do my next study, then I can have more informality and look at things that are not necessarily published. When I am talking to my peers or to my schleppers or to -- you know, to my students, and we are looking at someone down the hall has data, so obviously that is not published, and we are looking at someone's data from down the hall, to look at, so then I have -- I am entitled to do whatever I want to do, but then I am not also publishing it in the public sphere necessarily.
But occasionally, of course, you do publish -- even in peer-reviewed publications, you might publish something and

say it's un- --
Q. Referring to unpublished data?
A. You may refer to unpublished data, but then you say that it is, but then it doesn't carry the same weight. It doesn't carry the same weight, and it's subject to criticism, and you can never be certain about it, and it doesn't have the same veracity or the same, you know, confidence, et cetera.
And as I have said, I have had my own articles. You know, I once thought I had the solution to colon cancer, you know, which got turned down by 12 journals in a row, and before I finally got through my head that it really was wrong.
MR. LASKER: Well, that's -- we are running out of tape, so why don't we take a break here, because the tape is going to run out, and if it's not being taped, it doesn't actually count.
So, let's take a break and we'll start again.
THE VIDEOGRAPHER: The time is 3:36 p.m. We are off the record.
(Recess taken.)

THE VIDEOGRAPHER: The time is 3:42 p.m. We are on the record.
BY MR. LASKER:
Q. Dr. Neugut, I just want to follow up on something you said before we went on the break. I first want to put my microphone on, and then I'm going to say it again.
Before we took a break, you were talking about reaching or conducting assessments for public policy, public health issues; correct? I think that was one of the things you mentioned. Where you are trying to reach an assessment for public health determination, you would follow the IARC criteria; correct?
A. Yes.
Q. And part of this public health analysis that you are doing is intended to provide a level of precaution for populations; correct?
A. Yes.
Q. And there is something called the precautionary principle. You are familiar with that?
A. No.

Q. Now, you also, though, in other contexts would do an assessment of a potential causal inference where you are not looking at a public health question, but you are trying to zero in on a scientific assessment of what the true answer is, as opposed to what it might be; correct?
A. Possibly.
Q. When you are conducting an assessment of the epidemiological literature for this other purpose, for a scientific assessment, to dig down and be able to reach a scientific as opposed to a public health conclusion, you might have a different methodology that you would use. Is that fair to say?
A. Possibly.
Q. With respect to the -- I just have one more question on --
A. I might add to that, that we are not in a scientific context here either. Here we are -- we are in a legal context, and the rules for the law are different than the rules for science. And I am not a lawyer.
But, for example, you know, when --

when IARC says that something is a probable carcinogen, that is well beyond what would be legalese, in my -- in my unexpert opinion, that would be well beyond what would be sufficient to define a causal association for legal purposes. So, if we are going to start fooling around with definitions of different causal definitions, based on different contexts, then you are going to have to change -- you are going to have to define what context we are standing in, to be able to define what are the rules by which we are going to play the game.

Q. Okay. And it would be fair then for me to understand that you have followed a methodology in this case that is not a methodology that would be as -- what one would do for purposes of science, but is one that you -- in your understanding, is sufficient for purposes of the legal question in this case. Is that fair?

A. I would say, if anything, it's more -- it's more rigorous than would be necessary for legal purposes, because again, the IARC rules are -- in my understanding,

are beyond -- are more stringent than legal rules.

Q. And that understanding has --

A. That's my understanding, not as a lawyer, as a, I don't know, scientist or academic.

Q. And that understanding has helped determine how you approached the question of -- in your analysis of the epidemiological literature for this case.

A. I am approaching it from that perspective here. Again, whether that applies or does not apply for your purposes or for their purposes, or in the context of cases when they come up in subsequent litigation, is different, and if modifications will then be necessary in terms of how to use unpublished data or things like that, it -- because we'll then be in a different context or different framework, that may or may not be necessary or reasonable.

Q. Understood.

So, I just want to finish up, though, on the NAPP slide deck, which is

Exhibit 14-20, because we were looking at the third page from the end, this proxies versus self-respondents, and there was another column here that I want to ask you about, because they have the results for proxy and self-respondents, and then they have a separate column that is self-respondents only. Do you see that?

A. Yes.

Q. And do you agree with Dr. Blair, and he testified to this in his deposition, we can look at it if you would like, that in epidemiological analyses, information provided by cases are generally considered more reliable than information provided by proxies?

A. Yes.

Q. So, when the NAPP investigators focused on the data without proxies and cases only, or the pooled data from McDuffie and De Roos 2003, they found an ever-never odds ratio for glyphosate and non-Hodgkin's lymphoma of 0.95; correct?

A. Yes.

Q. And so, this most reliable odds

ratio for ever-never use of glyphosate from the U.S. and Canadian case-control studies is to the left, if you will, of the null finding or below 1.0; correct?

MR. TRAVERS: Objection to form.

A. Well, you know, you give up something when you -- that's true, but you're also -- it means you have more empty spaces, too. You have more unanswered -- I don't know that -- again, as I said before, I don't know this data. I'm not looking at tables. That means there is going to be more empty boxes in your -- there are going to be more non-respondents in both the cases -- in the cases and the controls, so you have given up something as well.

Q. Power. You have given up some power; correct?

A. It goes beyond power. It goes -- again, we were talking before about random classification. You have empty cells. It's -- there is -- nothing is free.

Q. But as between proxy and self-respondent data, and self-respondent data alone, you can have, at least with

respect to the information reported, more confidence in the data that is reported by the respondents; correct?
A. The validity of the data is better.
Q. And you are aware that the North American Pooled Project has published in the peer-reviewed literature its findings for the U.S. and Canadian case-control studies for glyphosate and multiple myeloma; correct?
A. I know they published some of their results. I don't know offhand specifically which. I will take your word for it.
Q. And you are aware that the Agricultural Health Study has also published its findings, updated findings, for other types of pesticides and non-Hodgkin's lymphoma; correct?
A. Yes.
Q. And sitting here today, you cannot say that any of the methodologies that were used in the 2013 AHS data that we discussed, or in this North American Pooled Project slide deck that we just discussed for glyphosate and non-Hodgkin's lymphoma, differs from the methodologies that were used

in these peer-reviewed published studies; correct?
A. Correct.
Q. Let's look at the Eriksson study. I know we have looked at it before, but I have a few more questions.
A. Eriksson?
Q. Eriksson, and I don't know what number that is. 14-13.
Now, this is also, like the McDuffie study, an exploratory analysis; correct?
A. Exploratory meaning that they did not start off with a particular specific pesticide or herbicide in mind to test, if that's what you mean.
Q. Correct.
A. Is that what you mean?
Q. Yes.
A. Yes.
Q. And in your expert report, you state that the odds ratios in this study were adjusted to account for possible confounding from use of other pesticides; correct? It's page 16 of your report, if that helps.

A. Yes.
Q. Now, in fact, the only adjusted odds ratio -- the only odds ratio that is reported in Eriksson that was controlled for the bounding by other pesticides is in that single table seven on page 1661 of the study; correct? Where they have the multivariate findings.
A. Yes.
Q. So, none of the other odds ratios reported in Eriksson, other than that multivariate odds ratio reported in table seven, are adjusted for confounding by other pesticides; correct?
A. That's correct.
Q. And if I could direct you to page 1658, in the left-hand column, all the way to the bottom, when they are talking about their statistical methods. Do you see that?
A. Yes.
Q. And the last three lines on that column, in the univariate analysis, and that is the analysis that they use in presenting all the other odds ratios in this report; correct?

A. Yes.
Q. In the univariate analysis, different pesticides were analyzed separately, and the unexposed category consisted of subjects that were unexposed to all included pesticides.
Do you see that?
A. Yes.
Q. That was the same issue we saw in the Hardell 2002 study; correct?
A. I don't recall, but okay.
Q. And that is, as you testified with respect to Hardell, a methodological flaw, because it prevents any analysis that accounts for other pesticide exposures; correct?
A. I'm not following.
Q. If the unexposed category is defined as individuals unexposed to all included pesticides, and the exposed category for glyphosate can include individuals with glyphosate exposures who were also exposed to other pesticides, that is a methodological flaw in the study; correct?
A. Why?

Q. Because in a case-control study, you are trying to pull populations of exposed individuals from the same population. You want to have the controls be from the same population as the cases; correct?
A. But that's not a flaw in the study. That is simply the reality of the universe and of people in the population. I mean, people are exposed or they are unexposed.
Q. Well, I understand that. But if you are defining "unexposed" to exclude individuals with exposures to other pesticides, and you are not doing that for the cases --
A. Then that would mean then that -- so, so that essentially what you are saying then is, if I may analogize, if you want to -- let's say we took asbestos and cigarette smoking and lung cancer --
Q. Sure?
A. -- as an analogy, and I said I wanted to know what the effect of asbestos was on lung cancer, but I wanted to control for tobacco use, so I could only take cigarette smokers, I would have to have

everybody be a smoker both in the case group and the control group, because if I had someone who wasn't exposed to cigarette smoking, I wouldn't know what to do with them.
Q. No, I think it would be a little bit --
MR. TRAVERS: He is still talking, I think.
A. No, I was finished.
Q. It would be a little bit different, I guess. If you were to do a study of asbestos and tobacco, smokers, and you had for your exposed group individuals with exposure to asbestos who might be exposed to cigarettes, but for your unexposed group you excluded anybody who had exposure to cigarettes, as a definition, that would be a problem; correct?
A. I don't agree. I mean, I think the best you can do is, you can put the exposures in everybody's way. You know, you can take a group where everyone has got an equal chance of being exposed to all the exposures. That's the way to do a -- that's the, shall

we say, the methodologically appropriate and sound way to do it.
Q. Okay.
A. As opposed to, let's say, taking people who live on -- in the 10021 area code, where they are never going to see, you know, herbicides in any meaningful way, as the control group for farmers, so to speak. So, you want to take everybody, let's say, being a farmer, where everybody has an equal chance of being exposed to herbicides.
Now, it may well turn out that in one particular farmer or that some group of farmers isn't going to use herbicides, because they are organic --
Q. Understood, understood.
A. -- or something like that. So, that's fine. They're still -- they're still fine. They're still in the thing. To say that therefore, they are screwing up your study in some methodological way is not fair. That's -- if that's what you are implying, then --
Q. No. I think you are misunderstanding me.

A. Then I am misunderstanding you.
Q. Let's go back to this.
The statement in the Eriksson study is that for the unexposed category, for the unexposed group --
A. Unexposed to herbicides.
Q. Well, the unexposed for glyphosate would be unexposed to glyphosate; correct?
A. But I think here they are talking about unexposed to any pesticide.
Q. Right.
So, each of the different pesticides was analyzed separately, so you look at a group that was exposed to that pesticide, and you are looking at, as your unexposed group, an individual that is not exposed to any pesticides. So, there you have farmers --
A. But he is a farmer and he chose not to be exposed. That was his -- that's life. That's his lifestyle or whatever choice.
Q. Well, no, I understand if they happen to have somebody who is not exposed. That is one thing. But here, in order to be part of the analysis, they define "unexposed"

as requiring that there is no exposure to other pesticides; correct? That's what Eriksson is stating here.
A. The unexposed were not exposed to other pesticides, yes.
Q. Any pesticides.
A. Any pesticides, right.
Q. So, that would be taking a non-farmer and putting them in the exposed group --
A. No.
Q. -- and having a farmer in the exposed group.
A. I don't agree. It would be taking, as I said, a farmer who wasn't exposed to pesticides. Well, I don't know. What was the control group? Maybe I am -- maybe I am misunderstanding what the control group is here.
Q. Well, let me --
A. Oh, I see. These are just general population controls. Okay. So, these are people who are not exposed to any pesticides, yeah.
Q. If the analysis or case-control

study allows for exposure to other pesticides when you are measuring, let's say glyphosate, as an exposed case, you can have somebody who is exposed to glyphosate and also exposed to 2,4-D and malathion, but for your control -- for your unexposed, I'm sorry, you are not allowing them to be counted if they have exposures to any pesticide. Then your unexposed population now is not the same population as your exposed population; correct? You are drawing from different populations now.
A. So, but you are allowed to do that as long as you create the same condition for both the cases and the controls. So, therefore, you could specify that, if you also specify that the case group cannot be exposed to any other herbicide.
Q. If you define "unexposed," though, as not allowing for exposures to any other pesticides at all --
A. Except for glyphosate.
Q. No. The unexposed would be none. The exposed group would have glyphosate and others.

A. And no other herbicide.
Q. Okay. So, if the exposed group is glyphosate and no other pesticide --
A. Correct.
Q. -- and the unexposed group is no pesticide, that's fine.
A. Correct. That's legal. That's, that's -- that is -- wrong word. That's --
Q. Allowed.
A. Allowed.
Q. If the exposed group, though, is exposure to glyphosate and other pesticides, then it would not be proper to --
A. Correct.
Q. -- define "unexposed" as having no pesticide exposures.
A. Absolutely right.
Q. And if that's what was done in the Eriksson study, that would be a flaw.
A. Right. And, you know, recognizing that you're -- what word would I use -- manipulating or playing with the data to some degree or -- and since, as you said at the beginning when we picked up this paper, this is an exploratory study, the term -- that is

precisely what an exploratory study is all about. It allows you to explore to see what's going on and to do sort of the subgroup analyses to see what happens if you do this or if you do that, as long as you adhere to some reasonable guidelines to make everything kind of logical and commonsensical, and not be too biased, if you will, in terms of how you play the data or play the subgroups against each other.
Q. And so, for all of the analyses that are reported in Eriksson, other than that one multivariate analysis on table seven, they have used this methodological design that you need to keep in mind and might be okay for an exploratory analysis; is that correct?
A. I think that's fair, yes. Wait. Are we still in -- wait. Is this the first one?
Q. Eriksson two thousand and --
A. Yes.
Q. -- eight.
But in analyzing Eriksson 2008, you would also want to be aware of the fact that

because of the way they defined the unexposed population, that that creates an issue as far as how you can actually analyze the findings in the study; correct?

A. You can interpret, I would say.

Q. Why don't we just put that aside. Let's start that again, and maybe you can just put your wallet --

A. I'm cool, I'm cool. I'm sorry.

Q. So, for Eriksson 2008, because of this fact, that they defined unexposed alone as not having exposure to any other pesticides, that -- that fact has to be taken into account in how you interpret all of the data reported in that study; correct?

A. All the data?

Q. Other than the multivariate analysis on table seven.

A. That is one analysis, and again, as long as they apply the same rules to both the cases and the controls, they can do whatever they like, or that would be a legitimate analysis, and then you -- as I told you earlier, in epidemiology you have the freedom to do whatever you like, as long as it has

logic, common sense, and intellectual validity to it.

Someone else may think it's silly. They are welcome to think whatever they like. And you can interpret or not, and think it reasonable or not think it reasonable, that you are free -- that you are -- that's your -- that's your freedom, you know, to do.

Q. Just so the record is clear, though, in the Eriksson study, the only analysis that does not define "unexposed" as being unexposed to all pesticides is that one data point in table seven for the multivariate analysis. All of the other data presented in that table uses this experimental approach of defining "unexposed" as unexposed to all pesticides; correct?

MR. TRAVERS: Objection to form, asked and answered.

A. So in table two, when they do the ten days versus greater than ten days, that is excluding anyone with any other herbicide exposure?

Q. Yeah. If you look at the univariate analysis on table seven, you can

actually cross-reference. You will see that the univariate odds ratios in table seven, and the univariate is where they do the analysis defining "unexposed" that way --

A. Okay.

Q. -- they match up. Correct?

A. All right.

Q. So, I am correct that for all of the analyses other than the one multivariate analysis on table seven, Eriksson uses this sort of exploratory methodology in which they define "unexposed" as unexposed to all other pesticides; correct?

A. Yes, but --

Q. And that's okay for an exploratory analysis. Isn't that your testimony?

A. And it may well turn out that that is, as I say -- depending on how you want to think or how you want to analyze it, that may be -- maybe this is the smartest analysis or the best analysis. It depends on how -- how you think through how glyphosate operates or how one -- I mean, if you are concerned about confounding by other herbicide, then perhaps taking all the herbicides out of the picture

in this way is the smartest. I'm not saying it is or it isn't. I'm saying at least that is one approach to how to analyze the data that addresses that question, and see what the answer is, is one way to address that issue.

Q. Just to be clear, we are not taking all the other pesticides out, because the exposed population, exposed to glyphosate, also has exposures to other pesticides; correct?

A. If they did that, then I would say it wasn't a legitimate analysis. I mean, as I said, if you are going to take it out of the control -- whatever you do to the case-control group, you have to do to the case group. You have to be consistent between cases and controls.

Q. And between exposed and unexposed with respect to other pesticides; correct?

A. So again, here, this is a case-control study.

Q. Right.

A. So, again, whatever you do to the cases, you have to do to the controls.

Q. Right.
A. So, if you are taking all herbicide exposures aside from glyphosate out of the picture, you have to do it to both groups.
Q. And with respect to the --
A. Aside from glyphosate.
Q. And if you are doing that, by the same token, if you are taking all the other pesticide exposures out of the unexposed group in this study, you would need to take all those other pesticide exposures out of the exposed group for your analysis; correct?
A. Yes, but that wouldn't be the way you would -- I would say in a case-control study, you wouldn't -- that wouldn't be the logical way to approach it.
Q. Right.
A. I mean, you might get that as the out -- that might be the way it would end up, but that wouldn't be the way you would logically approach it.
Q. Okay. So, it wouldn't be logical to define -- if you are going to have exposed -- allow for exposure to other pesticides, it wouldn't be logical for your

unexposed to an individual pesticide to exclude all other pesticides; correct?
A. No.
Q. Okay. So, with respect to the Eriksson study, the odds ratios, all the other odds ratios that are reported, except for this hierarchal odds ratio, are also -- they are not adjusted for smoking or drinking or any other lifestyle factors; correct?
A. No.
Q. They are only adjusted for age, sex and year of diagnosis; correct?
A. Age, sex, year of -- yes.
Q. And virtually every one of the approximately 20 different pesticides that Eriksson looked at is reported to have unadjusted odds ratios above 1.0; right?
A. So, are we now back in table two or table --
Q. All of the tables.
A. Huh?
Q. All of the tables.
A. Yes.
Q. Is it your testimony that every one of, looks like maybe 20 or more different

herbicides and insecticides and rodenticides and fungicides that are looked at in Eriksson 2008 cause non-Hodgkin's lymphoma?
A. I'm not addressing these other agents, so I don't have testimony regarding them.
Q. Is it your opinion, based upon the Eriksson study, based upon the findings of that study, that all of the -- every one of these 20 or so different herbicides, insecticides, rodenticides and fungicides cause non-Hodgkin's lymphoma?
A. DDT probably does. So, if we are going to add by analogy to the Bradford Hill criteria -- I won't do that, but the answer is, you know, I don't know, but it's not --
Q. Let me ask you this, Dr. Neugut. When a study uniformly reports odds ratios in excess of 1.0, for every exposure that it reports out, without controlling for confounding, that points to the possibility of a systematic bias in the study, doesn't it?
A. Yes.
Q. And --

A. It points to a concern. I mean, you know, again, if everything -- if all the exposures are related to each other in some significant way, or if most of them are, they don't all have to be, but if most of them are, then it's not totally inconceivable that they do elevate some risk.
But the answer is yes, generally speaking, that the -- that's what is referred to as specificity in the Bradford Hill criteria, and it would -- it should raise a concern that it's not purely -- that it's not -- that it's not -- well, that it's not a causal association, that there is something else going on that is methodological or statistical rather than causal.
Q. If there is confounding by other pesticide exposures, it's impossible from this study results to identify any one of the studied pesticides, including glyphosate, as having a true association with non-Hodgkin's lymphoma; correct?
A. Say that question again.
Q. If there is confounding by other pesticide exposures, it's impossible from

this study to identify any one of individually studied pesticides, including glyphosate, as having a true association with non-Hodgkin's lymphoma; correct?

A. I would not worry about confounding here. That is not -- or at least that would not be my -- I don't know that that would be the issue I would be concerned about. I mean, the --

Q. What issue would you be concerned about?

A. We have already said these are farmers. Farmers have a higher risk of lymphoma than the general population. The control group is the general population. So, you are seeing a slight increase in, if you want to call it an occupational risk, then -- so, this is -- this is an occupational risk ratio. You are seeing that farmers have an elevated risk of lymphoma.

Over and above that, the question is, do herbicides, within the farming group, or within the farmers, also convey an additional risk ratio over and above being a farmer. So, that is a question that the

study can address over and above.

Q. But this study, because of its design, can't provide you with that answer; correct?

A. Because?

Q. Because everything is above one in the study, so you can't actually differentiate any finding with respect to a specific pesticide; correct?

A. Well, you can see if the risk ratio for specific subgroups are higher than they are for the over -- for the overall group. If farmers exposed to glyphosate have a higher risk than farmers not exposed to glyphosate, I would worry about glyphosate. If -- again, we are talking about an exploratory study. If, if -- if there is a dose -- if people who have five times the amount of glyphosate as compared to those who have one-tenth the amount of glyphosate, have a higher risk than those --

Q. I understand. Sure.

A. -- then, as I said before, you have to apply your thinking and your logic and your common sense to looking at the data.

That's why it's called exploratory or -- and all of that, to see what makes sense within the data.

Q. But specifically with the Eriksson 2008 study, because of what we are seeing with elevated odds ratios, and if you look at table seven, glyphosate is in the middle, I guess, of the different pesticides, as far as the reported odds ratios, because of this systemic bias in the Eriksson study, it's impossible to reach any conclusion with respect to glyphosate; correct?

MR. TRAVERS: Objection to the compound question.

A. I would say that with this paper in general, I would be -- I might be concerned about all of these things, you know.

Q. Okay.

A. These are pretty high risk -- we are already getting up into higher risk ratios than I might expect purely from biases alone.

Q. How about with respect to when you have every finding above 1.0, so you have evidence of a systemic bias in the study,

it's impossible to reach a conclusion with respect to any individual exposure reported out of this study; correct?

A. I would say that that would be true of any -- I would have said that before I did the study, or it would have been impossible to reach a conclusion before I did the study no matter what I found.

Q. Because it's an exploratory study?

A. Correct.

Q. Now, with respect to the analysis here of latency, there is analysis of exposures for the categories of one to ten years, and then there is a category of greater than ten years; correct? And that is reported, I believe, on -- where is this document? Page 1659. 1658 and 1659.

A. Yes.

Q. But for -- and they report here, or Eriksson reports here on MCPA, 2,4,5-T, 2,4-D, and glyphosate; correct? In this analysis.

A. The question is what?

Q. The Eriksson paper reports results in this latency analysis for glyphosate, for

MCPA, and for 2,4,5-T and 2,4-D; correct?
A. Yes.
Q. But for MCPA, 2,4,5-T and 2,4-D, there were no exposed cases in that one- to ten-year latency period; correct? That's on the top of page 1659.
A. Yeah.
Q. So, we know for these pesticides at least that they could not have confounded the results for glyphosate within one to ten years of diagnosis; correct?
A. Okay. Yes. Um-hum.
Q. And the glyphosate odds ratio for that one- to ten-year latency period was 1.11. That's not even remotely close to statistical significance. That is a null result; correct?
A. Yes.
Q. Now, for the latency period of greater than ten years, the glyphosate odds ratios reported by Eriksson could be confounded by exposures to MCPA, 2,4,5-T and 2,4-D; correct?
A. Yes.
Q. And in your expert report, you note

in particular that MCPA is commonly used together with glyphosate; correct?
A. Yes.
Q. Eriksson reported an odds ratio for MCPA of 2.81 for that greater than ten-year latency period, which is higher than the unadjusted odds ratio reported for glyphosate for that same greater than ten-year period; correct?
A. Yes.
Q. And it's impossible to tell from Eriksson whether the odds ratio for glyphosate, if it had been controlled for the use of MCPA, would be elevated at all for greater than ten years latency; correct?
A. Yes.
Q. Now, in your expert report, you also point to the dose-response analysis in the Eriksson study for glyphosate; correct?
A. Yes.
Q. And this -- again, this dose-response analysis reported by Eriksson is not controlled or not adjusted for potential confounding by exposure to other pesticides; correct?

A. Correct.
Q. And if the data from De Roos 2005 is correct in showing higher exposure levels to other pesticides with higher exposure level to glyphosate, the finding of increased odds ratios at higher exposure levels of glyphosate could be an artifact due to confounding; correct?
A. Could be.
Q. And Eriksson also does not report any -- does not conduct any analysis to determine whether the findings for glyphosate exposure of less than ten days are statistically different than the finding for glyphosate, the odds ratio of greater than ten days; correct?
A. I mean that's -- the numbers are really too small to do anything statistically, to address what you just said.
Q. And going back to what we were discussing earlier, with respect to the Lee study, which had those two different odds ratios or point estimates.
A. Right.
Q. There is really no way to tell from

the glyphosate -- or from the data in Eriksson whether there is any meaningful difference between the reported odds ratios for less than ten days exposure as opposed to greater than ten days exposure of glyphosate; correct?
A. No, but I mean, you can't statistically confirm it.
Q. And just like you said in the Lee paper, when you can't statistically differentiate the two groups. It's not appropriate to say, as an epidemiologist, that you have shown that they are actually different; correct?
A. You can't say with definitiveness.
Q. Let's talk about the meta-analysis, and you talk about those on page 17.
First of all, the -- each of those meta-analyses that were presented, and this would be both Schinasi and the Chang and Delzell 2016 paper, they limited their analyses only to the most updated and comprehensive analysis of each epidemiology study population; correct?
A. Yes.

Q. Now, you are aware, are you not, that Chang and Delzell have updated their meta-analysis to include the data from the 2013 Agricultural Health Study and from the NAPP study; right?
A. I'm aware of it, but I haven't seen the -- I don't believe I have seen it.
Q. Were you not provided with the 2017 Chang and Delzell meta-analysis that was provided to your counsel with Monsanto's expert reports?
A. I didn't read Monsanto's expert reports.
Q. So, you have not looked at the Chang and Delzell study that is cited in those reports?
A. No.
MR. LASKER: Let me mark as the next exhibit in line, 14-21.
(Exhibit 14-21, Exponent, May 24, 2017 Meta-Analysis of Glyphosate Use and Risk of Non-Hodgkin Lymphoma marked for identification, as of this date.)
Q. And Dr. Neugut, if you look to page seven of this document, Exhibit 14-21, this

is --
A. I'm sorry, where am I looking?
Q. Page seven.
A. Page seven.
Q. This is analysis by Dr. Chang and Dr. Delzell; correct?
A. Yes.
Q. And if you look on page four, at the very top, they state that for purposes of this analysis, they are using "the same meta-analysis statistical methods as described in our publication Chang and Delzell, 2016." Correct?
A. Yes.
Q. And that is the meta-analysis that you cite to in your expert report; correct?
A. Yes.
Q. Now, plaintiffs' -- Dr. Ritz, plaintiffs' other epidemiology expert, stated in her expert report, and we can go back to her report, Dr. Ritz's report, at page 15 and 16, I believe. She is talking about the NAPP data again.
A. Um-hum.
Q. And on the -- on page 16, she notes

that the NAPP data were not included in any of the meta-analyses. Do you see that?
A. Are you in the middle of 16 or --
Q. Sort of the top, maybe one-third of the way down. The bottom of that last carryover paragraph, the final sentence.
A. Up here or down here?
Q. Right up here, the top paragraph. At the very end, it says, "The study results were published in 2014, and as such were not included in any of the meta-analysis." Correct?
A. The study results of the NAPP is she referring to?
Q. Yes. Well, you should confirm that for yourself, because that's what is discussed on page 15 and 16, but that is my understanding. I want to make sure that is your understanding as well of Dr. Ritz's --
A. Okay. Yes, okay.
Q. So, Dr. Ritz is pointing to the fact that, as we have discussed, using the methodology for meta-analyses that was used in the studies and was used both by Schinasi and Chang and Delzell, you would use the most

recent updated complete dataset for the meta-analysis; correct?
A. Yes.
Q. And so the NAPP dataset then would be used as the pooled analysis as compared to the De Roos 2003 and the McDuffie 2001 studies; correct?
A. Yes.
Q. And if the NAPP data -- and let me actually go back to Exhibit 14-21 for you. That is the 2017 meta-analysis. If you go back -- if you can go to the pages, page nine and page ten.
A. That is in the Exponent section?
Q. Yes. In Chang and Delzell, 2017. Pages nine and ten list all of the epidemiological studies that we have been discussing today, with the number one, Alavanja 2013, being the 2013 AHS data. Number two is the De Roos 2003, which is the De Roos case-control study. Are you with me?
A. Yeah, I just found it. Alavanja, De Roos.
Q. And then number three is De Roos 2005 AHS study; correct?

A. Yes.
Q. Number four is Eriksson 2008.
A. Um-hum.
Q. Number five is Hardell 2002.
A. Yes.
Q. Number six is Hohenadel, and Hohenadel did an analysis of -- another analysis of McDuffie; correct? The same data set. Correct?
A. Yes.
Q. McDuffie 2001; correct?
A. Yes.
Q. Orsi 2009?
A. Um-hum.
Q. And then number nine is Pahwa, et al, 2015, and that is the NAPP data; correct?
A. Yes.
Q. And so they then conduct, using the same methodology as they did in the 2016 meta-analysis that you cite in your report, they do meta-analysis looking at these different studies and considering different studies for -- to determine what the meta-relative risk is with those different

studies; correct? And they identify which studies they are including in the meta-analyses; correct?
A. Yes.
Q. So, for their model 26, if you can look at that, that's on page 11, using their same meta-analysis methodology that they used for the 2016 publication, and they are looking here now at studies three, four, five, eight and nine, so they have used the NAPP data in place of De Roos 2003 and McDuffie, but then continuing to use the 2005 Agricultural Health Study data; correct?
A. Yes.
Q. So, if you were to use the NAPP and substitute that for -- for De Roos 2003 and McDuffie per the -- per the normal methodology for a meta-analysis, you find that there is a meta-relative risk of 1.2 that is not statistically significant; correct?
A. Yes.
Q. And if you look at model 21 of their meta-analyses, this is the finding if you were to use both the 2013 Agricultural

Health Study data and the NAPP data and then all of the other studies that you analyzed; correct?
A. I'm not -- are we talking about --
Q. Model 21.
A. Back here?
Q. And you should reference it back, so what they have done in this analysis, if I understand it correctly, but you should correct me if I am wrong, is that they used the updated AHS analysis from 2013 in place of the 2005 analysis, and they have used the pooled analysis for the North American Pooled Project in place of the studies that were pooled into that study, McDuffie and De Roos; correct?
A. To be honest, I'm -- it's a little difficult for me to absorb all of this as I sit here.
Q. The reported finding at least, and I understand that you have not had a chance to look at this -- well, let me strike that.
I understand that you haven't looked at this, but the analysis, as reported by Chang and Delzell, 2017, for a

meta-analysis, when you look at the most updated AHS data and the most recent pooled data from North America, and in combination with the rest of the glyphosate epidemiology, your meta-relative risk is 1.0 with a confidence interval of 0.86 to 1.2; correct?
A. Yes.
Q. And that is a null finding for the meta-analysis; correct?
A. Yes.
Q. And that finding that Chang and Delzell report is consistent with what Dr. Blair testified that he would expect a meta-analysis to show, using that updated AHS data and updated Pooled Project data; correct? In his deposition testimony.
A. Yes.
Q. So, this 2017 meta-analysis finding of Chang and Delzell with the most updated epidemiological data does not provide evidence of an association between glyphosate and non-Hodgkin's lymphoma; correct?
MR. TRAVERS: Objection to form.
A. I don't know that it does or it doesn't. Again, I am not -- I haven't

incorporated it into my opinion and am not -- and you are putting into it data that I am not including in my opinion, and so, if you are asking me to form my opinion based on it, I am not willing to.

Q. And that's because you are following the methodology prescribed by IARC; correct?

A. Plus this is also not peer reviewed or published or -- and it's including data that wasn't itself peer reviewed or published.

Q. And we went through this before, but are you aware of any guidelines -- I know your -- the meta-analysis guidelines that you cite to in your report talk about using unpublished data in the meta-analysis. Are you aware of any guidelines for meta-analysis that state you should not consider unpublished studies in a meta-analysis?

A. So, you run the risk of -- what about the study that they didn't include?

Q. Let me -- let me ask the question again, and let me see if I have an answer.

Are you aware of any guidelines for

meta-analyses that state that you should not consider unpublished studies in your meta-analysis?

A. No.

Q. Let me turn to pages 17 to 20 of your expert report.

A. I'm sorry, where?

Q. Seventeen to 20 of your expert report. And this is where you are dealing with toxicity studies and mechanisms, and I think this may be a quick line of questions, but I want to make sure.

The type of evidence that you are presenting on pages 17 through 20, this is dealing with toxicological studies; correct?

A. Oh, this isn't --

Q. In your report, your own report again. Sorry.

A. I'm sorry. I'm looking at the Dr. Ritz report.

Q. Let's go back again. In your report, on pages 17 to 20, you are reporting on certain toxicity studies; correct?

A. Yes.

Q. And am I correct in my

understanding that you have basically taken this data from the IARC, IARC monograph?

A. Primarily. I mean, some of it may have come also from some of Portier's stuff or from other sources of a similar ilk.

Q. But it would be fair to say that this type of cited data is outside of your expertise as an epidemiologist?

A. It's not what I deal with on a daily basis, but I am familiar with this sort of data, and certainly to the degree of being able to incorporate it into, say, biological plausibility arguments, and I have a Ph.D. in chemical carcinogenesis, so, you know, at least going back, I have a fairly good familiarity with this sort of data, at least fundamental. I don't work in a lab anymore, and I wouldn't want to, but -- but I understand it fair enough. But it's not primarily what I deal with.

Q. Okay. And would I be correct in my understanding that you haven't actually read any of the toxicity studies or mechanistic studies for glyphosate?

A. I did read a couple of them, just

there were one or two that I probably went back and did read. But I did not -- I did not certainly do the literature review and then summarize it here.

Q. And you have not, for purposes of your opinion here, you don't purport to have done an expert analysis of the toxicity data or the mechanistic data. You are deferring to other experts for that; correct?

A. That's correct.

Q. Let's talk about your Bradford Hill analysis. And that is -- I believe it starts on page 20.

Now, Bradford Hill, we talk about Bradford Hill criteria. Bradford Hill is not a location, it's actually a person; right?

A. It's actually what?

Q. A person. There is a Sir Bradford Hill; correct?

A. Austin Bradford Hill.

Q. Austin Bradford Hill, right.

And he came up with these criteria for causation in a speech or presentation that he gave in 1965; correct?

A. Yes.

Q. And that is the source of the Bradford Hill, what we know as the Bradford Hill criteria; correct?
A. Yes.
Q. And in that seminal article laying out his criteria, Sir Bradford Hill stated that you should not even consider the criteria he specifies for determining whether or not there is causation unless you first have a statistically significant finding that cannot be explained by confounding or bias; correct?
A. It's a long time from 1965 to 2017. I mean, so, you know, that's like saying, you know, we are still doing what George Washington told us to do, and then based on that is how we are now interpreting the Constitution.
Q. Okay. There's two -- well, that is a separate issue that I am not going to go into. But let's just make sure I understand the answer to my question.
A. Yes.
Q. Because I think you are answering a different question.

So, Bradford Hill, when he set forth his criteria, it was his statement that you should not go move on to consider those other criteria unless you first have epidemiological findings that are statistically significant, positive findings that cannot be explained by confounding or bias; correct?
A. I don't recall. I mean, I'm not going to tell you I read the paper yesterday.
Q. You might not be surprised to learn that we are going to be looking at the paper right now. Expect nothing different.
A. Here we go down memory lane.
MR. LASKER: 14-22.
(Exhibit 14-22, Section of Occupational Medicine, Meeting January 14, 1965, The Environment and Disease: association or Causation?, marked for identification, as of this date.)
Q. And this is in fact the president's address by Sir Bradford Hill that sets forth the Bradford Hill criteria; correct?
A. Yes.
Q. And in the second column on the

first page in 295, Sir Bradford Hill, in introducing his -- these criteria that we will be discussing, states, "As a predicate, our observations reveal an association between two variables perfectly clearcut and beyond what we would care to attribute to the play of chance." Correct?
A. Yes.
Q. So, for Sir Bradford Hill, for -- under his analysis, the first threshold question is: Do you have a statistically significant finding; correct?
A. Yes.
Q. And also, that you have a clearcut finding that would not be explained by bias or confounding; correct?
A. Yes.
Q. And then you would move on to the criteria that he lays out and you lay out in your expert report; correct?
A. Yes.
Q. Let's move on then to -- well, strike that.
I'm correct in my understanding that you did not apply that predicate

requirement for your decision then to consider the Bradford Hill criteria; is that fair?
A. I think Bradford Hill would be absolutely appalled that about 90 percent of the causal things that are now commonplace in modern epidemiology, if he were to apply those criteria 50 years after the statement. He was working with regard to tobacco and lung cancer, where the relative risk is ten to 20, and would have been totally -- I think, you know, wouldn't have had any concept of thinking about risk ratios in even the two to three range, much less in the under two range, to be able to talk about such issues, if he wouldn't be able to read a modern epidemiology textbook.
So, to apply his -- this from 1965 to now, to make it some kind of criterion for how to approach causal thinking, I mean, certainly if this were true, we wouldn't have to even be sitting here talking, but that's out of -- it's so out of date --
Q. Let me just break this down, because you are using the Bradford Hill

criteria in your expert report; correct?
A. I'm not -- I mean, that's like saying I'm using Koch's postulates for figuring out whether someone has an infection with tuberculosis bacillus.
Q. My guess is that's not going to be meaningful to anybody who listens to this, so let me ask the question again.
You are using -- Bradford Hill in this paper lays out various criteria for making a causation assessment; correct?
A. Yes.
Q. And you follow that methodology and look at the same criteria in making your causation assessment; correct?
A. Yes.
Q. But in making your assessment in this case, you do not require as a predicate, the way Sir Bradford Hill would, that you start off with a statistically significant increased risk that cannot be attributed to chance or -- to confounding or bias; correct?
A. I think in modern epidemiology, it's not necessarily required, and I will base it on the -- the meta-analysis that says

that there is an elevated association.
Q. Let me just make sure I understand your testimony. With respect to the Bradford Hill criteria, you are -- you do not consider there to be, or maybe you do, but in conducting your analysis, am I correct in my understanding that you do not believe you need to have a statistically significant increased risk that cannot be attributed to confounding or bias, to then consider the Bradford Hill criteria?
A. You would never know, you can never know ever whether something is causal or not with 100 percent surety. That is the whole point. So, when -- what would be causal or not?
Q. Well, I think we are missing each other. I'm asking a simple question here.
In applying the Bradford Hill criteria in this case, am I correct that you did not require for -- before reaching the criteria, the -- that you start off, as Sir Bradford Hill states in his setting forth of the methodology, with an association that is statistically significant, positive, that

cannot be explained by confounding and bias.
A. That doesn't exist.
Q. Okay. So am I correct then that you do not believe that you need to have an observation that reveals an association between two variables that is perfectly clearcut and beyond what we would care to attribute to the play of chance before considering the Bradford Hill criteria?
MR. TRAVERS: Objection, asked and answered.
A. If there were a statistical association between two variables that could not be explained by bias or confounding, then it would almost -- you almost wouldn't have to have the Bradford Hill criteria to discuss it further.
It's -- secondly, the Bradford Hill criteria are not criteria in the sense of requirements. They are guidelines in the sense of how to approach thinking about causality. Whether you are quoting some speech of his, the point is that they're -- they're guidelines for how to think, how to think about causality, not how -- they are

not rules that are required, you have to have this, you have to have that, you have to have a third thing.
Some, they -- are judgment criteria, rules of judgment that we apply in thinking about whether the association between an exposed -- putative association and outcome are associated with each other, that I can evaluate -- you can evaluate or some other -- your expert can evaluate, and we can agree or disagree about.
Q. But just so I am clear, because it's a pretty long answer, you do not consider in your approach to the Bradford Hill criteria, you do not believe that you would need to have this association between two variables that are perfectly clearcut and beyond what we care to attribute to the play of chance before then going to the criteria laid out. Is that correct?
MR. TRAVERS: Objection, asked and answered.
A. I think they need to have an association -- a putative association or a suspected association between an exposure and

an outcome, where there may or may not be the possibility of bias or confounding, and I am evaluating whether bias or confounding are playing a role or whether causality or some other association or some other factor is leading to the association.

Q. So, your methodology then in applying the Bradford Hill criteria, at least to that extent, is different than the methodology that Dr. Bradford Hill would have followed. Is that fair to say?

A. Different than Dr. Bradford Hill would have applied in 1965.

Q. Correct?

A. Possibly.

Q. Now, with respect to these criteria, the first Bradford Hill criteria you discuss in your expert report is temporality; correct?

A. Yes.

Q. And you state in your expert report that there is no doubt that this criteria was met with the glyphosate epidemiology; correct?

A. Yes.

Q. But as we discussed earlier, with respect to cancer epidemiology, temporality also has to consider latency issues; correct?

A. Does it?

Q. Well, that's a question to you. If there is a latent disease, like cancer, and you are trying to determine whether an exposure is in the proper time frame to be a causal association -- for a causal association to be --

A. Well, since I don't -- again, since I am agnostic on the subject of latency, latency to me is not a key issue here personally. Again, Dr. Weisenburger or Dr. Ritz can address it in their own rules.

To me, the question is, did glyphosate exposure precede the onset of non-Hodgkin's lymphoma. That's what temporality means to me. And I think in at least all the studies that I am seeing, that was -- that was pretty clearcut.

Q. Okay. Well, if I -- just if I understand correctly, and I understand you have said you are agnostic on the issue of latency, which means you don't -- you haven't

formed an opinion one way or the other on latency; correct?

A. With regard to how long the latency needs to be.

Q. Right.

So, depending on the answer to that question of latency, for non-Hodgkin's lymphoma and glyphosate, temporality may be satisfied or it may not be satisfied for some of the glyphosate epidemiology; correct?

A. The question is whether there is -- if there is an association between glyphosate and non-Hodgkin's lymphoma -- the question is whether there is an association between glyphosate and non-Hodgkin's lymphoma. If there is an association between the two, then either glyphosate precedes non-Hodgkin's lymphoma, or non-Hodgkin's lymphoma precedes glyphosate.

So either glyphosate is -- now, from all the studies that we seem to have been reading, people, as you yourself have pointed out, and for most of the studies, 15 years, ten years, five years, whatever, glyphosate exposure preceded the onset of the

disease. Now, if there is an association, indeed it seems like that would be consistent with the causal association.

Our other interpretation or Plan B would be to say that getting a lymphoma makes you want to have glyphosate. Monsanto could have another remedy, could have another use for using Roundup to give to people who have lymphoma, if that's their preference, but the arrow has to go one way or the other. It's either glyphosate precedes lymphoma, or lymphoma precedes glyphosate.

Q. Dr. Neugut, to be clear, what you are purporting to try to do with Bradford Hill is answer the question of causation, not association; right?

A. Association, I think what Bradford Hill was saying, or what you were interpreting in his paragraph earlier, is that there -- that the -- that to address the question of causality, first there has to be an association between the exposure and the outcome.

Q. And then you look at temporality as one of the factors.

A. Then you look at these criteria to see what the interpretation of the association is, whether it's causal or confounding or bias or some other -- or whether the arrow goes in the opposite direction, protopathic bias or something of that sort.

Q. With respect to temporality for cancer outcome, for it to support a conclusion of causation, you would want to consider latency; isn't that fair?

A. Yes, but since latency can be anything or can be -- I don't see that it's an issue in this particular case.

Q. When you did your breast cancer epidemiological research, if you were looking at somebody and they said I used pesticides yesterday and then today I went to the doctor -- the first time I used it, and today I went to the doctor and they diagnosed me with breast cancer, would you say that temporality had been met for that exposure?

A. Of course not. But now you are talking about something absurd.

Q. Okay. So, it's not just the case

that exposure has to be before the diagnosis. It has to be before the diagnosis in the proper time frame for latency; correct?

A. I think in this particular instance, with regard to glyphosate and lymphoma, I think the criteria is fairly straightforward.

Q. And you say that without having any opinion one way or the other on what the latency period is.

A. If it's more than a couple of years, then I think that that is a fair statement. The ambiguity with regard to temporality in most cancer epidemiology studies arises in the context of physiologic phenomena, not in the context of external exposures.

So, I mean, when you are talking about something like weight loss, where you don't know if someone lost weight because they had the disease or if the weight loss somehow led to the disease, you can have ambiguity with regard to what the direction of the arrow is, if the two are associated with each other. So, there you can have

ambiguity.

If you are talking about being exposed to cigarette smoking and lung cancer, so either you are going to say that the cigarette smoking causes the lung cancer, or you are going to say that having lung cancer makes you -- cigarette smoking makes someone with lung cancer feel better when they smoke, so you have your choice of which way to interpret the association between the two.

So, on some level, if you want to say that glyphosate follows -- glyphosate exposure follows having a lymphoma, that may be your interpretation of the association between the two. But I don't think that is the logical, or that is not what seems to arise from the various case-control and cohort studies here.

Q. Dr. Neugut, that wasn't what I said, and I am not sure why we are miscommunicating here.

For purposes of cancer, when you are looking at epidemiological studies, and we have already discussed the fact that cancer epidemiology studies will include

things like lag time; correct?

A. Yes.

Q. In the analysis, and a variety of different analyses, in cancer epidemiology in particular, to make sure that you have taken into account --

A. Yes. Yes.

Q. -- latency; correct?

MR. TRAVERS: Objection.

A. But latency can be as little as a year.

Q. I understand that. But for you, for glyphosate and non-Hodgkin's lymphoma, you don't have an opinion about what the latency is. It could be a year, it could be ten years, you don't know. Is that your testimony?

A. That's correct, but --

Q. And --

A. But the key thing is that the exposure to glyphosate was more than a year prior to the development of lymphoma.

Q. Or more than ten years prior.

A. Or more than ten years, fine. I'm happy with that, too.

Q. And if that were the criteria, that the exposure of glyphosate for temporality has to be more than ten years before exposure, then at least for De Roos 2003, we don't have temporality that has been satisfied; correct?

MR. TRAVERS: Objection, asked and answered.

A. Disagree.

Q. There are no exposures in the De Roos or -- study, or that would have exposures more than ten years before diagnosis.

A. Temporality is not a question of whether latency applies. Temporality is a question of does the cause precede the effect. As long as the glyphosate exposure is prior to the disease, temporality is met.

Q. Let's talk about the next criteria you mention, which is -- Bradford Hill criteria, which is consistency; correct?

A. Correct.

Q. And this is -- now, again, Sir Bradford Hill in his assessment, when he was talking about consistency, he was looking to

consistency across studies finding statistically significant results; correct?

A. Yes.

Q. You do not define in your methodology "consistency" that way; is that correct?

A. The modern epidemiologic -- in modern epidemiology, statistical significance isn't considered essential.

Q. That is not my question. In your application of the Bradford Hill criteria, you are defining "consistency" differently than Bradford Hill did; correct?

MR. TRAVERS: Objection, asked and answered.

A. I don't know how he exactly defined it, but I would assume that he was more strict about statistical significance.

Q. And you have stated in your report, as a basis for your conclusion that there is consistency in the epidemiological studies, that all of the reported odds ratios --

(Telephone interruption.)

A. Sorry.

Q. I will start again.

You have stated in your report that you believe the criteria for consistency to be met, because the reported odds ratios in each -- all of the reported odds ratios in the epidemiological literature that you reviewed were above 1.0; correct?

A. Yes.

Q. Now, first of all, that would not include the dose-response analysis in the 2005 De Roos study; correct?

A. In the --

Q. The 2005 De Roos study, the dose-response analysis, the highest exposures were below 1.0 for the odds ratio; correct? So that finding in De Roos 2005 is inconsistent.

A. Okay.

Q. Is that correct?

A. Yes.

Q. And in order for you to also reach the conclusion -- well, strike that.

Your conclusion that all of the odds ratios are above 1.0 is based upon your analysis following the IARC methodology and not considering the updated Agricultural

Health Study data; correct?

A. Yes.

Q. And it also doesn't consider the self-respondent data that we looked at for the North American Pooled Project; correct?

A. Yes.

Q. And if those analyses are considered, there is no consistency among the epidemiological studies; correct?

MR. TRAVERS: Objection, mischaracterizes.

A. I don't know.

Q. Well, there would be then the AHS study, updated study that's below 1.0; correct?

A. So, again, I don't know the quality of the study or whether to consider it or how to consider it.

Q. I understand.

A. So, I am not going to give credit to a study that I don't know anything about or that I don't know much about.

Q. But just to understand your consistency analysis, and I understand you can't opine, you didn't look at the AHS 2013,

you didn't look at the NAPP data, but I'm just understanding your definition of "consistency."

If we were to consider the updated AHS data from 2013, that has an odds ratio of 0.9, so that would be below 1.0; correct?

MR. TRAVERS: Objection, assumes facts not in evidence.

A. Yes.

Q. And we would have the Orsi study, which is exactly 1.0; correct?

A. Yes.

Q. And we would have the NAPP data, which is either just above 1.0, if we include proxy respondents, or just below 1.0, if we only look at self-respondents; correct?

A. Yes.

Q. And then we would have the Swedish case-control study, the Eriksson study, which would be slightly above 1.0; correct?

A. Um-hum. Yes.

Q. So those data points, if those were the correct data points, and I understand you have not reviewed some of them, but those data points would not be consistent; correct?

A. Might or might not be. Again, I haven't looked at them, so I am not willing to opine on that.

Q. But we would have some above one, some below one, some directly at one; correct?

A. Um-hum.

Q. Yes?

A. Yes.

Q. And we already talked about dose-response. We talked about biological plausibility, and biological plausibility, I take it you defer to the toxicologists; correct?

A. To the degree that I am able to opine, I think it seems decent to me, but I would defer.

Q. And then the final criteria you discuss is strength of association; correct? In your expert report, that is the final criteria you mentioned.

A. Don't I mention specificity?

Q. You may mention specificity. You say that is not important.

A. I don't?

Q. Okay. Well, we will talk about specificity then.

In your opinion, you believe -- let me see if I am correct. It's your opinion that glyphosate has not been associated with any cancer other than non-Hodgkin's lymphoma; correct?

A. That is specificity?

Q. Well, I'm asking this question.

A. Or is that strength?

Q. Is it your opinion that glyphosate and glyphosate-based herbicides have not been shown to be a cause of any type of cancer other than non-Hodgkin's lymphoma?

A. That's my sense of the literature, yes.

Q. So, if glyphosate or glyphosate-based herbicides causes any cancer, it would be non-Hodgkin's lymphoma. That is the only --

A. Based on the literature as I have read it to date, yes. I mean, obviously, everything I am saying today is based on --

Q. Your review.

A. -- what I have read until today.

If anything changes --

Q. Right, I understand that.

But you looked at, for example, the IARC monograph, and they reviewed other types of cancer as well, and you agree that there is no association shown there between glyphosate and those other types of cancer, correct, besides NHL?

A. Yes.

Q. So, then for you, is it -- am I correct in my understanding that you think specificity has been met because if it causes any cancer, it only causes non-Hodgkin's lymphoma?

A. Yes.

Q. You would agree that there are lots of other causes for non-Hodgkin's lymphoma, though; correct?

A. I don't know lots. I mean, I have trouble thinking of more than a few, but I don't know how many would apply generally, but --

Q. Non-Hodgkin's lymphoma, certainly it's not a signature disease for glyphosate; correct. Like mesothelioma or -- and

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asbestos.
A. I don't know how to answer that question.
Q. Okay. Well, that's fair.
Is it your opinion that non-Hodgkin's lymphoma may be a signature disease for glyphosate?
A. I don't know what a signature disease means.
Q. Ah, okay. You would agree that there are lots of other causes for non-Hodgkin's lymphoma, either known or unknown, besides glyphosate; correct?
A. I think most lymphoma is unexplained.
Q. So, you can't say that if you see NHL, you would think that it would have to be glyphosate; correct?
A. No, that's correct.
Q. All right. So then the -- you are correct, the fifth, I think, of the criteria, you talk about analogy, which you say is not applicable, and then specificity. But before that, you talk about strength; correct?
A. Yes.

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Q. And that in fact is the first criteria that Dr. Bradford Hill, or Sir Bradford Hill discusses, correct, in his criteria?
A. I didn't follow his order.
Q. That's fine.
And with respect to strength, you are pointing to that range of 1.3 to 1.5; correct?
A. Yes.
Q. And that is based upon that earlier meta-analyses that you not take into account the 2013 AHS data or the NAPP data; correct?
A. It did not take into account the follow-up AHS data, correct.
Q. Now, with respect to that, that -- those numbers, 1.3 to 1.5, you would agree that that is not a very convincing number with respect to strength; correct?
A. Call it modest to moderate.
Q. You would agree it did not provide a strong push towards causality; correct?
A. It's not an overwhelming number, no.
Q. In fact, I think you have testified

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in other cases that that 1.3 to 1.5 is, I think the term you used was bupkis; right?
A. Have I used that expression?
Q. You've used that expression with respect to 1.3 to 1.5, haven't you?
A. I don't know. But as I say, it's not a large number.
Q. So, 1.3 to 1.5 is not what you would -- well, strike that.
When you have a number like 1.3 to 1.5, you would have concerns that those findings can be explained by something other than causation, such as bias and confounding; correct?
A. I would have that concern for even larger numbers, but -- so, again, the number that you see, we are talking about ever/never, generally we are talking about ever/never. You know, when you see a number like that number, there is also the issue of dose-response. So that means there are those who are more exposed and therefore potentially have higher risk. So that may reflect a subgroup that might have a significantly higher risk within it, but on

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the whole, it's a modest risk.
Q. I mean, we have talked about dose-response. We can go back to that. That is a separate criteria for Bradford Hill; correct?
A. Yes.
Q. But as far as the strength criteria is concerned, it would be fair to say that even with your understanding of the glyphosate literature, that is not a particularly powerful finding for that criteria for Bradford Hill; correct?
A. It's not a number that would -- that would build your confidence that this was a -- that there was a causal relationship. It's enough, it's -- what do they say -- it's sufficient, but not -- but not something that would add to your -- add to your confidence that there were a causal association.
MR. LASKER: Why don't we take a break now? I'm just going to look and see what more questions I have.
MR. TRAVERS: Yeah, sure.
THE VIDEOGRAPHER: The time is

5:12 p.m. We are off the record.
(Recess taken.)
THE VIDEOGRAPHER: The time is 5:27 p.m. We are on the record.
MR. LASKER: Dr. Neugut, I have no further questions. Thank you very much.
THE WITNESS: Oh, thank you.
MR. TRAVERS: Excellent.
I have just got a few follow-up questions. Let's see. Do we have exhibit stickers?
I want to enter as an exhibit, this is the Blair paper from 2011.
MR. LASKER: So what number is this?
MR. TRAVERS: 14-23.
(Exhibit 14-23, NIH Public Access, Impact of Pesticide Exposure Misclassification on estimates of Relative Risks in the Agricultural Health Study marked for identification, as of this date.)
EXAMINATION
BY MR. TRAVERS:
Q. And do you recognize this paper,

Dr. Neugut?
A. Yes.
Q. And this paper deals with the non-differential misclassification bias; is that correct?
A. Yes.
Q. And this paper authored by -- and you see that Aaron Blair is the lead author on this paper; correct?
A. Yes.
Q. And it's referencing the AHS study cohort?
A. Yes.
Q. And I would just like to refer you to the conclusion of this paper, and page six. You have been there.
The last paragraph on page six, it states, "We draw several conclusions from our methodological work in the AHS. First, the accuracy of reporting of pesticide use by farmers is comparable to that for many other factors commonly assessed by questionnaire for epidemiological studies."
MR. LASKER: I lost track. Where are you?

MR. TRAVERS: Sorry. The last paragraph, page six.
MR. LASKER: Okay. Starting, "First, the accuracy."
MR. TRAVERS: Yeah.
MR. LASKER: Okay.
BY MR. TRAVERS:
Q. Then it goes on to say, "Second, except in situations where exposure estimation is quite accurate, i.e., correlations of .7 or greater with true exposure, and true relative risk of 3.0 or more, pesticide misclassification may diminish risk estimates to such an extent that no association is obvious, which indicates false negative findings might be common."
Do you see that?
A. Yes.
Q. And with that bias in the AHS study, how would that affect the findings on glyphosate from the De Roos 2005 study?
A. Well, since we are talking about a relative risk in a range of 1.3 or -- or theoretically, a relative risk in the range

of 1.3 to 1.5, and misclassification error, then it would be very easy, based on the degree of misclassification error that they are talking about, for that kind of a risk ratio to be attenuated and to disappear in this study, which is basically what they are -- what they are describing.
Q. So, if there is a negative finding --
A. A null finding.
Q. Okay. And you said you read the deposition of Aaron Blair; correct?
A. Yes.
Q. And do you recall he is an author of the NAPP abstract?
A. Yes.
Q. And he is a lead investigator on the AHS, AHS study?
A. Yes.
Q. And it was still his opinion as the chair of the IARC working group that glyphosate was a probable human carcinogen; correct?
MR. LASKER: Objection to form.
A. Yes.

Q. And do you recall at the end of his deposition, he stated that his opinion had not changed at all after questioning by defense counsel? Do you recall that?
A. I recall that.
Q. And does Aaron Blair's testimony support your -- or support your opinion that Roundup can cause cancer in humans?
A. Yes.
Q. And after the almost seven hours of questioning, do you stand by the conclusion in your expert report?
A. Yes.
Q. Okay. I would like to get Exhibit 14-21, and this is the memo by Exponent, the updated meta-analysis.
MR. LASKER: Excuse me just a second.
Q. And is Exponent a peer-reviewed journal?
A. Exponent is a company, to my knowledge.
Q. And you are not aware of this paper being submitted for peer review?
A. I don't know anything about it.

Q. And I would like to ask, if you could, to read footnotes one and two. You don't have to read them out loud. If you can review footnotes one and two.
A. On the first page?
Q. Yes.
A. Okay.
Q. And if you recall from earlier in the testimony, this -- this memo to Hollingsworth, or this meta-analysis, the only updated information was the unfinished draft manuscript of the 2013 AHS study and the abstract from the NAPP study; correct?
A. Yes.
MR. LASKER: Objection to form, misstates the document.
Q. And reviewing footnotes one or two, can you tell who provided those documents to Chang and Delzell?
A. Mr. Lasker.
Q. And generally, when you are conducting a scientific study that you would submit for peer review, if you are going to update a study, would you rely solely on data provided by an attorney you are consulting

for?
A. Not commonly.
Q. Okay. Go back to Aaron Blair's deposition. If you could go -- if you could go to page 206.
A. 206?
Q. Yes. If you go to line 20, Mr. Lasker asked of Aaron Blair:
"But just so the record is clear, IARC was not relying upon the most updated analysis that you are aware from the AHS data with respect to glyphosate and non-Hodgkin's lymphoma; correct?"
And then Aaron Blair answers:
"Now you present it as if the analysis were completed. Analyses were done, manuscripts are in description, but the work wasn't finished, which means it's incomplete, and that you don't want to be reporting on, and we didn't."
Does that support your decision not to rely upon the 2013 unpublished manuscript?
A. Yes. You know, data that is not peer reviewed or published is not peer reviewed or published. You don't know why

it's not. It might not have been finished, might not have been accepted by the journal, it might not have been in good shape. You have no idea why it's not published.
Q. I just want to clarify, when you reference -- we talked a lot about the AHS study. But when you reference the AHS study in your report, what are you referring to?
A. 2005 paper.
Q. Okay. And I would just like -- if you have got your report, I would like to go to page three.
MR. LASKER: Just a moment. Page three?
MR. TRAVERS: Yes.
Q. And at the top, it says you were asked to review the scientific literature on glyphosate and glyphosate-based formulations and to provide an opinion to a reasonable degree of medical and scientific certainty as to whether glyphosate and glyphosate-based formulations can cause non-Hodgkin's lymphoma; correct?
A. Yes.
Q. If you were to do a literature

review for scientific journals, say like the Lancet, would you rely on unpublished, unpeer-reviewed data?

A. I might under certain circumstances report a fact or a bit of information, citing it as un- -- unpublished, but -- but as a -- almost as a -- more in the context of a bit of information, not in the context necessarily of, say, in a data table or something of that sort. So, I might express an opinion by someone or -- that is not published, or a factoid, but I don't think I would express data per se that was not published.

Q. And in your report, you also talk about meta-analyses, and there are meta-analyses in the IARC report as well; correct?

A. Yes.

Q. Those are in fact statistically significant; correct?

A. Yes.

Q. Okay. And in the -- and also in your report, you note that McDuffie shared an odds ratio, a statistically significant odds

ratio of 2.12 for people who used glyphosate greater than two days per year; correct?

A. Yes.

Q. And Eriksson showed an odds ratio of 2.36 for people who used glyphosate longer than ten years; correct?

MR. LASKER: Objection to form.

A. Yes.

MR. LASKER: I don't think that's what you meant to say. More than ten years?

MR. TRAVERS: Who used glyphosate longer than ten years.

MR. LASKER: Is that what he says in his report? Where are you reading?

MR. TRAVERS: Page 22.

MR. LASKER: Hmm. Okay. It is what he has in his report.

Q. And you have worked -- you have worked with the Miller Firm before on the Actos case; correct?

A. Yes.

Q. Have you ever worked for defendants as an expert?

A. Yes.

Q. What percentage of cases would you say are for defendant -- that you take are for defendants compared to plaintiffs?

A. Nowadays, I do about two-thirds plaintiff and about a third defendant.

Q. All right. Have you ever turned down -- have you ever turned down cases from plaintiffs' firms?

A. Sure. And from Miller.

Q. And defense counsel showed you an article from 1965 by Bradford Hill. Let's see. Has the application of Bradford Hill been modified at all from 1965 to present time?

MR. LASKER: Objection to form.

A. I mean, I don't want to say it's been modified in terms of its skeletal structure, but the interpretation of the nomenclature and the, the intent or the -- the interpretation of the criteria that are there have certainly been modified and adapted and adjusted over the years. They are not the same as they were in 1965.

I mean, remarkably, it's actually retained its -- the nomenclature has actually

stayed more or less the same as -- for 50 years, but the words don't necessarily -- are not applied -- the terminology and the applications are not applied in the same way now as they were 50 years ago.

Q. And that would be, what you are saying would be, that would be the general consensus of the scientific community?

MR. LASKER: Objection to form.

A. Sure. I would think so, yes.

Q. Would you -- do you agree with the following statement? Would you -- I'm sorry.

Would you agree that IARC is a well-regarded international public health agency?

A. Sure.

Q. Would you agree that when IARC monographs are available, they are generally recognized as authoritative?

A. The ones on carcinogenesis, yes.

Q. Let's see. And would you agree that IARC is one of the most well-respected and prestigious scientific bodies?

MR. LASKER: Objection to form.

A. When you say "most," you sort of

have to have a concluding phrase.
Q. Would you agree that IARC is a well-respected and prestigious scientific body?
A. Yes.
MR. TRAVERS: Those are all the questions I have got.
EXAMINATION
BY MR. LASKER:
Q. Just a few follow-ups, Dr. Neugut.
You do state in your expert report that Eriksson showed, on page 22, an odds ratio for -- of 2.36 for people who were -- used glyphosate longer than ten years. Does Eriksson actually report that data? Because I don't remember that from the glyphosate study.
A. What page are you on?
Q. In your report, page 22, you say that Eriksson showed an odds ratio of 2.36 for people who used glyphosate longer than ten years. You were asked that by plaintiffs' counsel and agreed that's what Eriksson found. It's on page 22, under strength of association.

A. If I said it, then I must have thought it.
Q. Okay. I believe, and you can -- you can correct me if I am wrong, that at least the number you are citing there is greater than ten days, not ten years, from Eriksson's report, and this is table two.
A. You are right. It's greater than ten days. I apologize, it's an error.
Q. Just so we are clear, that is a mistake in your expert report.
A. Um-hum.
Q. And that 2.36 number that we -- for greater than ten days, that is the number that we were talking about previously that you agreed there is no measure or indication that that is statistically different than the odds ratio for less than ten days; correct?
A. There is no number for that, but yes, it's larger.
Q. So, we don't know if -- we don't have any statistical indication from this study from Eriksson that there is a greater odds ratio with greater exposure, because we don't have that statistical analysis;

correct?
A. Right.
Q. With respect to the 2013 AHS study, did you rely upon anything that Dr. Blair said in his deposition in deciding not to consider or not to even look at that data?
A. What's the -- oh, the AHS follow-up?
Q. Yes.
A. No.
Q. With respect to -- plaintiffs' counsel asked you about the Chang and Delzell 2017 analysis, and he pointed out that the AHS 2013 analysis and the NAPP analysis were provided to Exponent by myself.
Now, just to be clear, you agree that I did not create that data; correct?
A. You did not --
Q. Create that data.
A. I assume not.
Q. And you have read Dr. Blair's deposition. You know that this was data that Dr. Blair had in his files; correct?
A. Yes.
Q. And this was data that Dr. Blair

did not disclose to IARC; correct?
A. Yes.
Q. And this is data that Dr. Blair did not disclose to the EPA; correct?
A. I don't recall offhand about EPA, but -- I don't know about that. I don't recall.
Q. And there was no way for investigators who were conducting a meta-analysis prior to the deposition of Dr. Blair, where this data became public, for any investigator at IARC or elsewhere doing a meta-analysis to include that 2013 data or the NAPP data; correct?
A. Correct.
Q. With respect to Exhibit 14-23, which is the paper, the Blair paper on exposure misclassification, plaintiffs' counsel asked you a couple of questions about that. Do you recall?
A. Which document?
Q. This would be Exhibit 14-23, and it is a paper by Blair entitled "Impact of pesticide exposure misclassification on estimates of relative risks in the

Agricultural Health Study." Correct?
A. Yes.
Q. And this study again is referring to the possibility of misclassification biasing results towards the null; correct?
A. I wouldn't use the word "biasing." I would say --
Q. Shifting towards the null.
A. Okay.
Q. And as we discussed previously, if the reported odds ratio is below 1.0, then this type of exposure misclassification would bump those numbers up a little bit.
MR. TRAVERS: Objection.
Q. And if it's above 1.0, this type of exposure misclassification might lower it. Correct?
MR. TRAVERS: Objection.
A. Yes.
MR. TRAVERS: Asked and answered, mischaracterizes his previous testimony.
Q. And with respect to the Agricultural Health Study, to the extent that there are odds ratios reported for glyphosate and non-Hodgkin's lymphoma below 1.0, the

type of exposure misclassification that is discussed in the Blair paper would bump those numbers up; correct?
MR. TRAVERS: Objection, asked and answered, mischaracterizes previous testimony.
A. A misclassification error would work on the opposite side as well.
Q. It would work in both directions.
A. Yes.
Q. And in fact, in this paper, at page 11, they have tables that show that if the risk ratio is below one, this misclassification would -- would tend to increase those numbers to make them higher; correct?
A. Yes.
Q. And so, with the Agricultural Health Study, both the 2005 study for their dose-response and the 2013 analysis for all of its findings, they reported odds ratios for glyphosate and non-Hodgkin's lymphoma that were below 1.0; correct?
A. Yes.
Q. So, the impact of this

misclassification, if it occurred, to -- for those numbers in the AHS studies for glyphosate and non-Hodgkin's lymphoma would actually push those numbers up; correct?
A. Yes.
Q. The Blair paper, the 2011 paper, Exhibit 14-23, also states that if the relative risks are -- the true relative risk is 1.0, misclassification -- the misclassification that they are discussing here does not actually impact the results at all; correct?
A. That's correct.
Q. And the other finding in this paper is that the attempt to make some measurement of intensity of exposure, which is what is done in the Agricultural Health Study, does improve the study as compared to just asking whether or not an individual had used or been exposed to pesticide in the past; correct?
A. I'm sorry, say that one again.
Q. That the Blair 2011 paper reports that when they look to their intensity measure in the Agricultural Health Study, intensity of exposure, that did correlate

with exposure levels better than simply asking the individual whether they had been exposed or not; correct?
A. I don't recall that, but -- I don't recall seeing that.
Q. Well, take a look to the last page, is actually where you were being asked questions by plaintiffs' counsel, on page six. And it is right where he stopped off on his questioning of you.
It states, "Third, it appears that an algorithm that incorporates several exposure determinants into an estimate of exposure intensity predicts urinary levels better than the individual exposure determinants considered here and would result in less attenuation of relative risk estimates." Correct?
A. Yes.
Q. One of the findings in this analysis by Blair is that the AHS, through using an algorithm to try to estimate intensity of exposure, does reduce this potential bias as compared to studies that don't include an intensity measure; correct?

A. Yes.
Q. And the case-control studies that we talked about for glyphosate, none of them included any algorithm to try and assess intensity of exposure; correct?
A. I don't think any of them did, no.
Q. The Blair paper in 2011, that resulted in modifications for the algorithm for intensity that was used in agricultural study analyses going forward; correct?
A. I don't know.
MR. LASKER: Let's mark as Exhibit -- I'm sorry.
(Exhibit 14-24, An Updated Algorithm for Estimation of Pesticide Exposure Intensity in the Agricultural Health Study marked for identification, as of this date.)
Q. This is a 2011 paper by Coble, et al, including Dr. Blair as well, "An updated algorithm for estimation of pesticide exposure intensity in the Agricultural Health Study." Correct?
A. Yes.
Q. And it states in this abstract that

an algorithm developed to estimate pesticide exposure intensity for use in epidemiological analyses was revised based on data from two exposure monitoring studies; correct?
A. Yes. But I am -- it's a little hard for me to absorb. This is a pretty complicated paper. It's a little hard for me to sit here and absorb here now.
Q. Okay. But it does appear, and I recognize that you have not reviewed this in connection with reaching your opinion, but it does appear that in response to some of the analyses that were in the paper we looked at, 14-23, there was an update in the algorithm for the Agricultural Health Study for intensity of exposure; correct?
A. Perhaps. I don't know, and I don't know for what particular exposures, and in particular, I don't know whether it applies to glyphosate in particular or not.
Q. And with respect to -- and let's -- I don't think we marked it, but I think we are going to have to now. The 2013 Agricultural Health Study analyses, do you know whether or not that analysis used the

algorithm that was being discussed in the paper you cited, 14-23, or the updated algorithm that was derived subsequently?
A. I don't know anything about the 2013 analysis.
Q. Okay. If in fact the 2013 analysis used an updated algorithm cited here in the Coble paper, that would at least potentially address some of the issues that you raised with respect to the Blair 2011 paper; correct?
A. Again, I would have to beg off on that. I don't know.
Q. Okay.
(Continued on next page with witness jurat.)

MR. LASKER: I have no further questions. We are done.
THE VIDEOGRAPHER: The time is 6 p.m. We are off the record.
oOo
I, ALFRED NEUGUT, M.D., , the witness herein, do hereby certify that the foregoing testimony of the pages of this deposition to be a true and correct transcript, subject to the corrections, if any, shown on the attached page.

_____

Subscribed and sworn to before me this _____day of _____,_____.

_____
NOTARY PUBLIC

STATE OF NEW YORK) Pg. of Pgs.
COUNTY OF NEW YORK)

I wish to make the following changes for the following reasons:

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ALFRED NEUGUT, M.D.,

C E R T I F I C A T E

STATE OF NEW YORK)
: SS.
COUNTY OF NEW YORK)

I, BONNIE PRUSZYNSKI, a Notary Public with and for the State of New York, do hereby certify:

That ALFRED NEUGUT, M.D., , the witness whose deposition is hereinbefore set forth, was duly sworn by me and that such deposition is a true record of the testimony given by the witness.

I further certify that I am not related to any of the parties to this action by blood or marriage, and that I am in no way interested in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 7th of August, 2017.

_____
Bonnie Pruszynski

H

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

IN RE: ROUNDUP PRODUCTS LIABILITY LITIGATION	MDL No. 2741 Case No. 16-md-02741-VC
This document relates to: ALL ACTIONS	**MONSANTO COMPANY'S AMENDED NOTICE TO TAKE ORAL AND VIDEOTAPED DEPOSITION OF DR. ALFRED NEUGUT**

To: All MDL plaintiffs, by and through, the Court's appointed co-lead counsel, Robin Greenwald of Weitz & Luxenberg, PC, Michael Miller of The Miller Firm, LLC, and Aimee Wagstaff of Andrus Wagstaff, PC

Please take notice that, pursuant to Rule 30 and Rule 45 of the Federal Rules of Civil Procedure, defendant Monsanto Company shall take the videotaped deposition upon oral examination of **Dr. Alfred Neugut on August 7, 2017** before a person duly authorized to administer oaths. The deposition shall commence at **9:00 a.m. ET at Weitz & Luxenberg PC, 700 Broadway, New York, NY 10003**. The conduct of the deposition, including its continuation if necessary, shall be governed by Pretrial Order No. 7: Deposition Protocol (ECF No. 103) and Rule 30 of the Federal Rules of Civil Procedure. Dr. Neugut shall produce any documents identified in Schedule A attached to his Document Subpoena, at least 7 days prior to the deposition. *See* July 27, 2017 Document Subpoena for Dr. Alfred Neugut.

DATED: July 28, 2017

Respectfully submitted,

/s/ Heather A. Pigman
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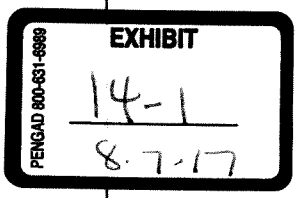
MONSANTO COMPANY



AO 88B (Rev. 02/14) Subpoena to Produce Documents, Information, or Objects or to Permit Inspection of Premises in a Civil Action

UNITED STATES DISTRICT COURT

for the

Northern District of California

IN RE: ROUNDUP PRODS. LIABILITY LITIG.
Plaintiff
v.
Defendant

Civil Action No. 16-md-2741-VC

SUBPOENA TO PRODUCE DOCUMENTS, INFORMATION, OR OBJECTS OR TO PERMIT INSPECTION OF PREMISES IN A CIVIL ACTION

To: Dr. Alfred Neugut

(Name of person to whom this subpoena is directed)

☑ *Production:* **YOU ARE COMMANDED** to produce at the time, date, and place set forth below the following documents, electronically stored information, or objects, and to permit inspection, copying, testing, or sampling of the material: SEE ATTACHED SCHEDULE A

Place: Hollingsworth LLP, 1350 I St., NW Washington, D.C. 20005	Date and Time: 07/31/2017 5:00 pm

☐ *Inspection of Premises:* **YOU ARE COMMANDED** to permit entry onto the designated premises, land, or other property possessed or controlled by you at the time, date, and location set forth below, so that the requesting party may inspect, measure, survey, photograph, test, or sample the property or any designated object or operation on it.

Place:	Date and Time:

The following provisions of Fed. R. Civ. P. 45 are attached – Rule 45(c), relating to the place of compliance; Rule 45(d), relating to your protection as a person subject to a subpoena; and Rule 45(e) and (g), relating to your duty to respond to this subpoena and the potential consequences of not doing so.

Date: 07/27/2017

CLERK OF COURT

OR

Signature of Clerk or Deputy Clerk

/s/ Heather Pigman
Attorney's signature

The name, address, e-mail address, and telephone number of the attorney representing *(name of party)* Monsanto, who issues or requests this subpoena, are:

Heather Pigman, 1350 I Street, NW Washington, D.C. 20005, hpigman@hollingsworthllp.com, 202-898-5800

Notice to the person who issues or requests this subpoena

If this subpoena commands the production of documents, electronically stored information, or tangible things or the inspection of premises before trial, a notice and a copy of the subpoena must be served on each party in this case before it is served on the person to whom it is directed. Fed. R. Civ. P. 45(a)(4).

Civil Action No. 16-md-2741-VC

PROOF OF SERVICE

(This section should not be filed with the court unless required by Fed. R. Civ. P. 45.)

I received this subpoena for *(name of individual and title, if any)* _____

on *(date)* _____ .

❒ I served the subpoena by delivering a copy to the named person as follows: _____

_____

_____ on *(date)* _____ ; or

❒ I returned the subpoena unexecuted because: _____

_____ .

Unless the subpoena was issued on behalf of the United States, or one of its officers or agents, I have also tendered to the witness the fees for one day's attendance, and the mileage allowed by law, in the amount of $ _____ .

My fees are $ _____ for travel and $ _____ for services, for a total of $ 0.00 .

I declare under penalty of perjury that this information is true.

Date: _____

_____
Server's signature

_____
Printed name and title

_____
Server's address

Additional information regarding attempted service, etc.:

Federal Rule of Civil Procedure 45 (c), (d), (e), and (g) (Effective 12/1/13)

(c) Place of Compliance.

(1) ***For a Trial, Hearing, or Deposition.*** A subpoena may command a person to attend a trial, hearing, or deposition only as follows:

(A) within 100 miles of where the person resides, is employed, or regularly transacts business in person; or

(B) within the state where the person resides, is employed, or regularly transacts business in person, if the person

(i) is a party or a party's officer; or

(ii) is commanded to attend a trial and would not incur substantial expense.

(2) ***For Other Discovery.*** A subpoena may command:

(A) production of documents, electronically stored information, or tangible things at a place within 100 miles of where the person resides, is employed, or regularly transacts business in person; and

(B) inspection of premises at the premises to be inspected.

(d) Protecting a Person Subject to a Subpoena; Enforcement.

(1) ***Avoiding Undue Burden or Expense; Sanctions.*** A party or attorney responsible for issuing and serving a subpoena must take reasonable steps to avoid imposing undue burden or expense on a person subject to the subpoena. The court for the district where compliance is required must enforce this duty and impose an appropriate sanction—which may include lost earnings and reasonable attorney's fees—on a party or attorney who fails to comply.

(2) ***Command to Produce Materials or Permit Inspection.***

(A) *Appearance Not Required.* A person commanded to produce documents, electronically stored information, or tangible things, or to permit the inspection of premises, need not appear in person at the place of production or inspection unless also commanded to appear for a deposition, hearing, or trial.

(B) *Objections.* A person commanded to produce documents or tangible things or to permit inspection may serve on the party or attorney designated in the subpoena a written objection to inspecting, copying, testing, or sampling any or all of the materials or to inspecting the premises—or to producing electronically stored information in the form or forms requested. The objection must be served before the earlier of the time specified for compliance or 14 days after the subpoena is served. If an objection is made, the following rules apply:

(i) At any time, on notice to the commanded person, the serving party may move the court for the district where compliance is required for an order compelling production or inspection.

(ii) These acts may be required only as directed in the order, and the order must protect a person who is neither a party nor a party's officer from significant expense resulting from compliance.

(3) ***Quashing or Modifying a Subpoena.***

(A) *When Required.* On timely motion, the court for the district where compliance is required must quash or modify a subpoena that:

(i) fails to allow a reasonable time to comply;

(ii) requires a person to comply beyond the geographical limits specified in Rule 45(c);

(iii) requires disclosure of privileged or other protected matter, if no exception or waiver applies; or

(iv) subjects a person to undue burden.

(B) *When Permitted.* To protect a person subject to or affected by a subpoena, the court for the district where compliance is required may, on motion, quash or modify the subpoena if it requires:

(i) disclosing a trade secret or other confidential research, development, or commercial information; or

(ii) disclosing an unretained expert's opinion or information that does not describe specific occurrences in dispute and results from the expert's study that was not requested by a party.

(C) *Specifying Conditions as an Alternative.* In the circumstances described in Rule 45(d)(3)(B), the court may, instead of quashing or modifying a subpoena, order appearance or production under specified conditions if the serving party:

(i) shows a substantial need for the testimony or material that cannot be otherwise met without undue hardship; and

(ii) ensures that the subpoenaed person will be reasonably compensated.

(e) Duties in Responding to a Subpoena.

(1) ***Producing Documents or Electronically Stored Information.*** These procedures apply to producing documents or electronically stored information:

(A) *Documents.* A person responding to a subpoena to produce documents must produce them as they are kept in the ordinary course of business or must organize and label them to correspond to the categories in the demand.

(B) *Form for Producing Electronically Stored Information Not Specified.* If a subpoena does not specify a form for producing electronically stored information, the person responding must produce it in a form or forms in which it is ordinarily maintained or in a reasonably usable form or forms.

(C) *Electronically Stored Information Produced in Only One Form.* The person responding need not produce the same electronically stored information in more than one form.

(D) *Inaccessible Electronically Stored Information.* The person responding need not provide discovery of electronically stored information from sources that the person identifies as not reasonably accessible because of undue burden or cost. On motion to compel discovery or for a protective order, the person responding must show that the information is not reasonably accessible because of undue burden or cost. If that showing is made, the court may nonetheless order discovery from such sources if the requesting party shows good cause, considering the limitations of Rule 26(b)(2)(C). The court may specify conditions for the discovery.

(2) ***Claiming Privilege or Protection.***

(A) *Information Withheld.* A person withholding subpoenaed information under a claim that it is privileged or subject to protection as trial-preparation material must:

(i) expressly make the claim; and

(ii) describe the nature of the withheld documents, communications, or tangible things in a manner that, without revealing information itself privileged or protected, will enable the parties to assess the claim.

(B) *Information Produced.* If information produced in response to a subpoena is subject to a claim of privilege or of protection as trial-preparation material, the person making the claim may notify any party that received the information of the claim and the basis for it. After being notified, a party must promptly return, sequester, or destroy the specified information and any copies it has; must not use or disclose the information until the claim is resolved; must take reasonable steps to retrieve the information if the party disclosed it before being notified; and may promptly present the information under seal to the court for the district where compliance is required for a determination of the claim. The person who produced the information must preserve the information until the claim is resolved.

(g) Contempt.

The court for the district where compliance is required—and also, after a motion is transferred, the issuing court—may hold in contempt a person who, having been served, fails without adequate excuse to obey the subpoena or an order related to it.

For access to subpoena materials, see Fed. R. Civ. P. 45(a) Committee Note (2013).

SCHEDULE A

DEFINITIONS

1. The term "Communication," as used in these Requests, is intended to have the broadest possible meaning and shall include any contact or act by which information or knowledge is transmitted or conveyed between two or more persons and includes, without limitation: (1) written contact, including but not limited to letters, memoranda, PowerPoint presentations, email, text message, telegram, telex, internet-based meetings, or other written or electronic documents or files; (2) oral contact, whether by face-to-face meetings, internet-based meetings, video conferences, telephonic conversations, or otherwise; and (3) nonverbal acts intended to communicate or convey any meaning, understanding or other message.

2. "Concerns," "concerning," "relates," or "relating" shall mean and include contain or containing, constitute or constituting, describe or describing, discuss or discussing, refer or referring, state or stating, assess or assessing, and record or recording.

3. "Documents" shall be construed in the broadest sense and includes, but is not limited to, the original and any non-conforming copies of any and all written, printed, typed, graphic, photographic, visual or otherwise recorded matter of any kind or nature, and all microfilm, or electronic sound recording or transcripts thereof however produced or reproduced, including non-identical copies, whether different from the original by reason of any notation made on such copies or otherwise, writings, drawings, records and recordings of every kind and description, whether inscribed by hand or by mechanical, electronic, microfilm, photographic or other means, as well as audio or visual reproduction of all statements, conversations or events including, but not limited to, agreements, bids, bonds, bulletins, calendars and appointment books, checks, circulars, communications, contracts, correspondence, statements, telegrams, receipts, returns, summaries, data books, accounting records, including ledgers, vouchers and books of account, computer printouts, information storage, media diaries and diary entries, drawings and charts, including additions and revisions, estimates, evaluations, financial statements and records, instructions, inter- and intra-office communications, invoices, job site reports, investigative reports, audits, logs, memoranda of any type, minutes of all meetings, notes

of all types, orders, including change, proceed and purchase orders, questionnaires and surveys, photographs, price sheets, records, results of investigations, schedules including additions and revisions, statistical records, reports, analyses and studies of any kind, tape recordings, including any form of any recording of any telephone or other conversation, interview, conference, or meeting, and all contract and working papers as well as drawings, papers and files. A reference herein to any one or more of these types of documents shall be construed to include all other types of documents without limitations.

4. Words used in the singular shall, where the context permits, include the plural, and words used in the plural shall, where the context permits, include the singular.

5. "You" and "your" refers to the person served with and responding to these Requests.

6. "Roundup®/ glyphosate litigation" refers to any lawsuit, litigation, or other matter, including, but is not limited to, the multidistrict litigation captioned, *In re Roundup Products Liability Litigation*, Case No. 3:16-md-02741-CV (N.D. Cal.), in which an individual has asserted or will assert, a claim against Monsanto Company ("Monsanto") asserting that the use of Monsanto's Roundup®-branded products has caused their hematopoietic malignancies, including non-Hodgkin's lymphoma ("NHL") or other cancers that have been or will be alleged.

REQUESTS FOR PRODUCTION

As stated in the foregoing Subpoena, you are required to produce the following documents:

1. All documents provided to you, or that you have, related to the Roundup®/ glyphosate litigation that are not publicly or otherwise available.

2. All studies, literature, materials, research files, or any other documents that are not publicly or otherwise available that you have reviewed and upon which you rely and/or intend to rely upon as a basis for the opinions that you intend to offer in the Roundup®/ glyphosate litigation.

3. All publications, literature, treatises, or other documents reviewed by you in working on, or rendering opinions in, the Roundup®/ glyphosate litigation that are not publicly or otherwise available. This request includes all documents not cited in your expert reports that contain data or other information considered by you in the course of formulating your opinions.

4. Your most recent curriculum vitae.

5. All billing records, invoices, or other documents reflecting time spent and/or fees charged by you (either directly or through your employer or other entity) in connection with the Roundup®/ glyphosate litigation.

6. Any retainer letter, contract, agreement, or other document setting forth the retention of you to work in the Roundup®/ glyphosate litigation.

7. A copy of all abstracts, articles, books or book excerpts of which you are an author, co-author or editor, and any correspondence you have written to or exchanged with members of any regulatory or legislative body, which has as all or part of its subject matter any hematopoietic malignancies, glyphosate, and/ or Roundup®, that are not publicly or otherwise available.

8. A copy of all handouts, power points or other documents used by you at any lecture you have given in the past five (5) years relating to hematopoietic malignancies, including NHL, that are not publicly or otherwise available.

9. A copy of all handouts, power points or other documents used by you at any lecture you have given on pesticides, including glyphosate and/ or Roundup®, that are not publicly or otherwise available.

10. A copy of all handouts, power points or other documents used by you at any lecture you have given relating to the United States Environmental Protection Agency (EPA), the International Agency for Research on Cancer (IARC), The European Food Safety Authority (EFSA), or other risk-assessment bodies that include discussion on policies and practices surrounding risk assessment. This request is limited to documents that are not publicly or otherwise available.

11. Any communications and documents relating to communications between you and any or all of the following individuals regarding glyphosate and/ or Roundup®, which are not publicly or otherwise available: Beate Ritz; Christopher Portier; Chadi Nabhan; Charles Jameson; Dennis Weisenburger; Aaron Blair; Matthew Ross.

12. A copy of all handouts, power points or other documents used by you at any lecture you have given in the past five (5) years relating to case control studies, cohort studies, pooled studies, meta-analysis, or Bradford Hill analysis that are not publicly or otherwise available.

DATED: July 27, 2017

Respectfully submitted,

/s/ Heather A. Pigman

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MONSANTO COMPANY

Declaration of Alfred I Neugut, M.D., Ph.D

1. I am a board-certified medical oncologist and a cancer epidemiologist, specializing in the study of cancer etiology in populations, and the evaluation of the risk and strength of association of known and suspected carcinogens. Currently, I am a full Professor of Epidemiology at the Columbia University Mailman School of Public Health. I am an author of over 450 peer-reviewed published articles on issues related to cancer. A copy of my curriculum vitae has been attached hereto and is incorporated by reference.

2. I have reviewed Monograph 112 from the World Health Organization's International Agency for Research on Cancer ("IARC"). Monograph 112 details IARC's review of all relevant and publically available data regarding the association between glyphosate and non-Hodgkin lymphoma. IARC concluded that glyphosate was a probable human carcinogen based on human studies, animal studies, and strong mechanistic evidence. Carcinogens are chemicals that cause cancer. I would equate the term "probable" as used in the IARC monograph as corresponding to my understanding of the legal term "within a reasonable degree of medical certainty".

3. I have also independently reviewed the scientific literature and agree with the IARC assessment that glyphosate is a probable human carcinogen.

4. IARC is a prestigious and esteemed scientific body that produces a definitive list of human carcinogens. My colleagues and I rely on the assessments from IARC in both cancer research and the formation of public policy regarding cancer prevention..

5. IARC utilizes a rigorous methodology for the evaluation of potential carcinogens. IARC uses the well accepted Bradford-Hill Criteria when assessing whether an agent can cause cancer.

6. In reviewing Monograph 112, it is my opinion that IARC continued its tradition of rigorous, transparent analysis and used a sound methodological approach when reviewing the evidence on glyphosate. IARC's assessment on glyphosate provides a reliable scientific basis for an opinion that glyphosate does cause non-Hodgkin lymphoma in humans.

7. It is my opinion to a reasonable degree of medical certainty that glyphosate does cause non-Hodgkin lymphoma in humans.

8. As the case develops, I plan on reviewing additional material relevant to the question of causality and reserve the right to supplement and amend my opinion in this matter.

9. This declaration does not constitute a full report of my opinion, methodology and materials relied upon. I will complete and issue an expert report during the appropriate time as determined by the trial schedule.

Date: 4/28/16

Alfred I. Neugut, M.D., Ph.D.

Exhibit E

February 17, 2017

Michael J. Miller, Esq.
The Miller Firm
108 Railroad Avenue
Orange VA 22960

Re: Glyphosate

Bill for services rendered in above case

Review of documents and papers, literature review, phone calls, preparation of tables, meetings with attorneys

Doctoral assistant	51 hrs@$225/hr	$11475
	10 hours@$450/hr	$4500

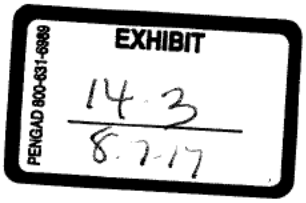
Balance due $15975

Please make check payable to Alfred I. Neugut

[redacted]

Thank you.

Alfred I. Neugut, MD, PhD
722 West 168th Street, Room 725
New York NY 10032



WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

PREAMBLE

LYON, FRANCE
2006

CONTENTS

Amended January 2006

Last update September 2015

PREAMBLE

The Preamble to the *IARC Monographs* describes the objective and scope of the programme, the scientific principles and procedures used in developing a *Monograph*, the types of evidence considered and the scientific criteria that guide the evaluations. The Preamble should be consulted when reading a *Monograph* or list of evaluations.

A. GENERAL PRINCIPLES AND PROCEDURES

1. Background

Soon after IARC was established in 1965, it received frequent requests for advice on the carcinogenic risk of chemicals, including requests for lists of known and suspected human carcinogens. It was clear that it would not be a simple task to summarize adequately the complexity of the information that was available, and IARC began to consider means of obtaining international expert opinion on this topic. In 1970, the IARC Advisory Committee on Environmental Carcinogenesis recommended ' . . . that a compendium on carcinogenic chemicals be prepared by experts. The biological activity and evaluation of practical importance to public health should be referenced and documented.' The IARC Governing Council adopted a resolution concerning the role of IARC in providing government authorities with expert, independent, scientific opinion on environmental carcinogenesis. As one means to that end, the Governing Council recommended that IARC should prepare monographs on the evaluation of carcinogenic risk of chemicals to man, which became the initial title of the series.

In the succeeding years, the scope of the programme broadened as *Monographs* were developed for groups of related chemicals, complex mixtures, occupational exposures, physical and biological agents and lifestyle factors. In 1988, the phrase 'of chemicals' was dropped from the title, which assumed its present form, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*.

Through the *Monographs* programme, IARC seeks to identify the causes of human cancer. This is the first step in cancer prevention, which is needed as much today as when IARC was established. The global burden of cancer is high and continues to increase: the annual number of new cases was estimated at 10.1 million in 2000 and is expected to reach 15 million by 2020 (Stewart & Kleihues, 2003). With current trends in demographics and exposure, the cancer burden has been shifting from high-resource countries to low- and medium-resource countries. As a result of *Monographs* evaluations, national health agencies have been able, on scientific grounds, to take measures to reduce human exposure to carcinogens in the workplace and in the environment.

The criteria established in 1971 to evaluate carcinogenic risks to humans were adopted by the Working Groups whose deliberations resulted in the first 16 volumes of the *Monographs* series. Those criteria were subsequently updated by further ad-hoc Advisory Groups (IARC, 1977, 1978, 1979, 1982, 1983, 1987, 1988, 1991; Vainio *et al.*, 1992; IARC, 2005, 2006).

The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been

established as being effective during previous *Monograph* meetings but remain, predominantly, the prerogative of each individual Working Group.

2. Objective and scope

The objective of the programme is to prepare, with the help of international Working Groups of experts, and to publish in the form of *Monographs*, critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures. The *Monographs* represent the first step in carcinogen risk assessment, which involves examination of all relevant information in order to assess the strength of the available evidence that an agent could alter the age-specific incidence of cancer in humans. The *Monographs* may also indicate where additional research efforts are needed, specifically when data immediately relevant to an evaluation are not available.

In this Preamble, the term 'agent' refers to any entity or circumstance that is subject to evaluation in a *Monograph*. As the scope of the programme has broadened, categories of agents now include specific chemicals, groups of related chemicals, complex mixtures, occupational or environmental exposures, cultural or behavioural practices, biological organisms and physical agents. This list of categories may expand as causation of, and susceptibility to, malignant disease become more fully understood.

A cancer 'hazard' is an agent that is capable of causing cancer under some circumstances, while a cancer 'risk' is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. The *Monographs* are an exercise in evaluating cancer hazards, despite the historical presence of the word 'risks' in the title. The distinction between hazard and risk is important, and the *Monographs* identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.

In the *Monographs*, an agent is termed 'carcinogenic' if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The induction of benign neoplasms may in some circumstances (see Part B, Section 3a) contribute to the judgement that the agent is carcinogenic. The terms 'neoplasm' and 'tumour' are used interchangeably.

The Preamble continues the previous usage of the phrase 'strength of evidence' as a matter of historical continuity, although it should be understood that *Monographs* evaluations consider studies that support a finding of a cancer hazard as well as studies that do not.

Some epidemiological and experimental studies indicate that different agents may act at different stages in the carcinogenic process, and several different mechanisms may be involved. The aim of the *Monographs* has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms. Information on mechanisms may, however, be used in making the overall evaluation (IARC, 1991; Vainio *et al.*, 1992; IARC, 2005, 2006; see also Part B, Sections 4 and 6). As mechanisms of carcinogenesis are elucidated, IARC convenes international scientific conferences to determine whether a broad-based consensus has emerged on how specific mechanistic data can be used in an evaluation of human carcinogenicity. The results of such conferences are reported in IARC Scientific Publications, which, as long as they still reflect the current state of scientific knowledge, may guide subsequent Working Groups.

Although the *Monographs* have emphasized hazard identification, important issues may also involve dose–response assessment. In many cases, the same epidemiological and experimental studies used to evaluate a cancer hazard can also be used to estimate a dose–

response relationship. A *Monograph* may undertake to estimate dose–response relationships within the range of the available epidemiological data, or it may compare the dose–response information from experimental and epidemiological studies. In some cases, a subsequent publication may be prepared by a separate Working Group with expertise in quantitative dose–response assessment.

The *Monographs* are used by national and international authorities to make risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes and decide among alternative options for public health decisions. The evaluations of IARC Working Groups are scientific, qualitative judgements on the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which public health decisions may be based. Public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations.

3. Selection of agents for review

Agents are selected for review on the basis of two main criteria: (a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity. Mixed exposures may occur in occupational and environmental settings and as a result of individual and cultural habits (such as tobacco smoking and dietary practices). Chemical analogues and compounds with biological or physical characteristics similar to those of suspected carcinogens may also be considered, even in the absence of data on a possible carcinogenic effect in humans or experimental animals.

The scientific literature is surveyed for published data relevant to an assessment of carcinogenicity. Ad-hoc Advisory Groups convened by IARC in 1984, 1989, 1991, 1993, 1998 and 2003 made recommendations as to which agents should be evaluated in the *Monographs* series. Recent recommendations are available on the *Monographs* programme website (http://monographs.iarc.fr). IARC may schedule other agents for review as it becomes aware of new scientific information or as national health agencies identify an urgent public health need related to cancer.

As significant new data become available on an agent for which a *Monograph* exists, a re-evaluation may be made at a subsequent meeting, and a new *Monograph* published. In some cases it may be appropriate to review only the data published since a prior evaluation. This can be useful for updating a database, reviewing new data to resolve a previously open question or identifying new tumour sites associated with a carcinogenic agent. Major changes in an evaluation (e.g. a new classification in Group 1 or a determination that a mechanism does not operate in humans, see Part B, Section 6) are more appropriately addressed by a full review.

4. Data for the *Monographs*

Each *Monograph* reviews all pertinent epidemiological studies and cancer bioassays in experimental animals. Those judged inadequate or irrelevant to the evaluation may be cited but not summarized. If a group of similar studies is not reviewed, the reasons are indicated.

Mechanistic and other relevant data are also reviewed. A *Monograph* does not necessarily cite all the mechanistic literature concerning the agent being evaluated (see Part B, Section

4). Only those data considered by the Working Group to be relevant to making the evaluation are included.

With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed. The same publication requirement applies to studies originating from IARC, including meta-analyses or pooled analyses commissioned by IARC in advance of a meeting (see Part B, Section 2c). Data from government agency reports that are publicly available are also considered. Exceptionally, doctoral theses and other material that are in their final form and publicly available may be reviewed.

Exposure data and other information on an agent under consideration are also reviewed. In the sections on chemical and physical properties, on analysis, on production and use and on occurrence, published and unpublished sources of information may be considered.

Inclusion of a study does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results, and limitations are clearly outlined in square brackets at the end of each study description (see Part B). The reasons for not giving further consideration to an individual study also are indicated in the square brackets.

5. Meeting participants

Five categories of participant can be present at *Monograph* meetings.

(a) The Working Group is responsible for the critical reviews and evaluations that are developed during the meeting. The tasks of Working Group Members are: (i) to ascertain that all appropriate data have been collected; (ii) to select the data relevant for the evaluation on the basis of scientific merit; (iii) to prepare accurate summaries of the data to enable the reader to follow the reasoning of the Working Group; (iv) to evaluate the results of epidemiological and experimental studies on cancer; (v) to evaluate data relevant to the understanding of mechanisms of carcinogenesis; and (vi) to make an overall evaluation of the carcinogenicity of the exposure to humans. Working Group Members generally have published significant research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts. Working Group Members are selected on the basis of (a) knowledge and experience and (b) absence of real or apparent conflicts of interests. Consideration is also given to demographic diversity and balance of scientific findings and views.

(b) Invited Specialists are experts who also have critical knowledge and experience but have a real or apparent conflict of interests. These experts are invited when necessary to assist in the Working Group by contributing their unique knowledge and experience during subgroup and plenary discussions. They may also contribute text on non-influential issues in the section on exposure, such as a general description of data on production and use (see Part B, Section 1). Invited Specialists do not serve as meeting chair or subgroup chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations.

(c) Representatives of national and international health agencies often attend meetings because their agencies sponsor the programme or are interested in the subject of a meeting. Representatives do not serve as meeting chair or subgroup chair, draft any part of a *Monograph,* or participate in the evaluations.

(d) Observers with relevant scientific credentials may be admitted to a meeting by IARC in limited numbers. Attention will be given to achieving a balance of Observers from constituencies with differing perspectives. They are invited to observe the meeting and

should not attempt to influence it. Observers do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations. At the meeting, the meeting chair and subgroup chairs may grant Observers an opportunity to speak, generally after they have observed a discussion. Observers agree to respect the Guidelines for Observers at *IARC Monographs* meetings (available at http://monographs.iarc.fr).

(e) The IARC Secretariat consists of scientists who are designated by IARC and who have relevant expertise. They serve as rapporteurs and participate in all discussions. When requested by the meeting chair or subgroup chair, they may also draft text or prepare tables and analyses.

Before an invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests to report financial interests, employment and consulting, and individual and institutional research support related to the subject of the meeting. IARC assesses these interests to determine whether there is a conflict that warrants some limitation on participation. The declarations are updated and reviewed again at the opening of the meeting. Interests related to the subject of the meeting are disclosed to the meeting participants and in the published volume (Cogliano *et al.*, 2004).

The names and principal affiliations of participants are available on the *Monographs* programme website (http://monographs.iarc.fr) approximately two months before each meeting. It is not acceptable for Observers or third parties to contact other participants before a meeting or to lobby them at any time. Meeting participants are asked to report all such contacts to IARC (Cogliano *et al.*, 2005).

All participants are listed, with their principal affiliations, at the beginning of each volume. Each participant who is a Member of a Working Group serves as an individual scientist and not as a representative of any organization, government or industry.

6. Working procedures

A separate Working Group is responsible for developing each volume of *Monographs*. A volume contains one or more *Monographs*, which can cover either a single agent or several related agents. Approximately one year in advance of the meeting of a Working Group, the agents to be reviewed are announced on the *Monographs* programme website (http://monographs.iarc.fr) and participants are selected by IARC staff in consultation with other experts. Subsequently, relevant biological and epidemiological data are collected by IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems such as PubMed. Meeting participants who are asked to prepare preliminary working papers for specific sections are expected to supplement the IARC literature searches with their own searches.

Industrial associations, labour unions and other knowledgeable organizations may be asked to provide input to the sections on production and use, although this involvement is not required as a general rule. Information on production and trade is obtained from governmental, trade and market research publications and, in some cases, by direct contact with industries. Separate production data on some agents may not be available for a variety of reasons (e.g. not collected or made public in all producing countries, production is small). Information on uses may be obtained from published sources but is often complemented by direct contact with manufacturers. Efforts are made to supplement this information with data from other national and international sources.

Six months before the meeting, the material obtained is sent to meeting participants to prepare preliminary working papers. The working papers are compiled by IARC staff and sent, prior to the meeting, to Working Group Members and Invited Specialists for review.

The Working Group meets at IARC for seven to eight days to discuss and finalize the texts and to formulate the evaluations. The objectives of the meeting are peer review and consensus. During the first few days, four subgroups (covering exposure data, cancer in humans, cancer in experimental animals, and mechanistic and other relevant data) review the working papers, develop a joint subgroup draft and write summaries. Care is taken to ensure that each study summary is written or reviewed by someone not associated with the study being considered. During the last few days, the Working Group meets in plenary session to review the subgroup drafts and develop the evaluations. As a result, the entire volume is the joint product of the Working Group, and there are no individually authored sections.

IARC Working Groups strive to achieve a consensus evaluation. Consensus reflects broad agreement among Working Group Members, but not necessarily unanimity. The chair may elect to poll Working Group Members to determine the diversity of scientific opinion on issues where consensus is not readily apparent.

After the meeting, the master copy is verified by consulting the original literature, edited and prepared for publication. The aim is to publish the volume within six months of the Working Group meeting. A summary of the outcome is available on the *Monographs* programme website soon after the meeting.

B. SCIENTIFIC REVIEW AND EVALUATION

The available studies are summarized by the Working Group, with particular regard to the qualitative aspects discussed below. In general, numerical findings are indicated as they appear in the original report; units are converted when necessary for easier comparison. The Working Group may conduct additional analyses of the published data and use them in their assessment of the evidence; the results of such supplementary analyses are given in square brackets. When an important aspect of a study that directly impinges on its interpretation should be brought to the attention of the reader, a Working Group comment is given in square brackets.

The scope of the *IARC Monographs* programme has expanded beyond chemicals to include complex mixtures, occupational exposures, physical and biological agents, lifestyle factors and other potentially carcinogenic exposures. Over time, the structure of a *Monograph* has evolved to include the following sections:

1. Exposure data
2. Studies of cancer in humans
3. Studies of cancer in experimental animals
4. Mechanistic and other relevant data
5. Summary
6. Evaluation and rationale

In addition, a section of General Remarks at the front of the volume discusses the reasons the agents were scheduled for evaluation and some key issues the Working Group encountered during the meeting.

This part of the Preamble discusses the types of evidence considered and summarized in each section of a *Monograph*, followed by the scientific criteria that guide the evaluations.

1. Exposure data

Each *Monograph* includes general information on the agent: this information may vary substantially between agents and must be adapted accordingly. Also included is information on production and use (when appropriate), methods of analysis and detection, occurrence, and sources and routes of human occupational and environmental exposures. Depending on the agent, regulations and guidelines for use may be presented.

(a) General information on the agent

For chemical agents, sections on chemical and physical data are included: the Chemical Abstracts Service Registry Number, the latest primary name and the IUPAC systematic name are recorded; other synonyms are given, but the list is not necessarily comprehensive. Information on chemical and physical properties that are relevant to identification, occurrence and biological activity is included. A description of technical products of chemicals includes trade names, relevant specifications and available information on composition and impurities. Some of the trade names given may be those of mixtures in which the agent being evaluated is only one of the ingredients.

For biological agents, taxonomy, structure and biology are described, and the degree of variability is indicated. Mode of replication, life cycle, target cells, persistence, latency, host response and clinical disease other than cancer are also presented.

For physical agents that are forms of radiation, energy and range of the radiation are included. For foreign bodies, fibres and respirable particles, size range and relative dimensions are indicated.

For agents such as mixtures, drugs or lifestyle factors, a description of the agent, including its composition, is given.

Whenever appropriate, other information, such as historical perspectives or the description of an industry or habit, may be included.

(b) Analysis and detection

An overview of methods of analysis and detection of the agent is presented, including their sensitivity, specificity and reproducibility. Methods widely used for regulatory purposes are emphasized. Methods for monitoring human exposure are also given. No critical evaluation or recommendation of any method is meant or implied.

(c) Production and use

The dates of first synthesis and of first commercial production of a chemical, mixture or other agent are provided when available; for agents that do not occur naturally, this information may allow a reasonable estimate to be made of the date before which no human exposure to the agent could have occurred. The dates of first reported occurrence of an exposure are also provided when available. In addition, methods of synthesis used in past and present commercial production and different methods of production, which may give rise to different impurities, are described.

The countries where companies report production of the agent, and the number of companies in each country, are identified. Available data on production, international trade and uses are obtained for representative regions. It should not, however, be inferred that those areas or nations are necessarily the sole or major sources or users of the agent. Some identified uses may not be current or major applications, and the coverage is not necessarily

comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their therapeutic efficacy.

(d) Occurrence and exposure

Information on the occurrence of an agent in the environment is obtained from data derived from the monitoring and surveillance of levels in occupational environments, air, water, soil, plants, foods and animal and human tissues. When available, data on the generation, persistence and bioaccumulation of the agent are also included. Such data may be available from national databases.

Data that indicate the extent of past and present human exposure, the sources of exposure, the people most likely to be exposed and the factors that contribute to the exposure are reported. Information is presented on the range of human exposure, including occupational and environmental exposures. This includes relevant findings from both developed and developing countries. Some of these data are not distributed widely and may be available from government reports and other sources. In the case of mixtures, industries, occupations or processes, information is given about all agents known to be present. For processes, industries and occupations, a historical description is also given, noting variations in chemical composition, physical properties and levels of occupational exposure with date and place. For biological agents, the epidemiology of infection is described.

(e) Regulations and guidelines

Statements concerning regulations and guidelines (e.g. occupational exposure limits, maximal levels permitted in foods and water, pesticide registrations) are included, but they may not reflect the most recent situation, since such limits are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that that country does not have regulations with regard to the exposure. For biological agents, legislation and control, including vaccination and therapy, are described.

2. Studies of cancer in humans

This section includes all pertinent epidemiological studies (see Part A, Section 4). Studies of biomarkers are included when they are relevant to an evaluation of carcinogenicity to humans.

(a) Types of study considered

Several types of epidemiological study contribute to the assessment of carcinogenicity in humans — cohort studies, case–control studies, correlation (or ecological) studies and intervention studies. Rarely, results from randomized trials may be available. Case reports and case series of cancer in humans may also be reviewed.

Cohort and case–control studies relate individual exposures under study to the occurrence of cancer in individuals and provide an estimate of effect (such as relative risk) as the main measure of association. Intervention studies may provide strong evidence for making causal inferences, as exemplified by cessation of smoking and the subsequent decrease in risk for lung cancer.

In correlation studies, the units of investigation are usually whole populations (e.g. in particular geographical areas or at particular times), and cancer frequency is related to a summary measure of the exposure of the population to the agent under study. In correlation studies, individual exposure is not documented, which renders this kind of study more prone

to confounding. In some circumstances, however, correlation studies may be more informative than analytical study designs (see, for example, the *Monograph* on arsenic in drinking-water; IARC, 2004).

In some instances, case reports and case series have provided important information about the carcinogenicity of an agent. These types of study generally arise from a suspicion, based on clinical experience, that the concurrence of two events — that is, a particular exposure and occurrence of a cancer — has happened rather more frequently than would be expected by chance. Case reports and case series usually lack complete ascertainment of cases in any population, definition or enumeration of the population at risk and estimation of the expected number of cases in the absence of exposure.

The uncertainties that surround the interpretation of case reports, case series and correlation studies make them inadequate, except in rare instances, to form the sole basis for inferring a causal relationship. When taken together with case–control and cohort studies, however, these types of study may add materially to the judgement that a causal relationship exists.

Epidemiological studies of benign neoplasms, presumed preneoplastic lesions and other end-points thought to be relevant to cancer are also reviewed. They may, in some instances, strengthen inferences drawn from studies of cancer itself.

(b) Quality of studies considered

It is necessary to take into account the possible roles of bias, confounding and chance in the interpretation of epidemiological studies. Bias is the effect of factors in study design or execution that lead erroneously to a stronger or weaker association than in fact exists between an agent and disease. Confounding is a form of bias that occurs when the relationship with disease is made to appear stronger or weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease. The role of chance is related to biological variability and the influence of sample size on the precision of estimates of effect.

In evaluating the extent to which these factors have been minimized in an individual study, consideration is given to a number of aspects of design and analysis as described in the report of the study. For example, when suspicion of carcinogenicity arises largely from a single small study, careful consideration is given when interpreting subsequent studies that included these data in an enlarged population. Most of these considerations apply equally to case–control, cohort and correlation studies. Lack of clarity of any of these aspects in the reporting of a study can decrease its credibility and the weight given to it in the final evaluation of the exposure.

Firstly, the study population, disease (or diseases) and exposure should have been well defined by the authors. Cases of disease in the study population should have been identified in a way that was independent of the exposure of interest, and exposure should have been assessed in a way that was not related to disease status.

Secondly, the authors should have taken into account — in the study design and analysis — other variables that can influence the risk of disease and may have been related to the exposure of interest. Potential confounding by such variables should have been dealt with either in the design of the study, such as by matching, or in the analysis, by statistical adjustment. In cohort studies, comparisons with local rates of disease may or may not be more appropriate than those with national rates. Internal comparisons of frequency of disease among individuals at different levels of exposure are also desirable in cohort studies, since

they minimize the potential for confounding related to the difference in risk factors between an external reference group and the study population.

Thirdly, the authors should have reported the basic data on which the conclusions are founded, even if sophisticated statistical analyses were employed. At the very least, they should have given the numbers of exposed and unexposed cases and controls in a case–control study and the numbers of cases observed and expected in a cohort study. Further tabulations by time since exposure began and other temporal factors are also important. In a cohort study, data on all cancer sites and all causes of death should have been given, to reveal the possibility of reporting bias. In a case–control study, the effects of investigated factors other than the exposure of interest should have been reported.

Finally, the statistical methods used to obtain estimates of relative risk, absolute rates of cancer, confidence intervals and significance tests, and to adjust for confounding should have been clearly stated by the authors. These methods have been reviewed for case–control studies (Breslow & Day, 1980) and for cohort studies (Breslow & Day, 1987).

(c) Meta-analyses and pooled analyses

Independent epidemiological studies of the same agent may lead to results that are difficult to interpret. Combined analyses of data from multiple studies are a means of resolving this ambiguity, and well-conducted analyses can be considered. There are two types of combined analysis. The first involves combining summary statistics such as relative risks from individual studies (meta-analysis) and the second involves a pooled analysis of the raw data from the individual studies (pooled analysis) (Greenland, 1998).

The advantages of combined analyses are increased precision due to increased sample size and the opportunity to explore potential confounders, interactions and modifying effects that may explain heterogeneity among studies in more detail. A disadvantage of combined analyses is the possible lack of compatibility of data from various studies due to differences in subject recruitment, procedures of data collection, methods of measurement and effects of unmeasured co-variates that may differ among studies. Despite these limitations, well-conducted combined analyses may provide a firmer basis than individual studies for drawing conclusions about the potential carcinogenicity of agents.

IARC may commission a meta-analysis or pooled analysis that is pertinent to a particular *Monograph* (see Part A, Section 4). Additionally, as a means of gaining insight from the results of multiple individual studies, ad-hoc calculations that combine data from different studies may be conducted by the Working Group during the course of a *Monograph* meeting. The results of such original calculations, which would be specified in the text by presentation in square brackets, might involve updates of previously conducted analyses that incorporate the results of more recent studies or de-novo analyses. Irrespective of the source of data for the meta-analyses and pooled analyses, it is important that the same criteria for data quality be applied as those that would be applied to individual studies and to ensure also that sources of heterogeneity between studies be taken into account.

(d) Temporal effects

Detailed analyses of both relative and absolute risks in relation to temporal variables, such as age at first exposure, time since first exposure, duration of exposure, cumulative exposure, peak exposure (when appropriate) and time since cessation of exposure, are reviewed and summarized when available. Analyses of temporal relationships may be useful in making causal inferences. In addition, such analyses may suggest whether a carcinogen

acts early or late in the process of carcinogenesis, although, at best, they allow only indirect inferences about mechanisms of carcinogenesis.

(e) Use of biomarkers in epidemiological studies

Biomarkers indicate molecular, cellular or other biological changes and are increasingly used in epidemiological studies for various purposes (IARC, 1991; Vainio *et al.*, 1992; Toniolo *et al.*, 1997; Vineis *et al.*, 1999; Buffler *et al.*, 2004). These may include evidence of exposure, of early effects, of cellular, tissue or organism responses, of individual susceptibility or host responses, and inference of a mechanism (see Part B, Section 4b). This is a rapidly evolving field that encompasses developments in genomics, epigenomics and other emerging technologies.

Molecular epidemiological data that identify associations between genetic polymorphisms and interindividual differences in susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. If the polymorphism has been demonstrated experimentally to modify the functional activity of the gene product in a manner that is consistent with increased susceptibility, these data may be useful in making causal inferences. Similarly, molecular epidemiological studies that measure cell functions, enzymes or metabolites that are thought to be the basis of susceptibility may provide evidence that reinforces biological plausibility. It should be noted, however, that when data on genetic susceptibility originate from multiple comparisons that arise from subgroup analyses, this can generate false-positive results and inconsistencies across studies, and such data therefore require careful evaluation. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent being evaluated, data on this phenotype may be useful in making causal inferences.

(f) Criteria for causality

After the quality of individual epidemiological studies of cancer has been summarized and assessed, a judgement is made concerning the strength of evidence that the agent in question is carcinogenic to humans. In making its judgement, the Working Group considers several criteria for causality (Hill, 1965). A strong association (e.g. a large relative risk) is more likely to indicate causality than a weak association, although it is recognized that estimates of effect of small magnitude do not imply lack of causality and may be important if the disease or exposure is common. Associations that are replicated in several studies of the same design or that use different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (such as differences in exposure), and results of studies that are judged to be of high quality are given more weight than those of studies that are judged to be methodologically less sound.

If the risk increases with the exposure, this is considered to be a strong indication of causality, although the absence of a graded response is not necessarily evidence against a causal relationship. The demonstration of a decline in risk after cessation of or reduction in exposure in individuals or in whole populations also supports a causal interpretation of the findings.

A number of scenarios may increase confidence in a causal relationship. On the one hand, an agent may be specific in causing tumours at one site or of one morphological type. On the other, carcinogenicity may be evident through the causation of multiple tumour types. Temporality, precision of estimates of effect, biological plausibility and coherence of the

overall database are considered. Data on biomarkers may be employed in an assessment of the biological plausibility of epidemiological observations.

Although rarely available, results from randomized trials that show different rates of cancer among exposed and unexposed individuals provide particularly strong evidence for causality.

When several epidemiological studies show little or no indication of an association between an exposure and cancer, a judgement may be made that, in the aggregate, they show evidence of lack of carcinogenicity. Such a judgement requires firstly that the studies meet, to a sufficient degree, the standards of design and analysis described above. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results should be considered and excluded with reasonable certainty. In addition, all studies that are judged to be methodologically sound should (a) be consistent with an estimate of effect of unity for any observed level of exposure, (b) when considered together, provide a pooled estimate of relative risk that is at or near to unity, and (c) have a narrow confidence interval, due to sufficient population size. Moreover, no individual study nor the pooled results of all the studies should show any consistent tendency that the relative risk of cancer increases with increasing level of exposure. It is important to note that evidence of lack of carcinogenicity obtained from several epidemiological studies can apply only to the type(s) of cancer studied, to the dose levels reported, and to the intervals between first exposure and disease onset observed in these studies. Experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.

3. Studies of cancer in experimental animals

All known human carcinogens that have been studied adequately for carcinogenicity in experimental animals have produced positive results in one or more animal species (Wilbourn *et al.*, 1986; Tomatis *et al.*, 1989). For several agents (e.g. aflatoxins, diethylstilbestrol, solar radiation, vinyl chloride), carcinogenicity in experimental animals was established or highly suspected before epidemiological studies confirmed their carcinogenicity in humans (Vainio *et al.*, 1995). Although this association cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there is *sufficient evidence of carcinogenicity* in experimental animals (see Part B, Section 6b) also present a carcinogenic hazard to humans. Accordingly, in the absence of additional scientific information, these agents are considered to pose a carcinogenic hazard to humans. Examples of additional scientific information are data that demonstrate that a given agent causes cancer in animals through a species-specific mechanism that does not operate in humans or data that demonstrate that the mechanism in experimental animals also operates in humans (see Part B, Section 6).

Consideration is given to all available long-term studies of cancer in experimental animals with the agent under review (see Part A, Section 4). In all experimental settings, the nature and extent of impurities or contaminants present in the agent being evaluated are given when available. Animal species, strain (including genetic background where applicable), sex, numbers per group, age at start of treatment, route of exposure, dose levels, duration of exposure, survival and information on tumours (incidence, latency, severity or multiplicity of neoplasms or preneoplastic lesions) are reported. Those studies in experimental animals that are judged to be irrelevant to the evaluation or judged to be inadequate (e.g. too short a

duration, too few animals, poor survival; see below) may be omitted. Guidelines for conducting long-term carcinogenicity experiments have been published (e.g. OECD, 2002).

Other studies considered may include: experiments in which the agent was administered in the presence of factors that modify carcinogenic effects (e.g. initiation–promotion studies, co-carcinogenicity studies and studies in genetically modified animals); studies in which the end-point was not cancer but a defined precancerous lesion; experiments on the carcinogenicity of known metabolites and derivatives; and studies of cancer in non-laboratory animals (e.g. livestock and companion animals) exposed to the agent.

For studies of mixtures, consideration is given to the possibility that changes in the physicochemical properties of the individual substances may occur during collection, storage, extraction, concentration and delivery. Another consideration is that chemical and toxicological interactions of components in a mixture may alter dose–response relationships. The relevance to human exposure of the test mixture administered in the animal experiment is also assessed. This may involve consideration of the following aspects of the mixture tested: (i) physical and chemical characteristics, (ii) identified constituents that may indicate the presence of a class of substances and (iii) the results of genetic toxicity and related tests.

The relevance of results obtained with an agent that is analogous (e.g. similar in structure or of a similar virus genus) to that being evaluated is also considered. Such results may provide biological and mechanistic information that is relevant to the understanding of the process of carcinogenesis in humans and may strengthen the biological plausibility that the agent being evaluated is carcinogenic to humans (see Part B, Section 2f).

(a) Qualitative aspects

An assessment of carcinogenicity involves several considerations of qualitative importance, including (i) the experimental conditions under which the test was performed, including route, schedule and duration of exposure, species, strain (including genetic background where applicable), sex, age and duration of follow-up; (ii) the consistency of the results, for example, across species and target organ(s); (iii) the spectrum of neoplastic response, from preneoplastic lesions and benign tumours to malignant neoplasms; and (iv) the possible role of modifying factors.

Considerations of importance in the interpretation and evaluation of a particular study include: (i) how clearly the agent was defined and, in the case of mixtures, how adequately the sample characterization was reported; (ii) whether the dose was monitored adequately, particularly in inhalation experiments; (iii) whether the doses, duration of treatment and route of exposure were appropriate; (iv) whether the survival of treated animals was similar to that of controls; (v) whether there were adequate numbers of animals per group; (vi) whether both male and female animals were used; (vii) whether animals were allocated randomly to groups; (viii) whether the duration of observation was adequate; and (ix) whether the data were reported and analysed adequately.

When benign tumours (a) occur together with and originate from the same cell type as malignant tumours in an organ or tissue in a particular study and (b) appear to represent a stage in the progression to malignancy, they are usually combined in the assessment of tumour incidence (Huff *et al.*, 1989). The occurrence of lesions presumed to be preneoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed. If an agent induces only benign neoplasms that appear to be end-points that do not readily undergo transition to malignancy, the agent should nevertheless be suspected of being carcinogenic and requires further investigation.

(b) Quantitative aspects

The probability that tumours will occur may depend on the species, sex, strain, genetic background and age of the animal, and on the dose, route, timing and duration of the exposure. Evidence of an increased incidence of neoplasms with increasing levels of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms.

The form of the dose–response relationship can vary widely, depending on the particular agent under study and the target organ. Mechanisms such as induction of DNA damage or inhibition of repair, altered cell division and cell death rates and changes in intercellular communication are important determinants of dose–response relationships for some carcinogens. Since many chemicals require metabolic activation before being converted to their reactive intermediates, both metabolic and toxicokinetic aspects are important in determining the dose–response pattern. Saturation of steps such as absorption, activation, inactivation and elimination may produce non-linearity in the dose–response relationship (Hoel *et al.*, 1983; Gart *et al.*, 1986), as could saturation of processes such as DNA repair. The dose–response relationship can also be affected by differences in survival among the treatment groups.

(c) Statistical analyses

Factors considered include the adequacy of the information given for each treatment group: (i) number of animals studied and number examined histologically, (ii) number of animals with a given tumour type and (iii) length of survival. The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto *et al.*, 1980; Gart *et al.*, 1986; Portier & Bailer, 1989; Bieler & Williams, 1993). The choice of the most appropriate statistical method requires consideration of whether or not there are differences in survival among the treatment groups; for example, reduced survival because of non-tumour-related mortality can preclude the occurrence of tumours later in life. When detailed information on survival is not available, comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the time the first tumour was discovered) can be useful when significant differences in survival occur before tumours appear. The lethality of the tumour also requires consideration: for rapidly fatal tumours, the time of death provides an indication of the time of tumour onset and can be assessed using life-table methods; non-fatal or incidental tumours that do not affect survival can be assessed using methods such as the Mantel-Haenzel test for changes in tumour prevalence. Because tumour lethality is often difficult to determine, methods such as the Poly-K test that do not require such information can also be used. When results are available on the number and size of tumours seen in experimental animals (e.g. papillomas on mouse skin, liver tumours observed through nuclear magnetic resonance tomography), other more complicated statistical procedures may be needed (Sherman *et al.*, 1994; Dunson *et al.*, 2003).

Formal statistical methods have been developed to incorporate historical control data into the analysis of data from a given experiment. These methods assign an appropriate weight to historical and concurrent controls on the basis of the extent of between-study and within-study variability: less weight is given to historical controls when they show a high degree of variability, and greater weight when they show little variability. It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls, particularly when historical controls show high between-study variability and are, thus, of little relevance to the

current experiment. In analysing results for uncommon tumours, however, the analysis may be improved by considering historical control data, particularly when between-study variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, gender and strain, as well as other factors such as basal diet and general laboratory environment, which may affect tumour-response rates in control animals (Haseman *et al.*, 1984; Fung *et al.*, 1996; Greim *et al.*, 2003).

Although meta-analyses and combined analyses are conducted less frequently for animal experiments than for epidemiological studies due to differences in animal strains, they can be useful aids in interpreting animal data when the experimental protocols are sufficiently similar.

4. Mechanistic and other relevant data

Mechanistic and other relevant data may provide evidence of carcinogenicity and also help in assessing the relevance and importance of findings of cancer in animals and in humans. The nature of the mechanistic and other relevant data depends on the biological activity of the agent being considered. The Working Group considers representative studies to give a concise description of the relevant data and issues that they consider to be important; thus, not every available study is cited. Relevant topics may include toxicokinetics, mechanisms of carcinogenesis, susceptible individuals, populations and life-stages, other relevant data and other adverse effects. When data on biomarkers are informative about the mechanisms of carcinogenesis, they are included in this section.

These topics are not mutually exclusive; thus, the same studies may be discussed in more than one subsection. For example, a mutation in a gene that codes for an enzyme that metabolizes the agent under study could be discussed in the subsections on toxicokinetics, mechanisms and individual susceptibility if it also exists as an inherited polymorphism.

(a) Toxicokinetic data

Toxicokinetics refers to the absorption, distribution, metabolism and elimination of agents in humans, experimental animals and, where relevant, cellular systems. Examples of kinetic factors that may affect dose–response relationships include uptake, deposition, biopersistence and half-life in tissues, protein binding, metabolic activation and detoxification. Studies that indicate the metabolic fate of the agent in humans and in experimental animals are summarized briefly, and comparisons of data from humans and animals are made when possible. Comparative information on the relationship between exposure and the dose that reaches the target site may be important for the extrapolation of hazards between species and in clarifying the role of in-vitro findings.

(b) Data on mechanisms of carcinogenesis

To provide focus, the Working Group attempts to identify the possible mechanisms by which the agent may increase the risk of cancer. For each possible mechanism, a representative selection of key data from humans and experimental systems is summarized. Attention is given to gaps in the data and to data that suggests that more than one mechanism may be operating. The relevance of the mechanism to humans is discussed, in particular, when mechanistic data are derived from experimental model systems. Changes in the affected organs, tissues or cells can be divided into three non-exclusive levels as described below.

(i) Changes in physiology

Physiological changes refer to exposure-related modifications to the physiology and/or response of cells, tissues and organs. Examples of potentially adverse physiological changes include mitogenesis, compensatory cell division, escape from apoptosis and/or senescence, presence of inflammation, hyperplasia, metaplasia and/or preneoplasia, angiogenesis, alterations in cellular adhesion, changes in steroidal hormones and changes in immune surveillance.

(ii) Functional changes at the cellular level

Functional changes refer to exposure-related alterations in the signalling pathways used by cells to manage critical processes that are related to increased risk for cancer. Examples of functional changes include modified activities of enzymes involved in the metabolism of xenobiotics, alterations in the expression of key genes that regulate DNA repair, alterations in cyclin-dependent kinases that govern cell cycle progression, changes in the patterns of post-translational modifications of proteins, changes in regulatory factors that alter apoptotic rates, changes in the secretion of factors related to the stimulation of DNA replication and transcription and changes in gap–junction-mediated intercellular communication.

(iii) Changes at the molecular level

Molecular changes refer to exposure-related changes in key cellular structures at the molecular level, including, in particular, genotoxicity. Examples of molecular changes include formation of DNA adducts and DNA strand breaks, mutations in genes, chromosomal aberrations, aneuploidy and changes in DNA methylation patterns. Greater emphasis is given to irreversible effects.

The use of mechanistic data in the identification of a carcinogenic hazard is specific to the mechanism being addressed and is not readily described for every possible level and mechanism discussed above.

Genotoxicity data are discussed here to illustrate the key issues involved in the evaluation of mechanistic data.

Tests for genetic and related effects are described in view of the relevance of gene mutation and chromosomal aberration/aneuploidy to carcinogenesis (Vainio *et al.*, 1992; McGregor *et al.*, 1999). The adequacy of the reporting of sample characterization is considered and, when necessary, commented upon; with regard to complex mixtures, such comments are similar to those described for animal carcinogenicity tests. The available data are interpreted critically according to the end-points detected, which may include DNA damage, gene mutation, sister chromatid exchange, micronucleus formation, chromosomal aberrations and aneuploidy. The concentrations employed are given, and mention is made of whether the use of an exogenous metabolic system *in vitro* affected the test result. These data are listed in tabular form by phylogenetic classification.

Positive results in tests using prokaryotes, lower eukaryotes, insects, plants and cultured mammalian cells suggest that genetic and related effects could occur in mammals. Results from such tests may also give information on the types of genetic effect produced and on the involvement of metabolic activation. Some end-points described are clearly genetic in nature (e.g. gene mutations), while others are associated with genetic effects (e.g. unscheduled DNA synthesis). In-vitro tests for

tumour promotion, cell transformation and gap–junction intercellular communication may be sensitive to changes that are not necessarily the result of genetic alterations but that may have specific relevance to the process of carcinogenesis. Critical appraisals of these tests have been published (Montesano *et al.*, 1986; McGregor *et al.*, 1999).

Genetic or other activity manifest in humans and experimental mammals is regarded to be of greater relevance than that in other organisms. The demonstration that an agent can induce gene and chromosomal mutations in mammals *in vivo* indicates that it may have carcinogenic activity. Negative results in tests for mutagenicity in selected tissues from animals treated *in vivo* provide less weight, partly because they do not exclude the possibility of an effect in tissues other than those examined. Moreover, negative results in short-term tests with genetic end-points cannot be considered to provide evidence that rules out the carcinogenicity of agents that act through other mechanisms (e.g. receptor-mediated effects, cellular toxicity with regenerative cell division, peroxisome proliferation) (Vainio *et al.*, 1992). Factors that may give misleading results in short-term tests have been discussed in detail elsewhere (Montesano *et al.*, 1986; McGregor *et al.*, 1999).

When there is evidence that an agent acts by a specific mechanism that does not involve genotoxicity (e.g. hormonal dysregulation, immune suppression, and formation of calculi and other deposits that cause chronic irritation), that evidence is presented and reviewed critically in the context of rigorous criteria for the operation of that mechanism in carcinogenesis (e.g. Capen *et al.*, 1999).

For biological agents such as viruses, bacteria and parasites, other data relevant to carcinogenicity may include descriptions of the pathology of infection, integration and expression of viruses, and genetic alterations seen in human tumours. Other observations that might comprise cellular and tissue responses to infection, immune response and the presence of tumour markers are also considered.

For physical agents that are forms of radiation, other data relevant to carcinogenicity may include descriptions of damaging effects at the physiological, cellular and molecular level, as for chemical agents, and descriptions of how these effects occur. 'Physical agents' may also be considered to comprise foreign bodies, such as surgical implants of various kinds, and poorly soluble fibres, dusts and particles of various sizes, the pathogenic effects of which are a result of their physical presence in tissues or body cavities. Other relevant data for such materials may include characterization of cellular, tissue and physiological reactions to these materials and descriptions of pathological conditions other than neoplasia with which they may be associated.

(c) Other data relevant to mechanisms

A description is provided of any structure–activity relationships that may be relevant to an evaluation of the carcinogenicity of an agent, the toxicological implications of the physical and chemical properties, and any other data relevant to the evaluation that are not included elsewhere.

High-output data, such as those derived from gene expression microarrays, and high-throughput data, such as those that result from testing hundreds of agents for a single end-point, pose a unique problem for the use of mechanistic data in the evaluation of a carcinogenic hazard. In the case of high-output data, there is the possibility to overinterpret changes in individual end-points (e.g. changes in expression in one gene) without considering the consistency of that finding in the broader context of the other end-points (e.g. other genes

with linked transcriptional control). High-output data can be used in assessing mechanisms, but all end-points measured in a single experiment need to be considered in the proper context. For high-throughput data, where the number of observations far exceeds the number of end-points measured, their utility for identifying common mechanisms across multiple agents is enhanced. These data can be used to identify mechanisms that not only seem plausible, but also have a consistent pattern of carcinogenic response across entire classes of related compounds.

(d) Susceptibility data

Individuals, populations and life-stages may have greater or lesser susceptibility to an agent, based on toxicokinetics, mechanisms of carcinogenesis and other factors. Examples of host and genetic factors that affect individual susceptibility include sex, genetic polymorphisms of genes involved in the metabolism of the agent under evaluation, differences in metabolic capacity due to life-stage or the presence of disease, differences in DNA repair capacity, competition for or alteration of metabolic capacity by medications or other chemical exposures, pre-existing hormonal imbalance that is exacerbated by a chemical exposure, a suppressed immune system, periods of higher-than-usual tissue growth or regeneration and genetic polymorphisms that lead to differences in behaviour (e.g. addiction). Such data can substantially increase the strength of the evidence from epidemiological data and enhance the linkage of in-vivo and in-vitro laboratory studies to humans.

(e) Data on other adverse effects

Data on acute, subchronic and chronic adverse effects relevant to the cancer evaluation are summarized. Adverse effects that confirm distribution and biological effects at the sites of tumour development, or alterations in physiology that could lead to tumour development, are emphasized. Effects on reproduction, embryonic and fetal survival and development are summarized briefly. The adequacy of epidemiological studies of reproductive outcome and genetic and related effects in humans is judged by the same criteria as those applied to epidemiological studies of cancer, but fewer details are given.

5. Summary

This section is a summary of data presented in the preceding sections. Summaries can be found on the *Monographs* programme website (http://monographs.iarc.fr).

(a) Exposure data

Data are summarized, as appropriate, on the basis of elements such as production, use, occurrence and exposure levels in the workplace and environment and measurements in human tissues and body fluids. Quantitative data and time trends are given to compare exposures in different occupations and environmental settings. Exposure to biological agents is described in terms of transmission, prevalence and persistence of infection.

(b) Cancer in humans

Results of epidemiological studies pertinent to an assessment of human carcinogenicity are summarized. When relevant, case reports and correlation studies are also summarized. The target organ(s) or tissue(s) in which an increase in cancer was observed is identified. Dose–response and other quantitative data may be summarized when available.

(c) Cancer in experimental animals

Data relevant to an evaluation of carcinogenicity in animals are summarized. For each animal species, study design and route of administration, it is stated whether an increased incidence, reduced latency, or increased severity or multiplicity of neoplasms or preneoplastic lesions were observed, and the tumour sites are indicated. If the agent produced tumours after prenatal exposure or in single-dose experiments, this is also mentioned. Negative findings, inverse relationships, dose–response and other quantitative data are also summarized.

(d) Mechanistic and other relevant data

Data relevant to the toxicokinetics (absorption, distribution, metabolism, elimination) and the possible mechanism(s) of carcinogenesis (e.g. genetic toxicity, epigenetic effects) are summarized. In addition, information on susceptible individuals, populations and life-stages is summarized. This section also reports on other toxic effects, including reproductive and developmental effects, as well as additional relevant data that are considered to be important.

6. Evaluation and rationale

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms. The strength of the mechanistic evidence is also characterized.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency). A classification may change as new information becomes available.

An evaluation of the degree of evidence is limited to the materials tested, as defined physically, chemically or biologically. When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of the degree of evidence.

(a) Carcinogenicity in humans

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the

Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

When the available epidemiological studies pertain to a mixture, process, occupation or industry, the Working Group seeks to identify the specific agent considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.

(b) Carcinogenicity in experimental animals

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals.

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*.

A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.

Limited evidence of carcinogenicity: The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

Inadequate evidence of carcinogenicity: The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

Evidence suggesting lack of carcinogenicity: Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied.

(c) Mechanistic and other relevant data

Mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is highlighted. This may include data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–activity relationships, metabolism and toxicokinetics, physicochemical parameters and analogous biological agents.

The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated, using terms such as 'weak', 'moderate' or 'strong'. The Working Group then assesses whether that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans derive from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

The conclusion that a mechanism operates in experimental animals is strengthened by findings of consistent results in different experimental systems, by the demonstration of biological plausibility and by coherence of the overall database. Strong support can be obtained from studies that challenge the hypothesized mechanism experimentally, by demonstrating that the suppression of key mechanistic processes leads to the suppression of tumour development. The Working Group considers whether multiple mechanisms might contribute to tumour development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals and whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumours observed in experimental animals are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating a favoured mechanism.

For complex exposures, including occupational and industrial exposures, the chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The Working

Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(d) Overall evaluation

Finally, the body of evidence is considered as a whole, in order to reach an overall evaluation of the carcinogenicity of the agent to humans.

An evaluation may be made for a group of agents that have been evaluated by the Working Group. In addition, when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of agents if the strength of the evidence warrants it.

The agent is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent is a matter of scientific judgement that reflects the strength of the evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data.

Group 1: The agent is *carcinogenic to humans.*

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

Group 2A: The agent is *probably carcinogenic to humans.*

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Group 2B: The agent is *possibly carcinogenic to humans.*

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is *not classifiable as to its carcinogenicity to humans.*

This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4: The agent is *probably not carcinogenic to humans.*

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

(e) Rationale

The reasoning that the Working Group used to reach its evaluation is presented and discussed. This section integrates the major findings from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic and other relevant data. It includes concise statements of the principal line(s) of argument that emerged, the conclusions of the Working Group on the strength of the evidence for each group of studies, citations to indicate which studies were pivotal to these conclusions, and an explanation of the reasoning of the Working Group in weighing data and making evaluations. When there are significant differences of scientific interpretation among Working Group Members, a brief summary of the alternative interpretations is provided, together with their scientific rationale and an indication of the relative degree of support for each alternative.

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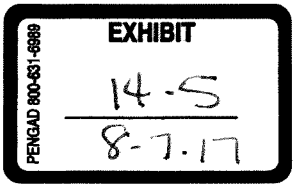
First author, date	Number of cases in the study (all NHL cases combined)	Number of controls in the study
Cocco, 2013	1869	2462
Pahwa, 2015 (commonly known as the NAPP study)	1690	5131
Eriksson, 2008	910	1016
Lee, 2004	872	2336
De Roos 2003	650	1933
Cantor, 1992	622	1245
McDuffie, 2001	517	1506
Hardell, 2002	515	1141
Hohenadel, 2011	513	1506
Hardell, 1999	404	781
Orsi, 2009	244	426
Nordstrom, 1996	111	400
De Roos, 2005 (commonly known as the AHS study)	92	(54223)*

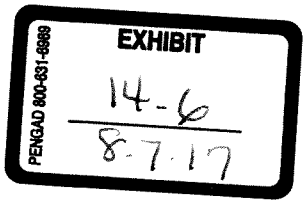


UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

IN RE: ROUNDUP PRODUCTS LIABILITY LITIGATION	MDL No. 2741 Case No. 16-md-02741-VC
This document relates to: ALL ACTIONS	

EXPERT REPORT OF ALFRED I. NEUGUT, MD, PHD

IN SUPPORT OF GENERAL CAUSATION ON BEHALF OF PLAINTIFFS



Expert Report on Glyphosate and Non-Hodgkin Lymphoma

Alfred I. Neugut, MD, PhD

I. Qualifications

I am currently the Myron M. Studner Professor of Cancer Research and Professor of Medicine and Epidemiology at Columbia University, and Associate Director for Population Sciences for the Herbert Irving Comprehensive Cancer Center at Columbia. I am also the Director of Junior Faculty Development for the Department of Epidemiology at the Mailman School of Public Health, overseeing about 30 assistant professors.

I am a medical oncologist with a particular interest in gastrointestinal tract cancers, especially colorectal and gastric cancers. Under the auspices of Columbia's Medical Scientist Training Program, I received my MD and a Ph.D. in Pathobiology in 1977. My PhD was in the laboratory of Dr. I. Bernard Weinstein, an authority in chemical carcinogenesis, and I studied growth control of cancer cells in vitro. I then trained in Internal Medicine at the Albert Einstein College of Medicine and fellowship in Medical Oncology at Memorial Sloan-Kettering Cancer Center.

I returned to Columbia for an M.P.H. in Epidemiology in 1983, and then joined the faculty at Columbia with appointments in Medicine and Epidemiology. My research has centered on cancer epidemiology and prevention. I initiated a series of important studies focused on risk factors for the occurrence and recurrence of colorectal adenomatous polyps (adenomas). These studies extended into the use and yield of colonoscopy and fecal occult blood testing for routine screening and diagnosis. An editorial I wrote in 1988 was the first to suggest the use of colonoscopy for routine screening of asymptomatic adults, a common practice now. My second major research focus was the occurrence of second malignancies, especially the impact of radiation therapy. I was also the co-PI of the Long Island Breast Cancer Study Project which investigated the high rate of breast cancer on Long Island and generated over 100 papers on environmental risk factors and breast cancer.

At the present time, a significant amount of my research is centered on studying quality of care in the use of chemotherapy and radiotherapy for cancer in the elderly and others. My group has found significant effects of age, race/ethnicity, as well as financial status and the level of co-payments in leading to lower quality care and decreased adherence to prescribed chemotherapy and hormonal therapy. I currently also have several projects ongoing in South Africa on the effect of HIV infection on cancer outcomes.

I have published over 500 peer reviewed chapters and papers. I have received over $50 million in funding from the National Cancer Institute, American Cancer Society, Department of Defense, and various foundations. I have led two NCI-funded training grants for predoctoral and postdoctoral trainees for over 25 years that have trained over 80 trainees who are now in various academic, government and industrial positions; I have also mentored over 15 K or K equivalent junior faculty award recipients. I am a recent recipient of the Distinguished Achievement Award of the American Society of Preventive Oncology. I have served on innumerable government grant review committees. My Curriculum Vitae is attached as Attachment A.

I have been asked to review the scientific literature on glyphosate and glyphosate-based formulations and to provide an opinion to a reasonable degree of medical and scientific certainty as to whether glyphosate and glyphosate-based formulations can cause non-Hodgkin lymphoma.

This review took as its takeoff the IARC report of 2015, and reviewed the studies and materials cited in that report. Further literature searches were conducted following up references in the key publications cited in the IARC report and a search conducted for any publications published subsequent to the IARC report. See References Section. We also reviewed the EPA (2016) report, the European Food Safety Authority (2015) report and the commentary by Portier (2015). In addition, I reviewed the transcripts of deposition of Aaron Blair of NIEHS, Donna Farmer of Monsanto and John Acquavella of Monsanto. With the exception of the deposition transcripts this would be the general approach utilized if one were doing a literature review for a scientific publication. More details are given in the text.

My assistant, Ayana K. April Sanders, MPH, a doctoral student in the Department of Epidemiology at Columbia University's Mailman School of Public Health, assisted with the tasks described above, compilation of the tables, and some of the writing. I reviewed all of the studies, and all opinions, analyses and conclusions are mine and mine alone.

II. Cancer Epidemiology

Epidemiology is the study of disease in populations, including its distribution, determinants, natural history, and survival. Rather than the individual patient, its perspective is that of public health. The traditional focus and goal of cancer epidemiology has been the determination of the incidence and mortality rates of cancer in different populations and subgroups, as well as the identification of risk factors for the purpose of disease prevention and control through primary prevention and screening interventions.

Much of epidemiology involves the assessment of cancer risk. A person can be at increased risk of cancer because of extrinsic or intrinsic factors, or a mix thereof.

- Extrinsic influences are factors outside of the individual's own body, such as environmental pollutants, cultural/lifestyle habits, medication use, infectious factors, and diet.
- Intrinsic influences are factors unique to each person, such as genetics.

From an epidemiologic perspective, an etiologic agent or risk factor is anything that increases the probability that an individual will develop the disease. These risk factors can include demographic characteristics (e.g., increasing age or race/ethnicity) or lifestyle and behavioral factors, such as smoking. They also include endogenous factors, such as genetic mutations that have been identified as predisposing a person for a disease, such as a deleterious *BRCA1* or *BRCA2* mutation. Most cancers undoubtedly arise from a combination of genetic and exogenous factors that interact to define certain demographic patterns.

III. Cancer characteristics

My report focuses on characteristics which are specific or idiosyncratic or more relevant to cancer as opposed to other areas of epidemiology (infectious disease, cardiovascular, psychiatric, etc).

a. Epidemiologists start with a definition of cancer which is a synonym for those diseases which involve malignancy (in contrast to being benign). While there may be various characteristics or ways in which to define this phenomenon, a good general definition would be that it is a disease in which the cell loses control of growth and proliferation. Benign cells or growths will stop growing when they reach some boundaries or limits, but malignant cells know no such limits and, in theory, will divide and proliferate forever. In many or most circumstances this is also associated with more rapid growth than in a normal cell, but this is not necessary – the defining characteristic is loss of growth control.

b. As a corollary to the above, cancers are all generally potentially fatal. This is because if you allow uncontrolled growth of a tumor (a growth) to proceed for an unlimited amount of time, it will ultimately reach a size where it will kill the host in some fashion, either because the size of the tumor (or tumors) will compete with the normal cells of the body for nutrition and oxygen, and malignant cells are always better than normal cells at this so the normal cells and tissues will starve to death (a phenomenon known as cachexia in terminal cancer patients). An alternative way in which people die from cancer is that the tumors block vital organs or passageways or replace normal functioning organs so one dies from organ failure. The tumor may be so slow growing that you would not die from it till you are very elderly and you may die from a different disease beforehand, but the point is that all malignant cancers, by definition are potentially fatal.

c. Cancer is a disease of the cell, i.e., in general, the pathophysiologic problem arises within the cell of origin as opposed to being a disease of an organ or system. All other diseases are pathologically problems of deterioration or inflammation or infection or some other disorder arising in the organ or in a system – the pancreas, the lung, the heart, the cardiovascular system, the immune system, etc. A cancer may arise in the context of an organ problem, e.g., liver cancer arising in the context of liver cirrhosis, but the cancer itself is a disorder of the liver cell.

d. Cancer cells are basically aberrant normal cells. That is, a cancer cell can retain initially many of the characteristics of the cell of origin. As it gets more aggressive or more advanced, it becomes less and less like the original normal cell.

e. From a public health and population perspective, individual cancers are uncommon, even rare. The four most common cancers in the US – breast, prostate, colorectal, lung - all occur at an age and sex-adjusted rate of about one case per 1000 population/year. From an epidemiologic perspective, this makes the use of cohort studies or intervention trials extremely difficult and expensive and indeed, such studies are uncommon. As described below, to get sufficient endpoints in such a study even with one of these "more common" cancers, one would need to follow tens of thousands of people for years. For other cancers, which are much less common, the use of cohort studies or intervention trials are

extremely uncommon and difficult to undertake and difficult to interpret unless risk ratios are very strong.

f. The latency period for a cancer can be very long, often on the order of decades. This exacerbates the problem of the use of cohort and intervention trials as described in the prior paragraph. There are, however, both tumor initiators and tumor promoters, the latter of which are short term carcinogens which can raise the risk of a cancer within very short time frames, even within a year or two. This is particularly true when looking at the hematopoietic malignancies.

g. More so than for most diseases, the diagnosis for malignant diseases is pathology-dependent, and hence highly accurate. Indeed, because it depends on histology and pathology, the subclassification of most tumors is also highly accurate. Thus to the degree that an epidemiologic study is trying to ascertain the association between a given exposure and a given disease, the width of the 95% confidence interval (i.e., the uncertainty with which one measures the association between the two variables) is increased by the uncertainty by which one estimates the presence of the exposure and the uncertainty by which one ascertains the presence of the disease. At least for studies of cancer, in most studies, more so than for most diseases, the definition and ascertainment of the disease is highly valid.

h. There are two major histologic types of cells or tissues – epithelial tissue and connective tissue. Malignancies of epithelial tissue are referred to as carcinomas, while malignancies of connective tissue are referred to as sarcomas. Both blood and lymphocytes fall under the rubric of connective tissue and hence malignancies of blood (leukemias) and malignancies of lymphocytes (either leukemias or lymphomas) are under the general category of sarcomas.

IV. Lymphoma

a. Lymphocytes are a type of white blood cell which constitute part of the immune system. There are two major types of lymphocytes. B cells are cells which respond to antigens and ultimately mature into plasma cells which make antibodies, while T cells have other functions, such as being killer cells (directly attacking foreign invaders and toxins). Lymphocytes both circulate in the blood stream, where they constitute about 15-25% of circulating white blood cells, and are concentrated in lymph nodes along the lymphatic system. These are located in contiguity with every organ and act as drainage or sewage systems for each organ in terms of disposal of toxins or invading microorganisms and are often the first sites of local metastasis.

b. Lymphocytes can become malignant in different phases and ways. Lymphocytes that are circulating in the blood stream that become malignant form lymphocytic leukemias. Lymphocytes in lymph nodes that become malignant form lymphomas, either Hodgkin lymphoma or non-Hodgkin lymphoma (NHL).

Plasma cells that become malignant (and emit antibodies) constitute the malignant cell of multiple myeloma.

c. The large majority of NHL arise from B cells as opposed to T cells but there are multiple varieties of NHL based on histology, precise cell of origin, genetic mutations or oncogenes present.

V. Basics of Causation in Epidemiology

Epidemiologic studies use a multi-step process to establish causal inferences. First, principles of causal inference are used to construct our theories, which then help us to formulate testable hypotheses. We then design studies to test causal hypotheses as rigorously as possible. The objective of an epidemiologic study is to obtain a valid and precise estimate of the frequency of a disease or of the effect of an exposure on the occurrence of a disease in the source population of the study (Rothman, 2008). Epidemiologic studies ask 'is there a statistical association between the exposure and outcome?'

In analytic epidemiology, observational studies are carried out to ascertain whether associations exist between an exposure and an outcome. Although a statistical association may exist between the two, there is always concern that this may reflect bias in the way the study was conducted or the presence of confounding factors. Confounding factors are factors associated with both the exposure and the outcome and can lead to an observed association, which is not truly a relationship between the two. For example, a study may show that asbestos workers have an elevated risk of lung cancer compared with the general population. However, one must be concerned that asbestos workers may be heavier smokers than other individuals in the general population and cigarette smoking is associated with lung cancer risk; thus, smoking may confound the observed association. Therefore, it is important in a study that looks at this exposure and outcome to collect smoking information so that it can be statistically controlled and the individual effect of asbestos exposure can be appropriately measured.

Multicausality (aka multifactorial): Certainly it is well known and well accepted that virtually every disease or condition can and does have multiple causes and its etiology can be spoken of as a multicausal phenomenon. Some of these causes are obvious and can be thought of as almost trivial (though they are not really trivial) such as age or gender. For example, virtually all epithelial malignancies (known as carcinomas) occur in adults and are usually age-dependent. Thus age is a risk factor for most carcinomas. Being a female is a risk factor or cause for female specific cancers, like ovarian cancer, which sounds trivial, but it is also a major risk factor for breast cancer, which can occur in males.

What is important to appreciate about the multicausal nature of disease is that all the causes contribute to the probability or risk of the disease occurring and thus any or all can be important in a given individual in whom they are present. Thus if one has a 60 year old obese male who is hypertensive, has a chronic elevated cholesterol, smokes cigarettes, is sedentary, and has a family history of coronary heart disease, and he develops a myocardial infarction (heart

attack), one may ask: What caused his heart attack? The correct answer is that all of these factors did and theoretically, if one removed any one of them from his past history, he might not have developed the disease. This is not to say, they were all equally contributory – how much they each contributed may vary and would be a function of the risk ratio associated with that particular exposure.

A common example of where this multicausal phenomenon occurs is in situations that address the question of whether asbestos exposure causes lung cancer. Many people with significant asbestos exposure in asbestos mines or other occupational settings have also been cigarette smokers, obviously a well-known lung carcinogen, and the argument has been made that the tobacco was responsible for the cancer, not the asbestos exposure. The correct causal analysis of this scenario would be that certainly the cigarette smoking contributed significantly to the development of the lung cancer, but that the asbestos exposure contributed significantly as well.

VI. Types of Epidemiologic Studies

a. Cohort and Case-control Studies

Epidemiologic observational studies fall into two broad categories: cohort studies and case-control studies. Participants in cohort studies are categorized based on their exposure and then followed to determine whether the outcome develops differently in the exposed and unexposed groups. Case-control studies enroll participants who have the outcome or disease under study, in addition to a control group of healthy participants. Both groups are then assessed for exposure. Both types of studies have their advantages and disadvantages. In both types, one must try to avoid bias or directional error. For example, in a case-control study, a patient with cancer may be inclined to give a positive answer more frequently than a control participant to a question regarding smoking history—this is referred to as recall bias.

As a general rule, cohort studies are preferred when the exposure is uncommon and the outcome is common, while case-control studies are preferable with uncommon outcomes. Since the incidence of most cancers, even the most common ones, is relatively low, case-control studies usually are used in cancer research. Their disadvantage is that they are often ambiguous on the temporal relationship between the exposure and the cancer. If you compare 100 patients with colon cancer to 100 patients without colon cancer for their intake of saturated fat, it can be unclear whether a decreased intake in the cases is related to the disease or preceded the disease. In a cohort study, where the exposure is ascertained before the subjects have developed the cancer, one can be more confident that any observed association preceded the development of disease.

Advantages to a Cohort Study

- Results can be used to calculate incidence

- Results can be used to calculate prevalence
- Efficient for studying common diseases
- Can study multiple diseases/outcomes
- Ensures temporality
- Study time varying covariates
- Reduces some types of selection bias and recall bias

Disadvantages to a Cohort Study

- Expensive
- Time consuming
- Cohort studies can be ineffective for studying rare diseases, particularly when follow up time is short.
- Requires prohibitively large sample size to detect occurrence of rare diseases
- Loss to follow-up is a types of selection bias
- Information bias is detection/observer bias (as opposed to recall bias)

A case-control study is a design where two groups, known as cases and controls, are selected based on the presence and absence, respectively, of a disease/outcome of interest. The groups are then queried about various exposures that may have been a source of disease. Associations between exposures and outcomes are measured using odds ratios, which estimate the relative risk. There are several types of case-control studies that vary depending on whether the study is designed within a designated cohort or not within a designated cohort. Sampling must be independent of exposure otherwise selection bias can be a problem. As long as we sample independent of exposure for our classic case-control study, we should have a valid design to address our research question. Controls are selected as a representative sample of the population that gave rise to the cases

Advantages of classic case-control studies

- Efficient for studying rare diseases (requires smaller sample than cohort study)
- Relatively fast
- Reduces the problem of follow-up bias
- Better able to deal with long latency periods
- Relatively inexpensive

Disadvantages of classic case-control studies

- Cannot calculate prevalence
- Inefficient for rare exposures
- Can only study one outcome
- Increased susceptibility to bias

1. Sampling assumptions (selection bias)
   - It is crucial to select cases and controls before gathering any information about exposures
2. Recall/information bias (potential error in recalling exposure
   - Case-patients may recall events differently than control patients

b. Meta-Analyses

Meta-analysis is a method for summarizing epidemiologic and other scientific evidence. "Meta-analysis [that] refers to the analysis of analyses...the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating findings. It connotes a rigorous alternative to the causal, narrative discussion of research studies which typify our attempts to make sense of the rapidly expanding literature..." (Glass, 1976). A meta-analysis is a statistical analysis that combines the results of multiple scientific studies.

The basic tenet behind meta-analyses is that there is a common truth behind all conceptually similar scientific studies, but which has been measured with a certain error within individual studies. The aim then is to use approaches from statistics to derive a pooled estimate closest to the unknown common truth based on how this error is perceived. In essence, all existing methods yield a weighted average from the results of the individual studies and what differs is the manner in which these weights are allocated and also the manner in which the uncertainty is computed around the point estimate thus generated. In addition to providing an estimate of the unknown common truth, meta-analysis has the capacity to contrast results from different studies and identify patterns among study results, sources of disagreement among those results, or other interesting relationships that may come to light in the context of multiple studies (Rothman, Greenland, & Lash, 2008).

A key benefit of this approach is the aggregation of information leading to a higher statistical power and more robust point estimates than is possible from the measure derived from any individual study. However, in performing a meta-analysis, an investigator must make choices which can affect the results, including deciding how to search for studies, selecting studies based on a set of objective criteria, dealing with incomplete data, analyzing the data, and accounting for or choosing not to account for publication bias (Walker, Hernandez, & Kattan, 2008).

Meta-analyses are often, but not always, important components of a systematic review procedure. For instance, a meta-analysis may be conducted on several clinical trials of a medical treatment, in an effort to obtain a better understanding of how well the treatment works. Here it is convenient to follow the terminology used by the Cochrane Collaboration (Van Tulder, Furlan, Bombardier, Bouter, & Group, 2003), and use "meta-analysis" to refer to statistical methods of combining evidence, leaving other aspects of 'research synthesis' or 'evidence synthesis', such as combining information from qualitative studies, for the more general context of systematic reviews.

We conduct meta-analyses to summarize published literature to create a more objective summary of literature than narrative reviews and produce a quantitative statistic demonstrating the estimate average effect of all of the available data. Meta-analyses also increase statistical power of the collection of studies, which results in a more precise estimate of effect size. Finally, conducting meta-analyses of observational studies can help to identify possible heterogeneity between studies.

Steps in Conducting a Meta-Analysis

- Identify objective and hypotheses
- Define outcome, exposure, population
- Formulate study inclusion criteria
- Formulate search strategy
- Extract data
- Assess study quality
- Estimate summary effect
    - Use published estimates [1] for each included study (RR-Risk Ratio/Relative Risk, OR-Odds Ratio, HR-Hazard Ratio)
    - Convert results to a common scale, if needed (z-transformation (standardization), log-transformation)
    - Combine estimates of effect using a weighted average of individual estimates to estimate summary effect (Fixed or Random Effects)

      Fixed effects assume that all studies are estimating the same underlying effect size (i.e., true effect) and that the variability between studies is due to sampling of people within each study. Random effects allow the studies to have different underlying effect, which vary around a mean over all studies and allows variation between studies as well as within studies.

      Selecting the correct statistical model (fixed or random effects) is critically important in a meta-analysis. If one cannot assume that all studies are sampled from the same population, then a random-effects model should be implemented for the meta-analysis. In fact, the random-effects model should be the logical starting point of a meta-analysis with the assumption that the true effect size may or may not vary from study to study and a fixed-effects model can follow as a form of sensitivity analysis.

[1] Measures of relative effect express the outcome in one group relative to that in the other. For all measures of relative effect, a value of 1 indicates that the estimated effects are the same for both comparative groups.
Risk ratio (aka relative risk; RR): the ratio of the risk of event in the two groups
Odds ratio (OR): the ratio of the odds of an event in two groups.
Hazard ratio (HR): the ratio of the hazard rates in the two groups.

There are two types of ways to summarize scientific evidence: 1) systematic review – meta-analysis of published data - and 2) pooled analysis – meta-analysis of individual level data.

Comparison of Meta-analyses and Pooled Analyses: Data Management/Analysis

Meta-Analyses	Pooled Analyses
Generally no contact with original study	Investigators of each study agrees to participate
Retrieve publication and extract data of interest -Study design -Population -Exposure, confounders -Risk estimates, confidence intervals	Obtain primary data -Outcomes -Exposures -Confounders
Check data abstracted for errors	Check primary data for errors
Differences in exposure, covariates, and contrasts across studies	Calculate risk estimates from primary data
	More standardized definitions for exposures, covariates, and contrasts across studies
	Standardize formatting of data
Check whether results are heterogeneous Check summary estimates, if appropriate Conduct sensitivity analyses	

VII. Review of Studies

a. Cohort Study (See Table 1)

De Roos et al. (2005) evaluated the association between exposure to glyphosate and cancer incidence on the Agricultural Health Study (AHS) cohort (A. J. De Roos et al., 2005).

Methods & Results
Population Description: The AHS is a prospective cohort study in Iowa and North Carolina, which includes 57, 311 private and commercial applicators who were licensed to apply restricted-use pesticides at the time of enrollment into the study. Recruitment of the applicators occurred between 1993 and 1997. Members of the AHS cohort were matched to cancer registry files in Iowa and North Caroline for case identification and to state death registries and the National Death Index to ascertain vital statistics.

Outcome Assessment: Incident cancers were identified for the time period from the date of enrollment (1993-1997) until December 31, 2001 and were coded according to the *International Classification of Disease*, 9th Revision (ICD-9). Cohort members who moved from the state were censored in the year they left.

The prevalence of ever-use of glyphosate was 75.5% (> 97% of users were men). In this analysis, exposure to glyphosate was defined as: (a) ever personally mixed or applied products containing glyphosate; (b) cumulative lifetime days of use, or "cumulative exposure days" (years of use × days/year, categorized in tertiles among users: 1-20, 21-56, 57-2,678)); and (c) intensity-weighted cumulative exposure days (years of use × days/year × estimated intensity level, categorized in tertiles: 0.1-79.5, 79.6-337.1, 337.2-18, 241). Poisson regression was used to estimate exposure–response relations between exposure to glyphosate and incidence of all cancers combined, and incidence of 12 cancer types: lung, melanoma, multiple myeloma, and non-Hodgkin lymphoma as well as oral cavity, colon, rectum, pancreas, kidney, bladder, prostate, and leukemia (results not tabulated). Exposure to glyphosate was not associated with all cancers combined (RR, 1.0; 95% CI, 0.9–1.2; 2088 cases). For non-Hodgkin lymphoma, the relative risk was 1.2 (95% CI, 0.7–1.9; 92 cases) when adjusted for age, and was 1.1 (95% CI, 0.7–1.9) when adjusted for multiple confounders (age, smoking, other pesticides, alcohol consumption, family history of cancer, and education); in analyses by cumulative exposure-days and intensity-weighted exposure-days, the relative risks were less than 1.0 in the highest tertiles. In summary, there was no association between glyphosate exposure and all cancer incidence or most of the specific cancer subtypes that were evaluated, including NHL. The strength of this analysis was the use of a large cohort with specific assessment of glyphosate and semi-quantitative exposure assessment. The De Roos et al. (2005) report demonstrates several major limitations that hinder the inferences made by the report: (1) a short follow up period of the cohort that does not allow for a meaningful evaluation of cancer risk; (2) the inability to determine disease latency in relation to glyphosate exposure and the risk of NHL; (3) using a comparison groups that is at an elevated risk of NHL; and (4) a potential for differential exposure misclassification.

(1) Short follow-up period: Participants who were licensed restricted use pesticide applicators were only enrolled in the study cohort from 1993-1997. Participants were followed to 2001, making the follow-up period for this data to range from 4-8 years. The report showed that the median follow-up period for this group was 6.7 years. Another important factor is that participants in the cohort were generally young with 46% being <50 years of age at the time of enrollment. These statistics suggest that the cohort may be too young to adequately evaluate cancer risk. Cancer epidemiology shows us that cancer incidence does not substantially increase until the ages of 50-55 years when we see an exponential increase in cancer incidence (Cancer Research UK, 2016). Thus, the study would have needed to follow this particular cohort for a much longer period of time in order to adequately evaluate cancer, and specifically NHL, risk from glyphosate exposure.

(2) Inability to determine disease latency period for NHL in AHS cohort: To determine the latency period between exposure to glyphosate and the onset of detectable NHL, the

investigators would have had to not only collect information on exposure to glyphosate, but also the time period of the initial exposure. Determining the latency period of the outcome is important in recognizing whether there is a meaningful increased risk in disease in a population because we can use that knowledge to rule out other causes of the disease.

(3) Elevated risk of NHL in control group: In comparison to the cases, it is expected that the control group used in the analysis for "ever/never" exposure to glyphosate would have an elevate risk for NHL. Evidence for this determination includes the following: A) Farmers who were licensed to use restricted-use pesticides comprise 91% of the controls in the De Roos et al., 2005 study. Several studies have demonstrated a significant increased risk of NHL in farmers (Morton et al., 2014; Orsi et al., 2009). B.) Factors considered a risk for increased likelihood of NHL in farmers was tested in the Hardell et al. (L. Hardell, Eriksson, & Nordstrom, 2002) study that ultimately found that the exposure to "all herbicides" is a risk factor for NHL, OR=1.75, 95% CI: 1.26-2.41. Theoretically, if farmers had not adopted glyphosate as an herbicide they were likely to use other herbicides and hence have an increased risk of NHL. C) Finally, and most specifically, the majority of the control group (53.3%) in De Roos et al. (2005) was exposed to 2,4-D, an herbicide with carcinogenic potential. The meta-analysis conducted by Schinasi and Leon (2014) indicated a NHL meta-risk of 1.40 (95% CI: 1.0-1.9) for 2,4-D exposure. IARC recently classified 2, 4-D as possibly carcinogenic to humans (category 2b). Therefore, the effect estimate reported by De Roos et al. (2005) would be an underestimate of the NHL risk in the "ever/never" glyphosate exposure analysis.

(4) Non-differential Exposure Misclassification

Intensity of exposure to glyphosate was collected only at enrollment from 1993 – 1997. Yet, with the movement of agriculture to genetically engineered crops in 1996, participants already using glyphosate would have a dramatic increase in their intensity of exposure. By not collecting follow-up data on exposure status the analysis of exposure to glyphosate and association with NHL would be underestimated.

b. Case-control Studies (See Table 1)

Cantor et al. (1992) conducted a case-control study of incident non-Hodgkin lymphoma (NHL) in 622 white men compared to 1245 population-based controls in Iowa and Minnesota (Cantor et al., 1992). The study measured the risk of NHL associated with farming occupation and specific agricultural exposures. Men who ever farmed had a relative increased risk of NHL than non-farmers (OR=1.2, 95% CI: 1.0-1.5) independent of crop or animal types. Men who ever handled glyphosate also showed a slight increased risk of NHL, but the association was not statistically significant (OR=1.1, 95% CI: 0.7-1.9) when adjusted for vital status, age, state, cigarette smoking status, family history of lymphohaemotapoietic cancer, high-risk occupations and high-risk exposures. A major strength of this analysis was that it used a large population-based sample in a farming community. However, the study had significant limitations. Specifically, there was low power to assess the risk of NHL with glyphosate with only 26 cases of NHL.

Interpretation of the results is also limited by lack of adjustment for other herbicides used by the cohort.

McDuffie et al. (2001) conducted a multisite population-based incident case-control design conducted in six Canadian provinces (McDuffie et al., 2001). The study investigated the associations between exposure to specific herbicides and NHL. A total of 517 male cases and 1506 controls were interviewed by phone. The risk of NHL was observed to be elevated but not statistically significant for men exposed to glyphosate [51 exposed cases (OR=1.26, 95% CI:0.87-1.81; adjusted for age and province) and (OR=1.20, 95% CI: 0.83-1.74; adjusted for age, province, high-risk exposure)]. In a frequency analysis of exposure to glyphosate, men with > 2 days of exposure per year had an increased risk of NHL (OR=2.12, 95% CI: 1.20-3.73; 23 exposed cases; adjusted for age and province) compared to those with ≤ 2 days of exposure. Overall, this study is strengthened by using a large population-based sample, but there was a low response rate, albeit having a non-differential effect on the reported estimates when respondents were compared to non-respondents.

Hardell et al. (2002) conducted a pooled analysis on two case-control studies in Sweden (Lennart Hardell, Eriksson, & Nordström, 2002), one of NHL (originally reported in (L. Hardell & Eriksson, 1999)) and another on hairy cell leukemia (HCL), a rare subtype of (originally reported in (Nordstrom, Hardell, Magnuson, Hagberg, & Rask-Andersen, 1998)). The pooled analysis of NHL and HCL was based on 515 cases and 1141 controls. In univariate analysis, glyphosate increased the risk of NHL and HCL (OR=3.04; 95% CI: 1.08-8.52; 8 exposed cases). After accounting for study, study area and vital status in multivariate analysis, the odds of disease due to exposure to glyphosate decreased to 1.85 (95% CI: 0.55-6.20). Although using the pooled analysis contributed to an overall stronger power for analysis, agent-specific exposures had minimal cases. The exposure frequency was low for glyphosate and limited the power to test the effect of the exposure.

De Roos et al. (2003) used pooled data from three case-control studies on NHL conducted in the 1980s in Nebraska (Zahm et al., 1990), Kansas (Hoar et al., 1986), and Iowa and Minnesota (Cantor et al., 1992) to examine pesticide exposure in farming as a risk factor for NHL among men (A. De Roos et al., 2003). The pooled sample population included 870 cases and 2,569 controls – the majority of cases (n=650) and controls (n=1933) were included for the analysis of 47 pesticides controlling for potential confounding by other pesticides. Logistic regression and hierarchical regression models (which provides more conservative estimates compared to logistic regression due to adjusting estimates based on prior evidence, from past IARC or EPA reports, that any of the 47 pesticides may cause *any type of cancer*) were used in data analysis and all models were adjusted for age, study site, and other pesticides. Reported use of glyphosate, as well as several individual pesticides, was associated with increased incidence of NHL. In the logistic regression model based on 36 cases, the odds ratios for association between exposure to glyphosate and NHL were 2.1 (95% CI: 1.1-4.0) and 1.6 (95% CI: 0.9-2.8) in hierarchical regression models. The pooled population used in this analysis was a considerable strength compared to single-population empirical studies limited by small cases sizes. Additionally, the study was population based. De Roos et al (2003) did

include an advanced methodological technique (hierarchical regression) for accounting for multiple exposures by adjusting for estimates based on prior distributions for the pesticide effects. However, this hierarchical regression method has limited scientific merit since the adjustments are based on prior evidence of factors that may cause any cancer and not specifically NHL, and the opinions of carcinogenicity of each pesticide can change over time. Therefore, the modeling is subject to the opinions on carcinogenicity at the time of analysis (i.e., the opinions about the carcinogenic potential of glyphosate and other herbicides in the late 1980's and early 1990's) and the result would likely be different from current opinions. Thus, the conservative odds ratios of the hierarchical regression may not be an accurate portrayal of the association between glyphosate and NHL and would limit how to interpret the findings of the hierarchical regression.

Lee et al. (2004) evaluated whether asthma acts as an effect modifier of the association between pesticide exposure and NHL (Lee, Cantor, Berzofsky, Zahm, & Blair, 2004). The study was conducted using a pooled analysis of population-based case-control studies in Iowa, Minnesota and Nebraska. The sample included both men and women; 872 cases with NHL from 1980 to 1986 and 2,381 frequency-matched controls. In-person interviews were conducted to collect exposure information on pesticide use and history of asthma. A total of 177 subjects (45 cases, 132 controls) reported having been told by a clinician that they had asthma. Asthmatics had a non-significantly lower risk of NHL than non-asthmatics (OR=0.5, 95% CI; 0.2-1.4), and there was no main effect of pesticide exposure (OR=1.0, 95% CI: 0.8-1.2). Overall, those with a history of asthma typically had large odds ratios associated with exposure to pesticides than subjects without a history of asthma. Among non-asthmatics, the odds ratio associated with glyphosate use was 1.4 (95% CI: 0.98-2.1; 54 exposed cases) and 1.2 (95% CI: 0.4-3.3; 6 exposed cases) for asthmatics when compared to non-asthmatic non-exposed farmers. There was no indication of effect modification, such that the main effect does not vary based on asthma status.

In a Swedish-based study, **Eriksson et al (2008)** reported the results of a population based case-control study of exposure to pesticides as a risk factor for non-Hodgkin lymphoma (Eriksson, Hardell, Carlberg, & Akerman, 2008). Men and women ages 18-74 years were included during December 1, 1999 to April 30, 2002. Incident cases of NHL were recruited from the University Hospitals in Lund, Linköping, Örebro and Umeå and controls were age and sex matched from the national population registry. Exposure to different agents was assessed by questionnaire. In total, 910 (91%) cases and 1016 (92%) controls participated in the study. Latency period calculations and multivariable analyses included agents with statistically significant increased odds ratios (OR) or with an OR > 1.5 and at least 10 exposed subjects. The odds of NHL for exposure to glyphosate was 2.02 (95% CI: 1.10-3.71) in univariate analysis and 1.51 (95% CI: 0.77-2.94) in a multivariable analysis. When considering exposure for more than 10n days per year, the OR was 2.36 (95% CI: 1.04-5.37). With a latency period of > 10 years, the odds ratio for exposure to glyphosate was 2.26 (95% CI: 1.16-4.40). Exposure to glyphosate was associated with increased odds for lymphoma subtypes and elevated odds of B-cell lymphoma (OR=1.87, 95% CI: 0.998-3.51) and the subcategory of small lymphocytic

lymphoma/chronic lymphocytic leukemia (OR=3.35, 95% CI: 1.42-7.89). Strengths of this study include having a population-based case-control study investigation, the ability to study different NHL subtypes and high response rate of cases and controls. Additionally, Eriksson et al. (2008) is one of the only studies to demonstrate elevated risk for glyphosate exposure in relation to several categories of NHL and evaluate the rick of NHL related to latency period. Limitations to interpreting the results derive from self-reported exposure assessment and possible confounding from use of other pesticides including MCPA – another herbicide that is commonly used together with glyphosate – but these were controlled for in the analysis. More so, it is expected that any residual confounding would result in an underestimation of the effect of a single pesticide. Given that the results demonstrated increased risk suggests there being a causal relationship despite confounding.

Orsi et al. (2009) reported the results of a hospital-based case-control study conducted in six clinics in France between 2000 and 2004 (Orsi et al., 2009). The study population included men and women aged 20-75 years and controls of the same age and sex as the cases were recruited in the same hospital – most were patients in the orthopedic and rheumatologically departments during the study period. In-person interviews and expert review of cases were used to evaluate pesticide exposure. The analysis included 491 cases (95.7% response rate; 244 cases of NHL, 87 cases of Hodgkin lymphoma, 104 cases of lymphoproliferative syndrome, and 56 cases of multiple myeloma) and 56 cases 456 age- and sex-matched controls. The study had a good response rate for the participants, but it enrolled hospital-based rather than population-based cases and controls. This could induce selection bias depending on whether individuals with high exposure to herbicide/pesticides, like glyphosate, (i.e., farmers) were more or less likely be hospitalized than the average person in the population that gave rise to the cases. A key limitation is that there was a small sample of participants reporting exposure to glyphosate thus limiting the power of the analysis to test for a true effect of glyphosate on any of the outcomes.

Cocco et al. (2013) reported on a pooled analysis of case-control studies conducted in six European countries between 1998-2004 (EPILYMPH, Czech Republic, France, Germany, Ireland, Italy, and Spain) investigating the role of occupational exposure to specific groups of chemicals in the etiology of lymphoma overall, B=cell lymphoma, and its most prevalent subtypes (Cocco et al., 2013). There was an approximately 1:1 ratio of cases (n=2,348) to controls (n=2.462) recruited by the six studies. Controls from Germany and Italy were randomly selected by sampling from the general population, whiles the other countries used matched hospital controls. Participation was adequate, 88% of cases participated and 81% of hospital controls and 52% of population controls participated. In-person interviews were conducted to collect detailed information on occupational history on farm-specific work related to type of crop, farm size, pest being treated, type of schedule of pesticide use. Industrial hygienists and occupational experts at each study center was used to assess exposure to specific groups of pesticides and individual compounds with assistance from agronomists. This method was used to reduce differential misclassification of exposure. Regression models were adjusted for age, sex, education, and study center. Lymphoma overall, and B-cell lymphoma were not

associated with any class of the investigated pesticides, while the risk of chronic lymphocytic leukemia was elevated among those ever exposed to inorganic and organic pesticides. The odds ratio for exposure to glyphosate and B-cell lymphoma was 3.1 (95% CI: 0.6-17.1; 4 exposed cases and 2 exposed control). The study was significantly limited in its power to assess the effects of glyphosate on risk of NHL due to substantially small sample of exposed cases.

c. Meta-analyses

In summary, the two published meta-analyses demonstrated statistically significant elevated risk of NHL in relation to glyphosate exposure. Estimates varied slightly based on the inclusion/exclusion of certain articles and the specific data points used in the meta-analyses.

Schinasi & Leon (2014) conducted a systematic review and a series of meta-analyses of approximately three decades of epidemiologic research on the relationship between NHL and occupational exposure to agricultural pesticide active ingredients and chemical groups, including glyphosate (Schinasi & Leon, 2014). The meta-analysis included six studies (A. De Roos et al., 2003; Eriksson et al., 2008; L. Hardell et al., 2002; McDuffie et al., 2001; Orsi et al., 2009) and yielded a meta risk-ratio of 1.5 (95% CI: 1.1-2.0) (See Fig. 1). Of note, the meta risk-ratio did not use the most fully adjusted estimates were from Hardell et al. (2002) and Eriksson et al. (2008) studies. The IARC Working Group re-assessed the meta-analysis by including the more adjusted estimates and generated similar but slightly diminished estimate (meta-RR=1.3, 95% CI: 1.03-1.65), I^2=0%, P for heterogeneity = 0.589].

Chang and Delzell (2016) used the same six studies as Schinasi and Leon (2014) to conduct a systematic review and meta-analysis examining the relationship between glyphosate exposure and risk of lymphohematopeoietic cancer including NHL, Hodgkin lymphoma, multiple myeloma and leukemia (Chang & Delzell, 2016). The meta-analysis yielded a meta-risk ratio of 1.3 (95% CI: 1.0-1.6) based on the six studies (Chang and Delzell, 2016 Figure 1). The investigators also conducted a meta-analysis substituting the logistic regression results of the De Roos et al. (2003) study for the hierarchical regression results and used the update data from McDuffie et al. (2001) and yielded a meta-risk ratio of 1.4 (95% CI: 1.0-1.8) (See Fig. 2).

VIII. Toxicity Studies

Animal Evidence (See Table 2)

Several rodent studies were conducted (EPA, 1985a, 1985b, 1986, 1991a, as cited in IARC Monograph 112) evaluating the effect of pure glyphosate exposure at varying concentrations. A significant positive trend for renal tumors in male CD-1 mice (EPA, 1985a), typically rare in mice, although there were no comparisons of any individual exposure group were statistically significant. In the Joint FAO/WHO Meeting on Pesticide Residues (JMPR, 2006) where CD-1 male and female mice were given diets containing glyphosate (purity,

98.6%), a significant positive trend for hemangiosarcoma in male CD-1 mice was reported. Again no individual exposure group was found to be statistically significant different from the control group. Finally, EPA's (EPA, 1991a, 1991b, 1991c, 1991d) reports saw a significant increase in the incidence of pancreatic islet cell adenomas in two studies in male Sprague-Dawley male and female rats that were exposed to increasing concentrations of 96.5% purity glyphosate diets. These reports also demonstrated increased thyroid gland adenoma in females and liver adenoma in males.

The IARC working group reached the conclusion of *sufficient evidence* of glyphosate carcinogenicity in animals based on the significance of trend tests. The European Food and Safety Authority (EFSA) concluded that based on lack of individual significant differences and consistency between historical control ranges that there is *no evidence of carcinogenicity* of glyphosate in animal studies. Guidelines for evaluating toxicity in animal studies and relevant scientific reports and publications recommended that the key data points are the use of concurrent controls and trend tests (OECD, 2012; European Chemicals Agency, 2015). Trend tests are more powerful than pairwise comparisons, particularly for rare tumors where data are sparse. Likewise, historical control data should be garnered from the studies in the same time frame, animal strain and preferably the same laboratory and reviewed by the same pathologist.

Carcinogenic Mechanisms in Humans (See Tables 3a & 3b)

The genotoxic potential for glyphosate has been studied in a variety of assays including human, non-human mammal and non-mammalian systems. In the following, we summarize the findings of studies carried out in exposed humans and in human cells in vitro (as cited in IARC Monograph 112).

Studies in exposed humans (see Table 3a)

Available publications assessing the effect of a glyphosate-based formulation have focused on communities where the agent was aerially-sprayed in areas of northern Ecuador (Paz-y-Miño et al., 2007)) and five regions in Colombia (C Bolognesi, Carrasquilla, Volpi, Solomon, & Marshall, 2009). In 24 exposed individuals in Ecuador, a statistically significant increase in DNA damage (DNA strand breaks) were observed in blood cells collected 2 weeks to 2 months after glyphosate was spayed in the area. Paz-y-Miño et al. (2011) studies continued by evaluating blood cells from 92 residents in 10 communities of northern Ecuador, sampled 2 years after the aerial spraying with an herbicide mix containing glyphosate (Paz-y-Miño et al., 2011). The results assessing chromosomal damage showed that the subject's karyotypes were similar to levels reported in the control group. In Colombia, 137 married couples (137 women of reproductive age and their 137 spouses) were recruited from five regions. In three regions with exposed to glyphosate-based formulations from aerial spraying, blood samples were taken from the same individuals at three time points – (1) before spraying (baseline), (2) 5 days after spraying, and (3) 4 months after spraying – to determine the frequency of micronucleus formation in lymphocytes. Compared to a reference region without use of pesticides, subjects residing in the three regions where there had been aerial spraying of glyphosate-based formulations and in a fourth region with pesticide exposure (but not administered aerially) had significantly higher baseline frequency of binucleated cells with micronuclei. Increased

frequency of micronucleus formation in peripheral blood lymphocytes compared to baseline frequencies was also reported in subjects from the three regions. Directly after aerial sprays with the glyphosate-based formulation, subjects showed higher frequency of binucleated cells with micronuclei. However, the observed increases in micronuclei formation was reported to be inconsistent with the rates of application used in the regions; there was no association between self-reported direct contact with pesticide sprays and frequency of binucleated cells with micronuclei. In one of the 3 regions, subjects' frequency of binucleated cells with micronuclei was significantly decreased 4 months after spraying compared to their frequencies immediately after spraying.

Studies in human cells in vitro (See Table 3b)

In studies using human cells in vitro, glyphosate induced DNA strand breaks (measured using the comet assay) in liver HEP-2 cells (F Mañas et al., 2009), lymphocytes (Alvarez-Moya et al., 2014; Mladinic, Berend, et al., 2009), GM38 fibroblasts, the HT1080 fibrosarcoma cell line (Monroy et al., 2005), and the TR146 buccal carcinoma line (Koller et al., 2012). DNA strand breaks were induced by AMPA in Hep-2 cells (Fernando Mañas et al., 2009), and by a glyphosate-based formulation in the TR146 buccal carcinoma cell line (Koller et al., 2012). AMPA, the degradation product of glyphosate and main metabolite of glyphosate, and glyphosate-based formulation also induces DNA strand breaks in Hep-2 cells and in the TR146 buccal carcinoma cells line, respectively. AMPA (F Mañas et al., 2009), but not glyphosate (Fernando Mañas et al., 2009), was found to produce chromosomal aberrations in human lymphocytes. Sister-chromatid exchange was induced by glyphosate (Bolognesi et al., 1997) and by a glyphosate-based formulation (Claudia Bolognesi et al., 1997; Vigfusson & Vyse, 1980) in human lymphocytes exposed in vitro. Glyphosate did not induce concentration-related increases in micronucleus formation in human lymphocytes at levels estimated to correspond to occupational and residential exposure (Mladinic, Perkovic, & Zeljezic, 2009).

Several studies have been conducted assessing the effect of glyphosate and its variations on oxidative stress, inflammation and immunosuppression. In studies examining the effects of glyphosate on oxidative stress parameters in the human keratinocyte cell line (HaCaT), a glyphosate-based formulation was found to be cytotoxic to HaCaT cell – addition of antioxidants reduced cytotoxicity (Gehin, Guillaume, Millet, Guyon, & Nicod, 2005). Another study showed that incubation of HaCaT cells with glyphosate at 21 mM (the half maximal inhibitory concentration for cytotoxicity, IC_{50}) for 18 hours increased production of hydrogen peroxide (H_2O_2) as shown by dichlorodihydrofluorescein diacetate assay (Elie-Caille, Heu, Guyon, & Nicod, 2010). Similar findings were reported by George & Shukla (2013) using 41% pure glyphosate up to 0.1 mM (George & Shukla, 2013). Dicholorodihydrofluorescein diacetate was used as a marker of oxidative stress limiting the validity of the findings (Bonini, Rota, Tomasi, & Mason, 2006; Kalyanaraman et al., 2012). The oxidative effects of glyphosate, AMPA, and a glyphosate-based formulation on oxidative stress in HepG2 cells was evaluated by Chaufan et al. (2014) and showed only the formulation had an adverse effects by increasing levels of reactive oxygen species, nitrotyrosine formation, superoxide dismutase activity, and glutathione, but did not have an effect on catalase or glutathione-S-transferase activities (Chaufan, Coalova, & Molina, 2014). Coalova et al (2014) found that exposing Hep2 cells to a formulation resulted in

various elevated parameters of oxidative stress. Exposure to the glyphosate-based formulation for 24 hours increased catalase activity and glutathione levels, with no effect on superoxide dismutase or glutathione=S-transferase activity (Coalova, de Molina, & Chaufan, 2014). Mladinic et al. (2009b) used blood samples from non-smoking male donors to examine the effects of in-vitro exposure to glyphosate on oxidative DNA damage in primary lymphocyte cultures and on lipid peroxidation in plasma. In both parameters glyphosate exposure significantly elevated the DNA damage when concentrations were 580 µg/mL or higher. Examining the effects of glyphosate, AMPA, and other related compounds in human erythrocytes collected from healthy donors, Kwiatkowska et al. (2014) found that exposed erythrocytes had increased production of reative oxygen species (Kwiatkowska, Huras, & Bukowska, 2014). One study was available investigating the effects of glyphosate on cytokine production in human peripheral blood mononuclear cells (Nakashima et al., 2002). At 1mM glyphosate had a slight inhibitory effect on cell perliferation and modestly inhibited the production of IFN-gamma and IL-2. The production of TNF-α and IL-1 β was not affected by glyphosate at concentrations that significantly inhibited proliferative activity and T-cell-derived cytokine production.

Several studies have been developed to assess the effect of glyphosate exposure on cell proliferation and death. George & Shulka (2013) found that a glyphosate-based formulation increased the number of viable cells in HaCaT keratinocytes(George & Shukla, 2013). Eight human cancer cell lines was inhibited cell growth when exposed to glyphosate and AMPA – the greatest loss of viability were in ovarian and prostate cell lines (Li et al., 2013). Immortalized prostate cell lines were not affected. Using t47D breast cancer cells, Thongprakaisang et al. (2013) saw an increased growth in the cancer cells when exposed to glyphosate only when endogenous estrogen was minimized in the culture medium (Thongprakaisang et al., 2013). The growth of hormone-independent cultured breast cancer cells was not affected by glyphosate. The effect on apoptotic cell death given glyphosate exposed has been studied in HepG2 human hepatoma cell line. Glyphosate-based formulations induced apoptosis, while glyphosate alone generally was ineffective or showed effects at considerably high concentrations (Chaufan et al., 2014; Coalova et al., 2014; Gasnier et al., 2009; Mesnage, Bernay, & Séralini, 2013). Formulations showed to be more cytotoxic than glyphosate alone in studies with glyphosate and nine different glyphosate-based formulations in three cell lines (Mesnage et al., 2013). In HUVEC primary neonate umbilical cord vein cells, and 293 embyonic kidney and JEG3 placental cell lines, Benachour & Séralini (2008) found that glyphosate at relatively high concentrations induced apoptosis (Benachour & Séralini, 2008). The umbilical cord HUVEC cells were the most sensitive (by about 100-fold) to the apoptotic effects of glyphosate. Heu et al. (2012) evaluated apoptosis in immortalized human keratinocytes (HaCaT) exposed to glyphosate (5–70 mM) (Heu, Berquand, Elie-Caille, & Nicod, 2012). Based on annexin V, propidium iodide and mitochondrial staining, exposures leading to 15% cytotoxicity gave evidence of early apoptosis, while increases in late apoptosis and necrosis were observed at higher levels of cytotoxicity.

IX. Bradford Hill Criteria for Causation

While studies may assess associations, the decision regarding whether causality, as opposed to reverse causality, confounding, or some other relationship exists between

a putative exposure and outcome reflects a judgment call on the part of an educated experienced observer. The issue of causation in science can be appreciated by how extensively it is discussed and expounded upon within the writings of various philosophers, thinkers, and scientists going back to Plato and Aristotle, but the discussion of this topic profoundly accelerated during the time frame of the Empiricists in the sixteenth to eighteenth centuries, reflecting the growth of true experimental science and observation and an effort to be able to systematize and understand it.

Prior to the twentieth century, in medicine, the scientific endeavors, such as they were, focused almost exclusively on infectious diseases, and even there causality was a major concern. One solution to this problem were the so-called Koch's Postulates, an algorithm by which to establish the etiologic agent for an infectious disease. It had a few instances of spectacular success, but in truth, it could not be often applied in human disease as it required that the infectious agent be introduced into a naïve host and cause the disease, something which was usually unacceptable, and today would almost always be unethical.

The advent of chronic diseases as the major health problems of the latter half of the twentieth century revived the causation issue, as again one could not apply any form of Koch's Postulates. Indeed, most scientists were skeptical of whether lifestyle or behavioral factors could even be responsible for disease, in contrast to infectious or toxic agents. Tobacco and lung cancer became the salient testing ground for this issue, and it proved difficult to convince both the scientific and lay public of the etiologic relationship between the two, especially in the face of fierce tobacco company opposition but with growing observational data in support of the hypothesis. For obvious reasons, it was impossible to undertake a study along the lines of Koch's Postulates.

In response to this problem there arose a set of criteria known as the Bradford Hill Criteria, published in 1965, named after their author, which became a checklist of sorts against which to weigh the collected evidence for a putative association in chronic disease epidemiology. They have remained to this day as the centerpiece of most circumstances in which a causal decision has to be made. Of particular relevance to this case is that they are also central to the methodology by which IARC reaches its judgments regarding carcinogenesis. We list them below and address each one in regard to the glyphosate/NHL question.

a. Temporality: This is always a key criterion for causality as it is an absolutely necessary condition, i.e., the cause must precede the effect. Certainly in this case, by the nature of the studies conducted, there is no doubt that this criterion was met. Exposure to glyphosate and its formulations preceded the development of NHL in all the human and all the animal studies.

b. Consistency: This criterion assesses whether the various studies essentially found similar results. Figures 1 and 2 summarize the findings of the case-control studies in Forest plots. If there were no association between glyphosate and NHL, i.e., if the two phenomena were truly random, then the measured associations in the studies should have randomly distributed themselves around 1. If one looks in the literature at exposures that have been shown not to be associated with certain outcomes, that is what one finds in the Forest plots. But that is not what one finds here. Here one finds that all the studies show a positive estimate of association between the exposure and the outcome. It is true that they are not all statistically significant. Many things attenuate the measurement of a statistical association ranging from any degree of misclassification in the measurement of the exposure or outcome to biases. But what is telling in the Forest plots is the ***consistency – they are primarily positive and to the right of 1.*** This consistency is amplified by the finding that when the data are meta-analyzed, they do indeed come out to be statistically significant.

c. Dose-Response: Two of the studies do suggest that there is a dose-response relationship, and that there is both a stronger association with increased exposure, as well as a statistically significant relationship. (See McDuffie (2002), Eriksson (2008)).

d. Biological Plausibility: Glyphosate has been shown to cause tumors in animal studies and there are at least two biological mechanisms (i.e., genotoxicity and oxidative stress) adduced for its mode of action. IARC considered this a strong rationale for carcinogenicity.

e. Strength: Meta-analyses suggest that the strength of association between ever use of glyphosate and NHL is in the range of 1.3-1.5. Of course, as mentioned in section c above, there is a dose-response so those exposed with high levels or for long durations have higher levels of risk. For example, Mc Duffie (2002) shows an OR=2.12 for people who used glyphosate greater than 2 days per year, and Eriksson (2008) showed an OR=2.36 for people who used glyphosate longer than 10 years.

f. Analogy: Not applicable.

g. Specificity: This is a criterion that is often not applicable in assessing a causal relationship and is ignored. However, this is one instance in which specificity does appear to apply. Glyphosate has not been associated with a broad range of malignancies, like epithelial cancers or even Hodgkin lymphoma, which would have suggested that methodological issues or biases in the studies could be the reasons rather than a true causal relationship. The fact that glyphosate has been linked **specifically** to NHL provides further reassurance that the association is causal.

X. Conclusions

My general view is that the approach and conclusions reflected in the IARC report of 2015 were reasonable and within the bounds of scientific and epidemiological normative practice and, with those practices in mind, reach the correct conclusion. While decisions regarding causal effects are, and usually will remain, judgement calls the epidemiologic and scientific evidence currently available leads to the conclusion to a reasonable degree of scientific certainty for most expert, objective, and reasonable viewers, myself included, that the use of glyphosate in its various combinations can cause non-Hodgkin lymphoma.

XI. Statement of Compensation and Previous Testimony

I am being compensated for my review and testimony at the rate of $450.00 per hour. The cases where I have testified at deposition or trial in the last four years are listed in Attachment B.

Dated: April 28, 2017

Alfred I. Neugut, MD, PHD

TABLE 1. OBSERVATIONAL HUMAN STUDIES OF GLYPHOSATE EXPOSURE AND NHL (Adapted from IARC Monograph 112)

Author	Year	Title	Study Design	Subjects	Location/ Enrollment Period	Exposure	Outcome	Risk Estimate (95% CI)
Cantor et al.	1992	Pesticides and other agricultural risk factors for non-Hodgkins lymphoma among men in Iowa and Minnesota	Case-Control	Cases: 622 (response rate, 89.0%); Iowa health registry records and Minnesota hospital and pathology records Controls: 1245 (response rate, 76–79%); population-based; no cancer of the lympho-haematopoietic system; frequency-matched to cases by age (5-year group), vital status, state. Random-digit dialing (aged < 65 years); Medicare records (aged ≥ 65 years); state death certificate files (deceased subjects) Exposure assessment method: questionnaire; in-person interview	Iowa and Minnesota, USA 1980–1982	Ever handled glyphosate	NHL	1.1 (0.7-1.9)
McDuffie et al.	2001	Non-Hodgkins Lymphoma and specific pesticide exposures in men cross-Canada study of pesticides and health	Case-Control	Cases: 517 (response rate, 67.1%), from cancer registries and hospitals Controls: 1506 (response rate, 48%); random sample from health insurance and voting records Exposure assessment method: questionnaire, some administered by telephone, some by post	Canada 1991–1994	Exposed to glyphosate Unexposed >0 and <= 2 days >2 days	NHL	1.2 (0.83-1.74) 1 1.0 (0.63-1.57) 2.12 (1.2-3.73)

Hardell et al.	2002	Exposure to pesticides as risk factor for non-Hodgkins lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies	Case-Control	Cases: 515 (response rate, 91% in both studies); Swedish cancer registry Controls: 1141 (response rates, 84% and 83%%); national population registry Exposure assessment method: questionnaire	Sweden; four Northern counties and three counties in mid Sweden 1987–1992	Ever glyphosate exposure (univariate) Ever glyphosate exposure (multivariate)	NHL and HCL	3.04 (1.08-8.5) 1.85 (0.55-6.2)
De Roos et al.	2003	Integrative assessment of multiple pesticides as risk factors for non-Hodgkins lymphoma among men	Pooled Case-Control	Cases: 650 (response rate, 74.7%); cancer registries and hospital records Controls: 1933 (response rate, 75.2%); random-digit dialing, Medicare, state mortality files Exposure assessment method: questionnaire; interview (direct or next-of-kin)	Nebraska, Iowa, Minnesota, Kansas, USA 1979–1986	Any glyphosate exposure	NHL	2.1 (1.1-4.0)
Lee et al.	2004	Non-Hodgkins lymphoma among asthmatics exposed to pesticides	Case-Control	Cases: 872 (response rate, NR); diagnosed with NHL from 1980 to 1986 Controls: 2381 (response rate, NR); frequency-matched controls Exposure assessment method: questionnaire; information on use of pesticides and history of asthma was based on interviews	Iowa, Minnesota and Nebraska, USA 1980–1986	Exposed to glyphosate - non-asthmatics / Exposed to glyphosate - asthmatics	NHL	1.4 (0.98-2.1) 1.2 (0.4-3.3)

De Roos et al.	2005	Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study	Prospective Cohort	54 315 (after exclusions, from a total cohort of 57 311) licensed pesticide applicators Exposure assessment method: questionnaire; semi-quantitative assessment from self-administered questionnaire	Iowa and North Carolina, USA1993–2001	Ever use 1-20 21-56 57-2678 Trend-test P value 0.73	NHL	1.1 (0.7-1.9) 1 (ref.) 0.7 (0.4-1.4) 0.9 (0.5-1.6)
Eriksson et al.	2008	Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis	Case-Control	Cases: 910 (response rate, 91%); incident NHL cases were enrolled from university hospitals Controls: 1016 (response rate, 92%); national population registry Exposure assessment method: questionnaire	Sweden, Four health service areas (Lund, Linkoping, Orebro and Umea) 1999–2002	Any glyphosate Any glyphosate* <=10 days per year use >10 days per year use 1-10 years >10 years B-cell lymphoma Lymphocytic lymphoma/B-CLL Diffuse large B-cell lymphoma Follicular grade I-III Other specified B-cell lymphoma Unspecified B-cell lymphoma T-cell lymphoma Unspecified NHL	NHL	2.02 (1.1-3.71) 1.51 (0.77-2.94) 1.69 (0.7-4.07) 2.36 (1.04-5.37) 1.11 (0.24-5.08) 2.26 (1.16-4.4) 1.87 (0.998-3.51) 1.63 (0.53-4.96) 1.47 (0.33-6.61) 2.29 (0.51-10.4) 5.63 (1.44-22)

Orsi et al.	2009	Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study	Case-Control	Cases: 491 (response rate, 95.7%); cases (244 NHL; 87 HL; 104 LPSs; 56 MM) were recruited from main hospitals of the French cities of Brest, Caen, Nantes, Lille, Toulouse and Bordeaux, aged 20–75 years; ALL cases excluded Controls: 456 (response rate, 91.2%); matched on age and sex, recruited in the same hospitals as the cases, mainly in orthopedic and rheumatological departments and residing in the hospital's catchment area Exposure assessment method: questionnaire	France 2000–2004	Any glyphosate exposure	NHL	1.0 (0.5-2.2)

Cocco et al.	2013	Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study	Case-Control	Cases: 2348 (response rate, 88%); cases were all consecutive adult patients first diagnosed with lymphoma during the study period, resident in the referral area of the participating centers Controls: 2462 (response rate, 81% hospital; 52% population); controls from Germany and Italy were randomly selected by sampling from the general population and matched to cases on sex, 5-year age-group, and residence area. The rest of the centers used matched hospital controls, excluding diagnoses of cancer, infectious diseases and immunodeficiency diseases Exposure assessment method: questionnaire; support of a crop exposure matrix to supplement the available information, industrial hygienists and occupational experts in each participating center reviewed the general questionnaires and job modules to assess exposure to pesticides	Czech Republic, France, Germany, Italy, Ireland and Spain 1998–2004	Occupational exposure to glyphosate	B-cell lymphoma	3.1 (0.6-17.1)

Schinasi et al.	2014	Non-Hodgkin lymphoma and occupational exposure to agricultural pesticide chemical groups and active ingredients: a systematic review and meta-analysis	Meta-Analysis	The meta-analysis for glyphosate included six studies (McDuffie et al., 2001; Hardell et al., 2002; De Roos et al., 2003; 2005a; Eriksson et al., 2008; Orsi et al., 2009)		NHL	1.5 (1.1–2.0)
Chang et al.	2016	Systematic review and meta-analysis of glyphosate exposure and risk of lymphohemato-poietic cancers	Meta-Analysis			LHC incl NHL Multiple Myeloma HL	meta-RR = 1.3 (1.0-1.6) meta-RR = 1.4 (1.0-1.9) meta-RR = 1.1 (0.7-1.6)

TABLE 2. ANIMAL EXPERIMENTS REGARDING CARCINOGENICITY OF GLYPHOSATE (Cited in IARC Monograph 112)

Author	Year(s)	Title	Species, strain (sex) Duration	Dosing regimen, Animals/groups at start	For each target organ: incidence (%) and/or multiplicity of tumors	Significance

EPA	1985a, b, 1986, 1991a	Glyphosate; EPA Reg.#: 524-308; Mouse oncogenicity study. Document No. 004370. EPA Reg.#: 524-308; Roundup; glyphosate; pathology report on additional kidney sections. Glyphosate; EPA Registration No. 524-308; Roundup; additional histopathological evaluations of kidneys in the chronic feeding study of glyphosate in mice. Document No. 005590. Second peer review of glyphosate.	Mouse, CD-1 (M, F) 24 mo	Diet containing glyphosate (technical grade; purity, 99.7%) at concentrations of 0, 1000, 5000, or 30 000 ppm, ad libitum, for 24 mo 50 M and 50 F/group [age, NR]	Males Renal tubule adenoma: 0/49, 0/49, 1/50 (2%), 3/50 (6%) Females No data provided on the kidney Report from the PWG of the EPA (1986): Males Renal tubule adenoma: 1/49 (2%), 0/49, 0/50, 1/50 (2%) Renal tubule carcinoma: 0/49, 0/49, 1/50 (2%), 2/50 (4%) Renal tubule adenoma or carcinoma (combined): 1/49 (2%), 0/49, 1/50 (2%), 3/50 (6%)	P for trend = 0.016; see comments [NS] [P=0.037; Cochran-Armitage trend test] [P=0.034; Cochran-Armitage trend test]

JMPR	2006	Glyphosate. In: Joint FAO/WHO Meeting on Pesticide Residues. Pesticide residues in food – 2004: toxicological evaluations. Report No. WHO/PCS/06.1. Geneva	Mouse, CD-1 (M, F) 104 wk	Diet containing glyphosate (purity, 98.6%) at doses of 0, 100, 300, 1000 mg/kg bw, ad libitum, for 104 wk 50 M and 50 F/group [age, NR]	Males Haemangiosarcoma: 0/50, 0/50, 0/50, 4/50 (8%) Histiocytic sarcoma in the lymphoreticular/haemopoietic tissue: 0/50, 2/50 (4%), 0/50, 2/50 (4%)	[P < 0.001; Cochran–Armitage trend test] NS
					Females Haemangiosarcoma: 0/50, 2/50 (4%), 0/50, 1/50 (2%)	NS
					Histiocytic sarcoma in the lymphoreticular/haemopoietic tissue: 0/50, 3/50 (6%), 3/50 (6%), 1/50 (2%)	NS

George et al.	2010	Studies on glyphosate-induced carcinogenicity in mouse skin: a proteomic approach.	Mouse, Swiss (M) 32 wk	Initiation-promotion study Skin application of glyphosate-based formulation (glyphosate, 41%; POEA, ~15%) (referred to as "glyphosate") dissolved in 50% ethanol; DMBA dissolved in 50% ethanol, and TPA dissolved in 50% acetone, used in the groups described below 20 M/group Group I: untreated control (no treatment) Group II: glyphosate only: 25 mg/kg bw topically, 3 × /wk, for 32 wk Group III: single topical application of DMBA, 52 µg/mouse, followed 1 wk later by TPA, 5 µg/mouse, 3 × /wk, for 32 wk Group IV: single topical application of glyphosate, 25 mg/kg bw, followed 1 wk later by TPA, 5 µg/mouse, 3 × /wk, for 32 wk Group V: 3 × /wk topical application of glyphosate, 25 mg/kg bw, for 3 wk, followed 1 wk later by TPA, 5 µg/mouse, 3 × /wk, for 32 wk Group VI: single topical application of DMBA, 52 µg/mouse Group VII: topical application of TPA, 5 µg/mouse, 3 × /wk, for 32 wk	Skin tumors [called "papillomas" by the authors, following gross examination only] Group I: 0/20 Group II: 0/20 Group III: 20/20*, 7.8 ± 1.1 Group IV: 0/20 Group V: 0/20 Group VI: 0/20 Group VII: 0/20 Group VIII: 8/20*, 2.8 ± 0.9	*P < 0.05 vs groups VI and VII *P < 0.05 vs group VI

Group VIII: single topical application of DMBA, 52 µg/mouse, followed 1 wk later by topical treatment with glyphosate, 25 mg/kg bw, 3×/wk, for 32 wk

Séralini et al.	2014	Republished study: long-term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize.	Rat, Sprague-Dawley (M, F) 24 mo	Drinking-water containing a glyphosate-based formulation at a concentration of 0 (control), 1.1 × 10−8% (glyphosate, 5.0 × 10−5 mg/L), 0.09% (glyphosate, 400 mg/L) or 0.5% (glyphosate, 2.25 × 103 mg/L), ad libitum, for 24 mo 10 M and 10 F/group (age, 5 wk)	Males No significant increase in tumor incidence observed in any of the treated groups Females Mammary tumors (mainly fibroadenomas and adenocarcinomas): 5/10 (50%), 9/10 (90%), 10/10 (100%)*, 9/10 (90%) Pituitary lesions (hypertrophy, hyperplasia, and adenoma): 6/10 (60%), 8/10 (80%), 7/10 (70%), 7/10 (70%)	NS *[P<0.05] NS
Chruscielska et al.	2000	Glyphosate - Evaluation of chronic activity and possible far-reaching effects. Part I. Studies on chronic toxicity	Rat, Wistar (M, F) 24 mo	Drinking-water containing ammonium salt of glyphosate (13.85% solution) [purity of glyphosate, NR] was used to make aqueous solutions of 0, 300, 900, and 2700 mg/L [Details on dosing regimen, NR] 55 M and 55 F/group (age, 6–7 wk)	No significant increase in tumor incidence observed in any of the treated groups	NS
JMPR	2006	Glyphosate. In: Joint FAO/WHO Meeting on Pesticide Residues. Pesticide residues in food – 2004: toxicological evaluations. Report No. WHO/PCS/06.1. Geneva	Rat, Wistar-Alpk:APfSD (M, F) 1 yr	Diet containing glyphosate (purity, 95.6%) at concentrations of 0, 2000, 8000, or 20 000 ppm, ad libitum, for 1 yr 24 M and 24 F/group [age, NR]	No significant increase in tumor incidence observed in any groups of treated animals	NS

JMPR	2006	Glyphosate. In: Joint FAO/WHO Meeting on Pesticide Residues. Pesticide residues in food – 2004: toxicological evaluations. Report No. WHO/PCS/06.1. Geneva	Rat, Sprague-Dawley (M, F) 104 wk	Diet containing glyphosate (purity, 98.7–98.9%) at doses of 0, 10, 100, 300, or 1000 mg/kg bw, ad libitum, for 104 wk 50 M and 50 F/group [age, NR]	No significant increase in tumor incidence observed in any groups of treated animals	NS
JMPR	2006	Glyphosate. In: Joint FAO/WHO Meeting on Pesticide Residues. Pesticide residues in food – 2004: toxicological evaluations. Report No. WHO/PCS/06.1. Geneva	Rat, Wistar-Alpk:APfSD (M, F) 24 mo	Diet containing glyphosate (purity, 97.6%) at concentrations of 0, 2000, 6000, or 20 000 ppm, ad libitum, for 2 yr 52 M and 52 F/group [age, NR]	No significant increase in tumor incidence observed in any groups of treated animals	NS

EPA	1991 A,B,C,D	Rat Sprague-Dawley (M, F) 24 mo	Diet containing glyphosate (technical grade; purity, 96.5%) at concentrations of 0, 2000, 8000, or 20 000 ppm, ad libitum, for 24 mo 60 M and 60 F/group (age, 8 wk) 10 rats/group killed after 12 mo	Males Pancreas (islet cell): Adenoma: 1/58 (2%), 8/57 (14%)*, 5/60 (8%), 7/59 (12%) Carcinoma: 1/58 (2%), 0/57, 0/60, 0/59 Adenoma or carcinoma (combined): 2/58 (3%), 8/57 (14%), 5/60 (8%), 7/59 (12%) Liver: Hepatocellular adenoma: 2/60 (3%), 2/60 (3%), 3/60 (6%), 7/60 (12%) Hepatocellular carcinoma: 3/60 (5%), 2/60 (3%), 1/60 (2%), 2/60 (3%) Females Pancreas (islet cell): Adenoma: 5/60 (8%), 1/60 (2%), 4/60 (7%), 0/59 Carcinoma: 0/60, 0/60, 0/60, 0/59 Adenoma or carcinoma (combined): 5/60 (8%), 1/60 (2%), 4/60 (7%), 0/59 Thyroid: C-cell adenoma: 2/60 (3%), 2/60 (3%), 6/60 (10%), 6/60 (10%) C-cell carcinoma: 0/60, 0/60, 1/60, 0/60	Adenoma, * $P \leq 0.05$ (Fisher exact test with Bonferroni inequality); see comments Adenoma, P for trend = 0.016; see comments NS Adenoma, P for trend = 0.031; see comments

EPA	1991 a,b,c,d	Second peer review of glyphosate Glyphosate; 2-year combined chronic toxicity/carcinogenicity study in Sprague-Dawley rats - List A pesticide for reregistration. Document No. 008390. Peer review on glyphosate. Document No. 008527. Glyphosate – EPA registration No. 524–308 – 2-year chronic feeding/oncogenicity study in rats with technical glyphosate. Document No. 008897.	Rat Sprague-Dawley (M, F) Lifetime (up to 26 mo)	Diet containing glyphosate (purity, 98.7%) at concentrations of 0 ppm, 30 ppm (3 mg/kg bw per day), 100 ppm (10 mg/kg bw per day), 300 ppm (31 mg/kg bw per day), ad libitum, up to 26 mo 50 M and 50 F/group [age, NR]	Males Pancreas (islet cell): Adenoma: 0/50 (0%), 5/49* (10%), 2/50 (4%), 2/50 (4%) Carcinoma: 0/50 (0%), 0/49 (0%), 0/50 (0%), 1/50 (2%) Adenoma or carcinoma (combined): 0/50 (0%), 5/49 (10%), 2/50 (4%), 3/50 (6%) Females Pancreas (islet cell): Adenoma: 2/50 (4%), 1/50 (2%), 1/50 (2%), 0/50 (0%) Carcinoma: 0/50 (0%), 1/50 (2%), 1/50 (2%), 1/50 (2%) Adenoma or carcinoma (combined): 2/50 (10%), 2/50 (2%), 2/50 (74%), 1/50 (2%)	Adenoma, *[P < 0.05; Fisher exact test] NS

TABLE 3A. STUDIES OF DIRECT EXPOSURE TO GLYPHOSATE-BASED FORMULATION IN HUMANS (Cited in IARC Monograph 112)

Author	Year(s)	Title	Cell type	End-point	Test	Description of exposure and controls	Test results/ Significance
Paz-y-Miño et al.	2007	Evaluation of DNA damage in an Ecuadorian population exposed to glyphosate	NA	DNA damage	DNA strand breaks, comet assay	24 exposed individuals in northern Ecuador, areas sprayed with glyphosate-based formulation (sampling 2 weeks to 2 months after spraying); control group was 21 non-exposed individuals	+/ P<0.001

Paz-y- Miño et al.	2011	Baseline determination in social, health, and genetic areas in communities affected by glyphosate aerial spraying on the northeastern Ecuadorian border	NA	Chromosomal damage	Chromosomal aberrations	92 individuals in 10 communities, northern border of Ecuador; sampling 2 years after last aerial spraying with herbicide mix containing glyphosate); control group was 90 healthy individuals from several provinces without background of smoking or exposure to genotoxic substances (hydrocarbons, X-rays, or pesticides)	-
Bolognesi et al.	2009	Biomonitoring of genotoxic risk in agricultural workers from five Colombian regions: association to occupational exposure to glyphosate	Lymphocytes	Chromosomal damage	Micronucelus formation	55 community residents, Nariño, Colombia; area with aerial glyphosate-based formulation spraying for coca and poppy eradication (glyphosate was tank-mixed with an adjuvant)	+ / P<0.001 *p-value for after spraying vs. before spraying in the same individuals
						53 community residents, Putumayo, Colombia; area with aerial glyphosate-based formulation spraying for coca and poppy eradication (glyphosate was tank-mixed with an adjuvant)	+ / P=0.01 *p-value for after spraying vs before spraying in the same individuals
						27 community residents, Valle del Cauca, Colombia; area where glyphosate-based formulation was applied through aerial spraying for sugar-cane maturation (glyphosate was applied without adjuvant)	+ / P<0.001 *p-value for after spraying vs before spraying in the same individuals

TABLE 3B. STUDIES OF GLYPHOSATE, AMPA, AND GLYPHOSATE–BASED FORMULATIONS EXPOSURE TO HUMAN CELLS IN VITRO (Adapted from IARC Monograph 112)

Author	Year(s)	Title	Tissue, cell line	End-point	Test	Results		Dose (LED or HID)	Significance
						Without metabolic activation	With metabolic activation		
GLYPHOSATE									
Mañas et al.	2009a	Genotoxicity of glyphosate assessed by the comet assay and cytogenetic tests	Liver Hep-2	DNA damage	DNA strand breaks, comet assay	+	NT	3mM [507.2 µg/mL]	P <0.01
Mladinic et al.	2009b	Evaluation of genome damage and its relation to oxidative stress induced by glyphosate in human lymphocytes in vitro.	Lymphocytes	DNA damage	DNA strand breaks, standard and hOGGI modified comet assay	+	+	3.5 µg/mL	P <0.01 (with hOGGI modified comet assay. + S9 at highest dose tested (580 µg/mL)
Alvarez-Moya et al.	2014	Comparison of the in vivo and in vitro genotoxicity of glyphosate isopropylamine salt in three different organisms.	Lymphocytes	DNA damage	DNA strand breaks, comet assay	+	NT	0.00007 mM [0.12 µg/mL]	P≤0.01
Monroy et al.	2005	Cytotoxicity and genotoxicity of human cells exposed in vitro to glyphosate	Fibroblast GM 38	DNA damage	DNA strand breaks, comet assay	+	NT	4mM [676 µg/mL]	P <0.01

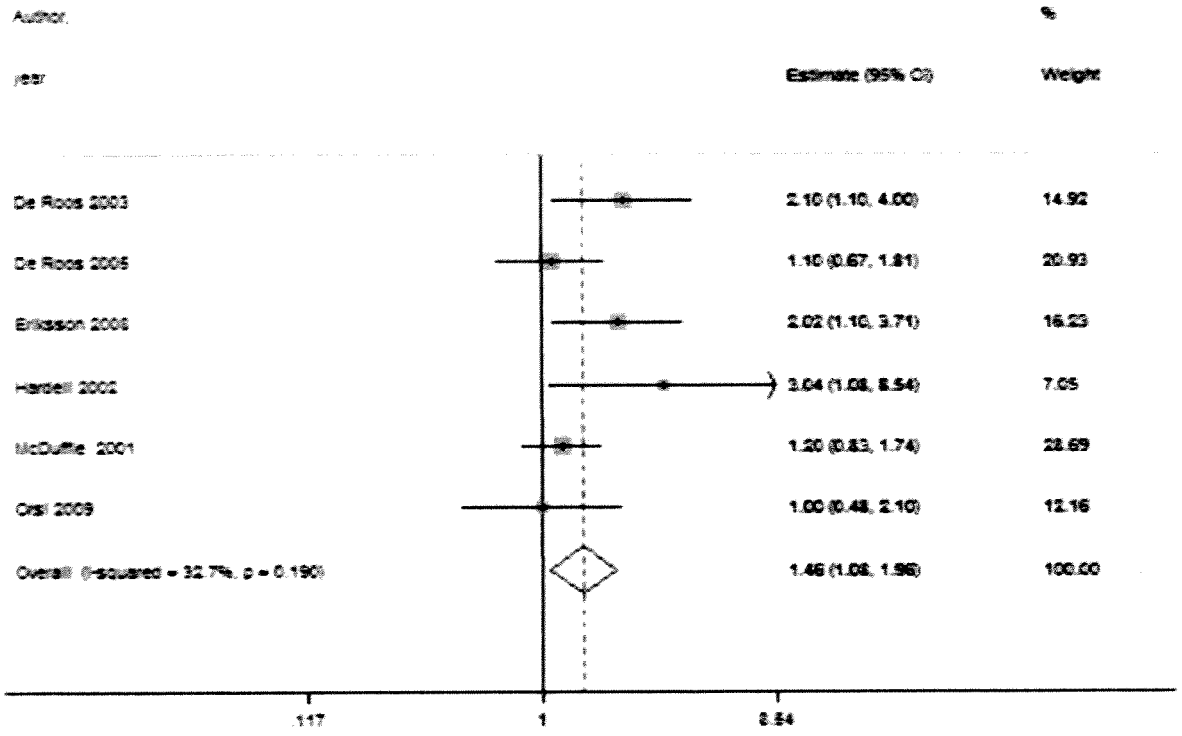
Lueken et al.	2004	Synergistic DNA damage by oxidative stress (induced by H2O2) and nongenotoxic environmental chemicals in human fibroblasts	Fibroblast GM 5757	DNA damage	DNA strand breaks, comet assay	+	NT	75 mM [12,680 µg/mL]	Not Reported
Monroy et al.	2005	Cytotoxicity and genotoxicity of human cells exposed in vitro to glyphosate	Fibrosarcoma HT1080	DNA damage	DNA strand breaks, comet assay	+	NT	4.75 mM [803 µg/mL]	P<0.001
Koller et al.	2012	Cytotoxic and DNA-damaging properties of glyphosate and Roundup in human-derived buccal epithelial cells	Buccal carcinoma TR146	DNA damage	DNA strand breaks, SCGE assay	+	NT	20 µg/mL	P≤0.05, dose-dependent increase
Mañas et al.	2009a	Genotoxicity of glyphosate assessed by the comet assay and cytogenetic tests	Lymphocytes	Chromosomal damage	Chromosomal aberrations	-	NT	6 mM [1015 µg/mL]	Not Significant
Mladinic et al.	2009a	Characterization of chromatin instabilities induced by glyphosate, acetochlor and carbofuran using cytome FISH assay	Lymphocytes	Chromosomal damage	Micronucleus formation	-	+	580 µg/mL	P <0.01 at highest exposure + S9
Bolognesi et al.	1997	Genotoxic activity of glyphosate and its technical formulation Roundup	Lymphocytes	Chromosomal damage	Sister-chromatid exchange	+	NT	1000 µg/mL	P < 0.05
AMPA									

Mañas et al.	2009b	Genotoxicity of AMPA, the environmental metabolite of glyphosate, assessed by the Comet assay and cytogenetic tests.	Liver Hep-2	DNA damage	DNA strand breaks, comet assay	+	NT	4.5 mM [500µg/mL]	P < 0.05 at 4.5 mM; P < 0.01 at up to 7.5 mM Dose-reponse relationship (p<0.05)
Mañas et al.	2009b	Genotoxicity of AMPA, the environmental metabolite of glyphosate, assessed by the Comet assay and cytogenetic tests.	Lymphocytes	Chromosomal damage	Chromosomal aberrations	+	NT	1.8 mM [200 µg/mL]	P <0.05
GLYPHOSATE-BASED FORMULATIONS									
Gasnier et al.	2009	Glyphosate-based herbicides are toxic and endocrine disruptors in human cell lines	Liver Hep-2	DNA damage	DNA strand breaks, comet assay	+	NT	5ppm	Not Reported
Koller et al.	2012	Cytotoxic and DNA-damaging properties of glyphosate and Roundup in human-derived buccal epithelial cells	Buccal carcinoma TR146	DNA damage	DNA strand breaks, SCGE assay	+	NT	20 µg/mL	Dose-dependent increase (P≤0.05)

Vigfusson & Vyse	1980	The effect of the pesticides, Decon, Captan and Roundup, on sister-chromatid exchanges in human lymphocytes in vitro	Lymphocytes	Chromosomal damage	Sister-chromatid exchange	+	NT	250 µg/mL	P < 0.001
Bolognesi et al.	1997	Genotoxic activity of glyphosate and its technical formulation Roundup	Lymphocytes	Chromosomal damage	Sister-chromatid exchange	+	NT	100 µg/mL	P < 0.05

AMPA, aminomethyl phosphonic acid; HID, highest ineffective dose; hOGG1, human 8-hydroxyguanosine DNA-glycosylase; LED, lowest effective dose; NR, not reported; NT, not tested;
S9, 9000 × g supernatant; SCGE, single cell gel electrophoresis; vs, versus

FIGURE 1. FOREST PLOT FOR GLYPHOSATE/NHL – SHINASI & LEON, 2014



(D)

Figure D. (Schinasi & Leon, 2014)Forest plots showing estimates of association between non-Hodgkins Lymphoma and occupational, agricultural exposure to (**D**) glyphosate.

FIGURE 2. FOREST PLOT – CHANG & DELZELL, 2016

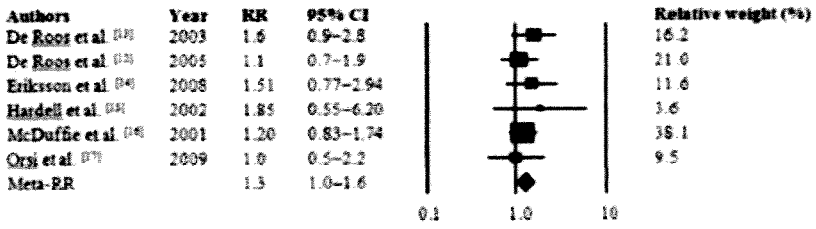


Figure 1. Forest plots of relative risk (RR) estimates and 95% confidence intervals (CIs) for the association between glyphosate exposure and risk of non-Hodgkin lymphoma. Meta-RRs were identical in random-effects and fixed-effects models.

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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

IN RE: ROUNDUP PRODUCTS LIABILITY LITIGATION	MDL No. 2741 Case No. 16-md-02741-VC
This document relates to: ALL ACTIONS	

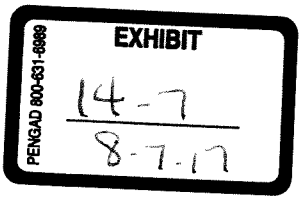
EXPERT REPORT OF DR. BEATE RITZ, M.D., Ph.D.

IN SUPPORT OF GENERAL CAUSATION

ON BEHALF OF PLAINTIFFS

1. Beate Ritz, MD, PhD, Background and Qualifications

I, Beate Ritz, MD, Ph.D., am Professor of Epidemiology at the UCLA Fielding School of Public Health, former Chair of the Epidemiology Department, and I hold co-appointments in Environmental Health Sciences and Neurology at the UCLA, School of Medicine. I was trained in Medicine at the University of Hamburg/Germany and received a doctoral degree from the University of Hamburg in Medical Sociology in 1986. I furthermore received another doctoral degree in Epidemiology from UCLA in 1995, and subsequently was hired as a faculty at UCLA. My faculty appointment at UCLA is one of several positions specifically assigned to the Center of Occupational and Environmental Health (COEH) mandated by the State of California to conduct research, teaching, and service to communities in California on occupational and environmental health issues. Hence, my primary research interests are health effects from occupational and environmental exposures with a focus on pesticides and air pollution and chronic diseases including cancers, reproductive outcomes, neurodevelopmental disorders and neurodegenerative diseases. I served for more than a decade as the co-director of the NIEHS-



funded UCLA Center for Gene-Environment Studies in Parkinson's disease (PD) and am currently the Director of the American Parkinson's Disease Association Center for Excellence in PD Research. In the past two decades, I was the principal investigator of numerous Parkinson's disease, pesticides and gene-environment epidemiology studies in California and also conducted research based on large databases (such as cancer registries) assembled in California and Denmark. As part of my research, I developed geographic information system (GIS) based exposure assessment tools to assess chronic health effects of long-term pesticide exposures and of air pollution in California. In the early 2000s, I served as a member of the external advisory committee for the NCI/NIEHS Agricultural Health Cohort Study and for one year chaired this committee. I also was a visiting scientist at IARC/Lyon in 2006-07. In 2007, I received the Robert M. Zweig M.D. Memorial Award (Clean Air Award) from the California South Coast Air Quality Management District and in 2008 I was awarded the "Excellence in Research" award from the American Parkinson's Disease Association. I served on multiple National Academy of Sciences/Institute of Medicine (NAS/IOM) committees evaluating Gulf War Illness – including IOM reviews of cancer and of amyotrophic lateral sclerosis (ALS). Recently, I served on the NAS/IOM committee on "Incorporating 21st Century Science into Risk-Based Evaluations" and I just newly began serving on the committee to assess "Health Effects in Vietnam Veterans from Agent Orange (herbicides)". I am a CA Governor appointed member of the scientific review board for the California Air Resources Board (CARB) panel on Air Toxics. I served on the editorial Board of the Journal *Epidemiology* as well as other journals (currently I am editing a section of the journal *Current Environmental Health Reports*) and I am the newly elected President Elect of the International Society for Environmental Epidemiology (ISEE). My Curriculum Vitae is attached as Exhibit A. A list of the materials I have reviewed, in addition to those set forth in my CV, are attached as Exhibit B. Exhibit C contains my billing rate and prior testimony.

2. Methodology

2.0 Definitions of statistical and methodological terms.

(Population-based) Case-control study. A case-control study is a study where the subjects are selected for inclusion based on their disease status. In other words, study subjects referred to as

cases are enrolled because they have the disease (in this case, NHL) and controls are subjects who at the time the cases are diagnosed are not afflicted by the disease of interest; additionally, a study is considered population-based if the controls are selected without bias from the same population from which all cases arose. After study enrollment, everyone is either asked to report their past exposures (in this case, glyphosate or Roundup) or – if possible – exposures are reconstructed from a record system (e.g. sales records or application records) or by experts who evaluate job tasks and titles among all study participants (generally referred to as a job exposure matrix).

Cohort study. In a cohort study, subjects are enrolled in the study based on their exposures (in this case, to glyphosate or Roundup), and followed over time to determine who develops the disease(s) of interest. At enrollment, all participants are asked to report their past exposures or exposure is reconstructed from records, basically similar as in the case-control study, except that at enrollment no study participant is allowed to suffer from the disease of interest yet i.e. at the time of exposure assessment. In some cohorts, exposure is only assessed at enrollment (baseline) while in others exposures continue to be assessed throughout follow-up until disease occurs.

Odds Ratio (OR). An odds ratio, or OR, is a measure of association between an exposure and a disease. It represents the odds that the disease will occur in a group of people given a particular exposure, in comparison to the odds of the disease in a group of people without the exposure. An OR of 1.00 is the null, meaning no effect. Thus, an OR of 1.40 as reported in one of the studies below, for example, represents a 40% increase in NHL from exposure to glyphosate. An OR of 3.10 in one of the studies below represents a 210% increase in the odds of NHL from exposure to glyphosate. An odds ratio is a "point estimate" or the 'central' estimate of the relationship between exposure and disease, in a given study (note: the OR is in the center of the upper and lower confidence limit boundaries, see below). Odds Ratios are the statistics that are used most often to analyze case-control studies, and they are often calculated using a statistical technique called logistic regression but can also be derived by simple calculations based on a 2x2 table of data.

Rate Ratio (RR). A rate ratio is the measure of association between exposure and disease that can be calculated from cohort study data. It compares the incidence rates of disease given an exposure, to the incidence rate of disease among people without the exposure. The incidence rate allows us to take time into account and may depend on how much time has passed from the start of the study until the point in time when disease is diagnosed (or until the end of the study), thus it not only uses information based on persons but based on person times time under observation (also known as 'persontime'). Therefore, a RR different from an OR inherently relies on measures that included time under observation (i.e. rates). However, the results are interpreted in the same way: a RR of 1.00 is the null (no effect); a RR of 1.40 is a 40% increase in the rate of disease, etc.

Risk Ratio (or Relative Risk) is a ratio of the risk in the exposed divided by the risk in the unexposed in a cohort - where risks are defined as the number of (un)exposed cases divided by the total number of (un)exposed. Thus, different from rate ratios, this measure uses the number of subjects rather than the number of person-years a subject contributes during follow-up as the denominator. This method is used for well-defined (similar length) follow-up periods in the exposed and the unexposed such that the time under observation will not contribute additional information and we can substitute persons for person-time.
NOTE: under certain circumstances often met especially for rare diseases, the odds ratio (OR), risk ratio (RR) and rate ratio (RR) are the same (albeit calculated as the ratio of odds, risks, or rates) and the interpretation of the estimates is also the same.

P-value. The p-value is the probability of obtaining an estimate at least as far from a pre-specified value (in case of the null hypothesis the 'null' value) as the estimate we have obtained, if the specified value were the true value (note: no p-value, for the null hypothesis or any other hypothesis, is the probability that the specified hypothesis is true). For example, a p-value of 0.04 means that, given the null hypothesis is true, if you repeatedly conducted 100 tests of samples drawn from the same population (people), then in 4% of your tests, you would obtain the results you got solely due to random error (chance). It is a metric intended to show the likelihood of random error. It *should not* be interpreted as the probability that an agent causes an outcome.

Confidence interval (CI). A confidence interval, or CI, is given around an OR or a RR to give the likely interval which potentially includes the unobservable true measure of effect. In other words, it is an interval estimate (as compared to a point estimate) of the true underlying relationship between exposure and disease, in a given study. In practice, most published estimates are 95% confidence intervals, which means that in 95 out of 100 times when sampling your study subjects, you will find the true result (effect estimate) within the given confidence interval.

Hierarchical regression is a type of statistical analysis that was used in the 2003 De Roos study.[1] It is used when there are many correlated exposures and as a means to adjust for multiple comparisons. In De Roos, there were many different pesticides used by farmers and pesticide applicators, and therefore use of one pesticide can be strongly correlated with the use of another pesticide. For example, imagine glyphosate is often used together with another pesticide, dicamba. If the Odds Ratio that is reported between glyphosate and cancer is 2.0, then dicamba –assuming it is mostly used together with glyphosate – would be a proxy for glyphosate exposure and its OR would also be close to 2.0, just because these pesticides tend to be used together even if dicamba is not a carcinogen. However, if both pesticides truly increase risk (both are carcinogens) and we put them into the same (regression) model, we would not be able to estimate their effects properly, since they would now both have an attenuated effect estimate (this is also referred to as correlated variables 'stealing variance from each other'). De Roos used hierarchical regression to tease apart such correlations in order to determine which pesticides are the ones that are driving increases in NHL and narrow down the long list of pesticides to find the "bad actors" which were increasing risk of NHL. But, this approach makes a number of assumptions, for example that either all pesticides considered or pesticides within certain groups have similar effects on the outcome which might be incorrect.

N (number). The number of people in a study.

Statistical power is the ability of a study to estimate an effect. In essence, it is a reflection of the sample size (number of subjects in a study – in cohorts also the number of cases), the prevalence

of exposure, and the expected effect size. Large sample sizes give us generally higher statistical power, which means they have narrower and more stable confidence intervals around point estimates. Smaller sample sizes have wider confidence intervals. Thus, larger studies are much more able to find statistically significant results especially when exposures or outcomes are rare and the expected size of the effect moderate or small in size.

Data pooling or pooled analysis. To pool data is to use the raw (un-analyzed or non-summarized) data from several studies and merge them together to conduct analyses. Data pooling is often done when there have been multiple small studies on a topic, because the pooling allows for larger sample sizes and a uniform approach to the analysis of the pooled data. In order to conduct data pooling, scientists need to have permission to access the data from the investigators of multiple studies. Pooled studies have greater statistical power than the original studies from which they draw.

Meta-analysis. In some instances, scientists are interested in pooling data but do not easily have access to the raw data from each study. This is, typically, because the studies were conducted many years earlier, or perhaps because the investigators do not know/trust each other or human subject restrictions do not allow for the sharing of raw data; it is quicker and more efficient to conduct a meta-analysis based on summary estimates from published reports. A meta-analysis uses the Odds Ratios or Rate Ratios and confidence intervals which were published in the original studies, and comes up with a summary estimate of the relationship between exposure and disease. Similar to pooled analyses, meta-analyses also have much greater statistical power than each study does on its own, but the authors do not have the option of re-analyzing the original data as could be done if raw data were available (such as lagging exposures or generating different exposure categories etc.).

Null hypothesis means no effect. In the studies described below, their null hypothesis was that NHL is not related to glyphosate/Roundup exposure. The statistical tests done in the studies described below aim to test the null hypothesis: they want to determine if there the null hypothesis can be rejected with adequate statistical certainty and whether they can determine

whether there any relationship between exposure to glyphosate/Roundup and the development of NHL is suggested by a study.

A Forest Plot is a visual representation of the main results of all studies on a topic. The purpose of grouping them all together visually is that it can give the reader a sense of overall size of the effect estimates and the direction of the associations in the existing literature. See pg. 14.

Dose-response. A dose-response association represents an increasing risk with an increasing dose, such as a larger number of days per year, or a longer number of years, being related to higher Odds Ratios. For example, the overall study Odds Ratio might be 1.40, but for people who used glyphosate more often, the Odds Ratio was 2.5 while for those using it less often it might have been 1.5. This is a sign of a dose-response effect.

Incident/incidence refers to newly diagnosed cases; while prevalent cases are any existing cases at any point in time or over a certain period in time.

Confounding is a bias that occurs because a risk factor for the outcome is also a cause or precursor of the exposure of interest such that the outcome is caused by this confounder and not by the exposure one is trying to assess. For example, if sex is a risk factor for NHL and sex is also associated with occupational exposure to pesticides, we would want to adjust all effect estimates for pesticides by sex to remove potential confounding bias.

Recall bias is one type of exposure misclassification that is considered 'differential' by epidemiologists. This means that cases and controls remember or report past exposures differently because they have or do not have the disease. Generally, it has been suggested that cases may put more effort into recalling exposures since they have a need to explain their disease or are more motivated to do so to help researchers while controls are less motivated to recall past exposures. However, this is most likely a problem if the diseased subject knows or suspects an agent to cause their disease. If the subject has no way to know which pesticide might have caused a cancer for example and is asked to report all chemicals they have ever used occupationally, it is unlikely that they would only recall one and not another chemical

differentially. Thus, if recall bias existed, we would expect all pesticides they reported to the researchers to show an association with the outcome and not just one amongst many, since the tendency to recall better or more exposures than controls would not be expected to be specific to one chemical. In fact, when recall has been compared with record based evaluations, differential recall that causes recall bias has generally not been shown to be a problem. *Note:* non-differential recall error such that both cases and controls misreport their exposures is known to cause mainly bias towards the null i.e. masking any true effect rather that enhancing them. These recall biases are one type of information bias (see below).

Other biases include information bias which is characterized as mismeasurement of exposures or outcomes which can severely distort results in both case-control and cohort studies. As long as mismeasurement is non-differential (see above) i.e. the same for cases and controls or for exposed and unexposed, such biases most often cause underestimation of true effect sizes i.e. bias results towards the null that can be severe. Finally, there is selection-bias if controls are not representative of the exposures in the population that gave rise to the cases in case-control studies, or when there is a large and differential (with regard to case status) loss to follow-up in cohort studies.

2.1 Literature search

To obtain all published studies on the relationship between non-Hodgkin's Lymphoma (NHL) and glyphosate (the active ingredient in Roundup), I undertook a literature search using the same method to search for articles that I normally use in my research. This is the same method that I teach my UCLA students to use. As such, I relied upon two search engines, PubMed (https://www.ncbi.nlm.nih.gov/pubmed) and Google Scholar (https://scholar.google.com/). PubMed is an excellent resource for finding papers on the exact topic one is interested in, but it does not do as well in finding papers which were largely about a different topic but may have also briefly reported on the topic of interest. Google Scholar does well in capturing every possible paper of interest, but will often provide many articles not relevant to the subject matter at hand. I use both search engines to be as thorough as possible, but also to identify the most relevant articles. These searches initially yielded 290 articles in PubMed and 9000+ articles in Google Scholar for epidemiological studies; and over 550 articles for

animal and mechanistic literature; and over 600 citations for cancer. [Most citations were not immediately relevant to the present question, due to their focus on topics such as effects in fish resulting from runoff; effects on pregnancy and child development; or effects on other cancer types.]

As is typical in most published meta-analyses and reviews, I took additional steps to ensure I did not miss any relevant articles by also reviewing other published papers to check their citations. For these, I relied on the IARC Glyphosate Monograph as well as the two meta-analyses on glyphosate and NHL, as well as other articles on the topic that were published more recently.[2-4]

Furthermore, I read the US EPA's Cancer Assessment Review Committee (CARC) report, however I disagreed with their results because they relied heavily on statistical significance in studies that were not sufficiently statistically powered to answer the question (more on this below).

2.2 Reliance on peer-reviewed literature

As I teach my students, the most relevant articles, and indeed the only articles I nearly ever review and cite in my own research, are those that have gone through peer review at a reputable journal. Each field has its own journals considered reputable; but in general, a reputable journal is a journal that is listed in the most well-known and respected indexing sources such as PubMed.[i] Typically, these journals have been published for many years and many are backed by well-recognized and respected medical or research non-profit organizations, such as the American Medical Association, the British Medical Association, the American Association for Cancer Research (AACR), the Union for International Cancer Control (UICC), or the American Cancer Society.

Peer review, as defined by Danzik, is "a system by which manuscripts submitted for publication are evaluated, using outside referees (peers), who comment on the manuscripts' merit, originality, significance, and appropriateness to the journal. The intent is to identify flaws

[i] PubMed is a service of the US National Institutes of Health (NIH). On their website (https://www.nlm.nih.gov/pubs/factsheets/j_sel_faq.html) they explain that NIH uses a committee, the Literature Selection Technical Review Committee, to review and recommend which biomedical and health- related life science journals are included. Criteria include relevant subject matter as well as journals that meet PubMed Central's scientific quality standard, described as "scientific and editorial character and quality of a journal."

in design and analysis or interpretation, to suggest improvements, to direct manuscripts to the most appropriate outlets, to discourage repetition in publishing, and to weed out poor science or scholarship."[5]

Independent peer review is the cornerstone of science in the United States and internationally, and has formed the basis for what is considered acceptable and reliable medical and scientific research. The peer review process, which is almost always done anonymously (the reviewer is nearly always anonymous, although the authors are usually not) provides the intellectual rigor required to ensure that manuscripts adhere to what is acceptable in the field with regards to reviewing the relevant literature, and examining the statistics, and determining whether research protocols apply widely accepted methods, report valid results and avoid or account for biases, and draw conclusions appropriate to the study's findings. Peer reviewers are responsible for deciding whether an article is acceptable for publication. Because of this, authors typically will first, only submit their best work; and secondly, authors have to respond to reviewer critiques and be willing to make changes as requested or argue against suggested changes if there is a compelling reason to not do so which must be explained and justified to and accepted by the journal editors. I have personally peer reviewed on hundreds of occasions and for more than 20 different journals. I have also served on the editorial boards of three journals: Epidemiology, Epidemiologic Perspectives and Innovations, and Environmental Health.

The system of peer review has been in practice for decades. Although it is not without imperfections, the revisions that are suggested improve the quality of published manuscripts, it heads off potential fraud, and its existence encourages honest and state-of-the-sciences work.[5]

It is usual that peer reviewers will assemble comments for the editors who will communicate these and the editor's own comments to the authors as requests for clarification and additional information with the intention to not only improve the manuscript but most importantly to allow them to assess research validity. When any validity issues spotted during the review process cannot be addressed sufficiently by the authors in their responses and/or a revised manuscript, the editor may decide that the manuscript is not ready for publication.

2.3 Conflicts of interest.

There have been several systematic reviews published on the role of conflicts of interest in medical research. In 2003, a review of 1140 original studies reported a strong relationship

between industry sponsorship and pro-industry conclusions, with industry-sponsored studies more than 3 times as likely to find conclusions sympathetic to industry [pooled Odds Ratio (OR): 3.60, 95% Confidence Interval (CI), 2.63-4.91].[6]

Similarly, a 2016 article in the British Medical Journal (BMJ), which analyzed the results of 190 clinical trials published in 2013, reported that the presence of a financial tie between study investigators and industry resulted in a threefold increase in a positive study result (OR=3.23, 95% CI 1.7-6.1).[7]

As these reviews show, and as is widely recognized across the medical and research communities, industry sponsorship and financial incentives are unequivocally related to study findings. For this reason, journals have increasingly required that investigators report conflicts of interest when they submit articles, and these conflicts are published for the reader to see and to take into account when drawing conclusions as to the verity of the findings or the interpretation of the presented data. This information is also made available to journal reviewers, because it may influence the choice to recommend a manuscript for publication i.e. it may contribute to assessing scientific validity of the reported research. Furthermore, this is what I as a professor teach my students, and UCLA teaches to students in bioethics courses and lectures.

I performed an analysis of the data contained in the literature review of Williams, et al. (2016) and provide my opinions on that and other data throughout this report. There is a clear conflict of interest with several of the authors, and my review of the Dr. William Heydens and Dr. John Acquavella transcripts shows that some of the authors failed to properly disclose these conflicts. Therefore, I put less weight on this group's conclusions since it suggests they lack an ability to be impartial.

2.4 Statistical significance.

If we start off a study assuming that there is no association between glyphosate/Roundup and NHL (the "null hypothesis"), then, after we do our statistical analysis, we can determine the p-value for the null hypothesis of our findings, which is the probability of obtaining an estimate at least as far from a pre-specified value (the null value in case of the null hypothesis) as the estimate we have obtained, if that specified value were the true value (note: no p-value, for the null hypothesis or any other, is the probability that the specified hypothesis is true). There is a convention to consider a $p<0.05$ as "statistically significant" however, this is simply a

convention which is sometimes replaced by other p-values such as $p<0.01$ or $p<10^{-7}$ (in genomic studies). What a p-value of 0.04 actually means is that, given the null hypothesis is true, if you repeatedly conducted 100 tests of samples drawn from the same population (people), then in 4% of your tests, you would obtain the results solely due to random error (chance). It is a metric intended to show the likelihood of random error. It *should not* be interpreted as the probability that glyphosate/Roundup causes NHL. Moreover, if $p>0.05$, this doesn't "prove" the null hypothesis; absence of proof is not proof of absence.

Similarly, when a (95%) confidence interval excludes 1.0 (such as OR=2.0, 95% CI=1.2-2.8) – because 1.0 (the null value) is outside of the confidence interval-- it would be considered "statistically significant". As with p-values, confidence intervals can be defined as 95% intervals or 90% or 80% etc. intervals. However, confidence intervals provide additional information that p-values do not provide, and this information is related to the precision of the estimates or what is also called the informativeness of the data. In practice, p-values and confidence intervals close to the null (for example, if one side of the confidence interval is between 0.9 to 1.1) are considered marginal in terms of significance. Importantly, however, the estimates least influenced by chance are not those with low p-values, but those with narrow confidence intervals.

Statistical significance testing has been widely used and often misused in the medical literature, and is use has thus been widely criticized. One journal now bans the use of all statistical tests and even confidence intervals.[8] In the last decade, there has been considerable debate on the merits and problems of significance testing,[9-29] and in many Schools of Medicine and Public Health such as UCLA, students have been taught for decades to not rely upon statistical significance to draw their conclusions in accordance with the writings of the faculty member Dr. Sander Greenland, an author of the most widely used textbook in Epidemiology Methods entitled "Modern Epidemiology."[30] At UCLA, we teach students to focus on the point estimate (e.g. the Odds Ratio or Rate Ratio) as a measure of the size of the association between exposure and disease and the confidence interval to gage the precision of this estimate and the informativeness of the data/study.

Also important to consider is the rarity of the disease, because the rarer a disease, the harder it is for a scientist to create a large enough study with enough cancer cases enrolled to have adequate statistical power. Cancer is by its nature a rare disease. The annual incidence rate

(number of new cases) of NHL is 19.7 cases per 100,000 people. This is why it is so hard to study NHL with a cohort study design, because you would have to follow hundreds of thousands of people for many years in order to find any result that would give us a $p<0.05$ if we assume that the effect estimate size is moderate (less 2). This is the main reason why most cancer studies are employing a case-control design which is much more efficient in terms of the necessary sample size for sufficient statistical power and in terms of costs in general.

Many of the case-control studies cited below in this review, particularly those that tried to recruit cases in rural areas, had a limited sample size simply because there are a finite number of cases of NHL in rural areas (with low population density). For example, the Nebraska study (which contributed to De Roos' pooled analysis) included 220 cases;[31] the Kansas study[32] included 200 cases. These are not large numbers, and the result is that we get wide confidence intervals, particularly when exposures are also rare (as they were in these two studies, with 6% of cases and 3% of controls reporting ever use of glyphosate).

As recognized by the US National Cancer Institute, wide confidence intervals are often seen in epidemiologic studies of rare diseases like NHL, but scientists are nonetheless encouraged to move forward and publish their results anyway. This is because smaller studies can later be used in pooled or meta-analyses, and those will have much improved statistical power to estimate precise effect estimates.

In addition, as we teach at UCLA, one study alone is never definitive. It is important for a reviewer to look at the information in the literature as a whole to understand relationships between exposure and disease. We teach students to consider point estimates (Odds Ratios) as indicators of associations and effect sizes, and to not dismiss or mis-interpret studies that have wide confidence intervals that may or may not include the null.

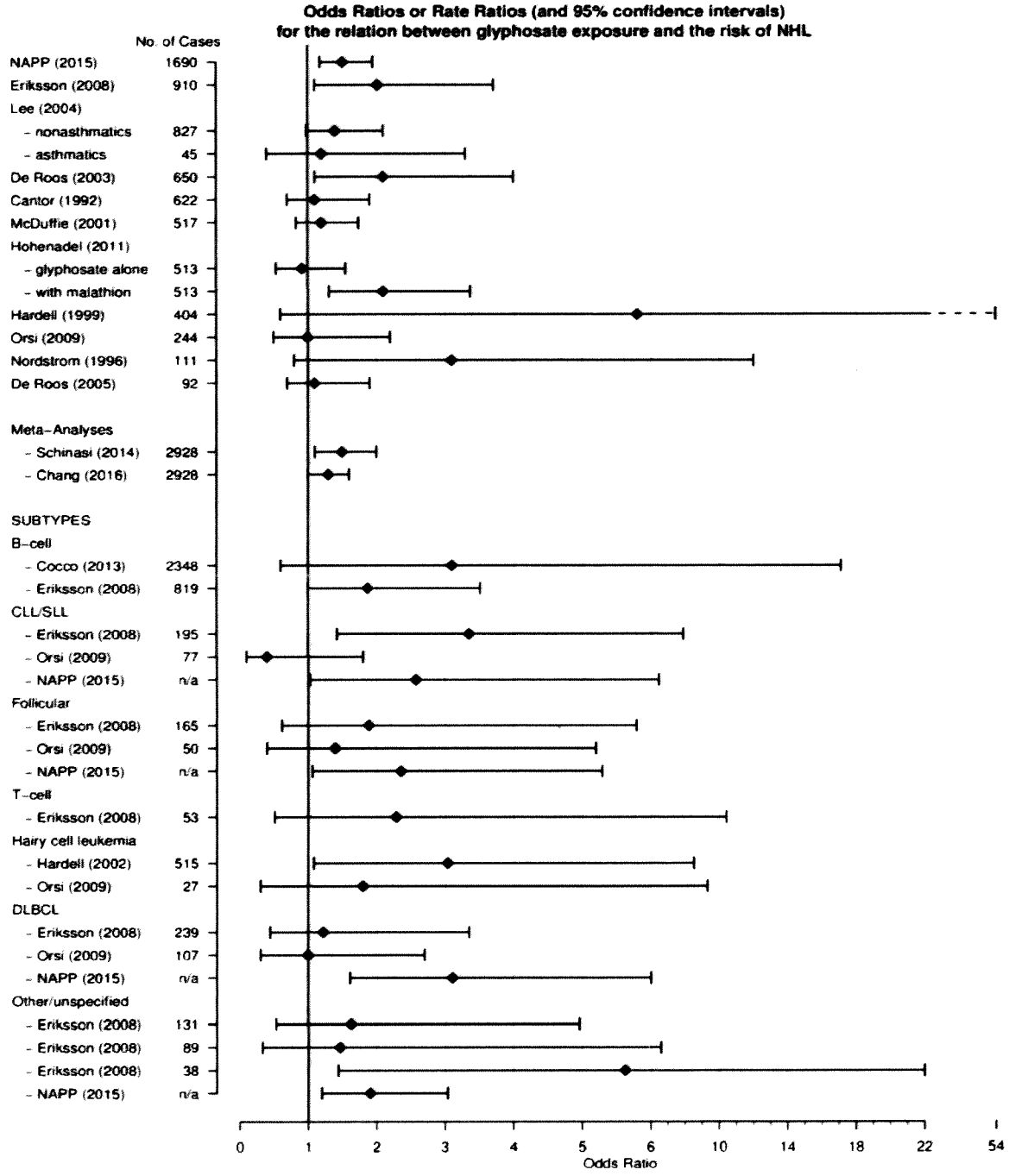
s2.5 Abstracts vs. full articles.

2.5 Abstracts vs. full articles.

Whenever possible it is preferable to examine and cite a full article over an abstract of the same study, because full articles have the space to provide a detailed overview of study methods and findings. If the full article is not yet published, however, it is common practice to cite abstracts.

3. Literature Review.

Here I summarize the findings of the epidemiologic studies on glyphosate and NHL in a forest plot, a graphical representation of all study results.



In reviewing the literature, the sample sizes and especially the number of cases should be noted, because of their bearing on 'statistical significance' and the width of confidence intervals. Because many of the smaller studies had suggestive findings but wide confidence intervals, it is particularly important to instead consider pooled and meta-analyses that summarize across these smaller studies and not only provide a much larger sample size but may allow us to assess NHL subtypes with sufficient precision. Here I show the sample sizes of each human study of glyphosate and NHL.

First author, date	Number of cases in the study (all NHL cases combined)	Number of controls in the study
Cocco, 2013	1869	2462
Pahwa, 2015 (commonly known as the NAPP study)	1690	5131
Eriksson, 2008	910	1016
Lee, 2004	872	2336
De Roos 2003	650	1933
Cantor, 1992	622	1245
McDuffie, 2001	517	1506
Hardell, 2002	515	1141
Hohenadel, 2011	513	1506
Hardell, 1999	404	781
Orsi, 2009	244	426
Nordstrom, 1996	111	400
De Roos, 2005 (commonly known as the AHS study)	92	(54223)*

* these are the N of unaffected cohort members, however we calculate person time and generally do not use person N in analyses.

Because sample size is so relevant in considering exposure-disease associations, an informative study to consider is Pahwa's pooled analysis of the North American and Canadian studies, the North American Pooled Project (NAPP).[33] This abstract was presented at the International Society for Environmental Epidemiology's annual conference, and hence was peer-

reviewed, as are all abstracts presented at this meeting. In this analysis of 1690 cases and 5131 controls, NAPP reported an elevated risk of all NHL with any glyphosate use (OR=1.51, 95% CI 1.18-1.95) and a dose-response effect was seen with greater use (>2 days/year, OR=2.66, 1.61-4.40). An OR of 2.66 means that glyphosate exposure increases the risk of developing NHL by more than 160%. With regards to NHL subtypes, increases were observed for small lymphocytic lymphoma (SLL; 2.58, 95% CI 1.03-6.48, among those using for more than 5 years), and for follicular lymphoma (OR=2.36, 95% CI 1.06-5.29), diffuse large B-cell lymphoma (DLBCL; OR=3.11, 95% CI 1.61-6.00), and other subtypes (OR=2.99, 95% CI 1.10-8.09) for use more than 2 days per year. These study results were published in 2014, and as such were not included in any of the meta-analyses.

There were three meta-analyses conducted on glyphosate and NHL. The first, by Schinasi and colleagues,[34] included 2928 cases from 6 studies[1,2,35-38] and reported increases in NHL risk with any glyphosate exposure (meta-RR: 1.5, 95% CI 1.1–2.0), similar to the results of the NAPP study. Particularly stronger increases were reported for B-cell lymphoma (meta-RR = 2.0, 95% CI 1.1-3.6). Notably, heterogeneity of study results was low, which means that the results across studies were highly consistent. This is important because it suggests that the increases in NHL risk were unlikely to be the result of random fluctuations of estimates across populations: when you see the same results in multiple studies across different settings, it improves confidence in the findings.

The IARC Working Group's Monograph on glyphosate[4] noted that the above meta-analysis did not always use the most "highly adjusted estimates" from each study. The most highly adjusted estimates (also known as "fully adjusted" models) are the estimates that adjust for as many confounding variables as possible, such as adjusting for age, sex, race, and also sometimes other pesticide exposures. This is relevant because it gives the reader confidence that the findings are most likely due to glyphosate/Roundup exposure, instead of another potential cause that acts as a confounder. As such IARC's Working Group conducted their own meta-analysis using solely the most highly adjusted estimates from the same studies,[1,2,35-38] and reported a meta risk-ratio of 1.3 (95% CI, 1.03–1.65), with consistent findings across studies (low heterogeneity). I concur with the IARC conclusions after conducting my own independent analysis of the studies included in the IARC review.

Also helpful to consider is the Swedish study by Eriksson,[2] which was large (N=910 cases) and in addition, this study examined cases diagnosed 1999-2002 and thus allowed for a longer time period to have elapsed between exposure and disease development (glyphosate first came on the market in 1974); this is known as the latency period between exposure and disease occurrence. Although a short latency period does not completely exclude the possibility of exposure-disease relationships in cancer, a longer latency period increases confidence in results due to increased biological plausibility i.e. typically we would generally expect a 5-10 year minimum latency between exposure and disease onset for blood system related cancers. (However, in an individual case the latency period could be as short as 1 year, and as long as 50+ years.) Eriksson reported a twofold increase in NHL risk with glyphosate exposure (OR=2.02, 95% CI 1.10-3.71). Notably, there was also evidence of a dose-response effect: with >10 days use, the risk was higher (OR=2.36, 95% CI 1.04-5.37) compared to less than 10 days of use (OR=1.69, 95% CI 0.70-4.07). This was the only study reviewed which conducted analyses and also accounted for latency (>10 years after use, OR=2.26, 95% CI 1.16-4.40) and these results are more convincing due to biologic plausibility; in the group in which less than 10 years had elapsed since exposure, the effect estimate was much lower, as would be expected since these exposures are less likely to contribute to disease onset (OR=1.10, 0.24-5.08).

Eriksson also stratified by NHL subtype; effect estimates were increased for every NHL subtype and confidence intervals overlapped, meaning that there was evidence for increased risk for all NHL types: B-cell lymphomas (OR=1.87, 95% CI 0.998-3.51); SLL/CLL (OR=3.35, 95% CI 1.42-7.89); follicular (OR=1.89, 95% CI 0.62-5.79); Diffuse large B-cell (OR=1.22, 95% CI 0.44-3.35); other specified B-cell lymphomas (OR=1.63, 95% CI 0.53-4.96); unspecified B-cell (OR=1.47, 95% CI 0.33-6.61); T-cell lymphomas (OR=2.29, 95% CI 0.51-10.4); unspecified NHL (OR=5.63, 95% CI 1.44-22.0).

An earlier Swedish study by the same research group[39] ascertained cases diagnosed 1987-1990; thus this population was distinct from those in Eriksson's analysis. This study was smaller (N=404 cases) and had few participants ever exposed to glyphosate, leading to wide confidence intervals (4 cases and 3 controls ever exposed; OR=2.3, 95% CI 0.4–13). The small sample size limits our ability to draw definitive conclusions, but it is interesting that the estimate effect size is quite similar to the one reported by the larger later study. Likely because of this limitation, authors later conducted a pooled analysis which grouped these cases with cases of hairy-cell

leukemia (a subtype of NHL), reporting a threefold increased risk of any NHL (OR=3.04, 95% CI 1.08-8.52).[36] An earlier report of only the hairy-cell leukemia cases also reported increases in risk with glyphosate exposure (OR=3.1, 95% CI 0.8-1.2), but relied on a quite small sample size (N=121 cases).[40]

The Canadian studies (McDuffie[35] and Hohenadel[41]) ascertained cases diagnosed 1991-1994 hence allowing for a latency period between first possible use of glyphosate and disease occurrence, however the sample size (N=517 cases) was smaller than that of the pooled US studies. McDuffie reported a weak increased risk of NHL with glyphosate exposure which was similar in size in minimally adjusted and fully adjusted models (OR=1.26, 0.95-1.90; OR=1.20, 0.83-1.74). This study had a variety of sources for controls and a control participation rate of 48%, which is of concern if this caused selection of controls that does not reflect the population exposure to glyphosate. To examine the accuracy of self-reported pesticide use, McDuffie conducted a validation study comparing questionnaire data from farmers to records from a local chemical supplier on pesticide purchases. They stated that concordance between self-reported and sales record based exposures was excellent, although more specific information was not provided.

Pesticides sometimes exert stronger health effects when mixed (co-exposure) with other pesticides than when used alone. McDuffie reported that when glyphosate exposure was mixed with dicamba, the risk was increased (OR=1.92, 95% CI 1.39-2.66, minimally adjusted model; OR=1.88, 95% CI 1.32-2.68; fully adjusted model) compared to dicamba exposure alone (OR=1.59 and 1.68, respectively).[35] Similarly, when glyphosate exposure was mixed with malathion (OR=2.10, 95% CI 1.31-3.37) it was stronger than when farmers only reported using glyphosate alone (OR=0.92, 95% CI 0.54-1.55).[41]

The study by Cocco was limited in how much we can glean from its results, as only 4 cases and 2 controls had ever used glyphosate. The prevalence may have been low in this study because the Cocco study included people with a range of occupations, unlike many of the other studies which focused on agricultural populations. Cocco reported increases in B-cell lymphoma with glyphosate use (OR= 3.1, 9% CI 0.6 to 17.1).[42]

Less informative for the current evaluation is the Cantor study[43] because, although it was carefully conducted, cases (in Iowa and Minnesota) were included that were diagnosed 1980-1983. Hence, only 6-10 years could have elapsed between a potential first glyphosate exposure

and NHL diagnosis, which for cancer epidemiologic studies is considered an inadequate latency period (see above) and one would want to see an at least the median latency period of 10 years. Again, for an individual the latency period may vary (1 year to many decades), but on average for a study one would prefer a minimum latency period of on average 10 years.

The Lee study[44] utilized Cantor's cohort to build upon by including subjects from Nebraska who were diagnosed July 1983 to June 1986, thus this study includes cases with a longer latency period, which improves confidence in results. Lee reported increases in NHL among non-asthmatics (OR=1.4, 95% CI 0.98-2.1, N cases=827) and a smaller elevated effect estimate in asthmatics with wide confidence intervals (OR=1.2, 95% CI 0.4-3.3) due to the small number of asthmatic cases (N=45).

De Roos 2003 reanalyzed the US studies[1] and used hierarchical regression in addition to conventional logistic regression models, a statistical technique (described above) which can account for co-exposures and correlations between pesticides but makes some strong assumptions about all pesticides or groups of pesticides having similar effects on the outcomes. Using regular logistic regression, De Roos reported an increased risk with glyphosate use (OR =2.1, 95% CI 1.1 to 4.0) and in the hierarchical regression analysis the effect estimate was smaller 1.6 and the 95% CI included the null value of 1 (95% CI =0.9-2.8). Notably, the OR for glyphosate was among the highest of 47 pesticides tested, which suggests that glyphosate may indeed be the pesticide most strongly related to NHL in these farmers among all pesticides they used. The selection of pesticides for this paper was based upon a "carcinogenic probability factor" developed for all cancers, not specific to NHL, so it is not clear whether the hierarchical regression represented the best analytic strategy for NHL since – as stated above – the model assumes that all pesticides included have a similarly strong effect on the outcome; thus we would expect the largest effect estimate to be pulled towards the null of 1 which is what happened. Also, in terms of possible exposure mismeasurement, a validation of questionnaire responses had previously been conducted which reported strong agreement between self-reported pesticide use in comparison to pesticide supplier records, and recall was similar between cases and controls.[45]

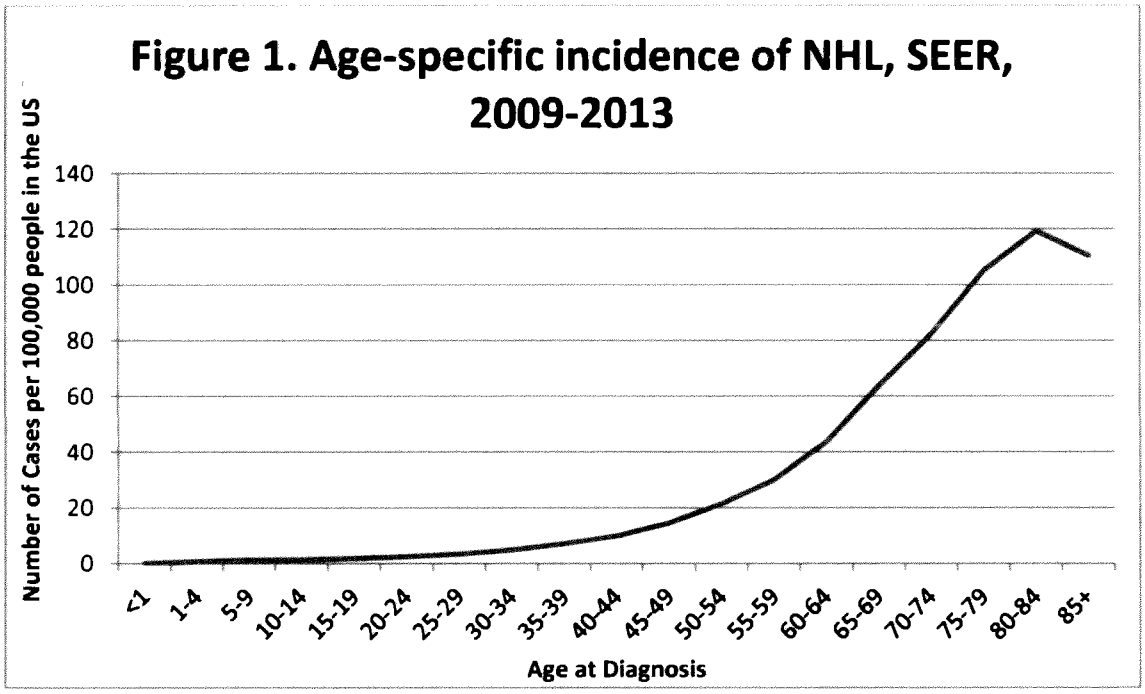
The French study by Orsi and colleagues[38] utilized a hospital-based study design, i.e. in this design cases and controls are recruited from among hospital patients. This is in contrast to nearly all of the other studies described above which used a population-based study design (with the exception of some countries within the Cocco study). Population-based studies are

considered superior to hospital based designs, because epidemiologic studies aim to select controls from the same population that gave rise to the cases, because it improves study validity. The patients who go to a hospital for NHL treatment may not live in the same area as the control patients selected; this can occur if the study hospitals are regional cancer centers which draw cases from a large geographic area. Orsi's study recruited controls who had been admitted largely from orthopedic and rheumatological admissions (mostly fractures, injuries and back pain). This may be problematic because orthopedic and musculoskeletal illnesses and injuries are conditions that typically do not require travel to a distant center for treatment, suggesting there was possible non-overlap between the case and control populations. In addition, hospital patients are an unusual group: they tend to be older, sicker, and have higher tobacco and alcohol use (and other behavioral/lifestyle differences) than the general population.[46-49] Consequently, the use of hospital controls can create unexpected and surprising findings (such as studies of cancer where the controls smoke more than the cases[48]). Further, biases can occur when the reasons for hospitalization are related to exposure. For example, if people exposed to glyphosate are more likely to be hospitalized (due to, perhaps, higher rates of time spent outdoors leading to greater injuries and back pain in farmers/gardeners) then this would bias the results. This may indeed be the case because there are known higher rates of musculoskeletal injuries among gardeners, and these people may also have higher glyphosate use.[50-52] Orsi and colleagues were unable to observe any association between glyphosate and NHL (OR=1.0, 95% CI 0.5 to 2.2; all NHL types combined). When authors examined risk by subtype, elevated risk with wide confidence intervals was reported for follicular lymphoma (OR=1.4, 95% CI 0.4-5.2) but not large diffuse large cell lymphoma (OR=1.0, 0.3-2.7). However, with 244 cases this study has only limited statistical power to conduct any subtype specific analyses.

De Roos 2005 is an analysis of the Agricultural Health Study (AHS).[37] Pesticide applicators were recruited for this study between 1993-1997 and followed for incidence of cancers up until December 2001, therefore active follow-up ranged from 4-8 years with a median follow-up period[ii] of 6.7 years, which is considered a short latency period in cancer epidemiology. Only 92 NHL cases had developed in the cohort by end of this follow-up period,

[ii] The follow-up period is the time that elapses between the start and the end of a study. Typically, participants are followed from the start date until 1) cancer diagnosis; 2) death; 3) study end; or 4) loss to follow-up (e.g. the study investigators cannot locate them or they drop out of the study), whichever comes first.

making this the smallest case sample size of any study reviewed; this is not surprising because the mean age at AHS study enrollment was 45.3 years.[53] NHL, like most other cancers, is a disease of aging, with dramatically higher incidence as people age. Figure 1 shows the incidence of NHL among Americans, with data taken from the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program.[54] It is not informative to follow a group of workers that young for only 4-8 years and draw meaningful conclusions about their cancer risk, especially for a rare cancer and an expected risk of moderate size (OR or RR of 1.5 to 2.5). The estimated RR was low and the confidence intervals were wide: the risk for any NHL was 1.2 (95% CI 0.7-1.9, adjusted for age; RR=1.1, 0.7-1.9, adjusted for age, demographic and lifestyle factors, and other pesticides).



AHS investigators collected information on 50 pesticides at enrollment (in 1993-1997); as the study description states, participants were asked about ever/never pesticide exposures and years of use and frequency of use (# of days per year) for 22 pesticides at enrollment and for another 28 pesticides in a take-home questionnaire that only 44% of applicators returned. The median time of employment involving mixing and applying any pesticide was 15 years at enrollment, and therefore the pesticide exposures occurring during the most relevant time period

for cancer development may not be known.[53] Among all pesticide applicators included in the analysis, 76% had ever used glyphosate, which made it among the most common pesticide used among applicators in this study. This is in line with other research on glyphosate, which reports that as of 1999, glyphosate was the highest selling crop-protection product on the market.[55] However, it is important to note that the first year genetically engineered, glyphosate-tolerant crops were planted commercially in the U.S. is 1996, and that prior to this date glyphosate accounted for just 3.8% of the total volume of herbicide active ingredients applied in agriculture[56] while glyphosate accounted for half of the total agricultural herbicide use in 2009 [see Coupe]. Also, in a 20-year timespan covered by EPA sales and usage reports (1987–2007), glyphosate use rose faster and more substantially than any other pesticide (in 2007, usage was in the range of 81.6–83.9 million kilograms, more than double the next most heavily sprayed pesticide (atrazine: ~33.1–35.4 million kilograms) making it the most heavily applied pesticide in the U.S. with 2/3 of the share of the total volume having been applied in just the last decade.[57-59]

Given the persistence of glyphosate in soil (with a half-life of 29-60 days[60,61]), the possibility of exposure to glyphosate due to drift from fields[iii] ,[62-64] and a possibility of contaminated water supplies,[65] it is plausible that passive exposure may have ultimately been much higher among agricultural communities and pesticide applicators than the 76% who reported ever use; more importantly, the baseline exposure assessment in the AHS only covered the first two years of very intensive use of glyphosate i.e. those who were enrolled in 1996/97. When exposure to an agent is extremely high—and potentially even ubiquitous as in a cohort of pesticide applicators, who spend their days in agricultural fields—it eventually becomes impossible to study its health effects since there are little or no exposure contrast to measure at

[iii] Studies of pesticide drift suggest the distance that pesticides travel depends upon several factors: first, the method of application, with air spraying by plane or helicopter (common due to its ease of use) leading to further drift than ground spraying, because the spraying occurs higher above crops; secondly, wind speed; and thirdly, pesticide droplet size, with smaller droplets travelling further. Estimates of pesticide drift vary from 74 meters in an area with low wind, up through >2400 meters under windy conditions. Studies of glyphosate pesticide drift suggest droplets can travel upwards of 800-1000 meters. According to the US EPA, spray drift has been reported to be a problem with glyphosate, as there have been multiple reports of damage from glyphosate to non-target crops.

least at the ever/never or cruder types of classification that do not rely on biomarker assays of dose.[iv],[66]

De Roos (2005) also conducted dose-response analyses by examining intensity-weighted exposure (years of use X days per year X intensity level), grouped into 3 levels (0.1-79.5; 79.6-337.1; and 337.2-18,241); and by cumulative exposure days (years of use X days per year), categorized into 3 groups (1-20, 21-56, 57-2,678). Authors decided to compare the cancer risk in these exposed groups not to that among the never exposed, but instead compared high exposure to low exposure. While this type of comparison attempts to control for and eliminate other risk factors that may distinguish non-exposed from exposed (hence reduce potential confounding bias) this type of approach also reduces any remaining exposure contrasts even further and thus reduces the ability to estimate risk increases with exposure and make the effect estimates also less comparable to those form other studies.

Industry-sponsored studies

A meta-analysis by Chang and Delzell was sponsored by Monsanto.[67] This meta-analysis found similar results to the above meta-analyses for any increases in NHL (meta-OR: 1.3, 95% CI 1.0-1.6) and particularly elevated risks for B-cell lymphoma (meta-OR: 2.0, 95% CI 1.1-3.6). This study also found extremely low heterogeneity across studies— unusual in most meta-analyses— supporting the consistency of findings across different settings.

Bradford-Hill criteria evaluation

The strength (effect size) criterion is partially met since the overall meta-analytical (point) effect estimates reported for ever never glyphosate use are between 1.3 and 1.5 reflecting a weak to moderate size association. However, the effect estimates for longer or more extensive use in several studies were larger i.e. between 2 and 3 and this can be considered a stronger endorsement of a causal relation; it is further supported by the observed dose response (biological gradient such that risk increases with dose - another Bradford Hill criterion) that these studies found (also note: a small association does not mean that there is not a causal effect,

[iv] Rose argues that when a risk factor is ubiquitous in a population, it may strongly influence the population incidence of a disease, but may not identify high-risk individuals within a population. For example, in a society where everyone smokes, smoking will not identify high-risk individuals for lung cancer.

though the larger the association, the more likely that it is unbiased and thus causal). In terms of consistency, this criterion is met since positive associations have been reported for different populations and in different places and different time periods which strengthens the likelihood of a true effect. Temporality i.e. that the cancer occurred after exposure and that there is an expected delay between the cause and effect has been shown i.e. all exposures were assessed and recorded for the periods prior to NHL occurrence. Unfortunately, only one study examined the influence of exposure lagging i.e. considered the latency period: that study found a strong association with a 10-year lag, which further corroborates causality in terms of cancer etiology. The specificity criterion (i.e. that one specific exposure causes one specific outcome) is hard to apply in the case of herbicide or pesticide exposure since almost none of the farmers/pesticide applicators is expected to solely be exposed to glyphosate, since most farming operations require the use of multiple pesticides over time. Also in the case of blood system cancers, one could argue that different pesticides have possible carcinogenic effects on different cell types. Nevertheless, it is of interest that NHL is one cancer reported consistently among farmers for the past 2 to 3 decades, and glyphosate is consistently the most widely used herbicide in farming especially after 1995 with the advent of genetically modified crops. Finally, some studies suggested that types of NHL that are showing T14/18 translocations in lymphocytes are the ones most likely caused by external agents including some pesticides and smoking and this increases also biologic plausibility for the action of genotoxic or oxidative stress pathways (see below) with certain pesticides such as glyphosate.

Biological plausibility.

Biomonitoring studies affirm that some (not all) persons who apply glyphosate occupationally have measurable glyphosate excreted in urine, and measurable glyphosate is also seen in farming household members who reside close to treated fields.[68-70] Research on exposed agricultural workers suggests increases in genomic instability (binucleated cells, micronuclei).[71] Rodent studies report increases in DNA oxidative damage (increases in 8-OHdG in either kidney or liver; lipid peroxidation) as well as cytogenetic damage (sister-chromatid exchanges, increases in micronuclei), and DNA single-strand breaks.[72-74] Cytotoxicity and genotoxicity are also reported in studies of human cells.[75]

Roundup vs. glyphosate. One study compared the effects in rodents of glyphosate to those of Roundup, and results were similar with regards to cytotoxic and genotoxic effects.[73] While a *plausible mechanism* between cause and effect is helpful, Bradford Hill noted that knowledge of the mechanism is often limited by current knowledge; nevertheless for glyphosate two mechanisms have recently been proposed, oxidative stress and genotoxicity, and been confirmed by the laboratory experiments listed above. Finally, while *coherence* between epidemiological and laboratory findings increases the likelihood of a true effect, Bradford Hill noted that "... lack of such [laboratory] evidence cannot nullify the epidemiological effect on associations". Due to ethical concerns, there will never be any human experimental evidence for glyphosate toxicity or carcinogenicity, but human cell based studies and animal experiments can substituted as model systems and have increasingly been used in the recent past.

4. Conclusions

The epidemiologic studies as a whole support an increased risk of NHL with exposure to glyphosate or glyphosate based formulations, including Roundup. Due to the rarity of this disease, many of the earlier studies were small in size, leading to wide confidence intervals; yet findings were consistent with nearly all studies having point estimates above 1.0. In the pooled and meta-analyses, results are consistent and unequivocal. Studies that assessed dose also generally found that higher levels of exposure were associated with increased risk and importantly in the one study that did assess the importance of having been exposed more than 10 years prior to a diagnosis of cancer, the results clearly pointed to those exposures as the relevant one as compared to the more recent exposures (within 10 years) increasing plausibility of associations greatly.

In my opinion, to a reasonable degree of scientific certainty, glyphosate causes NHL. Furthermore, to a reasonable degree of scientific certainty, glyphosate based formulations, including Roundup, cause NHL.

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EXHIBIT A

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EDUCATION

1995	Ph.D. in Epidemiology, School of Public Health, UCLA
1993	M.P.H. in Epidemiology, School of Public Health, UCLA
1987	Doctoral Degree in Medical Sociology, University of Hamburg.
1983	Medical Examination Certificate, Registration as a Physician (M.D.), Board of Health in Hamburg
1977-1983	Medical School, University of Hamburg, Germany

PROFESSIONAL POSITIONS AND APPOINTMENTS

2012- 2015	Chair, Department of Epidemiology, School of Public Health, University of California Los Angeles (UCLA)
2006-current	Professor, Departments of Epidemiology, Environmental Health, and Center for Occupational and Environmental Health, School of Public Health, and Neurology, School of Medicine, UCLA
2005-2012	Vice Chair, Department of Epidemiology, School of Public Health, University of California Los Angeles (UCLA)
2004-current	Appointment in the Department of Neurology, School of Medicine, UCLA
2002-current	Co-director of the UCLA-CGEP (UCLA center for Parkinson 's Disease Environmental Research (CCPDER- CNS)
2001 -2006	Associate Professor, Department of Epidemiology, Department of Environmental Health, and Center for Occupational and Environmental Health, School of Public Health, UCLA
1995-2001	Assistant Professor, Department of Epidemiology and Center for Occupational and Environmental Health, School of Public Health, UCLA
1993-1995	Assistant Researcher, Department of Epidemiology, School of Public Health, UCLA
1989-1991	Hochschulassistentin (Assistant Professor), Institute of Medical-Sociology, University of Hamburg, Germany.
1987-1988	Research Fellow and Resident, Psychiatric University-Hospital Eppendorf, Hamburg, Germany
1984-1986	Research Fellow, Institute of Medical Sociology, University Hospital Eppendorf, Hamburg, Germany

OTHER HONORARY PROFESSIONAL APPOINTMENTS

2002-2008	Editorial Board: EPIDEMIOLOGY
2004-2009	Editorial Board: Epidemiologic Perspectives & Innovations
2007-2010	Editorial Board: Environmental Health
2001-current	Chair (since 2005) and Member (since 2001) of the external advisory committee for the NCI/NIEHS Agricultural Health Cohort Study
2001-current	Board of Directors for the 'R. Lemelson Foundation for Psychocultural Research.' Annual awards of $800,000 for research and training including a UCLA training grant for cross-disciplinary studies in anthropology, psychology and neuroscience

2001-2002	Member of the external advisory committee for the California Biomonitoring Planning Project conducted by the Environmental Health Laboratory's Biomonitoring Project (CDHS)
2002	Member of the EPA Science Advisory Board for Human Health Research Strategy (HHRS)
2002-2004	Member of the external advisory committee for the California Environmental Health Surveillance System (Governor Davis appointee to expert working group for SB 702)
2003-2006	Member of the Ethic Committee for the International Society for Environmental Epidemiology
2003-2004	Member of NAS, IOM Committee on Gulf War and Health, Phase 3: Literature Review of Selected Environmental Particulates, Pollutants, and Synthetic Chemical Compounds
2002-2004	Member of the external advisory committee for the California Environmental Health Surveillance System (Governor Davis appointee to expert working group for SB 702)
2006	Member of NAS, IOM Committee on Gulf War and Amyotrophic Lateral Sclerosis
2006	Member of the Scientific Steering Committee for Pediatric BioBank in California
2007	Robert M. Zweig M.D. Memorial Award (Clean Air Award) from the California South Coast Air Quality Management District
2007	Appointed as a Collegium Ramazzini Fellow
2007	Scientific Organizing committee for the PPTOX conference in Faroe Island
2008	Scientific Organizing committee for the ISEE conference in Pasadena
2008	Member of the Environmental Exposures Working Group conducted by RTI International for the PhenX project of GWA research at NIH
2009	Member of NAS, IOM Committee on Gulf War and Health, Phase 4
2008-09	Member of the U.S. EPA CO standard setting panel for (CASAC: *Carbon Monoxide National Ambient Air Quality Standards*)
2009-2012	Elected Councilor for the International Society for Environmental Epidemiology (ISEE)
2010-current	Member of the Conference Organizing committee of the ISEE
2009	Award from the American Parkinson's Disease Association (APDA) for outstanding contributions to the medical and scientific communities towards the advancement of Parkinson's disease research
2010-2013	Member of the External Advisory Board for the Superfund site center grant at University of Washington
2010-2013	Member of the External Review Board for the Swiss Tropical and Public Health Institute in Basel
2013	Scientific Organizing committee for the ISEE conference in Basel/Switzerland
2012-current	Member of CA-EPA Scientific Review Panel on Toxic Air Contaminants
2012	Affiliate member of the Institute of the Environment and Sustainability
2014	Scientific Organizing committee for the ISEE conference in Seattle Washington
2014-current	Member of NAS/IOM committee on Incorporating 21st Century Science into Risk-Based Evaluations

FUNDED RESEARCH

NNH12ZDA006O-EVI3
Agency: NASA (PI: Ritz)
Total Direct Costs to UCLA: $1,294,244
Multi-Angle Imager for Aerosols (MAIA) 08/01/16-11/30/25
This project will assess air pollution and adverse birth outcomes using exposure data provided by Dr. Diner's group from the MAIA NASA project. UCLA researchers will be responsible for the modeling the effects of prenatal air pollution exposures on adverse birth outcomes derived from vital statistics records for multiple locations across the world.

1 U01 HD087221 (PI: Devaskar/UCLA Ob-GYN)
Agency: NIH/NICHD Period: 01/01/16-12/30/19
Total Direct Costs: $2,999,640
Imaging Innovations for Placental Assessment in Response to Environmental Pollution
The objective of this proposal is to develop and evaluate a suit of cutting-edge multi-parametric magnetic resonance imaging (mp-MRI) technologies and translate these novel placental imaging modalities to assessing the impact of environmental pollution exposure on prediction of placental insufficiency.

Psychosocial stressors, air pollution and childhood respiratory health in LAFANS
Agency: NIEHS R03ES025908 (PI: Ritz) Period: 07/01/15-06/30/17
Total Direct Costs $100,000
This study will add to the previous literature by constructing a more holistic measure of the stress perceived by the child, and use that measure to determine if a child's perceived stress modifies their risk of asthma or reduced lung function from air pollution.

Pesticide Exposures and Risk of Cerebral Palsy
Agency: NIEHS R03ES025904 (PI: Ritz) Period: 07/01/15-06/30/17
Total Direct Costs $100,000
Using records from the California Department of Developmental Services (DDS), we will identify children born 1995-2007 and diagnosed with CP in California until 2010. For ~10,000 CP cases we will randomly select 1:10 matched controls from the California birth certificates. Ambient pesticide exposure estimates pre-pregnancy, during pregnancy and/or first year of life for each child will be estimated using a Geographic Information System (GIS) model we previously developed based on the California Pesticide Use Reporting (PUR) system. We will examine specific vulnerable periods in pregnancy (trimesters or months of pregnancy) to assess pesticide exposure effects on CP.

Autism, Metabolomics, and Environment (AIME)
Agency: NIEHS R21ES25573 (PI: Ritz) Period: 07/01/15-06/30/17
Total Direct Costs $275,000
We will assess whether autism risk factors can be identified using metabolomic biomarkers of exposure in stored maternal serum samples from mid-pregnancy from 200 case and 200 control pregnancies in Central California and compare biomarker exposure patterns with modelled air pollution and pesticide exposures. Metabolomics analyses will be performed in a targeted as well as untargeted manner with high-resolution metabolomics that uses mass spectrometry and advanced data extraction algorithms to quantify up to 20,000 chemicals in small biologic extracts.

Air Pollution and Childhood Autism
Agency: NIEHS R21ES024006 (PI: Ritz/Ehrenstein – multiple PI) Period: 07/01/15-06/30/17
Total Direct Costs $275,000
We use highly sophisticated modeling and analytical techniques for the detailed spatial and temporal assessment of air pollution to examine their influence on neurodevelopment in a California birth cohort linked to autistic disorder records of the CA Department of Developmental Services.

Environment and cognitive decline in older Hispanics
Multi-PI: Ritz/Haan
Agency: NIEHS Type: R01- RES023451A Period: 04/01/15-03/31/19
Total Direct Costs: $ 2,000,000
The goal of the proposed research is to investigate whether long-term exposure to two ubiquitous environmental exposures, air pollution and pesticides, contribute to cognitive decline and dementia in elderly Mexican Americans (MA) from the "Sacramento Area Latino Study on Aging" (SALSA) cohort. We capitalize upon our expertise in modeling air pollution and pesticide exposure and plan to model 1) long and short term regional, local, and traffic related air pollution using monitored criteria pollutants, CALINE4 - emissions and land use regression (LUR) models; and 2) long-term exposures to pesticides of specific chemical classes with our GIS model; and 3) assess impairment in cognitive domains and the onset of dementia longitudinally based on multiple complex environmental exposure patterns while taking into account vulnerability due to genetic and physiologic risk factors for dementia.

Air Pollution and Autism in Denmark
PI: Ritz
Agency: NIEHS Type: R21 Period: 04/01/15-03/31/17
Total Direct Costs: $ 275,000
The goal of the proposed research is to utilize Danish nationwide population-based registers and sophisticated individual-level air pollution exposure measures to assess whether early life exposure to traffic-related and particulate air pollution during critical periods of fetal development are associated with autism risk. We will use the Danish National Birth Cohort (DNBC) which enrolled pregnant women and collected extensive prospective risk factor data during pregnancy and early life for ~100,000 children

among whom 720 are already diagnosed with ASD to examine potential confounding bias for a large number of risk factors assessed in pregnancy.

Air Pollution and Cardiovascular Diseases: Identification of Novel Biomarkers
Agency: NIEHS R21 ES024560 (PI: Zhu) Period: 05/01/15-04/30/17
Total Direct Costs $275,000
Objectives: The goal of this project is to identify novel and sensitive biomarkers of cardiovascular health effects, in association to air pollution exposures.
Role: Co-I

Environmental exposure, DNA methylation, and Parkinson's disease

Agency: NIEHS 21ES024356 (PI: Ritz/ Horvath) Period: 08/06/14 – 07/31/16

Total Direct Costs: $ 250,000

Environmental exposure, DNA methylation, and Parkinson's disease
Here we use a powerful new tool and systems biology analytic methods to identify signatures for toxic exposures that evoke long-term biologic responses. Using DNA methylation we will investigate specific epigenetic markers (CpGs) correlate with toxic exposures and the role these epigenetic changes play in PD progression using epigenome wide technologies combined with analytic tools to integrate these data. We will investigate epigenetic determinants of Parkinson's disease in over 800 subjects with existing biospecimens.
Role: PI

Maternal comorbidities, prescription drug use in pregnancy, and childhood cancer (COMPAC): a record linkage study in Denmark
PI: Heck
Agency: NIH/NCI Type: R21CA175959 Period: 04/01/14-03/31/16
Total Direct Costs: $ 275,000
This study aims to link several large-scale databases in Denmark to examine maternal health and medication use in pregnancy in relation to childhood cancers. We propose to examine common pregnancy conditions that have been linked to cancers in adults and children in other studies as well as common medications taken in pregnancy which are suspected carcinogens or linked to cancer in other studies.
Role: Co-I

Inflammatory Cytokine Polymorphisms, Air Pollution, and Very Preterm Birth
PI: von Ehrenstein
Agency: NIEHS Type: R21ES022734 Period: 07/01/13 - 06/30/15
Total Direct Costs: $ 275,000
We examine the hypotheses that maternal exposure to air pollutants during pregnancy is associated with an increased risk of very preterm birth (VPTB, <32 weeks gestation), and that polymorphisms in inflammatory genes modify the influence of air pollution on the risk of VPTB. We use data from the CA Very Preterm Birth (CVPTB) Study, a nested case-control study of VPTB from 5 counties in Southern CA known for high particulate matter, ozone, and traffic exposures that has genotyped SNPs related to PTB in 26 inflammatory/immune response pathway genes in mother-infant pairs and will utilize a combination of extensive air monitoring data and air pollution modeling approaches (land use regression (LUR), CALINE4, kriging) to estimate air pollution exposures in pregnancy for CVPTB Study subjects.
Role: CO-I

Pesticide Exposure and Childhood Autism
PI: von Ehrenstein
Agency: NIEHS Type: R21ES022389 Period: 01/01/14 - 12/31/15
Total Direct Costs: $ 275,000
We examine the hypothesis that exposure to specific pesticides during vulnerable periods, particularly during fetal development, determines risks of subsequent development of autistic disorder (AD). We developed a geographic pesticide exposure assessment tool (GRAPES) that utilizes the unique California Pesticide Use Report system, in combination with agricultural land-use maps, to derive record-based estimates of historical residential exposures, and expect to identify >20,000 autism cases with diagnoses up to the age of 72

months from the CA-DDS database born in CA 1997-2009 and >1,700 from agricultural areas as well as 1:10 age-sex match controls from birth records, the largest cohort ever to address hypotheses that exposures to specific chemicals (e.g. neurotoxic or endocrine disrupting agents) contribute to AD during vulnerable periods of development.
Role: CO-I

Parkinson's Susceptibility Genes and Pesticides (PEG-Renewal)
Principal Investigator: Ritz
Agency: NIEHS/NINDS Type:R01ES010544 03/01/11-11/30/15
Total Direct Costs: $ 2,500,000
In this renewal of an epidemiologic population-based case-control study we recruit 500 additional PD patients in three rural California counties and will assessed their exposures to pesticide exposures and the effects of gene-pesticide interactions.
Role: PI

Systems genetic and reverse phenotypic analysis of age and retirement.
PI: Horvath (UCLA)
Agency: NIA Type: R01AG042511-02 07/01/13 - 06/30/17
Total Direct Costs: $ 1,000,000
We will apply/develop state of the art computational, statistical, and bioinformatic approaches with which to investigate the association between genetic data and aging- related phenotypes. Specifically, the study uses data from the Health and Retirement Study (HRS) and a systems biology approach to identifying relevant SNPs and genetic pathways and machine learning techniques and reverse phenotyping methods to better understand the complex relationship between genetics and aging outcomes including cognition and wealth.
Role: CO-I

Exposure to C8-chemicals and autism, ADHD, and cerebral Palsy in the Danish Birth Cohort
PI: Jorn Olsen (UCLA and Aarhus University, Denmark)
Agency: Danish Medical Council
Total Direct Costs (at UCLA): $ 250,000 01/01/11 - 08/31/15
The overall goal of the project is to assess the impact of C8 persistent organic pollutants in maternal serum during pregnancy and childhood outcomes of autism, ADHD and cerebral palsy in the Danish Birth cohort using follow-up data from the National Danish medical registry systems.
Role: CO-I

A Cohort Study on Air Pollution and Breast Cancer in Los Angeles County
IIR13262718 Wu (co-PI) 02/13/14-02/150/17
Susan G Komen $217,728
The overall objective is to examine the role of air pollution and risk of breast cancer among whites and non-whites in Los Angeles using the large Multiethnic Cohort Study
Role: Co-Principal Investigator

Improvements in Air Quality and Health Outcomes among California Medicaid Enrollees Due to Goods Movement Actions — Phase I: Assessing Air Quality Changes
PI: Meng , UCLA
Agency: Health Effects Institute (HEI) #: 4914-RFA11-1/2-6 09/01/12 – 08/31/15
This phase of the project will evaluate the effect of goods movement emission reduction actions on ambient air quality in goods movement corridors, non-goods movement corridors, and areas outside of these two corridors in 10 major California counties between the 2003-2007 pre-policy and 2008-2012 post-policy years.

COMPLETED RESEARCH
Assessing and Reducing Taxi Drivers' Exposure to Ultrafine Particles
PI: Yifang Zhu (UCLA) Type: R21OH10196 09/01/12–08/31/14
Agency: CDC/NIOSH
Total Direct Costs: $ 275,000

Goal: The major goals of this project are to develop ultrafine particle exposure assessment instrument and explore novel low-cost ultrafine particle exposure mitigation strategies for taxi drivers.
Role: Co-I

Air Pollution and PD in Denmark
PI: Ritz Type: R21-ES022391 12/01/12-30/11/14
Agency: NIEHS
Total Direct Costs: $ 275,000
This study will use a sophisticated and validated GIS-based dispersion model, AirGIS, to assess exposure to traffic-related air pollution in PASIDA participants; i.e. NO_2/NO_x. Specific aims are to: (1) assess the influence of long-term traffic-related air pollution exposure on PD risk for 1,867 cases and 1,920 population controls combining existing PASIDA data with new exposure measures from AirGIS; and (2) investigate the combined action of air pollution and genetic variants in inflammatory genes previously linked to PD.
Role: PI

Parental Occupation and Childhood Cancers in Denmark
PI: Heck (UCLA) TYPE: R03 ES021643 4/15/12-3/31/14
Agency: NIEHS
Total Direct Costs: $ 50,000
The specific aims of this study are: 1) Create a linked database of all childhood cancers in Denmark diagnosed 1965-2010 with recorded information on parental employment. 2) Examine the relation between parental employment and childhood cancers focusing on maternal occupational exposures. 3) Examine specific hypotheses in childhood cancer risk (occupational social contact; contact with animals; organic dust; welding fumes; bitumen fumes; outdoor work; and several associations seen in previous literature (solvents, paints and pigments, motor vehicle exhaust related occupations)).
Role: Co-I

Pesticides and Childhood Cancers
Principal Investigator: Ritz (UCLA)
NIEHS R21- ES019986 4/1/11 – 12/31/13
Total Direct Costs: $ 275,000
The specific aims of this study are to examine associations between prenatal exposure to pesticides and specific childhood cancers in California between 1980-2009 using ambient measurement data using our GIS model of pesticide exposures based on land use maps and pesticide use report (PUR) data.

UCLA Center for Centers for Neurodegeneration Science (CNS; former CGEP)
Director: Chesselet, UCLA; Co-director: Ritz
NIEHS P01ES016732 09/15/08-08/31/13
Total Direct Costs: $5,000,000
We have previously shown associations between high levels of exposure to specific environmental pesticides and Parkinson's disease and will build on this knowledge to determine the mechanisms of action that may be causing this association. We will use an integrated, multidisciplinary approach to identify additional agricultural pesticides that are disrupting similar molecular pathways, and determine whether these also increase the risk of Parkinson's. This work is expected to shed light on the pathological processes involved in sporadic Parkinson's disease, the most frequent form of the disorder, and could have public health implications for precautions in the use of some pesticides.
Project 4: Pesticides and Genes in PD: Studies in Humans
Principal Investigator: Ritz
NIEHS 09/15/08-08/31/13
Total Direct Costs: $1,250,000
This project will use the existing PEG data to test biological candidate genes and newly identified putative environmental toxicants for association with PD. We will recruit and collect biological (DNA) samples from and construct exposures estimates for 400 additional population controls. This will enable us to test new hypotheses for rarer exposures to specific toxins and will allow us to investigate gene-gene (GxG) and gene-environment (GxE) interactions with sufficient power. Targeted toxins are either (a) interfering with the ubiquitin proteasomal system (UPS), (b) altering microtubule integrity, and/or (c) inhibiting the aldehyde/alcohol dehydrogenase. Targeted genes include UBE1 and UBE1L2; PSMC2, 3, 4, and 5; HIP2; SKP1A; GSK3B; CDK5; MAPT, Sirt2, and ALDH and ADH gene clusters.

Registry of Parkinson's Disease Study In Denmark (PASIDA)
Principal Investigator: Ritz
NIEHS RO1 - ES013717 09/01/06-08/31/13
Total Direct Costs: $5,600,000
We conduct 1) a case-control study of ~13,000 PD cases and age-gender matched controls from the Danish population via passive record linkage by unique ID between the National Patient Register, Pharmacy Database, and National Pension fund to identify risk factor information contained in these records (e.g. occupations, medication use, diseases prior to PD onset); and 2) recruit actively ~2500 of the most recently registered PD patients and population controls to collect additional risk factor information per interview and biological materials for gene-environment interaction analyses and to characterize PD patients phenotypically.

Air Pollution and Childhood Cancers
Principal Investigator: Heck (UCLA)
NIEHS R21- ES018960 4/1/10 – 12/31/13
Total Direct Costs: $250,000
The specific aims of this study are to examine associations between prenatal exposure to motor vehicle related air pollution toxics and specific childhood cancers in Los Angeles County and all of California between 1980-2009 using ambient measurement data, land use based regression (LUR) and CALINE4 models.

California Parkinson's Disease Registry Pilot Feasibility Study
Principal Investigator: Ritz
DOD 09/01/07-04/30/12
Total Direct Costs: $390,000
The primary goal is to conduct a pilot study for the legally mandated statewide population-based PD registry. We will identify PD cases in Kern, Tulare and Fresno counties from legally mandated sources (pharmacists, health care institutions, physicians and other providers). A secure prototype database will be established, and associations between PD and toxicant chemical exposure will be determined by linking to a database of toxicant chemicals established previously by UCLA based on California state data (e.g. the pesticide use databases).

UCLA UDALL Parkinson's Disease center
Principal Investigator: Chesselet, UCLA
NINDS Type: P50 NS38367 04/01/06-03/31/12
Total Direct Costs: $7,500,000
Project 6 within the center (budget of $ 500,000 annual direct costs): Progression and Health Impacts of PD Motor and Non-Motor Manifestations (C-PI Ritz)
Research goals are to assess whether development and progression of PD motor and non-motor manifestations in 300 PD patients ascertained in the PEG study (PI: Ritz see below) are influenced by environmental, behavioral, and social factors and by genetic variants of ApoE and serotonin transporter alleles; and to determine the relative contributions of progression of motor and non-motor manifestations of PD to changes in HRQOL over time.

Sunlight exposure and variations in vitamin D metabolic genes in Parkinson's disease
Principal Investigator: Ritz
NIEHS R03- ES017139 09/01/09-08/31/11
Total Direct Costs: $100,000
The goal of the proposed research based on the PEG study population is to examine the hypothesis that long-term low levels of vitamin D either through inadequate sunlight exposure or alterations in metabolic genes that influence physiological vitamin D levels increase the risk of PD. We will test associations between long-term UV exposure measures and PD and examine whether genetic alterations presumed to result in different physiological vitamin D activity in genes critical to the vitamin D pathway (VDR, CYP27B1 and CYP24A1) increase the risk of PD.

Traffic-Related Air Pollution and Ultrasound Measures of Fetal Growth
Principal Investigator: Wilhelm Turner (UCLA)

NIEHS R03- ES017314 04/01/09-03/31/11
Total Direct Costs: $100,000
The specific aims of this study are to estimate prenatal exposures to O3 and PM10 and pollutants originating from traffic (NOx) using CALINE4 air dispersion modeling and examine associations with fetal size throughout pregnancy using ultrasound measures to examine associations with weight, length, head circumference, fetal growth ratio, ponderal index, and cephalization index at birth.

Ambient Air Toxics and Adverse Birth Outcomes
Principal Investigator: Wilhelm Turner (UCLA)
NIEHS R03 ES017119-01 12/15/08 – 12/30/10
Total Direct Costs: $100,000
The specific aims of this study are to: (1) examine associations between prenatal exposure to motor vehicle air toxics and low birth weight (LBW) and preterm birth in women residing in Los Angeles County, California between 1994-2006 using both ambient measurement data and land use based regression (LUR) models; and (2) gain information about how LUR models built on NOx measurements reflect exposures to specific toxins thought to have biological relevance for these outcomes.

Exposure to mobile source air pollution and adverse birth outcomes in the Los Angeles Air Basin
Principal Investigator : Jun Wu (UCI)
NIEHS R21 ES016379 9/11/08 -12/31/10
Total Direct Costs: $250,000
The overall goal of the project is to improve exposure assessment of air pollution exposure in pregnant women and investigate the impact of air pollution exposure on adverse reproductive outcomes, such as preterm birth, low birth weight, and intrauterine growth retardation.

Disparity in asthma among Californians from pollutant exposures.
Principal Investigator: Meng, UCLA
California Air Resources Board 04/22/08- 12/31/10
Direct Costs: $270,000
The goal of the research is to conduct a population-based study to examine the effects of long-term air pollution exposure near residence on chronic severe asthma and asthma-like symptoms in vulnerable populations.

Development of Exposure and Health Outcome Indicators for Those with Asthma or Other Respiratory Problems
Principal Investigator: Meng, UCLA
EPA- R833629 09/01/07-12/31/10
Direct Costs: $410,000
The goal of this research is to investigate the feasibility of combining existing environmental monitoring and health survey data to develop indicators that signal trends in exposures and health for those with asthma or other respiratory problems

Neighborhood Effects on Children's Health & Access to Care
Principal Investigator: A. Pebley, UCLA
HRSA 09/01/07- 8/31/10
Total Direct Costs: $500,000
The goal of this study is to significantly advance our knowledge about the relative importance of specific family and neighborhood characteristics in the development of major child health problems. This project is based on the Los Angeles Family and Neighborhood Survey (L.A.FANS), a longitudinal study of neighborhoods, families, adults, and children in Los Angeles County

Traffic-Related Air Pollution and Asthma in Economically Disadvantaged and High Traffic Density Neighborhoods in Los Angeles County, California (with LA F.A.N.S.)
Principal Investigator: Ritz
California Air Resources Board 01/06/05-09/30/09
Total Direct Costs: $420,000
The objectives of this research are: (1) to conduct NO_x and NO_2 monitoring at 200 locations within LA County neighborhoods with varying levels of economic disadvantage and varying exposures to air

pollution originating from vehicular sources; (2) to use these monitoring data to help inform land use-based regression (LUR) models developed to predict traffic pollutant exposures; (3) to use geostatistical models to estimate regional background concentrations of O_3 and $PM_{2.5}$; (4) to evaluate associations between exposure to NO_x, NO and NO_2 and measures of lung function and asthma prevalence, exacerbation and possibly incidence in children ages 0-17 years in conjunction with the Los Angeles Family and Neighborhood Survey (L.A. FANS) study; and (5) to evaluate whether concentrations of the more regionally distributed background pollutants (O_3 and $PM_{2.5}$) confound or modify the effects of exposure to the more heterogeneously distributed traffic-related pollutants (NO_x, NO and NO_2) on lung function and asthma.

Aggregate Exposure Assessment: Longitudinal Surveys of Human Exposure-Related Behavior
Principal Investigator: Irva Hertz-Picciotto, UC Davis
EPA 01/12/04-11/30/09
Direct Direct Costs: $388,111
This project develops data collection platforms for longitudinal assessment of exposure-related behavior. The data characterize short-term, seasonal, and long-term changes in time-activities, food consumption habits, and use of household and personal care products. We assess exposure-related behaviors at multiple collection points over time, and evaluate a number of data collection methods for validity (accuracy), precision, completion rates, cost, feasibility, and user acceptability.

UCLA Center for Gene-Environment Studies in Parkinson's Disease (CGEP-part of the NIEHS CCPDER)
Director: Chesselet, UCLA; Co-director: Ritz
NIEHS 09/01/02-08/31/09
Total Direct Costs: $7,000,000
The overall objective of this Center is to understand how the detrimental effects of pesticides, a suspected environmental risk factor for Parkinson's disease, are modulated by genetic variations that impact dopamine homeostasis in nigrostriatal neurons. The center integrates 3 RO1 research projects that investigate these questions in fly, mouse, cell culture models and applies the results also to human genetics (project 1: PI Ritz)
Research Project I within the CGEP center "Environmental toxins and genes that influence dopamine in Drosophila and humans"
Principal Investigator: Ritz
NIEHS 09/01/02-08/31/09
Total Direct Costs: $1,000,000
This project examines interindividual variability of dopamine vesicular transporter (VMAT) expression due to promoter variants in two human populations in parallel with a reporter gene assay. These populations will be genotyped for functional VMAT2 variants and association analyses of gene-environment interactions and pesticide exposures collected in the parent grant will be conducted. In addition, Drosophila genetics will be used to determine how the expression of VMAT affects dopamine-mediated toxicity and identify genes that modulate VMAT function, which will then be examined in the human population for their relevance to increase risk of PD.

Parkinson's Susceptibility Genes and Pesticides (PEG)
Principal Investigator: Ritz
NIEHS/NINDS 10/01/00-09/30/07
Total Direct Cost: $2,653,852
We are testing the gene-environment interaction hypothesis for Parkinson's disease by conducting an epidemiologic population-based case-control study of 400 newly diagnosed PD patients from three rural California counties matched to population controls; in addition we are collecting data for unaffected sibling controls. Environmental and occupational pesticide exposure estimate are derived from California pesticide-use reporting (PUR) and other data. We are examining the effects of gene-environment interactions by testing for associations of PD using multiallelic repeat markers and genotyping intragenic single nucleotide polymorphisms (SNPs) and/or deletions in 50 candidate genes.

PD Consortium: Genetic and Environmental Factors in Parkinson's Disease
Principal Investigator: L. Nelson, Stanford
MJ Fox Foundation 10/01/04-09/30/07

Total Direct Costs $50,000
We established the Consortium for the Study of Genetic and Environmental Factors in Parkinson's disease, with the goal of organizing the collaborative efforts of five investigative groups that have who have conducted (or are conducting) seven case-control studies of PD. For approximately 1700 PD cases and 2100 gender- and age-matched control subjects, we investigate how the risk of developing PD varies according to tobacco and caffeine intake, as well as variants in ten candidate genes that code for proteins that may be involved in conferring the protective effect of these agents.

Alpha Synuclein and Environmental Exposures: A Study in Humans
Principal Investigator: Langston, The Parkinson's Institute
MJ Fox Foundation 01/01/05-12/31/07
Total Direct Costs $100,000
We are investigating the joint effects of: (1) consequences of alpha-synuclein over-production and enhanced mapping of the SNCA promoter region and (2) the biologic effects specific toxicants (e.g., rotenone, paraquat, organochlorine pesticides). We take advantage of two unique cohorts at high risk for pesticide exposure currently evaluated by members of the NIEHS-funded Collaborative Centers for Parkinson's Disease Environmental Research (CCPDER) at the Parkinson's Institute (PI) and UCLA, the Agricultural Health Study cohort and a population-based study of PD and pesticide exposure in rural Central California (the PEG study).

Prostate Cancer and Pesticide Exposure in Diverse Populations in California's Central Valley
Principal Investigator: Cockburn, USC
DOD 05/01/06-12/31/07
Total Direct Costs: 250,000$
This is a pilot study bringing an innovative collaborative approach to prostate cancer research. Specifically, this study will apply novel methods of pesticide exposure assessment using Geographical Information Systems (GIS), examine whether our proposed method of recruiting and approaching cases and controls for a large population-based case-control study will result in acceptable response rates, or whether our sample will be biased with respect to socioeconomic status, race, and disease characteristics, and whether we will be able to obtain sufficient DNA from mailed (Oragene) spit collection kits to assess effect modification by known relevant genes, and have sufficient stored DNA to assess the impact of genes that may be discovered in future.

Traffic-related Air Pollution and Adverse Birth Outcomes
Principal Investigator: Ritz
NIEHS 07/15/01-06/14/07
Total Direct Costs: $641,612
The objectives of this project are to determine whether exposures to elevated and traffic-related ambient air pollution during pregnancy result in low birth weight, preterm birth, intrauterine and postneonatal mortality, or cardiac defects in infants born to women living in the South Coast Air Basin (SoCAB). We performed a cohort study of all births (between 1995 and 1999), fetal and infant deaths (between 1989 and 1997), and conducted a nested case-control study of 2600 women who delivered children in LA in 2003 to collect additional exposure, confounder, and effects modifier data.

Ergonomic Interventions for Sewing Machine Operators
Principal Investigator: Ritz
CDC/NIOSH 10/01/02-09/31/06
Total Direct Costs: $868,262
We are conducting a randomized trial of a newly developed ergonomic intervention in sewing machine operators working in LA garment shops. The ergonomic intervention package includes changes in work-station design, training of employees, and suggestions of improvement in work procedures. We are examining whether interventions can reduce rates of upper extremity, neck (and lower back) musculoskeletal disorders, severity of pain and impairment, and lost-time compared to 'placebo' (control) interventions. This study will provide employers, employees and public agencies with evidence of the effectiveness of ergonomic interventions in order to guide health and safety policy.

Traffic-Related Air Pollution and Acute Respiratory Diseases and Asthma in Children Ages 0-5 in the SoCAB From 1990-2000

Principal Investigator: Ritz
California Air Resources Board 01/06/04-09/30/05
Total Direct Costs: $55,000
The aims of this study are to estimate the transient effects of traffic related and background air pollution in the South Coast Air Basin (SoCab) on the risk for hospitalization for acute respiratory illness and asthma in children ages 0-5 using a case- crossover study design and a time-series analysis.

Assessment of In-Traffic Exposures and Human Reproductive Health
Pilot project Principal Investigator: Ritz; SCEHSC Center Principal Investigator: Froines, UCLA
EPA 07/01/04-06/30/05
Total Direct Costs Pilot Project within the PM-center: $28,000
The goal of this project is to evaluate whether maternal in-vehicle air pollutant exposures during commutes (either in passenger cases, buses or other means of public transportation) affected the risk of low birth weight (LBW) and preterm birth in infants born to women living in Los Angeles County, California between 2003-2004. Commuting behavior (travel time, mileage and/or modeled routes) will be used to evaluate exposure to motor vehicle exhaust pollutants while in-transit

Molecular Epidemiology and Gene-Environment Interaction
Principal Investigator: Zhang, UCLA
NIH/NIEHS R21 ES 011667 04/01/02-03/31/05
Total Direct Costs: $450,000
This was a planning grant for molecular epidemiology in Environmental genome. The award was to establish a molecular epidemiology research program focusing on environmental genome.

Uncontrolled Asthma and Exposure to Air Pollutants: Linking Chronic Disease and Environmental Data Sources
Principal Investigator: Meng, UCLA
CDC/NIOSH/ 10/01/02-09/01/05
Total Direct Costs: $600,000
Based on the California Health Interview Survey (CHIS 2001) data, an extensive air monitoring network, and detailed information on traffic density we are conducting a population-based epidemiologic case-control study to: (1) ascertain the relationship between control of asthma and exposure to air pollutants in Los Angeles County and San Diego County, California; and (2) build and enhance the partnerships between public health and environmental agencies and local communities.

Center of Excellence for Environmental Public Health Tracking
Principal Investigator: Balmes, UCSF
CDC/ATSDR 10/01/02-09/01/05
Total Direct Costs (UCLA only): $300,000
The UCLA part of this center grant uses the data from 5,200 California Health Interview Survey (CHIS 2001) respondents who reported having been diagnosed with asthma at some point in their lives and live in the Greater Bay Area, San Joaquin Valley, and Los Angeles County. Criteria pollutant averages are employed as measures of background ambient air quality and linked with sociodemographic information and data on asthma management, access to care, and risk behaviors collected through CHIS for each targeted respondent.

Community Response to Maternal/Child Heath Disparities
Principal Investigator: Hobel, Cedars Sinai
NIH 04/1/03-9/30/05
The major goals of this study are to examine the interrelating biological and social-behavioral factors that contribute to health disparities in pregnancy outcomes and infant and early childhood mortality and morbidity. We will participate as one of five selected sites in the nation to plan for a multi-centered, community-based study examining the relationship between environmental factors and child health disparities.

Extension of the Rocketdyne/Al Worker Cohort Through 1999
Principal Investigator: Ritz
California Cancer Research Program 07/01/00-06/30/04

CRP award #00-00781V-20218
Total Direct Cost: $324,508
We extended the mortality follow-up of two previously established cohorts of workers employed at Rocketdyne/Atomics International (now Boeing North American) facility for an additional 5 years and added a cancer incidence component for the period 1972-1998. This study allowed evaluating the impact of radiation and some known animal carcinogens on cancer mortality and morbidity.

Assessment Scale for End-of-Life Care in End-Stage Dementia
Principal Investigator: Ackerman, UCLA
Alzheimer's Association 10/01/00-09/30/03
Total Direct Costs: $217,583
This pilot project developed a scale to assess end-of-life care for end-stage dementia patients and evaluated its performance using mortality data.

Pilot grant from Southern California Center for Airborne Particulate Matter (SCCAPM)
Principal Investigator: Froines, UCLA; Pilot grant Principal Investigator: Ritz
U.S.-EPA-Star grant 07/01/01-12/31/02
Total Direct Cost: $12,000
The pilot grant supported exposure assessment for an epidemiologic study of traffic related adverse birth outcomes.

Evaluation and Validation of Pesticide Use Reporting in California
Principal Investigator: Ritz
UC Toxic Substances Research & Teaching Program 07/01/99-06/30/01
Total Direct Costs: $ 50,000
The goal of this pilot grant was to use biomarker data to evaluate the validity of pesticide exposures estimates derived from geographic models of environmental exposure based on pesticide use reports and land use maps in California residents.

Identify and Reduce Work Hazards in Home Health Care Workers
Principal Investigator: Ritz
Institute of Labor and Employment Pilot Study 02/01/01-30/08/01
Total Direct Costs: $ 7,500
This pilot project developed and tested a survey instrument and collected preliminary data for a study of job hazards in 74,000 home health care workers in LA county.

Pilot Study for Gene-Environment Interaction and Parkinson's Disease Study
Principal Investigator: Ritz
APDA Center Pilot Grant 03/01/99-12/31/00
Total Direct Costs: $35,000
This pilot project involved establishing data resources to improve exposure measures for pesticides, and setting up of a county-wide networks to reach incident Parkinson's cases in rural California.

Development of a Temporary Parkinson's Disease Registry for Southern California
Principal Investigator: Ritz
APDA/Pilot Grant from the PD-center at UCLA 03/01/99-12/31/00
Total Direct Costs: $10,000
This pilot project established mechanisms to obtain incident Parkinson's cases in rural California using information provided by local health care providers, Parkinson's disease foundations, clinics, and Medicare, and to determine which data sources exist for the application of capture-recapture methods to validate coverage of a future PD registry.

Modeling Air Pollution and Birth Defects
Principal Investigator: Ritz
CBDMP Grant/SCEHS/NIEHS Pilot Grant 07/01/00-09/30/00
Total Direct Costs: $5,600
The objective of this project was to examine the usefulness of some advanced statistical modeling procedures in order to determine whether exposures to elevated levels of ambient air pollutants (PM10,

CO) at the levels found in the South Coast Air basin (SoCAB) basin caused defects of the cardiac system of fetuses.

Pesticide Exposure Modeling Based on Historical Use Reporting in California to Investigate Long-Term Health Effects
Principal Investigator: Ritz
UCLA-USC NIEHS-Center Pilot Grant 05/01/99-04/30/00
Total Direct Costs: $18,000
The objectives of this pilot grant were to develop a geographic model for pesticide exposure of California residents between 1950 and 1990 using satellite images of crops, aerial photographs, and Pesticide Use Reporting Data from the California Department of Pesticide Regulations.

Epidemiologic Study to Determine Possible Adverse Health Effects on Rockwell/Rocketdyne Workers from Exposure to Radioactive and Hazardous Substances
Principal Investigator: Morgenstern, UCLA
CPHF/DOE/DE-FG-03-91SF18983 01/10/93-03/31/99
Total Direct Costs: $740,000
The major goal of this study was to test the hypothesis whether exposure to toxic chemicals and ionizing radiation among Rockwell/Rocketdyne workers caused an excess of cancer mortality.

Hazard Surveillance in the Defense Nuclear Industry
Principal Investigator: Froines, UCLA
CDC/NIOSH/R01-CCR912034 09/01/95-08/31/99
Total Direct Costs: $1,244,745
The major goals of this project were to develop an integrated theory, approach, and methodology to exposure assessment and hazard surveillance in the U.S. defense nuclear industry.

The Influence of Air Pollution in the Los Angeles Metropolitan Area on the Occurrence of Birth Defects, 1990-1993
Principal Investigator: Ritz
SCEHSC/NIEHS/UCLA-USC NIEHS-Center Pilot Grant 09/01/97-09/30/98
Total Direct Costs: $24,000
The objective of this pilot project were to examine whether the exposure of pregnant women to elevated levels of ambient air pollutants (Ozone, NO2, PM10, CO) at the levels found in the Los Angeles Metropolitan Area or the South Coast Air basin (SoCAB) basin cause low birth weight or preterm birth.

RESEARCH CONDUCTED IN GERMANY (1984-1989)
Health effects of airborne-dioxin exposure in Hamburg nursery schools
Rheumatic disorders, working conditions and coping behaviors in female office workers
Work-related knee-joint and elbow injuries in pipe-fitters and welders
Back and neck pain, psycho-social and ergonomic stresses in nursing professions

HONORS AND AWARDS

1999	UCLA Faculty Career Development Award
1999	'Rothman' award presented at SER by C. Poole
1989-1992	Post-doctoral fellowship received from DAAD ("German Academic Exchange Office of the Ministry of Research and Technology")
2001	Delta-Omega Award
2007	Robert M. Zweig M.D. Memorial Award (Clean Air Award) from the South Coast Air Quality Management District (AQMD)
2009	Award from the American Parkinson's Disease Association for outstanding contributions to the medical and scientific communities and for my work towards the advancement of Parkinson's disease research

TEACHING

UCLA, School of Public Health, graduate courses, 1995-present
Epidemiology Methods (Core methods course (200B) in the UCLA Epidemiology program)
Environmental Epidemiology
Occupational Epidemiology
Advanced Methods in Occupational and Environmental Epidemiology
Seminar: Occupational and Environmental Cancers
Seminar: Policy Issues in Occupational and Environmental Health

University of Hamburg, Medical School, 1984-89
Lectures and seminars in Medical Sociology for medical students
Lectures and seminars in Psychiatry for medical students

ADVISING AND MENTORING OF DOCTORAL STUDENTS (PH.D) AND POSTDOCTORAL FELLOWS (SUBJECT OF DISSERTATION OR FELLOWSHIP)– *note: this list only includes primary advisees (i.e. chair of committee and not member of dissertation committee) and does not include master level students*
At UCLA:

1997 - 2001	Kurt Straif (Cancer mortality in the German rubber industry)
1998 - 2000	Timothy Clary (Pancreatic cancer mortality and pesticide use in California)
1998 - 2004	Michelle Wilhelm (Traffic-related air pollution and pregnancy related health effects)
1998 - 2004	Rudy Rull (GIS modeling of pesticide exposure and neural tube defects)
1998 - 2004	Anusha Krishnadsan (Occupational physical activity and prostate cancer incidence)
2001 - 2004	Yingxu Zhao (Work place exposures to chemicals and cancer incidence)
2003 - 2004	Gail Asleson Kang (*Movement Disorder Fellow*: Clinical characteristics of PD patients)
2002 - 2006	Pin-Chieh Jason Wang (Ergonomic interventions and health effects in LA garment workers)
2003 - 2006	Chad Lewis (TTHM contamination in drinking water and adverse birth outcomes)
2003 - 2005	Kathrine Hoggatt (co-mentored with Dr Greenland: Air pollution and adverse birth outcomes)
2004 - 2008	Angelika Wahner (Doctoral student & postdoctoral fellow: Parkinson's disease, genetic factors and anti-inflammatory drug use)
2004 - 2008	Marie Sharp (The Latina Paradox in Birth Outcomes)
2004 - 2008	Sadie Costello (Parkinson's disease and life style factors)
2005 - 2008	Shannon Rhodes (Doctoral student & postdoctoral fellow: Iron genetics and Parkinson's disease)
2008 - 2010	Nicole Gatto (Postdoctoral fellow: Vitamin D, sunlight and Parkinson's disease)
2004 - 2008	Amanda Colligan (Residential pesticide exposure and Parkinson's disease)
2005 - 2012	Anthony Wang (Occupational pesticide exposures and Parkinson's disease)
2007- 2011	JoKay Ghosh (Air toxics and adverse birth outcomes)
2008- 2013	Tracy Becerra (Autism and race ethnicity in Los Angeles)
2008- 2013	Erin Jacob-Marcotte (Pesticides in pregnancy and childhood cancers)
2011-2012	Anshu Shresta; post-doctoral fellow (Childhood cancers and the environment)
2011-2013	Pei Chen Lee; postdoctoral fellow (Air pollution and pregnancy biomarkers)
2009-2014	Shilpa Narayan (Progression in Parkinson's disease)
2009-2014	Christina Lombardi (Air pollution and childhood cancers)
2011-2014	Zeyan Liew: PFOA exposures in the Danish birth cohort and ADHD and autism)
2012 -present	Gretchen Bandoli (Stress, asthma and birth outcomes in LA)
2012 -present	Kristina Vanderwaal Hool (breast cancer and methylation patterns)
2011- present	Kim Paul (Gene-environment interactions in Parkinson's – PASIDA study)
2011- present	Xin Cui (Bias analysis in the PASIDA study of Parkinsons)
2011- present	Andrew Park (Pesticides and childhood cancers)
2012- present	Vivian Alonso (Nutrition, vitamins use and reproductive health)
2013- present	Yu-Hsuan Chuang (Parkinsons, gene methylation, and gene-environment interactions)
2013- present	Xiaoqing Xu (Pharmaceuticals and childhood cancers in Denmark)
2013- present	Matt Feaster (Occupations risk factors for childhood cancers)
2013- present	I-Fan Shih (Parkinsons and physical activity)
2013- present	Negar Omid (Childhood cancer risk factors)

2013- present Aline Duarte (Parkinson's non-motor symptoms)
2013- present Chenxiao Ling (Bias analysis in environmental epidemiology)
2014- present Cynthia Kuster (Parkinsons' and estrogen receptors)
2014- present Zuelma Esquivel (Childhood cancer risk factors)
At University of Washington:
2004-2006 Kathrine Carr (*Postdoctoral Fellow*: Bronchiolitis and air pollution in LA infants)
At UCI:
2011-2013 Jun Wu (junior faculty mentor for W. Rosenblith award given by HEI)
At the University of Copenhagen, Denmark:
2008-present Line Kenborg (Parkinson's disease and outdoors work and sunlight exposures)
2007-2009 Kathrine Rugbjerg (Parkinson's disease and head trauma and auto-immune diseases)
University of Umea/Sweden
2014 Opponent for doctoral student David Olsson (Air pollution and PTB and preeclampsia in Stockholm)

PARTICIPATION IN GRANT AND CENTER REVIEWS
Reviewer on a NCI Special Emphasis Panel "Improving Exposure Assessment in Environmental and Occupational Epidemiology of Cancer", May 2001
Reviewer of the NIEHS-funded Columbia University Environmental Health Sciences Center, May 2002
Reviewer of the Charles Harkin Award Application for Research in Thyroid Cancer, NIH, April 2003
Reviewer of the Wellcome Trust Application "Pre and post-natal exposure to particulate matter and pregnancy and infant outcomes: an historical cohort study", 2003
Reviewer of the Health Effects Institute's (HEI) Walter Rosenblith New Investigator Award application, April 2003
Reviewer of pilot grants for the Southern California NIEHS center grant (2004 and 2005)
Reviewer of pilot grants for the UCLA-CCPDER center (NIEHS funded) (2003 and 2005 and 2008)
Reviewer for NCI, Epidemiology of Cancer (2004/05 Council EPIC)
Reviewer for several NIH, Department of Health & Human Services meeting applications, 2003-2005
Reviewer (Chair of Review Committee) for a NIEHS-PO1 application (2004)
Appointment to Review Committee of the European Science Foundation (ESF) (2005)
Annual Review of SCEHSC Pilot Project Submission (permanent member 2004-current)
Institutional Patient-Oriented Career Development Programs in the Environmental Health Sciences [K12] (ES06-005). (2007)
Conference grant applications (2004-2007)
NIH reviewer for Outstanding New Environmental Scientist (ONES) award in the Environmental Health Sciences (2006)
Member of the EPA's Clean Air Scientific Advisory Committee (CASAC) Carbon Monoxide (CO) Review Panel (2008-current)
Grant review for an internal NIEHS scientist's application (Dr. Chen) (2007 and 2008)
Grant review for NIEHS special emphasis panels 2009-2010
Grant review for NIH-BCHI 2011
Pilot grant review for the Northern California Center for the National Children's Study –Pilot Projects Program August 2011
External Review of the Neurology Department at Columbia (NY), 2011
Scientific Review of Superfund Site Projects as EAC member for University of Washington, 2012
External Review of the Swiss Tropical and Public Health Institute (TPH), 2012 and 2013
External Review of the Epidemiology Branch at NIEHS, 2013
Review for Harvard NIEHS center pilot grant, 2014
Review of applications for Health Effects Institute (HEI Boston), Rosenblith awardees, 2014
Review for Mount Sinai (NY) NIEHS center pilot grants, 2014
Review for NIEHS USC-UCLAEnvironmental Health Science center pilot grants, 2014
Review of NIEHS conference grants July 2015
Review of Parkinson's disease grant for Parkinson's UK foundation in Great Britain

JOURNAL REVIEWER FOR:
American Journal of Epidemiology
Epidemiology
International Journal of Epidemiology
Annals of Epidemiology

Environmental Health Perspectives
Environmental Health
Occupational and Environmental Medicine
Archives of Neurology
Annals of Neurology
Neurology
Movement Disorders
Pediatrics
JAMA
Lancet
Parkinson's and Related Disorders
Pharmacogenetics and Genomics
Journal of the Air & Waste Management Association
Journal of Exposure Analysis and Environmental Epidemiology
Chemosphere
Zeitschrift Sozial- und Präventivmedizin (SPM)
Human Reproduction
Women & Health
Etc.

INVITED SEMINARS AND LECTURES (SELECTED)

1. The Health Effects of Low-level Ionizing Radiation, USC, Health Sciences 1996
2. Work Environment and Health, UCLA Health Sciences 1996
3. The Effects of Carbon Monoxide Exposure on Low Birth Weight in the LA Metropolitan Area, 1989-1993, USC, Southern California Environmental Health Sciences, 1997
4. Cancer Mortality in Radiation Workers, USC Southern California Environmental Health Sciences, 1997.
5. Basic Principles of Reproductive Epidemiology, European School of Risk Assessment in Reproduction" in Florence/Italy December, 1997.
6. The Rocketdyne/Al Worker Health Study: Results and Lesson's Learned, California Department of Health Services, Occupational Health Branch, 1998
7. Air Pollution and Low Birth Weight in Southern California, GSF Munich Germany, 1998.
8. Air Pollution and Adverse Birth Outcomes: Methodological Issues and First Results, Southern California Environmental Health Science Center, USC, 1998.
9. Gene-Environment Interaction and Parkinson's Disease, Neurology Grand Rounds, UCLA 1998
10. Air Pollution and Adverse Birth Outcomes in Southern California, Dept. of Reproductive Epidemiology, University of Michigan, East Lansing, 1999.
11. Methodologic Issues in Studying of Gene-Environment Interaction, GSF Munich Germany, 1999
12. Methodologic Aspects of Studying Cancer Mortality in Radiation Workers, Dept. of Epidemiology, University of Michigan, East Lansing, 2000.
13. Cancer Mortality in Fernald Uranium Workers, NIOSH, Cincinnatti, 2000.
14. GIS Modeling of Pesticide Exposures in California, Dept. Environmental Epidemiology, GSF Munich Germany, 2000
15. Traffic-related Air Pollution and Adverse Birth Outcomes in Southern California, Dept. Environmental Epidemiology, GSF Munich Germany, 2000
16. Studying Parkinson's disease in Populations; American Parkinson's Disease Association conference for patients and care providers at UCLA, 2001
17. From the Epidemiology of Parkinson's Disease to Gene-Environment Interactions, VA-PD conference, Woodland Hills, 2001
18. GIS Modeling of Air Pollution and Pesticide Exposures in California, USC-UCLA NIEHS Town hall meeting; Dec, 2001
19. GIS Modeling in the context of a Gene-Environment Interaction study of Parkinson's disease, Dept. Environmental Epidemiology, GSF Munich Germany, 2001
20. The Epidemiology of Parkinson's Disease, Conference of the Society for Research on Amyotrophic Lateral Sclerosis, Colorado May 2002
21. Traffic-related Air Pollution and Reproductive Health Effects: An Overview; Environmental Health Sciences seminar at UC Riverside, Feb. 2002
22. Reproductive Health Effects due to Carbon Monoxide Air Pollution in Southern California, NRC

Subcommittee on Health Effects from CO pollution meeting at UC Irvine, April 2002
23. Traffic-related Air Pollution and GIS Modeling in Southern California, USC-GIS Workshop Pasadena, May 2002
24. Health Effects Modeling with GIS, USC-GIS Workshop Public Forum at USC, May 2002
25. Dopamine Imbalance and Oxidative Stress in Parkinson's Disease, VA Research Conference on PD and Movement Disorders, Los Angeles 2002
26. The Center for Gene Environment Interaction in Parkinson's disease (CGEP) at UCLA: Dopamine Imbalance in Parkinson's Disease, Inaugural NIEHS Conference at the Parkinson's Institute in Sunnyvale CA, August 2002
27. Air pollution effects on birth outcomes: An overview. Health Effects Institute, Annual conference held at Georgetown University; 2003
28. Linking air pollution effects and adverse birth outcomes in the Los Angeles basin throughout the 1990s. U.S. EPA, Chapel Hill, NC; 2003
29. Air Pollution and Adverse Birth Outcomes in the South Coast Air Basin, 1989-2000; Conference of the Czech NAS meeting on air pollution effects (Dr. Sram), Prague, 2003.
30. Air pollution and adverse birth outcomes, an update on recent developments. Department of Preventive Medicine at the University of Southern California, 2003
31. GIS modeling of environmental exposures: applications to air pollution and pesticide exposures. Department of Environmental Health, Harvard, 2004
32. Air pollution models of adverse birth outcomes. Department of Epidemiology at the University of North Carolina, 2004
33. Parkinson's disease, metals and pesticides. Department of Toxicology, Symposium on Toxics Risks and Aging, Duke 2005
34. Air pollution and adverse birth outcome research in the SoCAB from 1995-2005. California Air Resources Board, Sacramento, Sept 2005
35. Parkinson's disease and pesticide exposure assessment in farming communities in the California Central Valley. Symposium of the Ramazzini Conference, Bologna, Italy Sept. 2005
36. Parkinson's disease and aging. UCLA Center on Aging Research Conference on Aging 2006.
37. Air Pollution and Asthma in Children. AQMD Asthma Impacts of Air Pollution Conference Los Angeles, Feb. 2006
38. Parkinson's disease and pesticides in the Central California Valley. NIEHS center at Columbia University, NY 2007
39. Assessing pesticides exposures for prostate cancers in the Central California Valley. IARC, Lyon 2007
40. Air pollution and adverse birth outcomes in LA. INSERM, Paris 2007
41. Gene Environment Interactions in Parkinson's disease. CREAL Institute, Barcelona 2008
42. Latest results on Gene Environment Interactions in Parkinson's disease. INSERM, Paris 2008
43. Re-assessing Gene Environment Interactions in Parkinson's disease. MDS conference symposium, Chicago 2008
44. Methodological Issues in studying risk factor for Parkinson's disease in populations. MDS conference symposium, Chicago 2008.
45. Environmental and occupational health studies in California. University of Dublin 2008
46. Air pollution, pregnancy and child health; Healthy Development and Ageing Workshop; British Foreign & Commonwealth Office, LA 2009
47. Air pollution, pregnancy and child health; Physician's for Social Responsibility Environmental training 2009
48. Air pollution and adverse pregnancy outcomes in LA; Annenberg School of Journalism 2009
49. Parkinson's disease and pesticides. George Washington University Environmental Health Program 2009
50. LUR model for traffic related exposures and adverse birth outcomes in LA. Helmholtz Center Munich 2010
51. Parkinson's disease and gene–pesticide interactions. Symposium on Predictive Health, Human Health: Molecules to Mankind. Emory University Atlanta Dec 2010
52. Air Pollution and Adverse Birth Outcomes, invited speaker at HEI annual conference Boston 2011
53. Parkinson's disease in Denmark; the PASIDA study; University of Odense Denmark, May 2011
54. Gene-environment interactions in Parkinson's disease, invited symposium speaker at the International Society for Environmental Epidemiology (ISEE), Barcelona 2011
55. Air Pollution and the Brain; invited plenary speaker at the annual conference of the International Society for Environmental Epidemiology (ISEE), South Carolina 2012

56. Air Pollution and Autism; invited speaker at the University of Aarhus, Denmark 2012
57. Air Pollution, Children and Women's Health in LA; invited speaker at the SCAMQD conference for stakeholders, LA 2013
58. How to be an Epidemiologist, invited speaker at SER, Boston 2013
59. Pesticides and Neurodegeneration; invited speaker at the Conference on safety of fumigated container shipping in Berlin, Germany 2014
60. History of Environmental and Occupational Epidemiology, invited speaker at SER, Seattle 2014
61. History of Air Pollution, Adverse Birth Outcomes and Children's Health in California; Invited Plenary Speaker for the ISEE Young Researcher Conference, Barcelona 2014
62. Environmental Causes of Adverse Neurodevelopment; Invited Speaker at the B-Debate Barcelona (Environment and Child Brain Development: the Challenges in the Global Context) Conference, Barcelona 2014
63. Autism Epidemiology; invited speaker at the annual CART meeting UCLA 2014
64. Epidemiology of Parkinson's disease, invited speaker at annual GEO-PD meeting Vancouver CA, 2014
65. Parkinson's Disease Epidemiology: a Gene-Environment Perspective, invited speaker at the Neurogenetics Institute of Luebeck/Germany, 2015

PUBLICATIONS

PEER REVEIWED JOURNAL ARTICLES (*indicates mentored students/fellows)

1. **Ritz B**. Humeral Epicondylitis Among Gas- And Waterworks Employees. Scandinavian Journal of Work, Environment and Health, 1995 Dec, 21(6): 478-86.
2. **Ritz B**, Heinrich J, Wjst M, Wichmann E, Krause C. Effect Of Cadmium Body Burden On Immune Response Of School Children. Archives of Environmental Health 1998,Jul-Aug; Vol 53: 272-280
3. **Ritz B**, Morgenstern H, Froines J, Young B. Effects Of Exposure To External Ionizing Radiation On Cancer Mortality In Nuclear Workers Monitored For Radiation At Rocketdyne/Atomics International. AJIM 1999, Jan; Vol 35: 21-31.
4. **Ritz B**, Yu F. The Effect Of Ambient Carbon Monoxide On Low Birth Weight Among Children Born In Southern California Between 1989 and 1993. Environmental Health Perspectives 1999 Jan, 107(1):17-25. PMCID: PMC1566307
5. Heinrich J, Hoelscher B, Wjst M, **Ritz B**, Cyrys J, Wichmann HE. Respiratory Diseases And Allergies In Two Polluted Areas In East Germany. Environmental Health Perspectives 1999,Jan; 107(1):53-62. PMCID: PMC1566314
6. **Ritz B**, Morgenstern H, Moncau J. Age At Exposure Modifies The Effects Of Low-Level Ionizing Radiation On Cancer Mortality In An Occupational Cohort. Epidemiology 1999, Mar; 10(2):135-140.
7. **Ritz B**. Radiation Exposure and Cancer Mortality In Uranium Processing Workers. Epidemiology, 1999, Sep; 10:531-538
8. **Ritz B**. Cancer Mortality Among Workers Exposed To Chemicals During Uranium Processing. JOEM 1999, Jul;41(7):556-566.
9. **Ritz B**, Morgenstern H, Froines J., Moncau J. Chemical Exposures Of Rocket Engine Test Stands Personnel And Cancer Mortality In A Cohort Of Aerospace Workers. JOEM, 1999 Oct; 41(10): 903-910.
10. Jacob B, **Ritz B**, Heinrich J, Hoelscher B, Wichmann HE. The Effect Of Low-Level Blood Lead On hematologic parameters In Children. Environmental Research, 2000 Feb, 82 (2): 150-159.
11. **Ritz B**, Yu F. Parkinson's Disease Mortality And Pesticide Exposure In California 1984-1994. International Journal of Epidemiology, 2000 Apr, Vol. 29:323-329.
12. Hoelscher B, Heinrich J, Jacob B, **Ritz B**, Wichmann HE. Gas Cooking, Respiratory Health And White Blood Cell Counts In Children. Int. J. Hygiene and Environ Health, 2000 Mar; 203 (1): 29-37.
13. **Ritz B**, Morgenstern H, Crawford-Brown D,Young B.The Effects Of Internal Radiation Exposure On Cancer Mortality In Nuclear Workers At Rocketdyne/Atomics International. Environ Health Perspect, 2000 Aug; 108(8):743-751. PMCID: PMC1638302
14. **Ritz B**, Yu F, Chapa G, Fruin S. Effect Of Air Pollution On Preterm Birth Among Children Born In Southern California Between 1989 And 1993. Epidemiology, 2000 Sep; 11(5):502-511.
15. Morgenstern H, **Ritz B**. Effects of Radiation And Chemical Exposures On Cancer Mortality Among Rocketdyne Workers: A Review of Three Cohort Studies. Occup. Med. 2001 Apr-Jun;16(2): 219-237.
16. **Ritz B**, Yu F, Chapa G, Fruin S, Shaw G, Harris J. Ambient Air Pollution And Risk of Birth Defects in Southern California. Am J Epidemiol 2002 Jan 1;155:17–25.

17. **Ritz B**, Hoelscher B, Frye C, Meyer I, Heinrich J. Allergic sensitization owing to 'second-hand' cat exposure in schools. Allergy 2002 Apr;57(4):357-61
18. Jacob B, **Ritz B,** Gehring U, Koch A, Bischof W ,Wichmann HE, Heinrich J for the INGA-Study group. Indoor Exposure To Molds And Allergic Sensitization. Environ Health Perspect. 2002 Jul;110(7):647-53. PMCID: PMC1240910
19. Clary T, **Ritz B**. Pancreatic Cancer Mortality And Organochlorine Pesticide Exposure In California, 1989-1996. Am J Ind Med. 2003 Mar;43(3):306-13.
20. Wilhelm M, **Ritz B.** Residential Proximity To Traffic And Adverse Birth Outcomes In Los Angeles County, California, 1994-1996. Environ Health Perspect. 2003 Feb; 111(2):207-16. PMCID: PMC1241352
21. Rull R, **Ritz B**. Historical Pesticide Exposure In California Using Pesticide Use Reports And Land-Use Surveys: An Assessment Of Misclassification Error And Bias. Environ Health Perspect. 2003 Oct; 111(13):1582-9. PMCID: PMC1241678.
22. Hashibe M, **Ritz B**, Le AD, Li G, Sankaranarayanan R, Zhang ZF. Radiotherapy For Oral Cancer As A Risk Factor For Second Primary Cancers. Cancer Letters 2005 Apr 8; 220(2):185–195.
23. **Ritz,B**, Tager I, Balmes J. Can Lessons From Public Health Disease Surveillance Be Applied To Environmental Public Health Tracking? Environ Health Perspect. 2005 Mar; 113(3):243-9. PMCID: PMC1253746
24. Kang G, Bronstein JM, Masterman DL, Redelings M, Crum JA, **Ritz B**. Clinical Characteristics In Early Parkinson's Disease In A Central Californian Population-Based Study. Mov Disord. 2005 Sep; 20(9):1133-42. PMCID: PMC3643967
25. Ponce NA, Hoggatt KJ, Wilhelm M, **Ritz B**. Preterm Birth: The Interaction Of Traffic-Related Air Pollution With Economic Hardship In Los Angeles Neighborhoods. Am J Epidemiol. 2005 Jul 15;162(2):140-8.
PMCID: PMC3636775
26. Wilhelm M, **Ritz, B**. Local Variations In CO And Particulate Air Pollution And Adverse Birth Outcomes In Los Angeles County, California, USA. Environ Health Perspect; 2005 Sep;113(9):1212-21. PMCID: PMC1280404
27. Rull RP, **Ritz B**, Shaw GM. Validation Of Self-Reported Proximity To Agricultural Crops In A Case-Control Study Of Neural Tube Defects. Journal of Exposure Analysis and Environmental Epidemiology; J Expo Sci Environ Epidemiol. 2006 Mar;16(2):147-55.
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EXHIBIT B

Studies excluded from the present review and the reasons for exclusion

Brown et al, "Pesticide exposures and multiple myeloma in Iowa men."[1]	Only provided results for multiple myeloma.
Fritschi et al, "Occupational exposure to pesticides and risk of non-Hodgkin's lymphoma." [2]	This paper did not report an effect estimate specific to glyphosate
Flower et al, "Cancer risk and parental pesticide application in children of Agricultural health study participants."[3]	Study took place in children; no specific glyphosate- lymphoma associations were reported.
Hoar et al, "Agricultural herbicide use and risk of lymphoma and self-tissue sarcoma."[4]	Results specific to glyphosate were not reported.
Kachuri et al, "Multiple pesticide exposures and the risk of multiple myeloma in Canadian men."[5]	Results only reported for multiple myeloma.
Landgren et al, "Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study."[6]	Monoclonal gammopathy of undetermined Significance (MGUS) is a precursor condition to multiple myeloma.
Sorahan, "Multiple Myeloma and Glyphosate Use: A Re-Analysis of US Agricultural Health Study (AHS) Data."[7]	Only provided results for multiple myeloma.
Waddell et al, "Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States)."[8]	This study did not report on glyphosate.
Zhang et al, 2016, "Health effect of agricultural pesticide use in China: implications for the development of GM crops."[9]	This article examined blood chemistry measures in relation to glyphosate, (markers for renal and hepatic function such as electrolytes, B vitamins, serum glucose, C-reactive protein, and peripheral nerve conduction). Not directly relevant for NHL

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EXHIBIT C

Compensation

My rates for expert work are $550.00/hour and $5,000.00/day for deposition and trial testimony.

Prior Testimony

I have not given a deposition or trial testimony in the last four years.

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1 EPIDEMIOLOGY AND PREVENTION

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Epidemiology is the study of disease in populations, including its distribution, determinants, natural history, and survival. Rather than the individual patient, its perspective is that of public health. The traditional focus and goal of epidemiology has been the determination of the incidence and mortality rates of cancer in different populations and subgroups, as well as the identification of risk factors for the purpose of disease prevention and control through primary prevention and screening interventions; more recently, the methods of epidemiology have been applied to clinical questions, including the assessment of treatment outcomes, such as survival, and the long-term sequelae of cancer and its treatment.

Because of its emphasis on populations, epidemiology generally uses rates (with denominator populations—rates standardized to a population—and time frames) or relative measures rather than absolute figures to measure relevant statistics. Descriptive epidemiology, the usual starting point for epidemiologists, encompasses incidence and mortality rates, survival rates, and time trends. Incidence and mortality rates are commonly expressed as the number of newly diagnosed patients or deaths per 100,000 in the group at risk.

These rates are usually age- and gender-adjusted, meaning they are mathematically adjusted to a standard population to remove the effects of a population's age and gender distribution, which may change over time. Cancer is primarily a disease of older people. With the extensive increase during the past 30 years in the number of people in the United States age 70 and older, the number of cancer cases occurring annually also has increased or only slightly diminished because cancer is an age-dependent disease. Furthermore, because women have a life expectancy 7 years longer than men, there are substantially more older women than men, so a difference in gender distribution would magnify or diminish with age as well. Thus, adjusting cancer rates for age and gender removes the effects of gender and age. As a result, a true change in cancer rates because of prevention, treatment, or new etiologic factors must be assessed by increases or decreases in age- and gender-adjusted incidence and mortality rates (Figs. 1-1, 1-2, and 1-3).[1,2]

Survival is defined as the time from diagnosis to death. A commonly used measure is the proportion of people alive at 5 years after diagnosis (Table 1-1). For some cancers, such as breast or prostate cancer, this time frame may be too short, as recurrences and deaths may continue to occur long after 5 years.

The American Cancer Society (ACS) publishes an annual estimate of the absolute number of new cancer cases and deaths.[2] These numbers are widely quoted, especially by the lay press. As noted above, it should be emphasized that these figures are not rates and are subject to fluctuations in the age and gender distribution of the population. ACS also publishes time trends of incidence and mortality rates for major cancers during the past 75 years; these figures can give interesting insights into the inroads made by primary prevention, screening, and treatment, as

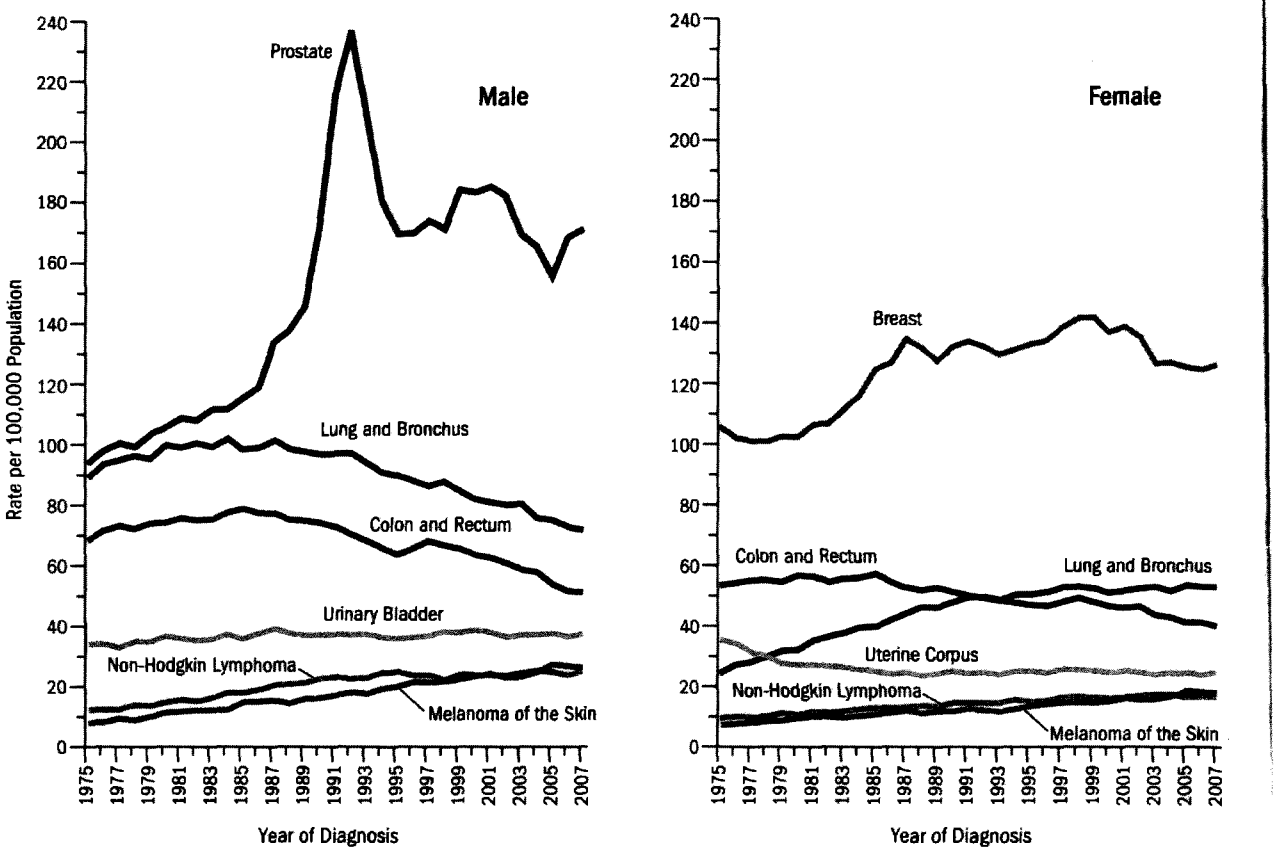

Fig. 1-1 U.S. annual age-adjusted cancer incidence rates (1975 to 2007) among men and women for selected cancers.[2]

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well as into changes brought about by increases or decreases in risk factors (Figs. 1-1, 1-2, and 1-3).[1,2]

Figures 1-2 and 1-3 show the changes in mortality for selected cancers since 1930. They illustrate the dramatic rise in mortality for lung cancer that accompanied the rise in tobacco use in the 20th century, peaking in men around 1985 and then falling 20 years after the Surgeon General's reports of 1964 and 1968, which publicized the hazards of cigarette smoking and its link to lung cancer. As tobacco use has fallen to around 20% in males, the lung cancer incidence and mortality rates have fallen and will continue to fall for the foreseeable future. Another dramatic change has been the fall in gastric cancer, which was the leading cause of cancer mortality in the United States prior to World War II. Most experts attribute this decline to the increased availability of the electric refrigerator and the concomitant increased consumption of fresh meat, fruits, and vegetables, as opposed to smoked and cured foods, which contain nitrites and other potentially carcinogenic agents.[3] One can also see among women a dramatic fall in uterine cancer, primarily reflecting the uterine cervix, and attributable to the widespread use of the Pap smear for screening after World War II. A decline in breast cancer mortality after the mid-1980s has been attributed to a combination of mammographic screening and advances in treatment, such as the use of adjuvant therapy.[4,5]

On the incidence figures (Fig. 1-1), the rise in prostate cancer incidence after 1985 is the most salient curve and reflects the introduction of prostate-specific antigen testing to the clinical laboratory and its widespread use for screening. A rise in the incidence of cutaneous melanoma in both men and women has been attributed to both a change in sun exposure patterns in the population and increased skin screening.[6,7]

Table 1-1 Definition of Terms Related to Survival

Survival time	Time from the initial diagnosis of cancer to death
Disease-free survival	Time from complete remission to relapse of disease
5-year survival rate	Proportion of patients who are alive 5 years after the time of diagnosis
Disease-specific survival rate	Proportion of patients who have not died of the specific disease (does not take into account deaths unrelated to the disease)
Overall survival rate	Proportion of patients who are alive at a specific time after the diagnosis (takes into account all causes of death)

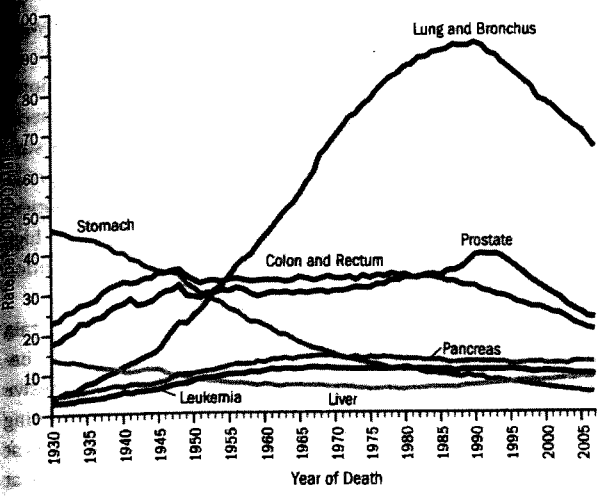

Fig. 1-2 U.S. annual age-adjusted cancer death rates (1930 to 2007) among men for selected cancers.[2]

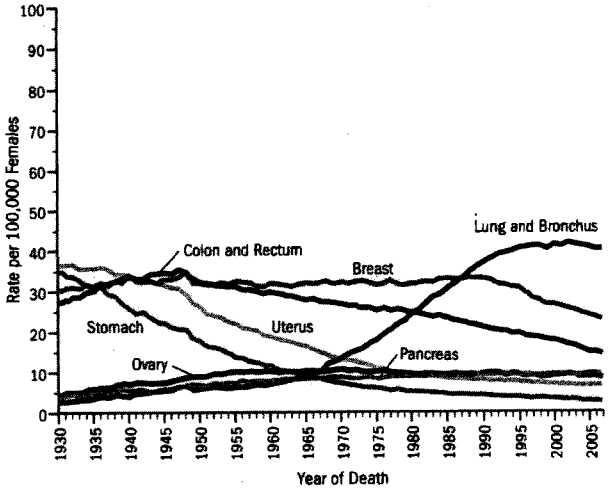

Fig. 1-3 U.S. annual age-adjusted cancer death rates (1930 to 2007) among women for selected cancers.[2]

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KEY POINTS

- Epidemiology is the study of the distribution, etiology, and natural history of disease in populations.
- Epidemiology can include assessment of treatment outcomes, disease prevention, and disease screening.
- Epidemiology addresses these issues with a public health and public policy perspective as opposed to the perspective of the individual patient.

RISK

Much of epidemiology involves the assessment of cancer risk. A person can be at increased risk of cancer because of either extrinsic or intrinsic factors, or a mix thereof.

- Extrinsic influences are factors outside of the individual's own body, such as environmental pollutants, cultural/lifestyle habits, medication use, infectious factors, and diet.
- Intrinsic influences are factors unique to each person, such as genetics.
- To assess etiology, risk is usually reported relative to another population. For example, in 2005, the breast cancer mortality rate for black women was 35.6 per 100,000, and the rate for non-Hispanic white women was 25.8 per 100,000. During that period, the relative risk of death for black women was 1.38 times that of white women (35.6 divided by 25.8).[8]

From an epidemiologic perspective, an etiologic agent or risk factor is anything that increases the probability that an individual will develop the disease. These risk factors can include demographic characteristics (e.g., increasing age or race/ethnicity) or lifestyle and behavioral factors, such as smoking. They also include endogenous factors, such as genetic mutations that have been identified as predisposing a person for a disease, such as *BRCA1* and *BRCA2*. Most cancers undoubtedly arise from a combination of genetic and exogenous factors that interact to define certain demographic patterns. These patterns are recognized as the populations in which a specific cancer is most likely to occur.

Certain genetic mutations occur with relatively high frequency but convey only a slight increase in probability of the cancer occurring. These are referred to as genetic polymorphisms and are usually thought to provide increased susceptibility to an environmental carcinogen or to modify risk in some other way. For example, genetic polymorphisms for the cytochrome P450 enzyme system that metabolizes carcinogens in cigarette smoke can cause variability in susceptibility to the effects of cigarette smoke. Better known are the uncommon genetic mutations that convey high risk for the development of malignancy, such as the mutations of the *BRCA* or familial adenomatous polyposis (FAP) genes. *BRCA*1 and *BRCA2* are genes with well-defined DNA sequences. Some *BRCA1* and *BRCA2* mutations increase the risk of breast and ovarian cancers and of certain other malignant diseases compared with risk for individuals without the mutations.[9] Advances in our knowledge regarding DNA methylation, histone modification, and other epigenetic phenomena may provide new insights into the effect of environmental factors on carcinogenesis and may suggest new targets for interventions.[10-12]

Knowledge regarding genetic risk factors for a particular cancer and the ability to predict the development of a particular cancer can help oncologists develop and select intervention options and to target high-risk populations for interventions. Table 1-2 lists selected low-prevalence, high-penetrance genetic syndromes with their associated cancers.

Knowledge of the risk factor also may present ethical dilemmas. These factors include conveying knowledge of risk to third parties in a patient's family, selection of embryos for implantation

during in vitro fertilization on the basis of genetic testing, or the use of amniocentesis for testing of known genes, the results of which could be followed by termination of the pregnancy. However, knowledge of the risk factor may allow for early interventions that could prevent disease or limit its severity.

To address risk from genetic factors, it is critical to take a good family history from patients with cancer. This is particularly important for younger patients, who are more likely to harbor a mutation. Such a history should include a census of all first-degree relatives at a minimum (i.e., parents, siblings, and children), with their genders, current age or age at death, any cancers diagnosed, and age at diagnosis. Family histories with cancers among the relatives that fit the pattern of a known genetic mutation or early age at diagnosis for certain cancers should lead to a referral to a genetic counselor for further evaluation and testing. The results of these evaluations have implications for the patient regarding risk of further cancers, as well as implications for other blood relatives in the patient's family.

Just as with genetic information, the clinician should make an effort to collect relevant risk-factor information for patients with cancer or for healthy patients who are undergoing wellness exams. Minimal information should include tobacco and alcohol use, height and weight, family history, and occupational history. Other factors should be included as relevant to a specific symptom or diagnosis (e.g., exposure to organic solvents such as benzene in those diagnosed with leukemia). This information can be used to provide advice and guidance to the patient (e.g., regarding tobacco cessation), to identify patients at high risk for certain cancers, to guide early detection and prevention strategies, and to assist with diagnosis of certain cancers.

Table 1-2 **Selected Hereditary Neoplastic Syndromes (Clinical Tests Available)**

Syndromes	Site(s) of Most Common Cancer(s)	Associated Gene(s)
Hereditary breast-ovarian cancer	Breast, ovary	*BRCA1, BRCA2*
Cowden	Breast, thyroid	*PTEN*
Li-Fraumeni	Brain, breast, adrenal cortex, leukemia, sarcoma	*TP53*
Familial adenomatous polyposis	Large bowel, small bowel, brain (Turcot), skin, bone (Gardner)	*APC*
Hereditary nonpolyposis colorectal cancer	Colorectal and endometrium, also ovary, pancreas, stomach, small bowel	*MSH2, MLH1, PMS1, PMS2, MSH6*
Multiple endocrine neoplasia (MEN1)	Pancreatic islet cell, pituitary adenoma, parathyroid adenoma	*MEN1*
MEN2	Medullary thyroid, pheochromocytoma	*RET*
Neurofibromatosis-1	Neurofibrosarcoma, pheochromocytoma	*NF1*
Von Hippel-Lindau	Hemangioblastoma, nervous system, renal cell	*VHL*
Retinoblastoma	Eye, bone	*RB1*
Melanoma, hereditary	Skin	*CDKN2/p16, CDK4*
Basal cell	Skin	*PTCH*

Chemoprevention and screening are options for certain high-risk populations, as is the modification of high-risk behavior. People at high risk for cancer may engage in intensive screening for the cancer in question. Although such screening may be clinically prudent, it may be less effective for patients at very high risk. In theory, a screening test might benefit those at risk for sporadic cancers and may not benefit patients at genetically high risk for a cancer. More importantly, a screening test proven effective for average-risk individuals is likely to be of greater value in those at higher risk. Certain tests may be of value in those at higher risk that would not be useful in average- or lower-risk individuals because of cost or other problems, such as high rates of false-positive results.

Population categorization is important in epidemiology. Populations can be delineated by gender, nationality, culture, race and ethnicity, socioeconomic status, age, and other characteristics. This is the basis of descriptive epidemiology—along with time trends—and is used to provide clues as to etiology. For example, a cancer that has a strong predominance in men may have a specific occupational component to it. Differences in incidence rates for various cancers found in both Japan and the United States have suggested hypotheses regarding diet and the consumption of green tea.[13]

Race and ethnicity are common ways of dividing populations in the United States. It should be remembered that race is a sociopolitical categorization.[14] The definitions used by U.S. investigators when generating population statistics are not formulated scientifically on the basis of characteristics such as genes, but rather reflect self-report by the individual and a mix of anatomical traits that often encompasses varying degrees of racial admixture. Much concern has arisen in the past 10 to 15 years regarding outcome disparities, in particular for a wide range of cancers and for black patients compared with white patients. In some instances, these disparities also reflect differences in incidence, but, in others, they may reflect differences in stage at diagnosis, access to treatment, or tumor biology. Race and ethnicity can correlate with other methods of categorization, such as poverty or prosperity, both of which are capable of changing the incidence of cancer and its related mortality.

Socioeconomic status and education also can be related to the risk of disease and death. Higher rates of breast cancer among white women in the San Francisco Bay area in California and on Long Island in New York were linked to a higher prevalence of professional women in those areas who, as a cohort, are less likely to have a full-term pregnancy by age 30, a known risk factor for breast cancer.[15] Socioeconomic status also has

been related to type of treatment received and subsequent outcomes for various cancers, although this variable is heavily confounded with race/ethnicity and education.[16] In a classic study, Ayanian et al.[17] found that women with breast cancer who were uninsured or on Medicaid had a 49% (95% CI [20, 84]) and 40% (95% CI [4, 89]) higher risk of death, respectively, than women with private insurance. A similar effect for socioeconomic status was found for survival of patients with colorectal cancer[18] and for quality of life for prostate cancer survivors.[19]

In analytic epidemiology, observational studies are carried out to ascertain whether associations exist between an exposure and an outcome. Although a statistical association may exist between the two, there is always concern that this may reflect bias in the way the study was conducted or the presence of confounding factors. Confounding factors are factors associated with both the exposure and the outcome and can lead to an observed association, which is not truly a relationship between the two. For example, a study may show that asbestos workers have an elevated risk of lung cancer compared with the general population. However, one must be concerned that asbestos workers may be heavier smokers than other individuals in the general population and cigarette smoking is associated with lung cancer risk; thus, smoking may confound the observed association. Therefore, it is mandatory in a study that looks at this exposure and outcome to collect smoking information so that it can be statistically controlled and the individual effect of asbestos exposure can be appropriately measured.

Epidemiologic observational studies fall into two broad categories: cohort studies and case-control studies. Participants in cohort studies are categorized on the basis of their exposure and then followed to determine whether the outcome develops differently in the exposed and unexposed groups. Case-control studies enroll participants who have the outcome or disease under study, in addition to a control group of healthy participants. Both groups are then assessed for exposure. Both types of studies have their advantages and disadvantages. In both types, one must try to avoid bias or directional error. For example, in a case-control study, a patient with cancer may be inclined to give a positive answer more frequently than a control participant to a question regarding smoking history—this is referred to as recall bias.

As a general rule, cohort studies are preferred when the exposure is uncommon and the outcome is common, while case-control studies are preferable with uncommon outcomes. Since the incidence of most cancers, even the most common ones, is relatively low, case-control studies commonly are used in cancer research. Their disadvantage is that they are often ambiguous on the temporal relationship between the exposure and the cancer. If you compare 100 patients with colon cancer to 100 patients without colon cancer for their intake of saturated fat, it can be unclear whether a decreased intake in the cases is related to the disease or preceded the disease. In a cohort study, where the exposure is ascertained before the subjects have developed the cancer, one can be more confident that any observed association preceded the development of disease. On the other hand, because of the low incidence of most cancers, a cohort study requires tens of thousands of subjects to be followed for years. One of the best-known cohort studies, the Nurses' Health Study, followed almost 90,000 nurses for 4 years to generate enough endpoints to determine the risk associated with dietary fat and breast cancer, the most common cancer.[20]

Molecular epidemiology—the use of sophisticated molecular and genetic markers in conjunction with the traditional tools of analytic epidemiology to investigate etiologic or other questions in cancer epidemiology—is a major field within cancer epidemiology. Biomarkers can be used to measure exposures or endpoints in place of the more traditional answers to questionnaires, and, in some instances, biomarkers can give a more objective unbiased assessment.

Many contemporary studies in clinical oncology use epidemiologic methodology to address clinical questions in oncology. When randomized trials may be difficult to conduct, observational studies, such as cohort or case-control studies, may be used to answer typical questions regarding the efficacy of a drug or the incidence of an adverse event from a drug, and also to ascertain the cost-effectiveness of a particular intervention. Therefore, an understanding of these analytic tools is imperative for the modern oncologist.

PATTERNS OF CARE, DISPARITIES, AND OUTCOMES RESEARCH

Although descriptive epidemiology and the determination of etiologic risk factors have been the traditional domains of epidemiology, the assessment of treatment outcomes in populations has become an important aspect of epidemiology. Clinical trials demonstrate "efficacy" of a treatment. How well the intervention works in the population as a whole in routine practice is referred to as "effectiveness." A phase II clinical trial can dem-

KEY POINTS

- Risk can be increased by both intrinsic and extrinsic influences.
- To assess etiology, a population risk is usually reported relative to another population.
- A key element in population statistics and rates is the presence of a denominator population.
- Germ-line genetic mutations have been identified for a number of cancers and can be identified in the clinical setting if one is alert to them.
- A good clinical history can also identify key exogenous risk factors, such as tobacco, alcohol, and certain occupational factors.
- Cohort studies and case-control studies are key tools in the conduct of observational research and the identification of risk factors for cancer.
- Differences in cancer risk exist across populations and individuals on the basis of various characteristics, including race/ethnicity, gender, age, socioeconomic status, and education.

onstrate the efficacy of a treatment intervention (e.g., tumor shrinkage), and a phase III study compares two interventions to determine which is superior. Prevention trials usually require phase III studies to show efficacy.

The study of patterns of care or treatments used is an aspect of outcomes research. Numerous studies often demonstrate geographic and regional differences in the preferred treatment of cancers. For example, for women with localized breast cancer, the decision to treat with lumpectomy and radiation therapy or with mastectomy may vary depending on the patient's geographic location.[21] Similar regional differences have been noted for prostate cancer screening and for the types of treatment used for localized prostate cancer.[22]

Health disparities generally can be defined as differences in outcomes related to a disease among a segment of the population compared with the general population. In current usage, the term is often used for subpopulations that are thought to be disadvantaged in some way, such as by race/ethnicity, increasing age, socioeconomic status, sexual orientation, rural residence, etc., and the public policy interest in disparities stems from an interest in finding avoidable and correctable causes for the disparities. For cancer-related disparities, such causes may reflect differences in risk-factor exposure, screening utilization, access to care, quality of care, or tumor biology. Most notably in this area, black patients are at increased risk of mortality from a wide variety of cancers.[23,24] Differences in tobacco usage have been responsible for disparities in mortality from squamous cell carcinoma of the esophagus between black and white patients.[25] A recent study from the Southwest Oncology Group found persistent racial disparities for women with breast and ovarian cancers entered on phase III trials despite similar stage, treatment, and follow-up, suggesting that biological differences may also play a role.[26]

Many of the disparities in outcomes among groups defined by race and socioeconomic status have been linked to differences in patterns of care. For example, treatment is less than optimal for a substantial proportion of patients with cancer who are poor or of certain ethnic backgrounds.[27] The reasons for these variations in care are complex. Some are the result of sociocultural differences in attitudes toward therapy. Patient–physician communication also can play a major role.[28] In other cases, poverty, lack of insurance, or underinsurance can make access to care difficult.[17,29] Logistical difficulties, such as a lack of adequate transportation to a treatment center, may play a role. Patients with severe comorbid disease or poor performance status may justifiably not be offered aggressive cancer treatments because they are at higher risk of a treatment-related morbidity.

CANCER PREVENTION

Prevention is intended to reduce cancer incidence and mortality. Primary cancer prevention is best defined as the use of interventions to reduce cancer incidence. Important to prevention is the fact that carcinogenesis is not a distinct event but rather a process that occurs over time. It is a cumulative continuum of discrete cellular changes resulting in uncontrolled growth. Primary prevention involves interventions or manipulations of the genetic, biologic, and environmental factors in the causal pathway of carcinogenesis. Smoking cessation, sun avoidance, diet modification, weight loss and increased physical activity, cancer virus vaccination, and chemoprevention (e.g., tamoxifen for breast cancer prevention) are primary prevention activities. Screening for asymptomatic cancers, which is intended to detect cancers earlier so that treatment can be introduced more promptly and effectively to reduce mortality, is considered secondary prevention. For some cancers, such as cervix cancer and colorectal cancer, intraepithelial neoplasia is an intermediate step in carcinogenesis, and treatment of this condition is a form of cancer prevention.[30]

KEY POINTS

- Most clinical trials are designed to determine "efficacy," meaning how well the treatment works in a selected environment. Some larger trials and outcomes studies are designed to show "effectiveness," meaning how well the treatment works in the population as a whole.
- Epidemiologic methodology, utilized in the field of health outcomes research, has been active in determining areas where disparities in incidence and mortality exist and possible causes for these disparities. With this information, interventions may be possible.

SMOKING CESSATION

Tobacco use is the most avoidable risk factor for cardiovascular disease, pulmonary disorders, and cancer. Smoking cessation and avoidance have the potential to save and extend more lives than any other public health activity. A smoker has a one-in-three lifetime risk of dying prematurely of a smoking-related disease. More human lives are lost because of cardiovascular disease caused by smoking than from smoking-related cancer. In addition to lung cancer, cigarette smoking has been linked to cancer of the larynx, oropharynx, esophagus, kidney, bladder, pancreas, and colon.[31]

The risk from tobacco smoke is not necessarily limited to the smoker. Epidemiologic studies suggest that environmental tobacco smoke, often called secondhand or passive smoke, may cause lung cancer and other pulmonary diseases in nonsmokers. The amount of smoke exposure, as well as the degree of inhalation of cigarette smoke, is correlated with the risk of mortality associated with lung cancer. Light and low-tar cigarettes are not safer because smokers tend to inhale them more frequently and deeply. Compared with their nonfiltered counterparts, filtered cigarettes allow smaller particles to get into the peripheral parts of the lung and cause different histologic subtypes of cancer,[32-34] specifically adenocarcinomas. Those who stop smoking almost immediately stop increasing their risk of cancer, although it takes some time before their risk of cancer declines. Some carcinogen-induced gene mutations, however, may persist for years.

The vast majority of adult American smokers begin smoking before age 18; two-thirds are nicotine dependent in their high school years.[35] Therefore, communicating health messages to the pediatric and adolescent population is a major public health challenge. Studies show that a physician's simple advice to avoid or quit smoking can improve the quit rate by two-thirds.[36] Despite this, a recent survey found that although more than 80% of oncologists assess smoking behavior in their patients, less than 20% feel confident enough to intervene in this important area.[37]

Among the most effective smoking cessation interventions are governmental actions. Tax increases on cigarettes and restrictions on venues where smoking is permitted have been very effective in reducing smoking prevalence rates.[38] Current smoker rates are down to 20% or less in the United States, and most tobacco-related cancers in this country now occur in former smokers. However, smoking remains a major factor globally, especially in Asia, and lung cancer is the leading cause of cancer mortality worldwide. Much concern has been raised in particular about smoking rates in India and China, and global efforts to reduce smoking rates are being initiated.[39,40]

Smoking is an addiction. It is easier for light smokers—the less addicted—to quit. Experts believe that heavy smokers generally need an intensive, broad-based cessation program that includes counseling, behavioral strategies, and drug therapy; if drug therapy is needed, the recommended first-line therapies are nicotine-replacement therapy, bupropion, and varenicline, with clonidine and nortriptyline as possible second-line therapies.[36] Most Americans who successfully quit smoking do so on their own, without participation in an organized cessation program, but this process can be strongly enhanced by even a small amount of encouragement from a health care provider. Smokers who stop completely are more likely to be successful than smokers who gradually reduce the number of cigarettes smoked or change to cigarettes containing lower amounts of tar or nicotine. The smoker who is quitting goes through a process with identifiable stages that include contemplation of quitting, an action phase during which the smoker quits, and a maintenance phase. As noted above, there now exist numerous effective strategies beyond counseling for advising and assisting the cooperative patient with his or her goals.[41,42]

Much of the literature focuses on the risks of cigarette smoking. Cigar smokers do not inhale, but the health risks associated with cigars are similar to those of cigarettes, especially the risks of oropharyngeal cancers.[43] Smokeless tobacco, or chewing tobacco, is the fastest-growing segment of the tobacco industry and represents a serious health risk. Chewing tobacco has been linked to dental caries, gingivitis, oral leukoplakia, and oral cancer. In addition, the nitrosamines found in this product have been shown to cause lung cancer in animal studies. Esophageal cancer is linked to the carcinogens in tobacco that dissolve in saliva, are swallowed, and then come into contact with the esophagus.

It is worth recognizing that alcohol ingestion plays a significant role in cancer etiology.[44] A major carcinogenic role for alcohol has been as a cofactor with tobacco in cancers of the upper aerodigestive tract, where the joint utilization of tobacco and alcohol can lead to synergistic risks. It is a significant carcinogen in its own right for hepatocellular carcinoma by the induction of cirrhosis, or as a risk factor for breast cancer.[45]

SUN AVOIDANCE

Results of epidemiologic studies show a correlation between the risk of nonmelanoma skin cancers (basal and squamous cell) and cumulative exposure to ultraviolet radiation. Possible risk factors for melanoma include a propensity to sunburn, a large number of benign melanocytic nevi, and atypical nevi. A history of severe sunburns, especially in childhood and adolescence, is associated with increased risk of melanoma in adulthood. Recently, concern has been raised about the increasing use of indoor tanning and tanning beds, and measures calling for their regulation have been sounded.[46,47] Reduction of sun exposure through the use of protective clothing and a change in one's pattern of outdoor activities to avoid the most intense and direct sunlight have been advocated as ways to reduce the risk of skin cancer. Although past studies have been inconclusive, a recent randomized trial confirmed that sunscreen use can reduce the risk of melanoma.[48]

DIET MODIFICATION

Rates of cancers of the breast, colon, endometrium, and prostate are higher in North America and western Europe than in Asia. Immigrants from Asia and their offspring acquire a higher risk for these cancers after they have been in the United States for some time. These observations, as well as data from animal studies, are the basis for the belief that dietary modification can significantly lower cancer risk for individuals in the United States.[49] Diet is a highly complex exposure to many nutrients and chemicals. Low-fat diets, which are usually low in red meat and high in fruits and vegetables, may render some protection through anticarcinogens found in vegetables, fruits, legumes, nuts, and grains. Potentially protective substances found in foods include phenols, sulfur-containing compounds, and flavones.[50] Although the cancer-prevention benefits are theoretical and not fully demonstrated, such a diet does lower the risk of cardiac disease. However, vitamins, minerals, or nutritional supplements in amounts greater than those provided by a good diet have not been demonstrated to be of value. Most randomized trials of vitamin supplements have not shown benefit in terms of prevention, and in some instances have even shown harm *(discussed in the "Chemoprevention" section below)*.

Despite correlative data, the dietary fat–cancer hypothesis has not been definitively demonstrated. Case-control and cohort epidemiologic studies yield conflicting results. No prospective clinical trial has demonstrated that cancer can be prevented through lowering dietary fat or increasing fiber intake. Studies, including randomized trials, have been consistent in showing no effect of dietary fiber intake on colon cancer risk.[51,52] The Women's Health Initiative, which included a randomized trial with a low-fat diet intervention, also did not indicate an effect on breast cancer or colon cancer risk.[53,54] Nonetheless, a randomized trial of more than 2,400 women with early-stage

breast cancer showed that patients randomly assigned to a low-fat diet, in addition to standard adjuvant therapy, had a significantly improved survival compared with women on a regular diet (hazard ratio [HR] 0.76, 95% CI [0.60, 0.98]).[55]

WEIGHT LOSS AND PHYSICAL ACTIVITY

A major public health concern has centered on the obesity epidemic in the United States. Obesity represents the effects of an individual's net caloric intake, which is the amount consumed versus the amount expended through physical activity. Changes in either of these variables will impinge on the measure of obesity, thereby affecting cancer risk. Obesity affects cancer risk through a number of mechanisms, including hormone metabolism, thereby affecting breast, endometrial, and prostate cancer risk, or by increasing esophageal reflux, which affects the occurrence of Barrett metaplasia and esophageal adenocarcinoma.[56,57]

OCCUPATIONAL CARCINOGENS

Since Percival Pott recognized an increased risk of scrotal cancer among chimney sweeps in 18th-century London, it has been understood that occupational exposures can increase the risk of certain cancers. The most important of the occupational carcinogens has been asbestos, exposure to which is prominent among construction workers, pipefitters, and shipyard workers. It has been closely linked to the incidence of mesothelioma, lung cancer, and possibly gastrointestinal tract malignancies. Another classic exposure has been radon inhalation, which occurs in uranium miners and potentially from home radon exposure, and increases the risk of lung cancer. Various other organic and aromatic chemicals are linked to the risks of leukemia and cancers of the urinary collecting system.

IONIZING RADIATION

As noted above, inhaled radon exposure can be carcinogenic to the lungs. The effects of other sources of radiation exposure and radiation carcinogenesis have been well recognized since their discovery at the turn of the 19th to 20th centuries, particularly on hematologic malignancies. The most prominent source of such exposure stemmed from the atomic bomb explosions in August 1945 in Japan, and much of what we know about radiation dosimetry, latency, and carcinogenic effects comes from the careful and meticulous studies undertaken in the wake of those events. The other major source of radiation exposure is therapeutic radiation, mainly in treatment of malignancies, hence the observation of second malignancies as a consequence. Exposure to ionizing radiation is associated with increased risk of breast, lung, esophageal, and bladder cancers, leukemia, sarcoma, and brain tumors. It has also been linked to thyroid cancer when there is exposure to radioactive iodine, as in the aftermath of the Chernobyl nuclear accident, which released radioactive iodine into the atmosphere.[58] Efforts to reduce the use of radiation therapy, to minimize the fields, and to avoid the joint use of an alkylating agent in combination with radiation therapy are well known in order to reduce the risk of these second malignancies.

CANCER VIRUS VACCINATION

Virally induced cancer has been recognized since the early part of the 20th century, with the discovery of Rous sarcoma virus in chickens. In humans, several viruses, including hepatitis B (hepatocellular carcinoma), hepatitis C (hepatocellular carcinoma), Epstein-Barr virus (Burkitt lymphoma), and human papillomavirus (HPV; cervix cancer, other anogenital squamous cell malignancies, and head and neck carcinoma) have been clearly established as carcinogenic. An understanding of retroviruses has broadened our appreciation of other viral agents, such as human herpesvirus-8 and Kaposi sarcoma.[59,60] In addition, the bacterium *Helicobacter pylori (H. pylori)* was found to be associated with gastric cancer. These are particularly exciting findings because these agents provide targets for vaccination as a means of primary prevention. This has been achieved for hepatitis B[61] and for HPV.[62] In Taiwan, where hepatoma is the leading cancer, hepatitis B vaccine was introduced in 1984 and the risk of hepatoma has so far been reduced by over 70% in those vaccinated.[63]

Another success has been the introduction of a vaccine for several subtypes of HPV. HPV vaccination is now recommended for young girls prior to becoming sexually active, which should reduce the incidence of cervix cancer by 70% or more, and the U.S. Centers for Disease Control and Prevention recently recommended the vaccine for boys as well. Because these same viruses are involved in other cancers, incidence of anal, vaginal, penile, and oropharyngeal cancers may also decline, particularly if male vaccination becomes common in the future.[64,65]

KEY POINT

- Avoidance of carcinogens is the most efficient way to prevent cancer. Smoking is the cause of nearly one-third of all cancers in the United States. Other environmental influences, such as sun overexposure, certain chemicals, and certain infectious agents, are associated with cancer causation.

CHEMOPREVENTION

Cancer chemoprevention is the use of natural or synthetic chemical agents to reverse, suppress, or prevent carcinogenesis before the development of an invasive malignant process.[66] Cancers are prevented through chemoprevention or, in certain cases, through surgical removal of the organ at risk. Although the concept that pharmacologic agents can prevent a cancer is relatively new, the idea that a compound can prevent chronic disease is not. Antihypertensive agents are used to prevent heart disease, kidney disease, and stroke. Lipid-lowering drugs are prescribed to prevent coronary artery disease.

The initial genetic changes of carcinogenesis are termed "initiation." This alteration can be inherited or acquired. Acquired genetic damage is the result of physical, infectious, or chemical carcinogens (Table 1-3). The influences that cause the initiated cell to change phenotypically are called promoters. Known

promoters include androgens linked to prostate cancer and estrogen linked to breast and endometrial cancers. The distinction between the initiator and promoter can sometimes blur; some components of cigarette smoke are referred to as "complete carcinogens" and serve as both initiators and promoters. Cancer can be prevented or controlled through interference with the factors causing disease initiation, promotion, or progression.

Compounds of interest in chemoprevention include anti-inflammatory agents, antioxidants, differentiating agents, or hormone antagonists. A long-term, randomized, placebo-controlled clinical trial is generally necessary to establish the efficacy of a chemopreventive agent, and several large clinical trials have been completed.[67-69] As discussed in the following sections, tamoxifen,[67] raloxifene,[69] and aromatase inhibitors[70] have been shown to reduce the incidence of breast cancer. In addition, nonsteroidal anti-inflammatory drugs reduce the occurrence of colorectal adenomas in various circumstances, and finasteride and dutasteride reduce the incidence of prostate cancer.[68,71] Retinoids may inhibit head and neck cancers.[72] Selenium and vitamin E were recently shown not to reduce prostate cancer risk.[73] Recent agents of interest for chemoprevention of breast, colon and other cancers include calcium and vitamin D.[74,75] Table 1-4 contains a list of selected large, randomized chemoprevention trials that have been conducted.

CANCERS OF THE LUNG, HEAD AND NECK, AND ESOPHAGUS

Tobacco smoking is the major cause of squamous cell cancers of the lung, head, neck, and esophagus. The risk of a second cancer of the lung, head, or neck is high—as great as 5% per year of smoking—for patients cured of these diseases. This is because of "field cancerization," meaning the carcinogens in tobacco smoke affect all tissues exposed to them. Even after smoking cessation, the tissues that have come in contact with smoke have residual molecular damage. For the esophagus, head, and neck, alcohol ingestion has an interactive effect with smoking. Other cancers of the lung (e.g., small cell and adenocarcinoma) also are associated with tobacco use. Very high rates of oral cancer are found in India in association with betel nut chewing. HPV infection, particularly the HPV-16 subtype, has been linked to oropharyngeal cancer[97]; a significant increase in incidence is anticipated in the coming years as a consequence, though the introduction of HPV vaccination may reduce this incidence.

In the United States, incidence rates for esophageal adenocarcinoma are among the most rapidly increasing since the late 1970s. This cancer occurs as a sequelae of Barrett esophagus and is thought to be the result of gastroesophageal reflux disease.[98] Esophagogastroduodenoscopy often is used as regular surveillance to detect Barrett esophagus in patients with gastroesophageal reflux disease; however, there is no convincing evidence that demonstrates a reduction in the subsequent incidence or mortality of esophageal adenocarcinoma.

Several large-scale studies have been launched to assess potential chemopreventive agents for patients at high risk for lung cancer. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial (ATBC)[77] and the Beta-Carotene and Retinol Efficacy Trial (CARET)[78] were prevention trials that showed the importance of testing even seemingly harmless chemoprevention agents, such as vitamins, before widespread use. The results of both trials are in contrast to numerous observational studies. The ATBC trial enrolled Finnish male smokers between

Table 1-3 Examples of Initiators and Promoters of Cancer

Carcinogen	Associated Cancer or Neoplasm
Alkylating agents	Acute myelocytic leukemia, bladder
Androgens	Prostate
Aromatic amines (dyes)	Bladder
Arsenic	Lung, skin
Asbestos	Lung, pleura, peritoneum
Benzene	Acute myelocytic leukemia
Chromium	Lung
Diethylstilbestrol (prenatal)	Vaginal (clear cell)
Epstein-Barr virus	Burkitt lymphoma, nasopharynx
Estrogens	Endometrium
Estrogen plus progesterone	Breast
Ethyl alcohol	Liver, esophagus, head and neck
Helicobacter pylori	Gastric
Hepatitis B virus	Liver
Hepatitis C virus	Liver
Human T-cell leukemia (HTLV)-1 virus	Adult T-cell leukemia, lymphoma
Human herpesvirus-8 (HHV-8)	Kaposi sarcoma
Human immunodeficiency virus (HIV)	Non-Hodgkin lymphoma, Kaposi sarcoma, squamous cell carcinoma of cervix
Human papillomavirus (HPV)	Squamous cell carcinoma of cervix, anogenital area, oropharynx
Immunosuppressive agents (azathioprine, cyclosporine, corticosteroids)	Non-Hodgkin lymphoma
Nitrogen mustard gas	Lung, head and neck, nasal sinuses
Nickel dust	Lung, nasal sinuses
Phenacetin	Renal pelvis, bladder
Polycyclic aromatic hydrocarbons	Lung, skin (especially squamous cell)
Schistosomiasis	Bladder (squamous cell)
Sunlight (ultraviolet)	Skin (squamous cell and melanoma)
Tobacco (including smokeless)	Upper aerodigestive tract, bladder, pancreas
Vinyl chloride	Liver (angiosarcoma)

These agents are thought to act as cancer initiators or promoters for the cancers with which they have been associated.

Table 1-4 Randomized Chemoprevention Trials

Author (Year, Trial Name)	Study Setting/ Endpoint	Number of Patients	Intervention	Primary Outcome
Head and Neck				
Hong et al (1990)[72]	Prior SCC	103	Isotretinoin (100 mg/m^2/d)	Positive (SPT)
Bolla et al (1994)[76]	Prior SCC	316	Etretinate (50, 25 mg/d)	Negative
Lung				
Virtamo et al (1994; ATBC Cancer Prevention Study)[77]	Lung cancer	29,133	Carotene (20 mg/d); vit E (50 mg/d)	Negative
Omenn et al (1996; CARET)[78]	Lung cancer	18,314	Carotene (30 mg/d); vit A (25,000 IU/d)	Negative
Pastorino et al (1993)[79]	Prior NSCLC	307	Vit A (300,000 IU/d)	Positive (SPT)
van Zandwijk et al (2000)[80]	Prior HNC, NSCLC	2,592	Vit A (300,000/150,000 IU/d); NAC (600 mg/d)	Negative
Lippman et al (2001)[81]	Prior NSCLC	1,166	Isotretinoin (30 mg/d)	Negative
Skin				
Levine et al (1997)[82]	Prior BCC/SCC	524	Isotretinoin (5-10 mg/d); vit A (25,000 IU/d)	Negative
Greenberg et al (1990)[83]	Prior BCC/SCC	1,805	Carotene (50 mg/d)	Negative
Tangrea et al (1992)[84]	Prior BCC	981	Isotretinoin (10 mg/d)	Negative
Moon et al (1997)[85]	AK	2,298	Vit A (25,000 IU/d)	Positive
Bavinck et al (1995)[86]	Renal transplant	38	Acitretin (30 mg/d)	Positive
Clark et al (1996)[87]	Prior BCC/SCC	1,312	Selenium (200 µg/d)	Negative
Breast				
Fisher et al (1998; BCPT)[67]	High risk/BC	13,388	Tamoxifen (20 mg/d)	Positive
Veronesi et al (1998)[88]	BC	5,408	Tamoxifen (20 mg/d)	Negative
Powles et al (1999)[89]	High risk/BC	2,471	Tamoxifen (20 mg/d)	Negative
Fisher et al (1999)[90]	DCIS/BC	1,804	Tamoxifen (20 mg/d)	Positive
Veronesi et al (1999)[91]	CBC	2,972	Fenretinide (200 mg/d)	Negative
Vogel et al (2006; STAR)[69]	High risk/BC	19,747	Raloxifene (60 mg/d) vs. tamoxifen (20 mg/d)	Equal
Goss et al (2011)[70]	High risk/BC	4,560	Exemestane (25 mg/d)	Positive
Colorectal				
Wactawski-Wende et al (2006)[92]	Colorectal cancer	36,282	Calcium (500 mg bid); vit D3 (200 IU bid)	Negative
Prostate				
Thompson et al (2003; PCPT)[68]	Prostate cancer	18,882	Finasteride (5 mg/d)	Positive
Andriole et al (2010)[71]	Prostate cancer	6,729	Dutasteride (0.5 mg/d)	Positive
Lippman et al (2009; SELECT)[73]	Prostate cancer	35,533	Selenium (200 mcg/d); vit E (400 IU/d)	Negative
Esophagus/Stomach				
Blot et al (1993; Linxian)[93]	Geographic risk	29,584	Multiple vitamins/minerals	Negative
Li et al (1993)[94]	Geographic risk	3,318	Multiple vitamins/minerals	Negative
All Cancer				
Hennekens et al (1996; PHS)[95]	Healthy men	22,071	Carotene (50 mg qod)	Negative
Lee et al (1999)[96]	Healthy women	39,876	Carotene (50 mg qod)	Negative

Abbreviations: AK, actinic keratosis; BC, breast cancer; BCC, basal cell carcinoma; bid, twice daily; CBC, contralateral breast cancer; d, day; DCIS, ductal carcinoma in situ; HNC, head and neck cancer; NAC, N-acetylcysteine; NSCLC, non-small cell lung cancer; SCC, squamous cell carcinoma; SPT, second primary tumor; qod, every other day; vit, vitamin.

Adapted from: Kufe DW, Bast RC Jr, Hait W, et al (eds). Holland-Frei Cancer Medicine, 7th Edition. *Hamilton, ON, and Lewiston, NY: BC Decker; 2006.*

age 50 and 69. Participants received alpha-tocopherol, beta-carotene, both, or placebo in a randomized, 2×2 factorial design. After a median follow-up of 6 years, there was a significant increase in lung cancer incidence and mortality for the participants who received beta-carotene. Alpha-tocopherol had no effect on lung cancer mortality. CARET enrolled 17,000 smokers and workers exposed to asbestos. Participants were randomly assigned to four arms and received beta-carotene, retinol, both, or placebo in a 2×2 factorial design. The results of the trial demonstrated a 28% increase in lung cancer and a 17% increase in deaths for the participants receiving beta-carotene. The reason for this outcome is uncertain; it occurred despite beta-carotene's role as both an antioxidant and as a precursor to retinol.

Retinoids have proven to be effective as chemopreventive agents for squamous cell malignancies of the head and neck, possibly by promoting terminal differentiation.[72] A study randomly assigned 102 patients with a first primary squamous cell carcinoma of the head and neck to 13-cis-retinoic acid, a retinoid analogue, or to placebo. At 3 years, there were two second primary head and neck cancers in the intervention group versus 12 in the placebo group ($p = 0.005$). Despite this study and later supportive trials, the retinoids have not become standard of care, mainly because of toxicities.

GASTRIC CANCERS

Heavy intake of smoked and cured meats and foods, limited consumption of fresh fruits and vegetables, and infection with *H. pylori* are associated with an increased risk of gastric cancer.[98] Gastric cancer was the most common cancer in the United States prior to World War II, but it is now much less common. This decline is thought to be caused by increased consumption of fresh meats, fruits, and vegetables and decreased consumption of cured/smoked foods. Experimental evidence of causality is scarce. Gastric cancer remains a very common malignancy in Japan, Latin America, China, and in other parts of the developing world. A randomized trial in China of eradication of *H. pylori* infection with a combination of omeprazole, amoxicillin, clavulanate, and metronidazole did not show a reduction in subsequent gastric cancer incidence. Nonetheless, patients who had no gastric pathology at study entry did show a significant reduction in gastric cancer incidence in subgroup analysis.[99] There are no randomized trial data to support screening for groups at high risk for *H. pylori* (e.g., Asian individuals), which would lead to the institution of eradication procedures to reduce the subsequent risk of gastric cancer. Studies are underway to further elucidate this question. Furthermore, the rates of cancer of the gastric cardia and esophageal adenocarcinoma are rising, and there is evidence to suggest that this may be a consequence of recent declines in the prevalence of *H. pylori*.[100] The reasons the cancers of the proximal stomach and distal stomach may have inverse associations with the presence of *H. pylori* are unclear. Nonetheless, it may be one reason why the incidence of distal gastric cancer in the United States has been declining while the incidence of proximal and gastroesophageal junction cancer incidence has been rising.[101]

COLON CANCER

Findings from epidemiologic studies suggest that nonsteroidal anti-inflammatory agents, such as piroxicam, sulindac, and aspirin, have protective effects against adenomatous polyps and invasive cancer.[102,103] The results of prospective intervention trials have demonstrated positive effects on the prevention of polyps; meta-analyses of randomized trials of aspirin designed to assess other endpoints have demonstrated that these agents prevent colon cancer.[103,104] In a placebo-controlled trial, high-dose celecoxib, a cyclooxygenase-2 (COX-2) inhibitor, was found to reduce the occurrence of colorectal polyps for patients with familial adenomatous polyposis.[105] A prospective randomized trial of patients with a history of colorectal adenomas demonstrated a 20% reduction in recurrence of polyps for patients who received celecoxib.[106] Trials to assess COX-2 inhibitors and other nonsteroidal anti-inflammatory agents for the prevention of colorectal adenomas have shown preventive benefits; however, these agents are associated with increased cardiovascular risk. A recent study suggested that the risk of colon cancer can be reduced even by doses of aspirin as low as 80 mg daily.[107] One observational study suggested that COX-2 inhibitors could improve mortality when used in patients with node-positive colon cancer[108]; a randomized trial is in progress to confirm this finding. This may be partly because of a beneficial effect on cancer metastasis.[109]

The Women's Health Initiative was a prospective, randomized study involving postmenopausal women randomly assigned to either combination estrogen plus progestin or to placebo. The rate of colorectal cancer was lower for women taking the study drug compared with women taking placebo.[110] However, the effect is offset by the life-threatening cardiovascular and breast cancer risks associated with treatment with estrogen plus progestin.[111]

The results of epidemiologic studies indicate that diets high in calcium are associated with a lower risk of colon cancer. However, in the Women's Health Initiative study, calcium and vitamin D supplementation did not lower the incidence of colorectal cancer.[92] Evidence from prospective randomized studies shows that calcium supplementation decreases the risk of recurrence of adenomatous polyps by approximately 20%.[112] Calcium binds bile and fatty acids, reducing intraluminal exposure to compounds that cause hyperproliferation of the colonic epithelium.

Obesity is associated with an increased risk of colorectal cancer. However, in another Women's Health Initiative randomized controlled trial, there was no difference in the incidence of colorectal cancer among women assigned to a low-fat diet as compared with controls.[54]

Colectomy is used as a preventive measure for individuals at extremely high risk of colon cancer as a result of a history of ulcerative colitis or of a genetic predisposition to the disease, such as familial adenomatous polyposis.[113]

No chemopreventive agent is currently recommended for prevention of colorectal cancer for individuals at average risk. The use of nonsteroidal anti-inflammatory agents for patients with familial adenomatous polyposis following colectomy may be reasonable in conjunction with endoscopic screening.

LIVER CANCER

Hepatitis B-induced hepatocellular carcinoma is one of the most commonly diagnosed cancers in Asia. The hepatitis B vaccine has been advocated for its ability to prevent the disease. Reductions in the incidence of hepatocellular carcinoma in Taiwan and elsewhere suggest some success.[63] Although hepatocellular carcinoma is much less common in the United States, there has been a rise in incidence rates because of an epidemic of hepatitis C, which also leads to hepatocellular carcinoma, but for which no vaccine is available.

BREAST CANCER

Tamoxifen has mixed estrogenic and anti-estrogen activities. It acts as an estrogen agonist in the endometrium and bone and as an estrogen antagonist in breast tissue. It also upregulates transforming growth factor-beta, which decreases breast cell proliferation. In randomized, placebo-controlled trials to assess tamoxifen as adjuvant therapy for patients with early-stage breast cancer, this drug was found to prevent new cancers in the contralateral breast. The Breast Cancer Prevention Trial was a randomized, placebo-controlled study of more than 13,000 women at high risk of breast cancer. After a median treatment of 69 months, tamoxifen was found to decrease the period risk of breast cancer by 49%. It also was associated with a reduction in bone fractures and with a small increase in risk of endometrial cancer, stroke, pulmonary emboli, and deep vein thrombosis.[67,114] A trial to compare tamoxifen with another selective estrogen-receptor modulator, raloxifene, for postmenopausal women, was completed (the Study of Tamoxifen and Raloxifene [STAR] Trial). Raloxifene decreased the risk of invasive breast cancer by amounts similar to tamoxifen but did not decrease the risk of noninvasive breast cancer. Compared with tamoxifen, raloxifene was associated with less risk of endometrial cancer, as well as with lower risk of thromboembolic events and cataracts.[69] A recent randomized trial showed that an aromatase inhibitor, exemestane, could also prevent breast cancer.[70] In a trial with 4,560 postmenopausal women randomly assigned to exemestane or placebo, exemestane reduced the risk of breast cancer compared to placebo by 65% (95% CI [0.18, 0.70]).

The Women's Health Initiative was discontinued early partially because of the increased risk of breast cancer (odds ratio 1.26) among women who were postmenopausal and who were taking active hormone-replacement estrogens with progestins.[110] A parallel trial of estrogen alone compared with placebo for women with a prior hysterectomy did not show an increased risk of breast cancer among women taking estrogen.[115]

Obesity also is associated with an increased risk of breast cancer, related to aromatase activity in fat tissue and increased estrogenic production.

Prophylactic bilateral mastectomy to prevent breast cancer has not been assessed by randomized trial. In a prospective series of 139 women with *BRCA1* and *BRCA2* mutations, 76 chose prophylactic bilateral mastectomy and 63 chose close surveillance. At 3 years, there was no breast cancer diagnosed in those who chose surgery; eight women in the surveillance group had been diagnosed with breast cancer. This study is small, of short duration, and, by design, prone to selection biases. However, it is fair to say that the short-term risk of breast cancer appears to be lower for women with certain *BRCA1* and *BRCA2* mutations who choose prophylactic mastectomy. Because this surgery leaves some breast tissue behind, a patient's risk is not reduced to zero. When coupled with prophylactic bilateral salpingo-oophorectomy, ovarian cancer risk is markedly decreased, and there is an added benefit for breast cancer prevention. Retrospective analysis of mastectomies for 214 women at high risk of breast cancer because of family history suggests that prophylactic mastectomy can lead to a 90% reduction in risk.[116] One large study of patients from 11 centers investigated 1,079 women with deleterious *BRCA* mutations and compared those who self-selected salpingo-oophorectomy to those who did not. With 3 years of follow-up, the prophylactic surgery was associated with an 85% reduction in risk of gynecologic cancer and a 72% reduction in risk of breast cancer in the *BRCA1* group, but no clear benefit for *BRCA2* carriers.[117]

A recent Cochrane review concluded that bilateral prophylactic mastectomy for those at very high risk of breast cancer (e.g., those with deleterious *BRCA* mutations) was effective in reducing the incidence and subsequent mortality from breast cancer.[118]

PROSTATE CANCER

Androgens stimulate prostate cell proliferation and, in laboratory animals, cause prostate carcinogenesis. Finasteride decreases androgenic stimulation of the prostate by inhibiting the production of 5-alpha-reductase. This enzyme, which is found in high amounts in the prostate, converts testosterone to the more potent dihydrotestosterone. Finasteride was tested as a preventive agent for prostate cancer in the Prostate Cancer Prevention Trial, a 10-year, randomized, placebo-controlled study involving 18,000 men age 55 and older. Results of the study showed that this drug was associated with a 24.8% reduction in the risk of prostate cancer during the treatment period. There were some initial concerns regarding an observed increased incidence of high-grade tumors that developed while patients were treated with finasteride.[68] Later re-analyses showed that these observations were a result of statistical methods, and that there are no true increases in high-grade tumors.[119,120] A recent study of another 5-alpha reductase inhibitor, dutasteride, also found a protective effect against prostate cancer.[71]

Findings from epidemiologic studies indicate a correlation between high intake of antioxidants, such as selenium and vitamin E, and lower risk of prostate cancer. The results of a small, randomized skin cancer prevention trial of selenium compared with placebo showed a significant decrease in the number of prostate cancers in men treated with selenium compared with men receiving placebo.[121] Eight years into the ATBC Prevention Trial, which enrolled 29,000 men, there were 99 cases of prostate cancer reported among men receiving vitamin E and 151 cases reported among men taking placebo. The cancers diagnosed were almost all detected as a result of the work-up of symptoms because there is no routine prostate cancer screening in Finland.[122]

The prostate cancer findings in both of these trials were incidental results of a secondary analysis. A prospective, randomized, placebo-controlled trial—the Selenium and Vitamin E Cancer Prevention Trial (SELECT)—assessed these drugs in 32,400 participants and reported no reduction in prostate cancer incidence.[73]

GYNECOLOGIC CANCER

Laser ablation, conization, or hysterectomy is used to treat cervix dysplasia or intraepithelial neoplasia, both of which are precursors to cervix cancer. Vaccines for HPV have been approved for young girls and will undoubtedly lower the incidence of cervix cancer.[62]

Studies have shown a strong protective effect against ovarian cancer for oral contraceptive hormone preparations.[123] However, there is no current recommendation for their use on a routine basis for prevention. For women at very high risk of ovarian cancer because of a *BRCA* genetic mutation, bilateral salpingo-oophorectomy after completion of child-bearing remains the treatment of choice (including fallopian tube removal).[124]

KEY POINTS

- Most randomized trials of vitamins or nutritional supplements as chemopreventive agents have proven negative.
- Hormone inhibitors for hormone-dependent cancers have proven efficacious as preventive agents and may have a role in clinical practice, though the benefits must be weighed against potential side effects.
- Drugs and vitamins to be used for prevention need to undergo the same rigorous assessment of efficacy and toxicity as do therapeutic agents prior to recommendation. Indeed, because they are generally administered to a healthy population, their toxicity profile must be safer than those of drugs used in the therapeutic setting.

CANCER SCREENING

Cancer screening is an attempt to detect cancer or its precursors early in asymptomatic individuals, with the goal of intervening and decreasing morbidity and mortality. A screening test is not typically diagnostic for cancer; rather, it determines whether cancer might be present and if additional testing, including a biopsy and staging, is necessary. To be of true benefit, screening must lead to earlier treatment that offers a better outcome, usually reduced mortality, compared with treatment that would occur at the onset of symptoms. Because of various biases *(discussed below)*, the ideal evaluation of a screening technology is through the assessment of disease-specific and overall mortality in a randomized clinical trial.

Early detection of an apparently localized cancer does not automatically confer benefit. There are screening tests for some diseases that have been found to be of no benefit, such as chest x-ray screening for lung cancer,[125,126] or urine screening for vanillylmandelic acid to detect neuroblastoma.[127] A number of common screening tests used in the United States offer undetermined benefit.

POTENTIAL BIASES

The evaluation of the benefits of a screening test is subject to several biases, including lead-time, length, and selection biases, the influences of which are reduced in a randomized trial.[128] These biases can lead one to believe that there is a benefit to a screening test when, in truth, there is none; there may even be a net harm. Screening, regardless of benefit, will usually increase the number of specific cancers diagnosed. It also can produce a shift in stage toward lower stages that will appear to improve survival statistics without reducing mortality (i.e., the number of deaths of a given cancer per number of people at risk of the disease). In such a case, the apparent duration of survival, measured from the date of diagnosis, would increase without lives truly being saved or life expectancy being changed.

When pure lead-time bias occurs, survival—the time from diagnosis to death—is increased, but treatment does not prolong life. Patients do not live longer; they are merely diagnosed at an earlier date. The screening test only prolongs the time the individual is aware of the disease and the time the individual is treated as a patient.

Length bias occurs when slow-growing, less-aggressive cancers are detected during screening. Cancers diagnosed as the result of the onset of symptoms between scheduled screenings are, on average, more aggressive, and treatment outcomes are not as favorable. An extreme form of length bias is termed overdiagnosis bias, or detection of pseudodisease. Some undetected slow-growing tumors fulfill the histologic criteria for cancer but would never be clinically significant or cause death. This phenomenon is compounded by the fact that the most common cancers are most frequent among older people. Other competing causes of death, such as heart disease, become more relevant. This is particularly common in prostate cancer.

Selection bias must be considered when assessing the results of any clinical trial. The group most likely to seek entry in the study may differ from the general population to which the study results might be applied. In an assessment of a group of individuals undergoing screening, individuals may have volunteered because of a particular risk factor not found in the larger population, such as a strong family history. In general, volunteers are more health-conscious and are likely to have better prognoses or lower mortality rates regardless of actually being screened; this trend is referred to as the "healthy volunteer effect."

ASSESSMENT OF SCREENING TESTS

As a result of the biases above, a screening intervention is best evaluated in a population-based, randomized, controlled screening trial with cause-specific mortality as the endpoint.[128] Because gold-standard randomized screening trials for cancer are perforce large (often involving thousands of people) and last for years, less-definitive study designs often are used to estimate the efficacy and effectiveness of screening practices.

In order of strength of evidence, efficacy can by assessed using the following:

- findings of internally controlled trials in which intervention-allocation methods other than randomization are used, such as allocation determined by birth date or by date of clinic visit;
- results of cohort or case-control analytic observational studies;
- findings of multiple time series studies, with or without the intervention; and
- opinions of respected authorities based on clinical experience, descriptive studies, or consensus reports of experts.

The last form of evidence is the weakest, because even experts can easily be misled by the biases described above.

POTENTIAL HARMFUL EFFECTS

Subjects can be harmed as a result of screening. A harmful effect can be associated with the test itself, the work-up of positive results of screening tests (both true-positive and false-positive results), and injuries from the treatment of true-positive results. Screening can detect some cancers that would never have caused medical problems; the unnecessary treatment of these cancers can be harmful. Aside from the adverse effects of screening and the subsequent work-up and extra treatment, there are the financial costs associated with screening and all of the above extra tests and treatments.

ACCURACY

The accuracy of any medical test is usually described using four indices: sensitivity, specificity, positive predictive value, and negative predictive value. The results of screening tests can be classified into four categories (Tables 1-5 and 1-6). Sensitivity and specificity are relatively independent of the underlying prevalence or risk of the population being screened, but the positive and negative predictive values are highly dependent on prevalence (Table 1-7). In other words, screening is most beneficial, efficient, and economical when targeting a cancer common to the general population or groups with a high prevalence (or high risk) of the specific disease being screened. Sensitivity need not be extremely high (Table 1-7). However, it is worth reiterating that the key criterion for the public health recommendation of a screening test is that it is able to reduce cancer mortality.[129]

A screening test that is not efficacious in reducing mortality in an average-risk population does not become efficacious if used in a high-risk population. It is certainly preferred to utilize screening tests in higher-risk populations (e.g., those with family history, or a lung cancer screening test in smokers) but this is because the yield will be higher, and thus the cost-effectiveness and, more importantly, the positive predictive value will be better (i.e., there will be fewer false positives). But if the screening test is not effective (i.e., does not reduce mortality), it will also not reduce mortality in higher-risk populations and should not be utilized. A good example is chest x-ray screening, which has been shown to not reduce lung cancer mortality.

Table 1-5 Indices for Describing the Accuracy of Screening Tests

Term	Definition	Ability of Test	Equation
Sensitivity	Proportion of people with the disease who have a positive result on a screening test	To detect disease when it is present	A / (A+C)
Specificity	Proportion of people who do not have the disease who have a negative result on a screening test	To correctly identify the absence of disease	D / (B+D)
Positive predictive value	Proportion of people with a positive result on a predictive value screening test who actually have the disease	To accurately predict the presence of disease	A / (A+B)
Negative predictive value	Proportion of people who have a negative result on a screening test who truly do not have the disease	To accurately predict the absence of disease	D / (C+D)

Abbreviations: A, true-positive result; B, false-positive result; C, false-negative result; D, true-negative result.

Table 1-6 Types of Results of Screening Tests

	Condition Present	Condition Absent
Positive Results	True positive (A)	False positive (B)
Negative Results	False negative (C)	True negative (D)

Table 1-7 Influence of Prevalence on Predictive Value

Positive Predictive Value for a Disease with Prevalence of 5 Affected Individuals per 1,000 Population			Positive Predictive Value for a Disease with Prevalence of 1 Affected Individual per 10,000 Population		
	Sensitivity			Sensitivity	
	0.8	0.95		0.8	0.95
Specificity			Specificity		
0.95	7%	9%	0.95	0.2%	0.2%
0.999	80%	83%	0.999	7%	9%

Its use in heavy smokers or asbestos workers would not make it "work" any better in those populations and it should not be used there. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial recently demonstrated that CA-125 and transvaginal ultrasound screening are not effective in reducing the mortality from ovarian cancer *(discussed below)*. Thus, the use of such screening in *BRCA* carriers would not be indicated despite their high risk.

KEY POINTS

- Evaluation of the benefits/efficacy of a cancer screening test is far more complicated than simply the performance of the test and the yield of localized cancers.
- The biases of screening are volunteer selection, lead-time, length, and overdiagnosis. These biases can make a screening test appear beneficial when there is actually no benefit, or even harm.
- To offset these biases, a randomized trial is the best way to assess a screening test with the endpoint of reduction in cancer-related mortality.

SCREENING FOR SPECIFIC CANCERS

Results from well-executed studies are convincing that screening for cervix, colorectal, and breast cancers is beneficial at certain ages for people at average risk. Although special surveillance of individuals at high risk for some specific cancers because of family history or genetic risk may be prudent, few studies have been carried out to assess its true worth.

A number of organizations have evaluated certain screening tests and considered whether to endorse routine use of such measures. The U.S. Preventive Services Task Force (USPSTF)[130] and the Canadian Task Force on Preventive Health Care[131] published screening recommendations after a rigorous review process. Each recommendation is made with a thorough, structured evaluation of the literature by screening experts. ACS publishes the most commonly quoted screening guidelines (Table 1-8).[132]

BREAST CANCER

Studies of breast self-examination have not shown that this practice decreases mortality.[133] The results of the largest randomized, controlled study of breast self-examination reported to date showed both an increased rate of biopsy and enhanced detection of benign lesions, but little or no stage shift and no reduction in breast cancer mortality.[134]

Findings from several randomized trials indicate that screening women older than age 50 with normal risk using mammography alone or mammography and clinical breast examination every 1 to 2 years decreases mortality by 20% to 30%. Each trial has been criticized for a certain aspect of its design but there is power in the consistency of the observations.[135]

Experts disagree on whether women of average risk between age 40 and 49 benefit from screening (Table 1-8). A meta-analysis of seven large randomized trials showed no benefit from mammography screening for women in this age group when assessed 5 to 7 years after trial entry.[136] There was a small benefit for women at 10 to 14 years after entry, which may have been the result of screening these women after they turned 50.[137] Nonetheless, current U.S. guidelines recommend initiating screening at age 40. There is no consensus on the age at which to cease screening. A recent re-analysis sponsored by the USPSTF suggested that screening before age 50 was not necessarily beneficial.[138] Although there was a potential 18% reduction in mortality, the number needed to screen to achieve this and the concomitant number of false positives that needed to be evaluated were so high that the USPSTF argued that the risk-benefit ratio for screening before age 50 was not worthwhile. The resulting disagreement from women's groups, political agencies, radiologists, and others has caused these guidelines not to be implemented as policy.

The results from outcomes studies show that there is substantial variation among U.S. radiologists regarding recommendations for additional testing or biopsy. This disparity is especially notable among younger women. In large cohorts, nearly half of all women between age 40 and 49 screened annually for 10 years will have false-positive mammograms necessitating repeat mammography, ultrasound examination, magnetic resonance imaging (MRI), or biopsy. In addition, the diagnosis of ductal carcinoma in situ has risen dramatically since the widespread introduction of mammographic screening for women younger than 50.

Mammography may not be as sensitive for detecting breast cancers among women with *BRCA1* or *BRCA2* mutations, possibly because these women tend to develop cancers at a younger age, when mammography is less sensitive. Studies have suggested that MRI has greater sensitivity than mammography or ultrasound. Its high cost and unproven survival benefit make it undesirable for general use, but it can increase yield in a cost-effective fashion for young *BRCA* mutation carriers[139,140] as well as for other women at increased risk for breast cancer.[141] ACS has developed guidelines[142] for the use of MRI for women who have a lifetime risk of breast cancer that is 20% to 25% or greater as determined by the BRCAPRO statistical model[143] or in some other way.

CERVIX CANCER

No randomized clinical trial has been conducted to determine whether cervix cancer screening with a Pap test reduces mortality, but findings from several cohort and case-control studies have shown the utility of this test in reducing mortality. Indeed, the introduction of this test in the late 1940s was accompanied by a dramatic decline in the incidence of cervix cancer in the United States (Fig. 1-1). Routine Pap testing is recommended for women who are sexually active or who are older than age 21. The recommended interval for Pap testing has recently been increased to 2 to 3 years by several organizations (Table 1-8). An upper age limit at which screening ceases to be effective is not known. In the United States, Pap testing has resulted in a decrease in cervix cancer incidence because screening usually finds and eliminates the precursor lesion, cervix intraepithelial neoplasia.

Table 1-8 Screening Recommendations for Asymptomatic Patients with Normal Risk*

Test or Procedure	U.S. Preventive Services Task Force	Canadian Task Force on Preventive Health Care	American Cancer Society
Fecal occult blood testing (FOBT) for colorectal cancer	Annual FOBT for individual age 50 or older	FOBT every 1 to 2 years for individual age 50 or older	Annually, FOBT or fecal immunochemical test (FIT) starting at age 50
Flexible sigmoidoscopy for colorectal cancer	Flexible sigmoidoscopy every 5 years for individual age 50 or older	Flexible sigmoidoscopy every 5 years for individual age 50 or older	Flexible sigmoidoscopy every 5 years, starting at age 50
Double contrast barium enema (DCBE) for colorectal cancer	Every 5 years for individual age 50 or older	No recommendation	Every 5 years, starting at age 50
Colonoscopy for colorectal cancer	Every 10 years for individual age 50 or older	Insufficient evidence	Every 10 years, starting at age 50
CT colonography for colorectal cancer	Insufficient evidence	Insufficient evidence	Every 5 years, starting at age 50
Digital rectal examination (DRE)	No recommendation	Poor evidence to include or exclude for men older than age 50	No recommendation
Prostate-specific antigen (PSA) and DRE for prostate cancer	Insufficient evidence to recommend	Insufficient evidence to include PSA in periodic health exam (PHE). Poor evidence to include or exclude DRE from PHE	Shared decision between physician and patient. Annually, starting at age 50 in men with a life expectancy of 10 or more years
Pap test for cervix cancer	Begin 3 years after the onset of sexual activity or age 21, whichever first. Pap smear every 3 years from age 21 to age 65, or alternatively Pap smear combined with HPV testing every 5 years starting at age 30	Annual screening to begin following initiation of sexual activity or at age 18. After two normal smears, screen every 3 years to age 69	Begin 3 years after a woman begins vaginal intercourse, but no later than age 21. Screen annually with conventional Pap tests or every 2 years with liquid-based Pap tests. At or after age 30, women with three normal tests in a row may screen every 2 to 3 years with cervix cytology alone, or every 3 years with HPV DNA test plus cervix cytology. Women age 70 and older who have had three or more normal Pap tests and no abnormal tests in the last 10 years and women who have had a total hysterectomy may choose to stop cervix cancer screening
Breast self-examination (BSE) for breast cancer	Recommends against clinicians teaching women how to perform BSE	Insufficient evidence to make recommendation	Beginning in their early 20s, women should be advised about the limitations and benefits of BSE. Women may choose not to do BSE or to do BSE irregularly or regularly
Clinical breast examination (CBE) for breast cancer	Insufficient evidence to recommend adding over and above mammography	Recommended with mammogram	Every 3 years for women in their 20s and 30s, annually for women age 40 and older
Mammography for breast cancer	Every 2 years for women age 50 to 74. Screening before age 50 should take into account patient context and patient values regarding specific benefits and harms	Mammogram and CBE every year for women age 50 to 69	Annually, starting at age 40
Cancer-related check-up	No recommendation	No recommendation	On the occasion of a PHE, cancer-related check-up should include exam for cancers of the thyroid, testicles, ovaries, lymph nodes, oral cavity, and skin. Counseling about tobacco cessation, sun exposure, diet and nutrition, risk factors, sexual practices, and environmental and occupational exposures should occur at the time of the health exam

*These recommendations were made for the general population—asymptomatic people who have no risk factors, other than age or gender, for the targeted condition.

Abbreviation: HPV, human papillomavirus.

In 2002, ACS revised its screening guidelines to recommend that screening start approximately 3 years after a woman begins having vaginal intercourse, but no later than age 21.[144] ACS recommends that cervix screening be performed annually in the case of regular Pap tests or every 2 years in the case of liquid-based cytologic tests. Women who have had normal results on three consecutive tests may be screened every 2 to 3 years. In March 2012, the ACS, USPSTF, and the American College of Obstetrics and Gynecology jointly released updated guidelines which endorsed screening every 5 years over age 30 with combined cytologic testing and HPV DNA testing. If normal by age 65, women could stop further screening. Women with certain risk factors, such as infection with HIV or a weakened immune system, might be screened more frequently.

The association of cervix cancer with HPV has led to the use of HPV DNA testing as the sole means of screening for cervix neoplasia. This has been recommended for use in resource-poor environments where Pap tests are difficult to conduct properly. In addition, HPV screening can be used to elucidate the diagnosis based on Pap tests that give equivocal outcomes.[145]

COLORECTAL CANCER

Several methods are recommended for colorectal cancer screening:

- Fecal occult blood testing
- Sigmoidoscopy
- Colonoscopy
- Radiographic barium contrast studies
- Computed tomography (CT) colonography

The results of randomized studies indicate that annual fecal occult blood testing can reduce colorectal cancer mortality by one-third.[146] The rate of false-positive results for fecal occult blood testing is 1% to 5%. Fewer than 10% of patients with occult blood found in stool analysis have cancer, and approximately one-fifth to one-third have adenomas.

Findings from two case-control studies found that screening sigmoidoscopy is associated with a decrease in mortality among participants age 50 and older.[147] The results from other studies show that approximately one-half of all polyps are found with the 35-cm flexible scope and two-thirds to three-quarters are found with a 60-cm scope. Diagnosis of polyps by sigmoidoscopy should lead to evaluation of the entire colon with colonoscopy.

Three randomized trials of sigmoidoscopy are in progress. One, from Great Britain,[148] showed a clear-cut mortality benefit for sigmoidoscopy that was quite dramatic, and may justify the use of sigmoidoscopy as a routine screening test, perhaps even as an alternative to colonoscopy. A second trial from Italy showed an 18% statistically significant reduction in colorectal cancer incidence and a 22% reduction in overall mortality that was not statistically significant.[149] The PLCO trial in the United States has just reported, in abstract form, the results of its randomized trial of sigmoidoscopy, the largest of the three studies with over 150,000 participants.[150] This study showed significant 21% and 26% reductions in overall colorectal cancer incidence and mortality. All three randomized trials showed dramatic and significant reductions in distal colon cancer incidence and mortality.

Several recent reports, all well-conducted observational studies, explored the benefits of colonoscopy in reducing mortality. At least four such reports found that although colonoscopy did reduce incidence and mortality in the left colon, it did not have the expected benefits on the right side of the colon which are the reasons for its use. The reasons for this finding are unclear and may represent differences in the biology of right-sided versus left-sided lesions, or differences in the expertise of endoscopists in examining the right side of the colon.[151] One recent study from Germany[152] did suggest a reduced incidence of right-sided neoplasia with the use of colonoscopy, so perhaps it is a population-specific phenomenon. No study has been done to evaluate this issue in the United States, where colonoscopies are overwhelmingly performed by gastroenterologists.

Although no study results have clearly demonstrated benefit, it is prudent to use colonoscopy as a screening tool for individuals at average risk for colorectal cancer. This rationale is an extension of the available data for sigmoidoscopy which show a mortality benefit almost exclusively for left-sided cancers, and no benefit for the right side of the colon where the sigmoidoscope does not reach.[153] Colonoscopy should be used for those at high risk, such as those with a genetic predisposition to colorectal cancer and those with inflammatory bowel disease. Little information is available on the utility of the barium enema as a screening tool. Recent interest has centered on CT (virtual) colonography as well. The evidence suggests that, in certain instances, it may substitute for colonoscopy.

Guidelines for colorectal cancer screening continue to evolve. Although ACS currently recommends the full range of screening tests listed above as options for screening, new guidelines were published in November 2008 by a working group composed of members from ACS, the American College of Radiology, and experts in gastroenterology.[154] These guidelines put increased emphasis on structural tests which could "detect adenomatous polyps and cancer" as opposed to "tests that primarily detect cancer," essentially suggesting that the fecal tests, guaiac-based occult blood testing and fecal immunochemical testing, were less desirable than endoscopy or CT colonography. It is notable that CT colonography was recommended along with endoscopy. Almost simultaneously, the USPSTF released its newest recommendations,[155] which include fecal occult blood testing, sigmoidoscopy, and colonoscopy, and conclude that the evidence is currently insufficient to recommend CT colonography. An excellent discussion of the relative merits and approaches of these two sets of recommendations can be found in an editorial accompanying the USPSTF report.[156]

LUNG CANCER

Screening for lung cancer with chest x-ray and sputum cytologic testing was evaluated in four randomized lung cancer screening trials in the 1960s and 1970s. No reduction in lung cancer mortality was seen in those studies.[157,158] A randomized trial of chest x-ray screening as part of the PLCO study was recently

conducted to re-evaluate its value. The results of this study reaffirm the absence of benefit for chest x-ray screening.[125]

Studies have shown that spiral CT can diagnose lung cancers at early stages, but it is unclear whether it will save lives.[159,160] This technology was evaluated in a large, randomized clinical trial of heavy smokers which compared CT screening to chest x-ray screening. These results were reported from the NLST trial[161] and showed a 20% reduction in mortality for the arm screened with CT. However, the number needed to screen to achieve this reduction in mortality as well as the rate of overdetection needs to be evaluated before this mode of screening will be recommended as policy for heavy smokers. Spiral CT also can detect many benign processes that cause noncalcified lung radiodensities; these are false-positive findings. Spiral CT does increase the number of lesions diagnosed and, thus, will increase the number of diagnostic and therapeutic procedures performed (*see Fig. 7-2 in Chapter 7: Lung Cancer*).[158,159]

OVARIAN CANCER

Adnexal palpation, transvaginal ultrasound, and measurement of serum CA-125 have been considered for ovarian cancer screening. No randomized prospective trial of screening for ovarian cancer has shown an improvement in ovarian cancer mortality. The results of such studies could lead to futile invasive diagnostic testing that might include laparotomy. A recent clinical trial (PLCO) randomly assigned over 78,000 women to screening with CA-125 and transvaginal ultrasound for 4 years or usual care, and found no difference in ovarian cancer mortality.[162]

PROSTATE CANCER

The digital rectal examination (DRE) and measurement of serum prostate-specific antigen (PSA) are commonly used in the United States, although most professional organizations advise caution in the use of such screening tools (Table 1-8). No well-designed, -conducted, and -analyzed study has been completed to test the true benefits of screening and treatment of prostate cancer.[163] Prostate cancer is prone to lead-time bias, length bias, and overdiagnosis. Whereas screening using PSA levels and DRE clearly detects many asymptomatic cancers, its ability to reliably distinguish tumors that could be lethal but are still curable from those that pose little or no threat to health is limited. It has been estimated that more than 30% of localized prostate cancers diagnosed during screening are indolent and clinically insignificant. Treatment of screen-detected cancers may cause morbidity, such as impotence and urinary incontinence, and carries a small risk of death.[164]

Most expert organizations do not recommend screening for prostate cancer. The USPSTF examined the evidence in support of screening and found there was insufficient evidence to recommend it.[164,165] ACS and the American Urological Association recommend that men older than age 50 at normal risk be offered screening and be allowed to make a choice after being informed of its potential risks and benefits (Table 1-8).

The interim results of two large randomized trials of prostate screening have been reported. The PLCO trial randomly assigned 76,693 men to 6 years of annual screening with PSA or regular management according to community standards. In essence, 85% of the men in the intervention group were screened while more than 40% of the men in the control arm were screened. After 7 to 10 years, there was no mortality benefit (HR 1.13, 95% CI [0.75, 1.70]).[166] The European Randomised Study of Screening for Prostate Cancer (ERSPC) randomly assigned 182,000 men in seven countries; each country had slight differences in study design. The intervention group was offered PSA screening every 4 years (every 2 years in Sweden), and 82% participated; a cut-off of 3 was used for the PSA rather than the usual 4. With a median follow-up of 9 years, the hazard ratio for mortality was 0.80 (95% CI [0.65, 0.98]). It is notable that 1,410 men needed to be screened (16% of patients being screened had an abnormal PSA and required biopsy and further evaluation) to prevent one death and 48 cases of prostate cancer were detected among those 1,410 men to save that one life.[167]

SKIN CANCER

No randomized study has been conducted to assess whether screening for skin cancer decreases mortality. Screening programs in Scotland and Australia may have caused the stage shift in diagnosed melanomas.[168] These programs also may reinforce sun avoidance and other prevention behaviors.

OTHER CANCERS

The dramatic rise in the incidence of esophageal adenocarcinoma during the past two decades has raised concerns regarding prevention. These tumors are known to arise from Barrett esophagus, a metaplastic change in the esophageal mucosa that later progresses to dysplasia and malignancy. The main risk factor for Barrett esophagus is gastroesophageal reflux disease, a condition that has increased dramatically, perhaps partially because of the epidemic of obesity. Thus, there has been a major effort to conduct esophagogastroduodenoscopy on patients with persistent gastroesophageal reflux disease to detect early-stage Barrett esophagus and to intervene in this pathway with the use of proton pump inhibitors and close surveillance with endoscopy. This has become a recommendation of the American Gastroenterological Association, despite the absence of any randomized trial or other high-quality evidence demonstrating a significant benefit from the point of view of cancer prevention or survival benefit.[169]

Although we have focused on cancer screening in the United States, it is worth noting that screening for some cancers may be worthwhile in other countries where these cancers are more common. One example is oral cancer, which is the most common cancer among men in India, largely because of the chewing of betel nuts. A randomized trial has shown that in this region the use of visual screening of the oral cavity reduced mortality significantly.[170] Hepatocellular carcinoma (HCC) is a common cancer in large portions of East Asia and Africa, related to chronic hepatitis B infection. A trial was conducted in Shanghai of over 18,000 carriers of hepatitis B, who were randomly assigned to a serum alpha-fetoprotein (AFP) test plus ultrasonography every 6 months or no screening. At 5 years, the HCC

mortality was reduced by 37% in the screened group (HR 0.63, 95% CI [0.41, 0.98]).[171]

Another common screening test is the use of photofluorography in Japan to screen for gastric cancer. No randomized trial has been conducted to confirm the efficacy of this test in reducing mortality.[172]

KEY POINTS

- The PLCO study yielded new data on screening for four cancers. It has confirmed that chest x-ray screening is ineffective for lung cancer, confirmed that sigmoidoscopy is efficacious in reducing mortality for colorectal cancer, provided definitive evidence that CA-125 and transvaginal ultrasound screening for ovarian cancer are not effective, and provided negative data on PSA screening for prostate cancer.
- Although mammography screening for breast cancer in women older than age 50 has significant evidence in its support, screening in women younger than age 50 and PSA screening in men for prostate cancer both remain controversial. In both circumstances, the absolute mortality reduction is small and the number needed to screen is large, making the risk-benefit ratio a major concern from a policy standpoint.
- New data from a randomized trial suggest that low-dose spiral CT screening may be a future approach to reducing lung cancer mortality among heavy smokers.
- The use of HPV DNA testing in conjunction with Pap smear testing can allow the prolongation of the interval between screening for cervix cancer to extend to 5 years.
- Randomized trial data is now substantial enough to support the use of both fecal occult blood testing and sigmoidoscopy as screening modalities for colorectal cancer.
- Despite its widespread use, the evidence supporting the use of colonoscopy for colorectal cancer screening is relatively weak.

SURVIVORSHIP

It is estimated that there are currently 12 million cancer survivors in the United States, and this number is likely to grow in the coming years. This is a good thing, of course, to the degree that it reflects the increasing success of treatment in curing (or at least prolonging life for) those diagnosed with cancer. The number of cancer survivors is also increasing because of the aging of the population with a concomitant increase in cancer cases, and because of the increased use of screening and diagnostic tests and thus the increased diagnosis of subclinical disease.

Cancer survivors share a substantial number of issues and problems that are currently the subjects of intensive research efforts, including their psychological needs, employment issues, appropriate surveillance, and management of long-term toxicities of treatment. It is also critical to bear in mind that they are at increased risk for second malignancies as an overall group. Some may be at increased risk for certain specific cancers.[173] They require, at the least, special attention to make sure that they obtain the screening studies that are recommended for the general population. For those who have special risks, they may require that special screening protocols be utilized. For example, MRI screening may be recommended for young breast cancer survivors who are at very high risk for a contralateral breast cancer.

It is mandatory that a good working relationship be established between the oncologist and the primary care physician.[174] Some studies have shown that regular wellness care may be neglected for cancer survivors under the stress and pressure of a cancer diagnosis and its treatment.[175-177] The standard protocols of good medical care, including hypertension, lipid, and other screening and vaccination protocols, should be followed for cancer survivors as they would be for any other adult. In addition, there is increasing evidence that improved lifestyle and other prevention activities, such as weight loss, tobacco cessation, increased physical activity, and a moderate diet, may improve the incidence of second malignancies, and they may reduce the recurrence of the initial primary cancer. In coming years, the medical oncologist is likely to play an increasing role as a primary and secondary prevention expert, similar to the ways in which cardiologists counsel their patients on tobacco cessation, weight loss, physical activity, and lipid management.[178]

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Etiology

Meta-analysis: Use of combined oral contraceptives in the past 10 years is associated with an increased risk for breast cancer

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Abstract

Objective

To determine whether an association exists between use of hormonal contraceptives and risk for breast cancer.

Data sources

Studies were identified from review articles, computer-aided literature searches, and colleagues.

Study selection

Studies were selected if they included at least 100 women with breast cancer and if information was obtained on the use of hormonal contraceptives and on reproductive history.

Data extraction

The principal investigators of all identified studies were invited to collaborate. If they agreed, they provided data on individual women pertaining to sociodemographic factors, use of hormonal contraceptives and hormone replacement therapy, family history of breast cancer, height, weight, age at menarche, reproductive history, menopausal status, age at menopause, gynecologic surgery, and tumor spread for those who had breast cancer.

Main results

54 studies involving 53 297 women with invasive breast cancer and 100 239 women without breast cancer provided data (90% of eligible studies). All analyses were stratified by study; age at diagnosis; parity; and, when appropriate, the age of the woman when her first child was born and the age at which she was no longer able to conceive. Overall, the relative risk (RR) for breast cancer in women who had used oral contraceptives compared with women who had never used them was 1.07 ($P < 0.001$). An increased risk for breast cancer existed in women who were currently using combined oral contraceptives (RR 1.24, 99% CI 1.15 to 1.33, $P < 0.001$), in those who had stopped using oral contraceptives 1 to 4 years previously (RR 1.16, CI 1.08 to 1.23, $P < 0.001$), and in those who had stopped using oral contraceptives 5 to 9 years previously (RR 1.07, CI 1.02 to 1.13, $P = 0.009$). No increased risk for breast cancer was found among women who had stopped using oral contraceptives for 10 or more years (RR 1.01, CI 0.96 to 1.05). The breast cancer diagnosed in women who had used oral contraceptives was less advanced than in those who had never used the contraceptives. For those who had used oral contraceptives compared with those who had not, the RR for tumors that spread beyond the breast compared with localized tumors was 0.88 (CI 0.81 to 0.95, $P = 0.002$). Duration of hormonal contraceptive use, age at first use, and the dose and type of hormone had little additional effect on the risk for breast cancer when recency of use was considered.

Conclusions

A small increased risk for breast cancer exists while women are taking combined oral contraceptives and in the 10 years after they stop. No evidence was found for an increased risk for breast cancer among women who stopped using oral contraceptives more than 10 years previously.

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Commentary

Concerns about the health effects of oral contraceptives have led to many studies that explore the effects on the risk for breast cancer. The results from most studies suggest a small risk from oral contraceptive use for younger women and no risk for older women.

As is usual for meta-analyses, the overall results do not substantially alter one's understanding of the previous studies and basically confirm a minimal, if any, increased risk for breast cancer. The real benefit of meta-analysis is in exploring subgroups. Here the results of the analysis indicate that the increased risk for breast cancer is limited to the time interval during which oral contraceptives were used and shortly thereafter, with no long-term effects, and that the excess number of cases of breast cancer seen are generally local disease.

It is important to consider the absolute risk associated with oral contraceptives. In particular, given the relatively low incidence of breast cancer among women in the age groups who most often use oral contraceptives, an excess risk of 20% to 30% still seems inconsequential, particularly if these breast cancers are at a very early stage (1). Certainly, the excess risk in terms of breast cancer incidence seems minuscule when compared with the potential hazards from cardiovascular or other adverse health events. For policy-making purposes, the effect of oral contraceptive use on breast cancer mortality would be useful.

Questions have recently been raised about whether epidemiologic methods can resolve concerns about small RRs (< 2) through use of observational studies. Meta-analyses, such as this one, are probably as good as we can do and at least suggest that there is not a greater cause for concern. Nonetheless, this study reminds me of what a professor of mine once said: We usually say that the difference was small but statistically significant. Perhaps we should say that the difference was statistically significant but small.

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REVIEW

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Meta-analysis: Its strengths and limitations

ABSTRACT

Nowadays, doctors face an overwhelming amount of information, even in narrow areas of interest. In response, reviews designed to summarize the large volumes of information are frequently published. When a review is done systematically, following certain criteria, and the results are pooled and analyzed quantitatively, it is called a meta-analysis. A well-designed meta-analysis can provide valuable information for researchers, policymakers, and clinicians. However, there are many critical caveats in performing and interpreting them, and thus many ways in which meta-analyses can yield misleading information.

KEY POINTS

Meta-analysis is an analytical technique designed to summarize the results of multiple studies.

By combining studies, a meta-analysis increases the sample size and thus the power to study effects of interest.

There are many caveats in performing a valid meta-analysis, and in some cases a meta-analysis is not appropriate and the results can be misleading.

THE AMOUNT OF INFORMATION generated in medical research is becoming overwhelming, even for experienced researchers. New studies are constantly being published, and clinicians are finding it nearly impossible to stay current, even in their own area of specialty.

To help make sense of the information, we are seeing more and more review articles that pool the results of multiple studies. When certain principles are followed and the data are quantitatively analyzed, these reviews are called meta-analyses. A PubMed search of the word "meta-analysis" in the title yielded 1,473 articles in the year 2007.

Combining available information to generate an integrated result seems reasonable and can save a considerable amount of resources. Nowadays, meta-analyses are being used to design future research, to provide evidence in the regulatory process,[1] and even to modify clinical practice.

Meta-analysis is powerful but also controversial—controversial because several conditions are critical to a sound meta-analysis, and small violations of those conditions can lead to misleading results. Summarizing large amounts of varied information using a single number is another controversial aspect of meta-analysis. Under scrutiny, some meta-analyses have been inappropriate, and their conclusions not fully warranted.[2,3]

This article introduces the basic concepts of meta-analysis and discusses its caveats, with the aim of helping clinicians assess the merits of the results. We will use several recent meta-analyses to illustrate the issues, including a controversial one[4] with potentially far-reaching consequences.

OBJECTIVES OF META-ANALYSIS

The main objectives of a meta-analysis are to:

- Summarize and integrate results from a number of individual studies
- Analyze differences in the results among studies
- Overcome small sample sizes of individual studies to detect effects of interest, and analyze end points that require larger sample sizes
- Increase precision in estimating effects
- Evaluate effects in subsets of patients
- Determine if new studies are needed to further investigate an issue
- Generate new hypotheses for future studies.

These lofty objectives can only be achieved when the meta-analysis satisfactorily addresses certain critical issues, which we will discuss next.

CRITICAL ISSUES IN META-ANALYSIS DESIGN

Four critical issues need to be addressed in a meta-analysis:

- Identification and selection of studies
- Heterogeneity of results
- Availability of information
- Analysis of the data.

Even small violations of the rules of meta-analysis can lead to misleading results

IDENTIFICATION AND SELECTION OF STUDIES

The outcome of a meta-analysis depends on the studies included. The critical aspect of selecting studies to be included in a meta-analysis consists of two phases. The first is the identification phase or literature search, in which potential studies are identified. In the second phase, further criteria are used to create a list of studies for inclusion. Three insidious problems plague this aspect of meta-analysis: publication bias and search bias in the identification phase, and selection bias in the selection phase. These biases are discussed below.

Publication bias: 'Positive' studies are more likely to be printed

Searches of databases such as PubMed or Embase can yield long lists of studies. However, these databases include only studies that have been published. Such searches are unlikely to yield a representative sample because studies that show a "positive" result (usually in favor of a new treatment or against a well-established one) are more likely to be published than those that do not. This selective publication of studies is called publication bias.

In a recent article, Turner et al[5] analyzed the publication status of studies of antidepressants. Based on studies registered with the US Food and Drug Administration (FDA), they found that 97% of the positive studies were published vs only 12% of the negative ones. Furthermore, when the nonpublished studies were not included in the analysis, the positive effects of individual drugs increased between 11% and 69%.

One reason for publication bias is that drug manufacturers are not generally interested in publishing negative studies. Another may be that editors favor positive studies because these are the ones that make the headlines and give the publication visibility. In some medical areas, the exclusion of studies conducted in non-English-speaking countries can increase publication bias.[6]

To ameliorate the effect of publication bias on the results of a meta-analysis, a serious effort should be made to identify unpublished studies. Identifying unpublished studies is easier now, thanks to improved communication between researchers worldwide, and thanks to registries in which all the studies of a certain disease or treatment are reported regardless of the result.

The National Institutes of Health maintains a registry of all the studies it supports, and the FDA keeps a registry and database in which drug companies must register all trials they intend to use in applying for marketing approval or a change in labeling. "Banks" of published and unpublished trials supported by pharmaceutical companies are also available (eg, **http://ctr.gsk.co.uk/welcome.asp**). The Cochrane collaboration (**www.cochrane.org/**) keeps records of systematic reviews and meta-analyses of many diseases and procedures.

Search bias: Identifying relevant studies

Even in the ideal case that all relevant studies were available (ie, no publication bias), a faulty search can miss some of them. In

searching databases, much care should be taken to assure that the set of key words used for searching is as complete as possible. This step is so critical that most recent meta-analyses include the list of key words used. The search engine (eg, PubMed, Google) is also critical, affecting the type and number of studies that are found.[7] Small differences in search strategies can produce large differences in the set of studies found.[8]

Selection bias: Choosing the studies to be included

The identification phase usually yields a long list of potential studies, many of which are not directly relevant to the topic of the meta-analysis. This list is then subject to additional criteria to select the studies to be included. This critical step is also designed to reduce differences among studies, eliminate replication of data or studies, and improve data quality, and thus enhance the validity of the results.

To reduce the possibility of selection bias in this phase, it is crucial for the criteria to be clearly defined and for the studies to be scored by more than one researcher, with the final list chosen by consensus.[9,10] Frequently used criteria in this phase are in the areas of:

- Objectives
- Populations studied
- Study design (eg, experimental vs observational)
- Sample size
- Treatment (eg, type and dosage)
- Criteria for selection of controls
- Outcomes measured
- Quality of the data
- Analysis and reporting of results
- Accounting and reporting of attrition rates
- Length of follow-up
- When the study was conducted.

The objective in this phase is to select studies that are as similar as possible with respect to these criteria. It is a fact that even with careful selection, differences among studies will remain. But when the dissimilarities are large it becomes hard to justify pooling the results to obtain a "unified" conclusion.

In some cases, it is particularly difficult to find similar studies,[10,11] and sometimes the discrepancies and low quality of the studies can prevent a reasonable integration of results. In a systematic review of advanced lung cancer, Nicolucci et al[12] decided not to pool the results, in view of "systematic qualitative inadequacy of almost all trials" and lack of consistency in the studies and their methods. Marsoni et al[13] came to a similar conclusion in attempting to summarize results in advanced ovarian cancer.

Stratification is an effective way to deal with inherent differences among studies and to improve the quality and usefulness of the conclusions. An added advantage to stratification is that insight can be gained by investigating discrepancies among strata.

There are many ways to create coherent subgroups of studies. For example, studies can be stratified according to their "quality," assigned by certain scoring systems. Commonly used systems award points on the basis of how patients were selected and randomized, the type of blinding, the dropout rate, the outcome measurement, and the type of analysis (eg, intention-to-treat). However, these criteria, and therefore the scores, are somewhat subjective. Moher et al[14] expand on this issue.

Large differences in sample sizes among studies are not uncommon and can cause problems in the analysis. Depending on the type of model used (see below), meta-analyses combine results based on the size of each study, but when the studies vary significantly in size, the large studies can still have an unduly large influence on the results. Stratifying by sample size is done sometimes to verify the stability of the results.[4]

Exclusion of nonpublished studies increases selection bias

On the other hand, the presence of dissimilarities among studies can have advantages by increasing the generalizability of the conclusions. Berlin and Colditz[1] point out that "we gain strength in inference when the range of patient characteristics has been broadened by replicating findings in studies with populations that vary in age range, geographic region, severity of underlying illness, and the like."

Funnel plot: Detecting biases in the identification and selection of studies

The funnel plot is a technique used to investigate the possibility of biases in the identification and selection phases. In a funnel plot

The funnel plot, a way to detect possible selection bias

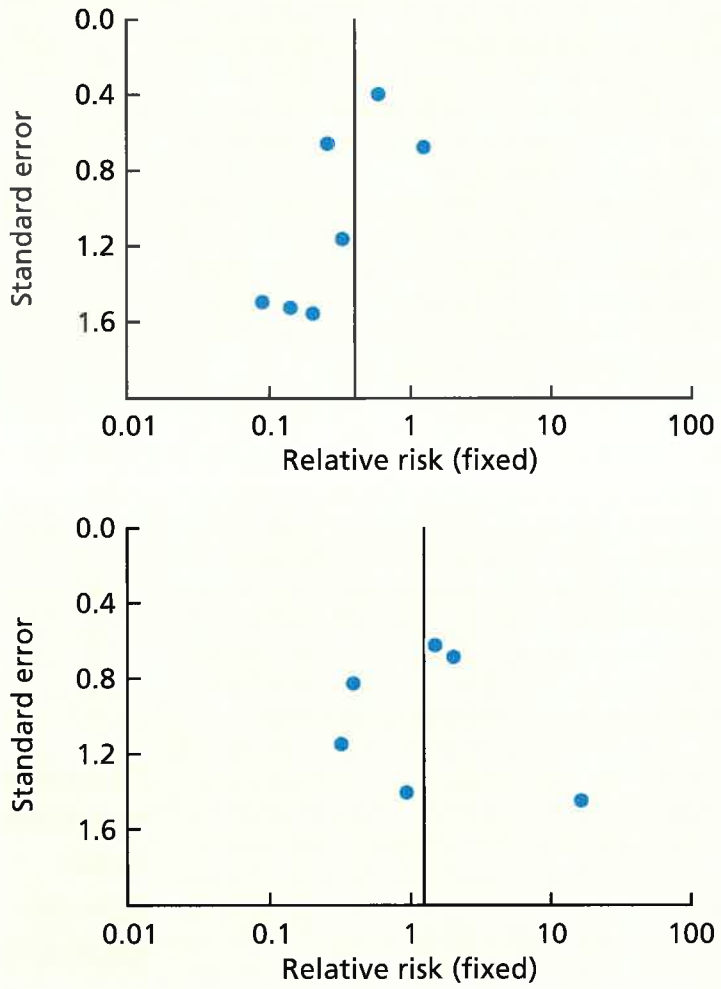

FIGURE 1. Top, a funnel plot of studies of anticoagulant prophylaxis that measured the outcome of symptomatic pulmonary embolism. The plot is asymmetrical, suggesting that small studies in which prophylaxis was associated with an increased risk are missing. **Bottom,** a funnel plot of studies with the outcome of major bleeding is symmetrical, suggesting absence of selection bias.

DENTALI F, DOUKELIS D, GIANNI M, ET AL. META-ANALYSIS: ANTICOAGULANT PROPHYLAXIS TO PREVENT SYMPTOMATIC VENOUS THROMBOEMBOLISM IN HOSPITALIZED MEDICAL PATIENTS. ANN INTERN MED 2007; 146:278–288.

the size of the effect (defined as a measure of the difference between treatment and control) in each study is plotted on the horizontal axis against standard error[15] or sample size[9] on the vertical axis. If there are no biases, the graph will tend to have a symmetrical funnel shape centered in the average effect of the studies. When negative studies are missing, the graph shows lack of symmetry.

Funnel plots are appealing because they are simple, but their objective is to detect a complex effect, and they can be misleading. For example, lack of symmetry in a funnel plot can also be caused by heterogeneity in the studies.[16] Another problem with funnel plots is that they are difficult to interpret when the number of studies is small. In some cases, however, the researcher may not have any option but to perform the analysis and report the presence of bias.[11]

Dentali et al[17] conducted a meta-analysis to study the effect of anticoagulant treatment to prevent symptomatic venous thromboembolism in hospitalized patients. The conclusion was that the treatment was effective to prevent symptomatic pulmonary thromboembolism, with no significant increase in major bleeding. FIGURE 1 shows the funnel plots for the two outcomes. Dentali et al[17] concluded that the lack of symmetry in the top plot suggests a lack of inclusion of small studies showing an increase in the risk of pulmonary thromboembolism, and thus, bias. The bottom plot shows the symmetry of the funnel plot for major bleeding, suggesting absence of bias.

HETEROGENEITY OF RESULTS

In meta-analysis, *heterogeneity* refers to the degree of dissimilarity in the results of individual studies. In some cases, the dissimilarities in results can be traced back to inherent differences in the individual studies. In other situations, however, causes for the dissimilarities might not be easy to elucidate. In any case, as the level of heterogeneity increases, the justification for an integrated result becomes more difficult. A tool that is very effective to display the level of heterogeneity is the forest plot. In a forest plot, the estimated effect of each study along with a line representing a confidence interval is drawn. When the effects are similar, the confidence intervals overlap, and heterogeneity is low. The forest plot includes a reference line at the point of no effect (eg, one for relative risks and odds ratios). When some effects lie on opposite sides of the reference line, it means

that the studies are contradictory and heterogeneity is high. In such cases, the conclusions of a meta-analysis are compromised.

The previously mentioned study by Dentali et al[17] presented several forest plots that display the level of heterogeneity of various outcomes. **FIGURE 2** shows the forest plot for the outcome of pulmonary embolism. Except for one, the estimated effects are on the same side of the unit line and the confidence intervals overlap to a large extent. This plot shows a low level of heterogeneity. **FIGURE 3** shows the forest plot for major bleeding. Here the effects are on both sides of the unit line, implying a high level of heterogeneity. Cochran's Q test is a statistical test used in conjunction with the forest plot to determine the significance of heterogeneity among studies.[18]

Gebski et al[19] performed a meta-analysis of randomized controlled trials comparing the survival of patients with esophageal carcinoma who received neoadjuvant chemotherapy vs those who underwent surgery alone. In only one of the eight studies included was neoadjuvant chemotherapy significantly beneficial. Three of the studies suggested that it was harmful, although the effects were not statistically significant. The pooled result was marginally significant in favor of the treatment ($P = .05$). This positive result was due largely to the fact that the only study with a significantly positive result study also was, by far, the largest (with 400 patients in each treatment group, vs an average of 68 per treatment group for the rest). Even though the test for heterogeneity was not significant, the marginal P value and the differences in study size make the results of this meta-analysis suspect.

AVAILABILITY OF INFORMATION

Most reports of individual studies include only summary results, such as means, standard deviations, proportions, odds ratios, and relative risks. Other than the possibility of errors in reporting, the lack of information can severely limit the type of analyses and conclusions that can be reached in a meta-analysis. For example, lack of information from individual studies can preclude the comparison of effects in predetermined subgroups of patients.

A low level of heterogeneity: Anticoagulation prevents pulmonary embolism

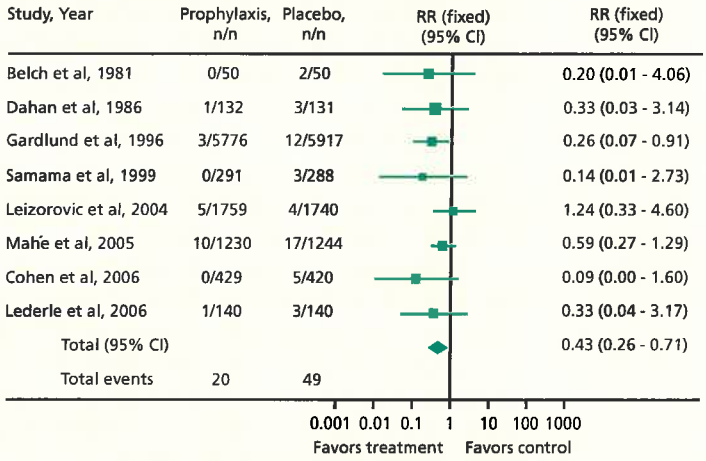

FIGURE 2. A forest plot of studies of anticoagulant prophylaxis with the outcome of pulmonary embolism. All except one of the studies show a better outcome with treatment than with placebo, indicating a low level of heterogeneity among the studies.

DENTALI F, DOUKELIS D, GIANNI M, ET AL. META-ANALYSIS: ANTICOAGULANT PROPHYLAXIS TO PREVENT SYMPTOMATIC VENOUS THROMBOEMBOLISM IN HOSPITALIZED MEDICAL PATIENTS. ANN INTERN MED 2007; 146:278–288.

A high level of heterogeneity: Does anticoagulation increase the risk of major bleeding?

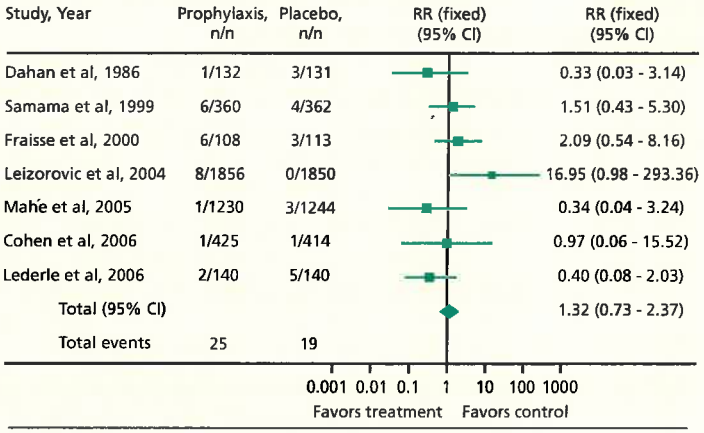

FIGURE 3. Risk of major bleeding in studies of anticoagulant prophylaxis. Some of the studies favor the control and others the treatment. This represents a high level of heterogeneity

DENTALI F, DOUKELIS D, GIANNI M, ET AL. META-ANALYSIS: ANTICOAGULANT PROPHYLAXIS TO PREVENT SYMPTOMATIC VENOUS THROMBOEMBOLISM IN HOSPITALIZED MEDICAL PATIENTS. ANN INTERN MED 2007; 146:278–288.

The best scenario is when data at the patient level are available. In such cases, the researcher has great flexibility in the analysis of the information. Trivella et al[20] performed a meta-analysis of the value of microvessel density in predicting survival in non-small-cell lung cancer. They obtained information on individual patients by contacting research centers directly. The data allowed them to vary the cutoff point to classify microvessel density as high or low and to use statistical methods to ameliorate heterogeneity.

A frequent problem in meta-analysis is the lack of uniformity in how outcomes are measured. In the study by Trivella et al,[20] the microvessel density was measured by two methods. The microvessel density was a significant prognostic factor when measured by one of the methods, but not the other.

RANDOMIZED CONTROLLED TRIALS VS OBSERVATIONAL STUDIES

'Data-mining' greatly increases the risk of false-positive results

Some researchers believe that meta-analyses should be conducted only on randomized controlled trials.[3,21] Their reasoning is that meta-analyses should include only reasonably well-conducted studies to reduce the risk of a misleading conclusion. However, many important diseases can only be studied observationally. If these studies have a certain level of quality, there is no technical reason not to include them in a meta-analysis.

Gillum et al[22] performed a meta-analysis published in 2000 on the risk of ischemic stroke in users of oral contraceptives, based on observational studies (since no randomized trials were available). Studies were identified and selected by multiple researchers using strict criteria to make sure that only studies fulfilling certain standards were included. Of 804 potentially relevant studies identified, only 16 were included in the final analysis. A funnel plot showed no evidence of bias and the level of heterogeneity was fairly low. The meta-analysis result confirmed the results of individual studies, but the precision with which the effect was estimated was much higher. The overall relative risk of stroke in women taking oral contraceptives was 2.75, with a 95% confidence interval of 2.24 to 3.38.

A more recent meta-analysis[23] (published in 2004) on the same issue found no significant increase in the risk of ischemic stroke with the use of oral contraceptives. Gillum and Johnston[24] suggest that the main reason for the discrepancy is the lower amount of estrogen in newer oral contraceptives. They also point out differences in the control groups and study outcomes as reasons for the discrepancies between the two studies.

Bhutta et al[25] performed a meta-analysis of case-control (observational) studies of the effect of preterm birth on cognitive and behavioral outcomes. Studies were included only if the children were evaluated after their fifth birthday and the attrition rate was less than 30%. The studies were grouped according to criteria of quality devised specifically for case-control studies. The high-quality studies tended to show a larger effect than the low-quality studies, but the difference was not significant. Seventeen studies were included, and all of them found that children born preterm had lower cognitive scores; the difference was statistically significant in 15 of the studies. As expected, the meta-analysis confirmed these findings (95% confidence interval for the difference 9.2–12.5). The number of patients (1,556 cases and 1,720 controls) in the meta-analysis allowed the researchers to conclude further that the mean cognitive scores were directly proportional to the mean birth weight ($R^2 = 0.51$, $P < .001$) and gestational age ($R^2 = 0.49$, $P < .001$).

ANALYSIS OF DATA

There are specific statistical techniques that are used in meta-analysis to analyze and integrate the information. The data from the individual studies can be analyzed using either of two models: fixed effects or random effects.

The fixed-effects model assumes that the treatment effect is the same across studies. This common effect is unknown, and the purpose of the analysis is to estimate it with more precision than in the individual studies.

The random-effects model, on the other hand, assumes that the treatment effect is not the same across studies. The goal is to estimate the average effect in the studies.

In the fixed-effects model, the results of

individual studies are pooled using weights that depend on the sample size of the study, whereas in the random-effects model each study is weighted equally. Due to the heterogeneity among studies, the random-effects model yields wider confidence intervals.

Both models have pros and cons. In many cases, the assumption that the treatment effect is the same in all the studies is not tenable, and the random-effects model is preferable. When the effect of interest is large, the results of both models tend to agree, particularly when the studies are balanced (ie, they have a similar number of patients in the treatment group as in the control group) and the study sizes are similar. But when the effect is small or when the level of heterogeneity of the studies is high, the result of the meta-analysis is likely to depend on the model used. In those cases, the analysis should be done and presented using both models.

It is highly desirable for a meta-analysis to include a sensitivity analysis to determine the "robustness" of the results. Two common ways to perform sensitivity analysis are to analyze the data using various methods and to present the results when some studies are removed from the analysis.[26] If these actions cause serious changes in the overall results, the credibility of the results is compromised.

The strength of meta-analysis is that, by pooling many studies, the effective sample size is greatly increased, and consequently more variables and outcomes can be examined. For example, analysis in subsets of patients and regression analyses[9] that could not be done in individual trials can be performed in a meta-analysis.

A word of caution should be given with respect to larger samples and the possibility of multiple analyses of the data in meta-analysis. Much care must be exercised when examining the significance of effects that are not considered prior to the meta-analysis. The testing of effects suggested by the data and not planned a priori (sometimes called "data-mining") increases considerably the risk of false-positive results. One common problem with large samples is the temptation to perform many so-called "subgroup analyses" in which subgroups of patients formed according to multiple baseline characteristics are compared.[27] The best way to minimize the possibility of false-positive results is to determine the effects to be tested before the data are collected and analyzed. Another method is to adjust the *P* value according to the number of analyses performed. In general, post hoc analyses should be deemed exploratory, and the reader should be made aware of this fact in order to judge the validity of the conclusion.

META-ANALYSIS OF RARE EVENTS

Lately, meta-analysis has been used to analyze outcomes that are rare and that individual studies were not designed to test. In general, the sample size of individual studies provides inadequate power to test rare outcomes. Adverse events are prime examples of important rare outcomes that are not always formally analyzed statistically. The problem in the analysis of adverse events is their low incidence. Paucity of events causes serious problems in any statistical analysis (see Shuster et al[28]). The reason is that, with rare events, small changes in the data can cause dramatic changes in the results. This problem can persist even after pooling data from many studies. Instability of results is also exacerbated by the use of relative measures (eg, relative risk and odds ratio) instead of absolute measures of risk (eg, risk difference).

With rare effects, even a small difference can seem large

In a controversial meta-analysis, Nissen and Wolski[4] combined 42 studies to examine the effect of rosiglitazone (Avandia) on the risk of myocardial infarction and death from cardiovascular causes. The overall estimated incidence of myocardial infarction in the treatment groups was 0.006 (86/14,376), or 6 in 1,000. Furthermore, 4 studies did not have any occurrences in either group, and 2 of the 42 studies accounted for 28.4% of the patients in the study.

Using a fixed-effect model, the odds ratio was 1.42, ie, the odds of myocardial infarction was 42% higher in patients using rosiglitazone, and the difference was statistically significant (95% confidence interval 1.03–1.98). Given the low frequency of myocardial infarction, this translates into an increase of only 1.78 myocardial infarctions per 1,000 patients (from 4.22 to 6 per 1,000). Furthermore,

when the data were analyzed using other methods or if the two large studies were removed, the effect became nonsignificant.[29]

Nissen and Wolski's study[4] is valuable and raises an important issue. However, the medical community would have been better served if a sensitivity analysis had been presented to highlight the fragility of the conclusions.

META-ANALYSIS VS LARGE RANDOMIZED CONTROLLED TRIALS

There is debate about how meta-analyses compare with large randomized controlled trials. In situations where a meta-analysis and a subsequent large randomized controlled trial are available, discrepancies are not uncommon.

LeLorier et al[6] compared the results of 19 meta-analyses and 12 subsequent large randomized controlled trials on the same topics. In 5 (12%) of the 40 outcomes studied, the results of the trials were significantly different than those of the meta-analysis. The authors mentioned publication bias, study heterogeneity, and differences in populations as plausible explanations for the disagreements. However, they correctly commented: "this does not appear to be a large percentage, since a divergence in 5 percent of cases would be expected on the basis of chance alone."[6]

Randomized trials are the gold standard, but meta-analyses provide valuable complementary information

A key reason for discrepancies is that meta-analyses are based on heterogeneous, often small studies. The results of a meta-analysis can be generalized to a target population similar to the target population in each of the studies. The patients in the individual studies can be substantially different with respect to diagnostic criteria, comorbidities, severity of disease, geographic region, and the time when the trial was conducted, among other factors. On the other hand, even in a large randomized controlled trial, the target population is necessarily more limited. These differences can explain many of the disagreements in the results.

A large, well-designed, randomized controlled trial is considered the gold standard in the sense that it provides the most reliable information on the specific target population from which the sample was drawn. Within that population the results of a randomized controlled trial supersede those of a meta-analysis. However, a well conducted meta-analysis can provide complementary information that is valuable to a researcher, clinician, or policy-maker.

CONCLUSION

Like many other statistical techniques, meta-analysis is a powerful tool when used judiciously; however, there are many caveats in its application. Clearly, meta-analysis has an important role in medical research, public policy, and clinical practice. Its use and value will likely increase, given the amount of new knowledge, the speed at which it is being created, and the availability of specialized software for performing it.[30]

A meta-analysis needs to fulfill several key requirements to ensure the validity of its results:

- Well-defined objectives, including precise definitions of clinical variables and outcomes
- An appropriate and well-documented study identification and selection strategy
- Evaluation of bias in the identification and selection of studies
- Description and evaluation of heterogeneity
- Justification of data analytic techniques
- Use of sensitivity analysis.

It is imperative that researchers, policymakers, and clinicians be able to critically assess the value and reliability of the conclusions of meta-analyses. ■

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UNITED STATES DISTRICT COURT

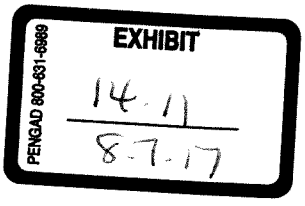
NORTHERN DISTRICT OF CALIFORNIA

IN RE: ROUNDUP PRODUCTS LIABILITY LITIGATION	MDL No. 2741 Case No. 16-md-02741-VC
This document relates to: ALL ACTIONS	

EXPERT REPORT OF DR. DENNIS WEISENBURGER, M.D.

IN SUPPORT OF GENERAL CAUSATION

ON BEHALF OF PLAINTIFFS



UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

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R. 26 EXPERT REPORT OF DENNIS D. WEISENBURGER, M.D.

I am a physician and pathologist specializing in the study of diseases of the hematopoietic and immune systems, with a special interest in non-Hodgkin lymphoma (NHL). My background, qualifications, academic accomplishments, and publications are fully detailed in my curriculum vitae. Briefly, I received a BA degree from the University of North Dakota in 1970 and an MD degree from the University of Minnesota in 1974. After a one-year internship in internal medicine (1974-1975) at Ohio State University, I pursued and completed training in anatomic and clinical pathology at the University of Iowa Hospitals (1975-78). Then, I completed a two-year hematopathology fellowship (1979-1981) with Dr. Henry Rappaport and colleagues at the City of Hope National Medical Center.

From 1984 to 2012, I was a faculty member in the Department of Pathology and Microbiology at the University Nebraska Medical Center (UNMC), and I was promoted to full professor in 1988. During the last 40 years, I have been actively engaged in the study of diseases of the hematopoietic and immune systems, including the pathology, genetics, epidemiology and clinical features of NHL. During this time, I was the chief pathologist for the Nebraska Lymphoma Study Group, and I directed the training program for hematopathology fellows at UNMC. I was also a member of the UNMC Eppley Institute for Research in Cancer and Allied Disease from 1988 to 2012, and the Center for Environmental Health and Toxicology from 1998 to 2012. I have served as a consulting hematopathologist for national lymphoma

clinical trials and research studies performed by the Cancer and Leukemia Study Group B (CALGB). In 2001, I served on the National Cancer Institute (NCI) Peer Review Group which assessed the future research needs for hematopoietic cancers including NHL.

During the last 40 years, I have been particularly interested in the pathobiological mechanisms of how leukemia and NHL develop in humans and the environmental exposures that may play a role in causing these cancers. When I first moved to Nebraska, I was told that there appeared to be an increased incidence of NHL in some counties of Nebraska. Therefore, I began an investigation of this observation and found that the incidence of NHL was increased in over one-half of the counties in eastern Nebraska, and that this increase appeared to correlate with the heavy use of pesticides and fertilizers in agriculture in those counties (1, 2). To study this further, in the mid 1980's, I organized and directed a large epidemiologic case-control study of NHL and related disorders in eastern Nebraska in collaboration with epidemiologists from the NCI. I then collaborated with the same NCI group in a large epidemiologic case-control study of cancers of the brain, stomach and lower esophagus in Nebraska. Later, I participated in a second large epidemiologic case-control study of NHL in Nebraska, and I am currently collaborating with an international consortium of investigators working on lymphoma epidemiologic studies (InterLymph).

In 2012, I became the Chairman of the Department of Pathology at the City of Hope National Medical Center in Duarte, CA. The City of Hope is an NCI-designated comprehensive cancer center, and a major center for the research study and treatment of hematopoietic cancers including NHL. I am also a member of the Beckman Research Institute at City of Hope. During my career, I have published over 300 papers on NHL in peer-reviewed journals, and over 50 papers on the epidemiology of NHL. Therefore, based on my extensive experience and research in the area of NHL, and my knowledge and review of the published scientific literature, I will render an expert opinion on whether the herbicide glyphosate and/or glyphosate-based formulations (GBFs), including Roundup, are a cause of NHL in humans exposed to these chemicals in the workplace or environment. A copy of my current Curriculum Vitae is attached as Exhibit A, a list of my testimony for the past four years and my billing rate is attached as Exhibit B, and a list of the additional materials I have reviewed is attached as Exhibit C.

Background

Glyphosate is a broad-spectrum organophosphate herbicide that is widely used to kill unwanted plants, both in agriculture and in non-agricultural landscapes. Glyphosate is the most heavily used herbicide in the world. Most GBFs, such as Roundup, are either made or used with a surfactant which helps glyphosate penetrate plant cells. A common surfactant used in Roundup is polyethyloxylated tallowamine (POEA), and this GBF was found to be more acutely toxic in animal studies than glyphosate alone (3). Users of GBFs including, but not limited to, farmers, nursery and forestry workers, landscapers and bystanders may be heavily exposed to GBFs during application, mainly by skin and inhalation exposures (4). Glyphosate biomonitoring of farmers has shown that 60% had low levels of glyphosate in their urine on the day of application (5). In another study (6), high concentrations of glyphosate were found in the urine of exposed individuals (average, 7.6 mg/L; range, 0-130 g/L), and there was a significant relationship between the manual application of glyphosate and urine concentrations. In California (1984-1990), glyphosate was the most commonly reported cause of pesticide illness among landscape maintenance workers, and the third most common cause among agriculture workers (3). Thus, people who apply or are otherwise exposed to GBFs can have significant biological exposures to the chemicals in these formulations including glyphosate.

In 2015, the International Agency for Research on Cancer (IARC), a part of the World Health Organization (WHO) and an authoritative body for the evaluation of carcinogenic hazards to humans (7), published its assessment of the carcinogenicity of glyphosate (4, 8). The IARC concluded that glyphosate and GBFs are probably carcinogenic to humans (Group 2A) based on limited epidemiological evidence in humans, mainly for NHL, and significant evidence of carcinogenicity in animals. The IARC also found strong evidence that glyphosate and GBFs can operate through two key characteristics of known human carcinogens, specifically genotoxicity to cells and the induction of oxidative stress. The IARC assessment of glyphosate has led to intense opposition from the pesticide industry, resulting in a series of industry-sponsored articles and reviews on this subject (9-15). Recently, the European Food Safety Authority (EFSA) and the US Environmental Protection Agency (EPA) found that glyphosate is not likely to be carcinogenic in humans (16-18).

Epidemiology in Humans

Numerous epidemiologic studies of the relationship of glyphosate exposure to cancer in humans have been reported, and these are summarized in the IARC and EPA reports (4, 18). These studies have been negative for most of the cancers studied including soft tissue sarcoma, leukemia, multiple myeloma, Hodgkin lymphoma, and cancers of the brain, stomach and esophagus, and prostate. However, most of the studies of NHL have shown a positive association with glyphosate exposure. Therefore, I will focus on the epidemiological studies of NHL in this report.

Six case-control studies of NHL and glyphosate exposure have been published (19-24) and the results of these studies are summarized in Table 1. Of these six case-control studies, five (19-22, 24) showed elevated odds ratios for NHL in workers exposed to glyphosate, whereas only one study (23) with limited statistical power showed no increase. Four of the five positive studies (19-22) showed statistically-significant increases in the risk for NHL (see bolded risk estimates), and the two studies (19, 22) in which a dose-response effect was evaluated showed significantly increased risks of NHL with an increased number of days that glyphosate was used (22) or days per year used (19). In all five positive studies, odds ratios of greater than 2.0 were demonstrated and these were statistically-significant in four of the studies. The only study with a non-significant increase had limited statistical power (24). In three of the five positive studies (20-23), the risk estimates for glyphosate were adjusted for the use of other pesticides but remained elevated. The results of these studies provide evidence for an etiological link between NHL and glyphosate exposure.

Table 1. Case-control studies of NHL and Glyphosate

Reference Location Time	Population Studied	Exposure Category	Exposed Cases	Risk Estimates (95% CI)	Covariants Controlled	Comments
1. McDuffie et al. (19) Canada 1991-1994	517 cases 1506 controls	Exposed ≤ 2 days/yr > 2 days/yr	51 28 23	1.2 (0.83-1.74)* 1.0 (0.63-1.57) **2.12 (1.2 -3.73)**	Age, province	Cross-Canada study; *adjusted for significant medical variables
2. Hardell et al. (20) Sweden 1987-1992	515 cases 1411 controls	Exposed Univariate Multivariate	8 8	**3.04 (1.08-8.52)** 1.85 (0.55-6.20)*	Age, county, study site, vital status	*Adjusted for other pesticides; limited statistical power
3. De Roos et al. (21) Midwest USA 1979-1986	650 cases 1933 controls	Exposed	36	**2.1 (1.1 -4.0)***	Age, study site	*Adjusted for other pesticides
4. Eriksson et al. (22) Sweden 1999-2002	910 cases 1016 controls	Exposed ≤ 10 days > 10 days	29 29 12 17	**2.02 (1.1 -3.71)** 1.51 (0.77-2.94)* 1.69 (0.7 -4.07) **2.36 (1.04-5.37)**	Age, sex, year of enrollment	*Adjusted for other pesticides; odds ratios also increased for all NHL subtypes
5. Orsi et al. (23) France 2000-2004	244 cases 454 controls	Exposed	12	1.0 (0.5 -2.20)	Age, site, socioeconomic category	Limited statistical power; odds ratios increased for some NHL subtypes
6. Cocco et al. (24) Europe 1998-2004	2348 cases 2462 controls	Exposed	4	3.1 (0.6 -17.1)*	Age, sex, site, education	Six countries; *B-cell NHL; limited statistical power

Only one large cohort study of licensed pesticide applicators, the Agricultural Health Study (25), has reported on the risk of NHL associated with glyphosate exposure. This study did not find a significantly elevated risk for cancer overall, or for most of the cancer types including NHL. The NHL risk estimate was 1.1 (0.7-1.9) for glyphosate with 92 exposed cases, and risk did not increase with the number of days glyphosate was used. However, the median follow-up time in this study was only 6.7 years, too short a time to detect a meaningful increase in NHL or other cancers associated with glyphosate. The average latency period for the development of NHL due to long-term exposure to carcinogenic chemicals, such as organic solvents for example, is about 20 years with a range of 10 to 30 years or more (26). However, short-term, high-dose exposures could result in a shorter latency period (26). In one pesticide study of NHL (22), a latency period of greater than 10 years was required to find excess cases of NHL. For glyphosate exposures of less than 10 years, the risk estimate was only 1.11 (0.24 -5.08), whereas it was significantly increased to 2.26 (1.16-4.40) for cases with a latency period of greater than 10 years (22).

Three meta-analyses of the six older epidemiological studies (19-23, 25) were also positive for an association between NHL risk and use of glyphosate. One study (27) showed a significantly increased meta-risk ratio of 1.5 (1.1-2.0), whereas reanalysis by the IARC Working

Group found a significant ratio of 1.3 (1.03-1.65) using fully adjusted risk estimates (4). An industry-sponsored study (9) also found the same risk ratio of 1.3 (1.0-1.9). Additional meta-analyses of two studies (21, 24) for an association of glyphosate use and risk for B-cell NHL were also significantly positive with a meta-risk ratio of 2.0 (1.1-3.6) in two separate analyses (9, 27). These findings provide additional evidence for an etiological link between NHL and glyphosate exposure.

Two industry-sponsored reviews (9, 13) and the EPA report (18) on these same epidemiological studies of NHL have suggested that the positive results are due to various methodologic issues such as study design, selection bias, recall bias, exposure misclassification, confounding and other issues. However, these case-control studies were performed by experienced epidemiologists using widely-accepted study designs and methods, were published in peer-reviewed journals, and I find them acceptable for review and consideration. The industry-sponsored and EPA reviews have given undue weight to the Agricultural Health Study (25) in their assessments, although admitting that the study duration was "relatively short". Taken together, the case-control studies provide evidence for a relationship between glyphosate exposure and risk of NHL, and this evidence cannot be simply dismissed due to the suggestion of possible methodologic issues or the negative results of the immature Agricultural Health Study.

Animal Studies

Glyphosate has also been tested for carcinogenicity in mice and rats in multiple studies (4, 17, 18, 28), and some studies have been positive for the development of tumors. The IARC Working Group (4) found a significant positive and dose-related trend in the incidence of renal tubule carcinoma ($p = 0.037$), and in renal tubule adenoma and carcinoma combined ($p = 0.034$), in males in a feeding study of CD1 mice. Renal tubule carcinoma is a rare tumor in this strain of mice. However, there was no increase in these tumors in female mice in that study. In another feeding study of CD-1 mice, IARC found a significant positive and dose-related trend in the incidence of hemangiosarcoma ($p < 0.001$) in males but not in females. Also, in a feeding study of Sprague-Dawley rats, IARC found an increase in the incidence of pancreatic islet cell adenoma at all doses of glyphosate in males, with a significant increase in the low dose group

Cancer Incidence among Glyphosate-Exposed Pesticide Applicators in the Agricultural Health Study

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Glyphosate is a broad-spectrum herbicide that is one of the most frequently applied pesticides in the world. Although there has been little consistent evidence of genotoxicity or carcinogenicity from *in vitro* and animal studies, a few epidemiologic reports have indicated potential health effects of glyphosate. We evaluated associations between glyphosate exposure and cancer incidence in the Agricultural Health Study (AHS), a prospective cohort study of 57,311 licensed pesticide applicators in Iowa and North Carolina. Detailed information on pesticide use and other factors was obtained from a self-administered questionnaire completed at time of enrollment (1993–1997). Among private and commercial applicators, 75.5% reported having ever used glyphosate, of which > 97% were men. In this analysis, glyphosate exposure was defined as *a*) ever personally mixed or applied products containing glyphosate; *b*) cumulative lifetime days of use, or "cumulative exposure days" (years of use × days/year); and *c*) intensity-weighted cumulative exposure days (years of use × days/year × estimated intensity level). Poisson regression was used to estimate exposure–response relations between glyphosate and incidence of all cancers combined and 12 relatively common cancer subtypes. Glyphosate exposure was not associated with cancer incidence overall or with most of the cancer subtypes we studied. There was a suggested association with multiple myeloma incidence that should be followed up as more cases occur in the AHS. Given the widespread use of glyphosate, future analyses of the AHS will allow further examination of long-term health effects, including less common cancers. *Key words:* cancer, cohort study, farming, glyphosate, pesticide. *Environ Health Perspect* 113:49–54 (2005). doi:10.1289/ehp.7340 available via *http://dx.doi.org/* [Online 4 November 2004]

Glyphosate [*N*-(phosphonomethyl)glycine], commonly sold in the commercial formulation named Roundup (Monsanto Company, St. Louis, MO), has been a frequently used herbicide on both cropland and noncropland areas of the world since its introduction in the 1970s (Williams et al. 2000). Roundup is a combination of the active ingredient and other chemicals, including a surfactant (polyoxyethyleneamine) that enhances the spreading of spray droplets when they contact foliage. Glyphosate is a broad-spectrum herbicide of which the primary mechanism is inhibition of the enzyme 5-enolpyruvoylshikimate 3-phosphate synthase, which is essential for the formation of aromatic amino acids in plants (Steinrucken and Amrhein 1980). Because this specific biologic pathway operates only in plants and microorganisms, the mechanism is not considered to be a risk for humans. Nevertheless, genotoxic, hormonal, and enzymatic effects in mammals have been reported (Bolognesi et al. 1997; Daruich et al. 2001; El Demerdash et al. 2001; Hietanen et al. 1983; Lioi et al. 1998a, 1998b; Olorunsogo et al. 1979; Peluso et al. 1998; Walsh et al. 2000; Yousef et al. 1995).

Results from genotoxicity studies of glyphosate have been conflicting. Glyphosate did not show any genotoxic activity in a battery of assays (Garry et al. 1999; Grisolia 2002; Li and Long 1988; Wildeman and Nazar 1982). However, other studies observed that glyphosate treatment of human lymphocytes *in vitro* resulted in increased sister chromatid exchanges (Bolognesi et al. 1997), chromosomal aberrations (Lioi et al. 1998b), and indicators of oxidative stress (Lioi et al. 1998b). Some studies found slightly greater toxicity of the Roundup formulation compared with glyphosate, in terms of both acute toxicity (Folmar et al. 1979; Martinez et al. 1990; Mitchell et al. 1987) and genotoxicity (Bolognesi et al. 1997; Vigfusson and Vyse 1980). Roundup was associated with increased DNA adducts in mice (Peluso et al. 1998) and a weak mutagenic effect in the *Salmonella* assay (Kale et al. 1995; Moriya et al. 1983; Rank et al. 1993), whereas glyphosate alone did not show these effects. Chronic feeding studies of glyphosate have not provided evidence of a carcinogenic effect in mice or rats (Williams et al. 2000).

The U.S. Environmental Protection Agency (U.S. EPA 1993) and the World Health Organization (WHO 1994) reviewed the toxicology data on glyphosate and concluded that glyphosate is not mutagenic or carcinogenic. The U.S. EPA classified glyphosate as category E, indicating "evidence of noncarcinogenicity for humans" (U.S. EPA 1993). Despite this conclusion, three recent case–control studies suggested an association between reported glyphosate use and the risk of non-Hodgkin lymphoma (NHL) (De Roos et al. 2003b; Hardell and Eriksson 1999; Hardell et al. 2002; McDuffie et al. 2001). Considering the widespread and frequent use of glyphosate in both the United States and the rest of the world, ongoing risk assessment is of importance. We studied site-specific cancer incidence associated with glyphosate use among pesticide applicators in the Agricultural Health Study (AHS) cohort.

Materials and Methods

Cohort enrollment and follow-up. The AHS is a prospective cohort study in Iowa and North Carolina, which includes 57,311 private and commercial applicators who were licensed to apply restricted-use pesticides at the time of enrollment. Recruitment of the applicators occurred between 1993 and 1997 (Alavanja et al. 1996). Cohort members were matched to cancer registry files in Iowa and North Carolina for case identification and to the state death registries and the National Death Index (National Center for Health Statistics 1999) to ascertain vital status. Incident cancers were identified for the time period from the date of enrollment until 31 December 2001 and were coded according to the *International Classification of Diseases,* 9th Revision (WHO 1977). If cohort members had moved from the state, they were censored in the year they left. The median time of follow-up was 6.7 years.

Exposure assessment. Using a self-administered enrollment questionnaire, we collected comprehensive-use data on 22 pesticides, ever/never use information for 28 additional pesticides, and general information on pesticide application methods, personal protective equipment, pesticide mixing, and equipment repair. Data were also collected on basic demographic

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and lifestyle factors. Applicators who completed this questionnaire were given a self-administered take-home questionnaire, which contained additional questions on occupational exposures and lifestyle factors. The questionnaires are available from the AHS website (National Institutes of Health 2004).

We constructed three glyphosate exposure metrics for this analysis: *a*) ever personally mixed or applied products containing glyphosate (ever/never); *b*) cumulative lifetime days of use, or "cumulative exposure days" (years of use × days per year, categorized in tertiles among users: 1–20, 21–56, 57–2,678); and *c*) intensity-weighted cumulative exposure days (years of use × days per year × intensity level, categorized in tertiles: 0.1–79.5, 79.6–337.1, 337.2–18,241). Tertiles were chosen *a priori* as the cut points with which to categorize exposure data, to avoid sparse data for rare cancers in the high-exposure categories. Intensity levels were estimated using questionnaire data from enrollment and measurement data from the published pesticide exposure literature, as follows: intensity level = [(mixing status + application method + equipment repair status) × personal protective equipment use] (Dosemeci et al. 2002).

Data analysis. Persons whose first primary cancer occurred before the time of enrollment (n = 1,074) were excluded from analyses, as were subjects who were lost to follow-up or otherwise did not contribute any person-time (n = 298) and applicators who did not provide any information on age (n = 7) or whether they had ever used glyphosate (n = 1,678). After exclusions, 54,315 subjects were available for inclusion in the age-adjusted analyses of cancer incidence in relation to glyphosate use; however, other analyses contained fewer observations because of missing data for duration and frequency of glyphosate use or for covariates.

We compared certain baseline characteristics among three types of pesticide applicators: *a*) those applicators who never personally used glyphosate; *b*) applicators with the lowest glyphosate exposure, defined as being in the lowest tertile of cumulative exposure days; and *c*) those with higher glyphosate exposure, defined as being in the middle or highest tertile of cumulative exposure days. The purpose of the comparison was to identify potential confounders of glyphosate exposure–disease associations for the various analyses we conducted. Differences between the exposure groups were tested using the chi-square statistics and associated p-values.

Poisson regression analyses were carried out for all cancers combined and specific cancer sites to estimate rate ratios (RRs) and 95% confidence intervals (CIs) associated with glyphosate exposure metrics; the effect of each metric was evaluated in a separate model for each cancer. We analyzed tertile exposure variables in separate models using either the lowest-tertile–exposed or never-exposed subjects as the reference category. We investigated specific cancer sites for which there were at least 30 cases with sufficient information for inclusion in age-adjusted analyses. These cancers were then evaluated for all the exposure metrics and in adjusted analyses, despite smaller numbers of cases upon further adjustment. For each exposure metric, RRs were adjusted for demographic and lifestyle factors, including age at enrollment (continuous), education (dichotomous: ≤ high school graduate or GED/education beyond high school), pack-years of cigarette smoking [indicator variables: never, pack-years at or below the median (12 pack-years), pack-years above the median], alcohol consumption in the past year [indicator variables: none, frequency at or below the median (72 drinks), frequency above the median], family history of cancer in first-degree relatives (dichotomous: yes/no), and state of residence (dichotomous: Iowa/North Carolina). There was insufficient variability in sex or applicator type to adjust for these factors.

Potential confounding from exposure to other pesticides was explored by adjusting for the five pesticides for which cumulative-exposure-day variables were most highly associated with glyphosate cumulative exposure days [(2,4-dichlorophenoxy)acetic acid (2,4-D), alachlor, atrazine, metolachlor, trifluralin]; these pesticide exposures were coded as variables indicating never, low, and high, with the split between low and high as the median of their cumulative exposure days. Additionally, of the pesticides for which only ever/never use

Table 1. Selected characteristics of applicators in the AHS by glyphosate exposure, based on data from the enrollment questionnaire (1993–1997).[a]

Characteristic	Never exposed (n = 13,280) No. (%)	Lowest exposed (n = 15,911)[b] No. (%)	Higher exposed (n = 24,465)[c] No. (%)
State of residence			
Iowa	9,987 (75.2)	9,785 (61.5)	15,336 (62.7)
North Carolina	3,293 (24.8)	6,126 (38.5)	9,129 (37.3)
Age (years)			
< 40	2,279 (17.2)	2,226 (14.0)	4,190 (17.1)
40–49	3,420 (25.8)	4,279 (26.9)	7,899 (32.3)
50–59	2,989 (22.5)	3,931 (24.7)	6,035 (24.7)
60–69	2,715 (20.4)	3,266 (20.5)	3,997 (16.3)
70	1,877 (14.1)	2,209 (13.9)	2,344 (9.6)
Sex			
Male	12,778 (96.2)	15,505 (97.5)	23,924 (97.8)
Female	502 (3.8)	406 (2.6)	541 (2.2)
Applicator type[d]			
Private	12,067 (90.9)	15,008 (94.3)	21,938 (89.7)
Commercial	1,213 (9.1)	903 (5.7)	2,527 (10.3)
Education			
High school graduate or GED	8,898 (68.7)	8,997 (57.9)	11,975 (50.1)
Beyond high school	4,060 (31.3)	6,530 (42.1)	11,936 (49.9)
Smoking history			
Never	7,298 (57.3)	8,241 (53.2)	12,751 (53.7)
≤ 12 pack-years	2,866 (22.5)	3,597 (23.2)	5,572 (23.5)
> 12 pack-years	2,567 (20.2)	3,643 (23.5)	5,439 (22.9)
Alcohol consumption in past year			
None	4,087 (32.7)	5,352 (35.6)	7,023 (29.8)
≤ 6 drinks/month	4,461 (35.7)	5,291 (35.2)	8,149 (34.5)
> 6 drinks/month	3,936 (31.5)	4,387 (29.2)	8,422 (35.7)
Family history of cancer			
No	8,701 (65.5)	9,520 (59.8)	14,668 (60.0)
Yes	4,579 (34.5)	6,391 (40.2)	9,797 (40.0)
Use of other common pesticides			
2,4-D	7,030 (53.3)	11,879 (75.2)	20,699 (85.1)
Alachlor	4,896 (39.7)	7,321 (50.9)	13,790 (59.7)
Atrazine	7,707 (58.5)	10,533 (66.6)	18,237 (75.0)
Metolachlor	3,890 (31.6)	6,172 (43.1)	12,952 (56.2)
Trifluralin	4,239 (34.0)	7,109 (49.7)	14,675 (63.5)
Carbaryl	4,110 (33.7)	8,515 (58.1)	15,139 (64.8)
Benomyl	510 (4.3)	1,418 (9.9)	3,391 (14.8)
Maneb	492 (4.1)	1,412 (9.9)	2,929 (12.9)
Paraquat	1,067 (9.0)	3,021 (21.2)	8,031 (35.2)
Diazinon	1,906 (16.0)	4,615 (32.4)	9,107 (40.0)

[a]Includes observations for subjects included in age-adjusted Poisson regression models of cancer incidence (n = 54,315). [b]Lowest tertile of cumulative exposure days. [c]Highest two tertiles of cumulative exposure days; the sum of the three tertiles of cumulative exposure days (n = 40,376) does not equal the total number of subjects who reported having ever used glyphosate (n = 41,035) because of missing data on duration and frequency of use. [d]"Private" refers primarily to individual farmers, and "commercial" refers to professional pesticide applicators.

information was available, we adjusted for the five pesticides that were most highly associated with ever use of glyphosate (benomyl, maneb, paraquat, carbaryl, diazinon). Where inclusion of all 10 other pesticides in a model changed a glyphosate exposure estimate by at least 20% (compared with a model restricted to the same observations), these results were presented as the final results for that cancer; otherwise, estimates adjusted only for demographic and lifestyle factors are presented.

Tests for trend across tertiles were conducted by creating a continuous variable with assigned values equal to the median value of cumulative exposure days (or intensity-weighted exposure days) within each tertile; the p-value for the trend test was that from the Poisson model coefficient for this continuous variable. We considered p-values < 0.10 as indicative of a trend.

Additional analyses were conducted for cancers for which we observed elevated RRs, and for NHL because of its association with glyphosate in previous studies. These included analyses stratified by state and analyses across quartiles and quintiles (where numbers allowed) of exposure days metrics.

Results

Selected characteristics of the glyphosate-exposed and never-exposed applicators are presented in Table 1. Among 54,315 subjects included in age-adjusted analyses, 41,035 (75.5%) reported having ever personally mixed or applied products containing glyphosate, and 13,280 (24.5%) did not. The cohort, both exposed and never exposed, was composed of primarily of male, middle-aged, private applicators. This is a population with relatively low smoking prevalence; in both the exposed and never-exposed groups, more than half of the subjects reported that they had never smoked. Significant differences ($p < 0.05$) existed between never-exposed and lowest-exposed subjects for all of the characteristics in Table 1. Lowest- and higher-exposed subjects ($p < 0.05$) also differed on several factors, the most notable being that higher-exposed subjects were more likely to be commercial applicators, to have consumed greater amounts of alcohol in the past year, and to have used other specific pesticides. However, lowest- and higher-exposed subjects were similar to each other ($p \geq 0.05$) in characteristics including smoking and family history of cancer in a first-degree relative. In addition, lowest- and higher-exposed subjects were more similar to each other than to their never-exposed counterparts (by qualitative comparison of percentages only) in factors including North Carolina residence, education beyond high school, and use of other pesticides. Because of relative similarities between lowest- and higher-exposed in factors associated with socioeconomic status and other exposures, we decided to conduct some analyses using lowest-exposed rather than never-exposed applicators as the reference group, in order to avoid residual confounding by unmeasured covariates. However, we decided *a priori* that any association should be apparent regardless of which reference group was used.

RRs for the association of all cancers combined and specific cancers with having ever used glyphosate are presented in Table 2. RRs adjusted for age only are presented, as well as RRs adjusted for demographic and lifestyle factors and, in some cases, for other pesticides. The incidence of all cancers combined was not associated with glyphosate use, nor were most specific cancers. There was an 80% increased risk of melanoma associated with glyphosate use in the age-adjusted analysis, which diminished slightly upon further adjustment. Adjusted risk estimates for colon, rectum, kidney, and bladder cancers were elevated by 30–60%, but these estimates were not statistically significant. There was more than 2-fold increased risk of multiple myeloma associated with ever use of glyphosate in adjusted analyses, although this is based on a small number of cases. The association between myeloma incidence and glyphosate exposure was consistent in both states (ever used glyphosate, fully adjusted analyses: Iowa RR = 2.6; North Carolina RR = 2.7).

Results from analyses of tertiles of increasing glyphosate exposure level are presented in Table 3. A decreased risk of lung cancer was suggested for the highest tertile of both cumulative and intensity-weighted exposure days (p-value for trend = 0.02); however, a similar trend was not observed in analyses using never exposed as the referent (results not shown). There was a 40% increased risk of colon cancer for the highest tertile of intensity-weighted exposure; however, no clear monotonic trend was observed for either exposure metric. Elevated risks of leukemia and pancreas cancer were observed only for the middle tertiles of both cumulative and intensity-weighted exposure days, with no increased risk among those with the highest exposure. The associations we observed in the analysis of ever use of glyphosate (Table 2) for melanoma, rectum, kidney, and bladder cancers were not confirmed in analyses based on exposure-day metrics; similarly, no exposure–response patterns were observed in analyses using never exposed as the referent or in analyses across quintiles of exposure (results not shown). No association was observed between NHL and glyphosate exposure in any analysis, including an analysis comparing the highest with the lowest quintile of exposure (> 108 vs. > 0–9 cumulative exposure days: RR = 0.9; 95% CI, 0.4–2.1).

Elevated RRs were estimated for multiple myeloma, with an approximate 2-fold increased risk for the highest tertile of both cumulative and intensity-weighted exposure days (Table 3); however, small numbers precluded precise effect estimation ($n = 19$ in adjusted analyses of exposure-day metrics). The estimated intensity-level component of the intensity-weighted exposure-day metric was not associated with multiple myeloma (highest vs. lowest tertile: RR = 0.6; 95% CI, 0.2–1.8), and observed positive associations of the intensity-weighted exposure-day metric with myeloma relied solely

Table 2. Association of glyphosate exposure (ever/never used) with common cancers[a] among AHS applicators.

Cancer site	Total no. of cancers[c]	Ever used glyphosate (% of total)	RR (95% CI)[b] Effect estimates adjusted for age ($n = 54,315$)[d]	RR (95% CI)[b] Adjusted for age, demographic and lifestyle factors, and other pesticides[d]
All cancers	2,088	73.6	1.0 (0.9–1.1)	1.0 (0.9–1.2)
Lung	204	72.1	1.0 (0.7–1.3)	0.9 (0.6–1.3)
Oral cavity	59	76.3	1.1 (0.6–2.0)	1.0 (0.5–1.8)
Colon	174	75.3	1.1 (0.8–1.6)	1.4 (0.8–2.2)[e]
Rectum	76	77.6	1.2 (0.7–2.1)	1.3 (0.7–2.3)
Pancreas	38	76.3	1.2 (0.6–2.5)	0.7 (0.3–2.0)[e]
Kidney	63	73.0	1.0 (0.6–1.7)	1.6 (0.7–3.8)[e]
Bladder	79	76.0	1.2 (0.7–2.0)	1.5 (0.7–3.2)[e]
Prostate	825	72.5	1.0 (0.8–1.1)	1.1 (0.9–1.3)
Melanoma	75	84.0	1.8 (1.0–3.4)	1.6 (0.8–3.0)
All lymphohematopoietic cancers	190	75.3	1.1 (0.8–1.5)	1.1 (0.8–1.6)
NHL	92	77.2	1.2 (0.7–1.9)	1.1 (0.7–1.9)
Leukemia	57	75.4	1.1 (0.6–2.0)	1.0 (0.5–1.9)
Multiple myeloma	32	75.0	1.1 (0.5–2.4)	2.6 (0.7–9.4)[f]

[a]Cancers for which at least 30 subjects had sufficient information for inclusion in age-adjusted analyses. [b]RRs and 95% CIs from Poisson regression models. [c]Frequencies among subjects included in age-adjusted analyses. [d]Numbers of subjects in these analyses are lower than in age-adjusted analyses because of missing observations for some covariates (models adjusted for demographic and lifestyle factors include 49,211 subjects; models additionally adjusted for other pesticides include 40,719 subjects). [e]Estimates adjusted for other pesticides are shown because inclusion of other pesticide variables in the model changed the effect estimate for glyphosate by at least 20%. [f]The estimate for myeloma was not confounded by other pesticides according to our change-in-estimate rule of ≥ 20%; however, the fully adjusted estimate is shown for the purpose of comparison with state-specific estimates (in the text), which were confounded by other pesticides and required adjustment.

on the exposure-day component; therefore, only results for cumulative exposure days are shown further. When using never exposed as the referent, the association between glyphosate use and multiple myeloma was more pronounced, with more than 4-fold increased risk associated with the highest tertile of cumulative exposure days (tertile 1: RR = 2.3; 95% CI, 0.6–8.9; tertile 2: RR = 2.6; 95% CI, 0.6–11.5; tertile 3: RR = 4.4; 95% CI, 1.0–20.2; p-value for trend = 0.09). Although the myeloma cases were sparsely distributed in analyses of quartiles and quintiles, the highest increased risks were observed in the highest exposure categories (full set of results not shown: upper quartile vs. never exposed: RR = 6.6; 95% CI, 1.4–30.6; p-value for trend across quartiles = 0.01).

Discussion

There was no association between glyphosate exposure and all cancer incidence or most of the specific cancer subtypes we evaluated, including NHL, whether the exposure metric was ever used, cumulative exposure days, or intensity-weighted cumulative exposure days. The most consistent finding in our study was a suggested association between multiple myeloma and glyphosate exposure, based on a small number of cases.

Although our study relied on self-reported exposure information, farmers have been shown to provide reliable information regarding their personal pesticide use (Blair et al. 2002; Blair and Zahm 1993; Duell et al. 2001; Engel et al. 2001; Hoppin et al. 2002). Investigators have used pesticide supplier reports (Blair and Zahm 1993) and self-reported pesticide use information provided earlier (Engel et al. 2001) to assess the validity of retrospectively reported pesticide use data. Among farmers in the AHS, Blair et al. (2002) reported high reliability for reports of ever use of a particular pesticide (ranging from 70 to > 90%). Agreement for duration and frequency of use was lower but generally 50–60% for specific pesticides. Hoppin et al. (2002) have demonstrated that farmers provide plausible data regarding lifetime duration of use, with fewer than 5% reporting implausible values for specific chemicals.

There were rather few cases of NHL for inclusion in this analysis (n = 92); nevertheless,

Table 3. Association of glyphosate exposure (cumulative exposure days and intensity-weighted exposure days) with common cancers[a] among AHS applicators.

	Cumulative exposure days[b]				Intensity-weighted exposure days[c]			
Cancer site	Tertile cut points	No.	RR (95% CI)[d]	p-Trend	Tertile cut points	No.	RR (95% CI)[d]	p-Trend
All cancers	1–20	594	1.0		0.1–79.5	435	1.0	
	21–56	372	1.0 (0.9–1.1)		79.6–337.1	436	0.9 (0.8–1.0)	
	57–2,678	358	1.0 (0.9–1.1)	0.57	337.2–18,241	438	0.9 (0.8–1.1)	0.35
Lung	1–20	40	1.0		0.1–79.5	27	1.0	
	21–56	26	0.9 (0.5–1.5)[e]		79.6–337.1	36	1.1 (0.7–1.9)[e]	
	57–2,678	26	0.7 (0.4–1.2)[e]	0.21	337.2–18,241	27	0.6 (0.3–1.0)[e]	0.02
Oral cavity	1–20	18	1.0		0.1–79.5	11	1.0	
	21–56	10	0.8 (0.4–1.7)		79.6–337.1	14	1.1 (0.5–2.5)	
	57–2,678	10	0.8 (0.4–1.7)	0.66	337.2–18,241	13	1.0 (0.5–2.3)	0.95
Colon	1–20	32	1.0		0.1–79.5	25	1.0	
	21–56	28	1.4 (0.9–2.4)[e]		79.6–337.1	20	0.8 (0.5–1.5)[e]	
	57–2,678	15	0.9 (0.4–1.7)[e]	0.54	337.2–18,241	30	1.4 (0.8–2.5)[e]	0.10
Rectum	1–20	20	1.0		0.1–79.5	16	1.0	
	21–56	17	1.3 (0.7–2.5)		79.6–337.1	18	1.0 (0.5–2.0)	
	57–2,678	14	1.1 (0.6–2.3)	0.70	337.2–18,241	16	0.9 (0.5–1.9)	0.82
Pancreas	0–20	9	1.0		0–79.5	6	1.0	
	21–56	9	1.6 (0.6–4.1)		79.6–337.1	16	2.5 (1.0–6.3)	
	57–2,678	7	1.3 (0.5–3.6)	0.83	337.2–18,241	3	0.5 (0.1–1.9)	0.06
Kidney	1–20	20	1.0		0.1–79.5	20	1.0	
	21–56	8	0.6 (0.3–1.4)		79.6–337.1	7	0.3 (0.1–0.7)	
	57–2,678	9	0.7 (0.3–1.6)	0.34	337.2–18,241	10	0.5 (0.2–1.0)	0.15
Bladder	1–20	23	1.0		0.1–79.5	14	1.0	
	21–56	14	1.0 (0.5–1.9)		79.6–337.1	8	0.5 (0.2–1.3)	
	57–2,678	17	1.2 (0.6–2.2)	0.53	337.2–18,241	13	0.8 (0.3–1.8)	0.88
Prostate	1–20	239	1.0		0.1–79.5	167	1.0	
	21–56	132	0.9 (0.7–1.1)		79.6–337.1	169	1.0 (0.8–1.2)	
	57–2,678	145	1.1 (0.9–1.3)	0.69	337.2–18,241	174	1.1 (0.9–1.3)	0.60
Melanoma	1–20	23	1.0		0.1–79.5	24	1.0	
	21–56	20	1.2 (0.7–2.3)		79.6–337.1	16	0.6 (0.3–1.1)	
	57–2,678	14	0.9 (0.5–1.8)	0.77	337.2–18,241	17	0.7 (0.3–1.2)	0.44
All lymphohematopoietic cancers	1–20	48	1.0		0.1–79.5	38	1.0	
	21–56	38	1.2 (0.8–1.8)		79.6–337.1	40	1.0 (0.6–1.5)	
	57–2,678	36	1.2 (0.8–1.8)	0.69	337.2–18,241	43	1.0 (0.7–1.6)	0.90
NHL	1–20	29	1.0		0.1–79.5	24	1.0	
	21–56	15	0.7 (0.4–1.4)		79.6–337.1	15	0.6 (0.3–1.1)	
	57–2,678	17	0.9 (0.5–1.6)	0.73	337.2–18,241	22	0.8 (0.5–1.4)	0.99
Leukemia	1–20	9	1.0		0.1–79.5	7	1.0	
	21–56	14	1.9 (0.8–4.5)[e]		79.6–337.1	17	1.9 (0.8–4.7)[e]	
	57–2,678	9	1.0 (0.4–2.9)[e]	0.61	337.2–18,241	8	0.7 (0.2–2.1)[e]	0.11
Multiple myeloma	1–20	8	1.0		0–79.5	5	1.0	
	21–56	5	1.1 (0.4–3.5)[e]		79.6–337.1	6	1.2 (0.4–3.8)[e]	
	57–2,678	6	1.9 (0.6–6.3)[e]	0.27	337.2–18,241	8	2.1 (0.6–7.0)[e]	0.17

[a]Cancers for which at least 30 subjects had sufficient information for inclusion in age-adjusted analyses. [b]Numbers of subjects in analyses vary depending on missing observations for cumulative exposure days and some covariates (models adjusted for demographic and lifestyle factors include 36,823 subjects; models additionally adjusted for other pesticides include 30,699 subjects). [c]Numbers of subjects in analyses vary depending on missing observations for intensity-weighted cumulative exposure days and some covariates (models adjusted for demographic and lifestyle factors include 36,509 subjects; models additionally adjusted for other pesticides include 30,613 subjects). [d]Relative rate ratios and 95% CIs from Poisson regression analyses. [e]Estimates adjusted for other pesticides are shown because inclusion of other pesticide variables in the model changed the effect estimate for glyphosate by at least 20%.

the available data provided evidence of no association between glyphosate exposure and NHL incidence. This conclusion was consistent across analyses using the different exposure metrics and in analyses using either never exposed or low exposed as the referent. Furthermore, there was no apparent effect of glyphosate exposure on the risk of NHL in analyses stratified by state of residence or in analyses of highly exposed groups comparing the highest with the lowest quintile of exposure. These findings conflict with recent studies. The first report of an association of glyphosate with NHL was from a case–control study, but the estimate was based on only four exposed cases (Hardell and Eriksson 1999). A pooled analysis of this initial study with a study of hairy cell leukemia showed a relationship between glyphosate exposure and an increased risk of disease [unadjusted analysis: odds ratio (OR) = 3.0; 95% CI, 1.1–8.5] (Hardell et al. 2002). A more extensive study conducted across a large region of Canada found an elevated risk of NHL associated with glyphosate use more frequent than 2 days/year (OR = 2.1; 95% CI, 1.2–3.7) (McDuffie et al. 2001). Similarly, increased NHL risk in men was associated with having ever used glyphosate (OR = 2.1; 95% CI, 1.1–4.0) after adjustment for other commonly used pesticides in a pooled analysis of National Cancer Institute–sponsored case–control studies conducted in Nebraska, Kansas, Iowa, and Minnesota (De Roos et al. 2003b). These previous studies were retrospective in design and thereby potentially susceptible to recall bias of exposure reporting. Our analysis of the AHS cohort had a prospective design, which should largely eliminate the possibility of recall bias. Differences in recall bias could account for discrepant study results; however, evaluation of the potential for recall bias in case–control studies of pesticides among farmers has not uncovered evidence that it occurred (Blair and Zahm 1993).

Our finding of a suggested association of multiple myeloma incidence with glyphosate exposure has not been previously reported, although numerous studies have observed increased myeloma risk associated with farming occupation (Boffetta et al. 1989; Brownson et al. 1989; Cantor and Blair 1984; Cerhan et al. 1998; Cuzick and De Stavola 1988; Eriksson and Karlsson 1992; Figgs et al. 1994; Gallagher et al. 1983; La Vecchia et al. 1989; Nandakumar et al. 1986, 1988; Pasqualetti et al. 1990; Pearce et al. 1985; Pottern et al. 1992; Reif et al. 1989; Vagero and Persson 1986). A possible biologic mechanism of how glyphosate might act along the causal pathway of this plasma cell cancer has not been hypothesized, but myeloma has been associated with agents that cause either DNA damage or immunosuppression (De Roos et al. 2003a). The association we observed was with ever use of glyphosate and cumulative exposure days of use (a combination of duration and frequency), but not with intensity of exposure. Estimated intensity of glyphosate exposure was based on general work practices that were not glyphosate specific, including the percentage of time spent mixing and applying pesticides, application method, use of personal protective equipment, and repair of pesticide application equipment (Dosemeci et al. 2002). Information on work practices specific to glyphosate use would clarify whether intensity of exposure contributes to myeloma risk.

The number of myeloma cases in our study was small, and it is plausible that spurious associations arose by chance; however, several aspects of our results argue against a chance association. The findings were internally consistent, with increased risk observed in both states. Adding to the credibility of the association, there was some indication of a dose–response relationship, with risk estimates increasing across categories of increasing exposure and stronger associations observed when using never-exposed subjects as the referent (as opposed to low exposed). Another possible explanation for spurious associations is unadjusted confounding. Our risk estimates were adjusted for some demographic and lifestyle factors and other pesticides. Of the other pesticides included in the fully adjusted model, only diazinon and trifluralin were important confounders of the glyphosate–myeloma association. It is certainly possible that an unknown risk factor for myeloma could have confounded our results; however, any unknown confounder would have to be linked with glyphosate use. Finally, the increased myeloma risk associated with glyphosate use could be due to bias resulting from a selection of subjects in adjusted analyses that differed from subjects included in unadjusted analyses. Table 1 shows that 54,315 subjects were included in age-adjusted models, whereas because of missing data for covariates, only 40,719 subjects were included in fully adjusted analyses. The association of glyphosate with myeloma differed between the two groups, even without adjustment for any covariates, with no association among the full group and a positive association among the more restricted group. Subjects who answered all the questions and were thus included in adjusted analyses differed from those who dropped out of such analyses in that they were more likely to be from Iowa (71.8% in included group vs. 44.6% in dropped group), were younger (average age, 51.5 vs. 57.9 years), and were more highly educated (46.7% educated beyond high school graduate vs. 30.2%); however, the two groups were similar in their use of glyphosate (75.9% vs. 74.5%). The increased risk associated with glyphosate in adjusted analyses may be due to selection bias or could be due to a confounder or effect modifier that is more prevalent among this restricted subgroup and is unaccounted for in our analyses. Further follow-up of the cohort and reevaluation of the association between glyphosate exposure and myeloma incidence after a greater number of cases develop will allow more detailed examination of the potential biases underlying the association.

Certain limitations of our data hinder the inferences we can make regarding glyphosate and its association with specific cancer subtypes. Although the AHS cohort is large, and there were many participants reporting glyphosate use, the small numbers of specific cancers occurring during the follow-up period hindered precise effect estimation. In addition, most applicators were male, precluding our ability to assess the association between glyphosate exposure and cancer incidence among women, for both non-sex-specific cancers and sex-specific cancers (e.g., of the breast or ovary). Our analysis provides no information on the timing of pesticide use in relation to disease, limiting the ability to sufficiently explore latency periods or effects resulting from glyphosate exposure at different ages. Despite limitations of our study, certain inferences are possible. This prospective study of cancer incidence provided evidence of no association between glyphosate exposure and most of the cancers we studied, and a suggested association between glyphosate and the risk of multiple myeloma. Future analyses within the AHS will follow up on these findings and will examine associations between glyphosate exposure and incidence of less common cancers.

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Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis

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We report a population based case–control study of exposure to pesticides as risk factor for non-Hodgkin lymphoma (NHL). Male and female subjects aged 18–74 years living in Sweden were included during December 1, 1999, to April 30, 2002. Controls were selected from the national population registry. Exposure to different agents was assessed by questionnaire. In total 910 (91%) cases and 1016 (92%) controls participated. Exposure to herbicides gave odds ratio (OR) 1.72, 95% confidence interval (CI) 1.18–2.51. Regarding phenoxyacetic acids highest risk was calculated for MCPA; OR 2.81, 95% CI 1.27–6.22, all these cases had a latency period >10 years. Exposure to glyphosate gave OR 2.02, 95% CI 1.10–3.71 and with >10 years latency period OR 2.26, 95% CI 1.16–4.40. Insecticides overall gave OR 1.28, 95% CI 0.96–1.72 and impregnating agents OR 1.57, 95% CI 1.07–2.30. Results are also presented for different entities of NHL. In conclusion our study confirmed an association between exposure to phenoxyacetic acids and NHL and the association with glyphosate was considerably strengthened.

Key words: phenoxyacetic acids; MCPA; glyphosate; insecticides; impreganting agents; non-Hodgkin lymphoma

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of lymphoid malignancies, where new classification systems based on immunohistochemistry, cytogenetics and evolving knowledge in clinical presentation and course has lead to modern classification systems.[1] Today, it is therefore more adequate to discuss NHL as many different diseases, which share some features but also differ in several aspects.

Interest in the etiology of NHL has been strengthened by an observed substantial increase in the incidence of the disease from the 1960's to the 1980's as reported from most countries with reliable cancer registries. However, this increase has clearly leveled off in many countries since the early 1990's, *i.e.*, in Sweden, Denmark and the USA.[2] The established risk factors for development of NHL include different immunosuppressive states, *e.g.*, human immunodeficiency virus (HIV), autoimmune diseases as Sjögren's syndrome and systemic lupus erythematosus (SLE), immunodepressants used after organ transplantation and some inherited conditions, for review see *e.g.*, Ref. 3. However, these causes may only explain a minority of cases, with a possible exception for HIV-related increases among younger persons in certain areas.[4]

It has been shown that Epstein-Barr virus (EBV) plays an essential role in the pathogenesis of lymphomas after organ transplantation.[5] A relation between lymphoma and elevated EBV-titers has been reported in a cohort.[6] Normally, EBV-production is held back by active cellular and humoral immune mechanisms. In immunodeficiency states this balance is disrupted and EBV-infected B-cells begin to proliferate.[7]

During the last decades, research on the etiology of NHL has been directed towards other potential causes such as pesticides, which may explain the impressive increase in the incidence. Today, it is also reasonable to consider the leveling off in incidence as a probable consequence of a reduced carcinogenic influence related to NHL. Furthermore, our emerging knowledge concerning the spectrum of NHL subgroups makes it reasonable to investigate causative agents for these different types of disease.

In 1981, we published results from a case–control study from Sweden, indicating statistically significant increased odds ratios for NHL and Hodgkin lymphoma (HL) in persons who had been exposed to phenoxyacetic herbicides or impregnating chlorophenols.[8] Our study was initiated by a case report.[9] Some of these chemicals were contaminated by dioxins, of which 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) has been recognised as a complete carcinogen by IARC.[10] Furthermore, these and several other related chemicals are immunotoxic.[11–15] Our results have been confirmed in some other studies, regarding phenoxyacetic herbicides from *e.g.*, Kansas[16] and Nebraska.[17]

Furthermore, in 1999 we reported a new case–control study performed to evaluate more recent exposure to pesticides and other chemicals, and we could thereby confirm our earlier findings regarding a relation with phenoxyacetic herbicides that was related to latency period.[18]

In that study, however, some newer compounds that are widely used today, such as the herbicide glyphosate, were still not very common. During the 1970's certain chemicals, *e.g.*, the phenoxy herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), chlorophenols, and the insecticide dichlorodiphenyltrichloroethane (DDT), were prohibited due to health concerns. Later also the phenoxy herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) was banned in Sweden. Reporting of these agents is therefore nowadays much less likely. It is also probable that the risk pattern has been influenced by protective measures during the last decades.

To further evaluate the relation between exposure to pesticides and other chemicals, focusing also on newer types of compounds, we have performed a new case–control study in Sweden. In our study we have also evaluated exposures in relation to different histopathological subtypes according to the most recent classification.[1]

Material and methods

The study covered 4 out of 7 health service regions in Sweden, associated with the University Hospitals in Lund, Linköping, Örebro and Umeå, and was approved by the ethics committees. Data were collected during December 1, 1999, to April 30, 2002, which was the time period for diagnosis of the cases. Regarding recruitment of cases and controls collaboration was established with another research group, which at the same time performed a parallel study on NHL in Sweden and Denmark.

Cases

All consecutive patients aged 18–74 years with newly diagnosed NHL, identified through physicians treating lymphoma and through pathologists diagnosing the disease, were approached if their physician did not judge this as less appropriate by ethical rea-

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sons. This was done regardless of whether the person had accepted to participate in the parallel study with which we collaborated in the recruitment procedure. If they accepted to participate they were included as potential cases, and went through the data assessment procedure described below. No cases were excluded because of specific conditions potentially associated with NHL, but no cases with *e.g.*, HIV or postransplantation NHL occurred. All the diagnostic pathological specimens were scrutinised by 1 out of 5 Swedish expert lymphoma reference pathologists, if they had not been initially judged by one of these 5. About 70% of all included cases were reviewed, whereas the remaining had been previously classified by one of the reference pathologists. If there was a disagreement from the original report the sample was reviewed by a panel of these pathologists. Therefore, some potential cases could later be excluded if a NHL diagnosis was not verified, and in those occasions all collected exposure information was disregarded. The pathologists also subdivided all NHL cases according to the WHO classification,[1] to enable etiological analyses also for the different diagnostic NHL entities. Since all lymphoma treating clinics and all lymphoma pathologists in the involved regions were covered by the study, it may well be regarded as population based, although the possibility of some individuals not reported through the case ascertainment system used.

Controls

From the population registry covering whole Sweden, randomly chosen controls living in the same health service regions as the cases were recruited during several occasions within the study period. The controls were frequency-matched in 10 years age and sex groups to mirror the age and sex distribution of the included cases, and to increase efficacy in the adjusted analyses. If they accepted to participate, they were included as controls.

Assessment of exposure

All subjects who accepted to participate received a comprehensive questionnaire, which was sent out shortly after the subjects had been telephone interviewed by the other research group we had collaboration with as stated earlier. Their interview, however, did not focus on work environment or chemical exposure, but rather dealt with other life style factors and diseases. Our questionnaire included a total work history with in depth questions regarding exposure to pesticides, organic solvents and several other chemicals. For all pesticides not only numbers of years and numbers of days per year, but also approximate length of exposure per day were questioned. Since most work with pesticides was performed in an individualized manner, no job-exposure matrix was judged to be applicable. Furthermore, the questionnaire also included questions on *e.g.*, smoking habits, medications, leisure time activities and proximity from home to certain industrial installations, but data on these factors are not included in this article.

Specially trained interviewers scrutinized the answers and collected additional exposure information by phone if important data were lacking, incomplete or unclear. These interviewers were blinded with regard to case/control status. All exposures during the same calendar year as the diagnosis and the year before were disregarded in the cases. Correspondingly, the year of enrolment and the year before were disregarded for the controls. As in our previous lymphoma studies we used a minimum criterion of one full day exposure to be categorized as exposed.[8,18]

Statistical methods

Unconditional logistic regression analysis (Stata/SE 8.2 for Windows; StataCorp, College Station, TX) was used to calculate odds ratios (OR) and 95% confidence intervals (CI). Adjustment was made for age, sex and year of diagnosis (cases) or enrolment (controls). In the univariate analysis, different pesticides were analyzed separately and the unexposed category consisted of subjects that were unexposed to all included pesticides. When analyzing subgroups of NHL all controls were used in the separate analyses. In the dose-response calculations made for agents with at least 20 exposed subjects, median number of days of exposure among controls was used as cut-off. Latency period calculations and multivariate analyses included agents with statistically significant increased OR, or with an OR > 1.50 and at least 10 exposed subjects.

TABLE I – NON-HODGKIN LYMPHOMA CASES DIVIDED ON HISTOPATHOLOGICAL SUBTYPES ACCORDING TO WHO CLASSIFICATION.

WHO diagnosis	Number of cases
B-cell lymphomas, total	819
Lymphocytic lymphoma/B-CLL (SLL/CLL)	195
Follicular, grade I–III (FL)	165
Diffuse large B-cell lymphoma (DLBCL)	239
Other specified B-cell lymphoma	131
Unspecified B-cell lymphoma	89
T-cell lymphomas	53
Unspecified non-Hodgkin lymphoma	38
Total	910

Results

In total, 1,163 cases were reported from the participating clinics. Of these, 46 could not participate because of medical conditions, 88 died before they could be interviewed. Since these were primarily excluded by the reporting physicians we had no information on *e.g.*, final WHO categories on these cases. Three NHL cases were not diagnosed during the study period, 1 lived outside the study area and 30 were excluded not being NHL (HL 20, acute lymphoblastic leukaemia 1, other malignancy 7 and unclear diagnosis 2). Of the finally included 995 cases with NHL, 910 (91%) accepted to participate and answered the questionnaire. Of these, 819 were B-cell, 53 T-cell and 38 unspecified lymphomas, Table I.

Among the 1,108 initially enrolled controls 92 did not respond to the mail questionnaire, resulting in 1,016 (92%) controls to be included in the analyses.

The medium and median age in cases was 60 and 62 years, and in controls it was 58 and 60 years, respectively. Of the cases, 534 were males and 376 females, and of the controls the corresponding numbers were 592 and 424.

This report presents exposure data regarding different types of pesticides.

Herbicides

Exposure to herbicides gave for all NHL OR 1.72 (95% CI 1.18–2.51), Table II. Exposure to phenoxyacetic acids yielded OR 2.04 (95% CI 1.24–3.36). This group was further subdivided in 3 categories; (*i*) 4-chloro-2-methyl phenoxyacetic acid (MCPA), which is still on the market and not known to be contaminated by dioxins; (*ii*) 2,4,5-T and/or 2,4-D which often were used together and were potentially contaminated with different dioxin isomers; (*iii*) other types. MCPA seemed to give the most pronounced increase in OR. Exposure to other herbicides, regardless if they also had been exposed to phenoxyacetic acids or not, also gave a statistically significant OR 1.82 (95% CI 1.08–3.06). In this category the dominating agent was glyphosate, which was reported by 29 cases and 18 controls, which produced OR 2.02 (95% CI 1.10–3.71). If both phenoxyacetic acids and glyphosate were excluded, exposure to other herbicides (37 different agents reported, but no one by more than 6 subjects at most) gave a nonsignificant OR of 1.22 (95 % CI 0.63–2.39).

Dose-response analyses regarding herbicides in total and glyphosate yielded an increased OR in the higher exposed group, Table II. For phenoxyacetic acids, however, no such association was demonstrated.

Regarding phenoxy herbicides and glyphosate an analysis was made taken the latency period for exposure into account. For the

latency period 1–10 years no exposed cases were found for MCPA and 2,4,5-T and/or 2,4-D. Regarding glyphosate OR 1.11 (95% CI 0.24–5.08) was obtained. Latency period >10 years yielded for MCPA OR 2.81 (95% CI 1.27–6.22), for 2,4,5-T and/or 2,4,-D OR 1.72 (95% CI 0.98–3.19), and for glyphosate OR 2.26 (95% CI 1.16–4.40).

When different NHL entities were analysed separately, the OR for the subtype small lymphocytic lymphoma/chronic lymphocytic leukaemia (SLL/CLL) was increased for both phenoxy herbicides and, especially, glyphosate, Table III. The entity diffuse large B-cell lymphoma (DLBCL) was significantly associated with exposure to phenoxyacetic acids, but not to other herbicides. On the other hand, the group follicular lymphoma was not clearly associated with phenoxyacetic acids, and only nonsignificantly with glyphosate. The category "other specified B-cell lymphoma" (*e.g.*, mantle cell lymphoma, marginal zone lymphoma) was significantly associated with exposure to phenoxyacetic acids, and an increased risk was also indicated for glyphosate. T-cell lymphomas seemed to be associated with all types of herbicides, but no statistically significant ORs were found due to relatively few exposed subjects. The least numerous categories ("unspecified NHL") yielded high and statistically significant ORs for phenoxy herbicides and glyphosate.

TABLE II – EXPOSURE TO VARIOUS HERBICIDES

Agents	Cases/controls	OR	CI
Herbicides, total	74/51	1.72	1.18–2.51
≤20 days	36/27	1.58	0.95–2.65
>20 days	38/24	1.87	1.10–3.18
Phenoxyacetic acids	47/26	2.04	1.24–3.36
≤45 days	32/13	2.83	1.47–5.47
>45 days	15/13	1.27	0.59–2.70
MCPA	21/9	2.81	1.27–6.22
≤32 days	15/5	3.76	1.35–10.5
>32 days	6/4	1.66	0.46–5.96
2,4,5-T and/or 2,4-D	33/21	1.61	0.87–2.97
≤29 days	21/11	2.08	0.99–4.38
>29 days	12/10	1.33	0.57–3.13
Other	7/7	1.21	0.42–3.48
Herbicides except phenoxyacetic acids	38/26	1.82	1.08–3.06
≤24 days	20/13	1.91	0.93–3.89
>24 days	18/13	1.73	0.84–3.60
Glyphosate	29/18	2.02	1.10–3.71
≤10 days	12/9	1.69	0.70–4.07
>10 days	17/9	2.36	1.04–5.37
Other herbicides	18/18	1.22	0.63–2.39
≤32 days	12/9	1.64	0.68–3.96
>32 days	6/9	0.80	0.28–2.29

Number of exposed cases/controls, odds ratios (OR) and 95% confidence intervals (CI). Agents with more than 20 exposed subjects were also divided in two groups based on median number of days among exposed controls. Adjustment was made for age, sex and year of diagnosis or enrolment.

Insecticides

In our study no overall increased OR was demonstrated for exposure to insecticides, OR 1.28 (95% CI 0.96–1.72), Table IV. The most reported insecticide DDT yielded OR 1.46 (95% CI 0.94–2.28). Increased risk was shown for mercurial seed dressing, OR 2.03 (95% CI 0.97–4.28).

In the dose-response analysis, OR 1.47 (95% CI 0.99–2.16) was found for the high category of insecticide exposure, Table IV. Similar trends were found for DDT and mercurial seed dressing.

Different NHL entities were analysed separately, Table V. Hereby, certain exposures seemed to be associated with subtypes of NHL. Thus, the group follicular lymphoma was associated with DDT, OR 2.14 (95% CI 1.05–4.40) and mercurial seed dressing, OR 3.61 (95% CI 1.20–10.9). Furthermore, exposure to DDT increased the risk also for T-cell lymphoma, OR 2.88 (95% CI 1.05–7.95).

Fungicides and rodenticides

Exposure to fungicides was not a risk factor in our study, neither in total, OR 1.11 (95% CI 0.56–2.23), Table IV, nor for different subtypes of NHL, Table VI. Furthermore, there were no single substances among 24 reported that significantly differed between cases and controls. Also for rodenticides no increased risk was found, Table IV.

Impregnating agents

Exposure to impregnating agents yielded a statistically significant OR 1.57 (95% CI 1.07–2.30), Table IV. In a dose-response calculation OR increased further in the high exposure group. Creosote showed a statistically significant OR for high exposure, OR 3.33 (95% CI 1.20–9.27).

Table VI presents results for different NHL entities. An increased risk for SLL/CLL was associated with exposure to impregnating agents in total, and most pronounced for creosote,

TABLE III – EXPOSURE TO VARIOUS HERBICIDES DIVIDED ACCORDING TO DIFFERENT LYMPHOMA ENTITIES

Lymphoma entities	Herbicides, total	Phenoxyacetic acids (ph)	MCPA	2,4,5-T and/or 2,4-D	Herbicides except ph	Glyphosate	Other
B-cell lymphomas, total (n = 819)	1.68 1.14–2.48	1.99 1.20–3.32	2.59 1.14–5.91	1.69 0.94–3.01	1.72 1.003–2.94	1.87 0.998–3.51	1.14 0.57–2.31
Lymphocytic lymphoma/B-CLL (n = 195) (SLL/CLL)	2.27 1.28–4.01	2.11 0.995–4.47	2.57 0.74–8.97	1.93 0.85–4.41	2.56 1.17–5.60	3.35 1.42–7.89	1.39 0.45–4.31
Follicular, grade I–III (n = 165) (FL)	1.78 0.88–3.59	1.26 0.42–3.75	–[1]	1.21 0.35–4.22	2.32 0.96–5.60	1.89 0.62–5.79	1.48 0.42–5.23
Diffuse large B-cell lymphoma (n = 239) (DLBCL)	1.44 0.81–2.59	2.16 1.08–4.33	3.94 1.48–10.5	1.65 0.71–3.82	1.20 0.51–2.83	1.22 0.44–3.35	1.00 0.33–3.03
Other specified B-cell lymphoma (n = 131)	1.62 0.82–3.19	2.60 1.20–5.64	3.20 0.95–10.7	2.21 0.90–5.44	1.38 0.51–3.73	1.63 0.53–4.96	1.15 0.33–4.03
Unspecified B-cell lymphoma (n = 89)	1.09 0.41–2.89	1.14 0.33–3.95	1.35 0.16–11.2	0.88 0.20–3.92	1.52 0.44–5.27	1.47 0.33–6.61	0.71 0.09–5.53
T-cell lymphomas (n = 53)	1.64 0.55–4.90	1.62 0.36–7.25	2.40 0.29–20.0	1.02 0.13–7.95	1.57 0.35–6.99	2.29 0.51–10.4	2.24 0.49–10.3
Unspecified non-Hodgkin lymphoma (n = 38)	2.86 1.001–8.18	3.75 1.16–12.1	9.31 2.11–41.2	3.21 0.85–12.1	5.29 1.60–17.5	5.63 1.44–22.0	1.88 0.23–15.4

Odds ratios (OR) and 95% confidence intervals (CI). Adjustment was made for age, sex and year of diagnosis or enrolment.
[1]No exposed cases

OR 2.91 (95% CI 1.01–8.33). Regarding follicular lymphomas and DLBCL, increased risks were also noted after creosote exposure, and for the latter subtype this was also the case for all impregnating agents together. T-cell lymphomas were also associated with impregnating agents, and it seemed to be specifically chlorophenols. In the group of patients whose lymphomas were not possible to classify histopathologically, increased risks were indicated for all types of impregnating agents.

TABLE IV – EXPOSURE TO VARIOUS OTHER PESTICIDES

Agents	Cases/controls	OR	CI
Insecticides, total	112/101	1.28	0.96–1.72
≤40 days	44/51	1.03	0.68–1.57
>40 days	65/50	1.47	0.99–2.16
DDT	50/37	1.46	0.94–2.28
≤37 days	20/19	1.17	0.62–2.22
>37 days	30/18	1.76	0.97–3.20
Mercurial seed dressing	21/11	2.03	0.97–4.28
≤12 days	7/6	1.27	0.42–3.83
>12 days	14/5	2.93	1.04–8.25
Pyretrine	15/10	1.74	0.78–3.91
≤25 days	8/5	1.86	0.60–5.75
>25 days	6/5	1.36	0.41–4.51
Permetrine	9/9	1.23	0.48–3.14
Other insecticides	28/26	1.25	0.72–2.16
≤33 days	9/14	0.79	0.34–1.85
>33 days	18/12	1.67	0.79–3.51
Fungicides	16/18	1.11	0.56–2.23
≤37 days	9/9	1.29	0.51–3.31
>37 days	7/9	0.94	0.35–2.57
Impregnating agents	70/51	1.57	1.07–2.30
≤45 days	27/25	1.23	0.71–2.16
>45 days	43/24	2.04	1.21–3.42
Chlorophenols	40/36	1.24	0.77–1.98
≤33 days	23/18	1.46	0.78–2.74
>33 days	17/17	1.08	0.54–2.15
Arsenic	7/5	1.63	0.51–5.20
Creosote	19/10	2.10	0.96–4.58
≤39 days	4/5	0.87	0.23–3.29
>39 days	15/5	3.33	1.20–9.27
Tar	8/5	1.84	0.59–5.69
Other impregnating agents	27/20	1.55	0.85–2.81
≤7 days	4/10	0.44	0.14–1.42
>7 days	22/10	2.55	1.19–5.47
Rodenticides	5/4	1.67	0.44–6.29

Number of exposed cases/controls, odds ratios (OR) and 95% confidence intervals (CI). Agents with more than 20 exposed subjects were also divided in two groups based on median number of days among exposed controls. In some subjects, number of days was not known (excluded in dose-response calculations). Adjustment was made for age, sex and year of diagnosis or enrolment.

Multivariate analysis

Since mixed exposure to several pesticides was more a rule than an exception, and all single agents were analyzed without adjusting for other exposure, a multivariate analysis was made to elucidate the relative importance of different pesticides. Criteria for agents to be included in this analysis are defined in Statistical Methods above. As seen in Table VII increased ORs were found but in general lower than in the univariate analysis.

Discussion

This was a population based case–control study on NHL, which is a strength of the investigation. Only living cases and controls were included, which was of advantage in comparison with interviewing next-of-kins. The study covered all new cases of NHL during a specified time. Pathologists in Sweden that were experts in lymphoma diagnosis confirmed all diagnoses. Thus, a main advantage compared with the earlier studies was the possibility to study the different NHL entities, classified according to the recently developed WHO classification system. The histopathological subgroups may well be regarded as separate in etiology and pathogenesis, as well as they are known to be different regarding course, prognosis and best treatment.

The frequency matching on age groups, gender and health service regions increased the efficacy of the study and ensured exposure conditions for the controls representative for the population in the included geographical areas. We achieved a high response rate among cases and controls, which is another advantage. A motivating introduction letter that was sent out with the questionnaire and with reminders if needed may explain this.

Exposures were assessed by questionnaires with information supplemented over the phone. Thereby use of different pesticides could be checked by information in *e.g.*, receipts and bookkeeping. However, no registries exist in Sweden on such individual use, which is a weakness in the assessment of exposure. Exposure to pesticides may be difficult to assess, and some misclassification regarding quantity of exposure has probably occurred, but such misclassification would most probably be nondependent of case/control status, and therefore only weaken any true risks. Use of protective equipment was not asked for which might have been a disadvantage of the study. However, such use would dilute the exposure and thus bias the result towards unity.

We have earlier published the results from 2 Swedish case–control studies on lymphomas, the first one on NHL and HL[8,19] and later on NHL.[18] These studies showed an increased risk for lymphomas as a result of exposure to herbicides belonging to the class phenoxyacetic acids. In the first study we also found correlation with chlorophenols and organic solvents. Several other studies,

TABLE V – EXPOSURE TO VARIOUS INSECTICIDES DIVIDED ACCORDING TO DIFFERENT LYMPHOMA ENTITIES

Lymphoma entities	Insecticides, total	DDT	Mercurial seed dressing	Pyretrine	Other
B-cell lymphomas, total (n = 819)	1.19	1.32	1.81	1.68	1.08
	0.88–1.61	0.83–2.10	0.84–3.93	0.73–3.86	0.60–1.94
Lymphocytic lymphoma/B-CLL (n = 195) (SLL/CLL)	1.46	1.39	0.75	2.40	1.57
	0.91–2.35	0.69–2.83	0.16–3.47	0.73–7.89	0.66–3.75
Follicular, grade I–III (n = 165) (FL)	1.37	2.14	3.61	2.60	0.28
	0.79–2.38	1.05–4.40	1.20–10.9	0.79–8.51	0.04–2.11
Diffuse large B-cell lymphoma (n = 239) (DLBCL)	1.23	1.24	2.20	1.25	1.31
	0.78–1.93	0.61–2.49	0.79-6.12	0.34–4.61	0.58–2.97
Other specified B-cell lymphoma (n = 131)	1.32	1.33	2.39	1.49	1.42
	0.77–2.27	0.57–3.10	0.73–7.81	0.32–6.94	0.53–3.80
Unspecified B-cell lymphoma (n = 89)	0.42	0.23	–[1]	–[1]	0.42
	0.15–1.18	0.03–1.75			0.06–3.18
T-cell lymphomas (n = 53)	1.61	2.88	2.08	2.20	1.59
	0.72–3.60	1.05–7.95	0.25–17.1	0.27–17.8	0.36–7.02
Unspecified non-Hodgkin lymphoma (n = 38)	1.91	2.39	5.43	3.14	4.70
	0.79–4.62	0.77–7.42	1.34–22.0	0.37–26.3	1.48–14.9

Odds ratios (OR) and 95% confidence intervals (CI). Adjustment was made for age, sex and year of diagnosis or enrolment.
[1]No exposed cases.

TABLE VI – EXPOSURE TO FUNGICIDES AND IMPREGNATING AGENTS DIVIDED ACCORDING TO DIFFERENT LYMPHOMA ENTITIES

Lymphoma entities	Fungicides	Impregnating agents, total	Chlorophenols	Creosote	Other
B-cell lymphomas, total (n = 819)	1.01	1.41	1.12	2.09	1.51
	0.48–2.09	0.95–2.11	0.69–1.84	0.94–4.64	0.82–2.78
Lymphocytic lymphoma/B-CLL (n = 195)	1.33	1.71	1.35	2.91	2.23
	0.43–4.12	0.94–3.11	0.64–2.85	1.01–8.33	0.97–5.13
Follicular, grade I–III (n = 165)	–[1]	1.49	0.91	2.56	1.80
		0.70–3.19	0.31–2.66	0.68–9.68	0.59–5.48
Diffuse large B-cell lymphoma (n = 239)	1.26	1.70	1.40	1.75	1.51
	0.45–3.47	0.97–2.96	0.70–2.78	0.54–5.74	0.62–3.67
Other specified B-cell lymphoma (n = 131)	1.56	1.24	0.95	2.58	1.09
	0.51–4.76	0.58–2.63	0.36–2.51	0.78–8.55	0.31–3.78
Unspecified B-cell lymphoma (n = 89)	–[1]	0.41	0.54	–[1]	0.54
		0.10–1.75	0.12–2.32		0.07–4.19
T-cell lymphomas (n = 53)	1.10	3.26	2.39	–[1]	2.07
	0.14–8.70	1.39–7.63	0.78–7.28		0.45–9.53
Unspecified non-Hodgkin lymphoma (n = 38)	3.73	2.52	2.02	4.94	1.40
	0.77–18.0	0.88–7.19	0.56–7.31	0.97–25.2	0.17–11.2

Odds ratios (OR) and 95% confidence intervals (CI). Adjustment was made for age, sex, and year of diagnosis or enrolment.
[1]No exposed cases.

TABLE VII – MULTIVARIATE ANALYSES INCLUDING AGENTS ACCORDING TO SPECIFIED CRITERIA, SEE TEXT

Agents	Univariate		Multivariate	
	OR	CI	OR	CI
MCPA	2.81	1.27–6.22	1.88	0.77–4.63
2,4,5-T and/or 2,4-D	1.61	0.87–2.97	1.24	0.68–2.26
Glyphosate	2.02	1.10–3.71	1.51	0.77–2.94
Mercurial seed dressing	2.03	0.97–4.28	1.58	0.74–3.40
Arsenic	1.63	0.51–5.20	1.17	0.34–4.02
Creosote	2.10	0.96–4.58	1.70	0.73–3.98
Tar	1.84	0.59–5.69	1.39	0.43–4.48

Odds ratios (OR) and 95% confidence intervals (CI). Adjustment was made for age, sex and year of diagnosis or enrolment.

but not all, from different research groups have supported our results, as reviewed,[20] and also confirmed later, *e.g.*, Ref. 21.

Furthermore, other groups have demonstrated associations between NHL and other classes of pesticides, especially different types of insecticides, *e.g.*, organophosphates,[22] carbamate,[23] lindane[24] and chlordane,[25] but also other groups of herbicides as atrazine.[26] Some case–control studies have found associations between several classes of pesticides, *e.g.*, Ref. 27 or merged groups of pesticides as in one recent study,[28] which demonstrate a significantly increased risk for NHL associated with exposure to "nonarsenic pesticides." These authors discuss the fact that several pesticides are chemically related and may exert their effects on humans through a similar mechanism of action, which may explain the wide range of pesticides that have been related to NHL over time in different countries and with different exposure conditions.

Several factors urged for a third Swedish study on the relation between pesticides, other chemicals and NHL, and the present study also used a somewhat changed methodology, which also may be of interest.

Thus, the use of phenoxyacetic herbicides, which earlier were dominating both as weed killers in agriculture and against hard wood in forestry, have substantially decreased during the last decades. 2,4,5-T, which was contaminated by TCDD, was prohibited in Sweden 1977, and 2,4-D was withdrawn from the market in 1990. MCPA, even if still used, has been largely substituted by other agents, among which glyphosate has been clearly dominating. This change of herbicide practice along with successively strengthened protection instructions has prompted our new study, reflecting also later years of exposure.

Furthermore, the changing trend of the incidence of NHL in many countries with reliable cancer registries, *e.g.*, Sweden, with a substantial and steady increase during the 1960's through 1980's but a leveling off or even slight decrease after that, makes it important to find etiological factors contributing to this shift in trend. Chlorinated compounds in the environment, which have been regulated during the 1970's and 1980's, may at least partly explain this trend, as discussed by us.[2] Phenoxyacetic herbicides with potential contaminating dioxins are examples of such substances. However, the prohibition of common environmental pollutants as polychlorinated biphenyls (PCB) and the following decline in the environment is probably more important to explain the leveling off of the incidence.[2]

In contrast to our 2 former case–control studies on NHL, this study included both genders and only consecutive living cases and living controls. In our earlier studies we have only studied male lymphoma cases, making the results of this study more representative for the whole population. To facilitate comparisons with our earlier results we also made additional analyses of herbicide exposure by gender. Only few women were exposed and separate analyses for both sexes still yielded an increased risk for NHL. Thus, in the total material herbicide exposure gave OR = 1.72, 95% CI 1.18–2.51 (n = 74 cases, 51 controls), whereas for men only OR = 1.71, 95% CI = 1.15–2.55 (n = 68 cases, 47 controls) and for women only OR = 1.82, 95% CI = 0.51–6.53 (n = 6 cases, 4 controls) were calculated.

In our study lymphocytic lymphoma/B-CLL was significantly associated with herbicides with highest OR for glyphosate but also creosote. Follicular lymphoma was significantly associated with DDT and mercurial seed dressing, diffuse large B-cell lymphoma with MCPA, and T-cell lymphoma with DDT and impregnating agents overall. Unspecified NHL was significantly associated with MCPA, glyphosate and mercurial seed dressing. It should be noted that several ORs were increased for herbicides; insecticides and impregnating agents but the calculations were hampered by low numbers of exposed cases and controls.

Our earlier results of exposure to phenoxyacetic herbicides as a risk factor for NHL were confirmed in our study. As in our previous lymphoma studies exposure to MCPA seemed to yield the highest OR among the different phenoxyacetic acids. This is of interest because MCPA is known not to be contaminated by dioxins, as 2,4-D and 2,4,5-T. At the same time MCPA is the only phenoxyacetic acid still in wider use in Sweden and many other countries.

Glyphosate is a broad-spectrum herbicide, which inhibits the formation of amino acids in plants.[29] The US Environmental Protection Agency[30] and the World Health Organization[31] have concluded that glyphosate is not mutagenic or carcinogenic. Since then, however, some experimental studies indicate genotoxic, hormonal and enzymatic effect in mammals, as reviewed.[32] Of particular interest is that glyphosate treatment of human lymphocytes *in vitro* resulted in increased sister chromatid exchanges,[33] chromosomal aberrations and oxidative stress.[34,35]

Glyphosate was associated with a statistically significant increased OR for lymphoma in our study, and the result was strengthened by a tendency to dose-response effect as shown in Table II. In our former study[18] very few subjects were exposed to glyphosate, but a nonsignificant OR of 2.3 was found. Furthermore, a meta-analysis combining that study with an investigation on hairy-cell leukaemia, a rare NHL variant, showed an OR for glyphosate of 3.04 (95% CI 1.08–8.52).[36] Recent findings from other groups also associate glyphosate with different B-cell malignancies such as lymphomas and myeloma.[32,37,38]

Glyphosate has succeeded MCPA as one of the most used herbicides in agriculture, and many individuals that used MCPA earlier are now also exposed to glyphosate. This probably explains why the multivariate analysis does not show any significant ORs for these compounds.

Exposure to insecticides was associated with a slightly increased OR, Table IV. In some other studies on the relation between pesticides and NHL, insecticides seem to be of some importance as causative agents.[27,37,38] Especially, different organophosphates were indicated as risk factors in those studies, with a Canadian study[37] showing statistical significant ORs for malathion and diazinon. In our study, only few subjects were exposed to different organophosphates, but we found a nonsignificant OR of 2.81 (95% CI 0.54–14.7) for malathion based on 5 exposed cases and 2 controls, not shown in Table.

The organochlorine DDT has shown suggestive but rarely significant association with NHL in some studies.[8,19,38–40] Our study showed a moderately but not significant increased OR for exposure to DDT.

Fungicides were not associated with the risk for NHL in our study, but few subjects were exposed to a wide range of different agents. In some earlier studies increased risks have also been noted for this group of pesticides.[16,18]

Exposure to impregnating agents produced a significant OR with a dose-response relation, Table IV. The highest risk was found for high exposure to creosote, which gave a significant OR. This finding was in contrast to our previous results on NHL,[18] but another Swedish study also found an association between creosote and NHL.[41] Chlorophenols have been the most common group of impregnating agents in Sweden, but were banned in 1977. In our first NHL study, reflecting exposures mainly during the time these substances were used, we found a strong association with NHL. As in the present study, however, no association was found in our second study on NHL.[18]

In conclusion, this study, which mirrors pesticide exposure during later years than in our previous studies, confirmed results of an association between exposure to phenoxyacetic herbicides and NHL. Furthermore, our earlier indication of an association between glyphosate and NHL has been considerably strengthened.

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Cancer Epidemiology, Biomarkers & Prevention

Non-Hodgkin's Lymphoma and Specific Pesticide Exposures in Men : Cross-Canada Study of Pesticides and Health

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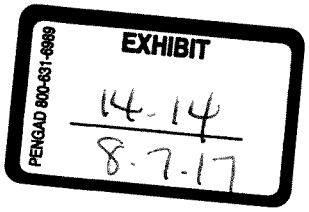

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Non-Hodgkin's Lymphoma and Specific Pesticide Exposures in Men: Cross-Canada Study of Pesticides and Health[1]

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Abstract

Our objective in the study was to investigate the putative associations of specific pesticides with non-Hodgkin's Lymphoma [NHL; International Classification of Diseases, version 9 (ICD-9) 200, 202]. We conducted a Canadian multicenter population-based incident, case (n = 517)-control (n = 1506) study among men in a diversity of occupations using an initial postal questionnaire followed by a telephone interview for those reporting pesticide exposure of 10 h/year or more, and a 15% random sample of the remainder. Adjusted odds ratios (ORs) were computed using conditional logistic regression stratified by the matching variables of age and province of residence, and subsequently adjusted for statistically significant medical variables (history of measles, mumps, cancer, allergy desensitization treatment, and a positive history of cancer in first-degree relatives). We found that among major chemical classes of herbicides, the risk of NHL was statistically significantly increased by exposure to phenoxyherbicides [OR, 1.38; 95% confidence interval (CI), 1.06–1.81] and to dicamba (OR, 1.88; 95% CI, 1.32–2.68). Exposure to carbamate (OR, 1.92; 95% CI, 1.22–3.04) and to organophosphorus insecticides (OR, 1.73; 95% CI, 1.27–2.36), amide fungicides, and the fumigant carbon tetrachloride (OR, 2.42; 95% CI, 1.19–5.14) statistically significantly increased risk. Among individual compounds, in multivariate analyses, the risk of NHL was statistically significantly increased by exposure to the herbicides 2,4-dichlorophenoxyacetic acid (2,4-D; OR, 1.32; 95% CI, 1.01–1.73), mecoprop (OR, 2.33; 95% CI, 1.58–3.44), and dicamba (OR, 1.68; 95% CI, 1.00–2.81); to the insecticides malathion (OR, 1.83; 95% CI, 1.31–2.55), 1,1,1-trichloro-2,2-bis (4-chlorophenyl) ethane (DDT), carbaryl (OR, 2.11; 95% CI, 1.21–3.69), aldrin, and lindane; and to the fungicides captan and sulfur compounds. In additional multivariate models, which included exposure to other major chemical classes or individual pesticides, personal antecedent cancer, a history of cancer among first-degree relatives, and exposure to mixtures containing dicamba (OR, 1.96; 95% CI, 1.40–2.75) or to mecoprop (OR, 2.22; 95% CI, 1.49–3.29) and to aldrin (OR, 3.42; 95% CI, 1.18–9.95) were significant independent predictors of an increased risk for NHL, whereas a personal history of measles and of allergy desensitization treatments lowered the risk. We concluded that NHL was associated with specific pesticides after adjustment for other independent predictors.

Introduction

NHL[4] has been epidemiologically associated with farming (1–8), with certain farm practices (9), with pesticide exposure (10–13), and with certain other occupations (14–17). The term pesticide is used to denote a wide variety of chemicals used to destroy weeds (herbicides), insects (insecticides), and mold (fungicides). Such chemicals are widely used in agriculture, horticulture, and forestry, and in the secondary processing of the products of these primary industries. Many of the NHL and pesticide case-control or cohort studies focused either on a small geographical area (1, 2, 4) or on one occupational group (2, 4, 5, 9). Our study encompassed six provinces of Canada with diverse agricultural practices and a number of different types of occupational and nonoccupational exposures to pesticides. Non-Hodgkin's lymphoma incidence rates have been increasing in Canada for the last 25 years reflecting a worldwide trend (18) that has not been explained by improved diagnostic (19) methods or record-keeping (20).

Materials and Methods

Study Population. We conducted a population-based case-control study among men resident in six Canadian provinces to

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[3] Dr. Choi was a collaborator who is now deceased.

[4] The abbreviations used are: NHL, non-Hodgkin's lymphoma; DDT, 1,1,1-trichloro-2,2-bis (4-chlorophenyl) ethane; STS, soft tissue sarcoma; HD, Hodgkin's disease; MM, multiple myeloma; 2,4-D, 2,4-dichlorophenoxyacetic acid; MCPA, 4-chloro-2-methylphenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; OR, odds ratio; OR_{adj}, adjusted OR; 95% CI, 95% confidence interval.

test the pesticide-exposure hypothesis related to four rare tumors. Incident cases among men, ages 19 years or over, with a first diagnosis of STS, HD, NHL [International Classification of Diseases, version 9 (ICD-9), code 200 or 202], or MM diagnosed between September 1, 1991, and December 31, 1994, were eligible. To balance the number of cases by geographical regions, each province was assigned a target number of cases in each tumor category. Each province ceased to ascertain cases when their preassigned target was reached. This report is based solely on cases diagnosed with NHL. Cases were ascertained from provincial Cancer Registries except in Quebec, for which hospital ascertainment was used. The Cancer Registries and hospitals provided information, including pathology reports, to confirm the diagnosis. Pathological material was reviewed and classified according to the working formulation by the reference pathologist. Misclassified and ineligible (*e.g.*, Kaposi's sarcoma, known HIV-positive) cases were excluded. Subjects for whom pathological material was unavailable remained in the study. After physician consent was received, postal questionnaires and informed consent forms were mailed to potential cases. Surrogates for deceased cases were not contacted.

Men, ages 19 years and older, selected at random within age constraints from the provincial Health Insurance records (Alberta, Saskatchewan, Manitoba, Quebec), computerized telephone listings (Ontario), or voters' lists (British Columbia) were potential controls. The random control subject selection was stratified by age ± 2 years to be comparable with the age distribution of the entire case group (STS, HD, NHL, and MM) within each province. Postal questionnaires and informed consent forms were mailed to potential controls. Surrogates for deceased persons were ineligible as controls. All of the participating control subjects were used in the statistical analyses of each cancer site.

Pilot Study. We conducted a pilot study (21) in each provincial region to test study procedures and to determine an operational definition of pesticide exposure to distinguish between environmental (which includes bystander and incidental) and more intensive exposure. Nonoccupational use of pesticides (home, garden, hobby) was included. There were few individuals who were completely free of being exposed to pesticides. Therefore, we constructed graphs that demonstrated that the most efficient definition of pesticide exposure, which discriminated (*a*) between incidental, bystander, and environmental exposure as compared with more intensive exposure and (*b*) between cases and controls, was a cumulative total of 10 h per year to any combination of pesticides. The screening questions in the postal questionnaire were used to trigger telephone interviews among those with cumulative exposure of ≥10 h/year to any combination of herbicides, insecticides, fungicides, fumigants, and/or algicides. The 68 cases and 103 controls who participated in the pilot study are not included in this report.

Pesticides. Pesticide is a generic term describing a variety of compounds of diverse chemical structures and biological modes of action. In this study, the term pesticide refers primarily to herbicides, insecticides, fungicides, and fumigants.

We conducted a validation pilot study of the modified questionnaires (21). Volunteer farmers ($n = 27$) completed the questionnaires and granted permission for us to access their records of purchases through their local agrochemical supplier. The concordance between the two sources was excellent and discordance was explainable by (*a*) the farmer paid in cash and the supplier discarded the record; (*b*) the farmer purchased the agrochemical in the United States, and, therefore, the local supplier did not have a record; (*c*) the farmer paid for professional ground or aerial spraying, and the account was listed in another name; or (*d*) the supplier had destroyed the records.

Questionnaires. The questionnaires were modified versions of the telephone interview questionnaire that was used in studies of pesticide exposure and rare tumors in Kansas (11) and Nebraska (13). With permission, we modified the questionnaire to create postal and telephone interview questionnaires. To control for the effects of other variables known or suspected to be associated with the development of NHL after conducting an extensive literature review, we used the postal questionnaire to capture demographic characteristics, antecedent medical history, family history of cancer, detailed lifetime job history, and occupational exposure history to selected substances, accidental pesticide spills, and use of protective equipment, as well as details of cigarette smoking history. The telephone questionnaire characterized exposure to individual pesticides. The pesticide data were collected at several levels beginning with the broadest categories (*e.g.*, minimal exposure, occupations with potential pesticide exposure) and progressing sequentially to major classes (*e.g.*, herbicides); to chemical groups (*e.g.*, phenoxy herbicides); and finally to individual compounds (*e.g.*, 2,4-D, MCPA, and 2,4,5-T).

In this report, we focus on lifetime exposure to individual pesticides classified by active ingredients and to major chemical classes of herbicides, insecticides, fungicides, and fumigants. We classified exposure by the number of herbicides, insecticides, fungicides, and fumigants reported by cases and controls as well as by the number of days per year of exposure to individual compounds.

Each subject who reported 10 h per year or more of exposure to pesticides (any combination of compounds) as defined by the screening questions, and a 15% random sample of the remainder was mailed a list of pesticides (both chemical and brand names) and an information letter. Each subject was subsequently telephoned to obtain details of pesticide use.

The listed pesticides were chosen for inclusion (22–25): (*a*) if the compound was ever registered for use in Canada and reviewed by the IARC; (*b*) if the pesticide was recently banned or restricted in Canada by the federal licensing agency; or (*c*) if the pesticide was commonly used in Canada for specific purposes.

To ensure consistency, we developed and distributed manuals for provincial study coordinators, interviewers, and data managers. Before commencing data collection, we held a 2-day workshop with provincial coordinators to review data collection procedures and policies, to practice interviewing skills, and to review SPSS-DE (Statistical Packages for the Social Sciences-Data Entry),[5] the custom data entry program that we used. On receipt of a postal questionnaire, the provincial coordinator reviewed it for internal consistency and completeness. Data were computer-entered and verified in the province of origin, transported to the coordinating center, and rechecked for completeness, after which statistical analyses were performed.

Copies of the questionnaires and additional information on pesticides that were not included in this report are available from the corresponding author.

Pathology Review. Pathologists in participating provinces were requested to send blocks or slides of tumor tissue removed at surgery to the reference pathologist. Ten subjects with Ka-

[5] SPSS-Data Entry II Statistical Package for the Social Sciences: Statistical Data Analysis. SPSS Inc., Chicago, Illinois, 1998.

Table 1 Comparisons of demographic, antecedent personal medical, general pesticide exposures and cigarette smoking history between cases of NHL and control subjects based on the postal questionnaire

	NHL, n = 517		Controls, n = 1506		OR[a] (95% CI)
	n	%	n	%	
Age, yr					
<30	64	12.4	356	23.6	
30–39	87	16.8	255	16.9	
40–49	111	21.5	238	15.8	
50–59	143	27.7	370	25.6	
>60	112	21.7	287	19.0	
Mean ± SD	57.7 ± 14		55.0 ± 16		
Residence on a farm at any time					
Yes	235	45.5	673	44.7	
No (reference)	279	54.0	828	55.0	1.06 (0.86–1.20)
Missing	3	0.6	5	0.3	
Pesticide exposure (screening question)					
<10 h/yr (reference)	379	73.3	1142	75.8	
≥10 h/yr	138	26.7	364	24.2	1.22 (0.96–1.55)
Smoking History					
Nonsmoker (reference)	160	30.9	526	34.9	
Ex-smoker	254	49.1	648	43.0	1.10 (0.86–1.41)
Current smoker	91	17.6	298	19.8	0.98 (0.72–1.33)
Missing data	12	2.3	34	2.3	
Current or ex-smoker	345	66.7	946	62.8	1.06 (0.86–1.20)
Medical History[b]					
Measles (yes)	251	48.5	888	59.0	**0.64 (0.51–0.79)**
Mumps (yes)	194	37.5	588	39.0	**0.75 (0.60–0.93)**
Previous cancer (yes)	73	14.1	87	5.8	**2.43 (1.71–3.44)**
Skin-prick allergy test	34	6.6	196	13.0	**0.52 (0.34–0.76)**
Allergy desensitization shots (yes)	18	3.5	114	7.6	**0.49 (0.29–0.83)**
Family history of cancer any first-degree relative (yes)	219	42.4	497	33.0	**1.31 (1.05–1.62)**

[a] OR stratified by age and by province of residence.
[b] Also tested and found to be unassociated: acne; asthma; celiac disease; chickenpox; diabetes; hay fever; mononucleosis; rheumatic fever; rheumatoid arthritis; ringworm; shingles; syphilis; tuberculosis; urinary tract infections; whooping cough; allergies; drug treatment for overactive thyroid; treatment for head lice, body lice, or scabies; medical implants; drug treatment for epilepsy; tonsillectomy; positive allergy prick skin test, patch skin test, or positive patch skin test for allergy.

posi's sarcoma were omitted on the basis of the etiological association with HIV infection. Any other known HIV-positive subjects had been previously excluded. Eighty-four % (436 of 517) of the NHL tumors were validated. Because of a change midstudy in some hospitals' policies regarding supplying pathological material without charge, we were unable to obtain the remaining samples.

Statistical Analyses. Data from the postal and telephone interviews were merged by using the identification number. Of the individuals selected randomly for a telephone interview, most had used one or no chemical pesticides. We reviewed these data and decided to include them in the statistical analyses because they might be informative with respect to low levels of exposure to pesticides and their inclusion maximized our sample size with respect to other known or suspected risk factors for NHL. We conducted descriptive analyses of each variable, which included, where applicable, frequencies, ranges, means ± SD, and median values for cases and controls separately.

To evaluate putative risk factors for NHL, conditional logistic regression was used to compute ORs and 95% CIs, stratifying by age groups and province of residence.[6] ORs were calculated for categorical variables related to medical history that were selected based on previous studies (*e.g.*, measles, mumps, previous cancer, allergy desensitization treatment, skin prick allergy test); pesticide exposure (<10 and ≥10 h per year); and smoking history. Using conditional logistic regression, ORs were also calculated for (*a*) major chemical classes of herbicides, insecticides, fungicides, and fumigants; and (*b*) for individual active chemicals. The statistically significant ($P < 0.05$) medical variables were used to adjust the effect of exposure to pesticides classified by major chemical group and by individual active chemical. Given the study sample size and the case-control ratio, *a priori* power calculations indicated that we had sufficient statistical power to detect an OR of 2 when at least 1% of the controls was exposed to a specific pesticide or chemical class of pesticide. Conditional logistic analyses (26) were conducted that retained in the model, all covariates for which the P was ≤.05. The criterion for entry into models was a $P \leq 0.20$ in bivariate age and province stratified analyses.

We created dose-response levels based on days/year of personally mixing or applying selected herbicides, insecticides, fungicides, and fumigants. We reported ORs stratified by age and province of residence. We created exposure categories for exposures to multiple different herbicides, insecticides, fungicides, and fumigants. For these analyses, the unexposed category was specific to the class of pesticide. We also created exposure categories for exposures to combinations of herbicides, insecticides, fungicides, and fumigants for which the reference group did not report exposure to any of those classes of pesticides.

[6] EGRET Intuitive Software for DOS Micros Statistics and Epidemiology Research Corporation, 1993.

Table 2 Herbicides: frequency of exposure to herbicides classified into major chemical classes and as individual compounds

The list includes only those reported by 1% or more of responders.

Major chemical classes	NHL n = 517		Controls n = 1506		OR[a] (95% CI)	OR_{adj}[b] (95% CI)
	n exposed	% exposed	n exposed	% exposed		
Phenoxyherbicides,[c] exposed	131	25.3	319	21.2	**1.46 (1.09–1.82)**	**1.38 (1.06–1.81)**
Individual phenoxyherbicides						
2,4-D	111	21.5	293	19.5	1.26 (0.97–1.64)	**1.32 (1.01–1.73)**
Mecoprop	53	10.2	81	5.4	**2.23 (1.38–3.07)**	**2.33 (1.58–3.44)**
MCPA	17	3.3	46	3.1	1.08 (0.59–1.94)	1.10 (0.60–2.00)
Diclofopmethyl	9	1.7	25	1.7	0.96 (0.42–2.20)	0.95 (0.41–2.22)
Phosphonic acid,[d] exposed	63	12.2	147	9.8	1.42 (0.95–1.90)	1.40 (0.94–1.89)
Individual phosphonic herbicides						
Glyphosate (Round-up)	51	9.9	133	8.8	1.26 (0.87–1.80)	1.20 (0.83–1.74)
Thiocarbamates,[e] exposed	21	4.1	49	3.3	1.41 (0.62–2.20)	1.46 (0.82–2.58)
Individual thiocarbamate herbicides						
Diallate (n exposed)	11	2.1	29	1.9	1.26 (0.59–2.67)	1.46 (0.68–3.14)
Phenols: Bromoxynil,[f] exposed	16	3.1	48	3.2	1.05 (0.41 1.69)	1.07 (0.58–1.99)
Dicamba,[g] exposed	73	14.1	131	8.7	**1.92 (1.39–2.66)**	**1.88 (1.32–2.68)**
Individual dicamba herbicides						
Dicamba (Banvel or Target)	26	5.0	50	3.3	1.59 (0.95–2.63)	**1.68 (1.00–2.81)**
Dinitroaniline,[h] exposed	11	2.1	31	2.1	1.17 (0.56–2.41)	1.20 (0.61–2.35)
Individual dinitroaniline herbicides						
Trifluralin	11	2.1	31	2.1	1.17 (0.56–2.41)	1.06 (0.50–2.22)

[a] ORs calculated with strata for the variables of age and province of residence.
[b] ORs adjusted for statistically significant medical variables (history of measles, mumps, cancer, allergy desensitization shots, and a positive family history of cancer in a first-degree relative), and with strata for the variables of age and province of residence.
[c] Phenoxyherbicides include the phenoxyacetic acids (*e.g.*, 2,4-D and MCPA), the phenoxy-2-propionic acids (*e.g.*, mecoprop); the phenoxybutanoic acids (*e.g.*, 2,4-DB) and other phenoxyalkanoic acids (*e.g.*, diclofopmethyl).
[d] Glyphosate is the only phosphonic acid herbicide reported by more than 1% of responders. Round-up, Touchdown, Victor, Wrangler, Laredo do not include dicamba, and Rustler is a mixture of dicamba and glyphosate.
[e] Thiocarbamate herbicides include diallate and triallate.
[f] Bromoxynil is the only phenol herbicide included.
[g] Dicamba as a major chemical class includes Banvel, and Target, and a mixture of dicamba and glyphosate (Rustler), or mixtures of dicamba, 2,4-D, and mecoprop (Dynel DS, Killex).
[h] Dinitroaniline herbicides include ethalfluralin and trifluralin.

Ethics. The protocol, letters of informed consent, questionnaires, and all other correspondence with potential subjects were approved by the relevant agencies in each province. All of the information that could be used to identify individuals remained within the province of origin under the control of the provincial principal investigators.

Results

Data from postal questionnaires based on responses from 517 NHL cases (67.1% of those contacted) and 1506 control subjects (48.0% of those contacted) were analyzed. Similar percentages of potential subjects resident in rural and urban areas responded. There were higher percentages of responders in the middle-age group than at either extreme among both cases and controls. Detailed information related to their pesticide exposure history was obtained by telephone interview from 119 NHL cases and 301 control subjects who indicated pesticide exposure of 10 h per year or more. A 15% random sample of cases and controls who indicated pesticide exposure of less than 10 h/year was also interviewed by telephone, resulting in detailed pesticide exposure information on 60 cases of NHL and on 155 controls. The total telephone interviewed sample consisted of 179 cases of NHL and 456 controls.

A summary of selected demographic, antecedent personal and familial medical history, general pesticide exposure as measured by the screening questions, and cigarette smoking history comparisons of NHL cases and population-based controls is shown in Table 1. Because all of the controls (age-matched for STS, MM, HD, and NHL) were used in the analysis, cases were older than controls. Cases and controls were similar in their smoking patterns. Cases were less likely to have a history of measles or mumps and more likely to have a personal history of a previous primary cancer. Cases were more likely than controls to have a positive family history of cancer, whereas more controls had undergone allergy desensitization injections. A slightly higher proportion of cases than controls indicated cumulative exposure to pesticides of $\geq$10 h per year.

Table 2 summarizes reported exposure to herbicides classified by major chemical classes (phenoxy, phosphonic acid, thiocarbamates, phenols, dicamba, and dinitroaniline) and by individual compounds for which at least 1% of responders reported exposure. ORs are also shown after adjustment for the statistically significant ($P < 0.05$) variables reviewed in Table 1, which included a history of measles, mumps, cancer, and allergy desensitization shots and a positive history of cancer in a first-degree relative. Cases experienced a significantly higher frequency of exposure to phenoxyherbicides, to dicamba or a mixture including dicamba, to 2,4-D, and to mecoprop.

Table 3 summarizes the insecticide exposure data. Exposure to two major chemical classes, carbamates and organophosphates, was statistically significantly associated with NHL, whereas exposure to organochlorines as a group was not.

Table 3 Insecticides: frequency of exposure to insecticides classified into major chemical classes and as individual compounds

Major chemical classes	NHL n = 517		Controls n = 1506		OR[a] (95% CI)	OR_{adj}[b] (95% CI)
	n exposed	% exposed	n exposed	% exposed		
Carbamates,[c] exposed	37	7.2	60	4.0	**1.95 (1.25–3.05)**	**1.92 (1.22–3.04)**
Individual carbamate insecticides						
Carbaryl	25	4.8	34	2.3	**2.05 (1.18–3.55)**	**2.11 (1.21–3.69)**
Carbofuran	9	1.7	18	1.2	1.58 (0.68–3.67)	1.64 (0.70–3.85)
Methomyl	6	1.2	13	0.9	1.86 (0.67–5.17)	1.65 (0.54–5.03)
Organochlorine, (1)[d] exposed	50	9.7	134	8.9	1.16 (0.81–1.66)	1.27 (0.87–1.84)
Individual organochlorine (1) insecticides						
Chlordane	36	7.0	105	7.0	1.06 (0.71–1.59)	1.11 (0.74–1.69)
Lindane	15	2.9	23	1.5	**2.05 (1.01–4.16)**	**2.06 (1.01–4.22)**
Aldrin	10	1.9	6	0.4	**3.81 (1.34–10.79)**	**4.19 (1.48–11.96)**
Organochlorine (2) diphenylchlorides[e] exposed	86	16.6	233	15.5	1.24 (0.94–1.65)	1.21 (0.90–1.62)
Individual organochlorine (2) diphenylchlorides						
Methoxychlor	65	12.6	201	13.3	1.08 (0.79–1.47)	1.02 (0.74–1.41)
DDT	32	6.2	59	3.9	**1.63 (1.03–2.57)**	**1.73 (1.08–2.76)**
Organophosphorus,[f] exposed	90	17.4	167	11.1	**1.69 (1.26–2.27)**	**1.73 (1.27–2.36)**
Individual organophosphorus insecticides						
Malathion	72	13.9	127	8.4	**1.77 (1.28–2.46)**	**1.83 (1.31–2.55)**
Dimethoate	22	4.3	50	3.3	1.20 (0.71–2.03)	1.20 (0.70–2.06)
Diazinon	18	3.5	28	1.9	1.72 (0.92–3.19)	1.69 (0.88–3.24)

[a] ORs calculated with strata for the variables of age and province of residence.
[b] ORs adjusted for statistically significant medical variables (history of measles, mumps, cancer, allergy desensitization shots and a positive family history of cancer in a first-degree relative), and with strata for the variables of age and province of residence.
[c] Carbamate insecticides include carbaryl, carbofuran, and methomyl.
[d] Organochlorine insecticides class one includes aldrin; chlordane; dieldrin; endrin; heptachlor; lindane; and a mixture of lindane, carbathiin, and thiram (Vitavex).
[e] Organochlorine (2) diphenylchloride insecticides include DDT and methoxychlor.
[f] Organophosphorus insecticides include malathion, chlorpyrifos, diazinon, dimethoate, parathion, methidathion, and trichlorfon.

Table 4 Fungicides: frequency of exposure to fungicides classified into major chemical classes and as individual compounds

Major chemical classes	NHL n = 517		Controls n = 1506		OR[a] (95% CI)	OR_{adj}[b] (95% CI)
	n exposed	% exposed	n exposed	% exposed		
Amide,[c] exposed	30	5.8	58	3.9	**1.69 (1.05–2.73)**	**1.70 (1.04–2.78)**
Individual amide fungicides						
Captan	20	3.9	24	1.6	**2.48 (1.33–4.63)**	**2.51 (1.32–4.76)**
Vitavax	10	1.9	39	2.6	0.88 (0.42–1.85)	0.88 (0.41–1.87)
Aldehyde,[d] exposed	7	1.4	25	1.7	0.85 (0.35–2.07)	0.92 (0.37–2.29)
Individual aldehyde fungicides						
Formaldehyde	7	1.4	255	1.7	0.85 (0.35–2.07)	0.92 (0.37–2.29)
Mercury Containing,[e] exposed	18	3.5	48	3.2	1.09 (0.61–1.95)	1.28 (0.70–2.27)
Mercury-containing fungicides						
Mercury dust (n exposed)	15	2.9	39	2.6	1.08 (0.57–2.04)	1.23 (0.64–2.35)
Mercury liquid (n exposed)	8	1.5	22	1.5	1.15 (0.49–2.69)	1.40 (0.74–3.22)
Sulphur Compounds	17	3.3	21	1.4	**2.26 (1.16–4.40)**	**2.80 (1.41–5.57)**

[a] ORs calculated with strata for the variables of age and province of residence.
[b] ORs adjusted for statistically significant medical variables (history of measles, mumps, cancer, allergy desensitization shots, and a positive family history of cancer in a first-degree relative), and with strata for the variables of age and province of residence.
[c] Amide fungicides include captan and a mixture of carbathiin, thiram, and lindane (Vitavax).
[d] Aldehyde fungicides include formaldehyde and a mixture of formaldehyde and iprodione (Rovral Flo).
[e] Mercury-containing fungicides include mercury dusts (Ceresan, Reytosan, and Agrox) and mercury liquids (Panogen, Leytosol, and PMAS).

Among individual carbamate compounds, exposure to carbaryl was statistically significantly associated with NHL. Among organochlorines, exposure to lindane, to aldrin, and to DDT was significantly associated with NHL. Malathion was the only individual organophosphate exposure statistically significantly associated with NHL.

Exposure to fungicides is summarized in Table 4. The fungicides with an amide group (OR_{adj}, 1.70; 95% CI, 1.04–2.78) were associated with NHL, whereas aldehydes and those containing mercury were not. Among individual amide-containing compounds, exposure to captan (OR_{adj}, 2.51; 95% CI, 1.32–4.76) was associated with NHL.

Malathion used as a fumigant was not associated with NHL (Table 5). There were fewer users of malathion as a fumigant compared with its use on crops. Carbon tetrachloride fumigant exposure (OR_{adj}, 2.42; 95% CI, 1.19–5.14) was associated with NHL.

Table 6 shows the results of a conditional logistic regres-

Table 5 Frequency of exposure to fumigants: individual compounds

Individual compounds+	NHL $n = 517$		Controls $n = 1506$		OR[a] (95% CI)	OR_{adj}[b] (95% CI)
	n exposed	% exposed	n exposed	% exposed		
Malathion[c]	12	2.3	23	1.5	1.49 (0.72–3.11)	1.54 (0.74–3.22)
Carbon tetrachloride[d]	13	2.5	18	1.2	**2.13 (1.02–4.47)**	**2.42 (1.19–5.14)**

[a] ORs calculated with strata for the variables age and province of residence.
[b] ORs adjusted for statistically significant medical variables (history of measles, mumps, cancer, allergy desensitization shots, and a positive family history of cancer in a first-degree relative) and with strata for the variables age and province of residence.
[c] Malathion is an organophosphorus insecticide which has been used indoors as a fumigant.
[d] Carbon tetrachloride was used as a grain fumigant.

Table 6 Most parsimonious model: conditional logistic regression analyses that contained major chemical classes of pesticides and important covariates ($P < 0.05$)

Phenoxyherbicides as a group, carbamate, and organophosphate insecticides, amide group containing fungicides, and carbon tetrachloride users/nonusers were included in the initial multivariate model and found not to contribute significantly to the risk of NHL.

Variable	Parameter Estimate ± SE	OR (95% CI)
Measles (yes)	−0.47 ± 0.11	**0.62 (0.50–0.78)**
Previous cancer (yes)	0.79 ± 0.18	**2.20 (1.54–3.15)**
First-degree relative with cancer (yes)	0.32 ± 0.11	**1.37 (1.10–1.71)**
Allergy desensitization shots (yes)	−0.65 ± 0.27	**0.52 (0.31–0.89)**
Dicamba mixtures (user)	0.67 ± 0.17	**1.96 (1.40–2.75)**

Table 7 Most parsimonious model: conditional logistic regression analyses that contained individual chemical pesticides and important covariates ($P < 0.05$)

Among individual pesticides, carbaryl, lindane, DDT, and malathion insecticides, and captan fungicide user/nonuser were included in the initial multivariate model and found not to contribute significantly to the risk of NHL.

Variable	Parameter estimate ± SE	OR (95% CI)
Measles (yes)	−0.48 ± 0.11	**0.50 (0.45–0.83)**
Previous cancer (yes)	0.80 ± 0.18	**2.23 (1.56–3.19)**
First-degree relative with cancer (yes)	0.32 ± 0.11	**1.38 (1.11–1.72)**
Allergy desensitization shots (yes)	−0.68 ± 0.27	**0.51 (0.30–0.87)**
Mecoprop (user)	0.80 ± 0.20	**2.22 (1.49–3.29)**
Aldrin (user)	1.23 ± 0.54	**3.42 (1.18–9.95)**

sion model that included major chemical classes of pesticides and all other covariates for which $P < 0.05$. The variables that remained statistically significantly associated with increased risk of NHL were a previous personal history of another malignancy, a history of cancer among first-degree relatives, and exposure to dicamba and mixtures containing dicamba. ORs for a personal history of measles or of allergy desensitization injections were significantly lower than those without this history. Table 7 summarizes a similar model that included individual pesticides and all of the other covariates for which $P < 0.05$ and in which mecoprop and aldrin exposure as well as the same covariates as in Table 6 were associated with NHL.

Table 8 shows the frequency of exposure to selected individual herbicides, insecticides, fungicides, and fumigants, stratified by the average number of days per year of exposure. In general, the results of these dose-response analyses are consistent with the exposed/nonexposed findings. Those compounds for which we found statistically significant case-control differences also have elevated ORs based on strata of the variable "days per year of exposure" (mecoprop, dicamba, malathion, DDT, captan, carbon tetrachloride, and sulfur). The exceptions were 2,4-D, for which there was no dose-response relationship, and glyphosate, which was not significant for exposure but for which we demonstrated a dose-response relationship.

Table 9 compares the frequencies of multiple herbicide, insecticide, fungicide, and fumigant use among cases and controls. Cases are significantly more likely to report exposure to between two and four herbicides or insecticides but not to five and more of either. An elevated OR was found for exposure to two or more fungicides. Table 9 also shows a dose-response relationship in comparisons of subjects who reported no pesticide exposure and those who reported using five or more pesticides.

Discussion

The hypothesis that farming (1–8), agricultural practices (9), and pesticide exposure (10–13, 22–25) are associated with NHL has been tested in a number of occupational studies. Not all of the studies confirm an association (27–29). Pesticides have diverse chemistry and biological modes of action. In addition to the active ingredients, there are emulsifiers, carriers, dispersants, and a variety of agents used to formulate liquids, granular and mists. The major chemical classes of *a priori* interest based on epidemiological studies (10–13, 22–25) were phenoxyherbicides, organophosphorus, organochlorines, aldehydes, and carbon tetrachloride. Occupational exposure to 2,4-D, 2,4,5-T, carbaryl, chlordane, DDT, diazinon, dichlorvos, lindane, malathion, nicotine, and toxaphene has been reported to be associated with NHL. In addition, our interest focused on pesticides classified as possibly or probably carcinogenic to humans based on evaluations by the IARC expert panels (Refs. 22–25; phenoxyherbicides including 2,4-D, MCPA, and 2,4,5-T as a group, atrazine, chlordane, DDT, dichlorvos, heptachlor, and pentachlorophenol). Our bivariate results for exposure to groups of phenoxyherbicides or dicamba-containing herbicides, for carbamates and organophosphorus insecticides, and for amide fungicides and for carbon tetrachloride were not attenuated when simultaneously adjusted for the important medical covariates (history of measles, mumps, cancer, allergy desensitization shots, and a positive history of cancer in a first-degree relative).

Among individual compounds, our results that related to exposure to 2,4-D, mecoprop, dicamba, malathion, DDT, carbaryl, lindane, aldrin, captan, and sulfur compounds were not attenuated after simultaneous adjustment for the same medical covariates. Clearly, we had few exposed men whose exposure was limited to one pesticide or to one class of pesticides. Our results show elevated risk for exposure to multiple herbicides, insecticides, and fungicides.

Table 8 Frequency of exposure to selected herbicides, insecticides, fungicides, and fumigants stratified by the number of days per year of exposure

Models that included the time variable "days per year" and stratification for age and province of residence were also assessed for the individual herbicide compounds bromoxynil, 2,4-DB, diallate, MCPA, triallate, and treflan. No significant associations were found.

Individual compounds	Days/yr	NHL		Controls		OR[a] (95% CI)
		n	%	*n*	%	
Herbicides						
2,4-D	Unexposed	406	78.5	1213	80.5	1
	>0 and ≤2	55	10.6	160	10.6	1.17 (0.83–1.64)
	>2 and ≤5	36	7.0	82	5.4	1.39 (0.91–2.13)
	>5 and ≤7	9	1.7	20	1.3	1.38 (0.60–3.15)
	>7	11	2.1	31	2.1	1.22 (0.60–2.49)
Mecoprop	Unexposed	464	89.8	1425	94.6	1
	>0 and ≤2	31	6.0	48	3.2	**2.27 (1.40–3.68)**
	≥2	22	4.3	33	2.2	**2.06 (1.17–3.61)**
Phosphonic acid: glyphosate	Unexposed	466	90.1	1373	91.2	1
	>0 and ≤2	28	5.4	97	6.4	1.00 (0.63–1.57)
	>2	23	4.5	36	2.4	**2.12 (1.20–3.73)**
Dicamba	Unexposed	491	95.0	1456	96.7	1
	≥1	26	5.0	50	3.3	1.58 (0.96–2.62)
Insecticides						
Malathion	Unexposed	445	87.0	1379	91.6	1.00
	>0 and ≤2	50	9.7	88	5.8	**1.82 (1.25–2.68)**
	≥2	22	4.3	39	2.6	**1.75 (1.02–3.03)**
DDT	Unexposed	485	93.8	1447	96.1	1.00
	>0 and ≤2	18	3.5	32	2.1	1.75 (0.96–3.21)
	>2	14	2.7	27	1.8	1.50 (0.77–2.91)
Fungicides						
Captan	Unexposed	497	96.1	1482	98.4	1.00
	>0 and ≤2	11	2.1	12	0.8	**2.69 (1.17–6.19)**
	>2	9	1.7	12	0.8	**2.80 (1.13–6.90)**
Sulphur	Unexposed	500	96.7	1485	98.6	1.00
	Exposed ≥1	17	3.3	21	1.4	**2.26 (1.16–4.40)**
Fumigant						
Carbon tetrachloride	Unexposed	504	97.5	1488	98.8	1.00
	>0 and ≤2	13	2.5	18	1.2	**2.13 (1.02–4.47)**

[a] ORs calculated with strata for the variables age and province of residence.

The strength of our results is enhanced by their internal consistency as we applied the strategy of assessing risk by different analytic approaches progressing from exposure to: (*a*) major chemical classes of herbicides, insecticides, fungicides, and fumigants; (*b*) individual compounds within those major chemical classes; and (*c*) individual compounds stratified by days per year of exposure. We constructed models that included potential confounders (*e.g.*, positive history of cancer in a first-degree relative). Generally, the same individual compounds or class of compounds was associated with case status. The risk estimates based on exposure to major chemical classes or to individual compounds tended to be precise, as indicated by the 95% CIs.

Our results confirm previously reported associations of NHL and a personal history of cancer (30, 31), of NHL and a history of cancer among first-degree relatives (32, 33), and of NHL and exposure to selected pesticides (1, 3, 5, 9–13). We were unable to find a previous report suggesting a protective effect of allergy desensitization shots. Koepsell *et al.* reported little association of the number of allergy desensitization shots and MM (34). The relationship between allergy and cancer is complex with well-designed studies reporting opposite results (35–38). Cigarette smoking was not a risk factor overall, confirming one study (39) and contradicting others (40, 41), although certain subtypes (39, 40) of NHL may be associated with cigarette smoking.

The limitations of this study relate to those inherent in the case-control design, specifically the potential for recall bias and for misclassification of pesticide exposure. Hoar *et al.* and Zahm *et al.* (11, 13), as well as others (27–29, 42–45), have dealt extensively with these issues among farmers. We have included individuals in many different occupations as well as home and garden users. These are groups for whom we did not find extensive validation studies. Their inclusion may have biased our dose-response findings toward the null, although the yes/no responses to individual pesticides would be less affected. We reduced the number of surrogate responders by excluding deceased persons from our definition of eligible subjects. This strategy was useful in decreasing the potential for misclassification of exposure.

A second limitation is the less-than-optimal response rates. We continued to recruit subjects in each province until the target numbers were achieved. We compared respondents to nonrespondents using postal codes as an indicator of rural residence, and we did not find a rural bias among respondents.

We reported results for a number of chemical agents and exposures, not all of which were specified in the hypothesis. Therefore, the statistical analyses related to these unspecified agents should be considered exploratory. As a consequence of conducting multiple comparisons, a small number of statistically significant results may be attributable to chance.

The two-tiered study design permitted us to obtain detailed information related to factors other than pesticides that are known or suspected of being etiologically associated with NHL. The mailing of a list of pesticides with both trade and generic chemical names followed by a telephone interview

Table 9 Distribution of numbers of exposures to multiple types of pesticides among cases and controls

	NHL		Controls		OR[a] (95% CI)
	n	%	*n*	%	
Multiple herbicide use					
Unexposed[b]	374	72.3	1148	76.2	1.00
Exposed 1	45	8.7	146	9.7	1.02 (0.70–1.47)
Exposed 2–4	73	14.1	151	10.0	**1.75 (1.27–2.42)**
Exposed ≥5	25	4.8	61	4.1	1.41 (0.84–2.35)
Multiple insecticide use					
Unexposed	370	71.6	1154	76.6	1.00
Exposed 1	44	8.5	127	8.4	1.24 (0.85–1.80)
Exposed 2–4	86	16.6	189	12.6	**1.58 (1.17–2.13)**
Exposed ≥5	17	3.3	36	2.4	1.46 (0.79–2.69)
Multiple fungicide use					
Unexposed	457	88.4	1361	90.4	1.00
Exposed 1	32	6.2	90	6.0	1.08 (0.70–1.67)
Exposed ≥2	28	5.4	55	3.7	1.61 (.99–2.63)
Multiple fumigant use					
Unexposed	487	94.2	1440	95.6	1.00
Exposed ≥1	30	5.8	66	4.4	1.45 (0.91–2.63)
Multiple pesticide use[c]					
Unexposed	357	69.1	1095	72.7	1.00
Exposed 1–4	77	14.9	230	15.3	1.09 (0.81–1.46)
Exposed ≥5	83	16.1	181	12.0	**1.57 (1.16–2.14)**

[a] ORs calculated with strata for the variables age and province of residence.
[b] With the exception of the variable multiple pesticide use, the "unexposed" referent category is specific to the class of pesticides.
[c] The unexposed referent category contains those who did not report exposure to herbicides, insecticides, fungicides, or fumigants.

allowed the collection of detailed information concerning pesticide exposure. The statistical power of our study was enhanced by the large number of cases and controls. In instances of rare exposures (<1% exposed), we had limited statistical power to detect associations. We restricted our analyses of individual pesticide compounds to those for which at least 1% of respondents indicated exposure.

The study was not restricted to pesticide exposure experienced by a specific occupational group. Occupational exposure was quite diverse; single *versus* multiple pesticides; indoor *versus* outdoor applications. For example, men who work in animal confinement buildings, grain elevators, and pesticide manufacturing have different exposure patterns in comparison with grain farmers and commercial applicators. Because this study encompassed a large geographical area of Canada, there was substantial diversity among agricultural enterprises and in the patterns and types of pesticide exposure.

Delineating the putative relationship between exposure to pesticides and NHL is complicated: (*a*) by the subject's exposure to a variety of different pesticides many of which are not mutagenic, teratogenic, or carcinogenic when tested as a single compound; (*b*) by the complexity of formulations of pesticides, the details of which are privileged proprietary information; (*c*) by the diversity of routes of possible exposure, which include ingestion, dermal, inhalation, and ocular; (*d*) by unexpected interactions among seemingly unrelated exposures, such as the increased permeability of rubber gloves to 2,4-D when exposed simultaneously to the insect repellent DEET and sunlight (46); and (*e*) by the role of differential genetic susceptibility.

Garry *et al.* (47) describe a potential mechanism to explain the relationship between exposure to specific pesticides and an increased risk of developing NHL. They have demonstrated specific chromosomal alterations in the peripheral lymphocytes of pesticide applicators exposed to a variety of pesticide classes. A higher frequency of chromosomal breaks involving band 18q21 was found in men who applied only herbicides compared with nonoccupationally exposed controls. Higher frequencies of rearrangements and breaks involving band 14q32 were found among men who applied herbicides, insecticides, and fumigants compared with controls. Reciprocal translocations between chromosomes 14q32 and 18q21 are frequently found in NHL patients.

Our results support previous findings of an association between NHL and specific pesticide exposures. Our strategy of assessing risk by several different approaches, beginning with general categories (*e.g.*, herbicides), proceeding through cumulative pesticide exposure to specific chemical classes, and proceeding further to specific chemicals, proved effective in delineating complex relationships. In our final models, NHL was associated with a personal history of cancer; a history of cancer in first-degree relatives; and exposure to dicamba-containing herbicides, to mecoprop, and to aldrin. A personal history of measles and of allergy desensitization treatments lowered risk.

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Pesticides and Other Agricultural Risk Factors for Non-Hodgkin's Lymphoma among Men in Iowa and Minnesota

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ABSTRACT

Data from an in-person interview study of 622 white men with newly diagnosed non-Hodgkin's lymphoma and 1245 population-based controls in Iowa and Minnesota were used to measure the risk associated with farming occupation and specific agricultural exposures. Men who ever farmed were at slightly elevated risk of non-Hodgkin's lymphoma (odds ratio = 1.2, 95% confidence interval = 1.0–1.5) that was not linked to specific crops or particular animals. Elevated risks were found, with odds ratio generally 1.5-fold or greater, for personal handling, mixing, or application of several pesticide groups and for individual insecticides, including carbaryl, chlordane, dichlorodiphenyltrichloroethane, diazinon, dichlorvos, lindane, malathion, nicotine, and toxaphene. Associations were generally stronger for first use prior to 1965 than more recently, and when protective clothing or equipment was not used. Small risks were associated with the use of the phenoxyacetic acid herbicide 2,4-dichlorophenoxyacetic acid, but the risks did not increase with latency or failure to use protective equipment. Exposure to numerous pesticides poses problems of interpreting risk associated with a particular chemical, and multiple comparisons increase the chances of false-positive findings. In contrast, nondifferential exposure misclassification due to inaccurate recall can bias risk estimates toward the null and mask positive associations. In the face of these methodological and statistical issues, the consistency of several findings, both within this study and with observations of others, suggests an important role for several insecticides in the etiology of non-Hodgkin's lymphoma among farmers.

INTRODUCTION

While farmers generally have low rates of morbidity and mortality, they appear to be at excess risk of selected cancers, particularly some of the hematopoietic tumors (1). Some studies suggest that the elevated risk of NHL[2] and leukemia among farmers may be associated with exposure to pesticides and other agricultural chemicals (2). To further evaluate these associations, we conducted parallel population-based case-control interview studies of men newly diagnosed with non-Hodgkin's lymphoma and leukemia in the states of Minnesota and Iowa. Findings for leukemia are reported elsewhere (3).

METHODS

Case Selection. All newly diagnosed cases of non-Hodgkin's lymphoma among men aged 30 or older were ascertained from Iowa State Health Registry records and a special surveillance of Minnesota hospital and pathology laboratory records. In Iowa, the diagnosis period for eligibility was March 1981 to October 1983, and in Minnesota, October 1980 to September 1982. In Iowa, all cases who resided in the state were eligible. In Minnesota, eligibility was restricted to cases who resided in places other than the cities of Minneapolis, St. Paul, Duluth, or Rochester at the time of diagnosis.

Pathology Review. A review panel of 4 experienced regional pathologists confirmed diagnoses and classified NHL cases as to morphological type using the Working Formulation for classification of NHL (4). NHL subtype was designated when at least 3 panelists agreed on a specific diagnosis, either at the initial review or a supplementary review conducted for more difficult cases. The case was considered "unclassifiable" if the pathology panel could not come to consensus on NHL subtype, or if the tissue sample was not adequate to differentiate among subtypes. The NHL subtypes were collapsed into categories as follows: follicular (combining small cleaved cell, mixed cell, and large cell follicular cases); diffuse (combining small cleaved cell, mixed cell, and large cell diffuse cases); small lymphocytic; and "other NHL" (combining large cell immunoblastic, lymphoblastic, small noncleaved, other, and unclassified NHL cases). Additional details regarding histopathology review procedures are presented elsewhere (5, 6).

Control Selection. A population-based control group of white men without a hematopoietic or lymphatic cancer was randomly selected and frequency-matched to NHL and leukemia cases by 5-year age group, vital status at time of interview, and state of residence. The sources of controls were: (*a*) random digit dialing for living subjects under age 65 at diagnosis, using the Waksberg method (7, 8) (data from the 1980 United States Census report that 96 and 97% of Iowa and Minnesota households, respectively, had telephones); (*b*) a 1% random listing from Medicare files provided by the Health Care Financing Administration for living subjects aged 65 and older [United States citizens 65 years of age and older are eligible for Medicare insurance and over 98% have been estimated to be in the roster (9)]; and (*c*) state death certificate files for deceased subjects.

Data Collection. Interviews were conducted during the period of August 1981 to May 1984. A trained interviewer administered an in-person structured interview, taking 45–60 min, to the subject, or the spouse, other close relative, or friend of deceased or incompetent subjects. We asked about sociodemographic characteristics, medical history, smoking habit, occupational history, residential history, familial history of cancer, and other known and suspected risk factors. In addition, we requested a detailed farming and pesticide use history of all subjects who had worked on a farm at least 6 months since age 18. For each farm that the respondent had worked, we recorded the years of farming activity, the total acreage, the number and types of livestock, and the crops grown, with average acreage for each and the number of years they had been grown on that farm. We also asked for a detailed history of pesticide use. Pesticide lists for the questionnaire were developed with the assistance of local agricultural experts. We named 23 specific insecticides used on animals, 34 insecticides applied to crops, 38 herbicides, and 16 fungicides. For each pesticide, we asked if it had ever been used; the first and last year of use; the method of application (aerial, surface application, incorporated into soil, other); whether the respondent had personally applied, mixed, or handled it; and the use of protective equipment.

Response Rates. Seven hundred eighty presumptive NHL cases were ascertained, and 694 (89%) were interviewed. After pathology review of interviewed cases, 622 were confirmed as NHL (438 living cases with direct interviews, 184 deceased or incompetent cases with proxy interviews). Among the 72 cases that could not be confirmed, 26 were

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[2] The abbreviations used are: NHL, non-Hodgkin's lymphoma; DDT, dichlorodiphenyltrichloroethane; CLL, chronic lymphocytic leukemia; OR, odds ratio; CI, 95% confidence interval; 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid.

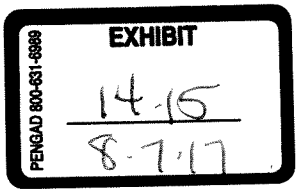

Table 1 *Characteristics of cases and controls from a study of non-Hodgkin's lymphoma in Iowa and Minnesota*[a]

	Cases		Controls	
	No.	(%)	No.	(%)
Type of NHL				
Follicular	195	(31)		
Diffuse	198	(32)		
Small lymphocytic	85	(14)		
Other	144	(23)		
Type of interview				
Direct	438	(70)	820	(66)
Surrogate	184	(30)	425	(34)
State of residence				
Iowa	293	(47)	603	(48)
Minnesota	329	(53)	642	(52)
Age				
<45	73	(12)	134	(11)
45–64	230	(37)	430	(35)
65+	319	(51)	681	(55)
Hair dye use (ever)?				
No	574	(92)	1194	(96)
Yes	48	(8)	51	(4)
Lymphopoietic cancer diagnosed in any first degree relative?				
No	557	(90)	1154	(93)
Yes	54	(9)	66	(5)
High risk occupation (ever)? [b]				
No	524	(84)	1174	(94)
Yes	98	(16)	71	(6)
Used high risk materials at least monthly for a year or more? [c]				
No	369	(59)	840	(67)
Yes	253	(41)	405	(33)
Cigarette smoking habit				
Never smoked	186	(30)	418	(34)
Past smoker	243	(40)	486	(39)
Current smoker	182	(30)	333	(27)

[a] Cases and controls numbered 622 and 1245, respectively. The number of respondents with missing values for selected characteristics is not explicitly listed.
[b] Persons ever employed at an occupation yielding an odds ratio of 1.5 or greater in Mantel-Haenzsel analyses adjusted for age (2 strata) and state of residence.
[c] Persons using one or more materials yielding an odds ratio of 1.5 or greater, from a list of 43 items that included paints, benzene, other organic solvents, resins, and others.

diagnosed as leukemia, and 46 with other conditions. Pathology review was not conducted on material of the persons who were not interviewed. Among random digit dialing controls, the household screening response rate was 87.5%, yielding 474 eligible persons, of whom 415 (87.6%) agreed to participate, for a net response rate of 76.7%. Among the 2 other control groups, 79% of the eligible controls selected from the Health Care Financing Administration rolls participated, and 77% of the eligible proxies for deceased controls provided complete interviews.

Statistical Analysis. The association between a variety of farm-related factors and risk of NHL was measured by the maximum likelihood estimate of the OR. ORs were adjusted for several known or suspected NHL risk factors, using unconditional logistic regression analysis with case-control status as the response variable (10, 11). OR for farmers who raised specific crops or animals, or were exposed to individual pesticides and families of pesticides, were calculated for all NHL and the NHL subtypes, comparing exposed persons to nonfarmers, except as noted. ORs for the histological subtypes of NHL were calculated using software for polychotomous logistic models developed by the Epidemiology and Biostatistics Program of the National Cancer Institute. Logistic models included the following potential confounding variables: vital status (alive, dead); state (Iowa, Minnesota); age (<45, 45–64, 65+); cigarette smoking habit (never, past, current); lymphopoietic cancer in a parent, sibling, or child (yes, no); nonfarming job related to NHL in this study (with OR of 1.5+); exposure to hair dyes (yes, no); and exposure to one or more other substances associated with NHL in this study [with OR of 1.5+, as calculated by standard methods with adjustment for age and state of residence (12)]. Tests for trend in the logistic analysis were obtained by categorizing the exposure variable and treating the scored variable as a continuous variable.

RESULTS

Study Population. Table 1 shows the distribution of the 622 cases and 1245 controls by type of NHL, type of interview, state of residence, age, hair dye use, having had a first degree relative with lymphopoietic cancer, employment in a high risk occupation (*a priori*), exposure to high risk materials (*a posteriori*), and cigarette smoking habit. Among the 622 respondent cases, the distribution of histological types was: 195 follicular (31.4%), 198 diffuse (31.8%), 85 small lymphocytic cell (13.7%), and 144 other and undefined lymphomas (23.2%).

We found elevated relative risks associated with certain occupational exposures and job classifications, hair dye use, as well as a history of familial cancer. These factors were entered as potential confounders in logistic regression models, as were variables for age, state of residence, and vital status of the study subject.

Farming. There was a small, but marginally significant increase in risk for all NHL (OR = 1.2, 95%, CI = 1.0–1.5) associated with ever living or working on a farm as an adult (Table 2). Fifty-seven % of the cases and 56% of controls reported some farm activity. When analyzed by NHL subtype, there was a small excess risk for each, but none was significant. Among subtypes, the highest observed risk for farming was found for small cell lymphocytic lymphoma (OR = 1.4, CI = 0.9–2.3).

No statistically significant trend by first and last year of farming activity, duration, or average yearly number of acres

Table 2 *OR and CI for non-Hodgkin's lymphoma according to ever having been a farmer, timing of farming occupation, and average size of farm (in acres)*[a]

	CO	CA	OR	CI
Nonfarmer	547	266	1.0	
Farmer	698	356	1.2	1.0, 1.5
First year farmed				
<1925	218	105	1.3	0.9, 1.8
1925–1934	200	92	1.1	0.8, 1.5
1935–1944	143	64	0.9	0.7, 1.3
1945+	136	94	1.4	1.0, 1.9
Missing	1	1		
Farmed until				
<1950	190	77	0.9	0.6, 1.3
1950–1969	190	113	1.4	1.1, 1.9
1970+	314	165	1.2	0.9, 1.6
Missing	4	1		
No. of years farmed				
<10	163	89	1.2	0.9, 1.6
10–39	289	153	1.2	0.9, 1.6
40+	239	112	1.2	0.9, 1.6
Missing	7	2		
Average no. of acres				
<120	129	62	1.1	0.8, 1.6
120–199	217	115	1.3	1.0, 1.7
200–319	183	96	1.2	0.9, 1.7
320+	140	72	1.1	0.8, 1.6
Missing	29	11		

[a] All OR relative to risk for subjects who were never farmers (266 cases, 547 controls). All ORs adjusted for vital status, age, state, cigarette smoking, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures in a logistic analysis.

during farming years was observed for all NHL or any subtype (Table 2). However, we observed slightly higher risks among men who farmed after 1949 than those who stopped before 1950. Men who operated medium-size farms (120–199 acres or 200–319 acres) were at slightly higher risk for all NHL and for most NHL subtypes than men farming smaller or larger establishments.

There was no notable association of risk for all NHL associated with the cultivation of any major crop, nor with the husbandry of the major types of livestock (data not shown). The patterns of OR for the lymphoma histological subtypes, as related to particular crops and livestock, followed the overall pattern for farming in general, with elevated (mostly nonsignificant) OR for small lymphocytic lymphoma associated with corn (OR = 1.4, CI = 0.9–2.4; 52 cases), wheat (OR = 1.5, CI = 0.8–2.9; 21 cases), flax (OR = 2.3, CI = 1.0–5.0; 15 cases), barley (OR = 1.5, CI = 0.7–3.1; 15 cases), and hay (OR = 1.4, CI = 0.8–2.4; 31 cases). Associations of other NHL subtypes with specific crops and livestock were weaker, as were associations of small lymphocytic lymphoma with specific types of livestock.

Among the 356 cases and 698 controls who had lived and worked on one or more farms as an adult, 323 cases (90.7%) and 636 controls (91.4%) reported that they were farm operators on at least one farm. Operators usually plan and execute pest control activities, and are more likely than hired hands to have direct knowledge of the chemicals used.

Pesticide Use (Ever). Among farmers, 300 cases (84%) and 603 controls (86%) reported use of at least one pesticide (for all NHL, OR = 1.2, CI = 0.9–1.4, relative to nonfarmers). The OR for use of one or more insecticides on livestock was 1.1 (CI = 0.9–1.4); for crop insecticide use, 1.2 (CI = 0.9–1.5); for herbicide use, 1.3 (CI = 1.0–1.6); and for fungicide use, 1.3 (CI = 0.8–2.0).

Pesticide Families. Table 3 shows the numbers of cases and controls, OR, and CI for use of one or more members of the listed chemical families of pesticides, by broad grouping of livestock insecticides, crop insecticides, and herbicides. Classification of pesticides into chemical families was done by us. All OR shown are relative to nonfarmers, numbering 266 cases and 547 controls. Significant risk elevations were found for several livestock insecticide families: chlorinated hydrocarbons (OR = 1.3), in particular the cyclodienes (OR = 1.7); natural products (OR = 1.5); and organophosphates (OR = 1.5), in particular the halogenated aromatic organophosphates (OR = 2.0). Among insecticides used on crops, the chlorinated hydrocarbon family showed significant elevation in risk (OR = 1.4). Although based on small numbers, use of nonhalogenated organophosphates on crops was associated with a nonsignificant OR of 3.1. Use of insecticides on livestock or crops resulted in a significant increased risk of NHL associated with chlorinated hydrocarbons (OR = 1.3) and organophosphates (OR = 1.5). No single family of herbicides was significantly associated with overall NHL risk.

The use, handling, or application of pesticides in selected chemical families was associated with elevated risk for several of the NHL morphological subtypes. Significantly elevated OR were found for diffuse NHL and: organophosphates used on crops (OR = 2.3, CI = 1.4–3.8; 26 cases, 101 controls); nonhalogenated aliphatic organophosphates for crops (OR = 2.2, CI = 1.3–3.8; 24 cases, 95 controls); cyclodiene chlorinated hydrocarbons used on livestock (OR = 2.2, CI = 1.1–4.5; 11 cases, 42 controls); and triazine herbicides (OR = 1.6, CI = 1.0–2.6; 25 cases, 133 controls). Small lymphocytic NHL was significantly associated with natural product insecticides used for livestock application (OR = 2.4, CI = 1.1–5.2; 10 cases, 70 controls) and halogenated aromatic organophosphates for livestock (OR = 5.2, CI = 1.9–14.3; 6 cases, 23 controls). Other and unclassified forms of NHL were significantly linked to the chlorinated hydrocarbon insecticide family used for crops (OR = 1.8, CI = 1.1–3.0; 26 cases, 157 controls); the cyclodienes (OR = 2.1, CI = 1.0–4.7; 15 cases, 111 controls) for crops; and halogenated aliphatic organophosphates used on livestock (OR = 2.3, CI = 1.0–5.3; 8 cases, 41 controls). No significant associations with use, handling, or application of pesticide families were found for follicular NHL.

Table 3 *OR[a] and CI for the use of pesticide groups in which at least one pesticide was handled by the respondent[b]*

	Cases	Controls	OR	CI
Insecticides used on livestock				
Carbamates	6	15	0.8	0.3, 2.2
Chlorinated hydrocarbons	112	198	1.3	1.0, 1.7
Cyclodienes	34	42	1.7	1.0, 2.8
Natural products	46	70	1.5	1.0, 2.2
Organophosphates	68	101	1.5	1.0, 2.1
Halogenated aliphatics	20	41	1.2	0.7, 2.0
Nonhalogenated aliphatics	43	67	1.3	0.9, 2.1
Halogenated aromatics	21	23	2.0	1.1, 3.7
Nonhalogenated aromatics	12	16	1.7	0.8, 3.6
Insecticides used on crops				
Carbamates	41	80	1.2	0.8, 1.8
Chlorinated hydrocarbons	96	157	1.4	1.0, 1.9
Cyclodienes	57	111	1.2	0.8, 1.7
Arsenicals	43	75	1.3	0.8, 2.0
Organophosphates	60	101	1.3	0.9, 1.9
Nonhalogenated aliphatics	56	95	1.3	0.9, 1.9
Nonhalogenated aromatics	7	4	3.1	0.9, 11.0
Insecticides used on crops and/or livestock				
Carbamates	43	85	1.1	0.8, 1.7
Chlorinated hydrocarbons	150	262	1.3	1.0, 1.7
Cyclodienes	70	124	1.3	0.9, 1.8
Organophosphates	96	144	1.5	1.1, 2.0
Halogenated aliphatics	21	41	1.2	0.7, 2.1
Nonhalogenated aliphatics	78	119	1.4	1.0, 2.0
Nonhalogenated aromatics	17	20	1.8	0.9, 1.8
Herbicides				
Amides	59	114	1.2	0.8, 1.7
Benzoic acids	53	98	1.3	0.9, 1.9
Carbamates	24	50	1.1	0.7, 1.9
Dinitroaniline	46	88	1.2	0.8, 1.8
Heterocyclics	20	49	0.9	0.5, 1.6
Phenoxyacetic acids	118	231	1.2	0.9, 1.6
Triazines	64	133	1.1	0.8, 1.6
Ureas	5	18	0.6	0.2, 1.6

[a] OR relative to nonfarmers, numbering 266 cases and 547 controls. All ORs adjusted for vital status, age, state, cigarette smoking status, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures in a logistic analysis.
[b] Individual pesticides were categorized into chemical families by the authors.

Selected Pesticides. Tables 4–6 show the numbers of cases and controls, with OR and CI for all NHL, from analyses of farmers who ever personally handled, mixed, or applied specific pesticides, and for farmers who first handled them prior to 1965 (1965 was chosen because it was 15–18 years prior to diagnosis, a reasonable minimal period for latency). Among livestock insecticides (Table 4), there were significantly elevated risks for *ever* handled, mixed, or applied for chlordane and lindane. Most other livestock insecticides had OR greater than 1.0. In general, first use prior to 1965 was associated with higher risk than ever use, and was significant for early reported use of chlordane, lindane, malathion, and nicotine. Among subjects who *ever* personally handled, mixed, or applied specific

Table 4 *Animal insecticides: ORs and CIs for ever having handled specific animal insecticides, and handled prior to 1965*

Insecticide	Ever handled				Handled prior to 1965			
	No. of cases	No. of controls	OR	CI	No. of cases	No. of controls	OR	CI
Chlordane	31	38	1.7	1.0, 2.9	22	22	2.2	1.2, 4.2
Coumaphos	13	18	1.6	0.8, 3.5	3	5	1.5	0.3, 6.3
DDT	79	149	1.2	0.9, 1.7	68	123	1.3	0.9, 1.8
Dichlorvos	20	38	1.2	0.7, 2.2	12	17	1.8	0.8, 3.9
Famphur	10	14	1.7	0.7, 4.0	1	1	2.4	0.1, 39
Lindane	55	90	1.4	1.0, 2.1	40	55	1.7	1.1, 2.7
Malathion	43	67	1.3	0.9, 2.1	25	30	1.8	1.0, 3.3
Methoxychlor	9	16	1.2	0.5, 2.7				
Nicotine	31	47	1.5	0.9, 2.5	28	36	1.8	1.0, 3.0
Rotenone	12	23	1.0	0.5, 2.2				
Toxaphene	8	19	0.8	0.3, 2.0				
Flyspray (NOS)	185	394	1.1	0.9, 1.4	173	368	1.1	0.9, 1.4

[a] OR relative to nonfarmers, numbering 266 cases and 547 controls. All ORs adjusted for vital status, age, state, cigarette smoking status, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures in a logistic analysis.

Table 5 *Crop insecticides: ORs and CIs for ever having handled specific insecticides, and handled prior to 1965*[a]

Insecticide	Ever handled				Handled prior to 1965			
	No. of cases	No. of controls	OR	CI	No. of cases	No. of controls	OR	CI
Aldrin	47	97	1.1	0.7, 1.7	34	59	1.3	0.8, 2.1
Carbofuran	29	65	1.0	0.6, 1.7	28	63	1.0	0.6, 1.7
Carbaryl	21	26	1.7	0.9, 3.1	7	4	3.8	1.1, 13.6
Chlordane	21	26	1.7	0.9, 3.2	12	16	1.6	0.7, 3.6
Copper acetoarsenate	36	63	1.3	0.8, 2.0	30	54	1.2	0.7, 2.0
DDT	57	75	1.7	1.2, 2.6	45	57	1.8	1.1, 2.7
Diazinon	27	39	1.5	0.9, 2.5	14	12	2.6	1.2, 5.9
Dieldrin	17	26	1.4	0.7, 2.8	10	13	1.9	0.8, 4.4
Fonofos[b]	15	30	1.1	0.6, 2.1				
Heptachlor	25	43	1.3	0.7, 2.2	14	25	1.3	0.6, 2.6
Lindane	21	23	2.0	1.0, 3.7	14	15	2.2	1.0, 4.7
Malathion	21	30	1.5	0.8, 2.7	11	9	2.9	1.1, 7.4
Phorate	21	48	1.0	0.6, 1.7	9	12	1.8	0.7, 4.5
Turbufos[b]	15	36	0.9	0.5, 1.7				
Toxaphene	10	13	1.5	0.6, 3.5	6	5	2.4	0.7, 8.2

[a] OR relative to nonfarmers, numbering 266 cases and 547 controls. All ORs adjusted for vital status, age, state, cigarette smoking status, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures in a logistic analysis.
[b] No reported use of fonofos or turbufos prior to 1965.

Table 6 *Herbicides: OR and CI for ever having handled specific herbicides, and handled prior to 1965*[a]

Herbicide	Ever handled				Handled prior to 1965			
	No. of cases	No. of controls	OR	CI	No. of cases	No. of controls	OR	CI
Alachlor	57	109	1.2	0.8, 1.7				
Atrazine	59	108	1.2	0.9, 1.8	19	32	1.3	0.7, 2.5
Bentazon	18	45	0.9	0.5, 1.6				
Butylate	22	44	1.2	0.7, 2.1	1	6	0.5	0.1, 4.3
Chloramben	39	70	1.3	0.8, 2.0	16	19	2.0	1.0, 4.0
Cyanazine	27	64	0.9	0.6, 1.5				
2,4-D	115	227	1.2	0.9, 1.6	86	153	1.3	0.9, 1.8
Dicamba	28	57	1.2	0.7, 2.0	7	7	2.8	0.96, 8.1
Glyphosate	26	49	1.1	0.7, 1.9				
Metribuzen	12	38	0.7	0.4, 1.4				
Popachlor	13	25	1.2	0.6, 2.5				
2,4,5-T	25	48	1.2	0.7, 1.9	13	18	1.7	0.8, 3.6
Trifluralin	45	87	1.2	0.8, 1.8	14	23	1.5	0.8, 3.1

[a] OR relative to nonfarmers, numbering 266 cases and 547 controls. All ORs adjusted for vital status, age, state, cigarette smoking status, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures in a logistic analysis.

insecticides for application on crops (Table 5), significant risk elevations were observed for DDT and lindane; and for use prior to 1965, carbaryl, DDT, diazinon, lindane, and malathion. We also calculated the OR for pre-1965 personal handling, mixing, or application of specific insecticides that could have been used on either animals or crops. Elevated risk was found for carbaryl (OR = 2.8, CI = 1.0–7.7; 9 cases), chlordane (OR = 1.8, CI = 1.1–3.1; 30 cases); DDT (OR = 1.4, CI = 1.0–1.8; 93 cases), dieldrin (OR = 2.2, CI = 1.0–4.9; 13 cases), lindane (OR = 1.7, CI = 1.1–2.7; 47 cases), and malathion (OR = 1.8, CI = 1.1–3.1; 31 cases). No significant risk elevations were observed for ever handling, mixing, or applying specific herbicides (Table 6). Among the herbicides marketed prior to 1965, use before 1965 of chloramben and dicamba was significantly associated with total NHL. The risk for *ever* having handled, mixed, or applied phenoxy acids was 1.2 for 2,4-D and for 2,4,5-T. For use and handling of these 2 chemicals prior to 1965, risks were 1.3 and 1.7, respectively. Analyses restricting the "exposed" group to farmers who reported that they had not used protective equipment in the handling of specific pesticides were conducted for pesticides showing associations with NHL in previous analyses, either for *ever* handling the pesticide, or

Table 7 *Pesticides ever handled with and without protective clothing or equipment: OR and CI for selected pesticides*[a]

Pesticide	Ever handled[b]				Handled without protective equipment			
	No. of cases	No. of controls	OR	CI	No. of cases	No. of controls	OR	CI
Animal insecticides								
Chlordane	31	38	1.7	1.0, 2.9	24	30	2.2	1.2, 4.2
DDT	79	149	1.2	0.9, 1.7	72	127	1.3	0.9, 1.8
Lindane	55	90	1.4	1.0, 2.1	45	67	1.6	1.0, 2.4
Malathion	43	67	1.3	0.9, 2.1	33	52	1.4	0.8, 2.2
Nicotine	31	47	1.5	0.9, 2.5	24	41	1.4	0.8, 2.3
Crop insecticides								
Carbaryl	21	26	1.7	0.9, 3.1	22	22	2.2	1.2, 4.2
Chlordane	21	26	1.7	0.9, 3.2	17	18	2.1	1.1, 4.3
DDT	57	75	1.7	1.2, 2.6	48	54	2.0	1.3, 3.1
Diazinon	27	39	1.5	0.9, 2.5	17	22	1.7	0.9, 3.2
Lindane	21	23	2.0	1.0, 3.7	16	14	2.6	1.2, 5.5
Malathion	21	30	1.5	0.8, 2.7	14	16	1.9	0.9, 4.1
Herbicides								
Chloramben	39	70	1.3	0.8, 2.0	31	44	1.7	1.1, 2.8
2,4-D	115	227	1.2	0.9, 1.6	89	175	1.2	0.9, 1.7
Dicamba	28	57	1.2	0.7, 2.0	19	32	1.4	0.8, 2.5
2,4,5-T	25	48	1.2	0.7, 1.9	18	30	1.4	0.7, 2.5

[a] OR relative to nonfarmers, numbering 266 cases and 547 controls. All ORs adjusted for vital status, age, state, cigarette smoking status, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures in a logistic analysis.
[b] Results for ever having used or handled these pesticides (with or without protective clothing or equipment) are from Tables 4, 5, and 6.

Table 8 *Selected pesticides first used prior to 1965: OR and CI for residents of Iowa and Minnesota, respectively*[a]

Pesticide	Iowa				Minnesota			
	No. of cases	No. of controls	OR	CI	No. of cases	No. of controls	OR	CI
Animal insecticides								
Chlordane	15	15	2.2	1.0, 4.8	7	7	2.2	0.8, 6.6
DDT	27	67	0.9	0.5, 1.5	41	56	1.7	1.1, 2.7
Lindane	33	47	1.5	0.9, 2.5	7	8	1.9	0.6, 5.5
Malathion	16	21	1.5	0.7, 3.1	9	9	2.0	0.7, 5.3
Nicotine	15	16	2.1	1.0, 4.6	13	20	1.4	0.7, 2.9
Crop insecticides								
Carbaryl	5	3	3.5	0.8, 15.5	2	1	4.9	0.4, 56
Chlordane	8	13	1.3	0.5, 3.3	4	3	3.1	0.7, 14.7
DDT	28	40	1.5	0.9, 2.6	17	17	2.3	1.1, 4.8
Diazinon	10	10	2.4	0.9, 6.2	4	2	3.8	0.7, 22
Lindane	9	13	1.4	0.6, 3.5	5	2	6.5	1.2, 35
Malathion	6	6	2.1	0.6, 7.0	5	3	4.1	0.9, 18.6
Herbicides								
Chloramben	7	10	1.6	0.6, 4.4	9	9	2.6	1.0, 6.8
2,4-D	51	96	1.2	0.8, 1.9	35	57	1.4	0.9, 2.3
Dicamba	4	5	2.1	0.6, 8.1	3	2	3.9	0.6, 24
2,4,5-T	9	16	1.2	0.5, 2.9	4	2	4.7	0.8, 26.4

[a] OR relative to nonfarmers, numbering 120 cases and 255 controls in Iowa, and 146 cases and 292 controls in Minnesota. All ORs adjusted for vital status, age, cigarette smoking status, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures in logistic analyses.

handling it prior to 1965, as well as for the 2 most commonly used phenoxyacetic acid herbicides (Table 7). Among insecticides used on livestock, all except one (nicotine) showed a stronger association among those who did not use protective equipment than for the entire exposed group. All of the crop insecticides showed stronger risk among farmers who did not use protective gear, as did 3 of 4 herbicides (the OR for 2,4-D remained the same).

We also calculated odds ratios for pre-1965 use and handling of selected pesticides separately for respondents from Iowa and Minnesota (Table 8). The pesticides with OR greater than 1.5 in both states were: the insecticides chlordane, lindane, and malathion applied to livestock; the insecticides carbaryl, DDT, diazinon, and malathion applied to crops; and the herbicides chloramben and dicamba. Findings from analyses of pre-1965 use of specific pesticides that included only direct respondents resembled results of OR calculations that included both direct and proxy respondents.

There was minimal evidence for confounding of results for any single pesticide by exposure to pesticides belonging to other chemical families. This was indicated by little change in OR when a variable for exposure to any of several pesticide families was added to logistic regression models for individual pesticides (for use, handling, or applying prior to 1965) that had shown statistically significant results.

DISCUSSION

We conducted this population based case-control study of NHL in 2 states with intensive agricultural activity to investigate risk factors for NHL among farmers. As compared with nonfarmers, farmers were at slightly elevated risk of NHL (OR = 1.2), in agreement with some population surveys (13, 14) and other case-control studies of NHL or CLL (3, 15–25), based on mortality records or incident cases. Other population surveys have found no risk elevation for farmers (26–31); some case-

control studies have observed elevated, though nonsignificant, risk elevations (32–36); and others, null or slightly lower risk for NHL (37–41). Among the studies that have found statistically significant positive associations for NHL or CLL among farmers, the risk ratios have generally been in the range of 1.2 to 1.9. In this study, the cell type with the strongest association with farming was small lymphocytic lymphoma (OR = 1.4), a NHL subtype morphologically similar to CLL. Farming occupation has been linked to CLL risk in several case-control studies, including the study parallel to this one (3) and others (21–23), with OR in the range of 1.4 to 1.8.

We found no striking differences or trends in NHL risk by several measures of the time or intensity of farming, including first year farmed, total duration of farming, or average number of acres farmed. However, the association among men who were farming after 1949 was slightly stronger than for those who stopped earlier. In addition, the NHL risk among farmers of midsized farms (average farm size of 120–199, or 200–319 acres) was slightly higher (OR of 1.3 and 1.2) than for men who farmed more acreage (OR of 1.1). This is consistent with findings from Saskatchewan, where NHL risk was higher among farmers of <300 acres than larger establishments (27). The findings that relate temporal period of farming and average farm size with NHL risk are consistent with associations with chemical pesticide use. There were increases in the use of agricultural chemicals after World War II (42, 43), and major usage occurred after 1950, increasing the opportunity for exposure among individuals who farmed more recently.

We observed no meaningful elevation or consistent trends in risk with average acreage of a number of major crops (including corn, wheat, and soybeans) or the average or maximum number of several types of livestock (including dairy cows, beef cattle, hogs, and chickens).

There were small elevations in risk for NHL among farmers who ever used pesticides, or who used pesticides belonging to very broad groups according to usage, including livestock insecticides, crop insecticides, herbicides, and fungicides. However, larger risks were observed when more specific definitions of pesticide exposure were used (*i.e.*, chemical classes or specific chemicals); when risk was measured by whether a farmer had personally handled, mixed, or applied the pesticides; and among farmers who did not use protective clothing or equipment. Among chemical classes of insecticides used on livestock, we found statistically elevated risk for the grouped chlorinated hydrocarbons, natural products, and organophosphates. Among the chlorinated hydrocarbons, larger OR occurred for the grouped cyclodienes (chlordane and dieldrin) and among the organophosphates, greater risks occurred for halogenated aromatics (chlorphyrifos, coumaphos, crufomate, ronnel, and tetrachlorvinphos). Among crop insecticide families that we evaluated, only the chlorinated hydrocarbons showed statistically elevated OR. No single family of herbicides was associated with NHL risk.

We found significantly elevated risks, with OR of 1.5 or more, for personal handling, mixing, or application of several individual insecticides, including carbaryl, chlordane, DDT, diazinon, lindane, malathion, and nicotine. Dieldrin, dichlorvos, famphur, and toxaphene also showed notable, though nonsignificant risk elevations. Patterns of risk from 3 other analyses were consistent with the hypothesis of an etiological role for these insecticides. Risk of NHL was greater for most chemicals among farmers who first used these chemicals before 1965 (15–18 years before diagnosis) and among those who did not use protective equipment, and there was notable consistency in the risk estimates from the 2 states. Associations with specific chemicals were not confounded by exposure to families of other pesticides. Other investigations of lymphopoietic cancer and pesticide exposure have also noted a rise in risk with increasing time since first exposure, suggesting the need for longer latency (3, 33, 39).

Three of the 4 chemicals that showed excesses, and are used both on crops and livestock, had larger OR associated with crops (DDT, lindane, and malathion), while for chlordane the OR was greater for use on animals. This contrasts with the parallel study of leukemia in Iowa and Minnesota, in which we generally found higher risks for chemicals used as animal insecticides (3).

Several insecticides associated with NHL in this study (chlordane, dieldrin, DDT, lindane, and toxaphene) are classified as having sufficient or limited evidence for carcinogenicity in animals by the International Agency for Research on Cancer (42). For some other insecticides associated here with NHL (carbaryl and malathion), information for evaluation is insufficient. With the exception of phenoxyacetic acid herbicides, the epidemiological literature regarding cancer risks from specific pesticide exposures is quite limited. Cancer risks have been assessed in cohort studies of insecticide manufacturing workers and applicators (44–55), but these are generally not useful in evaluating the risk of NHL associated with specific pesticides. In most cohort studies, the specific pesticide exposures experienced by individuals were not well documented, or the effects of multiple exposures could not be disentangled. In addition, most cohorts were too small or the follow-up period too brief to adequately assess risk of NHL. Hematopoietic and lymphopoietic cancers, however, have been elevated in some of these studies. In Northern Italy, incident lymphatic tissue cancers were in excess among agriculture and forestry workers licensed to use pesticides (Standardized Incidence Ratio = 1.4, CI = 1.0–1.9; 45 cases), especially among persons applying pesticides to only arable land (Standardized Incidence Ratio = 1.8, CI = 1.2–2.5; 31 cases) (47). Excess NHL risk was found in a cohort of United States grain industry workers (Standardized Mortality Ratio = 149), and within the cohort, a nested case-control study showed flour millers to be at especially high risk (OR = 4.2, CI = 1.2–14.2) (44). A variety of insecticides has been used in the grain industry, including DDT, hydrogen cyanide, ethylene dibromide, phosphine, and carbon tetrachloride. Among pesticide manufacturing workers exposed primarily to DDT (740 persons, 17,186.9 person-years of follow-up), no excess of all lymphopoietic and hematopoietic cancer was found (3 observed, 2.40 expected) (51).

Six case-control studies, 4 of NHL (19, 38, 39, 56) and 2 of CLL (3, 17), provide limited information on risk associated with exposure to specific insecticides or insecticide families. A third case-control study of CLL found a nonsignificant risk elevation among persons exposed to "pesticides," not further defined (57). Exposure to DDT was linked with CLL in 2 case-control studies (3, 17), and associated with NHL in 2 others (19, 56), with OR between 1.5 and 6.1. In the 2 other case-control studies, either DDT was not reported separately (39) or no association was found (0 exposed cases, 3 exposed controls) (38). In the current study, we found an association with ever handling, mixing, or applying DDT that was stronger for its use on crops than on livestock, and that was more pronounced for first exposure prior to 1965 than later. We found elevated

risk for pre-1965 application of DDT to crops in both Iowa and Minnesota.

The grouped chlorinated hydrocarbon insecticides were associated with small (nonsignificant) risk elevations for NHL in a Nebraska study (58). Other than DDT, the only chlorinated hydrocarbons reported specifically in other case-control studies are chlordane and lindane. Chlordane was significantly associated with NHL risk in Nebraska (OR = 2.1), and nonsignificantly in Washington State (OR = 1.61) (19). Lindane, another organochlorine, was significantly associated here with NHL when used either on crops or animals, and risks were elevated in both Iowa and Minnesota. Lindane has also been associated with NHL in a study from Kansas (2).

Risks associated with organophosphate exposure, either collectively, or as individual chemicals, were reported for CLL in the parallel study of leukemia in Iowa and Minnesota (3) and for NHL in a study with similar methods from Eastern Nebraska (39, 58). In the Nebraska study, the OR for organophosphate exposure study was 1.9 (OR = 1.1–3.1), and risk increased with days/year of use to OR = 3.1 for 21+ days. In Nebraska, 2 organophosphates, diazinon and malathion, showed significant positive associations with NHL, similar to our findings. In the parallel leukemia study in Iowa and Minnesota (3), elevated risk was found for CLL among farmers exposed to dichlorvos as an animal insecticide (OR = 2.2, CI = 1.0–4.6). We found significant associations for the grouped organophosphate insecticides used on livestock (OR = 1.5), especially halogenated aromatic organophosphates (OR = 2.0, CI = 1.1–3.7). The ORs for grouped nonhalogenated aromatic organophosphates used on livestock and crops were also elevated, but not statistically significant. Regarding specific organophosphate insecticides, we observed significant associations of NHL with use of malathion prior to 1965 on both crops and animals, and OR were above 1.5 for both types of application in Iowa and in Minnesota. In addition, we found significant OR for pre-1965 use of diazinon on crops, with comparable risk elevations in the 2 study states. Use of other organophosphates before 1965, including coumaphos and dichlorvos on livestock, and phorate on crops, also were associated with increased risk of NHL, although the 95% confidence interval for each included 1.0.

In the study from Nebraska (58), the carbamate insecticide family was significantly associated with NHL (OR = 1.8). We did not find significant associations with carbamates as a group. However, use of carbaryl prior to 1965 was associated with NHL (OR = 3.8, CI = 1.1–13.6), and risk was elevated in both study areas. However, the number of exposed subjects was small (7 cases, 4 controls).

Phenoxyacetic acid herbicides have been linked to NHL risk in several (19, 33, 39, 56), but not all (38, 59), case-control studies. Excesses have also been noted in 2 phenoxyacetic acid manufacturing cohorts, although few deaths occurred (60, 61). In our data, the risk of NHL associated with *ever* handling, mixing, or applying members of the phenoxy acid herbicide family, or the specific herbicides 2,4-D or 2,4,5-T, was small and about the same as for farmers overall. However, when latency was considered, the association with 2,4,5-T was somewhat stronger. Although our findings are not entirely negative, the risk of NHL with 2,4-D use is considerably weaker than observed in studies of similar design from Kansas and Nebraska (33, 39). Risks here were considerably lower and did not increase with latency or failure to use protective equipment. The reasons for the inconsistencies are not obvious. Use patterns of 2,4-D in Iowa and Minnesota may differ from Kansas or Nebraska. In the latter states, the bulk of 2,4-D is for postemergent application on small grains, whereas in Iowa it may be more frequently used on corn. It is unclear whether this difference affects exposures to farmers. It is also possible that the inconsistencies between this and other studies of 2,4-D are simply due to chance, since random variation in risk estimates among studies is to be expected.

Additional comments on the limitations of this study are warranted. Some associations found here may have arisen due to chance or bias. Numerous comparisons were made, and results must be evaluated in this context and judged against epidemiological rules of causality. Bias in selecting cases or controls was absent since eligibility for the study was unrelated to current or previous status as a farmer or the exercise of particular agricultural practices. However, willingness to participate could have been related to farm residence or occupation as a farmer. The fairly high and similar response rates in cases and controls, however, diminishes the possibility of such bias.

Bias due to differential response or recollection of cases and controls regarding specific pesticide exposure is possible. Such bias is unlikely because at the time interviews were held, respondents and interviewers were not aware of hypotheses regarding specific pesticides. Moreover, we found no excess risk for many pesticides but rather some internal consistency for elevated risk with others, such as some of the chlorinated hydrocarbons and organophosphates.

Nondifferential misclassification of specific pesticide exposures is a more likely source of distortion of risk estimates. For dichotomous measures of exposure, however, this distortion would tend to bias risk estimates toward the null (62) and is unlikely to yield false-positive findings. The effect of nondifferential misclassification on polychotomous measures can be more complex (63). There are many ways in which exposure misclassification may occur in studies of this design (64). Most, however, would yield false-negative findings. More than 90% of the farmers in this study operated one or more farms, in contrast to working as hired help. Most farm operators plan their own pest control operations, personally purchase pesticides, and mix and apply the chemicals themselves. They are thus more likely to remember names of specific chemicals that they used than most other pesticide users. However, when many different chemicals were involved, when their use was several decades in the past, and when the use of particular chemicals was brief or episodic, accuracy in reporting chemical names and the timing of application undoubtedly suffers. Proxy respondents not directly involved in farming operations may have been more prone to inaccurate responses than directly interviewed subjects. Among farmers, proxies responded for 28.9% of cases and 34.2% of controls. Among controls who had farmed, 18.4% of proxies did not know whether crop insecticides had been used, and 17.2% did not know about herbicide use. In contrast, 3.3% of directly interviewed farmers didn't know about crop insecticide use, and 3.1% didn't know about herbicide use. Among the controls who reported insecticide use on crops, DDT use was reported as unknown by 11 of 86 proxies (13%) but only 8 of 233 alive subjects (3.4%), and crop application of malathion was unknown by 16 of 86 proxies (19%) and 7 of 233 living subjects (3.0%). Among controls who ever used herbicides, 2,4-D use was reported as unknown by 9 of 88 proxies (10.2%) and 5 of 256 direct respondents (2.0%). Differential effects on risk estimates due to proxy responses among cases and controls should not occur because we adjusted for

type of respondent in the analysis.

This investigation supports findings from earlier studies that point to an elevated risk of non-Hodgkin's lymphoma among farmers, and our data strongly suggest a relationship with certain pesticide exposures. Interpretation of results regarding individual pesticides is fraught with difficulties, including the problems of interpreting risk of individual factors in the multiple exposure setting of modern agriculture as well as the chance occurrence of finding positive associations with multiple comparisons. Of equal concern is the possibility of missing important associations due to nondifferential exposure misclassification because of difficulties in accurate recall of past pesticide exposures. This would bias risk estimates toward the null. Despite these qualifications, the many internal consistencies of this study and concordance with observations of others support the notion that elevated NHL risk among farmers is associated with exposure to several insecticides, and support the use of protective equipment. The chemicals most strongly associated with risk of NHL were carbaryl, chlordane, DDT, diazinon, dichlorvos, lindane, malathion, nicotine, and toxaphene. Many of these insecticides are still in widespread use today, in the United States or elsewhere, and deserve further epidemiological evaluation.

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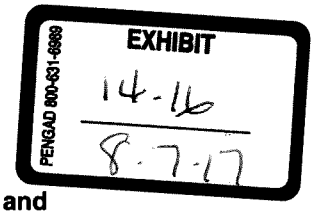
Original Contribution

Reported Residential Pesticide Use and Breast Cancer Risk on Long Island, New York



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Pesticides, common environmental exposures, have been examined in relation to breast cancer primarily in occupational studies or exposure biomarker studies. No known studies have focused on self-reported residential pesticide use. The authors investigated the association between reported lifetime residential pesticide use and breast cancer risk among women living on Long Island, New York. They conducted a population-based case-control study of 1,508 women newly diagnosed with breast cancer between August 1996 and July 1997 and 1,556 randomly selected, age-frequency-matched controls. Comprehensive residential pesticide use and other risk factors were assessed by using an in-person, interviewer-administered questionnaire. Unconditional logistic regression was used to calculate odds ratios and 95% confidence intervals. Breast cancer risk was associated with ever lifetime residential pesticide use (odds ratio = 1.39, 95% confidence interval: 1.15, 1.68). However, there was no evidence of increasing risk with increasing lifetime applications. Lawn and garden pesticide use was associated with breast cancer risk, but there was no dose response. Little or no association was found for nuisance-pest pesticides, insect repellants, or products to control lice or fleas and ticks on pets. This study is the first known to suggest that self-reported use of residential pesticides may increase breast cancer risk. Further investigation in other populations is necessary to confirm these findings.

breast neoplasms; case-control studies; environmental exposure; gardening; housing; pesticides

Abbreviations: CI, confidence interval; LIBCSP, Long Island Breast Cancer Study Project; OR, odds ratio.

The search for environmental factors associated with breast cancer is of great public interest. Pesticides are common environmental exposures that have been implicated in cancer etiology (1–3). Studies of breast cancer have primarily examined pesticide exposures among occupationally exposed individuals and among women in the general population (i.e., those not occupationally exposed) using biologic markers of exposure as well as indirect exposures such as residential proximity to pesticide exposure sources. However, to our knowledge, no investigation of lifetime, self-reported residential pesticide use has been published.

Numerous pesticides have shown carcinogenicity of varying levels (4–6). They have also been found to be genotoxic, tumor promoters, immunotoxic, and estrogenic (1). Organochlorine pesticides, which include dichlorodiphenyltrichloroethane (DDT), have been shown to have both

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estrogenic and carcinogenic properties (1, 7). This biologic plausibility and the fact that long-term exposure to organochlorine pesticides can be inferred from blood or adipose tissue levels account for why they are the most studied pesticide group in relation to breast cancer (1). However, epidemiologic studies have not provided convincing support for an adverse association with biomarkers of organochlorine pesticides (4–8). Many other pesticides commonly used in and around the home may have the potential to influence breast cancer risk but have not yet been studied. The use of biomarkers for many of these pesticides is limited since they may be short term or not available.

Therefore, a population-based, case-control study of the environment and breast cancer was conducted that assessed not only blood levels of organochlorine pesticides (9) but also a wide range of residential pesticide exposures through the use of an in-person, interviewer-administered questionnaire. The organochlorine pesticide biomarker investigation in the Long Island Breast Cancer Study Project (LIBCSP) population did not reveal an association with breast cancer risk (10). The analyses presented here investigate the relation between self-reported lifetime residential pesticide use and breast cancer risk among women living on Long Island, New York.

MATERIALS AND METHODS

Study population

Details of LIBCSP have been described previously (9). In brief, women who were residents of either Nassau or Suffolk Counties in New York State, newly diagnosed with invasive or in situ breast cancer between August 1, 1996, and July 31, 1997, were eligible as cases. Women residents of the same two counties during the same time period who had not been diagnosed with breast cancer were randomly selected as controls. Controls were frequency matched by 5-year age group to the expected age distribution of the cases. Controls were selected through random digit dialing if they were less than 65 years of age (screener response rate for random digit dialing = 77.9 percent) and were selected from Centers for Medicare and Medicaid Services (formerly the Health Care Financing Administration) rosters if 65 years of age or older. At the reference date (date of diagnosis for cases and date of identification for controls), women less than 65 years of age were required to have a residential telephone, and women 65 years of age or older were required to be Medicare participants.

Of 2,030 identified, eligible cases, 193 (9.5 percent) were not contacted because of physician refusal. Of those remaining, 1,508 cases (82.1 percent) were interviewed. Of 2,481 eligible controls, 1,556 (62.8 percent) completed the interview. For women less than 65 years of age, response rates were 89 percent for cases and 76 percent for controls. Among women 65 years of age or older, response rates were 72 percent for cases and 43 percent for controls. The most common reasons for both case and control nonparticipation were refusal and illness. The institutional review boards of all participating institutions approved the study protocol, and all participants provided informed consent.

Data collection

Trained interviewers administered a structured questionnaire that collected information on reproductive and medical history, occupational and residential history, and lifestyle and demographic characteristics. Detailed information on pesticide use, a primary focus of the study, was also obtained (http://epi.grants.cancer.gov/documents/LIBCSP/projects/ques/sectc.pdf). Participants were queried about pesticide use in and around their homes as well as their use of insect repellants, lice control products on themselves and others, and flea and tick control products on their pets. Usage patterns for seven lawn and garden pest categories and eight nuisance-pest categories were ascertained. For a particular pest category, participants identified all persons who applied the products, the various types of products applied, and the average yearly frequency of application and the number of years the products had been used. The number of lifetime applications for each individual category was derived by multiplying yearly application frequency by years of use.

Overall pesticide use (the sum of lifetime applications of all 15 categories), the two combined groups (lawn and garden and nuisance pest), and each of the 15 individual categories were considered in the analyses. Lifetime applications were categorized based on the control distribution. Women in the lowest quintile of overall pesticide use constituted the reference group in analyses of overall pesticide use. For the combined group analyses, women reporting no pesticide use for all individual pest categories within a combined group were the reference group. In this paper, individual category results are presented dichotomized as ever/never use because trends in breast cancer risk within each category were not observed. The use of two different combined group reference categories created reasonably sized groups of women who were unexposed regarding approximately half of the individual pest categories, which reduced exposure misclassification and provided more interpretable odds ratios because they were calculated by using the same reference group for a large number of categories. When odds ratios for individual pest categories were calculated based on all women who had not used pesticides for the category as the reference group, odds ratios were attenuated toward the null.

Patterns of pesticide use were examined in two ways: by applicator (self only/professional only/other or multiple applicators) and by product type (spray only/powder only/liquid only/other product or multiple types). Patterns of use could not be examined for two individual lawn and garden categories (other types of pesticides used outdoors and chemicals used on indoor plants) because of the infrequency of such pesticide use.

The analyses presented are based on 1,505 cases and 1,553 controls because three cases and three controls did not provide any pesticide information. To calculate total lifetime pesticide applications for women who reported pesticide use for an individual pest category but for whom data on use patterns were missing, the median value for the specific pattern variable was used (e.g., median years of weed killer use was used for women without reported duration of use); exclusion of these women did not materially change

estimates of association with lifetime applications. For all other analyses, women for whom data were missing were excluded.

Statistical analysis

Unconditional logistic regression was used to calculate odds ratios and 95 percent confidence intervals. Lifetime applications were entered into models as indicator variables for each quintile above the lowest. Characteristics assessed as possible confounders included race, marital status, religion, household income, age at menarche, parity, age at first birth, lactation, menopausal status, oral contraceptive use, hormone replacement therapy use, first-degree family history of breast cancer, history of benign breast disease, body mass index (weight in kilograms divided by height in meters squared) at the reference age and at age 20 years, alcohol use, smoking status, and physical activity. None of these factors were included in the final model because none resulted in at least a 10 percent change in the beta coefficient for the pesticide variables (11, 12). In addition to controlling all models for age, adjustment for education (defined as highest educational level attained: ≤high school graduate/some college/college graduate/postcollege) was included to control for possible confounding by socioeconomic status. Note that adjustment for education did not result in any substantial changes in the estimates of effect. Finally, models assessing one combined group (e.g., lawn and garden) were adjusted for the use of the other combined group (e.g., nuisance pests).

RESULTS

An increased breast cancer risk was associated with lifetime pesticide application for all pest groups combined (age- and education-adjusted odds ratio (OR) = 1.39, 95 percent confidence interval (CI): 1.15, 1.68 for quintiles 2–5 vs. quintile 1; table 1). However, there was no indication of increasing risk with increasing quintile of lifetime applications. Compared with never use of any lawn and garden pesticides, use of pesticides for these types of pests was associated with an elevated breast cancer risk (table 1). Adjustment for lifetime applications of nuisance-pest pesticides did not substantially change risk estimates. Although the age-adjusted odds ratio for ever use of combined nuisance-pest pesticides was elevated when compared with that for women who never used any pesticides for nuisance pests (age-adjusted OR = 1.20, 95 percent CI: 0.88, 1.63), further adjustment for use of lawn and garden pesticides reduced the odds ratio toward the null. No dose-response associations were observed for either combined group, and additional adjustment for education did not affect any odds ratios.

Individual lawn and garden categories

Ever use of pesticides for nearly all of the individual lawn and garden categories was associated with increased breast cancer risk (table 2). In general, within each category, no dose response was observed (data not shown). Little variation in breast cancer risk was observed for individual categories of lawn and garden pesticide application when classified according to the person who applied them (table 3). Women who exclusively self-applied lawn and garden pesticides were at a moderately increased risk of breast cancer (e.g., lawn insecticides OR = 1.56, 95 percent CI: 1.01, 2.43; chemicals for insects or diseases of outdoor plants OR = 1.58, 95 percent CI: 1.12, 2.22). However, these risk estimates were in the same range as those for pesticide use without consideration of applicator and were not generally different from those observed for women who had either professionals exclusively apply these pesticides (e.g., lawn insecticides OR = 1.41, 95 percent CI: 1.31, 1.77) or others perform the application (e.g., lawn insecticides OR = 1.32, 95 percent CI: 1.05, 1.67).

Overall, examination of breast cancer risk associated with use of different product types in the individual lawn and garden categories did not reveal any specific types as being associated with risk different from that observed without categorization by product type (table 3). For lawn insecticide application, exclusive use of the liquid form was associated with higher risk (OR = 1.77, 95 percent CI: 1.12, 2.77) than other product types. Women who used a combination of product types or some other product type for outdoor plant pest problems were at higher risk than women who used spray only (OR = 1.83, 95 percent CI: 1.27, 2.64).

Individual nuisance-pest categories

Lifetime applications of the individual categories of nuisance-pest pesticides did not appear to be related to breast cancer risk (table 2). Similarly, breast cancer risk was not elevated for nuisance-pest pesticide application when categorized by the person who performed the application or when classified by product types; the vast majority of the odds ratio estimates were at or near the null value (data not shown).

Subgroup analyses

We examined whether the relation of residential pesticide use and breast cancer varied within different subgroups of participants (data not shown). When the population was stratified by menopausal status (pre- vs. post-) or by length of residency (≥15 or <15 years in the current home) or was restricted to participants less than age 65 years, the associations between pesticide use and breast cancer risk in the subgroups were not considerably different from those for the entire sample. The relation was also examined according to stage of disease, that is, invasive cases only (84.4 percent) and in situ cases only. Associations for the invasive cases were nearly identical to those observed for all cases combined. Among in situ cases, the findings for breast cancer risk and use of pesticides for nuisance pests were similar to those found for invasive cases. However, the associations for all pest groups combined and the lawn and garden pest group were stronger for some, but not all, of the quantiles of use (OR = 1.91, 95 percent CI: 1.17, 3.13; OR = 1.97, 95 percent CI: 1.21, 3.21; OR = 2.03, 95 percent CI: 1.25, 3.30; OR = 1.23, 95 percent CI: 0.72, 2.08 for quartiles 1–4, respectively, vs. never use of lawn and garden pesticides).

TABLE 1. Adjusted odds ratios and 95% confidence intervals for breast cancer, according to lifetime applications of pesticides, among 3,058 women in Nassau and Suffolk Counties, New York, 1996–1997

	Lifetime applications (no.)			Cases (no.)	Controls (no.)	Adjusted for age, education, and other combined pest group*	
	Minimum	Median	Maximum			OR	95% CI†
All pest groups combined							
Quintile 1 (reference)	0	6	16	230	310	1.00	Reference
Quintiles 2–5				1,275	1,243	1.39	1.15, 1.68
Quintile 2	17	32	50	298	315	1.30	1.03, 1.64
Quintile 3	51	77	111	313	307	1.39	1.10, 1.76
Quintile 4	112	159	242	347	311	1.49	1.19, 1.88
Quintile 5	243	482	20,834	317	310	1.37	1.08, 1.72
Lawn and garden combined group‡							
Never used lawn and garden pesticides				240	305	1.00	Reference
Ever used lawn and garden pesticides				1,254	1,231	1.34	1.11, 1.63
Quartile 1	1	6	15	282	303	1.25	0.98, 1.59
Quartile 2	16	28	44	341	313	1.44	1.14, 1.82
Quartile 3	45	70	108	301	307	1.30	1.02, 1.64
Quartile 4	109	180	20,820	330	308	1.38	1.09, 1.75
Nuisance-pest combined group§							
Never used nuisance-pest pesticides				100	117	1.00	Reference
Ever used nuisance-pest pesticides				1,404	1,436	1.07	0.80, 1.42
Quartile 1	1	4	8	290	364	0.88	0.64, 1.20
Quartile 2	9	16	29	338	358	1.07	0.78, 1.46
Quartile 3	30	53	96	393	357	1.20	0.88, 1.65
Quartile 4	97	223	9,608	383	357	1.16	0.85, 1.58

* Odds ratios (ORs) for the category of all pest groups combined were adjusted for age and educational status only (≤high school graduate/some college/college graduate/postcollege).
† CI, confidence interval.
‡ Data for 11 cases and 17 controls were missing.
§ Data for one case were missing.

It is important to note that these latter measures were less stable because of the reduced sample size.

Insect repellants, lice control products, and flea and tick products used on pets

Breast cancer risk was not associated with frequent or long-term use of insect repellants (OR = 0.89, 95 percent CI: 0.60, 1.31 for ≥20 years vs. never use) or with use of lice control products (OR = 0.86, 95 percent CI: 0.71, 1.04 for use ≥2 times vs. never use). Likewise, no increased risk of breast cancer was associated with the use of flea and tick products on pets, when examined by frequency of application (OR = 1.08, 95 percent CI: 0.87, 1.33 for use ≥30 times vs. never use), type of product used, or person who applied the product (data not shown).

DISCUSSION

Overall, women who reported the highest (quintiles 2–5 combined) pesticide use in and around their homes had more than a 30 percent increased risk of breast cancer relative to women who reported the lowest use. Lifetime applications and patterns of use of pesticides for nuisance pests were consistently observed to have little or no association with breast cancer risk when examined as either a combined group or by individual categories. On the other hand, use of the combined lawn and garden pesticides as well as the majority

TABLE 2. Adjusted odds ratios and 95% confidence intervals for breast cancer, according to lifetime applications of pesticides for individual categories of pests,* among 3,058 women in Nassau and Suffolk Counties, New York, 1996–1997

Ever used pesticides for individual categories of pests	Cases (no.)	Controls (no.)	Adjusted for age, education,† and other combined pest group	
			OR‡	95% CI§
Never used any lawn and garden pesticides	240	305	1.00	Reference
Weeds	1,109	1,083	1.43	1.17, 1.75
Lawn insects	799	766	1.48	1.20, 1.82
Insects or diseases of trees	539	514	1.46	1.17, 1.81
Pests in vegetable or fruit gardens	298	259	1.58	1.24, 2.01
Insects or diseases of outdoor plants	261	232	1.54	1.20, 1.98
Any other type of outdoor pest	70	48	1.13	0.86, 1.49
Insects or diseases of indoor plants	121	112	1.48	1.08, 2.02
Never used any nuisance-pest pesticides	100	117	1.00	Reference
Ants, carpenter ants, or cockroaches	1,160	1,171	1.06	0.79, 1.42
Bees or wasps	599	610	1.05	0.77, 1.43
Flies or mosquitoes	328	310	1.12	0.81, 1.55
Moths, silverfish, or caterpillars	388	352	1.19	0.87, 1.64
Mice, rats, gophers, or moles	246	268	1.02	0.73, 1.42
Fleas or ticks, except on pets	377	394	1.06	0.91, 1.23
Termites	731	712	1.10	0.81, 1.48
Any other type of pest in the home	50	52	1.06	0.65, 1.71

* For all individual categories, some data were missing.

† Educational status: ≤high school graduate/some college/college graduate/postcollege.

‡ Each odds ratio (OR) was derived from a separate model. To create a common combined-pest-category reference group, a set of three mutually exclusive indicator variables was used: never used combined-pest-category pesticides (reference), used pesticides for individual categories of pests, used combined-pest-category pesticides but not for individual categories of pests.

§ CI, confidence interval.

of the individual pest categories in this group consistently showed an elevation in breast cancer risk. Finally, use of insect repellants, lice control products, or pet flea and tick control products was not related to breast cancer risk.

Interpretation of these findings in the context of other studies is limited because, to our knowledge, there are no published studies of self-reported residential pesticide use and breast cancer. A recent review of the numerous studies that have examined biologic markers of various organochlorine pesticides concluded that there was little support for a positive association between dichlorodiphenyldichloroethene or dichlorodiphenyltrichloroethane and breast cancer risk (13). Our own investigation of organochlorine levels among the LIBCSP population did not find increased breast cancer risk (10). The absence of an association for treatment of the home for termites in this analysis and in an earlier Long Island study that examined reported termiticide use (14) agrees with the lack of a breast cancer association with chlordane in the LIBCSP population (10). The observed null findings for lice control products is supported by the observed lack of association in the majority of epidemiologic studies that examined beta-hexachlorocyclohexane, a contaminant of lindane (gamma-hexachlorocyclohexane), and breast cancer risk (15–17).

Studies of agricultural workers, an occupational group with a high probability of pesticide exposure, have not shown an increased breast cancer risk among women (18–30). Many of the studies suffered from small sample size or lacked confounder information. Furthermore, occupation is a nonspecific indicator of pesticide exposure, possibly biasing results toward the null. In a recent study, breast cancer in farmers' wives was associated with their husbands' use of 2,4,5-trichlorophenoxypropionic acid, 2,4,5,-trichlorophenoxyacetic acid, and captan (31), pesticides that could have been used on Long Island. Thus, these findings support our observation of increased breast cancer risk and use of pesticides for weeds and fruit tree pests.

Other classes of popular pesticides have replaced organochlorines over the years in a continuing search for less toxic, but effective agents. Organophosphates were formerly among the most widely used household pesticides, accounting for about 22 percent of nonagricultural usage in 2001, so that many women in our study would almost certainly have been exposed in the past. However, because of health concerns, two major organophosphate pesticides, chlorpyrifos (widely used in lawns and against termites—the active ingredient in Dursban (Dow Agrosciences, LLC, Indianapolis, Indiana)) and diazinon, were restricted or banned for residential use after 2001 by the Environmental Protection Agency. Dichlorvos, formerly used in home foggers and aerosols and to control insects in passenger aircraft, is now classified by the Environmental Protection Agency as a "Restricted Use Pesticide" and may be purchased legally by certified applicators only. It is still used in no-pest strips, pet collars, and kennels. Dichlorvos has an Environmental Protection Agency carcinogenicity classification of B2 (probable human carcinogen (32)) and a rating of 2B (possibly carcinogenic to humans) from the International Agency for Research on Cancer. Organophosphates are mostly nonestrogenic, but mixtures of several organophosphates were found to affect birth weight and fetal viability. Chlorpyrifos was regarded as nonestrogenic until recently, when two studies showed possible evidence of weak estrogenicity (33, 34).

Carbamates, another class of widely used insecticides, include the Sevin (Aventis CropScience, Inc., Strasbourg, France) brand of carbaryl. Since Dursban was banned, it has become one of the most popular brands of carbaryl insecticides for home garden use. Carbaryl currently has a carcinogenicity rating of group III (unclassifiable as to human carcinogenicity) from the International Agency for Research on Cancer, although one study has reported an increased risk

TABLE 3. Adjusted odds ratios and 95% confidence intervals for breast cancer, according to lifetime applications of pesticides, person who applied the pesticides, and type of lawn and garden pesticide product in individual categories,* among 3,058 women in Nassau and Suffolk Counties, New York, 1996–1997

Use of pesticides for individual lawn and garden pest problems	Person who applied the pesticides	Cases (no.)	Controls (no.)	Adjusted†		Type of product applied	Cases (no.)	Controls (no.)	Adjusted†	
				OR‡	95% CI‡				OR	95% CI
Never used any lawn and garden pesticides		240	305	1.00	Reference		240	305	1.00	Reference
Weeds	Self only	101	110	1.21	0.88, 1.68	Spray only	292	300	1.30	1.02, 1.65
	Professional only	363	348	1.36	1.08, 1.71	Powder only	290	298	1.30	1.02, 1.65
	Other§	640	623	1.36	1.10, 1.67	Liquid only	77	73	1.40	0.97, 2.03
						Other¶	437	408	1.43	1.14, 1.79
Lawn insects	Self only	51	44	1.56	1.01, 2.43	Spray only	197	205	1.32	1.01, 1.72
	Professional only	402	373	1.41	1.13, 1.77	Powder only	193	195	1.38	1.06, 1.81
	Other	336	340	1.32	1.05, 1.67	Liquid only	53	40	1.77	1.12, 2.77
						Other	340	313	1.49	1.18, 1.88
Insects or diseases of trees	Self only	15	30	0.67	0.35, 1.29	Spray only	426	418	1.40	1.12, 1.75
	Professional only	372	343	1.45	1.15, 1.83	Powder only	0	0		
	Other	148	140	1.42	1.06, 1.9	Liquid only	25	25	1.41	0.78, 2.53
						Other	83	68	1.69	1.17, 2.44
Pests in vegetable or fruit gardens	Self only	87	85	1.41	0.99, 1.99	Spray only	115	94	1.64	1.18, 2.27
	Professional only	14	8	2.29	0.94, 5.58	Powder only	107	97	1.50	1.08, 2.09
	Other	195	166	1.56	1.18, 2.04	Liquid only	7	9	1.13	0.41, 3.11
						Other	68	59	1.60	1.08, 2.38
Insects or diseases of outdoor plants	Self only	101	86	1.58	1.12, 2.22	Spray only	127	107	1.58	1.16, 2.17
	Professional only	49	37	1.79	1.12, 2.84	Powder only	31	47	0.91	0.56, 1.49
	Other	106	107	1.29	0.93, 1.78	Liquid only	8	12	0.93	0.37, 2.33
						Other	91	66	1.83	1.27, 2.64

* For all individual categories, some data were missing.
† All models were adjusted for age, education, and combined-nuisance-pest pesticide use.
‡ OR, odds ratio; CI, confidence interval.
§ Any combination of appliers or some person other than self or professional only.
¶ Any combination of product types or some type other than spray, powder, or liquid only.

of non-Hodgkin's lymphoma in farmers who used this pesticide (35). Estrogenicity of carbamates has not been extensively investigated, although there is one report of inhibition of 17β-estradiol and progesterone activity in human breast and endometrial cancer cells (36).

Synthetic pyrethroids, common residential insecticides, have been found to possess estrogenic and antiprogestagenic properties in human breast cell assays (37, 38). These insecticides could have been included among categories of pesticides used for lawn and garden purposes for which an association with breast cancer was observed, such as problems on fruit trees, in vegetable gardens, and on outdoor as well as indoor plants. However, these insecticides could also have been used for nuisance-pest categories—such as ants, cockroaches, wasps, flies, mosquitoes, moths, silverfish, caterpillars, fleas, ticks, and termites—not associated with increased risks. Another insecticide, rotenone, possibly used by participants on fruit trees, vegetable gardens, and indoor plants, has been shown to cause mammary tumors in rats (39) but has also been shown to have anticancer action in human breast cell culture (40).

In LIBCSP, information was not collected on the time frame of pesticide use. This is a possible limitation because it has been proposed that exposures occurring between menarche and first birth may be the most influential in initiating breast cancer (41). However, we were not able to examine the effect of exposures occurring during a particular period of a woman's reproductive life cycle. Additionally, several of the individual pest categories included pests for which different pesticides would be used, and the same pesticide could have been used for several of the individual categories. For example, chlorpyrifos and diazinon could have been

used for lawn insects as well as to treat ants and cockroaches. Because we did not ascertain the specific chemicals applied for any of the pest problems, we were not able to assign any observed increased risk to the use of a specific pesticide.

Many women reported a combination of pesticide applicators as well as multiple types of products but did not rank the frequency of use of a particular applicator or product type. Thus, distributing lifetime applications according to multiple reported persons or product types was not possible. Assigning an equal distribution (e.g., if both self and professional were reported, half of the lifetime applications would be attributed to self and half to the professional) assumed information beyond what we collected and was most likely unrepresentative. Therefore, to avoid introducing additional exposure misclassification, we categorized women as combination users or exclusive users of an applicator or type. Future investigations of patterns of pesticide use should consider asking women to rank their use of multiple applicators or product types.

The "lifetime applications" variable represents exposure opportunity rather than an actual exposure dose. The detailed information required to calculate a received dose of pesticides was not, nor could it be, ascertained by a questionnaire alone. The categorized lifetime application variable used as the measure of pesticide exposure in these analyses allowed women to be ranked according to their reported use and allowed for exploration of trends. The variable also enabled both reported frequency and number of years of use to be combined into a single exposure variable.

Finding no dose-dependent relation between exposure and breast cancer risk may be due to the imprecision of the exposure measure. It is possible that ever use of pesticides for individual categories was recalled accurately, but the details of use were not. Thus, the ranking of women according to their lifetime applications may have been incorrect, thereby masking any underlying association. Furthermore, the combination of frequency and duration may not be the optimal approach to assess residential pesticide exposure for some of the pesticide categories. For example, the vast majority of women had only one lifetime application of termite control pesticides; thus, frequency and duration have little meaning.

The reliability of self-reported lifetime residential exposure among the participants must be considered. The design of the questionnaire required women to integrate a considerable amount of information over their lifetime, resulting in potentially imprecise reporting of their pesticide exposures. The time interval between exposure and recall, the amount of detail required, age, how memorable the exposure was, and the social desirability of reporting the exposure may all influence the reproducibility of residential pesticide use recall (42). The hypothesis of an adverse association between pesticides and breast cancer was widely publicized, so it is likely that this heightened awareness influenced cases' reporting. This issue could have resulted in recall bias such that the observed associations are biased away from the null. However, data from our study indicate that cases and controls were equally likely to believe that environmental factors were associated with breast cancer etiology. Examination of self-reported beliefs about the cause of breast cancer revealed no case-control differences in the reporting of at least one environmental factor (69 percent vs. 68 percent, respectively), suggesting that recall was not biased differentially.

The study's design lends many strengths to this investigation, including 1) a population-based design, which allows for generalizability of the results to the population of Long Island, New York, as well as similar populations; 2) a large sample size, which increases the power to detect associations; and 3) a comprehensive, in-person, interviewer-administered questionnaire, which provides well-measured confounding variables. Another strength of this study is long-term Long Island residency; nearly 60 percent of both cases and controls were residents of their current home for at least 15 years. For these long-term residents, pest problems they have encountered are likely to be stable over time (e.g., ant problems in the spring, wasp problems in the summer) so that a woman may have performed the same pesticide application routine for many years, making recall easier. When analyses were restricted to these women, the results were essentially the same, which could indicate that reporting of exposures was not differentially affected by length of residency, or it may reflect that the exposure assessment was not sensitive enough to capture any differences that may have existed.

Not all eligible women participated, and response rates varied by age (9). If the pesticide exposure of women who participated is different from that of those women who did not but does not differ by case-control status, then nondifferential misclassification would occur, biasing the estimates of association between pesticide use and breast cancer toward the null. On the other hand, if the response difference between the cases and controls is somehow related to pesticide use, then differential misclassification would occur, and the estimate of the association could be biased in either direction. The results do not appear to be biased because of age-related nonresponse, since results of analyses restricted to participants less than 65 years of age were not materially different.

A great deal of detail about residential and personal pesticide use was ascertained, which allowed investigation of not only overall pesticide use but also patterns of use for specific pesticide groups. However, information on use of actual chemical products was not ascertained because it was found during pilot testing that women could not recall them. This limitation prevents identification of specific pesticides that require further investigation in relation to breast cancer risk.

To our knowledge, our study is the first to suggest that self-reported residential pesticide use may be associated with elevated breast cancer risk. However, the weak association, the absence of a dose response, the lack of support from studies of biologic measures of exposures, and the possibility of chance findings due to multiple comparisons all indicate the uncertain nature of the observed association. Further investigation in other populations is necessary before any definitive conclusions can be reached.

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Exposure to Pesticides as Risk Factor for Non-Hodgkin's Lymphoma and Hairy Cell Leukemia: Pooled Analysis of Two Swedish Case-control Studies

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Increased risk for non-Hodgkin's lymphoma (NHL) following exposure to certain pesticides has previously been reported. To further elucidate the importance of phenoxyacetic acids and other pesticides in the etiology of NHL a pooled analysis was performed on two case-control studies, one on NHL and another on hairy cell leukemia (HCL), a rare subtype of NHL. The studies were population based with cases identified from cancer registry and controls from population registry. Data assessment was ascertained by questionnaires supplemented over the telephone by specially trained interviewers. The pooled analysis of NHL and HCL was based on 515 cases and 1141 controls. Increased risks in univariate analysis were found for subjects exposed to herbicides (OR 1.75, CI 95% 1.26–2.42), insecticides (OR 1.43, CI 95% 1.08–1.87), fungicides (OR 3.11, CI 95% 1.56–6.27) and impregnating agents (OR 1.48, CI 95% 1.11–1.96). Among herbicides, significant associations were found for glyphosate (OR 3.04, CI 95% 1.08–8.52) and 4-chloro-2-methyl phenoxyacetic acid (MCPA) (OR 2.62, CI 95% 1.40–4.88). For several categories of pesticides the highest risk was found for exposure during the latest decades before diagnosis. However, in multivariate analyses the only significantly increased risk was for a heterogeneous category of other herbicides than above.

Keywords: Non-Hodgkin's lymphoma; Hairy cell leukemia; Pesticides; Phenoxyacetic acids; Glyphosate; Impregnating agents

INTRODUCTION

Non-Hodgkin's lymphoma (NHL) is one of the malignant diseases with the most rapidly increasing incidence in the western world [1]. In Sweden, the mean age-adjusted incidence increased yearly by 3.6% in men and 2.9% in women during the time period 1958–1992 [2]. Hairy cell leukemia (HCL) was first described in 1958 and is regarded as a rare subgroup of NHL. HCL is more common in men with 23 male and 9 female patients reported to the Swedish Cancer Register in 1999 for the whole country [3].

The etiology of NHL is regarded to be multifactorial with different environmental exposures being part of it. Certain immunodefective conditions are established risk factors such as immunosuppressive medication after organ transplantation [4,5] and HIV-infection [6]. Also viral genesis, especially regarding Epstein–Barr virus (EBV) and endemic African Burkitt lymphoma has been indicated [7].

Regarding chemicals, exposure to phenoxyacetic acids, chlorophenols and organic solvents were associated with increased risk for NHL in Swedish studies [8–10]. In subsequent studies exposure to phenoxyacetic acids, particularly 2,4-dichlorophenoxyacetic acid (2,4-D), was associated with an increased risk for NHL [11,12]. These associations have been reviewed by us giving reference also to other studies [13].

We have now performed one case-control study on NHL, which did not include HCL [14], and another on HCL, specifically [15]. Both these studies focused interest especially on exposure to pesticides. In the NHL study, we found increased risks for subjects exposed to herbicides or fungicides. Among herbicides, phenoxyacetic acids

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TABLE I Number of exposed cases and controls, odds ratio (OR) and 95% confidence interval (CI) for exposure to pesticides and organic solvents

Agent	Number of exposed cases/controls	OR	CI
Herbicides	77/103	1.75	1.26–2.42
Phenoxyacetic acids	64/90	1.65	1.16–2.34
MCPA	21/23	2.62	1.40–4.88
2,4-D + 2,4,5-T	48/70	1.48	0.99–2.20
Glyphosate	8/8	3.04	1.08–8.52
Other	15/13	2.90	1.34–6.37
Insecticides	112/184	1.43	1.08–1.87
DDT	77/138	1.27	0.92–1.73
Mercurial seed dressing	20/33	1.40	0.77–2.47
Pyrethrins	13/27	1.16	0.57–2.25
Fungicides	18/17	3.11	1.56–6.27
Impregnating agents	104/162	1.48	1.11–1.96
Chlorophenols	66/106	1.37	0.98–1.92
Pentachlorophenol	64/101	1.40	0.99–1.98
Arsenic	8/10	1.75	0.66–4.54
Creosote	22/35	1.54	0.87–2.66
Other	40/67	1.35	0.88–2.04
Organic solvents	250/492	1.16	0.93–1.44

dominated. One subclass of these, 4-chloro-2-methyl phenoxyacetic acid (MCPA), turned out to be significantly associated with NHL. For several categories of herbicides, we observed that only exposure during the latest decades before diagnosis of NHL was associated with an increased risk for NHL. In the HCL study, we found increased risk for exposure to different categories of pesticides [15]. However, due to comparatively low number of study subjects, it was not meaningful to make further analyses of the tumor induction period.

Thus, the risk patterns for NHL and HCL in these studies, performed by the same methodology, showed similarities with respect to pesticides. Since the NHL study included patients with many different variants of NHL, it seemed motivated also to include HCL, as nowadays being regarded as a NHL subgroup, in a pooled analysis regarding risks in relation to pesticide exposure. The purpose was to enlarge the study size thereby allowing more precise risk estimates.

MATERIALS AND METHODS

Cases

The NHL study encompassed male cases aged ≥25 years with NHL diagnosed during 1987–1990 and living in the four most northern counties of Sweden and three counties in mid-Sweden [14]. They were recruited from the regional cancer registries and only cases with histopathologically verified NHL were included, in total 442 cases. Of these cases 192 were deceased.

From the national Swedish Cancer Registry, 121 male patients with HCL diagnosed during 1987–1992 were identified from the whole country [15]. One case later turned out to have been diagnosed in 1993, but was included in the study. Only living cases were included.

Controls

For living NHL cases two male controls matched for age and county were recruited from the National Population Registry.

For each deceased case two deceased controls matched also for year of death were identified from the National Registry for Causes of Death. For deceased subjects interviews were performed with the next-of-kin.

Similarly, four male controls matched for age and county were drawn to each case of HCL from the National Population Registry.

Assessment of Exposure

In both studies a similar questionnaire was mailed to the study subjects or next-of-kin for deceased individuals. A complete working history was asked for as well as exposure to different chemicals. If the information was unclear a trained interviewer supplemented the answers over the phone, thereby using written instructions. Years and total number of days for exposure to various agents were assessed. Also names of different agents were carefully asked for. If necessary, the Swedish Chemical Inspectorate was contacted to obtain information on the chemical composition of different brands of pesticides and other agents. A minimum exposure of one working day (8 h) and a tumor induction period of at least one year were used in the coding of chemicals. Thus, total exposure less than one day as well as exposure within one year prior to diagnosis (corresponding time for the matched control) were disregarded. The questionnaires were blinded as to case or control status during the interviews and coding of data.

Statistical Analysis

Conditional logistic regression analysis for matched studies was performed with the SAS statistical program (SAS Institute, Cary, NC). Thereby odds ratios (OR) and

TABLE II Exposure to different types of herbicides with dose-response calculations. High exposure is defined as > median number of days for exposed subjects. Range of exposure in days given within parenthesis

Agent	Total OR (CI)	Median number of days	OR (CI) Low	OR (CI) High
Herbicides	1.75 (1.26–2.42)	33 (1–709)	1.74 (1.10–2.71)	1.79 (1.15–2.79)
Phenoxyacetic acids	1.65 (1.16–2.34)	33 (1–709)	1.65 (1.01–2.66)	1.67 (1.02–2.69)
MCPA	2.62 (1.40–4.88)	25 (1–491)	1.94 (0.79–4.55)	3.61 (1.49–9.05)
2,4-D + 2,4,5-T	1.48 (0.99–2.20)	30 (1–709)	1.87 (1.08–3.20)	1.20 (0.68–2.08)
Other	2.90 (1.34–6.37)	11 (1–220)	2.26 (0.76–6.77)	3.37 (1.08–11)

95% confidence intervals (CI) were obtained. Both univariate and multivariate analyses were done. In this pooled analysis adjustment was made for study, study area and vital status. When risk estimates for different pesticides were analyzed only subjects with no pesticide exposure were taken as unexposed, whereas subjects exposed to other pesticides were disregarded.

RESULTS

The questionnaire was answered by 404 cases (91%) and 741 controls (84%) in the NHL study. Regarding HCL 111 cases (91%) and 400 controls (83%) participated. In the following results are given for the pooled analysis containing 515 cases and 1141 controls.

An increased risk was found for exposure to herbicides, insecticides, fungicides and impregnating agents, Table I. Regarding specific agents OR was highest for glyphosate and MCPA.

For herbicides dose-response calculations were also performed by comparing high and low dose exposures divided by the median exposure time in days, Table II. Exposure to MCPA gave a dose-response effect. Also for the group constituting of other herbicides than phenoxyacetic acids the risk was highest in the group with high exposure.

For herbicides in total and phenoxyacetic acids as a group the highest risks were seen when first exposure occurred 10–20 years before diagnosis, Table III. This was also the case for insecticides and impregnating agents. Within the latter group, however, an induction period of 20–30 years gave the highest risk for both creosote and pentachlorophenol.

Time to diagnosis from last exposure to different agents was also used in the calculation of risk estimates, Table IV. For phenoxyacetic acids the OR was highest for exposure 1–10 years prior to diagnosis whereas no increased risk was seen for those with last exposure >20 years from the time of diagnosis.

TABLE III Exposure to phenoxyacetic acids, insecticides, impregnating agents and organic solvents. Calculations are made with exposure divided according to time span from first exposure to diagnosis (induction period)

Agent	Induction period, years 1–10 OR (CI)	>10–20 OR (CI)	>20–30 OR (CI)	>30 OR (CI)
Herbicides	1.00 (0.05–11)	2.32 (1.04–5.16)	1.63 (0.87–2.98)	1.70 (1.12–2.58)
Phenoxyacetic acids	–*	2.88 (1.11–7.72)	1.54 (0.85–2.76)	1.50 (0.94–2.37)
MCPA	–* –	5.36 (1.57–21)	0.89 (0.20–3.03)	3.77 (1.49–9.99)
2,4-D + 2,4,5-T	–† –	2.87 (0.81–11)	1.87 (0.98–3.53)	1.15 (0.67–1.93)
Insecticides	1.20 (0.25–4.70)	2.84 (0.95–8.54)	2.19 (1.14–4.17)	1.31 (0.96–1.77)
DDT	–† –	2.64 (0.61–11)	1.63 (0.80–3.26)	1.17 (0.82–1.65)
Impregnating agents	1.20 (0.37–3.49)	2.27 (1.15–4.49)	1.89 (1.07–3.30)	1.23 (0.85–1.75)
Chlorophenols	–†	1.91 (0.82–4.44)	1.90 (0.98–3.65)	1.13 (0.73–1.71)
Pentachlorophenol	–†	1.91 (0.82–4.44)	2.13 (1.07–4.25)	1.13 (0.73–1.72)
Creosote	–*	0.88 (0.04–7.27)	5.33 (1.26–27)	1.34 (0.69–2.49)
Organic solvents	1.51 (0.65–3.37)	1.38 (0.84–2.24)	1.46 (1.00–2.12)	1.02 (0.79–1.30)

* No exposed cases, one exposed control.
† No exposed subjects.

TABLE IV Exposure to phenoxyacetic acids, impregnating agents and organic solvents. Calculations are made with exposure divided according to time span from last exposure to diagnosis

	Time span, last exposure-diagnosis, years			
Agent	1–10 OR (CI)	>10–20 OR (CI)	>20–30 OR (CI)	>30 OR (CI)
Herbicides	2.53 (1.38–4.64)	1.68 (0.88–3.14)	1.22 (0.66–2.19)	1.84 (0.95–3.51)
Phenoxyacetic acids	3.22 (1.59–6.65)	2.06 (1.03–4.09)	1.01 (0.54–1.81)	1.26 (0.57–2.62)
MCPA	3.52 (1.58–7.99)	2.33 (0.56–9.09)	0.92 (0.13–4.39)	–*
2,4-D + 2,4,5-T	4.31 (1.12–21)	1.85 (0.90–3.78)	1.04 (0.54–1.94)	1.41 (0.65–2.92)
Insecticides	2.37 (1.40–4.02)	0.87 (0.48–1.53)	1.45 (0.85–2.41)	1.46 (0.94–2.24)
DDT	1.45 (0.65–3.10)	1.13 (0.62–1.97)	1.46 (0.83–2.50)	1.20 (0.69–2.02)
Impregnating agents	1.92 (1.30–2.82)	0.79 (0.40–1.46)	1.67 (0.88–3.11)	1.19 (0.61–2.21)
Chlorophenols	–†	1.52 (1.02–2.25)	1.36 (0.61–2.86)	0.84 (0.32–1.96)
Pentachlorophenol	–†	1.59 (1.06–2.37)	1.28 (0.58–2.67)	0.81 (0.29–2.01)
Creosote	2.56 (0.85–7.67)	0.93 (0.13–4.17)	1.17 (0.36–3.43)	1.54 (0.60–3.75)
Organic solvents	1.17 (0.91–1.50)	1.00 (0.66–1.50)	1.39 (0.84–2.25)	0.99 (0.56–1.69)

* one exposed case, one exposed control.
† No exposed case or control.

Furthermore, exposure to phenoxyacetic acids during different decades from the 1940s was analyzed. Increased risk was found during recent decades, Table V.

No statistically significant increased risk was found for the whole group of organic solvents in this pooled analysis, but when the solvents were subgrouped according to specific substances there were increased risks for vanolen (OR = 1.91, CI = 1.03–3.49; $n = 20$ cases) and aviation fuel (OR = 3.56, CI = 1.03–12; $n = 6$ cases).

Multivariate analysis of exposure to phenoxyacetic acids, insecticides, fungicides and impregnating agents is presented in Table VI. An increased risk persisted for exposure to herbicides, fungicides and impregnating agents, however not statistically significant.

A separate multivariate analysis was performed on exposure to herbicides. Lower risk estimates were obtained although all herbicides still constituted risk factors for NHL, Table VII.

DISCUSSION

The cases in this study were identified by using the Swedish Cancer Registry, which is composed by six regional registries. In Sweden, the reporting of malignant diseases to the Cancer Registry is compulsory, which makes it likely that most incident cases in the study area were identified. Controls were selected from the National Population Registry and, in order to minimize recall bias, deceased controls were used for deceased cases in one of the studies [14] which were the basis for this analysis. In the other only living cases were included [15]. Recall bias is always a matter of concern in a case-control study with self-reported exposures. Farmer as occupation did not increase the risk in this pooled analysis (OR = 1.19, CI = 0.95–1.49) which indicates that the risk increase for pesticides was not explained merely by misclassification of exposure. All interviews and coding of data were performed blinded as to case or control status in order to minimize observational bias.

TABLE V Exposure to phenoxyacetic acids during different decades. Note that one subject may occur during several decades

Decade	Cases/controls	OR	CI
1940s	4/6	1.46	0.37–5.23
1950s	35/53	1.44	0.91–2.26
1960s	43/58	1.68	1.10–2.55
1970s	32/33	2.37	1.42–3.95
1980s	16/33	3.25	1.53–7.07

TABLE VI Multivariate analysis of exposure to pesticides

	Univariate		Multivariate	
Agent	OR	CI	OR	CI
Herbicides	1.75	1.26–2.42	1.39	0.96–2.02
Insecticides	1.43	1.08–1.87	1.07	0.78–1.45
Fungicides	3.11	1.56–6.27	2.02	0.97–4.23
Impregnating agents	1.48	1.11–1.96	1.30	0.98–1.72

TABLE VII Multivariate analysis of exposure to herbicides. Odds ratios (OR) and 95% confidence intervals (CI) are given

	Univariate		Multivariate	
Agent	OR	CI	OR	CI
MCPA	2.62	1.40–4.88	1.67	0.77–3.57
2,4-D + 2,4,5-T	1.48	0.99–2.20	1.32	0.88–1.96
Glyphosate	3.04	1.08–8.52	1.85	0.55–6.20
Other herbicides	2.90	1.34–6.37	2.28	1.02–5.15

This study was a pooled analysis of two case-control studies, one on NHL [14] and the other on HCL [15] to provide larger numbers, which would allow more detailed analyses regarding the timing of exposure and adjustment of multiple exposures. This method was justified since HCL is a type of NHL and similar methods and questionnaires were used in both studies. Also the findings regarding pesticide exposure were relatively homogenous for both studies. The smaller HCL study had a somewhat higher prevalence of exposure and therefore has in this pooled analysis more weight than one would expect.

Conditional logistic regression analysis was performed since both studies in this pooled analysis were matched. Heterogeneity in findings was averaged after stratification by study. Since the NHL study included also deceased cases and controls adjustment was made for vital status. Finally, in the HCL study the whole Sweden was included as study base whereas in the NHL study only parts of Sweden were included. Thus, adjustment was made for geographical area for cases and controls, i.e. county.

In the multivariate analysis exposure to herbicides, fungicides and impregnating agents increased the risk although OR was lower than in the univariate analysis. Significantly increased risk remained only for the heterogeneous group of "other herbicides". The results in multivariate analysis must be interpreted with caution since exposure to different types of pesticides correlate. Multivariate analysis is mainly useful to estimate the risk factors that seem to be most important.

Several previous studies have associated exposure to phenoxyacetic acids, primarily 2,4-D and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), with an increased risk for NHL [8–12,16–18]. Concerning MCPA data are sparse although in our first study on NHL, we found an increased risk [9,10].

In this pooled analysis, most subjects were regarding herbicides exposed to phenoxyacetic acids, mostly the combination of 2,4-D and 2,4,5-T. 2,4-D was withdrawn from the Swedish market in 1990 and 2,4,5-T was prohibited in 1977. Also MCPA, the phenoxy herbicide still commonly used in Sweden, increased the risk for NHL. Glyphosate is the herbicide now mostly used in Sweden. In this study, exposure to glyphosate was a risk factor for NHL. Thus, regarding herbicides lymphomagenesis seems not to be depending on contaminating dioxins, i.e. 2,3,7,8-TCDD in 2,4,5-T. A contributing effect of such exposure cannot be excluded, although not supported by mortality results in a cohort of workers exposed to 2,3,7,8-TCDD [19]. IARC classified recently 2,3,7,8-TCDD as a human carcinogen, Group I [20].

In the univariate analysis exposure to insecticides, mostly DDT, increased the risk for NHL. In the multivariate analysis no risk was found. This is in accordance with our previous results [9,10] and a pooled analysis of three case-control studies concluded that DDT is not a risk factor for NHL [21]. Furthermore, analysis of serum DDT/DDE has not given a clear association with NHL [22,24,25].

Regarding fungicides an increased risk for NHL has previously been reported from USA [11]. Our result with increased risk for NHL needs to be further studied since the finding was based on few subjects exposed to several types of fungicides.

Chlorophenols, which are chemically related to phenoxyacetic acids and have been used as e.g. wood preservatives, were banned in Sweden in 1978. An increased risk for NHL was found in this pooled analysis, but also for exposure to arsenic and creosote. Both chlorophenols and creosote have been associated with NHL [26,27].

An association between exposure to organic solvents and NHL has been described [9,10,28–30]. However, such an association was not confirmed now although an influence of tumor induction period can not be ruled out, *c.f.*, below. Another possibility might be that solvents used during later years are less toxic than previously, e.g. water based, and that they are more cautiously handled [31].

To further elucidate mechanisms in lymphomagenesis analysis of tumor-induction period (latency) and also time from last exposure to diagnosis was performed. Thereby the corresponding year for diagnosis was used for the matched control. For 2,4-D, 2,4,5-T and chlorophenols no subject had first exposure during 1–10 years prior to diagnosis due to restrictions in the use of these chemicals in Sweden during that time period. For fungicides such calculations were not meaningful due to low number of exposed subjects.

The highest risk for exposure to herbicides, insecticides and impregnating substances was found for last exposure 1–10 years prior to diagnosis. Correspondingly, in general the lowest risks were found for the longest tumor induction periods.

Do these results cast further light on the etiology of NHL? Certainly, exposure to some chemicals is of significance in lymphomagenesis. Furthermore, bearing in mind that several of these chemicals are immunotoxic, e.g. certain pesticides and chlorophenols [27,32,33] and immunosuppression is an established risk factor for NHL [34] such toxicity might be of importance for chemical agents.

Viruses have been associated with lymphomas in animals [35,36] and more specifically EBV for humans [7,37]. Virus proliferation in lymphocytes is held back by the immune system and immunosuppression may be followed by development of both B-cell and T-cell

lymphoma in animals [38–39]. For renal transplant patients treated with immunosuppressive drugs the risk for NHL is highest during the first years after transplantation and then declines [40].

Timing of exposure in relation to risk of NHL, particularly in regard to higher risk for recent exposures, seemed to be an interesting result regarding lymphomagenesis. Several interpretations are possible such as chance finding, late stage in lymphomagenesis, type of exposure or interaction with other factors. Certainly immunmodulation by pesticides [32,33] is one hypothesis which should be more elaborated on, possibly with interaction with latent virus infection such as EBV. This might explain the short tumor induction period. In fact, results from the included HCL-study showed interaction between EBV-infection and exposure to such chemicals [41,42]. Additionally, polychlorinated biphenyls [22,24,25] and chlordanes [23,24], chemicals that are immunotoxic [43,44], have been associated with an increased risk for NHL.

The etiology of NHL is multifactorial and further studies should consider immunotoxic effects by the studied chemicals as well as tumor induction period and interaction with virus infection, e.g. EBV.

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ELECTRONIC PAPER

Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men

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Background: An increased rate of non-Hodgkin's lymphoma (NHL) has been repeatedly observed among farmers, but identification of specific exposures that explain this observation has proven difficult.

Methods: During the 1980s, the National Cancer Institute conducted three case-control studies of NHL in the midwestern United States. These pooled data were used to examine pesticide exposures in farming as risk factors for NHL in men. The large sample size (n = 3417) allowed analysis of 47 pesticides simultaneously, controlling for potential confounding by other pesticides in the model, and adjusting the estimates based on a prespecified variance to make them more stable.

Results: Reported use of several individual pesticides was associated with increased NHL incidence, including organophosphate insecticides coumaphos, diazinon, and fonofos, insecticides chlordane, dieldrin, and copper acetoarsenite, and herbicides atrazine, glyphosate, and sodium chlorate. A subanalysis of these "potentially carcinogenic" pesticides suggested a positive trend of risk with exposure to increasing numbers.

Conclusion: Consideration of multiple exposures is important in accurately estimating specific effects and in evaluating realistic exposure scenarios.

Farming occupation has been associated with an increased risk of non-Hodgkin's lymphoma (NHL) in the United States and other countries.[1–4] Specific farming exposures contributing to the excess risk have not been clearly discerned, but pesticides have received considerable attention. Associations have been observed between NHL risk and exposure to phenoxyacetic acids, most notably 2,4-dichlorophenoxyacetic acid (2,4-D).[5–10] Organochlorine, organophosphate, carbamate, and triazine pesticides have also been implicated.[8 9 11–14]

There are several analytical challenges in studying health effects of pesticide exposures among farmers. Farmers are typically exposed to multiple pesticides during a lifetime, and pesticides are frequently used together or during the same growing season, posing a challenge for identifying specific risk factors. Although multiple and simultaneous exposures are common in epidemiology and the situation regarding pesticides is not unique, they do require large numbers to successfully identify risks from specific exposures. Many of the past studies of NHL and pesticides had limited power to adjust for potential confounding by associated pesticide exposures. Limited study power has also hindered investigation of the risk associated with common pesticide combinations.

In principle, multiple pesticide exposures should be modelled simultaneously to account for their probable correlation; however, modelling multiple pesticides can lead to imprecise estimates, particularly where exposures are infrequent. In addition, some estimates are expected to be very inaccurate, either due to chance or systematic error (such as recall bias). Hierarchical regression models, also known as multilevel or multistage models, allow the researcher to specify prior distributions for multiple effect parameters of interest (for example, pesticide effects), and to adjust the observed likelihood estimates towards these prior distributions with the objective of obtaining increased precision and accuracy for the ensemble of estimates.[15–17] Although the true prior distributions are rarely known, factors hypothesised to determine or explain the magnitude of the true effects of interest can be used to specify the form of the prior distributions, whose magnitudes are then estimated.[15]

During the 1980s, the National Cancer Institute conducted three population based case-control studies of NHL in Nebraska,[5] Iowa and Minnesota,[11] and Kansas.[7] Each of these studies focused on farming exposure to pesticides, and data from the three studies have been pooled. In the pooled data, certain organophosphate[12] and carbamate[13] insecticides were positively associated with the risk of NHL. Lindane use was associated with slightly increased incidence of NHL,[18] whereas DDT use was not.[19] There was also a slightly increased incidence associated with atrazine exposure.[20]

We used these pooled data to conduct an analysis of exposure to multiple pesticides in farming as risk factors for NHL among men. The larger sample size provided adequate numbers of exposed persons to analyse a set of pesticide exposures simultaneously, using hierarchical regression to adjust estimates based on prior distributions for the pesticide effects. In addition, effects of the number of pesticides used and of common pesticide combinations were explored to assess the risk associated with realistic scenarios of farmers' exposures to multiple pesticides.

METHODS

Study population

The three case-control studies had slightly different methods of subject recruitment. In Nebraska,[5] all cases of NHL diagnosed between July 1983 and June 1986 among white subjects 21 years of age and older, and living in one of the 66 counties of eastern Nebraska were identified through the Nebraska Lymphoma Study Group and area hospitals. In Iowa and Minnesota,[11] all newly diagnosed cases of NHL among

Abbreviations: 2,4-D, 2,4-dichlorophenoxyacetic acid; NHL, non-Hodgkin's lymphoma; OP, organophosphorus

white men aged 30 years or older were ascertained from records of the Iowa State Health Registry from 1981 to 1983, and a special surveillance system of Minnesota hospitals and pathology laboratories from 1980 to 1982. In Kansas,[7] a random sample of cases diagnosed between 1979 and 1981 among white men age 21 years or older was selected from the statewide cancer registry run by the University of Kansas Cancer Data Service. Population based controls were randomly selected from the same geographical areas as the cases, frequency matched to cases by race, sex, age, and vital status at the time of interview. Potential controls were identified by random digit dialing and from Medicare records, and for deceased cases, from state mortality files.

Only one study included women; in this pooled analysis we excluded female cases and controls. Those who lived or worked on a farm when younger than 18 years of age, but not after age 18, were not asked about their pesticide use in the Nebraska study; persons with this history from any of the three studies were therefore excluded from analyses of the pooled data. Following exclusions, the study population included 870 cases and 2569 controls.

Interviews

Interviews were conducted with the subjects or their next of kin if the subjects were dead or incapacitated. In each study, detailed questions were asked about the use of agricultural pesticides as well as other known or suspected risk factors for NHL. In Nebraska, information was obtained through questioning about the use of any pesticide, followed by prompting for selected specific pesticides, with details on the total number of years of use and average number of days per year. In Iowa and Minnesota, use was assessed by a direct question about a selected list of specific pesticides. Pesticide users were also asked the first and last year each pesticide was used. In Kansas, use of pesticides was assessed by an open ended question without prompting for specific pesticides, and duration of use and days per year were obtained for groups of pesticides (herbicides, insecticides, and fungicides), but not for each pesticide individually.

Statistical analyses

Each pesticide for which there were data from all three studies, and to which 20 or more persons were exposed, was included in the pooled analysis. The set of pesticides examined included 47 insecticides and herbicides. Exposure to each pesticide was coded as an indicator variable for exposed (1) or not exposed (0). Because these analyses of multiple pesticides modelled the pesticides simultaneously, any subject with a missing or "don't know" response for any one of the 47 pesticides of interest was excluded from all analyses. Following exclusion of subjects with missing data, analyses of multiple pesticides included 650 cases (74.7%) and 1933 controls (75.2%). We employed two approaches to our analyses: standard logistic regression (maximum likelihood estimation) and hierarchical regression, calculating odds ratios to estimate the relative risk associated with each pesticide. All models included variables for age (coded as a quadratic spline variable with one knot at 50 years)[21] and indicator variables for study site. Other factors known or suspected to be associated with NHL, including first degree relative with haematopoietic cancer, education, and smoking, were evaluated and found not to be important confounders of the associations between NHL and pesticides. The standard logistic regression models did not assume any prior distribution of pesticide effects, in contrast to the hierarchical regression modelling.

Hierarchical regression of multiple pesticide exposures

In the first-level model of the hierarchical regression analysis, NHL disease status was regressed simultaneously on the 47 pesticide exposures, age, and study site. The maximum likelihood estimates for the 47 pesticides from the first-level model were regressed in a second-level linear regression model as a function of prespecified prior covariates for each of the pesticides. The second-level model should incorporate what is known about each true effect parameter prior to seeing the study data.[15 22] Information derived from the second-level model was used to adjust the beta coefficient for each pesticide exposure according to its "prior distribution"; the beta for each pesticide was adjusted in the direction of its prior mean, or expected value (from the second-level model), with the magnitude of shrinkage dependent on the precision of its likelihood estimate (from the first-level model) and a prespecified variance of the assumed normal distribution for that parameter. SAS Proc GLIMMIX was used to run the hierarchical models. This program can be adapted for the purpose of hierarchical modelling of multiple exposures, and uses a penalised likelihood function to fit the first- and second-level models by an iterative procedure.[23]

Information on pesticides that would give a priori reason to believe that the true effect parameters for certain specific pesticides would be more or less similar to each other was constructed into a matrix for use in the second level of the hierarchical regression analysis (table 1). The second-level, or prior covariates, were factors hypothesised to determine the magnitude of, or explain some of the variability between, the individual true effects. The covariates were indicators of pesticide class, structure, and toxicity, used to define categories of pesticide effects which would be regarded as "exchangeable", or as draws from a common prior distribution.[15 22] These "categories of exchangeability" included the groupings: insecticides (versus herbicides), organochlorines, organophosphates, carbamates, phenoxyacetic acids, triazines, amides, and benzoic acids (see table 1). In addition to categories of exchangeability, we defined a prior covariate incorporating prior evidence for carcinogenicity of the pesticide. Based on data from the United States Environmental Protection Agency's (US EPA) Integrated Risk Information System (http://www.epa.gov/iris/) and the International Agency for Research on Cancer's Program on the Evaluation of Cancer Risks to Humans (http://monographs.iarc.fr/), carcinogenic probability for any cancer (not limited to NHL), was defined as a continuous variable ranging between 0 and 1 (algorithm for variable definition is included as footnote to table 1).

Another component of each pesticide effect's prior distribution was a value for the residual variance, which captures effects above and beyond those accounted for by the "group" effects of the second-level covariates, and determines the degree of shrinkage of a likelihood estimate toward its prior mean.[15 22] This residual variance was defined as a value relating to a range of probable values for the true effect parameter. We assumed, with 95% certainty, that the rate ratio for each pesticide, after adjusting for the second-level covariates, would fall within a 10-fold range around its prior mean (for example, between 0.5 and 5.0), by defining the prior residual variance as 0.35 (note: for a 10-fold range, residual variance = $((\ln(10))/3.92)^2 \cong 0.35$), assuming normality).

Because our prior covariates were crudely defined, and because there is little information on factors that would be expected to affect the magnitude of the effect of pesticides on NHL incidence, we also performed a hierarchical regression analysis of multiple pesticides using an intercept-only model, in which all pesticide effects were assumed to arise from a common prior distribution, with a prior residual variance of 0.35. In other words, this modelling strategy assumed that there was no a priori reason to believe that any specific pesticide was more likely to be associated with NHL incidence than any other pesticide in the model.

Number of pesticides used

We conducted analyses to estimate NHL incidence associated with the number of pesticides used, out of the total number of

Table 1 Second-level matrix for hierarchical regression analysis, showing values of "prior covariates" for each pesticide of interest*†

Pesticides	Insecticides	Organo-chlorines	Organo-phospates	Carbamates	Phenoxy-acetic acids	Triazines	Amides	Benzoic acids	Carcinogenic probability
Insecticides									
Aldrin	1	1	0	0	0	0	0	0	0.6
Bufencarb	1	0	0	1	0	0	0	0	0.3
Carbaryl	1	0	0	1	0	0	0	0	0.3
Carbofuran	1	0	0	1	0	0	0	0	0.3
Chlordane	1	1	0	0	0	0	0	0	0.8
Copper acetoarsenite*	1	0	0	0	0	0	0	0	1.0
Coumaphos	1	0	1	0	0	0	0	0	0.3
DDT	1	1	0	0	0	0	0	0	0.8
Diazinon	1	0	1	0	0	0	0	0	0.3
Dichlorvos	1	0	1	0	0	0	0	0	0.8
Dieldrin	1	1	0	0	0	0	0	0	0.6
Dimethoate	1	0	1	0	0	0	0	0	0.3
Ethoprop	1	0	1	0	0	0	0	0	0.3
Famphur	1	0	1	0	0	0	0	0	0.3
Fly, lice, tick spray	1	0	0	0	0	0	0	0	0.3
Fonofos	1	0	1	0	0	0	0	0	0.3
Heptachlor	1	1	0	0	0	0	0	0	0.8
Lead arsenate*	1	0	0	0	0	0	0	0	1.0
Lindane	1	1	0	0	0	0	0	0	0.3
Malathion	1	0	1	0	0	0	0	0	0.3
Methoxychlor	1	1	0	0	0	0	0	0	0.3
Nicotine	1	0	0	0	0	0	0	0	0.3
Phorate	1	0	1	0	0	0	0	0	0.3
Pyrethrins	1	0	0	0	0	0	0	0	0.3
Rotenone	1	0	0	0	0	0	0	0	0.3
Tetrachlorvinphos	1	0	1	0	0	0	0	0	0.3
Toxaphene	1	1	0	0	0	0	0	0	0.8
Terbufos	1	0	1	0	0	0	0	0	0.3
Herbicides									
Alachlor	0	0	0	0	0	0	1	0	0.3
Atrazine	0	0	0	0	0	1	0	0	0.3
Bentazon	0	0	0	0	0	0	0	0	0.1
Butylate	0	0	0	1	0	0	0	0	0.3
Chloramben	0	0	0	0	0	0	0	1	0.3
Cyanazine	0	0	0	0	0	1	0	0	0.3
2,4-D	0	0	0	0	1	0	0	0	0.5
Dicamba	0	0	0	0	0	0	0	1	0.3
EPTC	0	0	0	1	0	0	0	0	0.3
Glyphosate	0	0	0	0	0	0	0	0	0.3
Linuron	0	0	0	0	0	0	0	0	0.5
MCPA	0	0	0	0	1	0	0	0	0.3
Metolachlor	0	0	0	0	0	0	1	0	0.5
Metribuzin	0	0	0	0	0	0	0	0	0.3
Paraquat	0	0	0	0	0	0	0	0	0.5
Propachlor	0	0	0	0	0	0	1	0	0.3
Sodium chlorate	0	0	0	0	0	0	0	0	0.3
2,4,5-T	0	0	0	0	1	0	0	0	0.5
Trifluralin	0	0	0	0	0	0	0	0	0.5

*Carcinogenic probability value is created by combining the classifications from the IARC Monographs Programme on the Evaluation of Carcinogenic Risks to Humans and the US EPA Integrated Risk Information System. Assignment of carcinogenic probability by order of priority: 1.0 = classified as a human carcinogen on either assessment; 0.9 = probable human carcinogen in both assessments; 0.8 = probable human carcinogen in one assessment and possible human carcinogen in other assessment; 0.6 = probable human carcinogen in one assessment and unclassifiable in the other; 0.5 = possible human carcinogen in both assessments, or possible human carcinogen in one assessment and not assessed by the other group; 0.3 = not assessed by IARC or US EPA IRIS, or deemed unclassifiable in one or both assessments; 0.1 = evidence for non-carcinogenicity in either assessment.
†Used the IARC assessment for arsenic and arsenic compounds.

86 pesticides reported in all three of the pooled studies (many of these 86 pesticides were not included in the multivariable analysis of the set of 47 specific pesticides because of their infrequent use). The number of pesticides was coded using indicator variables (1 pesticide, 2–4 pesticides, 5 or more pesticides). Similar analyses were conducted for the number of insecticides and herbicides used. For those pesticides showing positive associations with NHL in the hierarchical regression analysis of 47 specific pesticides (nine pesticides total, see table 3), we conducted a similar analysis of the number of pesticides used, restricted to these "potentially carcinogenic" pesticides. In addition to logistic regression analyses, we evaluated the effect of the number of pesticides used by hierarchical regression with an intercept-only model, in which all pesticide effects (those indicating number of pesticides, as well as the 47 specific pesticides) were assumed to have been sampled from a common prior distribution with an unknown mean and a residual variance of 0.35.

Combined pesticide exposures

We explored the risk associated with combined pesticide exposures, defined as two pesticides used by the same person, but not necessarily at the same time. For any two pesticides for which more than 75 persons reported use of both (representing the 5% most common of all possible combinations of the 47 pesticides), and at least 20 persons reported use of each of the two individual pesticides not in combination, we evaluated potential superadditivity of pesticide effects on NHL (the appendix contains a list of the pesticide combinations evaluated). Individual and joint effects were first estimated

Table 2 Characteristics of subjects in the study population* and those subjects included in analyses of multiple pesticides†

Characteristics	Pooled study			Included in analyses of multiple pesticides		
	Cases (n=870)	Controls (n=2569)	OR (95% CL)‡	Cases (n=650)	Controls (n=1933)	OR (95% CL)
Study site						
Iowa/Minnesota	520 (60.9%)	1039 (40.4%)	1.0	436 (67.1%)	895 (46.3%)	1.0
Kansas	153 (17.6%)	862 (33.6%)	0.3 (0.3 to 0.4)§	101 (15.5%)	596 (30.8%)	0.3 (0.3 to 0.4)
Nebraska	187 (21.5%)	668 (26.0%)	0.5 (0.4 to 0.7)§	113 (17.4%)	442 (22.9%)	0.5 (0.4 to 0.7)
Respondent status						
Self respondent	545 (62.6%)	1413 (55.0%)	1.0	449 (69.1%)	1166 (60.3%)	1.0
Proxy respondent	325 (37.4%)	1156 (45.0%)	0.7 (0.6 to 0.9)§	201 (30.9%)	767 (39.7%)	0.7 (0.6 to 0.8)
Age (years)						
<40	53 (6.1%)	280 (11.0%)	0.7 (0.5 to 1.0)§	40 (6.2%)	211 (10.9%)	0.7 (0.5 to 1.1)
40–59	196 (22.6%)	493 (19.3%)	1.5 (1.1 to 1.9)§	160 (24.6%)	388 (20.1%)	1.6 (1.2 to 2.1)
60–79	478 (55.1%)	1261 (49.4%)	1.4 (1.1 to 1.7)§	355 (54.6%)	969 (50.1%)	1.4 (1.1 to 1.8)
≥80	141 (16.2%)	521 (20.4%)	1.0	95 (14.6%)	365 (18.9%)	1.0
Educational level						
Less than high school graduation	387 (45.2%)	1126 (44.7%)	1.0	276 (43.0%)	806 (42.4%)	1.0
High school graduation or GED¶	226 (26.4%)	629 (25.0%)	1.0 (0.9 to 1.3)	171 (26.6%)	467 (24.6%)	1.1 (0.9 to 1.3)
Some college or vocational school	151 (17.6%)	457 (18.1%)	1.0 (0.8 to 1.2)	122 (19.0%)	368 (19.4%)	1.0 (0.8 to 1.2)
College graduate or more	93 (10.9%)	308 (12.2%)	1.0 (0.7 to 1.1)	73 (11.4%)	261 (13.7%)	0.8 (0.6 to 1.1)
Ever lived or worked on a farm as an adult						
No	243 (28.1%)	780 (30.4%)	1.0	243 (37.5%)	775 (40.1%)	1.0
Yes	621 (71.9%)	1780 (69.5%)	1.1 (0.9 to 1.3)	405 (62.5%)	1157 (59.9%)	1.1 (0.9 to 1.3)
First degree relative with haematopoietic cancer						
No	792 (92.5%)	2452 (96.8%)	1.0	594 (92.8%)	1863 (96.7%)	1.0
Yes	64 (7.5%)	80 (3.2%)	2.5 (1.8 to 3.5)	46 (7.2%)	63 (3.3%)	2.3 (1.5 to 3.4)
Histological subtype						
Follicular	243 (28.0%)			196 (30.1%)		
Diffuse	334 (38.5%)			233 (35.9%)		
Small lymphocytic	99 (11.4%)			77 (11.9%)		
Other	192 (22.1%)			144 (22.2%)		

*Pooled study population limited to males and following exclusions.
†Any observation with a missing value for any of the 47 multiple pesticides was not included in analyses.
‡Odds ratios (OR) and 95% confidence limits (CL).
§Odds ratios for the matching factors are not interpretable for their relation with NHL, but are presented for comparison to odds ratios for the subgroup included in analyses of multiple pesticides.
¶GED, General Equivalency Diploma.

using logistic regression in models including variables for the joint exposure and two individual exposures, the 45 other specific pesticides, age, and study site. Where the OR for the joint effect was 1.3 or higher, positive interaction on the additive scale was evaluated using the interaction contrast ratio ($ICR = OR_{\text{joint exposure}} - OR_{\text{individual exposure \#1}} - OR_{\text{individual exposure \#2}} + 1$).[24] ICR values above 0.5 were considered indicative of superadditivity, and these pesticide combinations were further analysed using hierarchical regression with an intercept-only model, in which all pesticide effects (those indicating joint and individual exposures to the two pesticides, as well as the other 45 specific pesticides) were assumed to have been sampled from a common prior distribution with an unknown mean and a residual variance of 0.35.

RESULTS

Table 2 shows characteristics of men in the pooled studies. In the control population, which was representative of this part of the midwestern United States, approximately 70% of the men had lived or worked on a farm as an adult. There was a 10% increased NHL incidence associated with living or working on a farm as an adult; this increase is similar in magnitude to meta-analyses of farming and NHL mortality and morbidity.[4 25] Cases were slightly more likely than controls to have been directly interviewed, to be between the ages of 40 and 79, and they were more than twice as likely to have a first degree relative with haematopoietic cancer. The subset of subjects included in analyses of multiple pesticides was less likely than those in the overall study population to be from the Kansas or Nebraska studies, to have lived or worked on a farm as an adult, or to have had a proxy respondent, and they were slightly more likely to be more highly educated; however, the relation of these factors with case status did not differ between the overall study and the subset included in the analyses of multiple pesticides.

Use of most specific pesticides was more frequent among cases than controls; however, most of the odds ratios were not increased in the multivariable models (table 3), primarily due to adjustment for study site, since both the frequency of pesticide use and case-to-control ratios differed by study site. The results of the hierarchical regression analysis of 47 pesticides were generally similar to, but had somewhat more narrow confidence intervals than results from the logistic regression model. Only a few pesticides were associated with a possible increased NHL incidence (judged by OR ≥1.3 and lower confidence limit ≥0.8), including the organophosphate (OP) insecticides coumaphos, fonofos, and diazinon, the organochlorine insecticides chlordane and dieldrin, the insecticide copper acetoarsenite, and the herbicides atrazine, glyphosate, and sodium chlorate. There was also a significantly decreased risk associated with aldrin exposure. These suggested effects occurred in both the logistic and hierarchical regression analyses. For pesticides that had wider confidence intervals in the logistic regression model, odds ratios from the hierarchical model were generally closer to the null value, based on a priori assumptions about the probable magnitudes of effect. For example, we assumed that the effect of sodium chlorate would be similar to that of other herbicides and other pesticides for which there was a low carcinogenic probability, and that after accounting for these prior covariates, the rate ratio would likely fall within a 10-fold range around its expected value. Based on these assumptions, a fourfold risk associated with the use of sodium chlorate in the logistic regression analysis was adjusted to a 1.8-fold risk using hierarchical regression. Although unstable estimates were adjusted, results of the

Table 3 Effect estimates for use of specific pesticides and NHL incidence, adjusting for use of other pesticides*

Pesticides	Exposed (n (%)) Cases (n=650)	Controls (n=1933)	Logistic regression OR (95% CL)†	Hierarchical regression OR (95% CL)
Insecticides				
Aldrin	47 (7.2%)	115 (5.9%)	0.5 (0.3 to 0.9)	0.6 (0.4 to 1.0)
Bufencarb‡	6 (0.9%)	12 (0.6%)	1.1 (0.3 to 3.7)	1.0 (0.4 to 2.3)
Carbaryl	30 (4.6%)	57 (2.9%)	1.0 (0.5 to 1.9)	1.1 (0.6 to 1.9)
Carbofuran	41 (6.3%)	96 (5.0%)	0.9 (0.5 to 1.6)	1.0 (0.6 to 1.7)
Chlordane	39 (6.0%)	65 (3.4%)	1.5 (0.8 to 2.6)	1.3 (0.8 to 2.1)
Copper acetoarsenite	41 (6.3%)	68 (3.5%)	1.4 (0.9 to 2.3)	1.4 (0.9 to 2.1)
Coumaphos	15 (2.3%)	22 (1.1%)	2.4 (1.0 to 5.8)	1.7 (0.9 to 3.3)
DDT	98 (15.1%)	226 (11.7%)	1.0 (0.7 to 1.3)	1.0 (0.7 to 1.3)
Diazinon	40 (6.1%)	62 (3.2%)	1.9 (1.1 to 3.6)	1.7 (1.0 to 2.8)
Dichlorvos	16 (2.5%)	37 (1.9%)	0.9 (0.4 to 2.0)	0.9 (0.5 to 1.7)
Dieldrin	21 (3.2%)	39 (2.0%)	1.8 (0.8 to 3.9)	1.4 (0.8 to 2.6)
Dimethoate‡	5 (0.8%)	11 (0.6%)	1.2 (0.3 to 5.3)	1.2 (0.5 to 2.8)
Ethoprop‡	4 (0.6%)	14 (0.7%)	0.7 (0.2 to 2.9)	0.9 (0.4 to 2.1)
Famphur	12 (1.8%)	34 (1.8%)	0.7 (0.3 to 1.7)	0.8 (0.4 to 1.5)
Fly, lice, or tick spray	162 (24.9%)	408 (21.1%)	0.9 (0.7 to 1.1)	0.9 (0.7 to 1.1)
Fonofos	28 (4.3%)	44 (2.3%)	1.8 (0.9 to 3.5)	1.5 (0.9 to 2.7)
Heptachlor	28 (4.3%)	53 (2.7%)	1.1 (0.6 to 2.4)	1.1 (0.6 to 2.0)
Lead arsenate	9 (1.4%)	25 (1.3%)	0.5 (0.2 to 1.2)	0.6 (0.3 to 1.3)
Lindane	59 (9.1%)	109 (5.6%)	1.2 (0.7 to 2.0)	1.2 (0.8 to 1.9)
Malathion	53 (8.1%)	100 (5.2%)	1.1 (0.6 to 1.8)	1.1 (0.7 to 1.7)
Methoxychlor	9 (1.4%)	20 (1.0%)	0.8 (0.3 to 2.1)	0.9 (0.4 to 1.9)
Nicotine	24 (3.7%)	50 (2.6%)	0.9 (0.5 to 1.6)	1.0 (0.6 to 1.6)
Phorate	28 (4.3%)	67 (3.5%)	0.8 (0.4 to 1.6)	0.9 (0.5 to 1.5)
Pyrethrins‡	6 (0.9%)	12 (0.6%)	1.0 (0.3 to 3.2)	1.0 (0.4 to 2.3)
Rotenone	10 (1.5%)	26 (1.4%)	0.7 (0.3 to 1.7)	0.8 (0.4 to 1.5)
Tetrachlorvinphos‡	3 (0.5%)	11 (0.6%)	0.4 (0.1 to 1.8)	0.8 (0.3 to 1.9)
Toxaphene	17 (2.6%)	34 (1.8%)	1.1 (0.5 to 2.4)	1.1 (0.6 to 2.0)
Terbufos	21 (3.2%)	50 (2.6%)	0.8 (0.4 to 1.8)	0.8 (0.5 to 1.6)
Herbicides				
Alachlor	68 (10.5%)	152 (7.9%)	1.1 (0.7 to 1.8)	1.0 (0.6 to 1.6)
Atrazine	90 (13.8%)	185 (9.6%)	1.6 (1.1 to 2.5)	1.5 (1.0 to 2.2)
Bentazon	22 (3.4%)	58 (3.0%)	0.7 (0.3 to 1.5)	0.8 (0.4 to 1.4)
Butylate	28 (4.3%)	56 (2.9%)	1.2 (0.6 to 2.3)	1.2 (0.7 to 2.0)
Chloramben	34 (5.2%)	81 (4.2%)	0.9 (0.5 to 1.6)	0.9 (0.5 to 1.5)
Cyanazine	37 (5.7%)	96 (5.0%)	0.6 (0.3 to 1.0)	0.6 (0.4 to 1.1)
2,4-D	123 (18.9%)	314 (16.2%)	0.8 (0.6 to 1.1)	0.9 (0.6 to 1.2)
Dicamba	39 (6.0%)	79 (4.1%)	1.2 (0.6 to 2.3)	1.2 (0.7 to 2.1)
EPTC + protectant	13 (2.0%)	29 (1.5%)	1.2 (0.5 to 3.1)	1.1 (0.5 to 2.3)
Glyphosate	36 (5.5%)	61 (3.2%)	2.1 (1.1 to 4.0)	1.6 (0.9 to 2.8)
Linuron	5 (0.8%)	22 (1.1%)	0.3 (0.1 to 1.2)	0.5 (0.2 to 1.2)
MCPA	8 (1.2%)	16 (0.8%)	1.0 (0.4 to 2.6)	0.9 (0.4 to 2.0)
Metolachlor	13 (2.0%)	37 (1.9%)	0.7 (0.3 to 1.6)	0.7 (0.4 to 1.5)
Metribuzen	20 (3.1%)	53 (2.7%)	0.8 (0.4 to 1.7)	0.8 (0.4 to 1.5)
Paraquat‡	2 (0.3%)	15 (0.8%)	0.1 (0.02 to 0.7)	0.5 (0.2 to 1.2)
Propachlor	20 (3.1%)	50 (2.6%)	1.0 (0.5 to 2.0)	1.0 (0.6 to 1.9)
Sodium chlorate‡	8 (1.2%)	7 (0.4%)	4.1 (1.3 to 13.6)	1.8 (0.8 to 4.1)
2,4,5-T	25 (3.9%)	63 (3.3%)	1.0 (0.5 to 1.9)	0.9 (0.5 to 1.6)
Trifluralin	52 (8.0%)	120 (6.2%)	0.9 (0.5 to 1.6)	0.9 (0.5 to 1.4)

*Each estimate is adjusted for use of all other pesticides listed in table 3, age, and study site.
†Odds ratios (OR) and 95% confidence limits (CL).
‡Criteria for inclusion in the models was a pesticide use frequency of ≥20; however, some pesticide use frequencies are <20 in the multivariable models since observations with missing values were dropped.

hierarchical model including prior covariates and those from the hierarchical intercept-only model were virtually identical (results for intercept-only model not shown), indicating that the prior covariates representing pesticide category and carcinogenic probability were not important determinants of the variability between the observed effects, and that adjustment of estimates primarily occurred because of the a priori restriction on their variance. Indeed, a linear regression analysis of the 47 logistic regression beta coefficients for the pesticides regressed on the prior covariates found no statistically significant associations (at a significance level of $p < 0.05$; results not shown).

Among the farmers who used pesticides, the number of total pesticides ever used ranged between 1 and 32, but approximately 50% of farmers reported using only one or two pesticides. There was no association between NHL incidence and either the total number of pesticides or herbicides used (see table 4). There was a 40% increased incidence associated with the use of five or more insecticides; however, there was no apparent exposure-response trend. In an analysis of the number of "potentially carcinogenic" pesticides, NHL incidence increased by the number of pesticides used by the subject. Subjects who reported using any five or more "potentially carcinogenic" pesticides were twice as likely to be NHL cases than controls, compared to those using no pesticides. The results for "potentially carcinogenic" pesticides were highly sensitive to removal of certain pesticides from the count, including dieldrin, atrazine, or glyphosate. For example, removal of glyphosate from the count resulted in a lack of trend for increasing number of "potentially carcinogenic" pesticides (1 pesticide: OR = 1.2; 2–4 pesticides: OR = 1.2; ≥5 pesticides: OR = 1.1).

Table 4 Effect of number of pesticides used on NHL incidence*

Number of pesticides used	Exposed [n (%)] Cases (n=650)	Controls (n=1933)	Logistic regression OR (95% CL)†	Hierarchical regression OR (95% CL)
Any pesticide				
0	370	1252	1.0	1.0
1	89 (13.7%)	230 (11.9%)	1.2 (0.8 to 1.8)	1.1 (0.9 to 1.7)
2–4	87 (13.4%)	221 (11.4%)	1.0 (0.6 to 1.6)	1.0 (0.7 to 1.5)
≥5	104 (16.0%)	230 (11.9%)	0.8 (0.4 to 1.9)	1.0 (0.5 to 1.8)
Any insecticide				
0	382	1292	1.0	1.0
1	114 (17.5%)	281 (14.5%)	1.3 (0.9 to 1.9)	1.2 (0.9 to 1.7)
2–4	86 (13.2%)	237 (12.3%)	1.0 (0.5 to 1.8)	0.9 (0.6 to 1.4)
≥5	68 (10.5%)	123 (6.4%)	1.9 (0.6 to 5.7)	1.4 (0.7 to 2.9)
Any herbicide				
0	489	1544	1.0	1.0
1	50 (7.7%)	132 (6.8%)	1.0 (0.6 to 1.9)	1.1 (0.7 to 1.7)
2–4	52 (8.0%)	132 (6.8%)	0.8 (0.4 to 1.9)	1.0 (0.6 to 1.6)
≥5	59 (9.1%)	125 (6.5%)	0.8 (0.2 to 3.3)	1.0 (0.5 to 2.2)
"Potentially carcinogenic" pesticides				
0	496	1632	1.0	1.0
1	74 (11.4%)	168 (8.7%)	1.6 (0.8 to 3.1)	1.1 (0.8 to 1.7)
2–4	68 (10.5%)	123 (6.4%)	2.7 (0.7 to 10.8)	1.3 (0.7 to 2.3)
≥5	12 (1.8%)	10 (0.5%)	25.9 (1.5 to 450.2)	2.0 (0.8 to 5.2)

*Each estimate is adjusted for use of all pesticides listed in table 3, age, and study site.
†Odds ratios (OR) and 95% confidence limits (CL).

The analysis of 48 pesticide combinations in relation to NHL incidence revealed few joint effects of 1.3 or higher that were indicative of superadditivity (table 5). Combined exposures to carbofuran and atrazine, diazinon and atrazine, and alachlor and atrazine had estimated joint effects that were more than additive (ICR ≥0.5), even following shrinkage in hierarchical regression analyses. Other joint pesticide effects which seemed indicative of superadditivity in results from logistic regression analyses, such as that for atrazine and dicamba, were probably misleading due to imprecision of estimates; these results did not hold up following shrinkage in hierarchical regression analyses, according to our prior distribution of complete exchangeability.

DISCUSSION

Incidence and mortality rates for NHL have been generally increasing in the United States and in most industrialised countries for several decades, with an 85–100% increase in

Table 5 Estimated individual and joint effects of pesticide combinations on NHL incidence*†

Individual and joint pesticide exposures	Exposed [n (%)] Cases (n=650)	Controls (n=1933)	Logistic regression OR (95% CL)‡	Hierarchical regression OR (95% CL)
Chlordane and DDT				
Neither	543	1687	1.0	1.0
Chlordane only	9 (1.4%)	20 (1.0%)	1.1 (0.4 to 2.7)	1.0 (0.5 to 1.9)
DDT only	68 (10.5%)	181 (9.4%)	0.9 (0.6 to 1.3)	0.9 (0.6 to 1.2)
Both	30 (4.6%)	45 (2.3%)	1.7 (0.7 to 3.2)	1.3 (0.8 to 2.3)
Carbofuran and atrazine				
Neither	557	1728	1.0	1.0
Carbofuran only	3 (0.5%)	20 (1.0%)	0.2 (0.1 to 1.1)	0.6 (0.3 to 1.3)
Atrazine only	52 (8.0%)	109 (5.6%)	1.4 (0.9 to 2.2)	1.3 (0.9 to 1.9)
Both	38 (5.9%)	76 (3.9%)	1.6 (0.8 to 3.3)	1.5 (0.9 to 2.7)
Diazinon and atrazine				
Neither	551	1730	1.0	1.0
Diazinon only	9 (1.4%)	18 (0.9%)	1.2 (0.5 to 3.1)	1.1 (0.5 to 2.3)
Atrazine only	59 (9.1%)	141 (7.3%)	1.5 (1.0 to 2.3)	1.3 (0.9 to 1.9)
Both	31 (4.8%)	44 (2.3%)	3.9 (1.7 to 8.8)	2.3 (1.2 to 4.2)
Alachlor and atrazine				
Neither	545	1695	1.0	1.0
Alachlor only	15 (2.3%)	53 (2.7%)	0.7 (0.3 to 1.3)	0.7 (0.4 to 1.3)
Atrazine only	37 (5.7%)	86 (4.5%)	1.3 (0.8 to 2.1)	1.2 (0.8 to 1.8)
Both	53 (8.2%)	99 (5.1%)	2.1 (1.1 to 3.9)	1.6 (1.0 to 2.7)
Atrazine and dicamba				
Neither	552	1729	1.0	1.0
Atrazine only	59 (9.1%)	125 (6.5%)	1.5 (1.0 to 2.4)	1.4 (0.9 to 2.0)
Dicamba only	8 (1.2%)	19 (1.0%)	0.9 (0.3 to 2.6)	1.0 (0.5 to 2.0)
Both	31 (4.8%)	60 (3.1%)	2.1 (1.0 to 4.7)	1.6 (0.9 to 2.9)

*Effects of combined pesticide exposures were estimated in models including terms for the joint exposure, two individual exposures, the use of each other pesticide listed in table 2, age, and study site.
†Pesticide combinations considered are listed in the appendix.
‡Odds ratios (OR) and 95% confidence limits (CL).

mortality among whites and non-whites from the late 1940s to the late 1980s,[26] a time period relevant for this study. This increase may be partially attributed to improved diagnosis and in later years to AIDS related lymphomas, but cannot be completely explained by these factors.[27] Environmental factors such as pesticides could play a role in this persistent increase, since their use became more widespread during this time period.[28–30] Several aetiological mechanisms of pesticides in relation to NHL have been proposed, including genotoxicity and immunotoxicity,[31 32] increased cell proliferation,[33] and chromosomal aberrations.[34] In our analysis of multiple pesticides in farming, we found only a small number of the pesticides to be risk factors for NHL, with the highest increased risks among subjects exposed to five or more of these "potentially carcinogenic" pesticides, or those with certain combined pesticide exposures.

The large number of exposed subjects in this pooled analysis allowed adjustment for the use of other pesticides, and hierarchical regression modelling resulted in estimates that were in some instances more stable than those from logistic regression models. However, the effect estimates from the logistic and hierarchical analyses were quite similar overall, with a few standout exceptions. The hierarchical results are more conservative than those from the logistic regressions, given the uninformed nature of the prior distributions we specified, particularly in analyses of the number of pesticides used and combined pesticide exposures. For example, in the hierarchical regression analysis of the number of pesticides used, we assumed that the use of any five or more pesticides was no more likely to be associated with NHL than use of any one pesticide. A less conservative prior distribution could have been specified in which a higher probability would be placed on a positive association for the greater number of pesticides used. However, the uninformed nature of these priors seemed appropriate in a largely exploratory analysis of multiple exposures for which there is little prior knowledge about how pesticide exposures interact in relation to the risk of NHL. Both analyses showed increasing odds ratios with the number of "potentially carcinogenic" pesticides used, but the relative risks in the upper category were substantially different—25.9 for the logistic regression and 2.0 for the hierarchical analysis—probably indicating inappropriate use of logistic regression for these sparse data.

Adjustment for multiple pesticides suggested that there were few instances of substantial confounding of pesticide effects by other pesticides. Nevertheless, some previous findings in our data appear to be due to confounding by correlated pesticide exposures. In particular, a previously reported positive association for carbaryl[13] was not replicated in the adjusted analyses. Further analysis here revealed that carbaryl and diazinon use were highly associated ($p < 0.001$), and previously reported associations of different carbaryl measures with NHL were eliminated by adjustment for diazinon, including carbaryl use, personal handling of carbaryl, and use longer than 10 years. In the previous analysis, estimates were adjusted for groups of pesticides, including a group for organophosphate insecticides,[13] but adjustment for specific pesticides here gave different results. Similarly, previous observations of increased NHL risk associated with use of the OP insecticides dimethoate and tetrachlorvinphos[12] were negligible on inclusion of other OP insecticides in the model. These findings underscore the importance of considering correlated pesticide exposures.

Our observation of increased risk associated with the use of certain OP insecticides, including coumaphos, diazinon, and fonofos, is consistent with previous analyses of the pooled data,[12 20] and also corroborates findings of other studies.[8 34] OP insecticides are known to cause cytogenetic damage, and could thereby contribute to NHL aetiology.[35] There are data from in vitro, animal, and human studies that show effects of several OP insecticides on the immune system,[36–40] indicating another potential mechanism. OP compounds may impair immune function through pathways involving cholinergic stimulation,[41] or inhibition of serine esterases found in monocytes, natural killer cells, and cytotoxic T lymphocytes,[42] but it is unknown whether such immune effects might be chemical specific or related to general OP toxicity. Our data do not indicate an aetiological mechanism for NHL common to all OP insecticides, since increased NHL incidence was associated only with certain OPs evaluated.

We observed a possible effect of the organochlorine insecticides chlordane and dieldrin. There is some evidence that chlordane is immunotoxic, causing decreased lymphocyte function in vitro.[43] The concentration of chlordane in adipose tissue was higher among NHL cases than controls in a small case-control study in Sweden,[44] but a larger study in the United States found no such association.[45] Although these chemicals have been banned in the United States, their continued use in some developing countries, and bioaccumulation of their chemical residues in the food chain,[46] justify further research on health effects.

Use of the herbicide atrazine was associated with increased risk of NHL. Increased risk was observed in each of the three pooled studies separately, but a previous analysis of the Nebraska study data found that the risk was diminished on adjustment for use of OP insecticides and 2,4-D.[20] There have been few other epidemiological studies of atrazine in relation to NHL. In a cohort of triazine herbicide manufacturing workers, there was an excess number of deaths from NHL ($n = 3$) among a group of men with definite or probable exposure; however, some of the cases worked in triazine related jobs for short time periods, thus clouding interpretation.[47] A recent NHL study where cases were further distinguished by presence or absence of the t(14;18) chromosomal translocation found that the risk of NHL associated with atrazine use was solely observed among t(14;18) positive cases, suggesting a cytogenetic mechanism.[14] However, there is only very limited evidence for genotoxicity of atrazine, although there are no studies in humans.[48] A small number of studies of atrazine on immune function in rodents and in vitro suggest a decreased lymphocyte count and cytokine production following exposure; however, these effects were not always dose dependent or statistically significant.[17 48 49] In our data, there was an indication of superadditive effects of atrazine in combination with carbofuran, diazinon, or alachlor. This is a factor to consider in future studies of this widely used pesticide.

Glyphosate, commercially sold as Roundup, is a commonly used herbicide in the United States, both on crops and on non-cropland areas.[50] An association of glyphosate with NHL was observed in another case-control study, but the estimate was based on only four exposed cases.[51] A recent study across a large region of Canada found an increased risk of NHL associated with glyphosate use that increased by the number of days used per year.[8] These few suggestive findings provide some impetus for further investigation into the potential health effects of glyphosate, even though one review concluded that the active ingredient is non-carcinogenic and non-genotoxic.[50]

Much attention in NHL research has focused on the herbicide 2,4-D as a potential risk factor, and several studies have observed positive associations with 2,4-D exposure.[6 8 9] Whereas an indicated effect of 2,4-D exposure on NHL was reported in NCI's Nebraska and Kansas studies,[5 7] this analysis of the pooled data found no association with having ever used 2,4-D. The null association does not result from adjustment for other pesticides, missing data, or from the hierarchical regression modelling approach, but is rather due to pooling data from the Iowa and Minnesota study, in which no association of 2,4-D with NHL incidence was observed, with data from the Nebraska and Kansas studies. The literature on the relation between 2,4-D and NHL is not consistent.[32 52] Some recent studies have reported excess risk among

manufacturers[33] and farmers,[8] while others have not.[31] The study in Nebraska,[5] however, observed that NHL risk increased by number of days per year of 2,4-D use, which we were unable to duplicate in the pooled analysis because of lack of such data from the other two studies. It is possible that a more refined metric incorporating frequency of use better captures relevant exposure. Some recent studies may shed light on potential mechanisms of 2,4-D in relation to NHL. A study of 10 farmers who applied 2,4-D and MCPA observed a significant reduction of several immune parameters, including CD4, CD8, natural killer cells, and activated CD8 cells (expressing the surface antigen HLA-DR), and a reduction in lymphoproliferative response.[34] Furthermore, a study of professional 2,4-D applicators in Kansas observed an increase in the lymphocyte replication index following application.[35]

This pooled study of multiple agricultural pesticides provided an opportunity to estimate the effect of each specific pesticide and certain pesticide combinations on NHL incidence, adjusted for the use of other pesticides. Overall, few pesticides and pesticide combinations were associated with increased NHL risk; this has several implications. First, it is consistent with results from bioassays where only a few of the pesticides tested have caused cancer in laboratory animals.[35] Although epidemiological data on cancer risks from exposure to specific pesticides are scant, it also suggests that while some pesticides may present a cancer risk to humans, many, maybe even most, pesticides do not. Second, the fact that there were few associations suggests that the positive results we observed are not likely to be due to a systematic recall bias for pesticide exposures, or selection bias for the subgroup included in the analyses of multiple pesticides. Third, although some of the positive results could be due to chance, the hierarchical regression analysis placed some restriction on the variance of estimates, theoretically decreasing the chances of obtaining false positive results. On the other hand, it is possible that the assumptions for the hierarchical regression are too restrictive and that this has increased the number of false negatives.

Certain limitations of our data hinder the inferences we can make regarding specific pesticides in their association with NHL. Our exposure metric of having ever used a pesticide is rather crude, offering no distinctions based on use by the number of years or the number of days per year. Further exploration of observed associations by more refined exposure metrics is warranted. In addition, this analysis provides no information on the timing of pesticide use in relation to disease onset or in conjunction with the timing of other pesticides used. This has particular relevance in our analysis of "combined pesticide exposures", in which two pesticides may or may not have been used at the same time or even during the same year. Lastly, if a study subject had a missing value for any one of the 47 pesticides evaluated, that person was excluded from analyses, resulting in analyses on a limited subset (about 75%) of the pooled study population. Although we have no way to evaluate potential bias due to missing data, some assurances are provided by the fact that cases and controls were equally likely to be included in analyses, and that there were similarities between the entire group of study subjects and subjects included our analyses, in terms of NHL status in relation to demographic factors (table 2). If simultaneous analysis of multiple exposures is to become standard, statistical techniques to impute values for subjects with "don't know" or missing responses should be further developed in order to prevent biased results.

Despite limitations of our study, certain inferences are possible. Our results indicate increased NHL incidence by number of pesticides used, only for the subgroup of "potentially carcinogenic" pesticides, suggesting that specific chemicals, not pesticides, insecticides, or herbicides, as groups, should be examined as potential risk factors for NHL. In addition, argument against an analysis approach focused on classes or groups of pesticides is provided by the fact that our prior covariates of pesticide classes and groups in the hierarchical regression model were not important predictors of the magnitude of observed pesticide effects. A chemical specific approach to evaluating pesticides as risk factors for NHL should facilitate interpretation of epidemiological studies for regulatory purposes. However, the importance of additionally considering multiple correlated exposures is clear.

APPENDIX

Table A1 shows the pesticide combinations considered in analyses of joint and individual exposures.

Table A1 Pesticide combinations considered in analyses of joint and individual exposures

Insecticides	Insecticide and herbicide	Herbicides
DDT and chlordane	Aldrin and alachlor	Alachlor and atrazine
DDT and lindane	Aldrin and atrazine	Alachlor and chloramben
DDT and malathion	Aldrin and 2,4-D	Alachlor and cyanazine
DDT and fly, lice, or tick spray	Aldrin and trifluralin	Alachlor and 2,4-D
DDT and aldrin	Carbofuran and alachlor	Alachlor and dicamba
Lindane and malathion	Carbofuran and atrazine	Alachlor and glyphosate
Lindane and aldrin	Carbofuran and 2,4-D	Alachlor and trifluralin
Malathion and aldrin	Chlordane and 2,4-D	Atrazine and cyanazine
	DDT and alachlor	Atrazine and 2,4-D
	DDT and atrazine	Atrazine and dicamba
	DDT and 2,4-D	Atrazine and glyphosate
	DDT and trifluralin	Atrazine and trifluralin
	Diazinon and atrazine	Chloramben and trifluralin
	Fly, lice, or tick spray and alachlor	Cyanazine and 2,4-D
	Fly, lice, or tick spray and atrazine	Cyanazine and trifluralin
	Fly, lice, or tick spray and 2,4-D	2,4-D and trifluralin
	Fly, lice, or tick spray and trifluralin	
	Lindane and alachlor	
	Lindane and atrazine	
	Lindane and 2,4-D	
	Lindane and trifluralin	
	Malathion and alachlor	
	Malathion and atrazine	
	Malathion and 2,4-D	

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NON-HODGKIN'S LYMPHOMA AMONG ASTHMATICS EXPOSED TO PESTICIDES

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We conducted a pooled analysis of population-based case-control studies in Iowa, Minnesota and Nebraska to investigate whether asthma modifies risk of non-Hodgkin's lymphoma (NHL) associated with pesticide exposures. Cases (n = 872) diagnosed with NHL from 1980 to 1986 and frequency-matched controls (n = 2,381) randomly selected from the same geographic areas as the cases were included. Information on use of pesticides and history of asthma was based on interviews. Unconditional logistic regression was used to calculate ORs, adjusted for age, state and vital status. Of all subjects, 177 (45 cases, 132 controls) reported having been told by their doctor that they had asthma. Subjects with an asthma history had a nonsignificantly lower risk of NHL than nonasthmatics (OR = 0.6, 95% CI 0.3–1.4), and there was no main effect of pesticide exposure (OR = 1.0, 95% CI 0.8–1.2). However, asthmatics tended to have larger ORs associated with exposure to pesticides than nonasthmatics. The OR among asthmatics was 1.8 (95% CI 1.1–3.2) for ever-use of crop insecticides, 2.7 (95% CI 1.0–7.2) for chlordane, 2.4 (95% CI 1.0–5.7) for lindane and 3.7 (95% CI 1.3–10.9) for fonofos. Among nonasthmatics, ORs were 1.1 (0.9–1.3), 1.5 (1.1–2.2), 1.3 (0.97–1.8) and 1.6 (1.0–2.4), respectively. Although there is limited power for assessing interaction, our results suggest that the risk of NHL among asthmatics with pesticide exposure may be higher than among nonasthmatics with pesticide exposure.

Key words: *asthma; insecticide; farmer; non-Hodgkin's lymphoma; pesticide exposure*

Incidence and mortality rates for non-Hodgkin's lymphoma (NHL) have been increasing worldwide over the past several decades.[1] Although the reasons for this increase are not fully understood, NHL is known to be associated with a compromised immune system, particularly acquired or genetic immunodeficiencies.[2,3] Medical conditions related to more subtle immune alteration, such as asthma and other allergic conditions, have also been studied as potential risk factors for NHL.[4–10] These reports have described a decreased risk for NHL among persons with a history of asthma or allergies,[4,5] no association[6–8] or an increase in risk.[9,10] Exposure to pesticides has also been suggested as a possible risk factor for NHL.[11–15] Pesticides may increase cancer risk by altering the immune system.[16–19] Because both asthma and pesticide exposure may change the risk of NHL by immunologic alterations, we investigated the relation between pesticide exposure, asthma and risk of NHL.

MATERIAL AND METHODS

Study population

We pooled data from 2 population-based case-control studies of NHL in 3 midwestern states in the United States, which have been described in detail previously.[20,21] In Iowa and Minnesota, all newly diagnosed cases of NHL among white men aged ≥30 were ascertained from records of the Iowa State Health Registry and a special surveillance system of Minnesota hospitals and pathology laboratories from 1980 to 1983 (n = 530). In Nebraska, all cases of NHL diagnosed between July 1983 and June 1986 among white men and women aged ≥21 in 45 eastern counties were identified through the Nebraska Lymphoma Study Group and area hospitals (n = 346). All cases were reviewed by pathologists, and only histologically confirmed cases were included in this analysis. Controls were randomly selected from the same geographic areas as cases with frequency matching by race, gender, age (5-year age group) and vital status at the time of interview. Control/case matching ratios were approximately 2:1 in Iowa and Minnesota and 4:1 in Nebraska. For living cases under the age of 65, controls were selected by 2-stage random digit dialing.[22] For living cases aged 65 and over, controls were selected from the records of the Health Care Financing Administration. Controls for deceased cases were selected from death records in each state, with additional matching for year of death. Persons whose underlying cause of death was NHL, Hodgkin's lymphoma, multiple myeloma, leukemia or malignancy of unknown sites were excluded as controls. A total of 2,357 controls (Nebraska 1,318, Iowa and Minnesota 1,039) were identified.

Interview

Interviews were conducted with subjects or their next-of-kin if subjects were dead or incapacitated. Interviews were held in person in Iowa and Minnesota and by telephone in Nebraska. Participation rates among cases were 89% in Iowa and Minnesota and 91% in Nebraska. Among controls, rates were 78% in Iowa and Minnesota and 85% in Nebraska. We used standardized and structured questionnaires to collect information on use of pesticides and other known or suspected risk factors for NHL. Questions included personal handling of groups of pesticides and individual pesticides used on crops or animals, with year of first and last use. We also asked whether subjects had ever been told by a doctor that they had asthma and, if so, their age at first diagnosis.

Statistical analysis

Subjects who did not have any information on asthma (n = 25) were excluded from the pooled data set, leaving 872 cases and 2,336 controls eligible for analysis. We used unconditional logistic regression to obtain odds ratios (ORs) and 95% confidence intervals (CIs) with Stata software (version 7.0).[23] The ORs for NHL among farmers exposed to pesticides with asthma were compared to those of nonfarmers without asthma (*i.e.*, individuals who had never lived or worked on a farm and did not have asthma) and to those of farmers without asthma. We estimated the risk of NHL by reported use of individual pesticides where sufficient numbers of exposed subjects were available. We present ORs for pesticides

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that were personally handled by at least 5 exposed cases. The logistic model included age (<60, 60–75, >75), state (Iowa, Minnesota, Nebraska) and vital status (alive, dead). Other variables, such as gender, smoking, having a first-degree relative with lymphohematopoietic cancer, ever having a job correlated with lymphohematopoietic cancers (*e.g.*, painting or welding) and use of protective equipment, were also evaluated as possible confounders. Adjustments of ORs for these variables had minimal impact on risk estimates of NHL, and the latter 2 variables have some missing cases. These variables were not included in the final model. To assess possible reporting bias, risks were estimated including and excluding proxy respondents. We also explored the risk of NHL by age at first diagnosis of asthma and duration of pesticide use.

RESULTS

Table I shows the distribution of the 872 cases and 2,336 controls by asthma history, age, gender, vital status, state of residence, having a first-degree relative with lymphohematopoietic cancer and type of NHL. Of the total subjects, 177 (5.5%) reported having been told by their doctor that they had asthma. Asthmatic NHL cases were more likely than asthmatic controls to be younger, male, alive at the time of interview and residing in Iowa. Nonasthmatic NHL cases were more likely than nonasthmatic controls to be male, to have family history of lymphohematopoietic cancer and to reside in Iowa/Minnesota.

We evaluated ORs for NHL by pesticide groups and asthma history (Table II). Among nonfarmers, subjects with asthma had a lower risk for NHL (not statistically significant) compared to nonfarmers without asthma (OR = 0.6, 95% CI 0.3–1.4). ORs for NHL among farmers without asthma were near 1.0 for all pesticide categories except chemical classes of insecticide. The risk of NHL was significantly increased for exposure to crop insecticides (OR = 1.8, 95% CI 1.1–3.2) and nonsignificantly increased for exposure to livestock insecticides (OR = 1.4, 95% CI 0.9–2.3), herbicides (OR = 1.5, 95% CI 0.9–2.5) and fungicides (OR = 1.4, 95% CI 0.5–4.3) among farmers with asthma. Only organophosphate insecticides had significant ORs among both asthmatics and nonasthmatics. The pattern was consistent by state of residence or interview type, although the results were limited by small numbers of cases (data not shown).

Table III presents ORs for NHL among farmers exposed to individual pesticides by asthma history. Among insecticides, risk of NHL was significantly elevated with exposure to chlordane (OR = 2.7, 95% CI 1.0–7.2), fonofos (OR = 3.7, 95% CI 1.3–10.9) and lindane (OR = 2.4, 95% CI 1.0–5.7) in asthmatics compared to nonfarmers without asthma. Many other insecticides (aldrin, carbaryl, carbofuran, diazinon, dieldrin, flyspray, heptachlor, malathion) also had larger ORs among farmers with a history of asthma than among those without asthma. However, none of these was significantly different from the risks in nonasthmatics. Among nonasthmatics, risk of NHL was also significantly elevated with exposure to chlordane, diazinon, fonofos and malathion; but the magnitude of risk was smaller than that among asthmatics. Use of individual herbicides was also associated with increased risk of NHL among asthmatics compared to nonasthmatics, but only cyanazine had a significant OR. No fungicide had 5 or more exposed cases and was significantly associated with NHL.

Analyses of pesticide exposure and asthma history among farmers only are presented in Table IV. The reference category was nonasthmatic farmers not exposed to each pesticide. Asthmatics with exposure to crop insecticides had significantly elevated risk of NHL (OR = 2.0, 95% CI 1.1–3.5), but the interaction risk for pesticide exposure and asthma was not statistically significant.

We explored the potential modifying effects of age at first diagnosis of asthma and duration of pesticide use on risk of NHL (Table V). Only asthmatic farmers exposed to pesticides were included in this analysis. Risks among subjects diagnosed with asthma after age 30 tended to be higher for all types of pesticide than those among subjects who had developed asthma relatively early. There was no clear pattern of ORs for NHL by duration of pesticide use and age at diagnosis of asthma. The results were limited due to the small number of asthmatic NHL cases, and further studies are needed to investigate these findings.

DISCUSSION

We found that farmers with potential exposure to pesticides and a history of asthma tended to have higher relative risks for NHL than pesticide-exposed farmers not reporting asthma. The excess risks among asthmatics with pesticide exposure were generally more pronounced when we analyzed by individual pesticides (*e.g.*,

TABLE I – CHARACTERISTICS OF CASES AND CONTROLS BY ASTHMA HISTORY

Characteristics	Nonasthmatics (n = 3,031)		Asthmatics (n = 177)	
	Cases (n = 827)	Controls (n = 2,204)	Cases (n = 45)	Controls (n = 132)
Age (years)				
<60	231 (27.9)[2]	585 (26.5)	18 (40.0)	24 (18.2)
60–75	348 (42.1)	875 (39.7)	17 (37.8)	51 (38.6)
>75	248 (30.0)	744 (33.8)	10 (22.2)	57 (43.2)
Gender				
Male	676 (81.7)	1,594 (72.3)	38 (84.4)	100 (75.8)
Female	151 (18.3)	610 (27.7)	7 (15.6)	32 (24.2)
Vital status				
Alive	572 (69.2)	1,486 (67.4)	34 (75.6)	71 (53.8)
Dead	255 (30.8)	718 (32.6)	11 (24.4)	61 (46.2)
State of residence				
Iowa	238 (28.8)	483 (21.9)	15 (33.3)	26 (19.7)
Minnesota	264 (31.9)	491 (22.3)	10 (22.2)	28 (21.2)
Nebraska	325 (39.3)	1,230 (55.8)	20 (44.5)	78 (59.1)
Family history of cancer[1]				
No	733 (90.7)	2,072 (95.4)	42 (93.3)	120 (92.3)
Yes	75 (9.3)	99 (4.6)	3 (6.7)	10 (7.7)
Histologic type				
Follicular	243 (29.5)	—	18 (40.9)	—
Diffuse	298 (36.1)	—	16 (36.4)	—
Small lymphocytic	90 (10.9)	—	4 (9.1)	—
Other	194 (23.5)	—	6 (13.6)	—

[1]Lymphohematopoietic cancers diagnosed in any first-degree relative.–[2]Percentage in parentheses.

TABLE II – RISKS OF NHL BY FARMING HISTORY, PESTICIDE USE AND ASTHMA HISTORY

	Nonasthmatics				Asthmatics			
	Cases	Controls	OR[1]	95% CI	Cases	Controls	OR	95% CI
Nonfarmers	259	684	1.0	Ref[2]	9	37	0.6	0.3–1.4
Farmers	560	1,510	1.0	0.8–1.2	36	95	1.1	0.7–1.6
No pesticide use	137	419	1.0	0.8–1.3	3	14	0.7	0.2–2.6
Pesticide use	423	1,091	1.0	0.8–1.2	33	81	1.1	0.7–1.7
Animal insecticides	363	900	1.0	0.8–1.2	28	52	1.4	0.9–2.3
Crop insecticides	239	572	1.1	0.9–1.3	23	32	1.8	1.1–3.2
Organochlorine	205	412	1.2	0.9–1.5	17	28	1.5	0.8–2.8
Organophosphate	149	269	1.4	1.1–1.7	14	17	2.0	1.0–4.2
Carbamate	79	154	1.3	0.9–1.7	8	9	2.2	0.8–5.9
Herbicides	260	639	1.0	0.8–1.3	23	43	1.5	0.9–2.5
Phenoxyacetic acid	176	409	1.0	0.8–1.3	17	33	1.3	0.7–2.4
Triazine	131	268	1.1	0.9–1.5	12	17	1.7	0.8–3.7
Amides	105	231	1.1	0.8–1.4	11	15	1.8	0.8–3.9
Fungicides	44	110	1.0	0.7–1.4	5	10	1.4	0.5–4.3

[1]OR adjusted for age, vital status and state.–[2]Ref, reference category was nonfarmers without asthma (259 cases, 684 controls) for all ORs.

TABLE III – RISKS OF NHL AMONG FARMERS EXPOSED TO INDIVIDUAL PESTICIDES[1] BY ASTHMA HISTORY

	Nonasthmatics				Asthmatics			
	Cases	Controls	OR[2]	95% CI	Cases	Controls	OR	95% CI
Nonfarmers	259	684	1.0	Ref[3]	9	37	0.6	0.3–1.4
Insecticides								
Aldrin	66	148	1.0	0.7–1.5	10	11	2.1	0.9–5.1
Carbaryl	42	77	1.4	0.9–2.0	6	6	2.4	0.8–7.6
Carbofuran	56	117	1.2	0.8–1.7	6	8	1.9	0.7–5.6
Chlordane	67	108	1.5	1.1–2.2	9	8	2.7	1.0–7.2
DDT	158	313	1.2	0.9–1.5	11	24	1.2	0.6–2.4
Diazinon	58	98	1.6	1.1–2.3	7	9	1.9	0.7–5.3
Dieldrin	30	63	1.2	0.7–1.9	5	3	4.2	0.98–18.2
Flyspray	189	442	0.9	0.7–1.1	14	27	1.1	0.6–2.2
Fonofos	41	69	1.6	1.0–2.4	8	6	3.7	1.3–10.9
Heptachlor	44	84	1.3	0.9–2.0	6	6	2.6	0.8–8.4
Lindane	84	146	1.3	0.97–1.8	11	11	2.4	1.0–5.7
Malathion	89	141	1.5	1.1–2.1	7	9	1.9	0.7–5.1
Herbicides								
2,4-D	172	402	1.0	0.8–1.3	17	33	1.3	0.7–2.5
2,4,5,-T	36	77	1.1	0.7–1.8	7	8	2.2	0.8–6.1
Alachlor	96	210	1.1	0.8–1.4	10	14	1.7	0.8–4.0
Atrazine	119	225	1.3	0.96–1.6	9	16	1.4	0.6–3.3
Butylate	38	75	1.1	0.7–1.7	5	6	2.0	0.6–6.9
Chloroamben	52	103	1.1	0.8–1.6	9	10	2.3	0.9–5.7
Cyanazine	53	131	0.9	0.6–1.3	8	7	2.8	1.0–8.1
Dicamba	49	106	1.0	0.7–1.5	6	7	2.0	0.6–6.0
Glyphosate	53	91	1.4	0.98–2.1	6	12	1.2	0.4–3.3
Trifluralin	73	168	1.0	0.7–1.3	8	10	1.9	0.7–4.8

[1]At least 5 cases handled each individual pesticide were included in this analysis.–[2]OR adjusted for age, vital status and state.–[3]Ref, reference category was nonfarmers without asthma (259 cases, 684 controls) for all ORs.

chlordane, fonofos, lindane, cyanazine) and occurred when either "nonfarmers" or "farmers" was used as the reference.

Although we had limited power for assessing effect modification, there might be synergism between asthma and pesticide exposure for developing NHL. One possible explanation is that there is immune deviation in asthma toward T-helper 2 (Th2) predominance, with elevated IL-4, IL-5 and IL-13, which might inhibit Th1 responses that could protect against cancer.[24,25] This skewing of the immune response toward the Th2 phenotype could exacerbate the effects of the pesticides, which may partly act as carcinogens, and may also inhibit the immune response, acting synergistically with the asthma. Some pesticides might also inhibit a different arm of the immune response, *e.g.*, cytotoxic T lymphocytes or natural killer (NK) cells,[26,27] so that the combination of asthma and pesticides exposure eliminates more than one mechanism of immunosurveillance. Moreover, IL-13, which is prominent in asthma, can also downregulate cytotoxic T lymphocyte–mediated tumor immunosurveillance,[28] reducing 2 arms of the immune response to cancer and specifically crippling immunosurveillance against cancer in a murine tumor model.

Various characteristics, such as history of allergy and serum IgE levels, between late-onset and early-onset asthma[29–31] might be related to higher risk of NHL among individuals diagnosed with asthma over age 30. Exposure to pesticides may influence the induction and aggravation of asthma through modification of autonomic control of airways.[32] Associations between asthma and use of cholinesterase-inhibiting pesticides were observed among Canadian farmers[33] and U.S. pesticide applicators.[34]

The strengths of our pooled study are a population-based design, high response rates and detailed information on pesticide use and potential etiologic factors for NHL. The relatively large sample size facilitated the simultaneous evaluation of asthma and pesticide use but was still not enough to carefully evaluate individual pesticides and asthma in relation to NHL.

We used self-reported information concerning prior asthma history. The sensitivity of ascertainment of physician-diagnosed asthma has been estimated at about 68% and the specificity at about 94% when validated against clinical diagnosis.[35] This type of misclassification is likely to cause underestimation of the asso-

TABLE IV – RISKS OF NHL AMONG FARMERS BY PESTICIDE EXPOSURE AND ASTHMA HISTORY[1]

	Nonasthmatics			Asthmatics			Interaction OR (95% CI)
	Cases	OR[2]	95% CI	Cases	OR	95% CI	
Any pesticide							
No	137	1.0	Ref[3]	3	0.7	0.2–2.5	
Yes	423	1.0	0.8–1.2	33	1.1	0.7–1.7	1.6 (0.4–6.2)
Crop insecticides							
No	252	1.0	Ref	12	0.9	0.5–1.8	
Yes	239	1.2	0.9–1.4	23	2.0	1.1–3.5	1.9 (0.8–4.6)
Animal insecticides							
No	143	1.0	Ref	6	0.8	0.3–2.1	
Yes	363	1.0	0.8–1.3	28	1.4	0.9–2.4	1.7 (0.6–4.9)
Herbicides							
No	232	1.0	Ref	12	1.0	0.5–1.9	
Yes	260	1.1	0.9–1.4	23	1.6	0.9–2.8	1.4 (0.6–3.4)
Fungicides							
No	433	1.0	Ref	28	1.2	0.8–1.9	
Yes	44	1.0	0.7–1.5	5	1.5	0.5–4.5	1.2 (0.4–4.2)

[1]Nonfarmers were excluded from this analysis.–[2]OR, adjusted for age, vital status and state.–[3]Ref, reference category was nonasthmatic farmers not exposed to each pesticide.

TABLE V – RISKS OF NHL AMONG ASTHMATIC FARMERS BY AGE AT FIRST DIAGNOSIS OF ASTHMA AND DURATION OF PESTICIDE USE[1]

Age at first diagnosis (years)	Duration of pesticide use					
	≤50th percentile			>50th percentile		
	Cases	OR[2]	95% CI	Cases	OR	95% CI
Any pesticide						
≤30	3	1.0	Ref[3]	8	4.5	0.7–27.3
>30	6	16.3	1.7–156.8	6	5.0	0.7–37.1
Crop insecticides						
≤30	4	1.0	Ref	6	2.5	0.3–19.6
>30	3	2.3	0.2–31.1	4	14.1	0.8–257.7
Animal insecticides						
≤30	3	1.0	Ref	6	2.8	0.4–19.5
>30	4	15.1	0.95–240.2	8	5.0	0.7–37.8
Herbicides						
≤30	2	1.0	Ref	6	1.7	0.1–29.4
>30	4	3.2	0.1–99.5	4	2.3	0.1–51.3

[1]Only asthmatic farmers exposed to pesticides were included in this analysis.–[2]OR adjusted for age, vital status and state.–[3]Ref, reference category was asthmatic farmers in the category of ≤30 years of age at first diagnosis of asthma and ≤50th percentile of each pesticide use.

ciation between asthma history and NHL risk. However, we think misclassification *per se* is unlikely to explain the observed effect of asthma because the reported prevalence of asthma in our study (5.5%) was consistent with that reported in other populations, ranging from 5% in the Agricultural Health Study in the United States[34] to 4–6% in rural Saskatchewan in Canada.[33,36] Asthma prevalence was also similar by self (5%) and proxy (6%) respondents.

Although farmers provide considerably accurate detail regarding past pesticide use,[37–39] misclassification of exposure is a concern. Use of proxy respondents may introduce nondifferential misclassification bias;[40] however, responses from proxies are reported to be adequate for epidemiologic studies of pesticides and cancer.[41] Our analyses based on direct interviews found the same pattern of results as seen for proxy respondents (data not shown). Based on a study of the quality of information on pesticide use provided by farmers or their proxy respondents,[42] the degree of misclassification was generally in the range observed for other factors obtained by interview in epidemiologic studies of such factors as diet and use of tobacco and alcohol. Therefore, it appears unlikely that misclassification of exposure could explain the observed increase in the risk of NHL among asthmatics exposed to pesticides.

Differential reporting bias is also a concern in case-control studies and could have resulted from an increased likelihood of cases to remember pesticide exposures compared to controls. However, comparison of reporting by cases and controls regarding pesticide use among our subjects provided no evidence of differential response bias.[37]

In summary, our findings suggest that the risk of NHL among asthmatics with pesticide exposure may be higher than that among nonasthmatics with pesticide exposure. Considering the widespread use of pesticides and the relatively high prevalence of asthma, further studies, particularly with carefully defined asthma diagnosis and biomarkers, such as cytokine levels and activity of different T and NK cells, are needed to confirm these findings and clarify the mechanisms involved.

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Occupational Cancer Research Centre

An Evaluation of Glyphosate Use and the Risk of Non-Hodgkin Lymphoma Major Histological Sub-Types in the North American Pooled Project

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Towards a cancer-free workplace

Disclosure of Competing Financial Interests

None

IARC Evaluation of Glyphosate

- Limited evidence of NHL in humans and sufficient evidence of cancer in animals
- Mechanistic evidence of genotoxicity and oxidative stress
- Classified as Group 2A (probably carcinogenic)

Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate

In March, 2015, 17 experts from 11 countries met at the International Agency for Research on Cancer (IARC; Lyon, France) to assess the carcinogenicity of the organophosphate pesticides tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate (table). These assessments will be published as volume 112 of the IARC Monographs.[1]

The insecticides tetrachlorvinphos to the bioactive metabolite, paraoxon, is similar across species. Although bacterial mutagenesis tests were negative, parathion induced DNA and chromosomal damage in human cells in vitro. Parathion markedly increased rat mammary gland terminal end bud density.[4] Parathion use has been severely restricted since the 1980s.

The insecticides malathion and diazinon were classified as "probably aggressive cancers after adjustment for other pesticides.[5] In mice, malathion increased hepatocellular adenoma or carcinoma (combined).[10] In rats, it increased thyroid carcinoma in males, hepatocellular adenoma or carcinoma (combined) in females, and mammary gland adenocarcinoma after subcutaneous injection in females.[4] Malathion is rapidly absorbed and distributed. Metabolism to the

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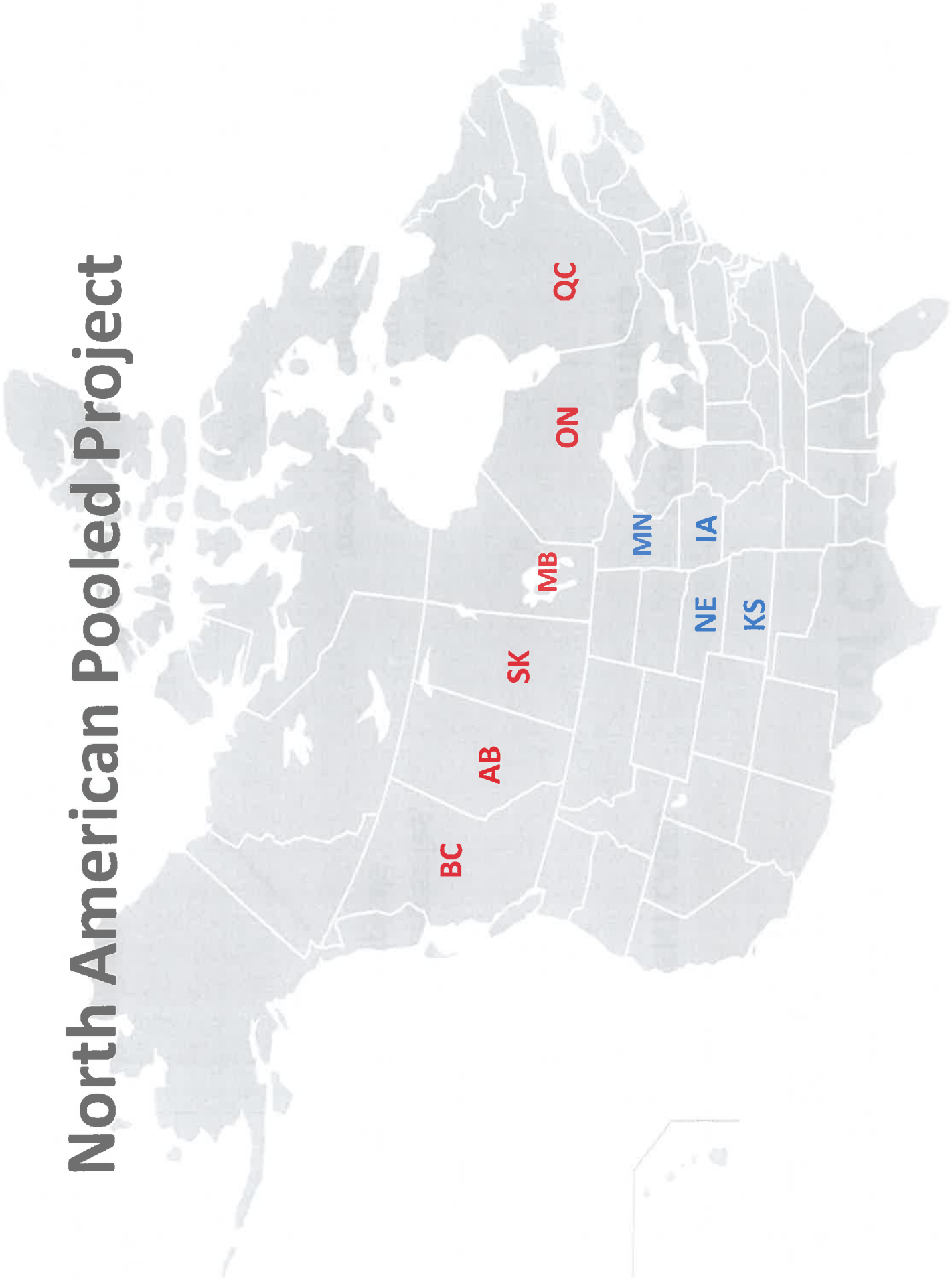
Towards a cancer-free workplace

International Survey of Herbicide Resistant Weeds: http://weedscience.org/graphs/geochart.aspx


North American Pooled Project
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KS

General Design of Case-Control Studies

INCIDENT CASES

Cancer registries, hospitals

POPULATION-BASED CONTROLS

Telephone lists, voters' lists, health insurance records, mortality records

QUESTIONNAIRE
(in person, phone, mail)

Glyphosate Use Information

	EVER/NEVER	DURATION # Years	FREQUENCY # Days/Year	LIFETIME DAYS # Years x # Days/Year
Iowa/Minnesota	✓	✓	X	X
Kansas	✓	X	X	X
Nebraska	✓	✓	✓	✓
Canada	✓	✓	✓	✓

Conceptual Framework for Analysis

Glyphosate Use

Ever/Never
Duration
Frequency
Lifetime days

NHL Risk

Overall
FL
DLBCL
SLL
Other

Covariates

Age, sex, state/province, lymphatic/hematopoietic cancer in a first-degree relative, proxy respondent use, any PPE use; *2,4-D, dicamba, malathion use*

Selected Characteristics of NHL Cases and Controls

Variable	Cases (N)	Controls (N)	OR* (95% CI)
N	1690	5131	
Histological sub-type			
Follicular (FL)	468		
Diffuse (DLBCL)	647		
Small lymphocytic (SLL)	171		
Other	404		
Location			
U.S.	1177	3625	
Canada	513	1506	
Respondent type			
Self	1140	3372	1
Proxy	533	1692	1.01 (0.89, 1.15)
Unknown/missing	17	67	
Lymphatic or hematopoietic cancer in a first-degree relative			
No	1493	4790	1
Yes	139	202	2.13 (1.69, 2.67)
Unknown/missing	58	139	

*ORs adjusted for age and location

Glyphosate Use and NHL Risks

NHL sub-type	Number of cases who reportedly ever used glyphosate	OR[a] (95% CI)	OR[b] (95% CI)
Overall	113	1.43 (1.11, 1.83)	1.13 (0.84, 1.51)
FL	28	1.00 (0.65, 1.54)	0.69 (0.41, 1.15)
DLBCL	45	1.60 (1.12, 2.29)	1.23 (0.81, 1.88)
SLL	15	1.77 (0.98, 3.22)	1.79 (0.87, 3.69)
Other	25	1.66 (1.04, 2.63)	1.51 (0.87, 2.60)

a. ORs adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, use of any personal protective equipment; b. ORs adjusted for all covariates in model (a) plus use of 2,4-D, use of dicamba, use of malathion

Duration (#Years) of Glyphosate Use and NHL Risks

# years	OR* (95% CI)				
	Overall	FL	DLBCL	SLL	Other
0	1	1	1	1	1
>0 and ≤3.5	1.59 (1.13, 2.22)	0.95 (0.52, 1.74)	2.02 (1.28, 3.21)	1.49 (0.63, 3.58)	2.08 (1.14, 3.78)
>3.5	1.20 (0.82, 1.75)	0.88 (0.46, 1.71)	1.19 (0.67, 2.12)	1.98 (0.89, 4.39)	1.32 (0.64, 2.71)
P-trend	0.03	0.96	0.03	0.08	0.14

*ORs adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, use of any personal protective equipment

Frequency (#Days/Year) of Glyphosate Handling and NHL Risks

# days/year handled	OR* (95% CI)				
	Overall	FL	DLBCL	SLL	Other
0	1	1	1	1	1
>0 and ≤2	1.03 (0.67, 1.60)	0.81 (0.35, 1.84)	0.95 (0.49, 1.81)	1.27 (0.42, 3.89)	1.49 (0.66, 3.32)
>2	2.42 (1.48, 3.96)	2.21 (0.99, 4.93)	2.83 (1.48, 5.41)	2.29 (0.66, 7.98)	2.26 (0.85, 5.99)
P-trend	0.02	0.07	0.04	0.21	0.85

*ORs adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, use of any personal protective equipment

Lifetime Days (#Years x #Days/Year) of Glyphosate Use and NHL Risks

Lifetime days	OR* (95% CI)				
	Overall	FL	DLBCL	SLL	Other
0	1	1	1	1	1
>0 and ≤7	1.20 (0.74, 1.95)	1.03 (0.43, 2.48)	1.14 (0.56, 2.30)	1.04 (0.24, 4.58)	1.93 (0.82, 4.51)
>7	1.55 (0.99, 2.44)	1.33 (0.60, 2.94)	1.51 (0.79, 2.88)	2.13 (0.76, 5.96)	1.69 (0.68, 4.15)
P-trend	0.02	0.02	0.10	0.01	0.33

*ORs adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, use of any personal protective equipment

Challenges

- Uncollected information about duration and frequency of glyphosate use in some locations
- Small numbers for certain stratified analyses
- Measurement error
- Potential recall bias and unmeasured confounding

Strengths

- Larger sample size = more statistical power to incorporate evaluations of NHL sub-types with detailed glyphosate use metrics
- Risk estimates adjusted for other pesticide uses *(results not presented)*
- Evaluated ORs based on data from self-respondents only and assessed effect modification of PPE use on glyphosate-NHL associations *(results not presented)*

Conclusions

- Glyphosate use may be associated with ↑ risk of NHL
- Some differences in risk by sub-type, but not consistent across different glyphosate use metrics
- Large sample size yielded more precise results than possible in previous smaller studies

Further Considerations

- Glyphosate use is projected to increase worldwide, especially in emerging large-scale agricultural economies in Latin America, Asia, and South Africa
- Use of glyphosate is important for global food supply

BUT…

- Glyphosate-resistant weeds are a concern and threat to its prolonged and isolated use
- The human (and environmental) health effects of newer herbicide formulations that contain glyphosate with ≥1 other active ingredient are largely unknown

Acknowledgements

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- **U.S. investigators:** Drs. Laura Beane Freeman, Aaron Blair, Shelia Hoar Zahm, Kenneth P. Cantor, Dennis D. Weisenburger
- **NAPP Executive Committee:** Drs. Shelley A. Harris, Laura Beane Freeman, John J. Spinelli
- **Data pooling:** Mr. Joe Barker (IMS Inc.)

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Towards a cancer free workplace

www.occupationalcancer.ca

About NHL and Glyphosate

NHL

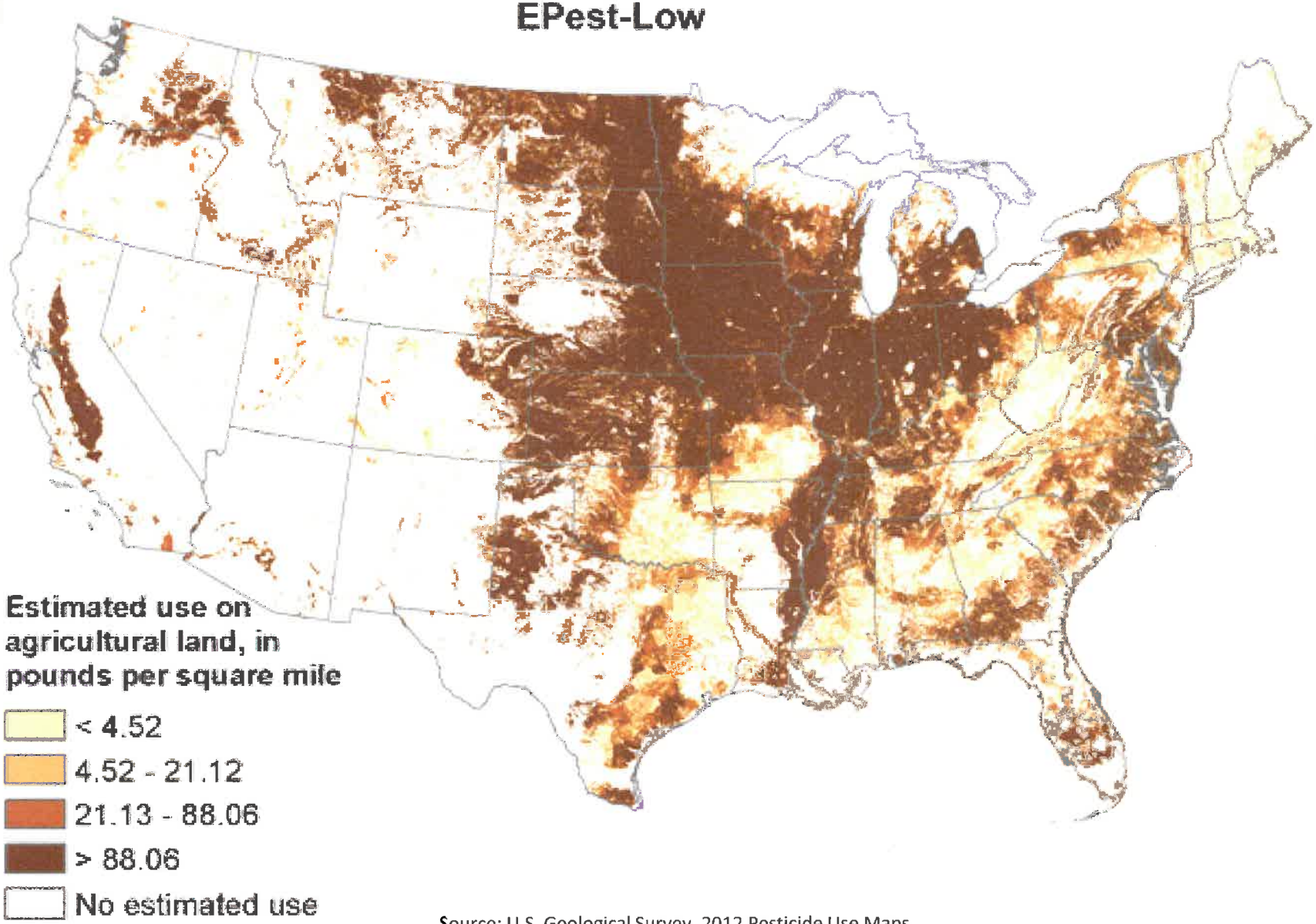
- A cancer that starts in the lymphocytes
- Heterogeneous, according to type of cell affected

Glyphosate

- A broad-spectrum herbicide
- Commonly known as “Roundup”
- The most frequently used herbicide in the world

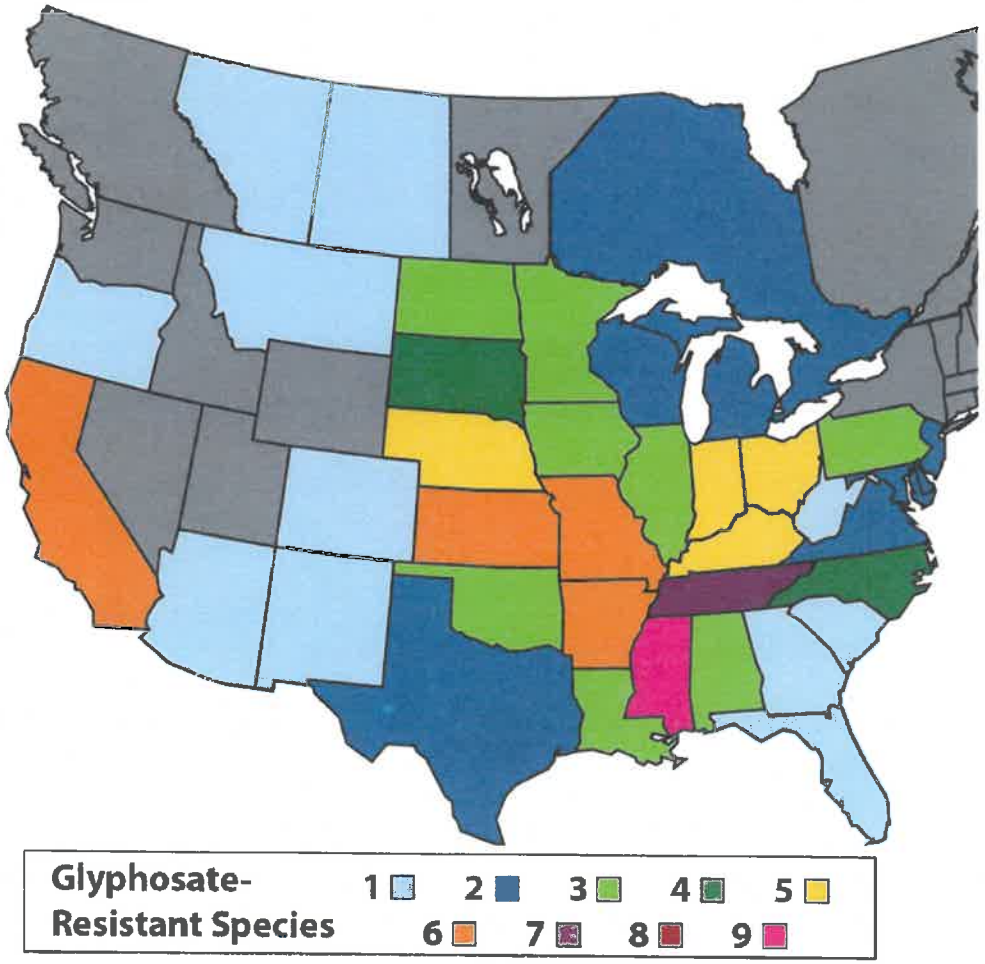
Estimated Agricultural Use for Glyphosate, 2012

EPest-Low



Source: U.S. Geological Survey. 2012 Pesticide Use Maps.
https://water.usgs.gov/nawqa/pnsp/usage/maps/show_map.php?year=2012&map=GLYPHOSATE&hilo=L

Glyphosate-Resistant Weed Species in North America



https://www.pioneer.com/home/site/mobile/plan/soybeans/weed-mgmt/

Proxy Respondent Analysis

Glyphosate Use

Ever/Never
Duration
Frequency
Lifetime days

Proxy and self-respondents
Self-respondents only

NHL Risk

Overall
FL
DLBCL
SLL
Other

Age, sex, state/province, lymphatic/hematopoietic cancer in a first-degree relative, use of any PPE, use of 2,4-D, use of dicamba, use of malathion

Covariates

Towards a cancer-free workplace

Selected Characteristics of NHL Cases and Controls (Continued)

Variable	Cases (N)	Controls (N)	OR (95% CI)
Ever lived or worked on a farm or ranch			
No	577	1840	1
Yes	1102	3276	1.06 (0.94, 1.20)
Unknown/missing	11	15	
Ever used any type of PPE			
No	374	1127	1
Yes	105	310	1.12 (0.86, 1.45)
Unknown/missing	1211	3694	

Proxy vs. Self Respondents

Glyphosate Use	OR (95% CI) for NHL Overall	
	Proxy and Self Respondents[a]	Self Respondents Only[b]
Never used	1	1
Ever used	1.13 (0.84, 1.51)	0.95 (0.69, 1.32)
Duration (# years)		
>0 and ≤3.5	1.28 (0.88, 1.84)	1.17 (0.79, 1.74)
>3.5	0.94 (0.62, 1.42)	0.78 (0.49, 1.24)
Frequency (# days/year)		
>0 and ≤2	0.74 (0.46, 1.19)	0.66 (0.39, 1.12)
>2	1.73 (1.02, 2.94)	1.77 (0.99, 3.17)
Lifetime days (# years x # days/year)		
0 and ≤7	0.87 (0.52, 1.45)	0.82 (0.46, 1.44)
>7	1.08 (0.66, 1.77)	1.06 (0.62, 1.81)

a. ORs adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, use of any PPE, use of 2,4-D, use of dicamba, use of malathion; b. ORs adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of any PPE, use of 2,4-D, use of dicamba, use of malathion

Future Research Priorities

- Evaluation of other agricultural exposures, confounding, and interactions
- Non-occupational exposures
- Factors that modify exposure, e.g. immune conditions

Acknowledgements

Canadian investigators

- Shelley A. Harris
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- John R. McLaughlin

U.S. investigators

- Laura Beane Freeman
- Aaron Blair
- Shelia Hoar Zahm
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May 24, 2017

Meta-Analysis of Glyphosate Use and Risk of Non-Hodgkin Lymphoma

This Technical Memorandum summarizes the results of a meta-analysis of glyphosate use and risk of non-Hodgkin lymphoma (NHL) using unpublished results from the Agricultural Health Study (AHS) cohort (Alavanja et al. 2013)[1]. For the purpose of sensitivity analysis, this meta-analysis also includes unpublished results from the North American Pooled Project (Pahwa et al. 2015)[2]. We used these two sets of results in place of other results that were included in our previously published systematic review and meta-analysis of the association between glyphosate use and NHL risk (Chang and Delzell 2016)[3]. That meta-analysis relied upon earlier, published results from the AHS cohort (De Roos et al. 2005)[4] and earlier, published results from the case-control studies that contributed to the North American Pooled Project (Cantor et al. 1992; De Roos et al. 2003; Hoar et al. 1986; McDuffie et al. 2001; Zahm et al. 1990)[5].

As stated in our paper (Chang and Delzell 2016), meta-analyses are not intended to identify, validate, or dispute causal relationships. They can provide a statistically precise summary measure of association across multiple studies and aid in identifying heterogeneity of results among studies; however, they also can obscure important differences in methods and results

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1 Alavanja MCR et al. DRAFT- Lymphoma risk and pesticide use in the Agricultural Health Study. March 15, 2013. Received by Exponent from Mr. Eric G. Lasker, Hollingsworth LLP.

2 Pahwa M et al. An evaluation of glyphosate use and the risk of non-Hodgkin lymphoma msajor histological subtypes in the North American Pooled Project. Presented at International Society for Environmental Epidemiology Conference, Sao Paolo, Brazil. August 31, 2015. Received by Exponent from Mr. Eric G. Lasker, Hollingsworth LLP.

3 Chang ET, Delzell E. Systematic review and meta-analysis of glyphosate exposure and risk of lymphohematopoietic cancers. J Environ Sci Health B 2016;51(6):402–434.

4 De Roos AJ et al. Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. Environ Health Perspect 2005;113(1):49–54.

5 Cantor KP et al. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. Cancer Res 1992;52(9):2447–2455.

De Roos AJ et al. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. Occup Environ Med 2003;60(9):E11.

Hoar SK et al. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA 1986;256(9):1141–1147. The estimated association between glyphosate use and NHL risk was not reported in this paper, although relevant data were available.

McDuffie HH et al. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. Cancer Epidemiol Biomarkers Prev 2001;10(11):1155–1163.

Zahm SH et al. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. Epidemiol 1990;1(5):349–356. The estimated association between glyphosate use and NHL risk was not reported in this paper, although relevant data were available.

among studies that can be more thoroughly evaluated in a detailed qualitative review of study strengths, limitations, and interpretations. In the presence of dissimilar studies, even if heterogeneity of results is not detectable using formal statistical tests, a single summary estimate may not be scientifically meaningful. Additionally, meta-analysis cannot overcome problems in the design and conduct of the underlying studies, and consistent findings across multiple studies may be due to shared biases rather than a true association.

In the meta-analysis described here, earlier results from the AHS cohort were replaced with results from Alavanja et al. (2013). In alternative models used for sensitivity analysis, earlier results from the North American case-control studies were replaced with results from Pahwa et al. (2015)[6]. However, Pahwa et al. (2015) did not describe in detail the eligibility criteria or the numbers of subjects included from each underlying study that contributed to their analysis. The numbers of total and reportedly glyphosate-exposed cases and controls in the North American Pooled Project, as reported by Pahwa et al. (2015), cannot readily be derived from the published numbers from the underlying studies. Due to the lack of transparency on this issue in the documents available to us[7], and our resulting lack of confidence in the results, we did not include the findings from Pahwa et al. (2015) in our primary analysis.

Differences between the analysis of Alavanja et al. (2013) and that of De Roos et al. (2005) include the following:

- Longer follow-up through 2008 (Alavanja et al. 2013) instead of 2001 (De Roos et al. 2005), resulting in the identification of more NHL cases (333 versus 92 in the complete cohort, respectively) and greater statistical power in Alavanja et al. (2013);
- Reporting of "high," "medium," and "low" glyphosate exposure versus none but not ever versus never glyphosate use (Alavanja et al. 2013) rather than tertiles of glyphosate exposure and ever versus never glyphosate use (De Roos et al. 2005);
- Use of a newer histopathological classification of NHL that includes chronic lymphocytic leukemia (CLL) and some other, less common subtypes (but not multiple myeloma) (Alavanja et al. 2013) that were excluded previously (De Roos et al. 2005);
- Adjustment for age, smoking status, number of livestock, driving of a diesel tractor, and state of residence in fully adjusted models (Alavanja et al. 2013) as opposed to

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[6] De Roos et al. (2003) included results from Cantor et al. (1992), Hoar et al. (1986), and Zahm et al. (1990) in their pooled analysis of multiple pesticides and NHL. Due to study overlap, and because Hoar et al. (1986) and Zahm et al. (1990) did not report associations between glyphosate use and NHL risk, we included only the results of De Roos et al. (2003) in our original meta-analysis (Chang and Delzell 2016).

[7] Other documents that we reviewed were an unpublished draft manuscript (Pahwa et al. An evaluation of glyphosate use and the risk of non-Hodgkin lymphoma major histological sub-types in the North American Pooled Project (NAPP). September 21, 2015; received by Exponent from Mr. Eric G. Lasker, Hollingsworth LLP; tables, figure, and appendix omitted) and a published abstract from the 2015 International Society for Environmental Epidemiology Conference in Sao Paolo, Brazil (http://ehp.niehs.nih.gov/isee/2015-868/).

adjustment for age, education, smoking pack-years, alcohol consumption, first-degree family history of cancer, state of residence, and use of 2,4-dichlorophenoxyacetic acid (2,4-D), alachlor, atrazine, metolachlor, trifluralin, benomyl, maneb, paraquat, carbaryl, and diazinon (De Roos et al. 2005); and

- Possible revision of the algorithm for estimating intensity of pesticide exposure using questionnaire data on mixing status, application, method, equipment repair, and use of personal protective equipment[8].

Differences between the analysis of Pahwa et al. (2015) and those of Cantor et al. (1992), De Roos et al. (2003), Hoar et al. (1986), McDuffie et al. (2001), and Zahm et al. (1990) include the following:

- Pooling of raw data for a unified analysis (Pahwa et al. 2015) instead of analyzing each contributing study separately (Cantor et al. 1992; De Roos et al. 2003; Hoar et al. 1986; McDuffie et al. 2001; Zahm et al. 1990), thereby resulting in greater statistical power in Pahwa et al. (2015);
- Inclusion of data on glyphosate exposure (Pahwa et al. 2015) that were not published by Hoar et al. (1986) and Zahm et al. (1990);
- Adjustment for age, sex, state/province, first-degree family history of lymphohematopoietic cancer, proxy respondent use, any personal protective equipment use, and use of 2,4-D, dicamba, or malathion in the unified dataset (Pahwa et al. 2015) as opposed to study-specific adjustment for age, state, vital status, cigarette smoking status, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures (Cantor et al. 1992); age, study site, and ten other pesticides (De Roos et al. 2003); age (Hoar et al. 1986; associations with glyphosate use not reported); age and province (McDuffie et al. 2001); or age (Zahm et al. 1990; associations with glyphosate use not reported);
- Inclusion of women (Pahwa et al. 2015), who were excluded from prior analyses (Zahm et al. 1990; De Roos et al. 2003);
- Possible inclusion of subjects who lived or worked on a farm when younger than 18 years of age, but not after age 18 (Pahwa et al. 2015), who were excluded from prior analyses (Zahm et al. 1990; De Roos et al. 2003);
- Use of logistic regression analysis in the unified dataset (Pahwa et al. 2015) versus use of either hierarchical or logistic regression analysis in one of the case-control studies (De Roos et al. 2003).

[8] Alavanja et al. (2013) cited Coble et al. (An updated algorithm for estimation of pesticide exposure intensity in the agricultural health study. Int J Environ Res Public Health 2011;8(12):4608–4622) as the source for this algorithm, whereas De Roos et al. (2005) cited Dosemeci et al. (A quantitative approach for estimating exposure to pesticides in the Agricultural Health Study. Ann Occup Hyg 2002;46(2):245–260).

We used the same meta-analysis statistical methods as described in our publication (Chang and Delzell 2016). Following those methods, the primary relative risk (RR) estimate that we chose to include based on data from Alavanja et al. (2013) was an estimate calculated by us that compared ever versus never use of glyphosate, using the fully adjusted model and the newer histopathological classification of NHL (from Supplemental Table 2 of Alavanja et al. (2013)). Because Alavanja et al. (2013) did not report RR estimates for ever versus never use of glyphosate, but instead reported RRs for low, medium, and high versus no exposure to glyphosate, we combined the RR estimates for the three different levels of exposure into a single estimate using random-effects meta-analysis. As shown in Table 1 below, the combined RR for ever versus never use of glyphosate in association with NHL risk in Alavanja et al. (2013) was the same after rounding (i.e., combined RR = 0.9, 95% confidence interval (CI) = 0.7–1.1) regardless of whether glyphosate exposure was classified using total days of exposure or intensity-weighted days of exposure, and whether the newer or an older classification of NHL was used.[9]

We conducted sensitivity analyses using four alternative RR estimates from Alavanja et al. (2013), namely, those comparing 1) "high" versus no exposure to glyphosate using intensity-weighted days of exposure, the newer NHL classification, and the fully adjusted model (from Supplemental Table 2 of Alavanja et al. (2013)); 2) "high" versus no exposure to glyphosate using unweighted days of exposure, the newer NHL classification, and the fully adjusted model (from Supplemental Table 2 of Alavanja et al. (2013)); 3) "high" versus no exposure to glyphosate using intensity-weighted days of exposure, the older NHL classification, and the age-adjusted model (from Supplemental Table 7 of Alavanja et al. (2013); results of fully adjusted model not reported); and 4) "high" versus no exposure to glyphosate using unweighted days of exposure, the older NHL classification, and the age-adjusted model (from Supplemental Table 7 of Alavanja et al. (2013); results of fully adjusted model not reported).

In our previously published meta-analysis, we prioritized the results of De Roos et al. (2003) based on a hierarchical regression model over the results from a logistic regression model because, according to the authors, hierarchical models can have "increased precision and accuracy for the ensemble of estimates" when modeling multiple pesticides simultaneously, and the more conservative prior assumptions specified in these models "seemed appropriate in a largely exploratory analysis of multiple exposures for which there is little prior knowledge about how pesticide exposures interact in relation to the risk of NHL." However, since 2003, the International Agency for Research on Cancer and the United States Environmental Protection

[9] De Roos et al. (2005) coded cancers according to the *International Classification of Diseases*, 9th Revision (1975), whereas the older classification used by Alavanja et al. (2013) was the *International Classification of Diseases for Oncology*, 3rd Edition (2000). These two classifications are not equivalent, although they are broadly similar for NHL overall (see http://apps.who.int/iris/bitstream/10665/96612/1/9789241548496_eng.pdf).

Agency have changed their classifications of the probable carcinogenicity of some pesticides, including glyphosate.[10] Because the prior covariates used by De Roos et al. (2003) probably would have changed in light of these revised classifications, we prioritized the results of the logistical regression model in the present meta-analysis.[11]

The RR estimate that we chose to include from Pahwa et al. (2015) was the fully adjusted estimate comparing ever versus never use of glyphosate using both self- and proxy respondents (RR = 1.13, 95% CI = 0.84–1.51).

Alavanja et al. (2013) also reported RRs for associations between glyphosate use (using unweighted days of exposure and the age-adjusted model) and risk of diffuse large B-cell lymphoma (DLBCL), CLL/small lymphocytic lymphoma (SLL)/mantle-cell lymphoma (MCL), and follicular lymphoma (FL) (from Table 3 of Alavanja et al. (2013)). Likewise, Pahwa et al. (2015) reported fully adjusted RRs for associations between ever versus never glyphosate use and risk of DLBCL, SLL, and FL. Therefore, we also calculated new meta-analysis results for these three NHL subtypes, with the results of Pahwa et al. (2015) included in sensitivity analyses but not in our primary analyses due to our concerns about subject inclusion criteria. For the primary analysis of NHL subtypes, we again combined the Alavanja et al. (2013) RR estimates for low, medium, and high versus no exposure (classified based on total days of exposure; results for intensity-weighted days of exposure not reported) into a single RR estimate for ever versus never glyphosate use using random-effects meta-analysis.

As shown in Table 1 and Figure 1, the primary random-effects meta-RR for the association between glyphosate use and risk of overall NHL, based on six independent studies[12], was 1.2 (95% CI = 0.91–1.6). Thus, compared with our originally reported meta-RR, which included the earlier AHS results of De Roos et al. (2005) and the hierarchical regression model results of De Roos et al. (2003) (meta-RR = 1.3, 95% CI = 1.0–1.6), the new meta-RR was attenuated and statistically nonsignificant. The attenuation is the result of the replacement of the results of De Roos et al. (2005) (RR = 1.1, 95% CI = 0.7–1.9 for ever use of glyphosate) with results of our

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[10] International Agency for Research on Cancer (IARC). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 112. Some Organophosphate Insecticides and Herbicides. Lyon: IARC, 2017.

[11] The RR for glyphosate use and NHL risk from the hierarchical model used by De Roos et al. (2003) was 1.6 (95% confidence interval (CI): 0.9–2.8) and that from the logistic regression model was 2.1 (95% CI: 1.1–4.0); thus, using the logistic regression results favored a higher estimated meta-RR.

[12] Alavanja et al. (2013); De Roos et al. (2003); Eriksson M et al. Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. Int J Cancer 2008;123(7):1657–1663; Hardell L et al.. Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies. Leuk Lymphoma 2002;43(5):1043–1049; McDuffie HH et al. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. Cancer Epidemiol Biomarkers Prev 2001;10(11):1155–1163; Orsi L et al. Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study. Occup Environ Med 2009;66(5):291–298.

analysis of data from Alavanja et al. (2013) (combined RR = 0.9, 95% CI = 0.7–1.1 for ever use of glyphosate).

Table 1 also shows the results of various sensitivity analyses using the alternative RR estimates from Alavanja et al. (2013); results from De Roos et al. (2005) instead of those from Alavanja et al. (2013); results from Hohenadel et al. (2011)[13] instead of those from McDuffie et al. (2001); and results from Pahwa et al. (2015) instead of those from De Roos et al. (2003) and McDuffie et al. (2001). All of the random-effects and fixed-effects meta-RRs for the association between glyphosate use and NHL risk were statistically nonsignificant, with little change in the point estimate and 95% CI (range of meta-RRs = 1.0–1.3, range of 95% confidence limits = 0.86–1.8) based on the inclusion of alternative RRs.

After inclusion of the results of Alavanja et al. (2013), meta-RRs from our primary analyses of the association between glyphosate use and risk of DLBCL, CLL/SLL with or without MCL, or FL also were statistically nonsignificant and attenuated (for DLBCL and CLL/SLL/MCL) or reversed from positive to inverse (for FL), compared with those reported our original meta-analysis (Table 1). In sensitivity analyses, two meta-RRs for SLL with or without CLL or MCL were statistically marginally nonsignificant or statistically significant, namely, models 4 and 5. However, both of these results were obtained using fixed effects models that included data of uncertain validity from Pahwa et al. (2015). In addition, given the presence of substantial and statistically significant heterogeneity among study-specific RRs in both of these analyses, the random-effects meta-analysis model is preferred[14]. In both analyses, the random-effects meta-RR was statistically nonsignificant and attenuated in comparison with the fixed-effects-meta-RR.

In summary, replacement of the results of De Roos et al. (2005) with the more recent results of Alavanja et al. (2013) resulted in weakened, statistically nonsignificant associations between glyphosate use and risk of all outcomes evaluated, including NHL, DLBCL, CLL/SLL/MCL, and FL.

Limitations

This analysis used non-peer-reviewed results from the AHS reported in a draft manuscript by Alavanja et al. dated March 15, 2013, and non-peer-reviewed, publicly presented results from the North American Pooled Project reported in a presentation by Pahwa et al. at the

[13] Hohenadel K et al. Exposure to multiple pesticides and risk of non-Hodgkin lymphoma in men from six Canadian provinces. Int J Environ Res Public Health 2011;8(6):2320–2330.

[14] Higgins JPT and Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. Updated March 2011. Available: http://handbook.cochrane.org/chapter_9/9_5_4_incorporating_heterogeneity_into_random_effects_models.htm.

International Society for Environmental Epidemiology Conference on August 31, 2015. We cannot verify the accuracy of these results or the published results of any of the other studies included in this analysis.

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Figure 1. Forest plot of meta-analysis of glyphosate use and non-Hodgkin lymphoma risk using unpublished results from Alavanja et al. (2013) in place of previously published results from De Roos et al. (2005) based on the Agricultural Health Study cohort. Some confidence limits are slightly different from those reported in original studies due to the recalculation of standard errors by the Comprehensive Meta-Analysis software (Biostat, Inc., Englewood, NJ).

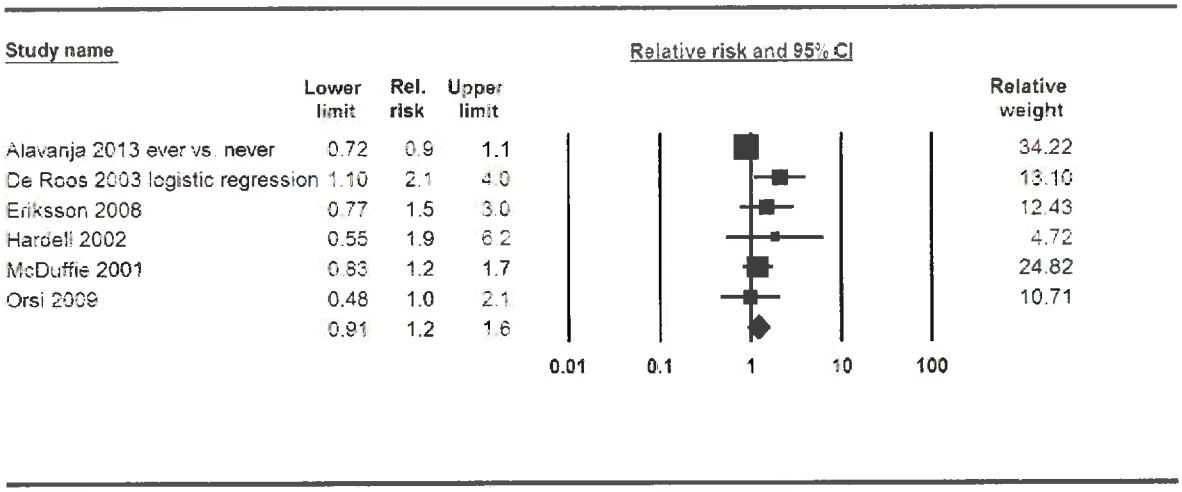

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Table 1. Results of meta-analysis of glyphosate use and non-Hodgkin lymphoma risk including unpublished results from Alavanja et al. (2013) and Pahwa et al. (2015)

Study #	Author	Year	Outcome	Number of exposed subjects	RR	95% CI
1	Alavanja et al.	2013	Non-Hodgkin lymphoma	82 cases highly exposed, 249 cases ever exposed based on intensity-weighted exposure, new classification 83 cases highly exposed, 250 cases ever exposed based on total exposure, new classification 60 cases highly exposed, 182 cases ever exposed based on intensity-weighted exposure, old classification 60 cases highly exposed, 183 cases ever exposed based on total exposure, old classification	a. 0.9 (ever vs. never random-effects meta-RR, intensity-weighted exposure, new classification) b. 0.9 (ever vs. never random-effects meta-RR, total exposure, new classification) c. 0.9 (ever vs. never random-effects meta-RR, intensity-weighted exposure, old classification) d. 0.9 (ever vs. never random-effects meta-RR, total exposure, old classification) e. 0.97 (intensity-weighted high exposure, new classification) f. 1.0 (total high exposure, new classification) g. 0.9 (intensity-weighted high exposure, old classification) h. 1.0 (total high exposure, old classification)	a. 0.7–1.1 (ever vs. never random-effects meta-CI, intensity-weighted exposure, new classification) b. 0.7–1.1 (ever vs. never random-effects meta-CI, total exposure, new classification) c. 0.7–1.1 (ever vs. never random-effects meta-CI, intensity-weighted exposure, old classification) d. 0.7–1.1 (ever vs. never random-effects meta-CI, total exposure, old classification) e. 0.7–1.4 (intensity-weighted high exposure, new classification) f. 0.7–1.4 (total high exposure, new classification) g. 0.6–1.4 (intensity-weighted high exposure, old classification) h. 0.7–1.4 (total high exposure, old classification)
2	De Roos et al.	2003	Non-Hodgkin lymphoma	36 cases, 61 controls	a. 2.1 (logistic regression) b. 1.6 (hierarchical regression)	a. 1.1–4.0 (logistic regression) b. 0.9–2.8 (hierarchical regression)
3	De Roos et al.	2005	Non-Hodgkin lymphoma	71 cases (total; not analytic cohort)	1.1	0.7–1.9
4	Eriksson et al.	2008	Non-Hodgkin lymphoma	29 cases, 18 controls	1.51	0.77–2.94
5	Hardell et al.	2002	Non-Hodgkin lymphoma	8 cases, 8 controls	1.85	0.55–6.20
6	Hohenadel et al.	2011	Non-Hodgkin lymphoma	50 cases, 133 controls	1.40 (ever vs. never random-effects meta-RR)	0.62–3.15 (ever vs. never random-effects meta-CI)
7	McDuffie et al.	2001	Non-Hodgkin lymphoma	51 cases, 133 controls	1.20	0.83–1.74
8	Orsi et al.	2009	Non-Hodgkin lymphoma	12 cases, 24 controls	1.0	0.5–2.2

9	Pahwa et al.	2015	Non-Hodgkin lymphoma	113 cases; controls NR	1.13		0.84–1.51		
	Meta-analysis model		**Outcome**	**Studies included**		**Meta-RR**	**95% CI**	I^2	$P_{heterogeneity}$
	***Model 1, random effects**		**Non-Hodgkin lymphoma**	**1a/b/c/d, 2a, 4, 5, 7, 8**	**1.2**		**0.91–1.6**	**42.2%**	**0.12**
	Model 1, fixed effects		"	"	1.1		0.90–1.3	"	"
	Model 2, random effects		"	1e, 2a, 4, 5, 7, 8	1.2		0.97–1.5	9.3%	0.36
	Model 2, fixed effects		"	"	1.2		0.98–1.5	"	"
	Model 3, random effects		"	1f, 2a, 4, 5, 7, 8	1.2		0.99–1.5	2.2%	0.40
	Model 3, fixed effects		"	"	1.2		0.99–1.5	"	"
	Model 4, random effects		"	1g, 2a, 4, 5, 7, 8	1.2		0.96–1.6	14.2%	0.32
	Model 4, fixed effects		"	"	1.2		0.97–1.5	"	"
	Model 5, random effects		"	1h, 2a, 4, 5, 7, 8	1.2		0.99–1.5	2.2%	0.40
	Model 5, fixed effects		"	"	1.2		0.99–1.5	"	"
	Model 6, random effects		"	1a/b/c/d, 2b, 4, 5, 7, 8	1.1		0.90–1.4	21.6%	0.27
	Model 6, fixed effects		"	"	1.1		0.90–1.3	"	"
	Model 7, fixed and random effects		"	1e, 2b, 4, 5, 7, 8	1.2		0.96–1.5	0.0%	0.61
	Model 8, fixed and random effects		"	1f, 2b, 4, 5, 7, 8	1.2		0.97–1.5	0.0%	0.67
	Model 9, fixed and random effects		"	1g, 2b, 4, 5, 7, 8	1.2		0.95–1.5	0.0%	0.56
	Model 10, fixed and random effects		"	1h, 2b, 4, 5, 7, 8	1.2		0.97–1.5	0.0%	0.67
	Model 11, random effects		"	1a/b/c/d, 2a, 4, 5, 6, 8	1.3		0.90–1.8	42.4%	0.12
	Model 11, fixed effects		"	"	1.1		0.88–1.3	"	"
	Model 12, random effects		"	1e, 2a, 4, 5, 6, 8	1.3		0.96–1.6	11.2%	0.34
	Model 12, fixed effects		"	"	1.2		0.96–1.6	"	"
	Model 13, random effects		"	1f, 2a, 4, 5, 6, 8	1.3		0.97–1.6	3.8%	0.39
	Model 13, fixed effects		"	"	1.2		0.97–1.6	"	"
	Model 14, random effects		"	1g, 2a, 4, 5, 6, 8	1.3		0.94–1.7	15.5%	0.31
	Model 14, fixed effects		"	"	1.2		0.95–1.6	"	"
	Model 15, random effects		"	1h, 2a, 4, 5, 6, 8	1.3		0.97–1.6	3.8%	0.39
	Model 15, fixed effects		"	"	1.2		0.97–1.6	"	"
	Model 16, random effects		"	1a/b/c/d, 2b, 4, 5, 6, 8	1.1		0.88–1.5	21.5%	0.27
	Model 16, fixed effects		"	"	1.0		0.87–1.3	"	"
	Model 17, fixed and random effects		"	1e, 2b, 4, 5, 6, 8	1.2		0.94–1.5	0.0%	0.59
	Model 18, fixed and random effects		"	1f, 2b, 4, 5, 6, 8	1.2		0.95–1.5	0.0%	0.64
	Model 19, fixed and random effects		"	1g, 2b, 4, 5, 6, 8	1.2		0.93–1.6	0.0%	0.54
	Model 20, fixed and random effects		"	1h, 2b, 4, 5, 6, 8	1.2		0.95–1.5	0.0%	0.64
	Model 21, fixed and random effects		"	1a/b/c/d, 4, 5, 8, 9	1.0		0.86–1.2	0.0%	0.42
	Model 22, fixed and random effects		"	1e, 4, 5, 8, 9	1.1		0.91–1.4	0.0%	0.71

	Model 23, fixed and random effects		"	1f, 4, 5, 8, 9	1.1	0.91–1.4	0.0%	0.75
	Model 24, fixed and random effects		"	1g, 4, 5, 8, 9	1.1	0.89–1.4	0.0%	0.64
	Model 25, fixed and random effects		"	1h, 4, 5, 8, 9	1.1	0.91–1.4	0.0%	0.75
	Model 26, fixed and random effects		"	3, 4, 5, 8, 9	1.2	0.94–1.5	0.0%	0.85

Study #	Author	Year	Outcome	Number of exposed subjects	RR	95% CI
1	Alavanja et al.	2013	Diffuse large B-cell lymphoma	22 cases highly exposed, 68 cases ever exposed based on total exposure	a. 1.0 (ever vs. never random-effects meta-RR, total exposure) b. 0.7 (total high exposure)	a. 0.7–1.4 (ever vs. never random-effects meta-RR, total exposure) b. 0.4–1.3 (total high exposure)
4	Eriksson et al.	2008	Diffuse large B-cell lymphoma	Not reported	1.22	0.44–3.35
8	Orsi et al.	2009	Diffuse large B-cell lymphoma	5 cases, 24 controls	1.0	0.3–2.7
9	Pahwa et al.	2015	Diffuse large B-cell lymphoma	45 cases; controls NR	1.23	0.81–1.88

Meta-analysis model	Outcome	Studies included	Meta-RR	95% CI	I^2	$P_{heterogeneity}$
***Model 1, fixed and random effects**	**Diffuse large B-cell lymphoma**	**1a, 4, 8**	**1.0**	**0.74–1.4**	**0.0%**	**0.94**
Model 2, fixed and random effects	"	1b, 4, 8	0.84	0.53–1.3	0.0%	0.61
Model 3, fixed and random effects	"	1a, 4, 8, 9	1.1	0.85–1.4	0.0%	0.89
Model 4, fixed and random effects	"	1b, 4, 8, 9	1.0	0.76–1.4	0.0%	0.49
Model 5, fixed and random effects	"	4, 8, 9	1.2	0.83–1.7	0.0%	0.94

Study #	Author	Year	Outcome	Number of exposed subjects	RR	95% CI
1	Alavanja et al.	2013	CLL/SLL/MCL	29 cases highly exposed, 90 cases ever exposed based on total exposure	a. 0.9 (ever vs. never random-effects meta-RR, total exposure) b. 1.1 (total high exposure)	a. 0.6–1.3 (ever vs. never random-effects meta-RR, total exposure) b. 0.6–1.8 (total high exposure)
4	Eriksson et al.	2008	CLL/SLL	Not reported	3.35	1.42–7.89
8	Orsi et al.	2009	CLL/SLL	2 cases, 18 controls	0.4	0.1–1.8
9	Pahwa et al.	2015	SLL	15 cases; controls NR	1.79	0.87–3.69

Meta-analysis model	Outcome	Studies included	Meta-RR	95% CI	I^2	$P_{heterogeneity}$
***Model 1, random effects**	**CLL/SLL/MCL**	**1a, 4, 8**	**1.2**	**0.41–3.3**	**78.6%**	**0.009**
Model 1, fixed effects	"	"	1.1	0.75–1.5	"	"
Model 2, random effects	"	1b, 4, 8	1.3	0.47–3.5	73.6%	0.02
Model 2, fixed effects	"	"	1.3	0.87–2.1	"	"
Model 3, random effects	"	1a, 4, 8, 9	1.3	0.64–2.7	72.7%	0.01

	Model 3, fixed effects		"	"	1.2	0.86–1.6	"	"
	Model 4, random effects		"	1b, 4, 8, 9	1.4	0.74–2.8	62.6%	0.05
	Model 4, fixed effects		"	"	1.5	1.0–2.1	"	"
	Model 5, random effects		"	4, 8, 9	1.6	0.59–4.2	67.6%	0.05
	Model 5, fixed effects		"	"	1.9	1.1–3.1	"	"

Study #	Author	Year	Outcome	Number of exposed subjects	RR	95% CI
1	Alavanja et al.	2013	Follicular lymphoma	12 cases highly exposed, 38 cases ever exposed based on total exposure	a. 0.7 (ever vs. never random-effects meta-RR, total exposure) b. 0.7 (total high exposure)	a. 0.4–1.1 (ever vs. never random-effects meta-RR, total exposure) b. 0.4–1.8 (total high exposure)
4	Eriksson et al.	2008	"	Not reported	1.89	0.62–5.79
8	Orsi et al.	2009	"	3 cases, 24 controls	1.4	0.4–5.2
9	Pahwa et al.	2015	Follicular lymphoma	28 cases; controls NR	0.69	0.41–1.15

Meta-analysis model	Outcome	Studies included	Meta-RR	95% CI	I^2	$P_{heterogeneity}$
***Model 1, random effects**	**Follicular lymphoma**	**1a, 4, 8**	**1.0**	**0.53–1.9**	**35.2%**	**0.21**
Model 1, fixed effects	"	"	0.88	0.57–1.4	"	"
Model 2, random effects	"	1b, 4, 8	1.1	0.60–2.1	75.0%	0.37
Model 2, fixed effects	"	"	1.1	0.60–2.0	"	"
Model 3, random effects	"	1a, 4, 8, 9	0.82	0.56–1.2	16.4%	0.31
Model 3, fixed effects	"	"	0.80	0.57–1.1	"	"
Model 4, random effects	"	1b, 4, 8, 9	0.86	0.56–1.3	10.5%	0.34
Model 4, fixed effects	"	"	0.84	0.57–1.2	"	"
Model 5, random effects	"	4, 8, 9	1.0	0.53–2.0	36.6%	0.21
Model 5, fixed effects	"	"	0.88	0.57–1.4	"	"

*Primary analysis

CI: confidence interval; CLL: chronic lymphocytic leukemia; MCL: mantle-cell lymphoma; RR: relative risk; SLL: small lymphocytic lymphoma

Meeting January 14 1965

President's Address

The Environment and Disease: Association or Causation?

by Sir Austin Bradford Hill CBE DSC FRCP(hon) FRS
(*Professor Emeritus of Medical Statistics, University of London*)

Amongst the objects of this newly-founded Section of Occupational Medicine are firstly 'to provide a means, not readily afforded elsewhere, whereby physicians and surgeons with a special knowledge of the relationship between sickness and injury and conditions of work may discuss their problems, not only with each other, but also with colleagues in other fields, by holding joint meetings with other Sections of the Society'; and, secondly, 'to make available information about the physical, chemical and psychological hazards of occupation, and in particular about those that are rare or not easily recognized'.

At this first meeting of the Section and before, with however laudable intentions, we set about instructing our colleagues in other fields, it will be proper to consider a problem fundamental to our own. How in the first place do we detect these relationships between sickness, injury and conditions of work? How do we determine what are physical, chemical and psychological hazards of occupation, and in particular those that are rare and not easily recognized?

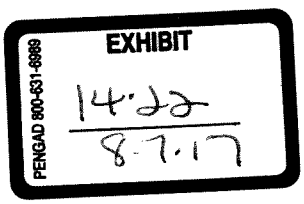
There are, of course, instances in which we can reasonably answer these questions from the general body of medical knowledge. A particular, and perhaps extreme, physical environment cannot fail to be harmful; a particular chemical is known to be toxic to man and therefore suspect on the factory floor. Sometimes, alternatively, we may be able to consider what *might* a particular environment do to man, and then see whether such consequences are indeed to be found. But more often than not we have no such guidance, no such means of proceeding; more often than not we are dependent upon our observation and enumeration of defined events for which we then seek antecedents. In other words we see that the event B is associated with the environmental feature A, that, to take a specific example, some form of respiratory illness is associated with a dust in the environment. In what circumstances can we pass from this observed *association* to a verdict of *causation*? Upon what basis should we proceed to do so?

I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of 'causation'. The 'cause' of illness may be immediate and direct, it may be remote and indirect underlying the observed association. But with the aims of occupational, and almost synonymously preventive, medicine in mind the decisive question is whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A. *How* such a change exerts that influence may call for a great deal of research. However, before deducing 'causation' and taking action we shall not invariably have to sit around awaiting the results of that research. The whole chain may have to be unravelled or a few links may suffice. It will depend upon circumstances.

Disregarding then any such problem in semantics we have this situation. Our observations reveal an association between two variables, perfectly clear-cut and beyond what we would care to attribute to the play of chance. What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?

(1) *Strength*. First upon my list I would put the strength of the association. To take a very old example, by comparing the occupations of patients with scrotal cancer with the occupations of patients presenting with other diseases, Percival Pott could reach a correct conclusion because of the *enormous* increase of scrotal cancer in the chimney sweeps. 'Even as late as the second decade of the twentieth century', writes Richard Doll (1964), 'the mortality of chimney sweeps from scrotal cancer was some 200 times that of workers who were not specially exposed to tar or mineral oils and in the eighteenth century the relative difference is likely to have been much greater.'

To take a more modern and more general example upon which I have now reflected for over fifteen years, prospective inquiries into smoking have shown that the death rate from cancer of the lung in cigarette smokers is nine to ten times the rate in non-smokers and the rate in heavy cigarette smokers is twenty to thirty times



as great. On the other hand the death rate from coronary thrombosis in smokers is no more than twice, possibly less, the death rate in non-smokers. Though there is good evidence to support causation it is surely much easier in this case to think of some features of life that may go hand-in-hand with smoking – features that might conceivably be the real underlying cause or, at the least, an important contributor, whether it be lack of exercise, nature of diet or other factors. But to explain the pronounced excess in cancer of the lung in any other environmental terms requires some feature of life so intimately linked with cigarette smoking and with the amount of smoking that such a feature should be easily detectable. If we cannot detect it or reasonably infer a specific one, then in such circumstances I think we are reasonably entitled to reject the vague contention of the armchair critic 'you can't prove it, there *may* be such a feature'.

Certainly in this situation I would reject the argument sometimes advanced that what matters is the absolute difference between the death rates of our various groups and not the ratio of one to other. That depends upon what we want to know. If we want to know how many extra deaths from cancer of the lung will take place through smoking (i.e. presuming causation), then obviously we must use the absolute differences between the death rates – 0·07 per 1,000 per year in non-smoking doctors, 0·57 in those smoking 1–14 cigarettes daily, 1·39 for 15–24 cigarettes daily and 2·27 for 25 or more daily. But it does not follow here, or in more specifically occupational problems, that this best measure of the effect upon mortality is also the best measure in relation to ætiology. In this respect the ratios of 8, 20 and 32 to 1 are far more informative. It does not, of course, follow that the differences revealed by ratios are of any practical importance. Maybe they are, maybe they are not; but that is another point altogether.

We may recall John Snow's classic analysis of the opening weeks of the cholera epidemic of 1854 (Snow 1855). The death rate that he recorded in the customers supplied with the grossly polluted water of the Southwark and Vauxhall Company was in truth quite low – 71 deaths in each 10,000 houses. What stands out vividly is the fact that the small rate is 14 times the figure of 5 deaths per 10,000 houses supplied with the sewage-free water of the rival Lambeth Company.

In thus putting emphasis upon the strength of an association we must, nevertheless, look at the obverse of the coin. We must not be too ready to dismiss a cause-and-effect hypothesis merely on the grounds that the observed association appears to be slight. There are many occasions in medicine when this is in truth so. Relatively few persons harbouring the meningococcus fall sick of meningococcal meningitis. Relatively few persons occupationally exposed to rat's urine contract Weil's disease.

(2) *Consistency:* Next on my list of features to be specially considered I would place the *consistency* of the observed association. Has it been repeatedly observed by different persons, in different places, circumstances and times?

This requirement may be of special importance for those rare hazards singled out in the Section's terms of reference. With many alert minds at work in industry today many an environmental association may be thrown up. Some of them on the customary tests of statistical significance will appear to be unlikely to be due to chance. Nevertheless whether chance is the explanation or whether a true hazard has been revealed may sometimes be answered only by a repetition of the circumstances and the observations.

Returning to my more general example, the Advisory Committee to the Surgeon-General of the United States Public Health Service found the association of smoking with cancer of the lung in 29 retrospective and 7 prospective inquiries (US Department of Health, Education & Welfare 1964). The lesson here is that broadly the same answer has been reached in quite a wide variety of situations and techniques. In other words we can justifiably infer that the association is not due to some constant error or fallacy that permeates every inquiry. And we have indeed to be on our guard against that.

Take, for instance, an example given by Heady (1958). Patients admitted to hospital for operation for peptic ulcer are questioned about recent domestic anxieties or crises that may have precipitated the acute illness. As controls, patients admitted for operation for a simple hernia are similarly quizzed. But, as Heady points out, the two groups may not be *in pari materia*. If your wife ran off with the lodger last week you still have to take your perforated ulcer to hospital without delay. But with a hernia you might prefer to stay at home for a while – to mourn (or celebrate) the event. No number of exact repetitions would remove or necessarily reveal that fallacy.

We have, therefore, the somewhat paradoxical position that the different results of a different inquiry certainly cannot be held to refute the

original evidence; yet the same results from precisely the same form of inquiry will not invariably greatly strengthen the original evidence. I would myself put a good deal of weight upon similar results reached in quite different ways, e.g. prospectively and retrospectively.

Once again looking at the obverse of the coin there will be occasions when repetition is absent or impossible and yet we should not hesitate to draw conclusions. The experience of the nickel refiners of South Wales is an outstanding example. I quote from the Alfred Watson Memorial Lecture that I gave in 1962 to the Institute of Actuaries:

'The population at risk, workers and pensioners, numbered about one thousand. During the ten years 1929 to 1938, sixteen of them had died from cancer of the lung, eleven of them had died from cancer of the nasal sinuses. At the age specific death rates of England and Wales at that time, one might have anticipated one death from cancer of the lung (to compare with the 16), and a fraction of a death from cancer of the nose (to compare with the 11). In all other bodily sites cancer had appeared on the death certificate 11 times and one would have expected it to do so 10–11 times. There had been 67 deaths from all other causes of mortality and over the ten years' period 72 would have been expected at the national death rates. Finally division of the population at risk in relation to their jobs showed that the excess of cancer of the lung and nose had fallen wholly upon the workers employed in the chemical processes.

'More recently my colleague, Dr Richard Doll, has brought this story a stage further. In the nine years 1948 to 1956 there had been, he found, 48 deaths from cancer of the lung and 13 deaths from cancer of the nose. He assessed the numbers expected at normal rates of mortality as, respectively 10 and 0·1.

'In 1923, long before any special hazard had been recognized, certain changes in the refinery took place. No case of cancer of the nose has been observed in any man who first entered the works after that year, and in these men there has been no excess of cancer of the lung. In other words, the excess in both sites is uniquely a feature in men who entered the refinery in, roughly, the first 23 years of the present century.

'No causal agent of these neoplasms has been identified. Until recently no animal experimentation had given any clue or any support to this wholly statistical evidence. Yet I wonder if any of us would hesitate to accept it as proof of a grave industrial hazard?' (Hill 1962).

In relation to my present discussion I know of no parallel investigation. We have (or certainly had) to make up our minds on a unique event; and there is no difficulty in doing so.

(3) *Specificity:* One reason, needless to say, is the specificity of the association, the third characteristic which invariably we must consider. If, as here, the association is limited to specific workers and to particular sites and types of disease and there is no association between the work and other modes of dying, then clearly that is a strong argument in favour of causation.

We must not, however, over-emphasize the importance of the characteristic. Even in my present example there is a cause and effect relationship with two different sites of cancer – the lung and the nose. Milk as a carrier of infection and, in that sense, the cause of disease can produce such a disparate galaxy as scarlet fever, diphtheria, tuberculosis, undulant fever, sore throat, dysentery and typhoid fever. Before the discovery of the underlying factor, the bacterial origin of disease, harm would have been done by pushing too firmly the need for specificity as a necessary feature before convicting the dairy.

Coming to modern times the prospective investigations of smoking and cancer of the lung have been criticized for not showing specificity – in other words the death rate of smokers is higher than the death rate of non-smokers from many causes of death (though in fact the results of Doll & Hill, 1964, do not show that). But here surely one must return to my first characteristic, the strength of the association. If other causes of death are raised 10, 20 or even 50% in smokers whereas cancer of the lung is raised 900–1,000% we have specificity – a specificity in the magnitude of the association.

We must also keep in mind that diseases may have more than one cause. It has always been possible to acquire a cancer of the scrotum without sweeping chimneys or taking to mule-spinning in Lancashire. One-to-one relationships are not frequent. Indeed I believe that multi-causation is generally more likely than single causation though possibly if we knew all the answers we might get back to a single factor.

In short, if specificity exists we may be able to draw conclusions without hesitation; if it is not apparent, we are not thereby necessarily left sitting irresolutely on the fence.

(4) *Temporality:* My fourth characteristic is the temporal relationship of the association – which is the cart and which the horse? This is a question which might be particularly relevant with diseases of slow development. Does a particular diet lead to disease or do the early stages of the disease lead to those peculiar dietetic habits? Does a

particular occupation or occupational environment promote infection by the tubercle bacillus or are the men and women who select that kind of work more liable to contract tuberculosis whatever the environment – or, indeed, have they already contracted it? This temporal problem may not arise often but it certainly needs to be remembered, particularly with selective factors at work in industry.

(5) *Biological gradient:* Fifthly, if the association is one which can reveal a biological gradient, or dose-response curve, then we should look most carefully for such evidence. For instance, the fact that the death rate from cancer of the lung rises linearly with the number of cigarettes smoked daily, adds a very great deal to the simpler evidence that cigarette smokers have a higher death rate than non-smokers. That comparison would be weakened, though not necessarily destroyed, if it depended upon, say, a much heavier death rate in light smokers and a lower rate in heavier smokers. We should then need to envisage some much more complex relationship to satisfy the cause-and-effect hypothesis. The clear dose-response curve admits of a simple explanation and obviously puts the case in a clearer light.

The same would clearly be true of an alleged dust hazard in industry. The dustier the environment the greater the incidence of disease we would expect to see. Often the difficulty is to secure some satisfactory quantitative measure of the environment which will permit us to explore this dose-response. But we should invariably seek it.

(6) *Plausibility:* It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the day.

To quote again from my Alfred Watson Memorial Lecture (Hill 1962), there was

'. . . no biological knowledge to support (or to refute) Pott's observation in the 18th century of the excess of cancer in chimney sweeps. It was lack of biological knowledge in the 19th that led a prize essayist writing on the value and the fallacy of statistics to conclude, amongst other "absurd" associations, that "it could be no more ridiculous for the stranger who passed the night in the steerage of an emigrant ship to ascribe the typhus, which he there contracted, to the vermin with which bodies of the sick might be infected". And coming to nearer times, in the 20th century there was no biological knowledge to support the evidence against rubella.'

In short, the association we observe may be one new to science or medicine and we must not dismiss it too light-heartedly as just too odd. As Sherlock Holmes advised Dr Watson, 'when you have eliminated the impossible, whatever remains, *however improbable*, must be the truth.'

(7) *Coherence:* On the other hand the cause-and-effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease – in the expression of the Advisory Committee to the Surgeon-General it should have coherence.

Thus in the discussion of lung cancer the Committee finds its association with cigarette smoking coherent with the temporal rise that has taken place in the two variables over the last generation and with the sex difference in mortality – features that might well apply in an occupational problem. The known urban/rural ratio of lung cancer mortality does not detract from coherence, nor the restriction of the effect to the lung.

Personally, I regard as greatly contributing to coherence the histopathological evidence from the bronchial epithelium of smokers and the isolation from cigarette smoke of factors carcinogenic for the skin of laboratory animals. Nevertheless, while such laboratory evidence can enormously strengthen the hypothesis and, indeed, may determine the actual causative agent, the lack of such evidence cannot nullify the epidemiological observations in man. Arsenic can undoubtedly cause cancer of the skin in man but it has never been possible to demonstrate such an effect on any other animal. In a wider field John Snow's epidemiological observations on the conveyance of cholera by the water from the Broad Street pump would have been put almost beyond dispute if Robert Koch had been then around to isolate the vibrio from the baby's nappies, the well itself and the gentleman in delicate health from Brighton. Yet the fact that Koch's work was to be awaited another thirty years did not really weaken the epidemiological case though it made it more difficult to establish against the criticisms of the day – both just and unjust.

(8) *Experiment:* Occasionally it is possible to appeal to experimental, or semi-experimental, evidence. For example, because of an observed association some preventive action is taken. Does it in fact prevent? The dust in the workshop is reduced, lubricating oils are changed, persons stop smoking cigarettes. Is the frequency of the associated events affected? Here the strongest

support for the causation hypothesis may be revealed.

(9) *Analogy:* In some circumstances it would be fair to judge by analogy. With the effects of thalidomide and rubella before us we would surely be ready to accept slighter but similar evidence with another drug or another viral disease in pregnancy.

Here then are nine different viewpoints from all of which we should study association before we cry causation. What I do not believe – and this has been suggested – is that we can usefully lay down some hard-and-fast rules of evidence that *must* be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?

Tests of Significance

No formal tests of significance can answer those questions. Such tests can, and should, remind us of the effects that the play of chance can create, and they will instruct us in the likely magnitude of those effects. Beyond that they contribute nothing to the 'proof' of our hypothesis.

Nearly forty years ago, amongst the studies of occupational health that I made for the Industrial Health Research Board of the Medical Research Council was one that concerned the workers in the cotton-spinning mills of Lancashire (Hill 1930). The question that I had to answer, by the use of the National Health Insurance records of that time, was this: Do the workers in the card-room of the spinning mill, who tend the machines that clean the raw cotton, have a sickness experience in any way different from that of other operatives in the same mills who are relatively unexposed to the dust and fibre that were features of the cardroom? The answer was an unqualified 'Yes'. From age 30 to age 60 the cardroom workers suffered over three times as much from respiratory causes of illness whereas from non-respiratory causes their experience was not different from that of the other workers. This pronounced difference with the respiratory causes was derived not from abnormally long periods of sickness but rather from an excessive number of repeated absences from work of the cardroom workers.

All this has rightly passed into the limbo of forgotten things. What interests me today is this: My results were set out for men and women separately and for half a dozen age groups in 36 tables. So there were plenty of sums. Yet I cannot find that anywhere I thought it necessary to use a test of significance. The evidence was so clear-cut, the differences between the groups were mainly so large, the contrast between respiratory and non-respiratory causes of illness so specific, that no formal tests could really contribute anything of value to the argument. So why use them?

Would we think or act that way today? I rather doubt it. Between the two world wars there was a strong case for emphasizing to the clinician and other research workers the importance of not overlooking the effects of the play of chance upon their data. Perhaps too often generalities were based upon two men and a laboratory dog while the treatment of choice was deduced from a difference between two bedfuls of patients and might easily have no true meaning. It was therefore a useful corrective for statisticians to stress, and to teach the need for, tests of significance merely to serve as guides to caution before drawing a conclusion, before inflating the particular to the general.

I wonder whether the pendulum has not swung too far – not only with the attentive pupils but even with the statisticians themselves. To decline to draw conclusions without standard errors can surely be just as silly? Fortunately I believe we have not yet gone so far as our friends in the USA where, I am told, some editors of journals will return an article because tests of significance have not been applied. Yet there are innumerable situations in which they are totally unnecessary – because the difference is grotesquely obvious, because it is negligible, or because, whether it be formally significant or not, it is too small to be of any practical importance. What is worse the glitter of the t table diverts attention from the inadequacies of the fare. Only a tithe, and an unknown tithe, of the factory personnel volunteer for some procedure or interview, 20% of patients treated in some particular way are lost to sight, 30% of a randomly-drawn sample are never contacted. The sample may, indeed, be akin to that of the man who, according to Swift, 'had a mind to sell his house and carried a piece of brick in his pocket, which he showed as a pattern to encourage purchasers'. The writer, the editor and the reader are unmoved. The magic formulæ are there.

Of course I exaggerate. Yet too often I suspect we waste a deal of time, we grasp the shadow and

lose the substance, we weaken our capacity to interpret data and to take reasonable decisions whatever the value of P. And far too often we deduce 'no difference' from 'no significant difference'. Like fire, the χ^2 test is an excellent servant and a bad master.

The Case for Action

Finally, in passing from association to causation I believe in 'real life' we shall have to consider what flows from that decision. On scientific grounds we should do no such thing. The evidence is there to be judged on its merits and the judgment (in that sense) should be utterly independent of what hangs upon it – or who hangs because of it. But in another and more practical sense we may surely ask what is involved in our decision. In occupational medicine our object is usually to take action. If this be operative cause and that be deleterious effect, then we shall wish to intervene to abolish or reduce death or disease.

While that is a commendable ambition it almost inevitably leads us to introduce differential standards before we convict. Thus on relatively slight evidence we might decide to restrict the use of a drug for early-morning sickness in pregnant women. If we are wrong in deducing causation from association no great harm will be done. The good lady and the pharmaceutical industry will doubtless survive.

On fair evidence we might take action on what appears to be an occupational hazard, e.g. we might change from a probably carcinogenic oil to a non-carcinogenic oil in a limited environment and without too much injustice if we are wrong. But we should need very strong evidence before we made people burn a fuel in their homes that they do not like or stop smoking the cigarettes and eating the fats and sugar that they do like. In asking for very strong evidence I would, however, repeat emphatically that this does not imply crossing every 't', and swords with every critic, before we act.

All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.

Who knows, asked Robert Browning, but the world may end tonight? True, but on available evidence most of us make ready to commute on the 8.30 next day.

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Impact of Pesticide Exposure Misclassification on Estimates of Relative Risks in the Agricultural Health Study

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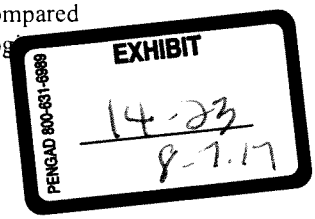
Abstract

Background—The Agricultural Health Study (AHS) is a prospective study of licensed pesticide applicators (largely farmers) and their spouses in Iowa and North Carolina. We evaluate the impact of occupational pesticide exposure misclassification on relative risks using data from the cohort and the AHS Pesticide Exposure Study (AHS/PES).

Methods—We assessed the impact of exposure misclassification on relative risks using the range of correlation coefficients observed between measured post-application urinary levels of 2,4-dichlorophenoxyacetic acid (2,4-D) and chlorpyrifos metabolite and exposure estimates based on an algorithm from 83 AHS pesticide applications.

Results—The correlations between urinary levels of 2,4-D and chlorpyrifos metabolite and estimated exposure intensity scores from the expert-derived algorithm were about 0.4 for 2,4-D (n=64), 0.8 for liquid chlorpyrifos (n=4), and 0.6 for granular chlorpyrifos (n=12). Correlations of urinary levels with individual exposure determinants (e.g., kilograms of active ingredient used, duration of application, or number of acres treated) were lower and ranged from −0.36 to 0.19. These findings indicate that scores from an *a priori* expert-derived algorithm developed for the AHS were more closely related to measured urinary levels than the several individual exposure determinants evaluated here. Estimates of potential bias in relative risks observed in the AHS based on the correlations from the AHS/PES and the proportion of the AHS cohort exposed to various pesticides indicate that nondifferential misclassification of exposure using the algorithm would bias some estimates toward the null, but less than the misclassification associated with individual exposure determinants.

Conclusions—Based on these correlations and the proportion of the AHS cohort exposed to various pesticides, the potential bias in relative risks from nondifferential exposure misclassification is reduced when exposure estimates are based on an expert algorithm compared to estimates based on separate individual exposure determinants often used in epidemiolog



studies. Although correlations between algorithm scores and urinary levels were quite good (i.e., correlations between 0.4 and 0.8), exposure misclassification would still bias relative risk estimates in the AHS towards the null and diminish study power.

Introduction

Exposure misclassification can limit the validity and precision of epidemiologic studies and diminish power to detect associations. The theory and mechanics of misclassification are well described[1–3] and the impact of exposure misclassification on relative risk estimates can be large.[4,5] In the AHS, as in many epidemiologic studies, there is no "gold standard" for exposure. In these cases, it is useful to relate estimates of exposure with actual measurements of current exposures (even if only at a single point in time) to provide an indication of the degree of exposure misclassification associated with surrogate indicators for exposures. Information from such methodologic efforts is of considerable assistance in the interpretation of epidemiologic data.

The Agricultural Health Study (AHS) is a long-term, prospective cohort study of licensed pesticide applicators and their spouses in Iowa and North Carolina.[6] The purpose of this paper is to use information from the AHS Pesticide Exposure Study (AHS/PES),[7] which compares urinary levels of pesticides with exposure estimates based on an expert-derived algorithm[8] and with several individual exposure determinants (kg of active ingredient used, hours of mixing and application, and number of acres treated) to evaluate effects of exposure misclassification on estimates of relative risks in the AHS.

Methods

Information on pesticide use and application procedures in the AHS was obtained by self-administered questionnaires (available at http://www.aghealth.org/questionnaires.html). Questionnaire information obtained at enrollment on pesticide use included pesticides used, application methods, mixing and applying, proportion of time personally mixed pesticides, first year of use, number of years and days per year personally applied, application method, and use of protective equipment. Information obtained on specific pesticides included ever used, mixing and application method, years used, average days per year of use, and first year of use. Monitoring information from the literature and from Pesticide Handlers Exposure Database was used to develop weights for important *a priori* exposure determinants identified from the literature, including mixing, application method, repair of application equipment, and use of personal protective equipment.[8] These weights were applied to information on pesticide use practices from AHS questionnaires to create quantitative pesticide exposure intensity scores. These scores were multiplied by the lifetime days of specific pesticide use to create intensity-weighted exposure metrics that have been used in a number of epidemiologic papers on various outcomes from this cohort (the AHS bibliography is available at: http://www.aghealth.org/.

Details of the AHS/PES monitoring effort and algorithm assessment study are provided elsewhere.[7,9] Briefly, the AHS/PES participants were individuals who had completed the AHS five-year follow-up interview between 1998 and 2003, had reported use of 2,4-D or chlorpyrifos, resided in selected counties in Iowa and North Carolina, and indicated they intended to use a product containing 2,4-D or chlorpyrifos during the upcoming season. Urine spot samples and 24-hour accumulations were collected prior to, during, and after an application of the target pesticides and analyzed for levels of 2,4-D and 3,5,6-trichloro-2-pyridinol (TCP) (a metabolite of chlorpyrifos). These pesticides were selected for the assessment study because they are important agricultural chemicals worldwide, used by many AHS participants with several different application methods, and may impact human

health.[10,11] The AHS/PES participants provided information on application practices at the time of application and, in addition, the AHS/PES monitoring team recorded application practices. Both sources of information and individual exposure determinants, were used to create exposure intensity scores using the previously developed algorithm[8], and each score was compared to post application urinary levels of 2,4-D and the chlorpyrifos metabolite (TCP) using Spearman correlation coefficients. Spearman rank order correlation values were calculated because the urinary biomarker measurements were not normally distributed and because a linear relationship between biomarker measurement and exposure intensity scores could not be assumed. In addition, the algorithm scores are not fully continuous because the algorithm variable weighting factors are combined in certain discrete combinations. The pesticide exposure section of the AHS/PES questionnaire mimicked that from the five-year followup questionnaire administered to the full cohort and included questions on determinants used in the algorithm.[8] Urinary concentrations have also been compared with several individual determinants.[7,12]

We assessed the impact of exposure misclassification on relative risks from the range of correlation coefficients (0.20, 0.40, and 0.70) observed between measured urinary levels of 2,4-D and chlorpyrifos and the algorithm scores, or individual exposure determinants. We considered nine scenerios based on proportions of applicators in the AHS reporting use of various pesticides (i.e., 20%, 40%, and 70%), a range of sensitivities that are possible with correlation coefficients of 0.20, 0.40, and 0.70, and on the range of relative risks that have been observed in the AHS are often seen in epidemiologic investigations (0.5, 1.0, 2.0, and 3.0). The calculations for relative risk attenuation based on these parameters are described in the appendix. This study was approved by the National Institutes of Health Special Studies Institutional Review Board (SSIRB), protocol number OH93-NC-N013, and also by Institutional Review Boards at the University of Iowa, Westat, Inc., RTI International, and Battelle, Inc. Informed consent was obtained from all participants prior to enrollment.

Results

Urinary biomarker measurement results have been previously reported for 2,4-D and chlorpyrifos applicators in the AHS/PES[7,9]. Geometric mean (geometric standard deviation) values in post-application urine samples were 25 (4.1) μg/L for 2,4-D applicators and 11 (2.3) μg/L TCP for chlorpyrifos. There was considerable range among the post-application measurements (greater than 600-fold for 2,4-D applicators (1.6 – 970 μg/L) and greater than 30-fold for chlorpyrifos applicators (2.5 – 80 μg/L)). Post-application geometric mean TCP levels for chlorpyrifos applicators were over seven times higher than geometric mean levels in the U.S. adult general population in the 2001 – 2002 period[13]. Geometric mean values for 2,4-D in the U.S. general population are not available due to the preponderance of non-detect values, but post-application geometric mean 2,4-D levels for 2,4-D applicators were about 20 times greater than the 95th percentile level in the U.S. adult general population[13]. Exposure intensity algorithm scores based on questionnaires were 10.3 ± 4.6 (range 1.8 – 20) for 2,4-D applicators and 9.4 ± 2.6 (range 6.6 – 14) for chlorpyrifos applicators.[9]

Spearman correlations between post application urinary levels of 2,4 D and chlorpyrifos metabolites and estimated exposure intensity scores based on monitoring team observations of AHS/PES participant activities were 0.39 for 2,4-D, 0.80 for liquid chlorpyrifos, and 0.60 for granular chlorpyrifos (Table 1).[9,12] Results were similar using exposure intensity scores based on information from participant-completed questionnaires with correlations of 0.42 for 2,4-D, 0.80 for liquid chlorpyrifos, and 0.58 for granular chlorpyrifos. Table 2 provides Spearman correlations between urinary levels of 2,4-D or chlorpyrifos metabolite among study participants and individual determinants of pesticide exposure used in some epidemiologic studies, e.g., kg of active ingredient, hours spent mixing and applying, and

number of acres treated.[12] These correlation coefficients were quite low and none was statistically significant. The correlations for 2,4-D were all less than 0.1 and those for chlorpyrifos were 0.19 for kg of active ingredient, −0.28 for hours of use per day, and −0.36 for acres treated.

Figure 1 shows the impact of exposure misclassification on relative risks considering the correlation between urinary levels and exposure estimates noted above and relative risks in a range relevant to the published results from the AHS. Correlations between estimated exposure intensity scores and urinary levels of 0.2 or less (dotted lines) and sensitivities of 0.9 or less would depress the relative risks considerably. Some lines do not provide information across the full range of possible sensitivities because they are undefined for certain combinations of prevalence of use, sensitivity, specificity, and correlation combinations. Many relative risks are so close to the null value that a reasonable interpretation would be that no association exists. For correlations of 0.4 (dashed lines), observed relative risks for the different sensitivity and exposure misclassification categories are somewhat closer to the true relative risks than for correlations of 0.2, but they still show substantial attenuation toward the null for sensitivities of 0.9 or less. Only for correlations of 0.7 (solid lines) do the observed relative risks approach the true relative risks. For true relative risks of 1.0, misclassification described here does not bias the relative risk regardless of the proportion exposed or the magnitude of the exposure misclassification, i.e., the estimated relative risk is always 1.0 and non-differential misclassification cannot create a positive association.

Discussion

Studies have evaluated the reliability and validity of farmers' self-reports of their pesticide application activities.[14–16] The reliability of farmers' recall of the types of pesticides used is between 60% and 80% for most pesticides.[14] Farmers can also provide considerable detail regarding their application practices, although as the questions get more detailed the reliability decreases.[14] Reliable reporting of the fact of pesticide use and application technique does not, however, provide assurance that exposure metrics and, more importantly, dose can be accurately estimated from such questionnaire data. Dose, i.e., the concentration at the target tissue, is the ultimate metric of interest in epidemiologic studies, but is largely unmeasurable.[17] Exposure and biologic factors both influence dose. Only one metabolite of chlorpyrifos (TCP) was monitored in the urine in this study and the concentration of other metabolites might also be important for health outcomes, although TCP is the major chlorpyrifos metabolite in humans. Chemical-specific biologic factors at the individual level, such as permeability of the skin and other tissues of first contact and metabolism are important, but largely unavailable for epidemiologic studies. Some information on exposure factors, such as type and condition of the equipment, use of protective equipment, type of clothing, and application rate, can be obtained by interview, but with reporting error. Estimates of pesticide exposure in the AHS were developed from an algorithm that included determinants that appeared, based on the literature, to affect exposure.[8] A concern about exposure estimates based on an algorithm is that the error associated with each determinant might multiply to something quite large and unreliable. If this was true, use of a simple, single exposure determinant might be preferable to a more complicated algorithm. Thus, an indication of the magnitude of misclassification from exposure estimates based on an algorithm derived from several determinants versus estimates based on a single determinant, e.g., acres treated, hours spent mixing and applying, or amount of active ingredient used, is essential for sound interpretation of data from epidemiologic studies and to provide guidance regarding exposure estimation efforts in future studies.[18]

Data from the recent AHS/PES methodologic study found moderate to high correlations (r=0.39 to 0.80) between measured levels in the urine and algorithm-derived estimates of pesticide exposure intensity based on information from self-reports by study participants or from observations by AHS/PES investigators during the monitoring of pesticide mixing and application activity.[9] These correlations between urinary levels and algorithm scores are similar to those reported for 2,4-D, glyphosate, and MCPA elsewhere[19–21] It is important to keep in mind that comparison of observational data and monitoring data collected at the time of application does not provide direct information on farmers' ability to recall past use of pesticides, which is critical for examining relationships between chronic diseases and pesticide exposure. Whatever the correlation is between urine measurements and a farmer's reporting of specific pesticide activities at the time of monitoring, it is likely that correlation with application activities in the past would be weaker because of increased uncertainty that occurs with the passage of time. Inclusion of frequency or duration of use of pesticides in cumulative exposure indices could introduce further misclassification that would typically lead to under-estimates of risk, as has been shown elsewhere.[22] On the other hand, it is also possible that recall of the details of pesticide use over many growing seasons might provide a better estimate of cumulative exposure over a long time period than a biologic measurement of exposure from a single application, particularly because urinary levels from non-persistent pesticide exposure reflect only recent use and are not necessarily a measure of long-term use. Several conclusions can be drawn from the evaluation of the impact of exposure misclassification on estimated relative risks in the AHS. First, the correlations between questionnaire, or observer information on pesticide use, and measured urinary levels are in the range found for other factors that are usually considered to be reliably obtained for epidemiologic studies, such as tobacco and alcohol use, diet, physical activity, and health assessments.[23–28] Second, exposure estimates from an algorithm based on several determinants thought to affect exposure are more highly correlated with measured levels of these pesticides in the urine than some specific individual determinants (i.e., kg of active ingredient used, hours of mixing and application, or number of acres treated) and would result in less attenuation of relative risks. In fact, in this example the correlations between these individual determinant measures and urinary levels of 2,4-D are so low (less than 0.1) that even if the true relative risk was 3.0, the calculated relative risk would only be about 1.1, making it very unlikely that any epidemiologic study could detect an association. The correlations between these individual determinants and urinary levels of chlorpyrifos are somewhat larger (-.36 to 0.19) than for 2,4-D (−0.09 to 0.09), but they are still considerably less than found for exposure intensity estimates based on the algorithm.[8] Third, the stronger correlations between urinary levels and algorithm exposure scores (e.g., 0.4 or 0.5) would still result in considerable attenuation of observed relative risks. For example, if the correlation between algorithm exposure intensity scores and measured urinary levels was 0.4 and the true relative risk was 3.0, the observed relative risks would be between 1.3 and 1.9 when sensitivity is in the 60 to 80% range. For a true relative risk of 2.0, the observed relative risks from correlations of 0.2 or 0.4 never rise above 1.4. For true relative risks of 0.5, correlations from 0.2 to 0.4 between exposure estimates and measurements yield estimates of relative risk between 0.7 and 0.9. All of these observed relative risks are in a range where a reasonable interpretation would be that no important association exists. In the AHS/PES exposure studies, only evaluation of chlorpyrifos in the liquid formulation had a correlation of 0.7 or greater and this may be inaccurate because the sample size was very small. The attenuation of relative risks from exposure misclassification would also reduce study power, which would necessitate larger investigations to meet study objectives.

There are additional considerations in assessing the accuracy of estimates of exposure intensities used in epidemiologic studies. First, for many chronic diseases, it is generally assumed that the critical exposure window occurs many years in the past. The correlations between estimates of exposure intensity and urinary levels in the AHS/PES[7,9] are based on

simultaneous collection of information on exposure determinants by questionnaire or observation and measurement of urinary levels of pesticides. Estimates of exposure intensity based on self-reported activities that occurred years in the past would probably be subject to greater error. Second, the correlations between algorithm scores and urinary levels varied by pesticide in each of the three recent methodologic studies[9,19–21] and the range was quite large, i.e., from r=0.12 to 0.80. Third the impact of misclassification on estimates of relative risks is influenced by the proportion of individuals exposed because this affects the sensitivity and specificity levels. For the range of exposure misclassification noted here, it appears that the proportion of the population exposed was less important than the accuracy of the exposure assessment. This conclusion, however, is based on relatively thin data and a more complete evaluation of this issue is needed.

Some cautions about these findings are warranted. The AHS/PES monitoring study provides information on farmer owner/operators and may not be relevant for other pesticide applicators. The number of measurements on chlorpyrifos is quite small and estimates are relatively unstable. The differences between urinary levels and individual determinants and algorithm scores we observed need further evaluation to see if they are generalizable to other situations. However, these data provide useful evidence regarding the reliability of the exposure metrics used in the AHS and for the interpretation of AHS findings.

We draw several conclusions from our methodologic work in the AHS. First, the accuracy of reporting of pesticide use by farmers is comparable to that for many other factors commonly assessed by questionnaire for epidemiologic studies.[23–28] Second, except in situations where exposure estimation is quite accurate (i.e., correlations of 0.70 or greater with true exposure) and true relative risks are 3.0 or more, pesticide misclassification may diminish risks estimates to such an extent that no association is obvious, which indicates false negative findings might be common. Third, it appears that an algorithm that incorporates several exposure determinants into an estimate of exposure intensity predicts urinary levels better than the individual exposure determinants considered here and would result in less attenuation of relative risk estimates. This provides some confirmation of the assumption that use of algorithms will improve exposure assessment. Finally, we note that even with the reduction in power from exposure misclassification, the AHS has identified some statistically significant links between various agricultural exposures and health outcomes.[29–35]

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Appendix

The plots in Figure 1 were developed based on the following procedure. Let X represent the true exposure, where X=1 denotes exposed and X=0 denotes unexposed, and similarly let Z represent the observed exposure. Suppose r denotes the correlation coefficient for X and Z, and Sen = P(Z=1 | X=1), the sensitivity, i.e., the probability an observed exposure is a true exposure. These quantities represent relationships in the general study population. Since X and Z are binary random variables, then by definition

$$r^2 = \frac{[P(Z=1, X=1) - P(Z=1)P(X=1)]^2}{P(Z=1)P(Z=0)P(X=1)P(X=0)}$$

which can be rewritten as

$$r^2=\frac{[\mathrm{Sen}-P(Z=1)]^2\,P(X=1)}{P(Z=1)\,P(Z=0)\,P(X=0)}$$

and as a quadratic equation in P(Z=1),

$$P(Z=1)^2\,[r^2+P(X=1)(1-r^2)]-P(Z=1)[r^2+P(X=1)(2\,\mathrm{Sen}-r^2)]+\mathrm{Sen}^2P(X=1)=0$$

that can be solved to obtain P(Z=1). Since P(Z=1) = Sen P(X=1) + (1-Sp) P(X=0), where Sp = P(Z=0 | X=0) is the specificity, i.e., the probability that an observed non-exposure is a true non-exposure, we can solve for Sp as

$$\mathrm{Sp}=\frac{1-P(Z=1)-P(X=1)\,(1-\mathrm{Sen})}{1-P(X=1)}$$

We assume misclassification is non-differential, which implies that Sen and Sp are not related to case status, that is, the same in the general population and in case subjects. Note that while Sen and Sp do not depend on case status, the correlation coefficient, r, does depend on the probability of exposure. Thus, r in cases will in general not equal r in the general population if the exposure factor is related to disease outcome.

For a cohort study and for disease outcome D, where D=1 denotes disease and D=0 denotes disease-free, the probability of disease for observed exposure Z=1, denoted P(D=1 | Z=1), can be expressed as

$$\begin{aligned}
P(D=1|Z=1)&=P(D=1,X=1|Z=1)+P(D=1,X=0|Z=1)\\
&=[\,P(D=1,X=1,Z=1)+P(D=1,X=0,Z=1)]/P(Z=1)\\
&=[\,\mathrm{Sen}\,P(D=1|X=1)\,P(X=1)+(1-\mathrm{Sp})\,P(D=1|X=0)\,P(X=0)]/P(Z=1)\\
&=[\,\mathrm{Sen}\,RR_{\mathrm{true}}P(X=1)+(1-\mathrm{Sp})\,P(X=0)]\,P(D=1|X=0)/P(Z=1)
\end{aligned}$$

where RR_{true} is the true relative risk and RR_{true} = P(D=1|X=1)/P(D=1|X=0). The third line follows from the assumption of non-differential misclassification, or equivalently that the observed exposure provides no additional information on disease outcome once the true exposure status is known, i.e., P(D|X,Z) = P(D|X).

Following a similar process, we obtain

$$P(D=1|Z=0)=[\,(1-\mathrm{Sen})\,RR_{\mathrm{true}}P(X=1)+\mathrm{Sp}\,P(X=0)]\,P(D=1|X=0)/P(Z=0)$$

Thus, the observed relative risk (RR_{obs}) can be expressed as

$$RR_{obs} = \frac{P(D=1|Z=1)}{P(D=1|Z=0)} = \frac{Sen\ RR_{true}\ P(X=1)+(1-Sp)\ P(X=0)}{(1-Sen)\ RR_{true}\ P(X=1)+Sp\ P(X=0)} \times \frac{P(Z=0)}{P(Z=1)}$$

For each P(X=1), sensitivity, RR_{true} and r, the corresponding RR_{obs} for the figure is obtained by first solving the quadratic equation for P(Z=1), then calculating RR_{obs} from the above equation.

In a similar way, a comparable expression can be developed for true and observed relative risks, OR_{true} and OR_{obs}, respectively, in a case-control setting, namely,

$$OR_{obs} = \frac{P(Z=1|D=1)\times P(Z=0|D=0)}{P(Z=1|D=0)\times P(Z=0|D=1)} = \frac{Sen\ OR_{true}\ P(X=1|D=0)+(1-Sp)\ P(X=0|D=0)}{(1-Sen)\ OR_{true}\ P(X=1|D=0)+Sp\ P(X=0|D=0)} \times \frac{P(Z=0|D=0)}{P(Z=1|D=0)}$$

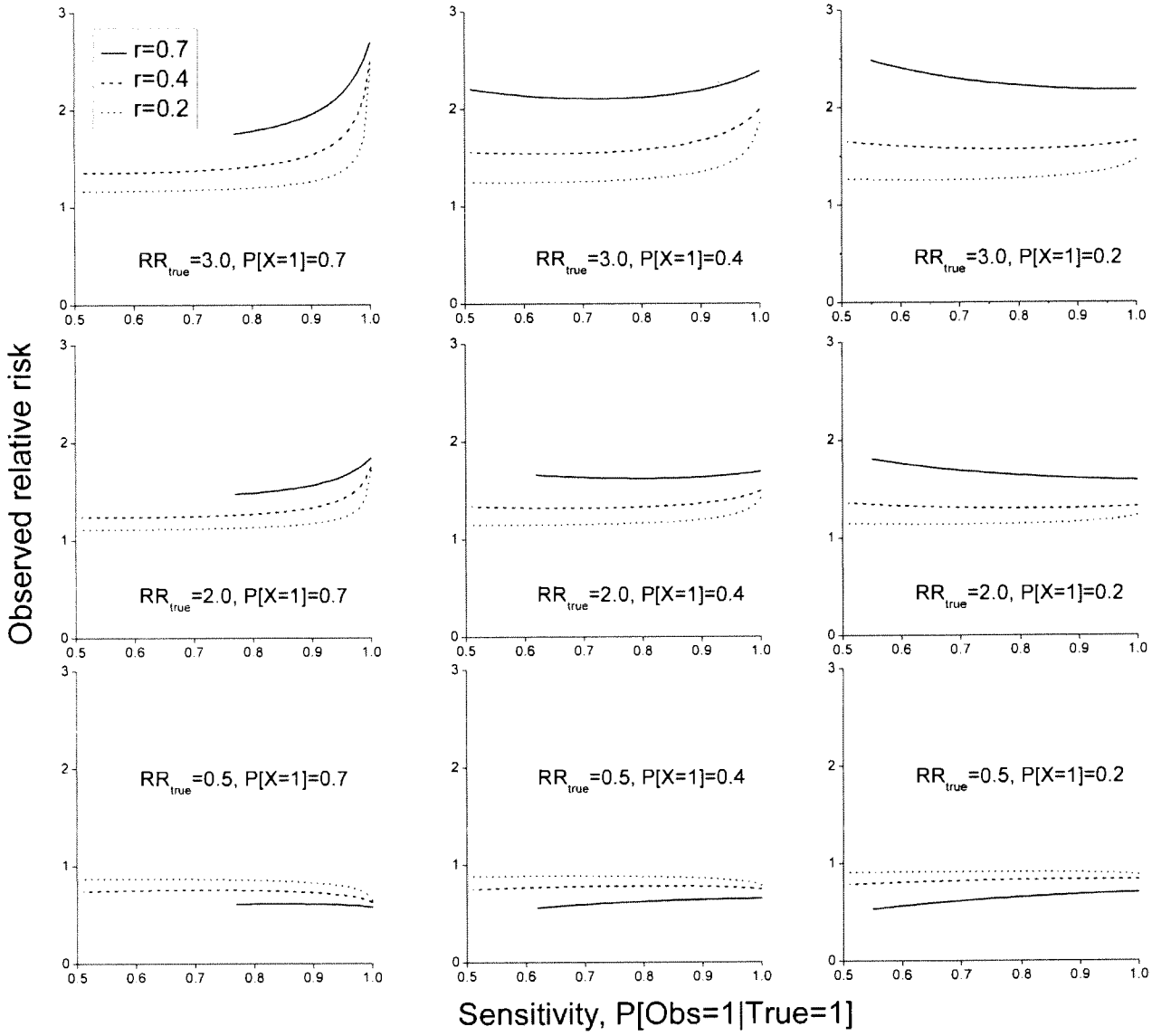

Figure 1.
Plots of observed relative risks based on different correlations between estimated exposure intensity scores and urinary levels (See appendix for further description of these plots).

Table 1

Spearman correlations between calculated pesticide exposure intensity scores and post-application urinary levels in the Agricultural Health Study Pesticide Exposure Study.[14]

Intensity Score Source	2,4-D (N=68)	Chlorpyrifos+ (Liquid formulation) (N=4)	Chlorpyrifos+ (Granular formulation) (N=12)
Observation	0.39**	0.80	0.60*
Questionnaire	0.42**	0.80	0.58*

*0.01<p<=0.05;

**p<=0.001

+Chlorpyrifos metabolite measured was 3,5,6-trichloro-2-pyridinol (TCP)

Table 2

Spearman correlations between exposure surrogates and post-application urinary levels in the Agricultural Health Study Pesticide Exposure Study (Thomas et al., Personal Communication).

Pesticide Applied	KG Active Ingredient	Hours Mixed or Applied	Acres Treated
2,4-D (N=63 to 68)[1]	0.05	0.09	−0.09
Chlorpyrifos (N=16)	0.19	−0.28	−0.36

[1] Number of individuals with monitoring data varied for the three determinants.

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Article

An Updated Algorithm for Estimation of Pesticide Exposure Intensity in the Agricultural Health Study

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Abstract: An algorithm developed to estimate pesticide exposure intensity for use in epidemiologic analyses was revised based on data from two exposure monitoring studies. In the first study, we estimated relative exposure intensity based on the results of measurements taken during the application of the herbicide 2,4-dichlorophenoxyacetic acid

(2,4-D) (n = 88) and the insecticide chlorpyrifos (n = 17). Modifications to the algorithm weighting factors were based on geometric means (GM) of post-application urine concentrations for applicators grouped by application method and use of chemically-resistant (CR) gloves. Measurement data from a second study were also used to evaluate relative exposure levels associated with airblast as compared to hand spray application methods. Algorithm modifications included an increase in the exposure reduction factor for use of CR gloves from 40% to 60%, an increase in the application method weight for boom spray relative to in-furrow and for air blast relative to hand spray, and a decrease in the weight for mixing relative to the new weights assigned for application methods. The weighting factors for the revised algorithm now incorporate exposure measurements taken on Agricultural Health Study (AHS) participants for the application methods and personal protective equipment (PPE) commonly reported by study participants.

Keywords: pesticides; exposure algorithm; epidemiology; 2,4-D; chlorpyrifos; captan

1. Introduction

The risk of adverse health effects associated with long-term exposure to pesticides is difficult to assess in epidemiologic studies due to various limitations that have been summarized in the literature [1]. A major challenge has been the development of reliable methods to estimate the duration and intensity of exposure to pesticides in large studies in which the direct measurement of exposure to all participants is not feasible [2-4]. The Agricultural Health Study (AHS) is a prospective cohort study of 57,310 licensed private and commercial pesticide applicators, primarily farmers, and 32,345 spouses, designed to investigate health effects associated with pesticides and other agricultural exposures [5]. At enrollment, pesticide applicators completed self-administered questionnaires to provide information on lifetime frequency and duration of use for 50 specific pesticides, frequency of mixing or loading of pesticides, application methods, frequency of repair of pesticide application equipment and use of personal protective equipment (PPE). To utilize the information collected on the enrollment questionnaire to estimate exposure intensity, we previously developed an exposure algorithm (denoted version 1) [6]. As described by Dosemeci *et al.*, the weighting factors in the algorithm were developed based primarily on expert judgment using published studies on pesticide exposure from the world's literature, including information from the Pesticide Handlers Exposure Database (PHED) [7]. The weighting factors (*i.e.*, numerical values), when used in the algorithm, convert categorical responses to specific questions from the enrollment questionnaire from each applicator into a relative exposure intensity score. The exposure intensity scores are multiplied by frequency and duration of use as reported on the questionnaire to calculate lifetime intensity-weighted days of pesticide use for epidemiological analyses.

The AHS algorithm has four variables that were combined as follows:

$$\text{Exposure Intensity Score} = ([\text{MIX}] + [\text{APPLY}] + [\text{REPAIR}]) \times [\text{PPE}])$$

where [MIX] represents exposure from mixing and loading operations prior to application, [APPLY] represents exposure from applying pesticides, [REPAIR] represents exposure from contact with contaminated surfaces during the repair of pesticide application equipment, and [PPE] represents an exposure reduction factor to account for use of PPE.

The reliability of the version 1 algorithm intensity scores for correctly rank ordering various application scenarios has been evaluated based on four field monitoring studies; (1) a study among Canadian farmers [8], (2) a study among Minnesota and South Carolina pesticides applicators [9], (3) the AHS Pesticide Exposure Study (AHS/PES) [10,11], and (4) the AHS Orchard Fungicide Exposure Study (AHS/OFES) [12-14]. Because the two field monitoring studies conducted on subgroups of AHS applicators after the algorithm was developed offered AHS-specific, quantitative measurements for various application characteristics, we used these data, in conjunction with the world's literature and PHED, to modify the algorithm weights, thereby reducing the need to rely exclusively on measurement data external to the cohort. The field monitoring results, in general, confirmed the underlying premise of the algorithm; *i.e.*, that algorithm scores based primarily on application method and the use of personal protective equipment can be used to identify applicators most likely to have encountered higher pesticide exposure levels, and thereby serve as an effective surrogate for exposure intensity. Nonetheless, the exposure measurements suggest that some modifications to the algorithm weights (denoted version 2) could be made that would improve agreement with the results of these field monitoring studies, and thereby potentially reduce exposure misclassification inherent in the use of any algorithm.

In the AHS/PES, we selected 2,4-D and chlorpyrifos because 2,4-D is one of the most important agricultural and residential herbicides and chlorpyrifos is one of the most important agricultural insecticides. In addition, the pharmacokinetics of these chemicals are relatively well understood. Both chemicals are widely used by AHS cohort members. Similarly, the AHS/OFES measured captan, the second most frequently used fungicide in the AHS. These studies included some of the most frequently used application methods in the cohort.

Measurement results from the AHS field studies were used to examine relative differences in urinary biomarker concentrations associated with the algorithm exposure variables. These comparisons enabled us to modify the algorithm weights using AHS-derived field study data while still relying on information from the literature and PHED for algorithm weights, particularly where AHS-specific field data was lacking. Decisions on changing any algorithm weights were based on the field study data in combination with the body of information from the literature and PHED. In addition, we re-scaled the algorithm scores and assigned weights for application methods reported by cohort members in follow-up questionnaires but not in the enrollment questionnaire. These enhanced algorithm weights provide the basis for updated exposure intensity scores currently used in AHS epidemiological analyses.

2. Field Studies

The methodology and measurement results for the AHS/PES have been previously described in detail [10]. The AHS/PES study selected applicators who reported agricultural use of 2,4-D or chlorpyrifos on the AHS Phase II questionnaire in 22 counties in eastern Iowa and 22 counties from eastern and central North Carolina. The AHS/PES study collected pre- and post-application urine

samples, as well as hand wipe, body patch and personal air samples [10]. The post-application urine sample was a composite sample collected from the beginning of a monitored application through the first morning void the next day. Results from 68 applicators for 88 applications of 2,4-D and from 16 applicators for 17 applications of chlorpyrifos were used in this analysis. Where repeat measurements were made on an individual, the interval between measurements ranged from one week to 14 months; however, as described previously [10], several applicators reported using the chemical in an unmonitored application within four days prior to the monitored application. All 2,4-D broadcast spray applications (N = 46) were made with tractor-mounted boom sprayers except for one truck-mounted boom sprayer and one highboy application and were grouped into a 'boom spray' category for this analysis. Hand spray applications of 2,4-D (N = 42) were made using vehicle-mounted or portable sprayers. In three applications, both boom spray and hand spray methods were used; these applications were placed in the hand-spray group for analysis. Chlorpyrifos application methods included in-furrow or banded applications of a granular formulation (n = 13), and spray applications of a liquid formulation by boom (N = 3) and airblast (N = 1) sprayers. For our purposes, we classified chlorpyrifos applications as either boom spray/liquid or in-furrow/granular. Applicators personally mixed and/or loaded pesticide products, except for five cases where someone else performed the mixing/loading. The AHS/OFES selected all orchard farmers in Iowa and North Carolina who reported growing apples or peaches on the AHS Phase 2 questionnaire [12]. The AHS/OFES measured captan, a fungicide, for 74 applicators on 144 days when it was applied to orchards using either hand spray or air blast methods [12-14]. Measurements included personal air, hand rinse and dermal patch samples, as well as pre-application and 24-h post-application urine samples. Both field studies were observational in design. Applicators in these studies followed their usual procedures with regard to mixing and application procedures, duration of the application, total amount of pesticide applied, and type of PPE worn during different phases of the application process. Information pertaining to the algorithm variables was obtained from observations by study personnel and, for the AHS/PES, using interviewer-administered questionnaires. AHS research was reviewed and approved as applicable by Institutional Review Boards at the National Cancer Institute, the University of Iowa, Battelle; RTI International, and the National Institute for Occupational Safety and Health.

2.1. Statistical Analysis

Arithmetic means, geometric means (GM) and geometric standard deviations (GSD) of post-application urine concentrations for AHS/PES applicators were calculated for application method and use of chemical-resistant or other waterproof gloves (referred to as CR gloves). We used a two-way analysis of variance procedure among study participants (GLM Procedure, SAS version 9.1, Cary, NC, USA) to evaluate whether CR-glove use or application method significantly affected the urine concentrations of the measured analyte, when controlling for the other factor. Urine concentrations were log-transformed to account for right skewed data.

We calculated the ratios of the GM's to evaluate the relative exposure intensity for (1) for boom spray compared to an in-furrow/granular application method and (2) the reduction in post-application urine concentrations attributable to glove use. Spearman correlation coefficients were calculated

between version 2 *vs.* version 1 algorithm scores for measurements of 2,4-D and chlorpyrifos in post-application urines.

To provide a secondary method to evaluate the revised weighting factors, we fitted a nonlinear regression model to assess the joint influence of the algorithm variables on post-application urine concentrations (Y) in μg/L:

$$Y = \{\alpha_0 + \alpha_1 \text{ Mix} + \alpha_2 \text{ Method} + \alpha_3 \text{ Repair}\} \times \{1 - (\beta_1 \text{ Gloves}) - (\beta_2 \text{ PPE other})\} \quad (1)$$

where α_0 represented the urinary concentration at the referent level of all factors, where α_1, α_2 and α_3 parameters represented the increase in Y for mixing (1 = yes, 0 = no), use of hand spray (method = 1) or boom spray (method = 0) for 2,4-D, or boom spray (method = 1) or in-furrow (method = 0) for chlorpyrifos, and repairing equipment (1 = yes, 0 = no), respectively, and where β_1 and β_2 parameters represented the reduction factors for use of CR gloves (1 = yes, 0 = no) and/or other PPE (1 = yes, 0 = no), respectively. We then compared the predicted values from the model to the algorithm scores. Because the regression coefficients were pesticide specific and based on relatively limited data in many of the exposure scenarios, we did not directly use the parameter estimates as weights, but rather to jointly assess the relative influences of the variables.

To evaluate the extent to which algorithm scores could be used to categorize applicators into exposure groups, we divided the 2,4-D applicators into three groups by algorithm score (<50, 50–100, >100), computed summary statistics, and conducted a nonparamteric test for trends based on rankings using the Stata nptrend command, an extension of the Wilcoxon rank-sum test. Due to a smaller number of applications and limited range of scores, the chlorpyrifos data were divided into two groups using a cut-point of 50.

3. Results and Discussion

3.1. Use of CR Gloves

CR glove use was associated with a significant difference in urinary 2,4-D GM levels overall, when controlling for application method ($p < 0.0001$). Among 2,4-D applicators who wore CR gloves, GMs of the post-application urine concentrations were 75% and 72% lower for boom (14 μg/L *vs.* 55 μg/L) and hand spray (23 μg/L *vs.* 81 μg/L) applicators, respectively, compared with those who did not wear CR gloves (Table1).

Among chlorpyrifos applicators, the GMs of 3,5,6-trichloro-2-pyridinol (TCPy) post-application urine concentrations were 50% and 56% lower with CR glove use for in-furrow (granular formulation) and boom spray (liquid formulation) application, respectively, (GM = 6 μg/L and GM = 14 μg/L) compared with no glove use (12 μg/L and 32 μg/L). While CR glove use was associated with lower GM TCPy levels, the results were not statistically significant ($p = 0.084$) when we controlled for application method.

Based on a reduction of 72% to 75% among the 2,4-D applicators, and of 50% to 56% among the chlorpyrifos applicators, the reduction factor for use of CR gloves was increased from 40% in the version 1 algorithm to 60% in version 2.

3.2. Application Method

Among 2,4-D applicators, the GMs for hand spray applicators were 1.6 times and 1.5 times higher than for boom spray applicators who did (23 µg/L *vs.* 14 µg/L) and did not wear CR gloves (81 µg/L *vs.* 55 µg/L) (Table 1). Although 2,4-D levels for hand spray were higher than for boom spray, the difference was not statistically significant after controlling for glove use (p = 0.092).

For chlorpyrifos applicators, the GMs for boom spray applicators were 2.3 and 2.7 times higher than for in-furrow applicators for those who did (14 µg/L *vs.* 6 µg/L) and did not (32 µg/L *vs.* 12 µg/L) wear CR gloves, respectively. Although boom spray results are based on only four observations, when we controlled for CR glove use, we observed a significantly higher GM concentration of TCPy associated with boom spraying *vs.* in-furrow application (p = 0.014).

Based on the ratio of the GM's by application method, we decided to increase the weighting factor for boom spray, thereby reducing the relative difference with hand spray from version 1 (*i.e.*, 3:9) compared to version 2 (*i.e.*, 40:90); and increasing the relative difference with in-furrow from version 1 (*i.e.*, 3:2) compared with version 2 (*i.e.*, 40:20).

Table 1. Post-application urine concentrations (µg/L) grouped by application method and CR glove use for 2,4-D [1] (N = 88) and chlorpyrifos [2] (N = 17) applications.

Application Method	CR Glove Use	N	AM	GM	GSD	CR Glove Use [3]	Application Method [3]
2,4-D							
Boom Spray	Yes	32	27	14	3.1	P < 0.0001	P = 0.092
	No	14	91	55	3.0		
Hand Spray	Yes	21	48	23	3.3		
	No	21	200	81	4.9		
Chlorpyrifos							
In-furrow (granular)	Yes	7	8	6	1.8	P = 0.084	P = 0.014
	No	6	14	12	1.8		
Boom Spray(liquid)	Yes	2	14	14	1.3		
	No	2	47	32	3.6		

[1] 2,4-D measured as a urinary biomarker for 2,4-D.

[2] TCPy measured as a urinary biomarker for chlorpyrifos.

[3] P values from two-way analysis of variance using (independent variables: glove use and application method).

Abbreviations: AM = arithmetic mean; CR = chemically-resistant; GM = geometric mean; GSD = geometric standard deviation; N = number of application days monitored.

In the version 1 algorithm, hand spray and air blast had the same weight (*i.e.*, 9); however, among captan applicators the AHS/OFES detected *cis*-1,2,3,6-tetrahydrophalimide (THPI), a metabolite of captan, in 77% of urine samples from 79 air blast applications (range, <1.7 to 32.0 µg/L) compared with 41% of samples from 59 hand spray applications (range, <1.7 to 29.9 µg/L) [13]. The percent detected was approximately 88% higher for airblast compared to hand spray. Due to the high percentage of non-detects among hand spray applicators, we did not estimate a GM; however, we

decided to increase the weighting factor for airblast to 150 so that it would be substantially higher than the weighting factor of 90 for hand spray in the version 2 algorithm (67% higher). The effect of this change was that an airblast applicator would be assigned a higher weight score (*i.e.*, 150) than a hand spray applicator, even if the hand spray operator both mixed/loaded and applied (*i.e.*, 50 + 90 = 140). Because the information from the captan study used in this assessment was based only on the percentage of detectable measurements for different application methods, no statistical analyses were performed for captan.

3.3. Version 2 Algorithm Weights

The version 2 algorithm retained the same four variables as version 1 because these variables were *a priori* determinants of interest and therefore had been collected for all applicators at enrollment. We made the following modifications to version 2: (1) rescaled the range of scores by a factor of 10; (2) increased the reduction for use of CR gloves; (3) increased the weights for boom spray and air blast application methods; and (4) reduced the weight for mixing (Table 2).

In the version 1 algorithm, intensity scores ranged from 0.1 to 20, with scores that included decimal values. To use only integers with a minimum value of 1, the version 2 algorithm weights were re-scaled by a factor of 10, so version 2 intensity scores range from 1 to 220. Rescaling was done primarily for convenience and had no effect of the relative ranking by algorithm score.

Table 2. AHS Pesticide Exposure Algorithm Weighting Factors. Algorithm Intensity Score = (MIX + APPLY + REPAIR) × PPE.

MIX	**Version 1**	**Version 2**
Did Not Mix	0	0
Mix <50% of the time	3	20
Mix >50% of the time	9	50
REPAIR	**Version 1**	**Version 2**
No	0	0
Yes	2	20
APPLICATION METHODS	**Version 1**	**Version 2**
Air blast	9	150
Hand Spray	9	90
Mist Blower Or Fogger	9	90
Fog Or Mist Animals	9	90
Greenhouse Sprayer	9	90
Pour Fumigant From Bucket	9	90
Powder Duster	9	90

Table 2. *Cont.*

MIX	Version 1	Version 2
Backpack Sprayer	8	80
Dust Animals	7	70
Pour On Animals	7	70
Garden Hose	None	50
Hand Held Squeeze Or Squirt Bottle	None	50
Watering Can/Sprinkling Can	None	50
Soil Injected Or Drilled	4	40
Spray Over Rows	4	40
Boom On Tractor	3	40
Broadcast Application	3	40
Personally Applied To Seed	2	40
Banded/Directed Spray (liquid)	2	30
Banded Application (granular)	2	20
Gas Canister	2	20
Hang Pest Strips In Barn	2	20
In-Furrow	2	20
Incorporated	2	20
Inject Animals	2	20
Seed Treatment	1	20
Hand Spreader Or Push Spreader	None	20
Planter Box	None	20
Aerial	1	10
PPE REDUCTION	**Version 1**	**Version 2**
Chemical Resistant or Rubber Gloves	40%	60%
Cartridge Respirator, Tyvek Coveralls	30% for use of 1 or more	10% each with max of 30%
Face Shield, Goggles, Boots, Apron, Other	20% for use of 1 or more	
Fabric/leather gloves	20%	none

[1] None indicates methods for which a version 1 weighting factor was not assigned

In the version 2 algorithm, the protection factor for glove use was increased from 40% to 60%. The increase was based on comparison of the GM urine concentrations for CR glove use relative to no CR glove use that ranged from 50% to 75% (Table 1). Data from the AHS/PES and the PHED data base generally demonstrate that personal protective equipment rarely reduce the amount of exposure

expected from a particular exposure scenario more than 90%. With the protective factor for CR rubber gloves increasing to 60%, we have assigned a further increase in protection with each additional piece of equipment, including coveralls, respirators, face shield/goggles and CR boots, up to 90% protection. We could not clearly distinguish between the levels of protection afforded by the various types of equipment so we assigned a 10 % reduction for each piece of equipment up to a maximum of 30%.

The enrollment questionnaire asked about use of "chemically" resistant gloves (for example, neoprene or nitrile gloves), and because we could not distinguish between different types of CR gloves based on the enrollment questionnaire, we assigned the same reduction for rubber, waterproof or disposable latex gloves as for CR gloves. The version 1 algorithm included a 20% reduction use of fabric/leather gloves. Data from our monitoring study AHS/PES study, however, did not support treating fabric/leather gloves as protective, and therefore, the version 2 algorithm does not assign any reduction in exposure for their use.

We increased the weight for boom spray application from 3 (on version 1 scale) to 40 (on version 2 scale) while retaining the banded/in-furrow application method weight at 2 (20 on the version 2 scale) to reflect the approximately 2-fold exposure difference observed in the chlorpyrifos data. Based on the detection frequency difference of THPI in the AHS/OFES, we increased the air blast application weight to 150 which was now 67% higher than the hand spray weight of 90. This change ensured that airblast would be the application method with the highest exposure potential under all exposure scenarios. Because post-enrollment AHS questionnaires expanded the number of application methods, we accommodated these additional methods in the version 2 algorithm by assigning weights based on similarities to previously assigned methods (Table 2).

In version 1, the weight for mixing equaled the weight for hand spray (previously the highest application method weight). In version 2, we assigned a relatively smaller weight of 50 for mixing (*versus* 90 for hand spray). This reduction increased the difference in intensity scores for applicators who both mixed and applied using different application methods. For example, version 1 scores for boom spray *versus* an in-furrow application for those who mixed were 9 (version 1 mix weight) + 3 (version 1 boom spray weight) = 12 *versus* 9 (version 1 mix weight) + 2 (version 1 in-furrow weight) = 11, respectively, a difference of less than 10%. The version 2 intensity scores were 50 (version 2 mix weight) + 40 (version 2 boom spray weight) = 90 and 50 (version 2 mix weight) + 20 (version 2 in-furrow weight) = 70, a difference of almost 30%.

Because only five 2,4-D applicators did not personally mix or load on the morning prior to monitoring, the amount of data available to assess exposure that occurs during mixing compared with the rest of the application process was limited. The GM of the post-application urine concentrations for applicators who mixed on the morning of urine collection was ~50% higher than those who did not mix, which is somewhat lower than previously reported in the literature [6,7]. Our revised weight for mixing is now less than the weight for hand spray method, and only slightly larger than the weight for boom spray application.

Repairing equipment increased exposure for 2,4-D applicators (GM = 34 µg/L, n = 26 who repaired *vs.* 28 µg/L, n = 62 who did not repair). Little difference was seen for chlorpyrifos (TCPy) (GM = 10 µg/L, n = 8 who repaired *vs.* 11 µg/L, n = 9 who did not repair), although the sample size was small. Given the limited data, we did not modify the algorithm weight for repair.

Spearman correlation coefficients between version 2 algorithm score and measurements of 2,4-D in post-application urine were greater than the Spearman correlation between version 1 algorithm scores and measurements of 2,4-D in post-application urine but not for chlorpyrifos (Table 3). Correlation coefficients for 2,4-D also increased for version 2 *vs.* version 1 for the hand, body and air (data not shown). Correlation coefficients were also increased for version 2 algorithm scores and measurements of chlorpyrifos on the hand and body (data not shown). Spearman correlation coefficients between version 1 and version 2 algorithm scores were very high for both 2,4-D (r = 0.95) and chlorpyrifos (0.97) applications.

Table 3. Spearman correlation coefficients between Version 1 algorithm scores and measurements of post-application urine 2,4-D and chlorpyrifos and modeled post-application urine concentrations for 2,4-D (N = 88) and chlorpyrifos (N = 17) and Version 2 algorithm scores with post-application urine concentrations and modeled post-application urine concentrations for 2,4-D and chlorpyrifos.

	Algorithm	
	Version 1	**Version 2**
2,4-D		
Version 1	1	
Version 2	0.95	1
Post-apply urine conc.	0.42	0.48
Predicted post-apply urine concentration [1]	0.96	0.97
Chlorpyrifos [2]		
Version 1	1	
Version 2	0.97	1
Post-apply urine conc.	0.53	0.52
Predicted post-apply urine concentration	0.52	0.59

[1] Modeled value from a non-linear regression mode l.

[2] TCPy measured as a urinary biomarker for chlorpyrifos.

We fitted a nonlinear model based on the algorithm formula (1) to compare the updated weights with parameter estimates from a joint analysis of all component variables simultaneously. Coefficients were in the expected direction and the application method and CR-glove PPE terms were significant (see Table 4 for parameter estimates). Use of CR gloves was statistically significant for both 2,4-D and chlorpyrifos with estimated reductions for use of gloves of 75% and 51%, respectively. Application method was also statistically significant, with higher urine concentrations for hand spray compared to boom spray for 2,4-D and for boom spray compared to in-furrow application for chlorpyrifos. For 2,4-D, the regression parameters for mix and repair were not statistically significant; however, the direction and relative magnitude of the estimates were consistent with their corresponding algorithm weights. For chlorpyrifos, all applicators mixed and applied, so the mix variable could not be evaluated

and the repair variable was also not statistically significant. The predicted concentrations from the model were highly correlated with the Version 2 algorithm scores (Table 3).

Table 4. Nonlinear regression of post-application urine concentration on algorithm.

$Y = [\{\alpha_0\} + \{\alpha_1\} \times mix + \{\alpha_2\} \times method + \{\alpha_3\} \times repair] \times [1 - \{\beta_1\} \times gloves - \{\beta_2\} \times ppe\_other]$.

2,4-D (n = 88)	**R-Squared = Regression**	**0.36**
Variable [1]	**Coefficient**	**P-value**
Intercept α_0	27	0.76
Mix α_1,	58	0.53
Method α_2	123	0.02
Repair α_3	32	0.59
Gloves β_1	0.75	<0.001
PPE other β_2	0.26	0.26
Chlorpyrifos (n = 17)	R-Squared =	0.77
Variable[1]	Regression Coefficient	P-value
Intercept α_0	8	0.22
Mix α_1,	Na [2]	Na [2]
Method α_2	33	0.006
Repair α_3	15	0.89
Gloves β_1	0.51	0.014
PPE other β_2	0.21	0.59

[1] α_0 represented the urinary concentration at the referent level of all factors, where α_1, α_2 and α_3 parameters represented the increase in Y for mixing (1 = yes, 0 = no), use of hand spray (method = 1) or boom spray (method = 0) for 2,4-D, or boom spray (method = 1) or in-furrow (method = 0) for chlorpyrifos, and repairing equipment (1 = yes, 0 = no), respectively, and where β_1 and β_2 parameters represented the reduction factors for use of CR gloves (1 = yes, 0 = no) and/or other PPE (1 = yes, 0 = no), respectively.

[2] na: all participants mixed chlorpyrifos and the regression omitted the variable.

When grouped by approximate tertile of the algorithm scores, we found a statistically significant trend ($p \leq 0.01$) in the post-application 2,4-D GM concentrations (Table 5). For chlorpyrifos, urine concentrations of TCPy were significantly higher among applicators with algorithm scores above 50 compared to the applicators with an algorithm score category less than 50 ($p = 0.03$).

Table 5. Arithmetic means, geometric means and geometric standard deviation of post-application urine concentrations by Version 2 algorithm score category.

2,4-D

Category	Range	N	AM	GM	GSD
<50	12–48	40	30	15	3.2
50–100	59–90	24	78	39	3.6
>100	110–160	24	178	69	4.7
All		88	84	30	4.2
p-trend	<0.01				

Chlorpyrifos [1]

Category	Range	N	AM	GM	GSD
<50	24–36	9	10	8	2.1
≥50	70–110	8	22	16	2.1
All		17	11	10.6	2.3
p-trend	0.03				

[1] TCPy measured as a urinary biomarker for chlorpyrifos.

Abbreviations: AM = Arithmetic Mean, GM = geometric mean, GSD = Geometric Standard Deviation.

3.4. Discussion

Developing estimates of pesticide exposure intensity for large-scale cohort studies is a challenging, but critical task for exposure–response analysis. The use of simple exposure metrics, such as duration, fails to account for large differences in cumulative exposure that can occur because of the amount and concentration of active ingredients in the pesticide products applied, mixing and application methods, equipment size and design, PPE use, individual work practices and personal hygiene [2,10,11,14,15]. Measurements from the AHS/PES demonstrated substantial variability in exposure as a indicated by 2,4-D post-application urine concentrations that ranged over three orders of magnitude (1.6 to 1,040 μg/L) [10]. Moreover, substantial variability in 2,4-D and chlorpyrifos urine concentrations was observed for applicators using the same application methods, which further highlighted the difficulty in predicting individual exposure levels from questionnaire data. However, when using an algorithm with multiple variables, we found correlations for version 2 algorithm scores and urine concentrations of 0.48 for 2,4-D and 0.52 for chlorpyrifos, and increasing GMs of urine concentrations by increasing categories of algorithm score, suggesting that our algorithm captures important components of applicators' exposure intensities.

Although we fitted a model to compare the updated algorithm weights with parameter estimates from a joint analysis of all component variables simultaneously, we did not use the coefficients from the model directly to change algorithm weight because coefficients were pesticide specific, based on relatively limited data and encompassed relatively few exposure scenarios. Nonetheless, coefficients were in the expected direction and the application method and PPE terms were significant, supporting the usefulness of the exposure algorithm.

Previous evaluations of the AHS algorithm (version 1) in both non-AHS and AHS applicators demonstrated its usefulness [8-15] in categorizing applicators into groups with significantly different

average exposure levels. Coble [8] compared algorithm scores for applicators of the herbicides 2,4-D and 2-methyl-4-chlorophenoxyacetic acid (MCPA) with post-application urine concentrations and found correlations of 0.49 for 2,4-D and 0.17 for MCPA, suggesting the potential for herbicide-specific differences. In Minnesota and South Carolina applicators [9], correlation coefficients for algorithm scores and urinary concentrations were 0.47 for glyphosate, 0.45 for 2,4-D and 0.42 for liquid chlorpyrifos, but 0.12 for any chlorpyrifos (*i.e.*, granular or liquid). In the AHS/OFES study, version 1 algorithm scores were predictive of dermal thigh patch levels, but not the post-application urine, hand, or air concentrations for captan [13]. An assessment of the version 1 algorithm within the AHS/PES data showed that algorithm scores and urinary concentrations were significantly correlated for both 2,4-D ($r = 0.42$) and chlorpyrifos ($r = 0.53$) [11]. Information collected from epidemiologic questionnaires spanning a working life-time necessarily constrains the number and type of variables that we can include in any exposure algorithm. We were thus unable to incorporate additional factors that may be predictive of exposure, such as, amount of active ingredient applied, application duration, number of tanks mixed/loaded, number of acres treated, formulation, spills or splashes and dermal contact with sprayed vegetation. These and other factors, including personal hygiene and other differences in work practices, increase uncertainties in exposure characterization; however, algorithm intensity scores in the AHS are not used alone; they are always applied to an estimate of lifetime days of use for each pesticide which serves as a measure of the relative amount of use in a lifetime.

Information about several commonly used application methods was obtained using the enrollment questionnaire. Additional application methods used by members of the cohort have been identified in subsequent follow-up data collections. Robust exposure measurement data were not available for assigning algorithm score weights for these methods, so scores previously developed for similar methods were assigned. The uncertainty in these assignments is a limitation of the updated algorithm.

Because liquid chlorpyrifos was always applied by spraying and granular chlorpyrifos was always applied using banded or in-furrow methods in the AHS/PES study, we could not distinguish between application method or formulation type. Both dermal measurements and urine concentrations were higher for liquid spray applications than for in-furrow granular applications. Formulation type was not included in the algorithm because it was not collected in the enrollment questionnaire.

While exposure levels varied by chemical, we lacked sufficient measurement data on determinants of exposure for multiple pesticides under different application scenarios to develop pesticide-specific weights, and therefore algorithm weights apply to all pesticides. In addition, differences in absorption, metabolism and excretion rates for different pesticides and tissue-specific effects did not allow algorithm intensity scores to estimate internal doses directly. Nonetheless, it was clear from the results that the algorithm scores, on average, provided an indicator of exposure intensity for applicators using the most commonly reported application methods in the AHS cohort. Epidemiologic analyses of the AHS cohort have used the algorithm score (version 1) extensively as a measure of exposure intensity (http://aghealth.nci.nih.gov/).

Both version 1 and 2 of the algorithm are based on an extensive review of the world's literature and the use of the Pesticide Handlers Exposure Database (PHED) which included many different chemicals (6). With the addition of revised algorithm weights derived from the two field studies within the AHS we were able to adjust the weights to account for local variations in farming practices and conditions. We judge version 2 to be superior to version 1 but the correlations between version 1 and version 2 are