EXHIBIT 57

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	

DEPOSITION OF DENNIS WEISENBURGER, M.D.
MONDAY, SEPTEMBER 11, 2017
9:13 A.M.

REPORTED BY: KATHERINE FERGUSON
RPR CSR NO. 12332
JOB NO. 128476

September 11, 2017
9:13 a.m.

Deposition of DENNIS WEISENBURGER, M.D., held at Courtyard by Marriott, 700 Huntington Drive, Monrovia, California, before Katherine Ferguson, Certified Shorthand Reporter.

I N D E X

E X H I B I T S

APPEARANCES:

FOR PLAINTIFF:
ANDRUS WAGSTAFF
BY: KATHRYN FORGIE, ESQ.
7171 West Alaska Drive
Lakewood, Colorado 80226

FOR MONSANTO:
HOLLINGSWORTH
BY: KIRBY GRIFFIS, ESQ.
BY: ELYSE SHIMADA, ESQ.
1350 I Street NW
Washington, DC 20005

ALSO PRESENT:
Rosa Trembour
Pearl Robertson (on speakerphone)
David Wool (on speakerphone)

MONROVIA, CALIFORNIA; MONDAY, SEPTEMBER 11, 2017
9:13 A.M.

THE VIDEOGRAPHER: Good morning. This is the start of tape labeled Number 1 in the videotaped deposition of Dr. Dennis Weisenburger in the matter of Roundup Products Liability Litigation. This case is before the United States District Court, the Northern District of California, MDL number 2741 and case number 16-MD-02741-VC.

This deposition is being held at Courtyard by Marriott at 17 -- 770 Huntington Drive in Monrovia, California. Today's date is September 11th, 2017. The time is approximately 9:12 a.m.

My name is Scott McNair from TSG Reporting Incorporated. I'm the legal video specialist. The court reporter today is Kathy Ferguson, also in association with TSG Reporting.

Counsel, please identify yourselves for the record.

MS. FORGIE: Kathryn Forgie for the plaintiffs.

MS. TREMBOUR: Rosa Trembour for the plaintiffs.

MR. GRIFFIS: Kirby Griffis, from

Hollingsworth, LLP, for Monsanto.

MS. SHIMADA: Elyse Shimada, from Hollingsworth, LLP, for Monsanto.

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

DENNIS WEISENBURGER, M.D.,
called as a witness by and on behalf of the Defendants, and having been first duly sworn by the Certified Shorthand Reporter, was examined and testified as follows:

EXAMINATION

BY MR. GRIFFIS:

Q Good morning, sir. We've just met, correct?

A Correct.

Q Would you state your name, please?

A Dennis Weisenburger.

Q How many times have you had your deposition taken before?

A Dozens of times.

Q How many times have you given testimony in court outside of the context of depositions?

A Three times.

Q How many expert reports do you believe you've created over the course of your career?

A 30 or so.

Q How many times do you think you've heard a lawyer make an objection?

A To what?

Q A question. Five hundred, two hundred?

MS. FORGIE: Objection.

A Many times.

MR. GRIFFIS: The objection?

MS. FORGIE: Yeah, I don't know if you're talking about in the context of a deposition or in general.

BY MR. GRIFFIS:

Q You understand, sir, from your extensive deposing experience, if you don't understand something in a question that I ask, you're free to ask for clarification from me, correct?

A Yes.

Q And if you don't know some fact that you need to know in order to answer a question of mine, you know that you're free to say so, correct?

A Yes.

Q You've been through this drill before?

A Yes.

Q When -- what did you do to prepare for this deposition?
A To prepare for the deposition?
Q Yes.
A I reviewed, again, all of the materials that I had accumulated on glyphosate and glyphosate based formulations, including reports from the IARC, EPA, EES -- FAA -- EFSA, whatever, the European Group and all the underlying epidemiologic data, the animal toxicology data, the mechanistic data. referenced in all of those more global papers as well as I did my own literature search multiple times to find anything that -- in addition or anything more recent.
Q And when did you do that preparation you just described?
A The preparation for the deposition?
Q Yes.
A Over the last week.
Q How many times did you meet with lawyers to get ready for the deposition?
A Twice.
Q When was that?
A Yesterday and this morning.
Q For how long a period each time?

A Yesterday, it was for about four and a half hours and today it was about half an hour.
Q You understand, sir, that if Ms. Forgie makes an objection and does not direct you not to answer the question, then you're to give me the best answer that you can to the best of your ability when she's done objecting, correct?
A Yes.
MR. GRIFFIS: I'm going to mark several exhibits, sir.
(Discussion off record.)
(Exhibit 16-1, retention agreement, was marked for identification.)
MS. FORGIE: Maybe what we can do, if you're going to mark a bunch of exhibits, we can get the phone plugged in and mark exhibits and take a break.
MR. GRIFFIS: I'm going to mark three, but we can pause it and --
MS. FORGIE: So why don't we take a short pause.
THE VIDEOGRAPHER: We're off the record at 9:16 a.m.
(Brief recess.)
THE VIDEOGRAPHER: We are back on the

record at 9:28 a.m.
BY MR. GRIFFIS:
Q Sir, we've marked as Exhibit 1 a retention agreement between you and the firm Andrus Wagstaff; is that correct?
A Yes.
Q And the date on that agreement is signed by Andrus Wagstaff on August 11th, 2015 and by you on August 12th, 2015, correct?
A Yes.
Q You are to be paid a rate of $500 per hour for your work and you got a $5000 retainer to start, right?
A Yes.
(Exhibit 16-2, 16-3, were marked for identification.)
BY MR. GRIFFIS:
Q Exhibit 2 to this deposition are the bills that you produced a few days ago, sir. And Exhibit 3, which we'll get to later, is a copy of your expert report.
Did I identify those correctly?
A That's correct.
MS. FORGIE: Let me see them for a second.
BY MR. GRIFFIS:

Q In 2015, you received $13,200 for your work?
A Yes, I think it's a retainer.
Q In 2016, you received $21,500?
A Yes.
Q 2017 through April, through your work, work through April 19th I guess -- do I have that end date right?
A I don't have that here.
Q Turn to the back of the page.
A Oh. Correct.
Q Through April 19th, you were paid $68,750, right?
A That's correct.
Q For a grand total, per math, of $103,450.
How many hours have you worked on this litigation since April 19th of this year?
A Over a hundred hours.
Q Sir, you are not a board certified epidemiologist, right?
A I'm not a board certified epidemiologist, but I have extensive experience in epidemiology.
Q You don't consider yourself to be a statistician, right?
A No, I'm not a statistician.

Q You don't have any formal training in epidemiology except for a three-week course you took once in Boston, right?
MS. FORGIE: Objection.
A That's true, although I've read a lot of epidemiology textbooks and articles and have interacted extensively with epidemiologists during the course of my career.
BY MR. GRIFFIS:
Q Yes, sir. It's correct that the only formal training in epidemiology you had was the three-week course you took once in Boston, right?
MS. FORGIE: Objection, asked and answered.
A That's correct.
BY MR. GRIFFIS:
Q And you've had no formal training after medical school in the field of biostatistics except for that three-week course you took once in Boston, right?
A I believe that's correct.
Q And you're not an expert on the design of epidemiology studies; is that fair to say?
A No, but when I've done studies, I've always worked with epidemiologists who assisted in the design.

Q Yes, sir. When you collaborate with people and your name is certainly on a number of epidemiology studies, when you collaborate with people on an epidemiology study, the design of the study is left to others, correct?
MS. FORGIE: Objection.
A Yes.
BY MR. GRIFFIS:
Q And you wouldn't be an expert either on the statistical analysis of the data collected in the epidemiology study, right?
A That's correct, although I understand how to interpret the data.
Q Yes, sir. The choice of what statistical tools to use and what tools to use to control for possible biases in the data and interpreting the data, those discussions would be made by others, correct?
MS. FORGIE: Objection.
A That's correct.
BY MR. GRIFFIS:
Q You would not be an expert on identifying the medical confounders for epidemiology studies, meaning saying this, this and this are the confounders in this particular set of data; is that

correct?
A I have general knowledge about what the risk factors are for Non-Hodgkin's Lymphoma, so I would say they would be the same ones that would be found in any epidemiological study that have been found.
Q Well, here's what I mean, sir. Some medical issues can be confounders in a particular set of data and not in a different set of data, correct?
A Yes.
Q So it would be someone else who would be the expert on figuring out which particular issues are confounders in a particular set of data by applying statistical tools to the data, correct?
A Yes.
MS. FORGIE: Objection, asked and answered.
A Yes, but I often was involved in those decisions.
BY MR. GRIFFIS:
Q And you would be involved primarily with identifying which things need to be looked for as potential confounders, right?
A Yes.
Q You don't have formal training in animal pathology, correct?

A No, but I've done -- human pathology and animal pathology is very similar and I've done quite a bit of animal pathology in my career.
Q As far as formal training, you don't have formal training in animal pathology, right?
MS. FORGIE: Objection, asked and answered. You can answer it again.
A No, but as I said, human pathology and animal pathology is very similar. The diseases are similar.
BY MR. GRIFFIS:
Q There is such a thing as training in animal pathology and training in human pathology and people do specialize in one or the other or both, correct?
A Veterinarians specialize in animal pathology.
Q And people who perform animal studies extensively as part of their career also specialize in animal pathology frequently, correct?
MS. FORGIE: Objection.
A Sometimes they do, sometimes they enlist animal pathologists or even human pathologists to assist in those studies.
BY MR. GRIFFIS:
Q You don't have board certification of any

kind in toxicology, right?
A I do not.
Q Or any formal training in toxicology, right?
MS. FORGIE: Objection.
A As part of my training in clinical pathology, we also are trained in toxicology. And I have extensive experience in the practical knowledge of toxicology and its application. I've done lots of reading on my own, textbook reading, article reading, I've done my own animal toxicology studies and I've participated in animal carcinogenesis tests as a pathologist and as a consultant.
BY MR. GRIFFIS:
Q Is your answer that although you don't have formal training in toxicology, you've got a lot of experience in the area?
A Yes.
MS. FORGIE: Objection, asked and answered, you can answer.
BY MR. GRIFFIS:
Q So the answer is yes as to no formal training in toxicology?
MS. FORGIE: Objection. You can answer again.

A I have practical training in toxicology and some formal training as part of my clinical pathology training.
Q When was that?
A When was that?
Q Yes, sir.
A That was during my pathology residency at the University of Iowa. I have to look on my CV to see exactly when it was, but it was during my pathology residency we trained in. Where we did our training in pathology, part of it was clinical pathology and part of that was toxicology.
Q No formal training after medical school in the science of risk assessment, correct?
MS. FORGIE: Objection.
A I have no formal training in the science of risk assessment.
BY MR. GRIFFIS:
Q And can you say a few words to the camera about what the difference is between hazard and risk assessment, in your view?
A Well, hazard assessment is a determination of whether a specific chemical has the potential to cause an illness or disease. And risk assessment looks at the risk associated with a certain dosage

and different dosages to give the actual risks of what that -- how often that disease would develop.
Q And you understand that IARC performed a hazard assessment on glyphosate, a non risk assessment, correct?
A Yes.
Q You understand that the various agencies, like EPA and EFSA, that have looked at the issue of glyphosate in human carcinogenicity have performed risk assessment, correct?
MS. FORGIE: Objection.
A Yes, I believe that's true.
BY MR. GRIFFIS:
Q You have no formal training in oncology, correct?
MS. FORGIE: Objection.
A Well, I have worked very closely with oncologists for all of my career and during my internship I spent about four months doing clinical oncology, so I have extensive experience in oncology, particularly in hematopoietic malignancies such as leukemia, lymphoma.
BY MR. GRIFFIS:
Q Do you treat patients?
A I have not treated patients since I was an

intern.
Q You don't consider yourself to be an oncologist, right?
MS. FORGIE: Objection.
A No, I'm not an oncologist.
BY MR. GRIFFIS:
Q Most of the -- you told us that you testified in many depositions earlier.
Most of your testifying has been on behalf of the plaintiffs; is that right?
MS. FORGIE: Objection.
A So it's been mixed. I testified on behalf of plaintiffs in a number of different lawsuits and I've also testified for the defendants in some lawsuits. So it's really been mixed.
BY MR. GRIFFIS:
Q It's accurate to say you've testified for a defendant before in a few cases, but most of the testifying you do is on behalf of plaintiffs, right?
MS. FORGIE: Objection, asked and answered.
A I haven't quantitated it, so I couldn't answer that.
BY MR. GRIFFIS:
Q You recall testifying in the Wendell versus Johnson & Johnson case that you've testified for a

defendant before in a few cases, but most of the testifying you do is on behalf of plaintiffs?
MS. FORGIE: Objection.
A I don't remember saying that. I've testified on both sides.
BY MR. GRIFFIS:
Q Do you disagree with that statement?
A Can I see it? Is this a statement I made?
Q I'll paraphrase it for you, sir. I've testified for defendants before in a few cases, but most of the testifying I do is on behalf of plaintiffs.
Do you disagree with that is the question?
MS. FORGIE: Objection, asked and answered.
A I don't disagree with it, no.
BY MR. GRIFFIS:
Q Now, the standard you would use for opinions in a medical article that you would put your name on and publish in the medical literature would be more rigorous than opinions in a litigation case, because otherwise it might not be accepted by the scientific reviewers who review the article, correct?
MS. FORGIE: Objection.
A That's correct.
BY MR. GRIFFIS:

Q And you believe that your experience qualifies you, but your training does not, to make causal assessments between occupational exposures and Non-Hodgkin's Lymphoma, correct?
MS. FORGIE: Objection.
A So self-training is a form of training, so I have had some formal training and I've done my own training and I've worked with people who have trained me in the practical aspects of those different disciplines.
BY MR. GRIFFIS:
Q So if we adjust for the self-training point and say that you would agree that it is your experience and not any formal training that you've received that qualifies you to make, in your opinion, causal assessments between occupational exposures and Non-Hodgkin's Lymphoma; you would agree with that?
MS. FORGIE: Wait. Objection, asked and answered. You can answer again.
A So we already talked about I have had some formal training.
BY MR. GRIFFIS:
Q What is the formal training you've had?
MS. FORGIE: Objection, asked and answered. You can answer again.

A Formal training in what?
BY MR. GRIFFIS:
Q In whatever you feel qualifies you to make causal assessments between occupational exposures and Non-Hodgkin's Lymphoma; what formal training are you referring to when you say no to my question?
A So I've had formal training and self-training in epidemiology and toxicology, of course pathology, and I have extensive experience in all the various clinical, biological aspects of lymphoma. So I have extensive experience.
Q The formal training in toxicology would be during your internship or medical school?
MS. FORGIE: Objection.
A During my medical school and residency, yes.
MS. FORGIE: Let me get my objection in. Objection, asked and answered.
BY MR. GRIFFIS:
Q The formal training in epidemiology would be that three-week course in Boston we talked about earlier, right?
A Yes.
MS. FORGIE: Objection, asked and answered.
A And training in medical school.

BY MR. GRIFFIS:
Q And you are -- you said in your expert report that you're working on some lymphoma epidemiology studies with InterLymph, correct?
A Yes.
Q Are you doing any work that includes or involves in any way glyphosate?
A No.
Q And I don't mean to just limit myself to InterLymph.
Are you doing any sort of scientific work or research, outside of your litigation consulting work, scientific work or research in any way that involves glyphosate?
A Well, I was principal investigator in the Nebraska epidemiology study which was part of the De Roos pooling paper --
Q Yes, and I'm --
MS. FORGIE: Let him finish his answer.
A And also --
MS. FORGIE: He's entitled to finish his answer.
A And also part of the NAPP study, which is an ongoing study. So that data is all part of -- my data is all part of that, so I have been involved.

BY MR. GRIFFIS:
Q I was going to cut you off to say I wasn't asking about the past. And I'll cover a lot of stuff on the past, I was asking about the future.
But perhaps you mean to talk about the future when you mentioned the NAPP study, do you?
A Well, the NAPP study is the present and the future.
Q What glyphosate data collection is going on currently with the NAPP study?
A The data has all been collected.
Q What glyphosate data analysis is going on with the NAPP study?
MS. FORGIE: Objection, you can answer to the extent that you're not giving away anything that's confidential and protected by academic privilege.
A So the analysis is continuing and data is being refined in that study.
BY MR. GRIFFIS:
Q Is there analysis and data refinement proceeding with regard to glyphosate?
A Yes.
Q Is anything in publication or being submitted for publication with regard to glyphosate?

MS. FORGIE: Objection, same objection about confidentiality.
A There's a draft manuscript that has not been finalized or submitted for publication.
BY MR. GRIFFIS:
Q And as far as glyphosate is concerned, what is the issue that's being examined; is it Non-Hodgkin's Lymphoma or some other condition?
MS. FORGIE: Same objection.
A It's Non-Hodgkin's Lymphoma.
BY MR. GRIFFIS:
Q So there's a publication that's been submitted using the NAPP data with regard to glyphosate and Non-Hodgkin's Lymphoma?
MS. FORGIE: Objection.
A The manuscript is in draft form, it's not been submitted.
BY MR. GRIFFIS:
Q The manuscript in draft form.
Are you one of the proposed coauthors in that draft manuscript?
A Yes.
Q Who are the other coauthors?
A The lead author's name is Pahwa, P-A-H-W-A. I can't, off the top of my head, name all of the

coauthors. Aaron Blair is a coauthor, a lady named Beane Freeman is the senior author. There are a variety of other authors from U.S. and Canada whose names I can't, off the top of my head, give you.
Q Yes, sir. And we'll talk about NAPP a little later and maybe it will refresh your memory about all the authors.
But is the publication that's in press the same data that Dr. Pahwa presented in a slide show in Brazil?
A It's not in press. It's in draft form.
Q I apologize. In draft form.
A It's substantially the same.
Q Okay. So we talked about -- I was trying to explore any scientific work that you're involved in currently or future involving glyphosate and you've identified this in-draft NAPP publication.
Is there anything else?
A No.
Q What do you know, if anything, about the Ramazzini Institute study on glyphosate?
A I don't know anything about it.
Q Have you ever been considered to be a fellow of the Ramazzini Institute?
A No.

Q Do you know what the Ramazzini Institute is?
A I don't.
Q Are you hearing the word for the first time from me?
A No, I've come across it before, but I don't know what it is.
Q What is your understanding of what it is?
A I don't know what it is.
Q Do you know where they are?
A I don't know for sure. Probably Italy with a name Ramazzini, but I don't actually know.
Q Do you know, for example, if Aaron Blair is a fellow?
A I don't know.
Q Do you know if Christopher Portier is a fellow?
A I don't know.
Q Do you know anyone who is a fellow?
A I don't.
MR. GRIFFIS: Yes, sir. I'm going to mark next --
(Exhibit 16-4, deposition notice, was marked for identification.)
MR. GRIFFIS: That's 5.

(Exhibit 16-5, Objections and responses to Schedule A, was marked for identification.)
BY MR. GRIFFIS:
Q Sir, I marked as Exhibit 4 a copy of a notice to take oral and videotaped deposition of Dr. Dennis Weisenburger that we issued to your counsel.
Have you seen this document before?
A Yes, I have.
Q Do you see, when you turn several pages back, there's a Schedule A with numbered pages and on page 2 a number of requests for production begin?
A Yes.
Q When did you first see those requests for production, sir, or hear about them?
A I don't remember precisely when it was. It was probably two weeks ago or so.
Q With regard to item 7 on page 3, "a copy of all abstracts, articles, books or book excerpts of which you are an author, coauthor 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," what

did you do to assemble documents in response to that request, sir, if anything?
A I determined that everything I had was publicly available and that I hadn't really had any of these exchanges.
Q For example, sir, do you have a copy of the Brazil slide show by Dr. Pahwa with regard to the NAPP study?
A Yes, we disclosed that.
Q And -- what do you mean by we "disclosed that"?
MS. FORGIE: Objection, don't answer about any discussions you had with me.
THE WITNESS: Okay.
MS. FORGIE: It's privileged.
BY MR. GRIFFIS:
Q Tell me what your understanding is of "we disclosed that."
A I provided that to Ms. Forgie.
Q Okay. Did you provide any other documents under seven here to Ms. Forgie?
MS. FORGIE: Don't say anything about any discussions that we've had.
A I provided all of the abstracts and slide presentations from the NAPP presentations to her.

BY MR. GRIFFIS:
Q Any other kinds of abstracts, slide presentations, books, book excerpts, et cetera?
A No.
Q So multiple things from NAPP is what you provided to Ms. Forgie?
A Yes.
Q All right. Item 8, "handouts, PowerPoints or other documents used by you at any lecture you have given in the past five years relating to hematopoietic malignancies, including NHL, that are not publicly or otherwise available," what did you do to respond to that request?
A Well, we felt this was -- I felt this was burdensome because I give many lectures, but none of the lectures that I've given in the last five years deal with glyphosate or any pesticide as an etiology from lymphoma. So I didn't really feel that providing all of this was really relevant to the case.
Q So there are such documents, but in your view they were not relevant; is that correct?
MS. FORGIE: Objection.
A That's correct.
BY MR. GRIFFIS:

Q Item 9 is, "a copy of all handouts, PowerPoints 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."
What did you do to respond to that request?
MS. FORGIE: Objection.
A I haven't given any such lectures in many years and I've never spoken in public on glyphosate or Roundup.
BY MR. GRIFFIS:
Q When is the last time you've given a lecture about any pesticides and possible etiology of Non-Hodgkin's Lymphoma?
A It would have probably been 10 years ago or more based on the studies we did in Nebraska, so the data and studies we did in Nebraska.
Q Did you provide any documents to Ms. Forgie --
MS. FORGIE: Objection.
Q -- in response to that one?
A No, I don't think I could even find these materials.
BY MR. GRIFFIS:
Q Item 11, sir, "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, Alfred Neugut, Charles Jameson, Chadi Nabhan, Aaron Blair, Matthew Ross; what, if anything, did you do to respond to that request?

MS. FORGIE: Objection.

A So I haven't had any communications with these people except for Dr. Portier. And the communications that we had were relating to the letter and the article that was written regarding the European decision. Frankly, all the e-mails are purged from my computer every so often when it gets overloaded and all of these communications with him would have been purged from my computer.

BY MR. GRIFFIS:

Q Did you do any search for communications with Mr. Portier?

MS. FORGIE: Objection.

A No.

BY MR. GRIFFIS:

Q Did you do a search for any communications that copied or included any of those other persons?

MS. FORGIE: Objection.

A I have not communicated with any of the other persons.

BY MR. GRIFFIS:

Q How many different e-mail addresses have you used for professional work that you could have received e-mails or sent e-mails to these people over the past 10 years?

MS. FORGIE: Objection.

A In when?

BY MR. GRIFFIS:

Q Over the past 10 years.

A Well, at City of Hope, I only use my work e-mail and in Nebraska I would have used my work e-mail, so it would have been just two.

Q So your work e-mail in Nebraska and work e-mail at City of Hope.

Do you know whether either of those institutions automatically backs up people's e-mail periodically?

MS. FORGIE: Objection.

A I don't know.

BY MR. GRIFFIS:

Q Did you make any effort to find out whether back up tapes exist with e-mail communications or other communications with these people?

MS. FORGIE: Objection.

A I did not.

BY MR. GRIFFIS:

Q Did you provide any communications in response to number 11 to Ms. Forgie?

MS. FORGIE: Objection.

A I did not.

BY MR. GRIFFIS:

Q When you say these are periodically deleted -- purged/deleted, do you mean by yourself?

A By my assistant on my behalf.

Q And what do you mean by getting too many e-mails that you need to purge, what happens?

MS. FORGIE: Objection.

A Well, my computer doesn't work when it has too much data in it, so I have to purge things from time to time. So it's usually stuff that's been accumulating.

BY MR. GRIFFIS:

Q Do you receive e-mails or do you access e-mails not only on a work computer but also on a laptop?

MS. FORGIE: Objection.

A I have an iPad, but I use the same e-mail address.

BY MR. GRIFFIS:

Q Yes, sir. And do you use any backup services that back up your data from the iPad or from your computer at work to the cloud?

MS. FORGIE: Objection.

A No, not that I know of.

BY MR. GRIFFIS:

Q And when you ask your secretary to purge e-mails, what instructions do you give to your secretary?

MS. FORGIE: Objection.

A Well, I would say, you know, please purge my e-mails from 2016 back, so I usually would keep my most recent e-mails.

BY MR. GRIFFIS:

Q So right now your e-mails would go back to some particular date and then you wouldn't have anything before that; is that correct?

A Right.

MS. FORGIE: Objection.

BY MR. GRIFFIS:

Q Item 13, "all communications and documents relating to the North American Pooled Project, including, but not limited to, all communications and documents" with a number of named persons here.

What, if anything, did you do to respond to that request, sir?

MS. FORGIE: Objection. Again, limit your answers to things that are nonconfidential in a sense that they relate to the academic privilege.

A So for this, I did do a search of my database and did find the presentations, I'd save those, the presentations, the various presentations that were given by people from NAPP and those I forwarded to Ms. Forgie. There were some e-mail communications. They'd all been purged as far as I know. And they were really not substantial in terms of the data because I have not been -- I would say I have not been highly active in formulating or critiquing the draft presentations.

BY MR. GRIFFIS:

Q Why is that; what is your role instead?

A My role --

MS. FORGIE: Objection. Only answer to the extent you're not giving away information that's confidential.

A Yeah. So my role was the original role as principal investigator of the Nebraska study, so the Nebraska study provided data and that data is part of the study. So as I said, most of the work of

analyzing the data, formulating the slides and the presentations was done by the group in Canada.

BY MR. GRIFFIS:

Q Yes, sir. And Ms. Forgie keeps telling you to only answer to the extent it doesn't violate what's called an academic privilege.

What's your understanding of the sort of information that you are not permitted to tell me because of an academic privilege?

MS. FORGIE: Objection. Don't answer that if it has anything to do with discussions you and I have had.

A I don't know. I don't know the answer to that question.

BY MR. GRIFFIS:

Q For example, the fact that a publication is in the works, that's not something that you consider to be academic privilege, correct?

MS. FORGIE: Objection, asked and answered. You can answer again.

A Correct.

BY MR. GRIFFIS:

Q Is the kinds of analyses that were performed something that you considered to be subject to the academic privilege?

MS. FORGIE: Objection.

A Yes.

BY MR. GRIFFIS:

Q Are the conclusions something you consider to be subject to the academic privilege?

MS. FORGIE: Objection.

A Yes.

BY MR. GRIFFIS:

Q Are which associations or absences of associations you chose to focus on something you consider to be subject to the academic privilege?

MS. FORGIE: Objection.

A Yes.

BY MR. GRIFFIS:

Q And the reason for the academic privilege in your understanding is what, sir?

MS. FORGIE: Objection. Again, don't discuss anything that you and I have discussed.

A Well, the data is in the process of being analyzed, it's not finalized. The manuscript is a draft manuscript that will probably undergo changes. So these are all privileged documents that are not really made available until -- usually until the manuscript has actually been accepted for publication at the earliest.

BY MR. GRIFFIS:

Q Yes, sir. Before your conversations with Ms. Forgie, if any, about the subject of academic privilege, what was your understanding about the scope of academic privilege?

A It was the same.

Q What was that understanding?

MS. FORGIE: Objection, asked and answered. You can answer again.

A That draft of the manuscript or substantial data from the manuscript should not be made available for public review or use until the manuscript is actually accepted for publication.

BY MR. GRIFFIS:

Q And what is your understanding of the reason for that role?

MS. FORGIE: Objection.

A Well, it's just convention. It's academic convention. This is the way academic people do things. I think the reason is that -- that if information is released prior to acceptance, it could be used in ways to affect whether something is accepted or not, questions the data could be misinterpreted. There are all kinds of reasons.

BY MR. GRIFFIS:

Q Could you turn to your expert report, sir. That's Exhibit 3.
A Expert report?
Q Yes. By the way, before we do that, you brought a folder with you today.
What do you have in the folder?
A Just my expert report.
Q What other documents are in there?
A Nothing.
Q The reason I'm asking about other documents is you have about six paperclips and two binder clips which makes me think --
MS. FORGIE: I asked the same question, but it's got exhibits.
A It's all the exhibits.
BY MR. GRIFFIS:
Q Fine. So the expert report there, Exhibit 3, would you turn to page 3 of the expert report, please.
A Page 3?
Q Yes. On pages 1 and 2 you're talking about your own background and on page 3 you start talking about glyphosate; is that right?
MS. FORGIE: Objection.
A Yes.

MR. GRIFFIS: To help my understanding, what is the nature of that objection?
MS. FORGIE: What happens is you keep making these declaratory statements before you ask the question and I object to the declaratory statements.
MR. GRIFFIS: That's utterly accurate.
MS. FORGIE: They're not appropriate and they're not necessarily accurate.
BY MR. GRIFFIS:
Q Page 3, sir, the -- on page 3, when you have a citation, you use parentheses and a number and a close parentheses to indicate where we can find the citation in your own notes, right?
A Yes.
Q So the first citation that you give when you start talking about glyphosate is to what, please?
A It's number 3.
Q What is it?
MS. FORGIE: Objection.
A What is the reference?
BY MR. GRIFFIS:
Q Yeah, what is the reference?
A This document by Cox, entitled "Glyphosate

fact sheets part 1, toxicology part 2, human exposure and ecological effects in the Journal of Pesticide Reform, 1995."
Q Now, do you know what the Journal of Pesticide Reform is?
A I don't.
Q You know that hasn't been published in more than a decade, but it was published by something called The Northwest Center for Alternatives to Pesticides?
MS. FORGIE: Objection.
A I didn't know that.
BY MR. GRIFFIS:
Q How did you find this article?
A I probably saw it in reference by another article.
Q The articles that you pulled together for your expert report, were any of those provided to you by plaintiff's counsel or anyone else?
A A few were provided, but most of them are ones that I found myself or looked for myself.
Q And the ones that were provided to you, are those ones you had a hard time finding and so you asked for help or are they ones they said take a look at this and sent them to you?

MS. FORGIE: Objection.
A Both.
BY MR. GRIFFIS:
Q Both.
Do you recall which ones that they suggested you take a look at?
MS. FORGIE: First of all, objection. Don't answer anything about any discussions you and I had or you had with any other lawyer, please.
A No, I don't remember which ones were which. They all were put together in piles and became part of one large accumulation of documents.
BY MR. GRIFFIS:
Q Okay. To get back to the Northwest Center for Alternatives to Pesticides, you never heard of that group before?
MS. FORGIE: Objection.
A I have.
BY MR. GRIFFIS:
Q So you don't know that it's a lobbying group opposed to pesticides?
A I didn't know that.
Q And you didn't know this journal was dedicated to that same cause?
MS. FORGIE: Objection, asked and answered.

You can answer again.
A I didn't know that.
BY MR. GRIFFIS:
Q Do you know if it purports to even be peer reviewed?
MS. FORGIE: Objection, asked and answered. You can answer it again.
A I assumed it was, but I don't actually know that for a fact.
BY MR. GRIFFIS:
Q Yes, sir. And the article you cite is by the Journal of Pesticide Reform editor, it wasn't something submitted to the editor but written by the editor of the journal, correct?
MS. FORGIE: Objection, asked and answered. You can answer it again.
A I don't know that.
BY MR. GRIFFIS:
Q You didn't notice that when you looked at the article?
A No.
(Exhibit 16-6, Carolyn Cox article, was marked for identification.)
BY MR. GRIFFIS:
Q Do you see, sir -- I've handed you Exhibit

6, the -- and this is the Cox article you cited, right?
MS. FORGIE: Objection, give him a chance to look, please.
A I don't know that it is. I don't think it is. Or it could be and mine was in a different format because it looks quite different, actually.
BY MR. GRIFFIS:
Q These are the glyphosate fact sheets, part 1 of 2 and part 2 of 2; do you see that on the top line, sir?
A Uh-huh.
Q And it says "Carolyn Cox and Glyphosate Fact Sheet, Part 1 and Part 2," that's your citation on page 13 of your expert report, correct?
MS. FORGIE: Objection, asked and answered. You can answer it again.
A I don't know whether it's the same document or not.
BY MR. GRIFFIS:
Q Your citation, sir, on page 13 of your expert report, is "Cox, C., Glyphosate Fact Sheets: Part 1, Toxicology; Part 2, Human Exposure and Ecological Effects. Journal of Pesticide Reform." Correct?

MS. FORGIE: Objection, asked and answered. This is bordering on badgering the witness.
A I don't see --
MS. FORGIE: Wait. Let me get my objection in. He said he doesn't know. Now you're badgering him.
You can answer it one more time.
A I don't know if it's different or not.
BY MR. GRIFFIS:
Q Sir, I asked a different question. I said the cite on page 13 is "Cox, C., Glyphosate Fact Sheets: Part 1, Toxicology; Part 2, Human Exposure and Ecological Effects" from the Journal of Pesticide Reform.
That's your cite on page 3?
MS. FORGIE: Objection, asked and answered.
A But Part 1 is not labeled "toxicology" here.
BY MR. GRIFFIS:
Q What we have as Exhibit --
A And Part 2 does not have a label either.
Q Yes, sir. What we have as Exhibit 6 -- and I understand you've seen a different version, sir, perhaps -- is labeled "Glyphosate Fact Sheet" and we have Part 1 and Part 2 and it's by Carolyn Cox in the

Journal of Pesticide Reform, correct?
MS. FORGIE: Objection, asked and answered. You can answer it again. You're badgering him.
A That's what your document says, but I'm not sure -- it looks different than the document that I -- that's all I can say. It might be the same, it might not. I don't know.
BY MR. GRIFFIS:
Q Do you see that it says "Carolyn Cox is JPR's editor"?
A Yes.
Q Okay. Now, are articles from the Journal of Pesticide Reform generally accepted as reliable in your field?
MS. FORGIE: Objection.
A I don't know the answer to that.
BY MR. GRIFFIS:
Q Do you know if it's generally accepted -- the Journal of Pesticide Reform, do you know if it's generally accepted as scientifically reliable?
MS. FORGIE: Objection, asked and answered. You can answer it again.
A I don't know the answer to that.
BY MR. GRIFFIS:
Q In your expert report, sir, on page 3, your

second citation -- I'll wait for you to get there. The second citation, Citation 4, is to the IARC Monographs, correct?

MS. FORGIE: He's not there yet.

A Yes.

BY MR. GRIFFIS:

Q Tell me how much you relied on the IARC Monographs and the IARC findings in reaching your conclusions about glyphosate and Non-Hodgkin's Lymphoma.

A Well, it was one of the documents I reviewed in the -- as well as many other things that I reviewed. And I reviewed it carefully and I pulled a lot of the articles that were referenced there as part of the materials that I reviewed. So I used it more as an information source than anything else, just like the other documents that I looked at.

Q Did you use it as kind of a guideline to which articles you should take a look at?

MS. FORGIE: Objection.

A It was a starting point, but, you know, then I did my own searches, I reviewed the EPA documents, the EFSA documents, all kinds of documents so --

BY MR. GRIFFIS:

Q And how influenced were you in reaching your own conclusions that IARC had reached the conclusions that they had after doing their review?

MS. FORGIE: Objection.

A I wasn't influenced. My strategy was to make up my own mind based on all the literature that I reviewed.

BY MR. GRIFFIS:

Q Are you relying on the fact that IARC went through this process and reached the conclusions that they did to support your views that glyphosate causes Non-Hodgkin's Lymphoma?

MS. FORGIE: Objection, asked and answered. You can answer it again.

A No.

BY MR. GRIFFIS:

Q So you won't be telling a jury or a judge that IARC reached these conclusions and that's one of the reasons that you should agree with me that glyphosate causes Non-Hodgkin's Lymphoma; is that correct?

MS. FORGIE: Objection, asked and answered. You can answer it again.

A Well, I think it is telling that IARC came to that conclusion, but I did not rely on the IARC

conclusion to draw my own conclusion.

BY MR. GRIFFIS:

Q Do you intend to argue to a judge or a jury that they should believe that glyphosate causes Non-Hodgkin's Lymphoma because IARC -- in part because IARC reached a conclusion like that?

MS. FORGIE: Objection, asked and answered. You can answer it again.

A No, I would give my own conclusions.

BY MR. GRIFFIS:

Q You read the deposition of Dr. Blair, correct?

A I did.

Q And you saw that he testified that the IARC working group spent only one or two days total in analyzing whether glyphosate causes cancer, right?

MS. FORGIE: Objection, mischaracterizes the deposition.

A I don't remember that. I know the IARC spent about a week reviewing four or five different pesticides, but how much time they spent on each one, I don't really know.

BY MR. GRIFFIS:

Q A week -- evaluating four or five would leave obviously less than a week for any one of them,

right?

MS. FORGIE: Objection.

A Depending on how the time was apportioned, it depends entirely on that. I wasn't part of the IARC, so I have no firsthand knowledge.

Q Yes, sir. If Dr. Blair testified, and it was true, that the IARC working group only spent one or two days total analyzing whether glyphosate can cause cancer, that's less time than you spent, right?

MS. FORGIE: Objection, mischaracterizes the deposition.

A Yes. But as I understand it, the IARC spent -- the different people in the IARC spent quite literally months analyzing data and writing draft reports prior to their meeting, so they -- they spent a lot of time in aggregate.

BY MR. GRIFFIS:

Q And did you see that Dr. Blair testified with regard to that issue, that the evaluation process didn't start until day 1 of the one-week meeting?

MS. FORGIE: Objection, mischaracterizes the deposition and asked and answered. You can answer it again.

A I don't remember that, but I think the

evaluation really started when people were reviewing documents and writing draft reports months before.
BY MR. GRIFFIS:
Q And you -- do you recall that Dr. Blair testified that the months before period was used for gathering studies and gathering information and not analysis?
A And writing draft reports.
MS. FORGIE: Wait. Is there a question?
MR. GRIFFIS: Yes.
BY MR. GRIFFIS:
Q Do you recall Dr. Blair testified to that?
MS. FORGIE: Objection, asked and answered and mischaracterizes.
A Repeat the question. I'm sorry.
BY MR. GRIFFIS:
Q Yes, sir. Do you recall that Dr. Blair testified that that month or longer period that you just referred to was, in fact, spent gathering studies and not analyzing them?
MS. FORGIE: Objection, asked and answered, mischaracterizes the deposition testimony.
A I don't remember that, but my recollection -- what I do recollect is that there were subgroup leaders who were analyzing data and

manuscripts and writing draft reports. So when they came to the meeting in Leon, they came with draft reports which had analyzed data.
Q So people who are not subgroup leaders then would be in the position of dealing with, as you understand the process, an already written draft report and having a day or two to analyze all that data and reach their own conclusions; is that fair?
MS. FORGIE: Objection, mischaracterizes his prior testimony and asked and answered.
A So I don't know what the other members were doing during that time. I assumed that they had access to the same documents, but I don't really know what they did.
BY MR. GRIFFIS:
Q Okay. Your first category of evidence that you set forth in your expert report is epidemiology; is that right?
A Yes.
Q Why is that?
A You have to start somewhere. I didn't -- I could have started with the animal toxicology as well. It was an arbitrary decision.
Q You would agree that epidemiologic studies in humans provides the best and most convincing data

linking environmental exposures to cancer, right?
MS. FORGIE: Objection.
A Well, epidemiology is one source of data. I'm not sure it's the best. In some studies it's the best. In some analyses it's the best, in others it's not the best.
BY MR. GRIFFIS:
Q Yes, sir. I'm not talking about any particular set of data. I'm talking about as a general proposition, as a comparison of classes of evidence, epidemiologic studies in humans provide the best and most convincing data linking environmental exposures to cancer, correct?
MS. FORGIE: Objection, asked and answered. You can answer it again.
A It depends entirely on the quality of the data.
BY MR. GRIFFIS:
Q Do you recall testifying in Wendell versus Johnson & Johnson that epidemiological studies in humans provide the best and most convincing data linking environmental exposure to cancer?
MS. FORGIE: Objection.
A I don't remember.
BY MR. GRIFFIS:

Q What is your view of the importance of epidemiology and the role of epidemiology in a body of evidence that includes epidemiology and animal studies and mechanistic evidence like genotoxicity or oxidative stress evidence?
A I think epidemiology is one of the disciplines that is important, but all the disciplines are important. And depending on the situation, one could be more important than the other depending on the quality and quantity of the data.
Q With regard to the quality and quantity of data that exists regarding Non-Hodgkin's Lymphoma, how do you rank epidemiology, animal studies and mechanistic data in terms of their importance in reaching a conclusion?
MS. FORGIE: Objection.
A I think they're all important.
BY MR. GRIFFIS:
Q They're all equally important?
A Yes.
MS. FORGIE: Counsel, at some point when it's convenient can we have a break?
MR. GRIFFIS: Now is fine.
MS. FORGIE: Thank you.
THE VIDEOGRAPHER: We are off the record at

10:20 a.m.
(Exhibit 16-7, Article, was marked for identification.)
THE VIDEOGRAPHER: We are back on the record at 10:32 a.m.
BY MR. GRIFFIS:
Q Sir, we established earlier that you've been paid so far in this litigation $103,450 and you told me that since April 19th, which is the last date on the bills you provided to us, you worked about a hundred hours, correct?
A Yes.
Q So just doing the math, a hundred hours at $500 an hour is $50,000; $103,000 plus $50,000 is the $153,000 that you've earned so far in this litigation, correct?
A Yes.
Q I've marked as Exhibit 7 the original article by Sir Austin Bradford Hill that became known as the Bradford Hill Criteria; do you recognize that, sir?
A Yes.
Q And in the right-hand column on the first page, page 295, this is before -- I'll back up a moment.

The Bradford Hill Criteria are a number of numbered criteria like strength, consistency, et cetera, and that starts in the third full paragraph on page 295 in the right-hand column, right?
MS. FORGIE: Objection.
A Yes.
BY MR. GRIFFIS:
Q And immediately before that, setting this up, Dr. Bradford Hill describes what it is that the criteria are for; is that right?
MS. FORGIE: Objection.
A I'd have to read the preamble. I don't know.
BY MR. GRIFFIS:
Q Let's -- I'll read that paragraph, the paragraph immediately before the numbered paragraph strength. And you just follow along and make sure I get it right, sir. "Disregarding then any such problem in semantics we have this situation. Our observations reveal an association between two variables, perfectly clearcut 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?" And then he goes

into the first criteria in strength, right?
A Yes.
Q Okay. So I read that correctly, sir?
A Yes.
MS. FORGIE: Objection. I object to the use of the word "criteria." You're looking at me like what is the grounds.
MR. GRIFFIS: I'm not looking at you anymore.
MS. FORGIE: Right, you looked at me?
MR. GRIFFIS: I did look at you. Then I stopped.
MS. FORGIE: You can look at me. I don't care. But that's the grounds.
BY MR. GRIFFIS:
Q You call them the Hill Criteria?
A Some people call them the Hill Criteria. I believe they're more guidelines that people should use rather than criteria. It's a matter of semantics.
Q In your expert report, you call them "these guidelines or criteria," correct?
A Yes.
MS. FORGIE: Objection.
BY MR. GRIFFIS:

Q Either term is right?
A Either term is right.
Q Okay. So the third sentence that I read, sir, "What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?"
Now, what Dr. Bradford Hill is doing here is pointing out that when two things are associated with one another, there's a difference between them being associated with one another and the one causing the other; is that right?
MS. FORGIE: Objection.
A That's right.
BY MR. GRIFFIS:
Q Association means we have observed that one happens and the other tends to happen more commonly and that might be due to a causal association or that might be due to something else; is that fair?
A Yes.
Q And among the things that it might be due to are some different causation that we're not seeing in the data or confounding or bias or the play of chance.
Those are all possibilities for the perceived association; is that right?

MS. FORGIE: Objection.
A That's right.
BY MR. GRIFFIS:
Q He says, "Our observations reveal an association between two variables, perfectly clearcut and beyond what we would care to attribute to the play of chance."
Dr. Bradford Hill is considered one of the founders of modern epidemiology; is that right?
A Yes.
Q And the association he's talking about here is an association seen in epidemiological data, right?
MS. FORGIE: Objection.
A People use these guidelines or criteria also with regard sometimes to animal data and other data. So they're sort of general guidelines criteria. Most often they're applied to epidemiology, but they can be applied to other disciplines as well.
BY MR. GRIFFIS:
Q When you say "applied to epidemiology," I want us to all understand each other.
Epidemiology is sort of a threshold, we find an association in epidemiology and then in

looking at the factors we pull in data from animal studies if it's available, mechanistic data if it's available from other disciplines, right?
MS. FORGIE: Objection.
A Or it could happen the other way. You could start with animal data that showed an association and then you might go and do your epidemiology later. There are different orders that things can happen in.
BY MR. GRIFFIS:
Q Okay, sir. Can you give me an example of a published Bradford Hill analysis, on any subject whatsoever, that starts with an association seen in animal data and then looks at other kinds of information?
MS. FORGIE: Objection.
A Not off the top of my head.
BY MR. GRIFFIS:
Q Can you give me an example of a published paper that uses -- applies the Bradford Hill analysis that starts with any kind of association other than epidemiology, not just animal studies?
MS. FORGIE: Objection.
A Not off the top of my head.
BY MR. GRIFFIS:

Q Okay. Let's talk about "perfectly clearcut and beyond what we care to attribute to the play of chance."
Modern epidemiologists have a number of statistical tools that they use to establish whether something is beyond what we would care to attribute to the play of chance, correct?
A Yes.
Q And statistical significance is one of those tools, correct?
A Yes.
Q And the -- although there are a number of confidence levels that people can select for particular studies based on their prior assumptions about the data, the most commonly used confidence interval in science is the 95 percent confidence interval, right?
MS. FORGIE: Objection.
A Yes.
BY MR. GRIFFIS:
Q And a 95 percent confidence interval means what?
A It means that you can have 90 percent confidence or 95 -- 95 percent confidence or 95 percent certainty that the value that you see is not

due to chance, but there's a five percent chance that -- there is a five percent possibility that it is due to chance.
Q Yes, sir. It doesn't say anything about causation in itself, correct?
MS. FORGIE: Objection.
A That's correct.
BY MR. GRIFFIS:
Q Okay. So what we mean by due to chance, when we're talking about a 95 percent confidence interval in the data, is if we did the same experiment again, there's a 95 percent chance that we would be in the same range; is that right?
MS. FORGIE: Objection.
A Yes.
BY MR. GRIFFIS:
Q And it could be that we would be in the same range because of some problem with the way we designed the study or because of confounding or because of bias or it could be that we would be in the same range because there's a true causal association here, we don't know without looking further; is that fair?
MS. FORGIE: Objection.
A You would have to repeat the question.

That was a complicated question.
BY MR. GRIFFIS:
Q Sure. Yes, sir. A 95 percent -- 95 percent chance that we would get the same results again, that could mean there's a 95 percent chance we would get it again if we ran the experiment again because the new experiment would have the same biases or confounding or other problems as the first experiment or it could be that there's a true causal association that we have seen and the second study would find it too, right?
MS. FORGIE: Objection.
A That's correct.
BY MR. GRIFFIS:
Q Okay. You remember, sir, that when you looked at the IARC Monograph, the IARC working group reached particular conclusions about the different types of evidence that they looked at; they had a conclusion about epidemiology that was limited to them, they had a conclusion about the animal studies and a conclusion about the mechanistic data, correct?
MS. FORGIE: Objection.
A That's correct.
BY MR. GRIFFIS:
Q And you recall -- I got it right that the

working group's assessment about the epidemiological evidence was that it was, quote, "limited," close quote, right?
A Yes, that's a term they use based on the criteria they use in general for IARC conclusions, so --
Q Yes, sir. Did you read the preamble that sets forth what those criteria were?
A Yes, I did.
Q Do you recall that the criteria for limited evidence of carcinogenicity in the human study, the epidemiology, it says "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, of which chance, bias or confounding could not be ruled out with reasonable confidence?
MS. FORGIE: Objection.
A That's the IARC definition.
BY MR. GRIFFIS:
Q And do you agree that the epidemiology evidence that exists with regard to glyphosate and Non-Hodgkin's Lymphoma is limited by the IARC definition?
MS. FORGIE: Objection.

A That's the IARC's definition.
BY MR. GRIFFIS:
Q Yes, sir. Do you agree that the evidence is limited if you were to apply the IARC definition?
MS. FORGIE: Objection.
A I would probably say it was sufficient, but I don't quibble with the IARC. They have their own terminology, their own rules and if you -- and so the IARC working group applied the IARC methodology and that's what they said.
BY MR. GRIFFIS:
Q I'll read the standards again. "Positive association has been observed between exposure to the agent and cancer."
You believe a positive association is demonstrated in the epidemiology, correct?
A Yes.
Q For which a causal interpretation is considered by the working group to be credible and you consider there to be a credible causal association in the epidemiology, correct?
A Yes.
Q But chance, bias or confounding could not be ruled out with reasonable confidence.
And do you agree or disagree with regard to

the epidemiology on glyphosate and Non-Hodgkin's Lymphoma, that chance, bias or confounding cannot be ruled out with reasonable confidence?
MS. FORGIE: Object.
A I don't use that convention when I evaluate the epidemiology data. That's the IARC's convention. That's the terminology they use.
BY MR. GRIFFIS:
Q Yes, sir. And you said you don't quibble with them on it.
I'm trying to find out whether you agree or disagree that -- is it your view, sir, that chance, bias or confounding can be ruled out with reasonable confidence in the epidemiology data in glyphosate and Non-Hodgkin's Lymphoma?
MS. FORGIE: Object to form.
A Yes.
BY MR. GRIFFIS:
Q So you disagree with IARC on that?
A Well, it's a matter of degree in terms of the confidence one has in the data. And IARC basically had two categories they could use: They could use 1 or the 2A and they didn't feel they had enough data to put it into one so they left it in 2A. But I think that the epidemiologic studies are

well-constructed, they're well-done and they took every precaution to, as best they can, eliminate bias, eliminate -- to account for confounding. And, you know, so we have to accept the studies on the basis of their quality and who performed them and, you know, the results.

Q Yes, sir. Is it your view that the evidence on epidemiology is sufficient, in part, because it's the best -- the information we have on epidemiology is the best epidemiology evidence available so we have to take it the way it is?

MS. FORGIE: Objection.

A The epidemiology data is high-quality data. I wouldn't necessarily use the term "best," but it -- they're well-done studies with very credible results, published in peer-reviewed journals and accepted by IARC and all the regulatory agencies as part of their reviews, so I accept it.

BY MR. GRIFFIS:

Q You read the deposition of Dr. Neugut, right?

A Yes.

Q Did you read the deposition of Dr. Portier?

A I did.

Q Do you agree with Dr. Neugut that the

epidemiology alone is not sufficient to say there's a causal association between glyphosate and Non-Hodgkin's Lymphoma?

MS. FORGIE: Objection, asked and answered. You can answer it again.

A Well, I would never look at the epidemiology alone. But what I did is I looked at the total body of information and epidemiology was one part, an important part.

BY MR. GRIFFIS:

Q Do you agree or disagree with Dr. Neugut's statement that epidemiology alone is not sufficient to say there's a causal association?

MS. FORGIE: Objection, asked and answered. You can answer it again.

A I would say by itself, it isn't. But no one would ever just do that kind of analysis.

BY MR. GRIFFIS:

Q Okay. And you know that Dr. Portier also said that the epidemiology alone is not sufficient to say there's a causal association and you agree with that, right?

MS. FORGIE: Objection, asked and answered. You can answer it again.

A Well, I just answered the question, I have

the same answer, that it's an important part of the information, but no one would just look at one piece of the information to come to a conclusion.

BY MR. GRIFFIS:

Q Do you agree with Dr. Portier that the genotoxicology alone is not sufficient to say there's a causal association?

BY MS. FORGIE: Objection.

A Yes.

BY MR. GRIFFIS:

Q I'm going to ask you some general questions of the same sort that I was asking when we were talking about the Bradford Hill paper, sir. This is not about this particular set of data before us, but about association and causation in general, all right.

Do you agree that associations with high relative risks are more likely to be causal assuming reasonably stable data?

MS. FORGIE: Objection.

A In general, yes.

BY MR. GRIFFIS:

Q And do you agree that significant associations may not be causal, significant meaning statistical significance, but causal associations

should be statistically significant?

MS. FORGIE: Objection.

A In general, that's true, yes.

BY MR. GRIFFIS:

Q Do you agree with Dr. Neugut, from his deposition, sir, that a positive epidemiology study is one with an odds ratio of greater than one that was statistically significant?

MS. FORGIE: Objection. Could I have that question read back?

MR. GRIFFIS: It was do you agree with Dr. Neugut.

A Could you repeat it?

BY MR. GRIFFIS:

Q Sure. Do you agree with Dr. Neugut, sir, from his deposition, that a positive epidemiology study is one with an odds ratio of greater than one and was statistically significant?

MS. FORGIE: Objection.

A That would be considered a positive study, yes.

BY MR. GRIFFIS:

Q And do you agree that you would not -- with Dr. Neugut from his deposition -- you agree with Dr. Neugut you would not label an exposure as being

even associated with an outcome unless there is a finding an increased risk of significance?
MS. FORGIE: Objection, mischaracterizes the deposition.
A So one can overinterpret the whole concept of statistically significant. And so sometimes results are not entirely -- they may be a borderline significance.
BY MR. GRIFFIS:
Q Is it necessary --
MS. FORGIE: Wait, let him finish.
A One has to look at the totality of the evidence. Some of it may be statistically significant, some of it might be borderline significant, some of it might be elevated but not significant. One has to look at all the data, the totality of the data. One cannot make decisions based on one data point.
BY MR. GRIFFIS:
Q Certainly there are a number of substances about which you can say, based on statistically significant data, unquestionably statistically significant data, that there is a positive causal association between that and a cancer, correct?
A Yes.

MS. FORGIE: Objection.
BY MR. GRIFFIS:
Q And glyphosate is not one of those substances, correct?
MS. FORGIE: Objection.
A With glyphosate, there are multiple epidemiologic studies, there are multiple animal studies, there are a number of mechanistic studies that all show statistically significance with regard to etiology.
BY MR. GRIFFIS:
Q So you believe that glyphosate does qualify as a substance for which there is unquestionably statistically significant data upon which you can rely in finding a true causal association?
MS. FORGIE: Objection, asked and answered. You can answer it again.
A I believe the data is convincing.
BY MR. GRIFFIS:
Q Are there any --
MS. FORGIE: Let him finish.
MR. GRIFFIS: Sorry, I thought you were.
THE WITNESS: I was.
BY MR. GRIFFIS:
Q Are there any epidemiology -- are there any

statistically significant associations between glyphosate and Non-Hodgkin's Lymphoma with an odds ratio of greater than one that are controlled for other pesticides?
MS. FORGIE: Objection.
A Yes.
BY MR. GRIFFIS:
Q Tell me what.
A Tell you one?
Q Tell me them.
A Well, they're shown in my table. The De Roos study has an elevation of 2.1 that's statistically significant. The Eriksson study has an elevation of 1.51 which was not statistically significant. And the Hardell has an increase of 1.85 that is not statistically significant. And although I don't have it listed here, if you look at the NAPP study, that shows a statistically significant increase risk for NHL and for diffuse large B-cell lymphoma that is adjusted for other pesticides. So, in fact, all four of the major studies has shown an increased risk ratio adjusted for other pesticides, two of which are significant --
Q The two that are significant --
MS. FORGIE: Wait. Were you finished?

A -- and two that are not.
BY MR. GRIFFIS:
Q The two that are significant in your view are De Roos, Item 3 on your chart, and the NAPP study that you didn't actually list on your chart; is that right?
MS. FORGIE: Objection.
A Right.
BY MR. GRIFFIS:
Q All right. We'll get to NAPP later.
Could you tell us briefly why you chose not to include that in your expert report?
A Yeah. It was an arbitrary decision. I felt like I would be sort of using it twice because the NAPP study is based on the McDuffie study and De Roos study. It's a pooling of that data. So it's really the same data. So I decided -- and the fact that it -- it has not been published, I decided not to use it. But I --
Q Okay.
A I'm happy to talk about it.
MS. FORGIE: Were you finished?
THE WITNESS: Yes.
BY MR. GRIFFIS:
Q To be fair, if we were to put NAPP into

your table, it would be, so that we don't double count, we need to delete McDuffie and De Roos because it's using the same data?

A Yes.

MS. FORGIE: Objection.

BY MR. GRIFFIS:

Q And some of these studies actually kind of have the same issue; they represent a combination of two or more older studies, right?

A Yes.

MS. FORGIE: Objection.

BY MR. GRIFFIS:

Q Do you agree, sir, it's important to have consistent findings across different epidemiologic studies to determine a causal relationship?

MS. FORGIE: Objection.

A Yes.

(Exhibit 16-8, Study - Etiologic Heterogeneity Among Non-Hodgkin Lymphoma Subtypes: The InterLymph Non-Hodgkin Lymphoma Subtypes Project, was marked for identification.)

BY MR. GRIFFIS:

Q Sir, I have marked as Exhibit 8 a study in the Journal of the National Cancer Institute Monographs, 2014, on which you are a coauthor, among

many other coauthors, entitled "Etiologic Heterogeneity among Non-Hodgkin's Lymphoma Subtypes: The InterLymph Non-Hodgkin's Lymphoma Subtype Project," correct?

A Yes.

Q And would you tell us, first of all, what your role was in this study?

A Well, I was involved in organizing the study, designing how the different subtypes were grouped. And I was actually a peer reviewer for about four or five of the other papers that were part of this monograph. So I was sort of, in a way, one of the editors. So this -- the whole monograph was based on pooled analyses of many epidemiological studies.

Q And by "monograph," you mean a single edition of the journal that was devoted to a common subject, multiple papers within --

A This is one of the papers, correct.

Q So you were a peer review on some of the other papers?

A Yes.

Q And please explain briefly what this study, the one I've marked as Exhibit 8, was doing.

A Well, study 8 took a look at all the data

globally and I think showed that some risk factors are important for some types, some subtypes, but not important for other subtypes. So that -- and this is something we've known from other data that certain risk factors are important for some subtypes, but don't have any -- don't have any role in other subtypes.

On the other hand, there are some risk factors which appeared to increase the risk for all subtypes, so --

Q So you can't really generalize about risk factors without actually looking at the data; is that fair?

MS. FORGIE: Objection.

A Right.

BY MR. GRIFFIS:

Q When you say "subtypes," what you're talking about is subtypes of Non-Hodgkin's Lymphoma, right?

A Yes.

Q Non-Hodgkin's Lymphoma is a heterogenous group of conditions, not a single unitary condition, right?

MS. FORGIE: Objection.

A Well, traditionally it's been thought of as

a single disease, but I think our concepts and ideas have changed about it so that we really believe now that some of the subtypes are quite distinctive, some subtypes are related to other subtypes, but other subtypes are not at all related to other subtypes. So it is a very heterogenous group of diseases.

Q And this study, Exhibit 8, sir, was a statistical analysis of a large amount of data about the etiology of various subtypes of Non-Hodgkin's Lymphoma, meaning things that cause those various subtypes of Non-Hodgkin's Lymphoma, right?

A Yes.

Q On page 138, sir --

A 138?

Q Yes. I'm in the "discussion" section.

A Okay.

Q I'm going to start with the second sentence in the "discussion" section, sir. "Based on a novel methodological approach to cluster NHL subtypes according to a broad spectrum of risk factors, the majority of risk factors showed differences in risk among NHL subtypes whereas fewer factors showed consistent risks among subtypes," correct?

MS. FORGIE: Objection.

A That's what it says. I have to read it

again to understand it.
BY MR. GRIFFIS:
Q Okay. And do you -- isn't that exactly what you were just telling me, that what you have found, based on this work and other work, that some risk factors are associated with particular subtypes and some risk factors are associated with multiple subtypes?
MS. FORGIE: Objection. Also, he's requested time to review which I think should --
A I think it says the same thing. You're right.
BY MR. GRIFFIS:
Q Okay. It goes on to say, "Overall, this approach most strongly distinguished T-cell from B-cell lymphomas with additional heterogeneity among specific types of B-cell lymphoma, although the patterns of effect heterogeneity varied substantially for the different risk factors," right?
A Yes, that's what it says.
Q Can you explain what that means, distinguishing -- "most strongly distinguish T-cell from B-cell lymphomas with some additional heterogeneity among specific types of B-cell lymphoma"?

A I haven't read this paper for a long time, but let me attempt here. It says --
MS. FORGIE: You can take your time to read it.
THE WITNESS: Let me read the comment again.
BY MR. GRIFFIS:
Q Let me be clear. What I -- my question is primarily asking you to make it clear to a relative lay person what T-cell and B-cell lymphoma means in the context of that sentence, because they may not know the difference.
MS. FORGIE: And make it clear you read as much as you need to read.
A Let me read the comment again.
BY MR. GRIFFIS:
Q Sure.
A So what it's saying is there seemed to be risk factors for B-cell lymphoma and there seemed to be risk factors for T-cell lymphoma. Those are two different immunologically types -- subtypes of Non-Hodgkin's Lymphoma. So there seemed to be some correlation of certain factors with more so with T or more so with B and then even within B, with some subtypes of B.

Q Okay.
A I think that's what it said.
Q It would be fair to say, sir, before we go and turn to the specific data on glyphosate, that the conclusion that different risk factors may or may not have heterogenous impact on Non-Hodgkin's Lymphoma would be true of glyphosate?
MS. FORGIE: Objection.
A So it could be true for glyphosate. We don't know. I mean, the -- there are a few studies that have looked at risk for B versus -- I think B or B versus T, but at least for B because B is the biggest group. And the NAPP actually looked at the large subtypes, because for the small subtypes you don't have enough cases so they aggregated those into one sort of very heterogenous group.
BY MR. GRIFFIS:
Q The other group?
A The other group, yeah.
Q So some of the studies have actually looked -- broken it down by subtype, but as a general proposition, it would be necessary to look at the data on glyphosate to figure out whether it was the kind of risk factor that affects different subtypes differently or whether it affects the subtypes the

same?
MS. FORGIE: Objection, mischaracterizes his testimony.
A So traditionally, in the past, epidemiologists looked at the NHL as a -- as an entity. But as a pathologist, one of the things that I really pushed hard in the InterLymph group was this idea of looking at subtypes, because we've learned a lot about how distinctive some of the various subtypes are, so it would make sense to look and see whether there aren't specific risk factors for subtypes. And for some types we have already known that. But looking at things, environmental things that might have more specificity for subtypes. That was one of the things that I really pushed hard into the InterLymph group. That was one of my contributions.
MR. GRIFFIS: I'm going to turn now, sir, to the epidemiology studies that you listed in Table 1 of your expert report. Let's take a five-minute break before we do that.
THE VIDEOGRAPHER: We are off the record at 11:06 a.m.
(Brief recess.)
THE VIDEOGRAPHER: We are back on the

record at 11:18 a.m.

(Exhibit 16-9, Cancer Epidemiology, Biomarkers & Prevention, was marked for identification.)

BY MR. GRIFFIS:

Q Sir, I've marked as Exhibit 9 the McDuffie article and this is the first of the epidemiology articles that you put into your expert report, Number 1 on your Table 1, your table of epidemiologic studies of Non-Hodgkin's Lymphoma and glyphosate and the first one you discussed, right?

A Yes.

Q And the study looked at many different substances at once, it wasn't specifically designed to test the hypothesis that glyphosate caused Non-Hodgkin's Lymphoma, right?

MS. FORGIE: Objection.

A Right.

BY MR. GRIFFIS:

Q Now, why is it important for an epidemiology study to describe at the outset which specific relationships are being investigated?

Let me rephrase that, because I don't mean that they should write it at the beginning of the paper, but why is it important for epidemiologists

and people performing epidemiology studies to decide up front which specific relationships are being examined and to declare that?

MS. FORGIE: Objection.

A Well, it can impact on how you design the study and how many cases and how many controls you need, so it's important to understand what your intent is for the study in order to design the study properly.

In this study, they -- the question generally was looking at whether a specific class is or even specific pesticides are associated with Non-Hodgkin's Lymphoma, so it was a more general approach rather than looking at one class of pesticides or one specific pesticide.

Q Yes, sir. And when they mentioned, when they were discussing how they set up the study, the specific classes and chemical groups and individual compounds they mentioned -- I'm over on page 1156, right-hand column.

A Okay.

Q And here they're talking about how they collected the pesticide data and how they drilled down from broadest categories of exposure to classes to chemical groups and finally individual compounds.

And that's at the end of the first paragraph, right?

A The pesticide data was collected at various levels -- separate levels, if that's what you're talking about.

Q Right. And the specific examples that they gave are of the phenoxyherbicides which don't include glyphosate and the individual compounds that they mentioned in the example also don't include glyphosate, right?

A Yes.

Q And the authors describe their analyses in the study as exploratory, right?

MS. FORGIE: Objection.

A Where do you see it?

BY MR. GRIFFIS:

Q Page 1161, sir.

A Oh, in the --

Q When you get there I'll direct you more specifically. 1161 -- sorry, are you there?

A Yeah.

Q Right-hand column, the second full paragraph, third paragraph. It says, "We reported results for a number of chemical agents and exposures, not all of which were specified in

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."

That's what they wrote, right?

A Yes.

Q The issue they're talking about here is when you gather a whole bunch of data about a whole bunch of possible association, you are likely, just by the play of chance, to see statistically significant association just due to the operation of chance, right?

MS. FORGIE: Objection.

A That's certainly a possibility, yes.

BY MR. GRIFFIS:

Q If you're using a 95 percent confidence interval, it would happen about one out of every 20 associations, right?

MS. FORGIE: Objection.

A Right.

BY MR. GRIFFIS:

Q And glyphosate isn't mentioned in the abstract or in the discussion section of this

article, right?
A I'd have to read through it to be sure.
Q Okay. Go ahead.
MS. FORGIE: Objection.
A Yeah, that's correct. Glyphosate is not mentioned, although they do comment that risks were found for a number of herbicides so they don't specify.
BY MR. GRIFFIS:
Q Now, Table 2, sir, is a listing of a number of individual herbicides with some associated odds ratios.
Would you explain the difference between the odds ratio A and the odds ratio B column in Table 2, sir?
A Yeah. So you have to look at the footnote and odds ratio A is sort of adjusted for -- it's adjusted for age and province or residence. And then -- so adjusted on two variables. And then B is adjusted on that, as well as I think they list a bunch of medical variables, as well as a positive history of cancer in first-degree relatives. So it's a more detailed adjustment.
Q It's more adjusted?
A More adjusted, yes.

Q Now, we established earlier that you wouldn't be the person to figure out exactly which things need to be adjusted for or to construct the statistical tools used to do the adjustment. But would you explain, please, why it is that the column B adjustment is more helpful than the column A adjustment.
MS. FORGIE: Objection.
A I think it's more helpful because it -- it adjusts for more variables and it equalizes the analysis in a better way. And, you know, a lot of the things they've adjusted for I don't think are important, but some of the things are important. You always want to adjust for age and province or state or residence just because there could be differences in different places. And it's good to adjust for a family history of -- not sure of a family history of cancer, but a family history of hematopoietic cancer would be a better thing to adjust for. So -- I don't know. I mean, the second adjustment is not really, to me, very much better than the first.
Q Yes, sir. You chose, when you created your chart in your expert report, your Table 1 listing, the epidemiology studies and some selected risk estimates pulled out of those epidemiology studies

and they were selected, right, assuming you didn't report every single risk assessment from the study?
A I didn't. No, I reported just for glyphosate.
Q And not every single one for glyphosate, you pulled particular ones out to show us, correct?
MS. FORGIE: Objection.
A Right.
BY MR. GRIFFIS:
Q For example, the very first one that you report from McDuffie is the 1.2 from the more adjusted odds ratio column, correct?
MS. FORGIE: Objection.
A Yes. You can see it's not much different than the one that's adjusted, seeing just a couple variables, it's almost the same.
BY MR. GRIFFIS:
Q It didn't change the numbers much, but it's a better figure because it adjusts for more relevant variables, right?
MS. FORGIE: Objection, asked and answered. You can answer that again.
A That's the reason I selected that one.
BY MR. GRIFFIS:
Q Yes, sir. Now, in your expert report, you

also point to an analysis from the McDuffie paper of the odds ratios for less than or equal to two days a year of exposure to glyphosate and one for greater than two days per year of glyphosate, right?
A Yes.
Q That is from Table 8 on page 1161, correct?
A Yes.
Q And they did not adjust -- those figures are not adjusted for exposure to other pesticides, right?
A That's correct.
Q And that is the 2.12 odds ratio with a confidence interval of 1.2 to 3.73 and you put that into your table and bolded it, right?
A Yes.
Q Now, that is certainly a major confounder for the issue of whether glyphosate can cause Non-Hodgkin's Lymphoma, right?
MS. FORGIE: Objection.
A What's a major confounder?
BY MR. GRIFFIS:
Q Exposure to other pesticides.
A Yes, it could be.
Q And they said -- the authors said, on page 1160, in the right-hand column at the bottom,

"clearly, we had few exposed men whose exposure was limited to one pesticide or one class of pesticides," right?

A Yes, that's what it says.

Q So confounding was certainly happening in this study, right?

MS. FORGIE: Objection.

A Well, it's potentially confounding. We don't really know it's confounding, but there's potential for confounding.

BY MR. GRIFFIS:

Q The 2.12, that you listed on your Table 1 and put into bold, wasn't even adjusted for the other medical variables that we saw adjusted for in Table 2, right?

MS. FORGIE: Objection.

A No, it was just adjusted for age and province of residence.

MR. GRIFFIS: I've been told we need to change the tape, so I'm going to pause and we can do that.

THE WITNESS: Okay.

THE VIDEOGRAPHER: This marks the end of Videotape Number 1 in the deposition of Dr. Dennis Weisenburger. We're off the record at 11:32 a.m.

(Brief recess.)

THE VIDEOGRAPHER: We are back on the record at 11:34 a.m. This marks the beginning of Videotape Number 2 in the deposition of Dr. Dennis Weisenburger.

BY MR. GRIFFIS:

Q Doctor, I'm on Table 8 in the McDuffie study.

A Okay.

Q Exhibit 9. And again, this is the table from which you pulled the 2.12 odds ratio that you put in Table 1 in your expert report and bolded.

The analysis that you cited in your expert report on the issue of dose response of glyphosate in Non-Hodgkin's Lymphoma, is it greater than zero, less than or equal to two versus greater than two, days per year of exposure, does not take into account the duration of exposure, correct?

MS. FORGIE: Objection.

A That's correct.

BY MR. GRIFFIS:

Q So, for example, a person could use glyphosate twice a year for each of 10 consecutive years and they'd be put in the low exposure group and someone who used it three times in their life but all three times in the same year on different days would

be put into the high exposure group, right?

MS. FORGIE: Objection.

A I'm not sure that's true. I'd have to look in the methods to see if they have any qualifiers --

BY MR. GRIFFIS:

Q Okay. Go ahead.

A -- to that. Based on what they say in the methods, you really can't know, but I would assume that's correct.

Q It's possible that the dose response analysis in this study could be backward with regard to these two groups, the low exposure group and the high exposure group could be backwards depending on how duration matches up with this measure that they chose of dates per year, right?

MS. FORGIE: Objection.

A So this parameter, less than or equal to two days and greater than two days, is a surrogate for dose intensity rather than total dose. So intensity is important as well as time and this looks more at intensity, so low intensity versus high intensity.

BY MR. GRIFFIS:

Q Well, sir, someone could be exposed to it, tiny amounts of glyphosate with a trivial exposure on

three different days in a year and put into the high risk group, or somebody could be massively exposed on two days during the year and be put into the low risk group, right?

MS. FORGIE: Objection, asked and answered. You can answer it again.

A It's certainly possible, but that's the way -- that's the way they did it in this study.

BY MR. GRIFFIS:

Q Yes, sir. It's possible, though, that the actual exposures, both in terms of total number of exposures and intensity of exposures, could be reversed between these two groups, correct?

MS. FORGIE: Objection, asked and answered. You can answer it again.

A Well, as I said, this is a measure of intensity of exposure, so it's looking at people who had more exposure in a short period of time, which is a year, versus those who had less exposure in a short period of time. So it -- it is what it is.

BY MR. GRIFFIS:

Q But my statement is correct, that the people that are placed in the low group and the people that were placed -- a person could be put in the lower exposure group having had a more meaningful

exposure to glyphosate than someone who is placed into the high exposure group, right?
A It's possible.
MS. FORGIE: Objection, asked and answered. You can answer it again.
A It's possible.
BY MR. GRIFFIS:
Q Sir, there's no odds ratio reported in this study between glyphosate and NHL, Non-Hodgkin's Lymphoma, that is statistically significant and is adjusted for other pesticides, right?
MS. FORGIE: Objection, asked and answered.
A That's correct.
MR. GRIFFIS: Exhibit 10 will be the Hardell study.
(Exhibit 16-10, Hardell study, was marked for identification.)
BY MR. GRIFFIS:
Q Sir, we talked earlier about how some of the epidemiology studies were actually groupings of smaller, older epidemiology studies and that's true of this one, right?
A Yes.
Q This Hardell 2002 study looked at the Hardell 1999 and the Nordstrom 1998 studies, right?

A Yes, and pooled them.
Q And this is like the McDuffie study, another study where data was gathered for a large group of herbicides and pesticides and other chemicals, not focussed on glyphosate, correct?
MS. FORGIE: Objection.
A Yes.
BY MR. GRIFFIS:
Q So you would expect to see multiple statistically significant associations just due to chance alone in such a grouping of data, right?
MS. FORGIE: Objection.
A You certainly could.
BY MR. GRIFFIS:
Q There were only eight people with Non-Hodgkin's Lymphoma exposed to glyphosate, even in this pooled analysis out of 404 total cases, right?
MS. FORGIE: Objection.
A That's correct.
BY MR. GRIFFIS:
Q And you say that -- in your Table 1 in your expert report, that there is limited statistical power to this study, right?
A Yes.
Q Is that because of the very small number of

people exposed?
A Yes.
Q And could you explain what "limited statistical power" means?
A Well, it means when you have a small number of exposed cases, your ability to detect significant differences is limited by the number of cases.
Q Yes, sir.
A So the power is weak.
Q And when power is weak, you can get false results in both directions, right; you can get seemingly false positive associations that are really based on how scant the data is and you can get seeming false negative associations that are really based on how scant the data is; fair?
MS. FORGIE: Objection.
A Yes, you can get either false positive or false negative results.
BY MR. GRIFFIS:
Q Now, Dr. Hardell and his colleagues did multivariate analysis adjust for confounders in this study, right?
A Yes.
Q What is multivariate analysis?
A Well, it's a form of analysis where you

can -- you can look at how different variables affect each other and you can modify the effects by the effects due to other variables. So you can come to a more -- a more, I guess, accurate appraisal of what the true result is.
Q Okay. In the -- and Table 7 reports the univariate and the multivariate analyses that they employ to get the various odds ratios that they reported for a number of specific substances, including glyphosate, right?
A Yes.
Q And you chose to put into your Table 1 in your expert report the 3.04, 1.08 to 8.52, from the univariate analysis; is that right?
A Yes.
Q And you also listed the multivariate one, 1.85, 0.55 to 6.2?
A Yes.
Q You bolded the 3.04 one and not the 1.85 one.
First of all, why are some things bolded and some things not bolded in Table 1 of your expert report?
A So I bolded the ones that were statistically significant.

Q Okay. And the better controlled one, the multivariate analysis, is not statistically significant in the Hardell study, right?
MS. FORGIE: Objection.
A Right.
BY MR. GRIFFIS:
Q And you say that the multivariate analysis that you report here, 1.85, not statistically significant, is adjusted for other pesticides, right?
A Yes.
Q Let's go to the statistical analysis section, so 1044 -- page 1044.
A Okay.
Q It goes over onto the next page. I showed you where the section starts, but the part I would like you to focus on is the second page, 1045. They talk about both univariate and multivariate analyses were done. We were just in the table that shows the results of that.
And they say, "in this pooled analysis, adjustment was made for study area and vital status," right.
A Right.
Q Vital status means alive or dead?
A Correct.

Q So they didn't control in the multivariate analysis for other pesticides, correct?
A If you read on, it says, "when risk estimates for different pesticides were analyzed." I'm assuming -- that's a good question.
Q They say in the next sentence --
MS. FORGIE: Wait, he's reading so he can answer your question.
A It's not clear from the methods, but in the results section, they talk about multivariate analysis. Tables 6 and 7, it says "multivariate analysis of exposure to phenoxyacetic acids, insecticides, fungicides" --
MR. GRIFFIS: Can you tell me where you're reading?
THE WITNESS: Yeah, it's the third paragraph on 1046.
A It says, "an increased risk persisted for exposure to herbicides, fungicides and impregnating agents. A separate multivariate analysis was performed for exposure to herbicides. Lower risk estimates were obtained, although all herbicides still constituted risk factors for NHL." It implies they did risk adjustment for other pesticides. I know -- I mean, other experts have also come to that

conclusion.
Q Do they say anywhere that they controlled for other pesticides?
MS. FORGIE: Objection, asked and answered. He just answered that question. You can answer it again.
A It doesn't clearly say.
BY MR. GRIFFIS:
Q On page 1047, sir, three paragraphs down from the table, Table 7 on the left-hand side, talking about the multivariate analysis as performed for herbicides, fungicides and impregnating agents. And two -- three sentences in, they say, "The results in multivariate analysis must be interpreted with caution since exposure to different types of pesticides correlate," correct?
MS. FORGIE: Objection. You left out part of the sentence.
MR. GRIFFIS: No, I read the whole sentence.
MS. FORGIE: No.
MR. GRIFFIS: The sentence says, "the results in multivariate analysis must be interpreted with caution since exposure to different types of pesticides correlate."

MS. FORGIE: But you started to read "in the multivariate analysis exposure to herbicides, fungicides and impregnated agents increased the risk" and you left out although OR was lower than the unit variant analysis.
MR. GRIFFIS: Okay. Now I'm focussed on the results.
MS. FORGIE: So skipping the first two sentences to the third sentence, is that what you're doing?
MR. GRIFFIS: Yeah, that's what I said I was doing.
A I don't know --
MS. FORGIE: Objection, asked and answered. You can answer it again.
A All I can say is that I assume the multivariate analysis included analysis for other pesticides and other people who reviewed this paper came to the same conclusions. So -- but I'm not sure at this point.
BY MR. GRIFFIS:
Q You agree with me, sir, they don't say anywhere that they controlled for other pesticides and they say that, hey, when you look at the multivariate analysis result you have to interpret

them with caution because there is, in fact, correlation with exposures to different pesticides, right?

MS. FORGIE: Objection, asked and answered. He's answered this twice. You can answer it a third time, but it's starting to be harassing.

A That's what they say.

BY MR. GRIFFIS:

Q And the statement that "the results in multivariate analysis must be interpreted with caution since exposure to different types of pesticides correlate" doesn't make sense if they have already controlled for the effective exposure to different types of pesticides in the multivariate analysis, right?

MS. FORGIE: Objection, asked and answered. You can answer it again.

A It doesn't make sense.

BY MR. GRIFFIS:

Q Now, whether Table 7 did or didn't control for other pesticides and herbicides, that odds ratio is not statistically significant, right?

A Correct.

Q It's certainly the case that there is no odds ratio in Hardell that shows a statistically

significant association between glyphosate and Non-Hodgkin's Lymphoma controlled for other pesticides; true?

MS. FORGIE: Objection.

A Well, the multivariate analysis for glyphosate is not statistically significant.

BY MR. GRIFFIS:

Q Is there any other odds ratio reported in this study that shows a statistically significant association between glyphosate and Non-Hodgkin's Lymphoma controlled for other pesticides?

MS. FORGIE: Objection, asked and answered. This is the fifth time he's explained it to you, many times.

A No.

BY MR. GRIFFIS:

Q The next thing I'm going to look at, Doctor, is the De Roos 2003. That's a little bit intricate and it's almost lunchtime.

Would you like to break?

A Sure.

THE VIDEOGRAPHER: We are off the record at 11:54 a.m.

(Lunch recess.)

THE VIDEOGRAPHER: We are back on the

record. The time is 12:48 p.m.

(Exhibit 16-11, De Roos 2003 study, was marked for identification.)

BY MR. GRIFFIS:

Q Sir, I've marked as Exhibit 11 the De Roos 2003 paper and this is the paper that appears in your expert report, Table 1, correct, Item 3?

A Yes.

Q And this study pooled three smaller older studies: The Cantor study from 1992, the Zahm study from 1990 and the Hoar study from 1986, correct?

A Yes.

Q Did I pronounce those names correctly?

A Yes.

Q And you were one of the coauthors on the De Roos 2003 paper, right?

A Yes.

Q And what was your role?

A So the Nebraska study is one of the three studies that they pooled and that was the study that I was the PI on. So it was all data from Nebraska. I helped organize the study, I managed the study, I did all the pathology on the study.

Q Okay. And is there a sense in which De Roos 2003 supersedes Cantor 92, Zahm 94, Hoar 86?

MS. FORGIE: Objection.

A I'm not sure I'd use that terminology. It pooled the data from those three studies so they're bigger numbers and more power to analyze. So in a way, yes, because I used it instead of the other three. And some of the other three don't maybe even look at glyphosate, so this one had enough cases to do that.

Q The idea of pooling, when you do it right like this, is to try to get more power and get more information than could be contained in the smaller studies by comparing like to like; is that fair?

A Yes.

Q That's the sense when I mean supersede; this, if it's done right, should be better than the sum of the parts; is that fair?

MS. FORGIE: Objection.

A Yes.

BY MR. GRIFFIS:

Q That was your intent anyway?

A Yes.

Q And none of the studies that went into this -- Cantor, Zahm or Hoar -- was designed to test the hypothesis that glyphosate specifically was associated with Non-Hodgkin's Lymphoma, right?

MS. FORGIE: Objection.
A That's correct.
BY MR. GRIFFIS:
Q This looked at -- they looked at and the De Roos 2003 pooled analysis looked at 47 pesticides simultaneously, right?
A Yes.
Q And as we discussed earlier, with so many comparisons going on, multiple comparisons, more than 20 comparisons, you would expect some false positives just by virtue of the fact that you're looking at so many different statistical comparisons at once, right?
MS. FORGIE: Objection.
A Yes.
BY MR. GRIFFIS:
Q Generally speaking, smaller studies with fewer patients are more prone to chance complicating their findings or falsifying their findings, right?
A Yes.
Q Now, in -- did you read the expert reports of any of the other expert witnesses in the litigation, sir?
A Yes.
Q Did you read the report of Dr. Neugut?

A Yes.
Q Did you see that Dr. Neugut said that the Cantor study, one of the ones that's pooled here, had low power because there were only 26 cases of Non-Hodgkin's Lymphoma with exposure to glyphosate?
MS. FORGIE: Objection.
A I don't remember that.
BY MR. GRIFFIS:
Q Okay. Well, let's set aside whether he said it.
Do you agree that the Cantor study has low power because there are only 26 cases in Non-Hodgkin's Lymphoma with exposure to glyphosate?
MS. FORGIE: Objection.
A I would actually probably have to look at the study. 26 cases is a fair number of cases even compared to the other cases we've been studying so --
Q Okay.
MS. FORGIE: Were you finished with your answer?
BY MR. GRIFFIS:
Q Hardell is one that you listed in your expert report as having low statistical power, right?
A Right.
Q And that was one with eight individuals

with exposure glyphosate in Non-Hodgkin's Lymphoma, right?
A Right.
Q So 26, you seem to have a different threshold perhaps than Dr. Neugut that at eight you would agree with him about the low statistical power, right?
MS. FORGIE: Objection.
A Yeah, I agree that eight is, as I said in my report, it has limited power.
BY MR. GRIFFIS:
Q And some of the other studies that you list on your Table 1 in your expert report have comparable or less than Hardell, right, like Cocco has only four individuals with exposure to glyphosate in Non-Hodgkin's Lymphoma?
A Yes.
Q And Orsi has only 12 exposure to glyphosate in Non-Hodgkin's Lymphoma?
A Yes.
Q Do you think Orsi has limited statistical power?
A Yes.
Q Now, I'm looking at your Table 1 in your expert report, sir. You report only one odds ratio

from the De Roos study and that is a 2.1 with a confidence interval of 1.1 to 4.0.
A Correct.
Q And that's bolded which in your -- in the rubric you were using means it was statistically significant. And there's an asterisk which refers us to the comment over on the right, "adjusted for other pesticides," correct?
A Yes.
Q And when I asked you earlier, are there any statistically significant findings with an odds ration of greater than one in testing for other pesticides, in the epidemiology literature you said yes, there's one in De Roos 2003, meaning this one, and there's also one in the North American Pooled Project data.
And although you didn't list it in your expert report, you were aware of that one, correct?
A Correct.
MS. FORGIE: Objection.
BY MR. GRIFFIS:
Q So those were the two.
Now, on page 2 of the De Roos study, we have the "statistical analyses" section and the data that was -- the odds ratios that were given in this

were controlled in two different ways, the logistical regression and hierarchical regression, correct?
A Yes.
Q And in the "statistical analysis" section, they explain -- it's explained that the pesticide -- other pesticide exposures were controlled in the hierarchical regression analysis, correct?
A Yes.
Q And not in the logistical regression analysis, right?
A They're controlled in both.
Q Where does it say that?
A I have to sit down and read the whole paper again to really be sure.
MS. FORGIE: Do you want him to read the whole paper to find it?
MR. GRIFFIS: Looking for him to finish his sentence.
A So on the title for Table 3, it says "Effect estimates for use of specific pesticides and NHL incidence, adjusting for use of other pesticides," and there's an asterisk. And the asterisk says, "Each estimate is adjusted for use of all other pesticides listed in Table 3, age and study site." Logistic regression and hierarchical

regression use slightly different methods to do basically the same thing.
Q Okay. Let's go to page 2 of 9, "statistical analysis" section.
A 209.
Q Two of 9?
MS. FORGIE: Page 2.
THE WITNESS: Page 2. I'm sorry.
BY MR. GRIFFIS:
Q And I'm looking at the first paragraph under "statistical analysis" first, about halfway down the paragraph where it says "we employed two approaches to our analysis: Standard statistical regression (maximum likelihood estimation), and hierarchical regression." And then it says, "all models included variables for age and indicator variables for study site." It goes on to explain that it was considered whether to control for first-degree relative with hematopoietic cancer, education and smoking, but those weren't important confounders; I'm right so far?
MS. FORGIE: No. Objection.
BY MR. GRIFFIS:
Q Is that correct so far?
A I think so, yeah.

Q Okay. And then "the standard logistic regression models did not assume any prior distribution of pesticide effects, in contrast to the hierarchical regression modelling;" did I read that correctly?
A Uh-huh.
Q Explain what that means.
A Well, I'm not really sure what it means. I think it means that they made adjustments for each of the pesticides, but they didn't really take into consideration how often they were covariates, how often they were used, whereas the other one, the hierarchical regression, was a more detailed analysis.
Q If you keep reading the next sentence under the title "Hierarchical regression of multiple pesticide exposures" gives us some more information saying "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."
Can you explain what it means to be regressed simultaneously on the 47 pesticide exposures?
A No, I can't. I'm not an expert on these

kind of multivariate analyses and differences.
Q Then please explain a little more -- I believe you said earlier that the logistic regression control for other pesticides was less thorough or less sophisticated or less complete than the hierarchical.
Would you explain what you meant by that if I even got it right?
MS. FORGIE: Objection.
A I think that's the best I can do.
BY MR. GRIFFIS:
Q Okay.
A They explain it in their -- on the end of the description of hierarchical regression. They say, "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. In other words, this modelling 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."

So it's a different way of doing it. I'm not sure -- I'm not sure it's better or more sophisticated or less sophisticated. That would be a question for an epidemiologist or a statistician.

Q Which of the people on the paper would that be a question for?

A It would be a question for De Roos or Zahm or Cantor or Blair, Burmeister also. They're all epidemiologists. Burmeister is a statistician.

Q When the -- I'm sorry, you were just reading from a paragraph that extends from page 4 over to page 5. And I'm now looking at the last sentence in that paragraph, sir, that's on page 5.

It says, "Indeed a linear regression analysis of 47 logistic regression beta coefficients for the pesticides regressed on the prior covariates found no statistical significant association at a significance level of P less than 0.05 results not shown." Can you explain --

A Where is that? I'm sorry.

Q You were reading from the paragraph that extends from page 4 to page 5.

A No, I was reading from page 2.

Q Were you?

A Uh-huh.

Q I was looking at an almost identical sentence that was extending from 4 to 5 talking about the linear intercept model. Anyway, if you turn to page 5 and look at the paragraph that ends there.

A So they looked at it one way and it was statistically significant and they looked at it a second way and it was still elevated, but it was no longer statistically significant.

Q And the linear regression analysis, which is another way they looked at it but did not show the results, found no statistically significant association, correct?

MS. FORGIE: Objection.

BY MR. GRIFFIS:

Q Do you need to know where I am, sir?

A I know where you're at. I need to read this again.

Q Sure.

A That's what it says. They used another method called "linear regression analysis," but it doesn't show the data.

Q Yeah, it says "data results not shown," right?

A Yeah.

Q So there could have been a column of logistic regression -- sorry, linear regression analysis next to the logistic regression and hierarchical regression, but none of those would have been statistically significant, right?

MS. FORGIE: Objection.

A That's what it says.

BY MR. GRIFFIS:

Q Okay. So there was -- to sum up, I think, if I got this correct, there were three different ways that the data was analyzed in this study: Statistical regression, hierarchical regression and linear regression; am I right so far?

MS. FORGIE: Objection.

A I believe so.

BY MR. GRIFFIS:

Q In the logistic -- and you believe that the logistic regression, hierarchical regression and linear regression all controlled for other pesticides, correct?

A Yes.

Q In the logistic regression, there was a statistically significant odds ratio, 2.1 with a confidence interval of 1.1 to 4.0, correct?

A Correct.

Q In the hierarchical regression, it was not statistically significant, correct?

A That's correct, but it was still elevated.

Q And in the linear regression, it was also not statistically significant, although we don't know what the numbers are, right?

A Correct.

Q Did you originally have access to those numbers?

MS. FORGIE: Objection.

A I never saw the numbers.

BY MR. GRIFFIS:

Q So you wouldn't have seen the -- a table with the linear regression analysis?

A No, I don't -- I don't remember. I don't think so, but I don't remember.

Q You don't generate these tables?

A No.

Q The value that you reported in your expert report was the one that is statistically significant and not the -- not either of the nonsignificant values, correct?

A Correct.

Q Why is that?

A Well, because, you know, I probably should have -- I probably should have listed both, but I listed the one that was statistically significant.
Q And is it fair to say you don't know which of the three regressions best controls for other pesticides exposures?
MS. FORGIE: Objection.
A I don't know which one does, no. They don't really talk about that.
BY MR. GRIFFIS:
Q Please explain what the North American Pooled Project is.
A Yeah, so the North American Pooled Project is a pooling project of studies -- the three studies in the De Roos 2003 paper and the McDuffie paper, so it's a pooling of Canadian and U.S. case control studies.
Q We talked a few minutes ago about how there's a sense in which the De Roos 2003 paper supersedes the three papers that it pooled, Cantor, the Zahm and Hoar.
In the same sense, does the North American Pooled Project supersede the De Roos 2003 and McDuffie papers?
MS. FORGIE: Objection.

A Yes, because it pools them and uses the data in bigger, more powerful study.
BY MR. GRIFFIS:
Q And again, the intent of pooling is to increase the power and increase the value of the statistical analyses performed on the data; is that fair?
MS. FORGIE: Objection.
A Yes.
BY MR. GRIFFIS:
Q Now, there hasn't been a publication yet from the North American Pooled Project, right?
MS. FORGIE: Objection.
A There's a publication that's actually been published.
BY MR. GRIFFIS:
Q On the subject of glyphosate and Non-Hodgkin's Lymphoma, there hasn't been a publication yet?
MS. FORGIE: Objection.
A No, there hasn't, not to my knowledge.
BY MR. GRIFFIS:
Q And that's what is, we were talking about earlier, that's in draft, right?
A Yes.

Q The findings -- and as we discussed earlier, the findings that are going to be published in the paper that's in draft right now have been presented at various scientific conferences and there are slide shows corresponding to that, right?
A Yes.
(Exhibit 16-12, slide show, was marked for identification.)
BY MR. GRIFFIS:
Q I've marked as Exhibit 12 a slide show from a presentation --
MS. FORGIE: Are we on 12? Sorry.
BY MR. GRIFFIS:
Q -- PowerPoint presentation that was done by Dr. Pahwa in Brazil; is that correct?
A Yes.
Q And you've seen these slides before, they were sent to you, right?
A Yes.
Q You got e-mails from Dr. Pahwa and others and sending e-mails back and forth discussing the slides attached, correct?
MS. FORGIE: Objection.
A Yes.
BY MR. GRIFFIS:

Q Now, unfortunately, the -- she didn't turn on page numbering on the slides, but if you'll turn to the ninth slide --
MS. FORGIE: You mean ninth by page number or double sides; which nine do you mean?
MR. GRIFFIS: Mine isn't. Mine's by page number.
MS. FORGIE: Okay. So it's going to be 18 for us.
MR. GRIFFIS: No. There aren't -- do you have page numbers on yours?
MS. FORGIE: No. We have double-sided.
BY MR. GRIFFIS:
Q What would be the ninth slide?
A Just show us.
MS. FORGIE: Yeah, just show us.
THE WITNESS: It's this one?
BY MR. GRIFFIS:
Q Yeah. So the ninth slide is showing glyphosate used and NHL risks for ever/never use of glyphosate, correct?
A Yes.
Q What is ever/never?
A So if they've ever been exposed, they're counted as exposed and if they've never been exposed,

they're counted as unexposed.
Q It's one of the ways that epidemiologists assess causation, correct, ever/never?
MS. FORGIE: Objection.
A Yes, sir, it's a rather crude method.
BY MR. GRIFFIS:
Q Yes, sir. And we have a column called "odds ratio A, 95 percent confidence interval" and one called "odds ratio B, 95 percent confidence interval," right?
A Yes.
Q The first column, odds ratio A, adjusts for age, sex, state province and lymphatic or hematopoietic cancer in first-degree relative, a proxy respondent and use of any personal protective equipment, correct?
A Yes.
Q And B adjusts for everything that I just said from A, plus use of 2,4-D, which is another pesticide, use of Dicamba, use of Malathion, two more pesticides, right?
A Correct.
Q And in the "adjusted for other pesticides" column, there are no statistically significant results, correct?

A That's correct.
Q And does that accurately reflect the draft data on ever/never use of pesticides?
MS. FORGIE: Objection.
A Yes. The numbers are different, but I think the findings are similar.
BY MR. GRIFFIS:
Q So for ever and never use of pesticides, the NAPP, North American Pooled Project, has a null finding for glyphosate and NHL overall, right?
MS. FORGIE: Objection.
A It's not a null finding, but it's not statistically significantly increased.
BY MR. GRIFFIS:
Q And if you look at the subtypes, the odds ratio for each subtype varied, correct?
A Yes.
Q And they were all nonsignificant, right?
A Yes.
Q And one was less than zero as a matter of fact -- less than one, correct?
A Yes.
Q And what does an odds ratio of less than one as compared to one that's greater than one mean?
A It doesn't mean much. It means that it's

less than one, so it's -- it could be equivalent to one, but you see the range goes between .4 and 1.15, so it's somewhere in that range.
Q Right. I'm probably just asking too simple a question.
For a jury or judge that doesn't know statistics, generally speaking, an odds ratio of greater than one is --
A Suggests risk.
Q -- suggests risks, all things being equal, and whether all things are equal or not is always a matter of debate, and an odds ratio of less than one suggests a decrease, all things being equal; is that fair?
MS. FORGIE: Objection.
A Well, I would say it means there's no increased risk, there's no increased risk. You could say a decreased risk, but we don't really believe that glyphosate prevents cancer.
BY MR. GRIFFIS:
Q Sir, turn to the third slide from the end, please. The title is "Proxy vs. Self Respondents."
A Start at the beginning.
Q Third from the end is the easiest way to get there. Start at the back, go in three.

A Oh, there. Got it.
Q So here we have two columns: One is "proxy and self respondents" and the other is "self respondents only," correct?
A Correct.
Q And there was an issue with some question about the value of the proxy responses as compared to the value of the self responses in this data, right?
MS. FORGIE: Objection.
A That was one of the things they -- that's one of the things they analyzed as a possible covariate.
BY MR. GRIFFIS:
Q And they found that the proxy responses were less reliable than the self respondents which is consistent with standard epidemiology, right?
MS. FORGIE: Objection.
A It's often -- that's often the case, although not always.
BY MR. GRIFFIS:
Q And it was in this data, right?
MS. FORGIE: Objection.
A Well, they don't actually show you the data for the proxy, but you would assume that that's true because the odds ratios are higher for -- well, for

some of them than when you add the proxies in than when you do the self respondents. But for others it's really no different.

Q Yes, sir. And I'm not asking you based on what's revealed on this slide, but based on your knowledge of this study and your knowledge of the underlying studies, the issues of less reliable data from proxy respondents was something that you all found and identified in that data, correct?

MS. FORGIE: Objection, asked and answered. You can answer it again.

A I don't think it was clear in the analysis frankly. There were some other -- there were some other slides -- there's another slide set that looked at it and really didn't seem there was any real difference. So here you see for some of them, the odds ratio were a little higher when you had the proxies, but for others it's really not. So I really can't answer that question with regard to the specific project based on this data.

Q Okay.

A I mean, if you aggregated all of this data together, it may not be much different.

Q Do you recall, sir, whether the NAPP scientists looked at the issue of proxy versus self

respondents and were concerned about unreliability, the relative unreliability of the proxy respondents?

MS. FORGIE: Objection, asked and answered. You can answer it again.

A They looked at it with that thought in mind, but I don't see anything here that would convince me that it's a major issue.

BY MR. GRIFFIS:

Q Okay. And I'm not asking about this slide, but your memory of the project.

Do you recall in the project that being identified as a concern and that the proxy data was, in fact, less reliable than the self respondent data?

MS. FORGIE: Objection, asked and answered. You can answer it again.

A No, I don't recall that. In fact, in the analyses they did, they used proxy as a covariate so they adjusted for it.

BY MR. GRIFFIS:

Q In which set?

A In almost all of the data sets.

Q When adjusted for proxy respondents, the statistical significance of statistically significant findings decreased, right?

MS. FORGIE: Objection, asked and answered.

You can answer it again.

A I don't know which data you're talking about.

BY MR. GRIFFIS:

Q I'm asking about your memory of the study in the data analyses therein.

MS. FORGIE: Objection, asked and answered.

A I remember the data that it wasn't a major issue.

BY MR. GRIFFIS:

Q Okay. So I want to look at the various measures -- what this chart is showing, in addition to proxy and self respondents in one column and self respondents in another, is several measures of intensity, right; we have never/ever in the first two rows; we have duration, number of years of use in the next two; frequency, which is something we saw from McDuffie in the next two; and then lifetime days, which is number of years times number of days per year in the last two, right?

MS. FORGIE: Objection.

A Right.

BY MR. GRIFFIS:

Q And the lifetime days is a measure that was not reported in the published studies that we've

looked at to date; is that right?

MS. FORGIE: Objection, there's two questions pending.

A That is correct.

BY MR. GRIFFIS:

Q The lifetime days analysis would adjust for the possible exposure, misclassification issue that we talked about with regard to McDuffie which was only measuring greater than zero, less than or equal to two days versus greater than two days per year, right?

MS. FORGIE: Objection, mischaracterizes.

A It's just a different parameter to measure that really -- it does a different -- it does a different thing.

BY MR. GRIFFIS:

Q It captures both the number of days per year and for how many years you've been using it?

A Right.

Q And it puts that information together so that people who have been exposed to glyphosate on more occasions over the course of their life and more frequently will be -- will tend to be put into a higher risk group than those who have not, correct?

MS. FORGIE: Objection.

A That's correct.
BY MR. GRIFFIS:
Q Now, the odds ratio for Non-Hodgkin's Lymphoma with exposure in the highest dose category of greater than seven days per year is 1.08 in the first column, proxy and first respondents, and 1.06 in the second column, self respondents, correct?
A Correct.
Q And neither one of those is statistically significant, right?
A Right.
Q Those are null results?
MS. FORGIE: Objection.
A Correct.
BY MR. GRIFFIS:
Q Do you recall Dr. Blair testifying in the deposition that you read that the self-reported data of proxies is less reliable than self-reported data of the individual who had the exposure?
MS. FORGIE: Objection, mischaracterizes the testimony.
A I don't remember that.
BY MR. GRIFFIS:
Q You agree that, generally speaking, that's correct?

MS. FORGIE: Objection.
A It's a concern that it has to be considered. It depends. In some studies it hasn't been a problem, in other studies it has. So it's always something to be considered.
BY MR. GRIFFIS:
Q Yes, sir. The ever/never odds ratio calculated for the self respondents was less than 1.0, correct?
A Yes.
Q When looking at the number of years of exposure, sir, duration in terms of number of years, you looked at greater than zero and less than or equal to 3.5 years of exposure versus more than 3.5 years of exposure, correct?
A Yes.
Q And there was, if anything, a negative trend in the data with people who had been exposed for a longer period of time having a lower odds ratio, correct?
MS. FORGIE: Objection.
A That's correct, although the numbers aren't so very different.
BY MR. GRIFFIS:
Q That was true for both proxy and self

respondents and self respondents, correct?
MS. FORGIE: Objection, asked and answered. You can answer it again.
A Correct.
BY MR. GRIFFIS:
Q And none of the figures were statistically significant, right?
A Correct.
Q Now, you mentioned there has been a publication by the North American Pooled Project for multiple myeloma, right?
A Yes.
Q And the findings were negative for glyphosate in multiple myeloma, right?
MS. FORGIE: Objection.
A Yes.
BY MR. GRIFFIS:
Q You don't claim, sir, that glyphosate or any glyphosate-containing product causes any kinds of cancer other than Non-Hodgkin's Lymphoma, correct?
MS. FORGIE: Objection.
A That's correct.
BY MR. GRIFFIS:
Q In other publications upon which you've been a coauthor, sir, you've expressed concerns about

proxy respondents, right?
MS. FORGIE: Objection.
A Proxies are always a concern. They have to be considered.
BY MR. GRIFFIS:
Q They're more likely to give don't know answers than self responders, right?
MS. FORGIE: Objection.
A Yes.
BY MR. GRIFFIS:
Q They are more likely to give unreliable answers with regard to pesticide exposure, right?
MS. FORGIE: Objection.
A I would say maybe less reliable. I wouldn't say unreliable.
MR. GRIFFIS: Take a two-minute break?
MS. FORGIE: Sure.
MR. GRIFFIS: Give me five if you prefer.
MS. FORGIE: I'd rather take five.
THE VIDEOGRAPHER: Off the record at 1:34 p.m.
(Brief recess.)
THE VIDEOGRAPHER: We are back on the record at 1:54 p.m.
(Exhibit 16-13, September 21, 2005 draft

publication, was marked for identification.)
BY MR. GRIFFIS:
Q Doctor, I've marked as Exhibit 13 a copy at the top where it says, "Date of last revision: September 21, 2015," draft publication on glyphosate used in risk of NHL, Non-Hodgkin's Lymphoma, major histological subtypes in the North American Pooled Project; did I identify that correctly?
A Yes.
Q This is one of the drafts that was exchanged among the coauthors of the North American Pooled Project of this potential publication of glyphosate and NHL, correct?
A Yes.
Q On page 8, sir, under "statistical analyses," the second paragraph, it says at the start, "It was possible that the use of other pesticides in the NAPP may confound the relationship between glyphosate used and NHL risk;" did I read that correctly?
A Yes.
Q And then at the end of the paragraph, it explains which pesticides were correlated with glyphosate as confounders saying, "Pesticides that were most strongly correlated with glyphosate,

defined in this study as Spearman coefficients greater than or equal to 0.35 and Cohen's Kappa value greater than or equal to 0.30, and that were significantly or strongly associated with NHL in previous studies were evaluated as confounders," and it identifies the herbicides 2,4-D and Dicamba and Malathion, right?
A Yes.
Q And it's correct that those were confounders in this data, correct?
MS. FORGIE: Objection.
A Well, they were considered to be confounded. I don't know the underlying data, but they were highly correlated with glyphosate and at least 2,4-D and I think others, too, have been reported as increasing risks, so they were considered potential confounders and that's why they adjusted for them.
BY MR. GRIFFIS:
Q When you say "increasing the risk," you mean increasing the risk of NHL?
A Yes.
Q Turn to page 10, please.
MS. FORGIE: You can take your time to review this if you need to.

A Okay.
BY MR. GRIFFIS:
Q I'm looking at the header "Glyphosate use and NHL risks overall and by major histological subtype." And the first paragraph reports a significant association between glyphosate used in risk of NHL overall and with regard to subtypes, it says the magnitude of risk differed by subtype.
A Yes.
Q And that's an accurate reflection of the data in the North American Pooled Project, right?
MS. FORGIE: Objection.
A Yes.
BY MR. GRIFFIS:
Q It goes on to say, "Associations were attenuated and no longer statistically significant when the model represented by odds ratio A was further adjusted for ever use of 2,4-D, Dicamba and Malathion," right?
A Yes.
Q So ever and never -- the ever and never association disappeared when it was controlled for confounding by these other pesticides, right?
A Correct.
Q The next paragraph discusses duration and

says "There was a general inverse trend in risks except for cases of SLL" -- what is SLL?
A Small lymphocytic lymphoma.
Q -- "where the odds increase with longer duration of glyphosate used."
And this trend was of borderline statistical significance, correct?
A Yes.
MS. FORGIE: Objection.
BY MR. GRIFFIS:
Q So glyphosate use examined by duration shows a general inverse trend for most of the subtypes examined, right?
MS. FORGIE: Objection.
A That's what it says.
BY MR. GRIFFIS:
Q And then that's an accurate description of the data, right?
MS. FORGIE: Objection.
A Yeah, it's an accurate -- apparently it's an accurate description of the data from this early version of the manuscript.
BY MR. GRIFFIS:
Q An additional adjustment for the chemicals 2,4-D, Dicamba and Malathion generally resulted in

attenuated risk estimates compared to models unadjusted for these pesticides, correct?
MS. FORGIE: Objection.
A Except for SLL.
BY MR. GRIFFIS:
Q Except for SLL for which the addition of these agents in logistic regression model had no substantial effect on risk, correct?
A Correct.
Q Was there a later draft of this document among the documents that you gave to Ms. Forgie?
A There's probably more than one.
(Phone ringing).
Q How recent would the drafts be dated, approximately?
MS. FORGIE: Objection.
A I don't know how many -- there had been -- there are more recent drafts, let me say that. I don't know how many.
BY MR. GRIFFIS:
Q I'm trying to understand generally, was this something that was worked on some in 2016 so there might be a draft or two or is it something that's being actively revised right now so there would be much more up-to-date drafts or what?

A It was definitely worked on in 2016 and even 2017.
Q Did you turn over drafts from 2016 and 2017?
MS. FORGIE: Objection.
A To who?
BY MR. GRIFFIS:
Q Ms. Forgie.
A No, I didn't.
Q Do you have drafts from 2016 and 2017?
A I do.
MS. FORGIE: To be clear, he didn't give me any.
BY MR. GRIFFIS:
Q The next paragraph, sir, on page 10, talks about frequency of glyphosate used, correct? This is the greater than or equal to two days and greater than zero, less than or equal to two days a year?
A Yes.
Q And the last sentence says, "The pattern of increased risks with more frequent glyphosate handling was still apparent for NHL overall and all subtypes, all the trends were no longer statistically significant upon adjusting for these three pesticides," correct?

MS. FORGIE: Objection.
A That's what it says.
BY MR. GRIFFIS:
Q Does that accurately reflect the data?
MS. FORGIE: Objection.
A It may have changed in subsequent manuscripts.
BY MR. GRIFFIS:
Q Do you claim that in the current manuscript, any of the associations between glyphosate and Non-Hodgkin's Lymphoma or any subtype that control for other pesticides is statistically significant?
A Yes.
Q Which?
A So for greater than two days, there's a statistically significant increase for NHL overall and for large B-cell lymphoma. And there are nonsignificant increase of the same magnitude for the other subtypes as well.
Q What do you mean by "nonsignificant increase of the same magnitude"?
A It means that if NHL overall was -- had a twofold increase risk that was statistically significant, the other subtypes had a similar

magnitude, twofold, greater or less, but not statistically significant.
Q Okay. So --
A So that should be actually reflected in table 2 in the manuscript here which you don't provide.
Q Which was not provided to us.
A Well --
Q So the data for duration, number of years of exposure, that shows a negative trend with increasing duration, correct, meaning most recent data?
MS. FORGIE: Objection.
A I don't -- I can't comment on it. I don't remember that precisely, but I do remember that duration was only significant for small lymphocytic lymphoma; for others, it didn't increase duration, it did not significantly increase risk. The risks might actually have gone down. I don't remember that data precisely without having it in front of me.
Q Well, we have Exhibit 12, the slide show --
MS. FORGIE: Well, objection.
Q -- on the table of proxy versus self respondents for duration, frequency and lifetime days.

MS. FORGIE: Objection, he's already stated there's tables missing from Exhibit 13.
BY MR. GRIFFIS:
Q You have drafts with these tables in them?
A I do.
Q I demand production of them.
MS. FORGIE: Don't respond.
BY MR. GRIFFIS:
Q That wasn't for you, that was for you.
The duration data, sir -- you can take a look at the slide show if that helps you, three pages from the back, looking at number of years of exposure -- there's a negative trend with increasing duration of exposure in the North American Pooled Project data, correct?
A Correct.
Q And that's reflected in the current drafts as well, right?
MS. FORGIE: Objection. You mean this draft?
MR. GRIFFIS: No, I mean the one on his computer.
A That's what the words in the draft say.
BY MR. GRIFFIS:
Q I'm not talking about this draft, I'm

talking about the most recent one on your computer.
MS. FORGIE: I'm going to object to that. That's confidential. I don't know how you got a copy of this draft, but that information is confidential. This is not a published document. It's unfair to be asking him things he may or may not have seen.
A I don't remember precisely. I do remember the duration was -- did not show any significant results except possibly for small lymphocytic lymphoma.
BY MR. GRIFFIS:
Q The data that you've been -- your group has been reporting publicly -- and you can see this in the slide show -- shows a negative trend with increasing duration, right?
A For NHL overall.
Q And it shows a positive trend for frequency when calculated in terms of number of days per year, correct?
A Yes.
Q And it shows nothing statistically significant when the two are summed, correct, number of years times number of days per year, right?
MS. FORGIE: Objection.
A That's correct.

BY MR. GRIFFIS:
Q So the direction of the trend, when you look at the number of years, is the opposite of the trend when you look at the number of days per year and when you combine the two, significance is extinguished, correct?
A Correct. I think we saw this same phenomenon on our paper on 2,4-D, so my impression of the data is intensity of exposure is a better -- is a better measure of risk than length of exposure.
Q Or it's a better way to get statistically significantly findings to report?
MS. FORGIE: Objection.
A That's what epidemiologists look to do.
BY MR. GRIFFIS:
Q Find the best significant risks to report?
MS. FORGIE: Objection.
A No, to find the truth.
BY MR. GRIFFIS:
Q Why is the truth the biggest number?
A I didn't say it was. I just said epidemiologists look at things in different ways to find the truth.
Q Okay. What you said was it seems that the intensity is the best measure. It also is the

measure that has a statistically significant finding associated with it.
Why, other than the fact that it's the only one that has a statistically significant increased trend, is it the best measure?
MS. FORGIE: Objection, asked and answered. You can answer it again.
A Well, this is my personal opinion, and that is that the intensity of the exposure is the most important feature of the exposure. If you get high doses over a short period of time, it is, in general, increases risk much more than lower exposures over a long period of time. So if you do the product of low exposures over a long period of time, you don't get -- often don't get much of an increase in risk. That's what we saw in 2,4-D. But if you look at high exposures over a short period of time, you see increased risk because it's the high exposures that really increase the risk.
BY MR. GRIFFIS:
Q What your data is measuring is not how much glyphosate people were exposed to, but on how many days during a particular year they were exposed, right?
MS. FORGIE: Objection.

A It's a surrogate for that.
BY MR. GRIFFIS:
Q And do you know of any data showing it's a useful surrogate or that it reliably correlates with the amount of glyphosate to which they were actually exposed?
A Not for glyphosate, no.
Q For any substance?
A Not that I can remember. But it's a commonly used surrogate.
Q On page 13, sir --
A Page 13?
MS. FORGIE: Back to Exhibit 13?
MR. GRIFFIS: Yes.
BY MR. GRIFFIS:
Q Second full paragraph, looking at the first two sentences, "a fairly consistent decrease in NHL risk was found when odds ratios were further adjusted for pesticides 2,4-D, Dicamba and Malathion. This observation suggested that elevated risk of NHL may be attributed in part to pesticides other than glyphosate;" did I read that correctly?
A Yes.
Q Is that a correct description of the data in the most recent draft?

MS. FORGIE: Objection.
A Yes, I think so.
BY MR. GRIFFIS:
Q Page 15, second full paragraph, starting with the second sentence, "NHL is a constellation of heterogenous cancers that each has its own causes, risk factors and etiologies" --
A Make sure I know where you're at.
Q Page 15, second full paragraph, starting with second sentence. "NHL is a constellation of heterogenous cancers that each has its own causes, risk factors and etiologies. Pesticides, including individual agents such as glyphosate, may exert different effects on these subtypes and the large size of the NAPP made it possible to parse this out;" did I read that correctly?
A Yes.
Q Is that an accurate description of the data included the most recent drafts?
MS. FORGIE: Objection.
A Yes. Although it only looked at the most common subtype -- the three most common subtypes.
(Exhibit 16-14, 8/26/15 e-mail, was marked for identification.)
BY MR. GRIFFIS:

Q Sir, I've marked as Exhibit 14 an e-mail from Aaron Blair dated August 26th, 2015 to multiple people, including yourself.
When Dr. Pahwa was headed to Brazil for her presentation, she circulated her slides to you and the other coauthors, right?
A Yes.
Q And Aaron Blair suggested to the group that the group should notify IARC that the presentation was coming, correct?
A Yes.
Q And nobody disagreed with that, right?
MS. FORGIE: Objection. I mean, in this e-mail?
A I don't remember. I don't think anybody disagreed, but I don't remember.
BY MR. GRIFFIS:
Q Why was it important to notify IARC?
A I don't know. It wasn't my idea. I think IARC was interested in the results of this study, so maybe they -- maybe they thought that it was appropriate to send the slides to IARC. I don't know.
Q Did you have any opinion on whether it was important to notify IARC?

A No.
(Exhibit 16-15, 8/27/15 e-mail, was marked for identification.)
BY MR. GRIFFIS:
Q Exhibit 15, sir, is an e-mail thread. If you look at the bottom of the first page, on August 26th, 2015 --
MS. FORGIE: Hold on, I have a problem with my mic.
BY MR. GRIFFIS:
Q On August 26th, 2015, Aaron Blair sent a number of talking points for consideration to the group, correct?
MS. FORGIE: Objection.
A Yes.
BY MR. GRIFFIS:
Q He said, "Below is a start of thinking about talking points to questions about IARC," right?
A Right.
Q And one of the things he said is "adjustment for other pesticides made the associations that you saw not significant," right?
A That's correct.
MS. FORGIE: Objection.
A That's for ever and never, I believe.

BY MR. GRIFFIS:
Q He said, "the association may differ by histological type and that FL was not linked to glyphosate at all," correct?
MS. FORGIE: Objection.
A That's what he says. I'm not sure that -- I'm not sure what he's basing that on.
BY MR. GRIFFIS:
Q You disagree that FL is not linked to glyphosate at all?
A I don't have -- I don't have an opinion one way or the other.
Q Do you have an opinion, one way or the other, whether FL is linked to glyphosate at all in the NAPP data?
A If you look at the greater than two days exposure, the odds are increased for FL. It's just not significant.
Q What is FL?
A Follicular lymphoma.
(Exhibit 16-16, 11/27/14 e-mail, was marked for identification.)
BY MR. GRIFFIS:
Q By the way, does this refresh your memory that you received e-mails from Aaron Blair?

MS. FORGIE: Objection. He already stated that.
A There were e-mails circulating --
MS. FORGIE: There's no question pending.
BY MR. GRIFFIS:
Q You remember earlier in the deposition you said you never got an e-mail from Aaron Blair?
MS. FORGIE: Objection, that mischaracterizes his testimony.
A No. What I said was that I had not communicated directly with Aaron Blair about -- these were group e-mails, okay, so they were going around to everyone. I didn't do any direct communication back and forth to Aaron Blair. These were all group e-mails.
BY MR. GRIFFIS:
Q So when you were interpreting our document requests for this deposition, you interpreted any communications with Chris Portier and Aaron Blair and others as meaning communications that were just the two of you going back and forth rather than e-mails coming to you and others from those people?
A They were group e-mails.
Q So you interpreted it to exclude any group e-mails; is that right?

MS. FORGIE: Objection. He's also stated he didn't save all these. How could he remember. This isn't fair.
MR. GRIFFIS: That's a speaking objection. I move to strike it.
A It's true, I don't have these e-mails in my computer anymore, so I didn't remember -- I didn't remember some of them, although I knew there was this group e-mail conversation, okay, and you have it here.
BY MR. GRIFFIS:
Q I have some of it.
Sir, do you know for a fact that there are no e-mails on your computer pertaining to glyphosate in any way that are to or from Aaron Blair or Chris Portier or the other people we listed with or without others copied?
MS. FORGIE: Objection, asked and answered.
A So the only things that I have are the PowerPoint presentations that were sent to Ms. Forgie and I assumed it had been sent on to you. So I gave her everything I had.
BY MR. GRIFFIS:
Q Were there e-mails associated with those PowerPoint presentations?

A With some of them there were, yes.
Q And the drafts of the NAPP study on glyphosate and NHL, are there e-mails associated with those?
MS. FORGIE: Objection. He never stated.
A You mean with the PowerPoint presentations?
BY MR. GRIFFIS:
Q I'm talking about the drafts of the in-press NAPP study on glyphosate.
MS. FORGIE: Objection, mischaracterizes his prior testimony.
A Sure there are e-mails associated with that because those were circulated in the group e-mails as well and people commented, made changes and this is -- this is normal.
BY MR. GRIFFIS:
Q Yes, sir. So you do have e-mails with some other people on our list that you're calling group e-mails that pertain to the exchanges about the drafts of the NAPP; is that right?
MS. FORGIE: Objection, mischaracterizes his testimony. Also, you've produced information that he would consider confidential and I do as well.
A I do as well.
BY MR. GRIFFIS:

Q Yes, sir. Is what I said correct, though?
MS. FORGIE: Objection. If it relates to confidential information about confidential drafts --
A I don't know. I didn't go back and look for manuscripts because we considered manuscripts confidential.
BY MR. GRIFFIS:
Q Yes, sir.
A And the conversations around manuscripts confidential. These are works in progress.
Q There are e-mails that are associated with the draft, for example, e-mails transmitting the drafts or commenting on the drafts between you and your coauthors with regard to the pending NAPP publication that is in press right now, correct?
MS. FORGIE: Objection, you're getting into confidential information. I've already told you he did not provide me any manuscripts because he considered them confidential. They didn't come to me and they're not going to you.
MR. GRIFFIS: I'm asking about the existence of any e-mails, not the content of e-mails.
A There were e-mails. I'm not sure if I have them on my computer or not.
BY MR. GRIFFIS:

Q I would ask you not to delete any e-mails that have the word "glyphosate."
MS. FORGIE: Don't respond.
MR. GRIFFIS: And I'll ask you to see that that that happens as counsel.
MS. FORGIE: You're not entitled to confidential information. I don't know where you received these e-mails. I don't know where you received these manuscripts. But I can tell you I did not receive any manuscripts from Dr. Weisenburger because that is confidential and you know it is. I don't have any draft manuscripts, but if I did, I would not produce them. It's privileged.
MR. GRIFFIS: Anything else?
MS. FORGIE: I'll probably think of something else.
MR. GRIFFIS: Save it for briefing.
MS. FORGIE: I think it's inappropriate. Have these been previously produced, Counsel, these draft manuscripts?
MR. GRIFFIS: Yes, it's all been produced.
MS. FORGIE: When were they produced?
MR. GRIFFIS: By Aaron Blair.
MS. FORGIE: That's not what I was told, but I'll look again. Thank you.

BY MR. GRIFFIS:
Q All right. I'm sorry. I've gotten a little confused. Can I see what you have marked in front of you.
So January 14th, 2016 e-mail from Kenneth Cantor to you, among other people, attaching five abstracts for the IARC meeting and these are NAPP abstracts, correct?
A Correct.
Q Tell me what the NAPP abstracts for the IARC meeting are.
A I'm not sure I can tell you all of them.
Q I don't mean list each one.
What's the IARC meeting and why is NAPP sending abstracts?
A So the IARC apparently has an annual meeting or a regular meeting in which new research is presented and the NAPP group targeted these five abstracts to the IARC meeting for presentation and one of them was the NHL abstract. The other ones, I don't know exactly what they were. I think one was myeloma. I don't know what the other ones were.
Q Was someone on the team tasked with putting these abstracts together?
MS. FORGIE: Objection.

A It was Pahwa and the Canadian group.
BY MR. GRIFFIS:
Q And Ken Cantor, Dr. Cantor writes, at the bottom of the first page here, "results in the second abstract (glyphosate) are less than convincing, given that control for other pesticides results in attenuated odds ratios which aren't in the abstract," correct?
A That's what it says.
Q And do you agree with that?
A I can't remember what was in that final abstract. These are drafts of abstracts. So apparently in the draft that he saw that was the case, but I don't remember.
(Exhibit 16-17, 8/22/16 e-mail, was marked for identification.)
BY MR. GRIFFIS:
Q Sir, on August 14th, 2016, you e-mailed Dr. Christopher Portier asking him the status of an EU glyphosate review and wanted to know the status?
A Correct.
Q Wanted to know if glyphosate had been approved for use and if there had been restrictions, right?
A Right. This is in followup to the letter

we had written as a group where he had been the first author and then the manuscript, so I was just curious to know whether there had been any action on the part of the EU, so it was a simple question.

Q Is this the only occasion on which you have directly corresponded with Portier directly, not with group e-mail, but you e-mailing him and him responding to you?

MS. FORGIE: Objection, asked and answered. You can answer it again.

A To the best of my knowledge. I've never met him, I've never -- so I don't really know him. This was in followup to the document that I was a cosignature on.

BY MR. GRIFFIS:

Q The document on which you're a cosignature, there were actually a couple of them, there was a letter to the EU commissioner and there was a followup publication letter, correct?

A Right.

Q And as to those, did you receive e-mails from Chris Portier to you and to others soliciting your signing on to those letters?

MS. FORGIE: Objection, asked and answered.

A I received an e-mail from someone. I don't

know who it was.

BY MR. GRIFFIS:

Q And did you just respond and say yes, I will sign off or was there an exchange on the subject?

MS. FORGIE: Objection.

A There was not an exchange. I read it -- I read -- I read one or two drafts, I made some suggested corrections in the drafts and sent them back to Portier. They weren't substantial changes. They were mainly grammar and phrasing of things.

BY MR. GRIFFIS:

Q Are they still on your computer, the edits?

A No.

Q He sent a draft document in Word format or some other format and you edited it on your computer and sent the changes back?

MS. FORGIE: Objection.

A It would have printed -- I don't do a lot of stuff on my computer so I did it manually. It probably would have been scanned and sent back to him.

BY MR. GRIFFIS:

Q Would there be a PDF image on your computer possibly?

A Yeah, but this is two or three years possibly. I don't have it on my computer.

Q Have you looked for it?

A I know it's not there because nothing -- practically nothing there from 2016 is still there. And this was prior to this. I don't know when it was. It's probably '15.

Q Dr. Portier responded to you and told you that the EU approved the use of glyphosate for 18 months while the European Chemical Agency reviews the data and then you forwarded that to Aaron Blair, correct?

A I did, that's right.

Q And you said, "It seems important to get our US/Canadian paper on this" -- meaning the NAPP data, right -- "submitted soon so it could be considered in this review." You just nodded, but the court reporter can't take that down.

A True, I was concerned it was taking a long time to get the NAPP data submitted, so I was trying to push the group, the NAPP group to get the data submitted so that it could be publicly available.

Q What do you consider the NAPP data to contribute to the picture on glyphosate in NHL?

A Well, it -- as we've discussed, it pools

the data from two large studies and it's able to do -- have a more powerful approach to analyzing some of the dose response and subtype data.

Q What is the information that is different in the NAPP data from what is available in the underlying data?

A Well, the data is very similar to what's been presented in the various meetings.

Q When you say "the various meetings," you're referring to, among others, the Brazil slide show?

A Right.

(Exhibit 16-18, 5/5/16 e-mail, was marked for identification.)

BY MR. GRIFFIS:

Q Sir, Exhibit 18, a May 5th, 2016 e-mail from Kathryn Forgie to you forwarding an article, correct?

A Yes.

Q And you responded saying, "when do you want to discuss your first case," correct?

A Correct.

Q What did you mean by "first case"?

A Well --

MS. FORGIE: I'm going to object. I think this is all privileged information. I'm going to let

him answer, but I'm not going to waive our privilege.
A She had some specific cases she wanted to discuss.
BY MR. GRIFFIS:
Q Like cases about the specific people rather than about general causation?
A Yes.
Q And you forwarded that to Aaron Blair and said "FYI;" why did you do that?
A Probably to let him know I was consulting with her. I'm not sure he knew that I was retained by her.
Q When is the last time you purged your e-mails, sir?
MS. FORGIE: Objection, asked and answered. You can answer it again.
A Maybe within the last few months. I'm not sure exactly when.
BY MR. GRIFFIS:
Q Now, we discussed earlier that there was an open letter to the EU commissioner that you signed off on at the request of either Chris Portier or someone else who e-mailed you, you couldn't remember whom. And later, there was a publication on differences between the IARC analysis and the

analysis performed by the European Food Safety Agency, correct?
MS. FORGIE: Let me stop for a second. I've just been advised there's a problem with phone interference. Is there any way we can check on that?
MR. GRIFFIS: We can go off the record.
THE VIDEOGRAPHER: Off the record at 2:31 p.m.
(Brief recess.)
THE VIDEOGRAPHER: We are back on the record at 2:45 p.m. This marks the beginning of Videotape Number 3 of the deposition of Dr. Weisenburger.
MS. FORGIE: I've been advised that the rough draft, which is exhibit -- I mean the draft manuscript, which is Exhibit 13, was, in fact, produced by Dr. Blair but not attached to his deposition which is why I didn't know about it. So I apologize. I stand corrected on that. We still believe that all of this information is privileged in terms of the academic privilege and we don't think it's appropriate to discuss it, nor would we produce -- nor have any drafts been produced to me because of that privilege. That's all.
(Exhibit 16-19, 9/10/17 e-mail, was marked

for identification.)
MS. FORGIE: 19 is the additional materials; is that right?
MR. GRIFFIS: Plus your cover e-mail.
MS. FORGIE: I haven't seen the cover e-mail.
BY MR. GRIFFIS:
Q Sir, Exhibit 19 is an e-mail that we received yesterday, which was a Sunday, at 12:56 p.m. Eastern time, attaching what was called "an additional materials list."
Do you recognize the additional materials list?
A Yes, I prepared these lists.
Q When did you review the materials on the additional materials list?
A Over the last few months.
Q And there are 45 citations on the additional materials list, right?
A Yes, I guess so. Let me look.
Q Okay. They're numbered.
A It looks different than what I sent.
Q Let me see, make sure I give you the right thing. Yeah, that's what we received.
A So it was actually three separate lists

which looks like they've been consolidated into one list.
Q When did you send the three lists, sir?
A It was within --
MS. FORGIE: Objection, that's privileged.
THE WITNESS: Did I send it, it's privileged?
MS. FORGIE: Yeah, communications between us are privileged.
MR. GRIFFIS: Please direct him not to answer that.
MS. FORGIE: Don't answer that.
BY MR. GRIFFIS:
Q Sir, did you send the first of those lists more than a week ago?
MS. FORGIE: Don't answer that. Actually, you can go ahead and answer it. Don't say anything about any communications we had, just the date.
A Yeah, so it would have been sent last Tuesday, the day after Labor Day.
BY MR. GRIFFIS:
Q All three lists?
A Yes.
Q Have you been -- and why were there three lists?

A One was additional materials reviewed, one was additional materials relied on and one was other additional things reviewed.
Q And what is the difference between reviewed, relied on and other additional things reviewed?
MS. FORGIE: Objection.
A Well, I can't tell -- I mean, I could show you the three lists. I have them with me.
MS. FORGIE: No, that's okay. Just if you -- if there's a difference, you can tell us. If not --
A So there was a list of manuscripts that I relied on that I would have referenced in my -- in my report, if I had them at the time I wrote the report, there was a list of materials I reviewed that I wouldn't have referenced in my report and then there was a list of other materials that I reviewed that I thought were important like the -- for example, the letter to the commissioner of the EFS -- whatever it is, EFSA, and the manuscript that I was a coauthor on with Portier. I also listed the Aaron Blair deposition -- no, that was on my other one. I listed the draft of the Agricultural Health Study that was attached to the Aaron Blair deposition, I listed the

most recent meta analysis that was done, things that I had reviewed since I wrote my report.
BY MR. GRIFFIS:
Q When you reviewed the Blair deposition, did it come with exhibits attached?
A I don't think it did. I don't think it did. Because otherwise I would have printed it. So when I reviewed the Blair deposition, I had only the deposition and then only later, fairly recently, did I ask for --
MS. FORGIE: Don't give any statements about communications between us.
A Okay. I didn't -- I had no access to it.
BY MR. GRIFFIS:
Q So you asked to have it provided to you?
A Yes.
Q How long ago was that?
MS. FORGIE: Just give him the date on communications, approximately.
A I don't know the date. It was a month or two ago, fairly recent.
BY MR. GRIFFIS:
Q Okay. So you -- you originally had a list that showed which materials you considered important enough you would have included them in your expert

report had you had them at the time; is that right?
MS. FORGIE: Objection.
A I would have referenced them in my report, yes.
BY MR. GRIFFIS:
Q Do you have anything to add to your expert report or change about your expert report in the light of the various materials that you reviewed that were disclosed to us yesterday?
A No, there wouldn't be any substantial changes.
Q So these would be additional references that you would be relying on with sufficient importance to put a parenthetical referenced to them in your report; is that right?
A Yes.
MS. FORGIE: Objection.
BY MR. GRIFFIS:
Q And do you remember which references those are looking at the list in front of you?
A Well, this is a consolidated list.
Q Yes, sir.
A I couldn't go and tell you which was which off the top of my head. I couldn't.
Q So you can't unscramble the list without

looking at what was provided to us?
MS. FORGIE: Objection.
A Probably not.
BY MR. GRIFFIS:
Q You told us that you sent those lists two weeks ago.
Were there any materials that you have seen since you sent those three lists to plaintiff's counsel that you consider important enough to be on the list?
A No.
MS. FORGIE: Objection.
A I sent the lists last Tuesday which would have been less than a week ago.
BY MR. GRIFFIS:
Q I'm sorry, I wrote two weeks ago about something else.
MS. FORGIE: That's why I objected. It was the day after Labor Day is when he sent them. I know that because it was my daughter's birthday.
BY MR. GRIFFIS:
Q Did you see anything since you sent the three lists last Tuesday?
A No, I didn't review anything, anything new.
Q Yes, sir. So with last Tuesday as the

bound farthest forward in time, how far back does your review of documents on that list go; months?

A Yeah, to the time that I wrote my report, submitted my report.

Q So it's a catchup of everything from the time of your report until now?

A Yes.

Q And the -- when we looked at your billings, the 2017 billing and the April 19th, did that match up in any way to your expert report drafting?

A So the biggest -- the last and biggest bill was submitted I think right after I submitted my report.

Q Okay. So the hundred hours since then that you estimated that you had worked since April 19th of 2017 would include your review of these materials and other work that you did; is that right?

A Yes.

MR. GRIFFIS: I'm going to make an objection on the record. This isn't for you to respond to, it's to put it on the record at this time. That is, that the Federal Rules of Civil Procedure require a timely disclosure of an expert's opinions and the bases, therefore, this certainly pertains to the bases, therefore, and that disclosure

has to be timely and updated in a timely fashion to permit appropriate cross-examination.

Because this was provided to us 45 substantial citations the day before your deposition and on a Sunday while we were traveling to get all the way across the country, we reserve the right to reopen your deposition at plaintiff's counsel's expense to question you about these 45 citations and the substance thereof.

In addition, we reserve the right to reopen your deposition at plaintiff's counsel's cost and expense with regard to e-mails for which we will seek disclosure, drafts of the NAPP document and other documents that we requested in the Notice of Deposition that we were told, in response to the Notice of Deposition, would be produced to the extent that we didn't already have them or that they were not otherwise objectionable. And we did not receive them.

We will be filing appropriate motions. That doesn't call for any response from you or any action from you.

MS. FORGIE: I'm going to respond to it. We, of course, don't agree with that. We think that every document that was not already publicly

available or already produced in the MDL was produced to you except for those for which we claim academic privilege. And we believe that the academic privilege does apply to draft manuscripts of the NAPP. And he's already stated there were no e-mails that were provided that were already -- weren't already produced to you that we're aware of. And with regard to the articles, he said they don't change his opinion, they're just additional reading, they didn't change his opinion in his expert report.

MR. GRIFFIS: And sir, with regard to the request that I made earlier, that you do not delete or get rid of any e-mails or documents, et cetera, that also doesn't call for a response from you, but it does trigger legal obligations and I advise you to speak to counsel about that, without me sitting around, about what obligations that produces on your behalf and her behalf and the rest of the plaintiff's committee.

MS. FORGIE: And we don't agree with that either. We'll take it up with him separately and privately.

MR. GRIFFIS: Thank you.

BY MR. GRIFFIS:

Q Sir, one of the things that you have published on in the past is an increase in the

incidence of Non-Hodgkin's Lymphoma nationwide that began in the 1950s, correct?

A Yes.

Q And that was something that -- a number of hypotheses were generated about what could be causing that, including such things as better reporting, better surveillance and those were pretty much ruled out as explanations for the increase, correct?

MS. FORGIE: Objection.

A Well, we really don't know why it increased dramatically in that sort of 20-year period. We don't really understand why. Part of it was probably HIV/AIDS, part of it was probably better reporting, better recognition of lymphomas by pathologists. But most of it we don't understand.

BY MR. GRIFFIS:

Q And the -- what do you consider to be the known causes of Non-Hodgkin's Lymphoma that are firmly established by science?

A Okay. One is immunosuppression, another one is a family history of hematopoietic cancer or lymphoma, certain autoimmune diseases increase risk, certain infections increase risk, HIV/AIDS is an example, ST (indecipherable) virus infection, infection of other viruss like HTL V1 or HH V8 or

hepatitis C, certain bacterial infections. And then there are a variety of chemicals, solvents, pesticides, maybe other things I'm not thinking of. That's a good portion of the list.

Q Solvents and pesticides, those are obviously very broad categories.

Do you consider all solvents and all pesticides to be causes of Non-Hodgkin's Lymphoma?

A No. But there are certain solvents and general exposure to solvents which increase risk. And for pesticides, there are some pesticides which are accepted risk factors and other ones which are suspected and other ones that probably aren't risk factors.

Q Which solvents do you consider to be accepted risk factors for Non-Hodgkin's Lymphoma?

A So -- trying to think of the terminology -- it's usually exposure to mixed solvents, often solvents including what are called mineral oils. There's some evidence for benzene. But most of the solvent literature is on general exposure to mixed solvents, so it's not parsed out very well.

Q Okay. So what pesticides do you consider to be accepted risk factors for Non-Hodgkin's Lymphoma?

MS. FORGIE: Objection.

A Well, I think -- there's good data on 2,4-D, there's data on Lindane, there's data on -- off the top of my head, I think Malathion is another one. I mean, I don't have an active list for pesticides. But those are some examples of people commonly associated with NHL.

BY MR. GRIFFIS:

Q Other than solvents and pesticides, what other environmental factors do you consider to be causes of Non-Hodgkin's Lymphoma?

A There's some data on exposure to diesel fumes which, in a way, would be exposure to petrochemicals and solvents, so it falls within the same category.

Q Do you consider that to be a generally accepted risk factor?

MS. FORGIE: Objection.

A It's a reported risk factor. I don't know whether it's generally accepted or not.

BY MR. GRIFFIS:

Q Okay. Go on.

A That's all I can think of at the moment.

Q This rising epidemic of Non-Hodgkin's Lymphoma that began in the 1950s, at least the first

part of the increase could not have been caused by glyphosate since glyphosate wasn't around yet, correct?

MS. FORGIE: Objection.

A That's correct.

BY MR. GRIFFIS:

Q Do you agree, sir, that most Non-Hodgkin's Lymphomas are spontaneous?

MS. FORGIE: Objection.

A Well, I think most -- I think most Non-Hodgkin's Lymphomas, we don't have an obvious etiology that we can point to.

BY MR. GRIFFIS:

Q You testified in the past that 80 to 90 percent -- 80 to 90 percent of Non-Hodgkin's Lymphoma cases are idiopathic, correct?

MS. FORGIE: Objection.

A As far as we know, but I think that that's changing because we're finding more causes over time.

BY MR. GRIFFIS:

Q What do you think the percentage is now?

MS. FORGIE: Objection.

A I don't know. Maybe 70 percent.

BY MR. GRIFFIS:

Q It's more than half?

A Yes.

(Exhibit 16-20, article, was marked for identification.)

BY MR. GRIFFIS:

Q Exhibit 20 is the Eriksson study that you listed on Table 1 in your expert report; is that right?

A Yes.

Q And this is another study, like the others we've been discussing, that looked at potential associations between Non-Hodgkin's Lymphoma and a wide variety of different herbicides, insecticides and other pesticides, right?

A Yes.

Q So like McDuffie, it was an exploratory study, correct?

MS. FORGIE: Objection.

A Yes.

BY MR. GRIFFIS:

Q And you report that Eriksson showed a statistically significant response?

A Yes.

Q And you were talking about data from Table 2 on page 1659, right?

A Yes.

Q So less than or equal to 10 days of exposure, there was an odds ratio of 1.69, greater than 10 days there was an odds ratio of 2.36, correct?
A Yes.
Q And that wasn't adjusted for other pesticides, right?
A That's correct.
Q And the odds that are -- the odds ratio given in Table 3, which break down by NHL subtype, also were not adjusted for other pesticides, right?
A That's correct.
Q You don't know if any of the odds ratios reported on either of those tables would be statistically significant if they were controlled for other pesticides; is that fair?
MS. FORGIE: Objection.
A Yes.
BY MR. GRIFFIS:
Q Now, the only odds ratio that is controlled -- the only adjusted odds ratio adjusted for exposure to other pesticides is the multivariate analysis in Table 7; is that right?
A That's correct.
Q The multivariate analysis there is not

statistically significant, correct?
A That's correct.
Q And Table 2, sir, exposure to various herbicides and Table 4, exposure to various other pesticides, virtually every substance looked at has an unadjusted odds ratio above one, right?
MS. FORGIE: Objection.
A That's true -- well, there's one that's under -- two under.
BY MR. GRIFFIS:
Q Yeah, I said virtually.
MS. FORGIE: Objection.
BY MR. GRIFFIS:
Q It's true that virtually every one is over one?
A To me, virtually every one means every one, but not every one.
MS. FORGIE: You're talking about what's in the table.
BY MR. GRIFFIS:
Q Talking about Table 2 and Table 4.
A Almost every one.
Q Okay. That would suggest the possibility of systemic bias in the study, right, the fact that almost everything is found to be greater than one?

MS. FORGIE: Objection.
A Well, it would suggest some kind of bias.
BY MR. GRIFFIS:
Q It's impossible to tell from this study whether the unconfounded odds ratio that they give for glyphosate exposure for more than 10 years would be statistically significant if it was controlled for other pesticides, right?
MS. FORGIE: Can I have that question read back, please.
(The requested portion of the record was read by the reporter at 3:15 p.m.)
MS. FORGIE: Objection.
A I don't know -- I don't know what number you're -- or what category you're talking about.
BY MR. GRIFFIS:
Q I need to fix it because I meant days, not years. Table 2, exposure to various herbicides, glyphosate less than or equal to 10 days and greater than 10 days.
MS. FORGIE: What's the question?
MR. GRIFFIS: I'm pointing him to the table.
BY MR. GRIFFIS:
Q The question is, there's no way to tell

whether the purportedly statistically significant finding for glyphosate exposure of greater than 10 days duration would be statistically significant if adjusted for other pesticides, correct?
MS. FORGIE: Objection.
A There's no way to know that's correct.
BY MR. GRIFFIS:
Q There's no statistically significant odds ratio greater than one that is controlled for other pesticides in this study, the Eriksson study, correct?
MS. FORGIE: Objection.
A I'm sorry, can you repeat that again?
BY MR. GRIFFIS:
Q There's no statistically significant association between glyphosate and Non-Hodgkin's Lymphoma or any subtype of Non-Hodgkin's Lymphoma in this study that is statistically significant greater than one and controlled for other pesticides, right?
A That's correct.
MS. FORGIE: Objection.
MR. GRIFFIS: Mark as Exhibit 1 the De Roos 2005 study.
MS. FORGIE: Exhibit 1?
MR. GRIFFIS: 21.

(Exhibit 16-21, article, was marked for identification.)
BY MR. GRIFFIS:
Q You discuss that in your expert report on page 5, but it's not in your Table 1, correct?
A That's correct.
Q And you report that the study did not find a significantly elevated risk of cancer overall or types of cancer including NHL, right?
A Yes.
Q And you have a couple of critiques of it. You said the median followup time in the study was only 6.7 years, too short a time to detect a meaningful increase in NHL or other cancers including glyphosate, right?
A Yes.
Q Can you explain what you mean by that, please?
A Well, usually you do a cohort study, you follow the individuals for a long period of time, say 20 or even 30 years. So this was a very early preliminary analysis of data.
Q Okay. How long a period of time do you need between an exposure of an environmental -- possible environmental risk factor for Non-Hodgkin's

Lymphoma and presentation of the disease in order to detect it?
MS. FORGIE: Objection.
A You mean on average or --
BY MR. GRIFFIS:
Q Let's talk about epidemiology studies first of all.
How long a period do you need for an epidemiology study to provide useful data?
MS. FORGIE: Objection.
A For NHL?
BY MR. GRIFFIS:
Q Yes, sir, for NHL.
A Well, I don't think I can answer that in a general fashion. I think depending on the intensity of the exposure -- depends on the intensity of the exposure and length of the exposure, one can see cases of NHL as early as two years after exposure and as long as 30 or more years after exposure. So it's a very wide -- it's a very wide interval.
Q When you say as early as two years and as long as 30 years, you're talking about individuals, correct?
MS. FORGIE: Objection.
A Yes.

BY MR. GRIFFIS:
Q So if an individual is -- and you were making an intensity distinction, correct, so that if someone's -- has an intense exposure, their latency period to presentation would probably be shorter than someone with less intense exposure?
A In general.
Q So for an individual patient, you would expect to see NHL more than two years, less than 30 years after exposure, depending on intensity?
MS. FORGIE: Objection.
A So for NHL, I would expect cases to start appearing maybe two years after exposure, but you could see cases for many years, more than 30 years.
BY MR. GRIFFIS:
Q Okay. So from greater than two and no outer bound; is that right?
A Yes.
MS. FORGIE: Objection.
BY MR. GRIFFIS:
Q For epidemiology. Epidemiology obviously collects multiple people, it's not looking at one individual.
To have a meaningful test of whether a particular -- let's say pesticides to be topical, for

the particular pesticide can cause NHL, how long a period of time do you think you need between the exposures and the cancers that you're measuring?
MS. FORGIE: Objection, asked and answered. You can answer it again.
A I don't think there's any accepted answer to that. Obviously the longer, the better, yeah. So obviously the longer the better. I can't give you a more specific answer than that.
BY MR. GRIFFIS:
Q 6.7 years is too short in your view, right?
MS. FORGIE: Objection.
A In my view it's too short, yes.
BY MR. GRIFFIS:
Q Is 10 too short?
MS. FORGIE: Objection.
A No, probably not. But -- probably not.
BY MR. GRIFFIS:
Q Okay. Where -- I understand that you have to draw a line and it would be a little bit arbitrary, but we have it down between 6.7 and 10, where would you draw that line?
MS. FORGIE: Objection, mischaracterizes his testimony.
A I couldn't draw a line. I think 6.7 years

is too short for a cohort study. For the design of any epidemiologic study, it would be best to have a longer exposure, the longer the better, but I don't have a specific number that I can apply to say this is the magic number.

BY MR. GRIFFIS:

Q Okay. The longer the better, 6.7 is too short, 10 is probably long enough and you couldn't draw a line -- you couldn't be more specific in between those two; is that fair? That's fair, sir?

A Yes.

Q Okay. And the relevant period of time is the period between when the people in the study were exposed to glyphosate and when the people in the study get cancer, that's the period of time we need to look at, right?

A Correct.

Q Now, the De Roos 2005 study, Exhibit 21, that's part of a much larger effort called "the Agricultural Health Study," right?

A That's correct.

Q This is one of multiple publications that's come out of the Agricultural Health Study, right?

A Yes.

Q And that's a National Cancer Institute,

National Institute of Environmental Health Sciences, et cetera, government-funded study, right?

A Yes.

Q And this is the only prospective cohort study that looks at, among other things, possible association between glyphosate and cancer, right?

A To my knowledge, yes.

Q And as you reported in your expert report, the results of the study were negative, there was no association found between glyphosate exposure and Non-Hodgkin's Lymphoma either in crude analysis or in analyses controlled for pesticide -- other pesticide exposures, right?

MS. FORGIE: Objection.

A That's correct.

BY MR. GRIFFIS:

Q You don't rely on this as a study that supports your conclusion that glyphosate can cause Non-Hodgkin's Lymphoma, correct?

A That's correct.

Q And when the De Roos 2005 study looked at higher exposures to glyphosate, looked at the issue of dose response, it found no dose response; is that right?

A That's correct.

Q And the total days of exposure to glyphosate of exposed members in the Agricultural Health Study cohort was significantly higher than those in the case controlled studies that we've been looking at so far, right?

MS. FORGIE: Objection.

A Are you talking about cumulative days?

BY MR. GRIFFIS:

Q Yes, sir.

A Yes, that's true.

Q I mean, the lowest exposure group -- I'm looking at Table 3 on page 52 -- was between 1 and 20 days of glyphosate exposure?

A Right.

Q And the next group was 21 to 56 days and the next one is 57 to 2678 days, right?

A Right.

Q And what they found was the risk in the highest exposed group, people exposed from 57 to 2678 days, had a lower odds ratio than those in the lowest exposure group, 1 to 20 days, right?

MS. FORGIE: Objection.

A That's correct.

BY MR. GRIFFIS:

Q Now, it's both for cumulative exposure days

and intensity weighted exposure days, correct?

A That's correct.

Q Do you have criticisms of the De Roos 2005 study other than the followup time of 6.7 years being too short?

A Well, there are a number of criticisms. One, the people that were followed were quite young. The median age was only, I think, 45, so such a young cohort would need longer followup than, say, a cohort with the median age of 65. So that's another reason why the followup is too short.

The other -- one of the other criticisms is that they compared the highest tertile to the lowest tertile rather than to those that were unexposed which would tend to decrease that kind of analysis -- that kind of analysis would tend to decrease to the null. There are some things that -- which lead one to sort of question these results from such a preliminary analysis of -- of the data.

Q So your three criticisms are median age of 45 being rather young, that they compared the highest tertile -- and that was in the Table 3 we were just talking about?

A Right.

Q Highest tertile to the lowest tertile and

not to the unexposed population?
A Right.
Q And you considered the 6.7 year median followup to be too short, correct?
MS. FORGIE: Objection.
A Right.
BY MR. GRIFFIS:
Q And the only one of those three criticisms you made in your expert report was the last, 6.7 year median being too short to follow up, right?
MS. FORGIE: Objection.
A It ties in with the age. They tie in together. That's the major criticism.
BY MR. GRIFFIS:
Q Did you formulate the first two criticisms after you wrote your expert report?
MS. FORGIE: Objection.
A No.
BY MR. GRIFFIS:
Q Okay. You just didn't put them in your expert report?
MS. FORGIE: Objection, mischaracterizes his testimony. He said they are in there.
MR. GRIFFIS: He said they're not.
MS. FORGIE: He said they tied in together.

BY MR. GRIFFIS:
Q The highest tertile to lowest tertile, that's not in there at all, right?
MS. FORGIE: Objection.
A No, I didn't mention that in my report, something -- yeah, I don't -- I -- it's probably something that I came upon after I wrote my report.
BY MR. GRIFFIS:
Q And you came upon it after you wrote your report how?
A Either by reading the paper or perhaps reading the other depositions. I don't remember.
Q You mentioned that -- never mind.
The followup time of 6.7 years in the De Roos study, that's the number of years after the aegis gathered information on prior exposures, right?
MS. FORGIE: Objection.
A Right, that's the followup with regard to their survival or status.
(Exhibit 16-22, article, was marked for identification.)
BY MR. GRIFFIS:
Q Exhibit 22, Doctor, that I've just marked as such, is published in Environmental Health Perspectives in April 1996. It's titled "The

Agricultural Health Study" and it gives general data about the Agricultural Health Study and its participants, correct?
A Yes.
Q If you look at Table 1, sir, page 365, one of the pieces of information they give is years that the participants first reply back to pesticide; do you see that?
A Yes.
Q Do you see that the median number of years that people participating is something on the order of 15 years with that data?
A Yes.
Q And the information collected, is it based on information that was collected in 1993 to 1997, according to the Exhibit 21, correct, under materials and methods, talking about when recruitment of the applicator occurred?
A Yeah, just let me --
MS. FORGIE: Take your time.
A Let me see the De Roos study here. 1993 to 1997.
BY MR. GRIFFIS:
Q When these initial questionnaires were done, which was '93 to '97, the median exposure to

pesticides in the cohort was already about 15 years, right?
MS. FORGIE: Objection.
A That's correct.
BY MR. GRIFFIS:
Q And glyphosate, at the time, had been on the market for 20 or more years, right?
A That's correct. Almost 20 years.
Q So the potential period of time in the De Roos 2005 study for which people could have been exposed to glyphosate, just at the time of data collection, was 15 to 20 years, right?
MS. FORGIE: Objection.
A But we don't really know what the data is for glyphosate.
BY MR. GRIFFIS:
Q It's potentially 15 to 20 years, right?
MS. FORGIE: Objection, asked and answered. You can answer it again.
A This is for pesticides in general. So we really don't know what the data is for glyphosate.
BY MR. GRIFFIS:
Q Is there a reason that the differential would skew towards later for glyphosate and not for other pesticides?

A Yes, because glyphosate was not really very highly used for many, many years. Only until the mid 1990s did it really take off as being used. So it was, I think, made up maybe three percent or four percent of all the pesticides used during those early years. So it's unlikely that it contributed 15 years. It's unlikely.

Q It's certainly not the case that the people in the De Roos study had 6.7 years between their exposure to glyphosate and developing cancer if they did develop cancer, right?

MS. FORGIE: Objection, asked and answered. You can answer again.

A Yeah, they would have had exposure because exposure goes back. But we don't know how far back it goes.

BY MR. GRIFFIS:

Q It could have gone, on average, further than 10 years, right?

MS. FORGIE: Objection, asked and answered. You can answer it again.

A It's possible.

BY MR. GRIFFIS:

Q You have no reason to say that it was 6.7 years and not greater than 10 years, your threshold

for a study yielding fruitful data on exposure to a substance and Non-Hodgkin's Lymphoma, correct?

MS. FORGIE: Objection, asked and answered. He just gave you a reason. You can give it to him again.

A I need to hear the question again.

BY MR. GRIFFIS:

Q Yes, sir. You have no reason to suppose that the true period of time for the people who were exposed to glyphosate, who developed Non-Hodgkin's Lymphoma, between their exposure and their diagnosis, was not 10 years or more, the period of time that you say it is, is a fruitful period for a study?

MS. FORGIE: Objection, asked and answered. You can answer it again.

A I have no way to know what it was.

BY MR. GRIFFIS:

Q The real number is not 6.7, right?

MS. FORGIE: Objection, asked and answered. You can answer it again.

A We really don't know what the number was. We really don't know what the number was because they could have -- they could have used glyphosate and they could have stopped before they were even enrolled in the study. So we really don't know what

the number is.

Q If the real number is 10 or greater as opposed to 6.7 you put in your expert report, then this is not an immature study, correct?

MS. FORGIE: Objection, asked and answered.

A It is an immature study because we -- for a cohort study of young applicators, it's very unlikely that you would see an increased odds ratio with such a short followup because you wouldn't have accumulated enough cases of NHL to do that.

BY MR. GRIFFIS:

Q And the followup, though, is only one part of the relevant time consideration, correct, the true time consideration is the time between exposure and the assessment of cancers, right?

MS. FORGIE: Objection, asked and answered several times. You're starting to badger. You can answer again.

A Yes, it's true. The exposure time is from the time -- it's actually the time from when they started the -- using the chemical to the time they stopped using the chemical. That's exposure time. And the latency would be the time they started using the chemical until they developed the cancer.

Q Okay. And that is a different number than

the time between the initial questionnaire and final followup; that's a different number, right?

MS. FORGIE: Objection, asked and answered. You can answer it again.

A You're asking now exposure time or latency?

BY MR. GRIFFIS:

Q Well, the 6.7 that you said was too short a time is based on followup, right?

MS. FORGIE: Objection, asked and answered. You can answer it again.

A Yes. That was the median followup time.

BY MR. GRIFFIS:

Q Okay. But the important figure is not how long between initial questionnaire and followup in a particular study, the important number for the issue of latency, which is your criticism, is between the initial exposure and the cancer assessment, correct?

MS. FORGIE: Objection, asked and answered like five times. You can answer it again.

A Yes.

BY MR. GRIFFIS:

Q How many years of followup, in addition to 6.7, do you think would make this no longer an immature study?

MS. FORGIE: Objection, asked and answered.

A I don't know the answer to that. I think -- I think the -- the best followup would be at least 20 years or more, but I think we don't really know the answer to that question.

MS. FORGIE: When you finish with AHS, can we take a quick break, when you're finished?

MR. GRIFFIS: Yeah. I'm seeing if I am. Okay.

THE WITNESS: Break.

THE VIDEOGRAPHER: We're off the record at 3:40 p.m.

(Brief recess.)

THE VIDEOGRAPHER: We are back on the record at 3:55 p.m.

(Exhibit 16-23, Draft publication, was marked for identification.)

BY MR. GRIFFIS:

Q I've marked as Exhibit 23 a draft of 2013 -- 2013 draft of updated data from the Agricultural Health Study; have you seen this before, sir?

A I have, yes. Thank you.

Q When did you see it?

A A few weeks ago.

Q And you saw it a few weeks ago because you

read about it in one of the depositions and asked for a copy?

MS. FORGIE: How did you know that?

A Well, I -- I knew about it because Aaron Blair was questioned about it and then I did see it referenced in other depositions and I -- so then I asked for a copy, yes.

BY MR. GRIFFIS:

Q The cancers assessed in the De Roos '05 April were done through December 31, '01, and these were in the 2013 data, they were assessed through December 31, 2008; did you see that when you reviewed these two papers?

A Yes.

Q It's another seven years of followup, correct?

A Correct.

Q 6.7 plus seven, even if we pay no attention to how long it was before initial questionnaires that people were initially exposed to glyphosate, would take us over your 10-year threshold for an effective epidemiology study on glyphosate and NHL, right?

MS. FORGIE: Objection.

A So I didn't -- I didn't give you any threshold, but it would -- it would put the followup

over 10 years.

Q Well, you told us that 6.7 was too short and you thought more than 10 would be too long and you couldn't tell us more specifically in between those two, right?

MS. FORGIE: Objection, mischaracterizes his testimony.

A I didn't give you any threshold.

BY MR. GRIFFIS:

Q So what is the --

A Other than 6.7 is too short and 10 would probably be a minimum number.

Q So 6.7 plus another seven is also too short?

MS. FORGIE: Objection, asked and answered. You can answer it again.

A Well, I don't know. I mean it's better than 6.7. It's longer than 10.

BY MR. GRIFFIS:

Q Do you feel that the data in the 2013 draft is immature and has too short a followup time?

MS. FORGIE: Objection.

A No, but there are other issues with this manuscript which are problematic.

BY MR. GRIFFIS:

Q Okay. The followup time is no longer a criticism?

MS. FORGIE: Objection.

A The followup time is better, much better, okay.

BY MR. GRIFFIS:

Q It's a much larger cohort than the De Roos 2005, right, as far as number of cases?

A Yes.

MS. FORGIE: Objection.

A Yes.

BY MR. GRIFFIS:

Q And the people in the study are older, people in the cohort are older in the status which addresses your concern about average age of 45-year-old applicators, correct?

MS. FORGIE: Objection.

A Right, but they're still pretty young.

BY MR. GRIFFIS:

Q They're in a much better age range with the 2013 data than they were with the De Roos 2005 data, right?

A Yes.

MS. FORGIE: Objection, asked and answered.

BY MR. GRIFFIS:

Q Okay. Sir, go to page 31, please. I'm going to show you some data tables and each time I'm going to take you to the first page of the table so we can see what it is and then the part of the table that has glyphosate data.

So on page 31, we have Table 2, which is pesticide exposure, lifetime days and intensity weighted lifetime days and the age adjusted risk of NHL, correct?

A Yes.

Q And if you go to page 34, you see the glyphosate data there?

A Yes.

Q And first of all, you see that there were 250 -- 89 plus 78 plus 83 -- cases with exposure to glyphosate in the various exposure groups, correct?

MS. FORGIE: Objection.

A Correct.

BY MR. GRIFFIS:

Q And do you see that in each case, there is no significant trend and no P value even above one in the data showing any sort of association between glyphosate and Non-Hodgkin's Lymphoma in this data, correct?

A That's correct.

Q That's true for all of the dosage groups, correct?

A Yes.

Q Go to page 36, Table 3. This shows exposure, lifetime days and the age adjusted risk of NHL.

And this time it's breaking down by Non-Hodgkin's Lymphoma type, correct?

MS. FORGIE: Objection.

A Here it says "lifetime days."

BY MR. GRIFFIS:

Q Are you on page 36, Table 3?

A Yes.

Q So lifetime days -- yes, sir, lifetime days.

But it's broken down by NHL subtype, right?

A Correct.

Q If you go to page 39, there are no statistically significant positive associations for any NHL subtype in these data, correct?

A That's correct.

Q And the P trend for diffuse large B-cell lymphoma is actually statistically significant negative, right?

MS. FORGIE: Objection.

A That's correct.

BY MR. GRIFFIS:

Q Page 53, this table is showing -- wait for you to get there.

A Yes.

Q Page 53, this table is showing pesticide exposures, total days and intensity weighted total days, fully adjusted of NHL, '92 through 2008.

And glyphosate data is presented on page 59, and again, there are no statistically significant associations in these data, correct?

MS. FORGIE: Objection.

A So how is this different from the first table we looked at?

BY MR. GRIFFIS:

Q These are -- these have confounder adjustments.

MS. FORGIE: Objection. I object to his statement. There's more to it than that.

A So where is the --

BY MR. GRIFFIS:

Q Glyphosate data?

A Yeah.

Q On page 59.

A Okay.

Q So my statement is correct, there are no statistically significant associations, positive associations in these data, correct?

MS. FORGIE: Objection.

A That's correct.

BY MR. GRIFFIS:

Q And to cut short the flipping through additional tables, you looked through these data tables and you found no statistically significant positive associations between glyphosate and Non-Hodgkin's Lymphoma in these data, correct?

A That's correct.

Q What are your criticisms of the 2013 AHS data?

A Well, I think the main criticism is that when they administered the followup questionnaire, 37 percent of the participants failed to respond, so they had a large number of participants that dropped out of the study. And so there are two approaches on how to deal with that; one is to just analyze the data for the other 63 percent, but that would result in a significant -- potential significant selection bias because you don't know what the exposures of the 37 percent would have been.

The other issue is that instead, they

decided to imputate, in effect guess, what the exposures would have been for that 37 percent. And that's a very questionable approach to the missing data because they're basing data on participants that they do have data on and they're basing the data on the fact that participants with the missing data are assumed to have continued to use glyphosate.

And another significant criticism is that right about this time, around 1996, the usage of glyphosate took off and began to go up at about a 45-degree angle. And they don't really capture much of that at all in this -- in this analysis. So the issue of significant people dropping out of the study with no data and imputating the data, or guessing what the data was, I think is a major problem with this manuscript and is probably one of the reasons why this manuscript hasn't gone anywhere.

Q Do you have any other criticisms besides the two that you identified?

A I think those are the major criticisms.

Q Did you come up with those two criticisms by your own analysis of this study or from looking at some work from other persons?

MS. FORGIE: Objection.

A Well, part of it was from my own analysis

and part of it was from reading the rebuttal written by Dr. Ritz who provided a much more detailed and sophisticated explanation than I have.

Q Yes, sir. Dr. Ritz, of course, is an epidemiologist?

A Yes.

Q Do you feel qualified to assess the imputation methodology that was used in the study and critique it or are you really relying on Dr. Ritz for that?

MS. FORGIE: Objection, asked and answered.

A I'm relying on her assessment.

BY MR. GRIFFIS:

Q Okay. And with regard to the increase in usage on glyphosate and whether -- it would be necessary for there to be a differential between the cases and the controls for the increase in glyphosate use to cause a relevant fuzzing of the statistics; is that fair to say?

MS. FORGIE: Objection.

A Say it again.

BY MR. GRIFFIS:

Q Yes, sir. It would be necessary for there to be a differential in increased glyphosate used between cases and controls for that to alter the

statistics in a study, right?

MS. FORGIE: Objection.

A No, it would -- most likely what would happen is they have nondifferential -- you don't -- first of all, you don't know what the real values are for a significant proportion of the participants and the methodology they use would have created a nondifferential misclassification which would have made it -- which would have lowered any risk ratios towards the null. So it's a major problem with this -- with this updated manuscript.

BY MR. GRIFFIS:

Q Same question as for your first criticism, are you assessing the nondifferential bias that you say may exist from increase use of glyphosate using your own epidemiological expertise or are you mostly relying on Dr. Ritz's analysis from her supplemental expert report?

MS. FORGIE: Asked and answered.

A I'm relying on my expertise.

BY MR. GRIFFIS:

Q And the -- is it your position, sir, that epidemiology can't be done anymore because so many people are exposed to glyphosate?

MS. FORGIE: Objection.

A It's my opinion that this is -- this has become a very flawed study due to loss of participants, that it is probably never going to be able to provide relevant results with regard to glyphosate.

BY MR. GRIFFIS:

Q I was asking about the other criticisms, sir, not that one, increasing glyphosate use.

A I'm sorry, ask your question. I must have been thinking ahead of you. I'm sorry.

Q Yes, sir. Is it your view that increased glyphosate use makes further epidemiology in the current era impossible because so many people are exposed?

MS. FORGIE: Objection.

A It makes it much more difficult to demonstrate differences, because in a study like this, you need to have enough unexposed participants to compare to the exposed participants. And if the majority, 70, 80 percent of the participants are exposed, it makes it more difficult to do the study because you need a much larger number of participants to get enough contrast in the exposures to see any difference.

BY MR. GRIFFIS:

Q Do you know, sir, that some data from -- not involving glyphosate, but involving other substances, was published in 2014 from this later data collection?
A Yes.
Q And that included what was published despite the dropout issue that you identified as your first criticism?
A Yes, but in that study, the imputation was likely more accurate because although we don't really know, it's a guesstimate there too, but it's likely more accurate because they had -- because of the pretty level use of the various different pesticides. In other words, you didn't have this dramatic increase in those pesticides like we know occurred for glyphosate.
Q Would you support the submission of this data for publication as something important for people to know about?
MS. FORGIE: Objection, speculation.
A I think they should -- I think they should publish it, but I think, you know, if it has adequate and critical peer review, it may not be accepted.
BY MR. GRIFFIS:
Q You saw Dr. Blair's testimony in his

deposition that he and the other authors discussed publishing it in advance of IARC so that IARC could review it and thought it would be important for IARC to review it; you saw his testimony saying that?
MS. FORGIE: Objection, mischaracterizes the testimony.
A I don't remember exactly what was -- I don't remember that from his -- from his deposition. If you want to show it to me, I'd be happy to see it, but I don't remember that specifically.
BY MR. GRIFFIS:
Q You don't remember them discussing the possibility of publishing it before IARC?
A I don't remember that.
Q Do you remember that he testified at his deposition that he didn't tell anyone at IARC about this data that he knew about?
MS. FORGIE: Objection, mischaracterizes the testimony.
A I think it was generally known that there was data out there.
BY MR. GRIFFIS:
Q You think it was generally known by the IARC participants that there was updated AHS data?
A That's what you do with cohort studies, you

update them periodically, so that's -- that's the natural evolution of reporting on cohort studies. So people knew the original cohort study was there and people, I think, were and have been waiting for followup publications. So I don't know what the IARC people knew or didn't know.
Q Do you know if they've even tried to have it published?
A I don't know that.
Q Do you know why?
A No.
Q You read Dr. Ritz's expert report, not supplemental, but expert report -- did you read her expert report?
A Yes.
Q Did you see she said the NAPP data should be considered in any analysis?
A I think once the NAPP data is published, it could be -- it could be included in a meta-analysis, yes. But prior to having it published, I would say no.
Q And you know that Dr. Blair testified -- if you read his deposition, did you see he testified if the NAPP data were included in a meta-analysis, the risk would have been nonsignificant?

MS. FORGIE: Objection, mischaracterizes his testimony.
A I don't think we know that until it's actually done. It wouldn't surprise me actually because it's the same data that's already in the meta-analysis, right? You're taking the NAPP and putting it in and taking the De Roos 2003 and the McDuffie out, so you're basically putting -- you're basically putting the same data back into the meta-analysis.
BY MR. GRIFFIS:
Q There are analyses and tranches of data reported in the NAPP data that don't show up at all in De Roos '03.
MS. FORGIE: There's no question.
Q Correct?
MS. FORGIE: Objection.
A The NAPP includes De Roos 2003 and the McDuffie --
Q McDuffie.
A -- groups. So it's -- you're really not changing the data very much.
Q For example, the combined data of intensity by year and by number of days of use during the year, that's new, it wasn't reported in McDuffie or in De

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Roos '03, right?
MS. FORGIE: Objection.
A That's true, that's new data that would contribute to a meta-analysis, but I doubt whether it would take the odds ratios down. It would keep them the same or even increase them because it's the same basic data.
BY MR. GRIFFIS:
Q When we say --
A But you have to do the analysis. It's hard to sort of guess what the results would be without doing it.
Q Why haven't the NAPP data been published yet?
MS. FORGIE: Objection, calls for speculation.
A Well, I wish I had the answer to that. It's been slow and methodical. As you know, I've been pushing hard to get it published and it's slow and methodical.
BY MR. GRIFFIS:
Q You don't know the reason for the holdup?
MS. FORGIE: Objection, asked and answered. You can answer it again.
A I don't. It's been slow and methodical.

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BY MR. GRIFFIS:
Q Do you know whether the AHS data is suffering from the same mysterious slowdowns?
MS. FORGIE: Objection.
A I don't know. I don't think so, but I don't know.
BY MR. GRIFFIS:
Q In your expert report, sir, the section on animal studies, it starts on page 6.
A Yes.
Q You say, "glyphosate has also been tested for carcinogenicity in mice and rats in multiple studies," and you give some sites, "and some studies have been positive for the development of tumors," right?
A Yes.
Q And what you mean by positive is statistically significant associations found for particular tumors in particular studies, right?
A Yes.
Q And as we've discussed, if a study looks at multiple end points, like dozens of cancers in a group of animals, about one out of 20 of those associations are going to be positive in any particular study, right?

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MS. FORGIE: Objection.
A That's possible.
BY MR. GRIFFIS:
Q That's true by the play of chance alone, it's a math thing, not a science thing?
A Right.
MS. FORGIE: Objection.
BY MR. GRIFFIS:
Q So it's really important to look at whether the number of associations exceeds the number that you would expect due to chance, whether the associations that you see are consistent across animal species, whether they're consistent across males and females, whether they're consistent with the tissues targeted, et cetera, correct?
MS. FORGIE: Objection, speculation.
A All of those things are important to consider, yes.
BY MR. GRIFFIS:
Q And none of those analyses appear in your expert report; is that fair?
A I think they do. I mean, I comment on whether things were statistically significant or not. I discuss whether they were males or females or both. What are the other issues that you brought

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up?
Q Whether the same associations are found across multiple studies.
A So I comment on that in my closing remarks on Bradford Hill.
Q And I think that might have been it. Do you say, in your section on animal studies, we have seen the consistent results targeting similar tissues in mice and in rats, in males and in females across multiple studies?
MS. FORGIE: Objection, asked and answered. You can answer it again.
A Well, yes, if you read through the animal studies, you'll see I do comment on that.
BY MR. GRIFFIS:
Q Show me where.
A So --
MS. FORGIE: You mean other than what he's already pointed out?
MR. GRIFFIS: He hasn't pointed out anything yet.
Q Show me where, please.
MS. FORGIE: Objection.
A Well, there -- you know, there is -- so for example, probably the best example is the lymphoma

studies on page 7, in the middle paragraph, where you see, in one study, lymphomas in both males and female mice. In another study, you see it in males, another study you see it in males and another study you see it in females. So, I mean, that's probably the best example.

Most of the tumors occurred in males and not in females. But there was -- and so I -- I summarized where there was a consistency in the -- under the Bradford Hill Criteria for replication of results where I say animal studies are replicated, the findings for pancreatic islet cell adenoma, cellular adenoma, hemangioma, hemangioma sarcoma and malignant lymphoma. And actually, there a couple other ones that were also replicated when I reviewed the more detailed toxicology studies of Portier and Jameson, T-cell tumors of the thyroid were replicated and kidney tumors were replicated.

Q You said the studies; do you mean the expert reports of Portier and Jameson?

A Yes, the expert reports of Portier and Jameson.

Q Are you relying on their expert reports for their --

A Yes, I am. It was something -- they

reviewed -- they reviewed the actual animal studies. I was limited, like IARC, to reviewing summaries of the studies, either from IARC or from EPA or from the EFSA or -- yeah, so those are the sources that I used to compile what I found.

Q Did you see in Dr. Portier's deposition that he said that the pooling methodology that he applied to malignant lymphomas did not work and did not show a significant trend when he applied it to 24-month studies as opposed to the 18-month studies?

MS. FORGIE: Objection. He didn't read that.

A His report?

BY MR. GRIFFIS:

Q His deposition.

Did you tell me earlier you read his deposition?

A That was a mistake. I didn't read his deposition.

Q You don't know what he said about his pooling results and what they didn't show in his deposition?

A No.

Q If he said the various things that he said in his expert report were not so in his deposition,

that would undermine your reliance on the expert report; would that be fair to say?

MS. FORGIE: Objection, mischaracterizes the deposition of Portier and -- well, I won't make a speaking objection, but you might want to ask him about timing of when he read things.

A So I'm mainly relying on my own evaluation of the published reports that I had in hand.

BY MR. GRIFFIS:

Q Okay. Now, you also said a little earlier, sir, that you didn't have available to you original animal data and that IARC also didn't have available to it original animal data.

Did you read the Greim paper?

MS. FORGIE: Objection.

A I did and I referenced it and I actually discussed it in my report.

BY MR. GRIFFIS:

Q Did you look at the raw data that was provided, the original data that was provided along with the Greim paper?

A The Greim, no, I did not.

Q That was available online, as it says in the Greim paper, and it's still available online and always available online since the Greim paper was

published; did you know that?

A Yes, I did.

Q Did you look at it?

A No, I did not.

Q And did you read, in the depositions of Dr. Blair and Dr. Ross and others who participated in IARC, that the Greim data was -- that they could have looked at it if they had chosen to, but it was too voluminous and they chose not to look at it?

MS. FORGIE: Objection, mischaracterizes the testimony.

A From the IARC report, what they said is it wasn't published in a peer-reviewed journal and it wasn't reviewed by another regulatory agency, so by their rules that IARC has, they would not review it and do an independent analysis. So I'm not -- I'm not sure what you said is true.

Q Okay.

A I'm not sure. Maybe you should rephrase it or ask me again.

Q Well, you may not be the right person to know about the details of IARC's procedures, and tell me if you're not, but do you know that IARC has a rule that if something as incorrect as Greim was at the time of the IARC review, they will review it?

MS. FORGIE: Objection.
A If they knew about it.
BY MR. GRIFFIS:
Q And do you know that they admitted that they knew about it, it was in their hands and there's e-mails proving it?
MS. FORGIE: Objection, mischaracterizes.
A I'm not privy to what happened at IARC.
BY MR. GRIFFIS:
Q Well, whatever happened at IARC and whatever their rules are, is it your rule that you won't look at animal data that's provided in an electronic annex along with the published article like the Greim report?
MS. FORGIE: Objection.
A I would probably rely on someone who -- like Portier or Jameson or somebody else who has more experience in doing this than I do.
BY MR. GRIFFIS:
Q Fair enough. So knowing that Dr. Portier, maybe Dr. Jameson have looked at that data and analyzed it and have more experience, you wouldn't look at the raw data yourself, you would rely on what they have done; is that fair?
MS. FORGIE: Objection.

A I probably wouldn't, no. I think, based on what's already been published in the review articles and in the analyses that IARC did and that EPA did and that EFSA did and the German group did, I mean -- and -- and in the reports of Jameson and Portier, there's an abundance of evidence, which I sort of listed here, that I'd like to say reduces tumors of various types in rats and mice. And there's some consistency in that. It was reproduced more than once, twice, three times for some tumors.
Q Sir, you don't have any problem philosophically with unpublished as opposed to published data, do you?
MS. FORGIE: Objection.
A I personally think that all data that's considered should be published and peer reviewed.
BY MR. GRIFFIS:
Q What do you mean "all data that's considered"?
A That's considered in any kind of evaluation like this, that's considered by the EPA, by IARC, by anybody. The data should be publicly available, peer reviewed and available for anybody to analyze and that has not been the case.
Q Okay, sir. I want to understand why you

have that view.
Is it because you think that that sort of data should be transparent to the general public and scientists so that anyone can look at it or you think that data that is unpublished is of a low quality, and therefore, shouldn't be looked at by regulators?
MS. FORGIE: Object to form.
A No, I think all the data should be looked at by regulators and judged based on its quality. And I think probably for the most part it is high quality, but one cannot know unless one has the opportunity to review it.
BY MR. GRIFFIS:
Q Okay. Well, when you said that all data that is looked at by EPA and by regulators should be published, why do you say that?
A Well, because then it would be publicly available. Then I could sit down and evaluate it, if I wanted to, or somebody like Portier could sit down and evaluate it or other regulatory agencies could sit down and evaluate it. If it's not publicly available, it -- you can't evaluate it for quality and you can't make up your own mind about, you know, what does the data really show, were the analyses done by the company pathologist, by the company

biostatisticians correct.
Q I know it's getting late and you're a little tired, but I want to be clear about this.
The reason that you say that all this data should be made public isn't because of -- isn't because the process of making it public improves its quality so much as you think that all such data should be available so that anyone who wants to can see, it's an open access sort of --
A Yes.
MS. FORGIE: Objection, mischaracterizes his prior testimony.
A There should be total transparency.
BY MR. GRIFFIS:
Q Okay. You understand, sir, that regulators very frequently do make decisions based on largely an unpublished data, correct?
MS. FORGIE: Objection.
A That's been the tradition, but I -- I think that transparency is a much better approach to this.
Q And -- late for me too. Take a few minutes.
MS. FORGIE: For all of us.
THE WITNESS: Are we taking a break?
MR. GRIFFIS: Sure.

THE WITNESS: Can I grab a coffee?
MR. GRIFFIS: Yeah, let's make it like two rather than 10 minutes.
THE VIDEOGRAPHER: Off the record at 4:34 p.m. This marks the end of Videotape Number 3 in the deposition of Dr. Dennis Weisenburger.
(Brief recess.)
THE VIDEOGRAPHER: We are back on the record at 4:39 p.m. This marks the beginning of Videotape Number 4 in the deposition of Dr. Dennis Weisenburger.
BY MR. GRIFFIS:
Q Sir, I'm looking at your expert report on pages 8 through 10, "mechanisms of carcinogenesis," and you describe several different kinds of studies here and the first is human in vivo genotox and then in vitro studies and then some studies in in vivo, in vitro mammals and other organisms, animals and plants both.
Which category is the most important and most relevant to assessing whether glyphosate can cause Non-Hodgkin's Lymphoma?
MS. FORGIE: Objection.
A For me, the most relevant is the studies done to humans, human cells, in mammals, in mammal

cells --
Q All right. And of those, which is the most important --
MS. FORGIE: Are you finished?
A And other living organisms.
BY MR. GRIFFIS:
Q What did you leave out? Was it without a rank order or was that just listing everything?
A It was sort of a rank order.
Q So the most important is in living humans, right?
MS. FORGIE: Objection, asked and answered. You can answer it again.
A The most important is in humans and mammals, in vivo and in vitro. And then other, how do you say it, other in vivo studies, non-mammals.
BY MR. GRIFFIS:
Q That's another rank of everything?
A Yes.
Q Of everything?
A More or less.
Q You say on page 8, the first two things you talked about are the Paz-y-Mino 2007 and Bolognesi 09 studies and you say they are particularly informative with regard to the genotoxicity of these chemicals in

humans in your expert report, right?
A Yes.
Q What do you mean by "particularly informative"?
A Well, they're both studies of workers and other people who were exposed to glyphosate that was sprayed. And in the first study, the exposures were quite high, perhaps like you would see in an animal study, and in the second study the exposures were lower. And in both cases, they saw significant increases in genotoxicity in cells of the humans who were exposed. So for me, this is strong evidence that the formulations that they were exposed to were genotoxic.
(Exhibit 16-24, article, was marked for identification.)
MR. GRIFFIS: That's Exhibit 24, right?
THE WITNESS: 24.
BY MR. GRIFFIS:
Q Exhibit 24, sir, is the Paz-y-Mino 2007 study. And the study reports the results of something called a comet assay test looking at blood samples from 24 individuals living in Ecuador near the Columbian border and comparing that to individuals in a control group not living near the

border, right?
A Yes.
Q Do you know where the controlled population lived?
A They lived in an area that wasn't sprayed with glyphosate. I'll see if they give more details to that. Unexposed control group consisted of 21 unrelated, healthy individuals living 80 kilometers away from the spraying area, similar exposed group, et cetera.
Q Where are you reading?
A It's top of 258, first paragraph on the left.
Q 258?
A I'm sorry, 458, third page.
Q They're similar to the exposed group regarding demographic characteristics and occupation, but were not matched controls, correct?
A Yes.
MS. FORGIE: Objection.
BY MR. GRIFFIS:
Q That's what it says, right?
A That's what it says.
Q And do you know if they had differences in income levels?

A No.
Q Do you know if they had differences in access to sanitation like indoor plumbing?
A No.
Q Do you know if they have differences in the degree to which they were urban or rural?
A Well, they were matched for demographic characteristics, so I'm assuming there was some matching. They don't give you the details, but urban and rural would fit into that category.
Q You consider urban and rural a demographic characteristic?
A Yes.
Q Do you know whether they match that?
A No.
Q Do you agree the differences in sanitation, like indoor plumbing, housing, income levels, et cetera, could affect general health and background level of genotoxicity?
MS. FORGIE: Objection.
A I don't know that without more specifics.
BY MR. GRIFFIS:
Q The only demographic information they give us about the cases and controls in the study in Table 1 are the gender and age, correct?

MS. FORGIE: Objection, mischaracterizes what he just said.
A They give the gender and age. In the next paragraph actually below the one we were just on, it says "neither the exposed or the control group smoked tobacco, drank alcohol, took prescription drugs or had been exposed to pesticides during the course of their normal daily lives and mainly worked at home, cultivating and harvesting crops, pesticides, other herbal substances" and then named activities. So it sounds like they were matched for activities and other -- other things that could affect genotoxicity studies.
Q It says --
A It doesn't say how they were matched, but it sounds like they were similar.
Q It says they were not matched controls in the previous paragraph, right?
A Right.
MS. FORGIE: Objection.
BY MR. GRIFFIS:
Q What's a matched control?
A Well, a matched control, it depends on what you match on. Usually you match at a minimum on age and sex, but you could match on many things.

Q The study population, the people living near the border who were sprayed were complaining of multiple acute illnesses, correct?
A Yes.
Q Page 457, left-hand column, intestinal pain and vomiting, diarrhea, fever, heart palpitations, headaches, dizziness, numbness, insomnia, sadness, burning of eyes or skin, blurred vision, difficulty in breathing, blisters or rash, correct?
A Correct.
Q And they didn't match controls for suffering from those symptoms or for level of illness, correct?
MS. FORGIE: Objection.
A No, because I think many of those symptoms were due to the pesticides that they were sprayed with.
BY MR. GRIFFIS:
Q Having intestinal pain and vomiting, having diarrhea, having heart palpitations, having systemic complaints significant enough to cause clinical symptoms can itself cause genotoxicity and occupational stress; is that right?
MS. FORGIE: Objection.
A Severe stress could do that, yes.

BY MR. GRIFFIS:
Q And whatever illnesses that they were suffering from, which you don't know, were due to pesticides could do that as well, right?
MS. FORGIE: Objection, asked and answered.
A It's very likely the illnesses were due to pesticides -- due to the sprayed pesticides.
BY MR. GRIFFIS:
Q And if genotoxicity was secondary to the symptoms that they were showing and not primarily caused by the pesticides, it would be not evidence of glyphosate-induced genotoxicity, right?
MS. FORGIE: Objection.
A Well, it would be hard for me to believe that any of these symptoms would cause enough oxidative stress to produce the kinds of measurable changes we saw in genotoxicity in this study. It would be hard for me to believe.
BY MR. GRIFFIS:
Q Do you know the degree to which systemic illness causes oxidative stress?
MS. FORGIE: Objection.
A It does increase the oxidative stress, but by and large, the body can deal with the oxidative stress that's -- that's generated from things like

that unless it's -- unless it's chronic oxidative -- chronic illness that causes increased oxidative stress. I'm talking in generalities though.
BY MR. GRIFFIS:
Q Yes, sir. Oxidative stress is damage to DNA caused by reactive oxidative species, correct?
MS. FORGIE: Objection.
A Well, oxidative stress is the physiologic term for the process that generates the free radicals, but otherwise what you said is true, yes.
BY MR. GRIFFIS:
Q The reason that we care about oxidative stress with regard to glyphosate is because the hypothesis has been generated that oxidative stress is a mechanism by which glyphosate can damage DNA and ultimately lead to cancer; is that right?
MS. FORGIE: Objection.
A Oxidative stress is one mechanism, another is direct genotoxicity.
BY MR. GRIFFIS:
Q Yes, sir, I'm talking about oxidative stress.
A Okay.
Q That's the hypothesis, right, that oxidative stress can cause damage to DNA, which after

an additional specific of events can potentially lead to cancer; is that right?
MS. FORGIE: Objection, asked and answered.
A That's one hypothesis.
BY MR. GRIFFIS:
Q Are there other hypotheses about how glyphosate, through oxidative stress, could cause cancer?
A No, through oxidative stress, that is the hypothesis.
Q And oxidative stress is something that's going on all the time in every cell in our body whether we're exposed to glyphosate or other substances or not, correct?
A That's right.
Q There are up to 10 thousand or more DNA lesions per cell throughout our body per day due to oxidative stress, correct?
MS. FORGIE: Objection.
A I don't know if that's correct. It's common and it occurs in all of us.
BY MR. GRIFFIS:
Q That number doesn't surprise you?
A It does surprise me, but it could be true.
Q Many lesions per cell, would that surprise

you, per day?
MS. FORGIE: Objection, speculation.
A Again, I don't know the answer to that. There would be -- if there was that much -- if there was that much stress, there probably would be many lesions. The good thing about it is the body has ways to compensate and either heal the lesions or the cell dies.
BY MR. GRIFFIS:
Q Too many lesions in DNA can be dealt with by the body in multiple ways by DNA repair which is going on all the time in every cell in our bodies, correct?
A Correct.
MS. FORGIE: Objection.
BY MR. GRIFFIS:
Q By various actions taken to remove a damaged cell from circulation being eaten by other cells or programmed to just die on its own, for example, correct?
MS. FORGIE: Objection.
A Yes.
BY MR. GRIFFIS:
Q And even if a DNA lesion survives and is reproduced, it would be necessary for it to be the

right kind of lesion to cause changes in the cell that are stable and lead to cells either to become immortal or to reproduce itself at a disproportionate rate in order for it to cause cancer; is that right?
MS. FORGIE: Objection.
A It would require one or more changes to have that kind, yes.
BY MR. GRIFFIS:
Q There are multiple steps in the process, right?
MS. FORGIE: Objection.
A Yes.
BY MR. GRIFFIS:
Q Our body has very robust mechanisms to make sure that cells don't become carcinogenic even if exposed to genotoxic substances or oxidative stressors, right?
MS. FORGIE: Objection.
A That's true.
BY MR. GRIFFIS:
Q It's only when those mechanisms are overwhelmed that we have a problem, right?
MS. FORGIE: Objection.
A Or fail.
BY MR. GRIFFIS:

Q Blood samples are -- on page 458 in your 2007 study -- blood samples were collected and processed from the controls, but not at the same time as the blood samples that were collected and processed in the exposed group, right?
MS. FORGIE: Objection.
BY MR. GRIFFIS:
Q I'm in the very first paragraph on page 458.
A Yeah. Blood samples were collected and processed as per the exposed group, but not concommonly.
Q You mean not at the same time, correct?
A Correct.
Q So we don't know if blood samples were drawn during the same kind of season with the same exposure to ultraviolet light during a sunny season versus a rainy season, et cetera, correct?
MS. FORGIE: Objection.
A We don't know that.
BY MR. GRIFFIS:
Q If blood samples from the exposed group were frozen, that would be an improper methodology for comet assay samples, correct?
MS. FORGIE: Objection.

A I don't know the answer to that question.
BY MR. GRIFFIS:
Q Okay. Have you done comet assays yourself?
A No.
Q So you don't know whether it would be a violation of methodology to freeze samples from the controls and not freeze samples from the -- I'm sorry, freeze samples from the exposed group and not freeze samples from the controls?
MS. FORGIE: Objection, asked and answered.
A Typically when you do a study, you want to handle the samples the same way. So I don't know whether it would affect the results, in some assays it doesn't and some assays it does, so you would have to know that. And I don't know that.
BY MR. GRIFFIS:
Q Right. The spray that was involved in the study, sir -- I'm on the first page -- was Roundup Ultra and Cosmo-Flux 411F, correct?
A Trying to see where you're at -- there it is. Yeah, POEA and Cosmo-Flux 411F.
Q And it says that's a proprietary Columbian component, right?
A Yes.
Q Do you know if Cosmo-Flux 411F is

genotoxic?
A I do not.
Q Do you know what's in it?
A No.
Q Do you know how long a comet assay can detect DNA damage purportedly caused by specific exposure?
A How long -- how long after the exposure?
Q Yeah.
A As long as the DNA damage is there, it can detect it.
Q Do you know how long DNA damage would remain without either being repaired or eliminated from the body?
MS. FORGIE: Objection.
A DNA damage can be repaired, it can be eliminated or it can persist.
BY MR. GRIFFIS:
Q Do you know how much DNA damage can persist months after an exposure?
MS. FORGIE: Objection, asked and answered. You can answer it again.
A No, but if the cells are -- don't repair it and it's not significant enough to kill the cell, then the cells can divide and proliferate and they

can carry the lesion and that can occur -- that can occur. That's how cancers develop.
Q So the only cells that would still be around a couple of months after an exposure would be cells that are proliferating with the genetic defect in them; is that right?
MS. FORGIE: Objection.
A That's true.
BY MR. GRIFFIS:
Q And that would be a whole lot fewer than the cells that were initially damaged; is that right?
MS. FORGIE: Objection.
A It would depend entirely on what their proliferate advantage would be.
BY MR. GRIFFIS:
Q Is there any indication that the investigators that were scoring the comet assay were blinded as to the scoring samples?
A I don't know. I would have to read the methods to tell you that. I don't remember.
MS. FORGIE: Do you want him to read the paper?
MR. GRIFFIS: No. I want to take pity on our court reporter.
BY MR. GRIFFIS:

Q If they weren't blinded, then that would be a flaw; is that right?
MS. FORGIE: Objection.
A Yes, they should be blinded.
BY MR. GRIFFIS:
Q And if it doesn't say they were blinded in here, you don't know whether they were or not; is that fair?
A That's fair.
Q Table 1 shows the data that was collected, correct?
MS. FORGIE: The data that was what? I didn't hear.
MR. GRIFFIS: Collected.
A Yes.
BY MR. GRIFFIS:
Q And in the final scoring, the median length of the comet assays in all but one of the 21 controlled subjects was identical, right, 25.0?
A Yes.
Q Which was not the case in the exposed glyphosate group, right?
A Yes.
Q That's virtually impossible for the median in 21, 20 different people to be identical in a comet

assay, right?
MS. FORGIE: Objection.
A They aren't identical. There's one that's higher. That might be the minimal level they measure at.
BY MR. GRIFFIS:
Q It says median, right?
MS. FORGIE: Objection, asked and answered.
A If it was the minimal level and they were all the same, then the median level would be the minimum, right.
BY MR. GRIFFIS:
Q So they were all 25 or shorter, 25 or longer, what?
A I don't know. I don't know -- I don't know why that has occurred. They don't comment on it in the papers I remember, but it might be the -- it might be the lower level of detection. I don't know.
Q Have you done comet assays so you know whether there is a lower limited detection?
A I have not done comet assays, no. But all the other values in the exposed are higher than 25 which would tell me that 25 is probably the lower limit of detection.
Q That's your guess, right?

MS. FORGIE: Objection.
A That's a guess.
BY MR. GRIFFIS:
Q Now, Dr. Paz-y-Mino performed a second study of people exposed to glyphosate containing compounds near the Columbian border, correct?
A Yes.
Q And have you reviewed that study?
A Yes.
Q When did you review it, sir? It wasn't listed in your report.
A Yeah, it was listed in my -- either in my other papers reviewed or maybe more in my -- or in the more recent list that you have. I can't remember where it's listed.
Q Okay. You didn't describe it in the body of your expert report or cite it there?
A No, I didn't rely on it; I didn't.
Q Why not?
A Because I didn't think it was useful.
(Exhibit 16-25, article, was marked for identification.)
BY MR. GRIFFIS:
Q This is a study in which the investigators from the first -- some of the investigators from the

first study looked at -- looked for geno -- indications of genotoxicity based on blood samples of people sprayed with glyphosate containing compounds near the Columbian border, right?
A Yes.
Q They say in the abstract -- this is near the end of the abstract -- "in conclusion, the study population did not present significant chromosomal and DNA alterations," correct?
A Correct.
Q They were looking for chromosomal fragmentation in karyotypes which is a step farther up the chain than genotoxicity, right?
MS. FORGIE: Objection.
A Yeah, it's a more specific assay.
BY MR. GRIFFIS:
Q Genotoxicity that it's going to lead to cancer is going to move through higher phases like that, like cause chromosomal damage, not just spot damage to detected --
A Correct.
Q So genotoxicity can be assessed at various levels at the very early stages of the process, damage occurring to the DNA and at higher levels looking at whether there's damage to chromosomes,

whether damage is persisting and being replicated, et cetera, right?
A Correct.
Q And they say at the end here several -- I'm sorry, I'm on page 50, the last paragraph of the study.
A Okay.
Q Several research studies related to glyphosate exposure have been conducted in Columbia, by Bolognesi, et al., and that's actually referring to one of the studies that you cited in your expert report?
A Correct.
Q Solomon, et al. And which stated the publications have low geotoxic risk associated with glyphosate, correct?
A That was --
MS. FORGIE: Objection.
A That was the conclusion of some of the studies, yes.
BY MR. GRIFFIS:
Q Regarding our study, you obtained results showing no chromosomal in the analyzed individuals?
A Right.
Q This is a negative study on the issue of

genotoxicity in the study that causes --
A Yes, this was a study done two years later. So I would be very surprised to see abnormalities in chromosomes or DNA alterations two years later unless the patients had cancer or something. So this is a long time after the exposure.
Q For genotoxicity, for genotoxic exposure to cause cancer it has to persist and they found no persistence in the study, right?
MS. FORGIE: Objection.
A It's a small sample size. I would say for the vast majority of us, the -- the damage is repaired and doesn't persist. So it's not surprising they didn't find anything. This is what I would have predicted.
Q And you recall from the Bolognesi study, which you also cite in your expert report, that they concluded in 2011 that the genotoxic risk potentially associated with exposure to glyphosate in areas where it is applied on it and was low, that was their conclusion, right?
MS. FORGIE: Objection.
A I'd like to see the conclusion but I --
Q Towards the end of the abstract, sir.
(Exhibit 16-26, article, was marked for

identification.)
MS. FORGIE: Is that a new exhibit?
THE WITNESS: Yeah, 26.
MS. FORGIE: Do you have another copy?
A That was their conclusion. The basis of that conclusion is kind of unclear.
BY MR. GRIFFIS:
Q They say, sir, in the abstract, overall data suggests that genotoxic damage associated with glyphosate as evidenced by small -- and appears to be transient, correct?
A Yes.
Q And they go on to say, potentially associated to glyphosate in areas where herbicide is applied is low, correct?
A That's what they say.
Q A little higher in the abstract, the increase in frequency of BMNN, that was one of their measures of genotoxicity, right?
A Yes.
Q Observed immediately after the glyphosate spraying was not consistent with the rates of application used in the regions and there was no association between self-reported direct contact with eradication sprays and frequency of BMNN, correct?

A That's what they say, but it's actually contradicted in another area where they actually contradict themselves. So again, it was a bit -- bit confusing.
Q It said in multiple places that greater -- I'm sorry, that there -- that the rates of BMNN that they observed was not consistent with rates of application used in the regions, correct?
MS. FORGIE: Objection.
A Yeah, but the other statement is the one I'm questioning.
Q That no significant association between self-reported direct contact and frequency of BMNN?
A Right. Unfortunately I don't know where they say that here.
Q Take a look at page 994, sir, right-hand column, the last full paragraph, second to last paragraph. There was no significant association between self-reported direct contact with eradication sprays and frequency of BMNN. The frequency of BMNN and participants who self-reported because they entered the field immediately after spraying to pick the copa leaves, felt spray drops in their skin who thought they were exposed was not significantly greater than folks living in the same areas who were

not present during spraying; that's what they reported, right?
A Right.
MR. GRIFFIS: What's our time?
THE VIDEOGRAPHER: 5:40.
MR. GRIFFIS: I'm going to pause for a minute.
THE VIDEOGRAPHER: Off the record at 5:13 p.m.
(Brief recess.)
THE VIDEOGRAPHER: We are back on the record at 5:18 p.m.
MR. GRIFFIS: Dr. Weisenburger, during the break, I was told that we have used 5 hours and 40 minutes of deposition time of seven hours, default under the federal rules. Because we have identified multiple areas of documents, including the documents that you had told us about that you had relied on yesterday -- this is going to be another one of those statements that don't require you to say anything, sir. There were multiple documents that you provided to us only yesterday for which we have not had time to even acquire the relevant documents in this location or review them or prepared to ask you questions about them for which you originally provided information about which ones you

considered important enough to put into that expert report. But that information is lost to us by the manner in which they were presented to us.
And the identification of multiple documents that reflect other areas of interest to us, such as drafts of NAPP study, e-mails with the authors of those studies, et cetera, things that were requested in the document production request and not produced, I'm going to reserve the remainder of my time to return and question you about those matters and forego a good deal of questioning I could do otherwise on remaining areas of your expert report, we feel that the newly disclosed and identified stuff that we can't get into today because we don't have it at all or because it was so recently disclosed is more important.
So I'm going to stop at this time and suspend my questioning of you at this time. There will probably have to be motions practice as to circumstances of our return, but I'll have an hour and 20 minutes. Turn it over to you.
MS. FORGIE: Yeah. And, of course, we don't agree with any of that. We are producing him today. We are prepared to complete the deposition and go forward in the other hour and 20 minutes and I highly intend that you do.

MR. GRIFFIS: I can do that only if you provided me with all the documents we asked for.
MS. FORGIE: We're not going to argue. We're going to take a two-minute break because we may have a few questions to ask.
THE VIDEOGRAPHER: We are off the record at 5:21 p.m.
(Brief recess.)
THE VIDEOGRAPHER: We are back on the record at 5:31 p.m.

EXAMINATION

BY MS. FORGIE:
Q Doctor, I have just a few questions for you.
You were asked some questions about expert work you have done for defendants in the past; do you remember those questions?
A Yes.
Q And have you reviewed literature for defendants with regard to asbestos and whether or not asbestos is a risk factor for Non-Hodgkin's Lymphoma?
A Yes, I've handled quite a number of cases alleging that asbestos causes Non-Hodgkin's Lymphoma and my position has always been that asbestos does

not increase the risk or cause Non-Hodgkin's Lymphoma.
Q And you gave those opinions to defendants, is that correct, defendant's lawyers?
A Yes.
Q You mentioned that you had read the expert's -- had read the expert report of Dr. Portier; do you remember that testimony?
A Yes.
Q And you also mentioned that you read the expert report of Dr. Jameson; do you remember that testimony?
A Yes.
Q Did you read those reports before or after you wrote your expert report?
A After -- after I wrote my report. Actually, I read them just recently.
Q But after you wrote your own report?
A Yes.
Q So you couldn't have relied on those reports in forming -- in drafting your report since you read them afterwards, correct?
MR. GRIFFIS: Objection, leading.
A That's correct.
Q With regard to your criticisms of the draft

manuscript of unpublished -- of the unpublished health study, you relied upon your review of the drafts in making your criticisms about the imputation of exposure data given the increased use of glyphosate; is that correct?

MR. GRIFFIS: Objection, leading.

A That's correct.

Q And you only relied upon the Ritz rebuttal report to confirm your opinion; is that correct?

MR. GRIFFIS: Objection, leading contrary to his testimony.

A Yes.

Q You were asked numerous questions about the NAPP study and the draft manuscripts of the NAPP study; do you remember those questions?

A Yes.

Q Do you recall if the NAPP study made a breakdown of odds ratios for people who used glyphosate for more than two days per year?

A Yes.

Q Do you remember approximately the odds ratio for people in the NAPP study for people who used glyphosate for more than two days per year?

A Yes, it was approximately two -- twofold increase and that was -- it was statistically

significant and had been adjusted for the other three pesticides.

Q Okay. And was that data presented in one of the slide shows that are publicly available in connection with the NAPP study?

A Yes.

Q Did you provide me any draft manuscripts of the NAPP study?

A No.

Q Why is that?

A Because it wouldn't have been ethical or correct or academically correct.

Q Why is that?

A Well, because it's -- it's -- can't think of the terminology. It's -- it's not academic practice to make preliminary publications available for public use.

Q Okay. And you were asked -- you provided additional studies to me that -- the day after Labor Day and then I provided them to the defense; do you remember that testimony?

A Yes.

MR. GRIFFIS: Objection, counsel's testifying.

MS. FORGIE: I'd love to, but I can't.

BY MS. FORGIE:

Q Where any of those additional studies necessary to your expert report?

A No.

Q And do any of those additional studies change any of the opinions that were expressed in your expert report?

A No.

MS. FORGIE: I don't have anything else.

RE-EXAMINATION

BY MR. GRIFFIS:

Q Did you discuss the content of any of these questions during the break just now?

MS. FORGIE: Objection, don't answer that. That's privileged.

MR. GRIFFIS: Questioning on a break during a deposition is privileged?

MS. FORGIE: Yeah, any discussions between us are privileged, you know, both by agreement and by the rules.

MR. GRIFFIS: No further questions.

MS. FORGIE: Thank you.

THE VIDEOGRAPHER: This concludes today's proceedings of Dr. Dennis Weisenburger. The total

number of videotapes used today was four and we're off the record at 5:36 p.m.

STATE OF CALIFORNIA)
) ss
COUNTY OF LOS ANGELES)

I, KATHERINE FERGUSON, Certified Shorthand Reporter, for the State of California, do hereby certify:

That prior to being examined, the witness named in the foregoing deposition, was by me duly sworn to testify the truth, the whole truth and nothing but the truth;

That the testimony of the witness and all objections made at the time of the examination were recorded stenographically by me;

That the foregoing transcript is a true record of the testimony and all objections made at the time of the examination.

Before completion of the deposition, review of the transcript [x] was [ ] was not requested. If requested, any changes made by the deponent (and provided to the reporter) during the period allowed are appended hereto.

I hereby certify that I am not interested in the event of the action.

IN WITNESS WHEREOF, I have subscribed my name this 13th day of September, 2017.

____
Katherine Ferguson, CSR 12332

NAME OF CASE: In re: Roundup Products Liability Litigation
DATE OF DEPOSITION: 9/11/2017
NAME OF WITNESS: Dennis Weisenburger, M.D.
Reason Codes:
1. To clarify the record.
2. To conform to the facts.
3. To correct transcription errors.
Page ______ Line ______ Reason ______
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ANDRUS WAGSTAFF
ATTORNEYS AT LAW

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www.AndrusWagstaff.com
7171 W Alaska Drive
Lakewood, Colorado 80226
Office: (303) 376-6360
Fax: (303) 376-6361

RETENTION AGREEMENT
EXPERT OPINIONS AND TESTIMONY

SCOPE: This agreement is to retain the services of Dennis Dean Weisenburger, M.D., to perform services all in conjunction with litigation related to an herbicide known as "Roundup" and related products and ingredients. For the purpose of this agreement, professional services shall include, but not be limited to medical record review; medical literature review; document review; research and analysis; pathology review; report preparation and revision; telephonic and/or personal consultation with the attorney; testimony preparation; deposition and court testimony, whether live, recorded or telephonic. Attorneys agree to be respectful and considerate of Dr. Weisenburger's busy practice when scheduling expert work. Dr. Weisenburger agrees to keep all conversations with attorneys (whether telephonic, via email or in person), strictly confidential, and to keep any documents shared with Dr. Weisenburger equally confidential. Dr. Weisenburger agrees not to disclose any such documents at any time, even after the termination of the litigation. With regard to the Roundup litigation Dr. Weisenburger agrees not to work with other attorneys or litigants.

FEES: Invoices are payable upon receipt, and are not contingent upon the outcome of the legal matter. Fees are charged as follows:

1. Professional Time for Dr. Weisenburger $500 per hour
2. Expenses of Weisenburger will also be paid as separate matters. Payment will be made within 30 days of submission by Dr. Weisenburger.

RETAINER: Attorneys agree to pay Dr. Weisenburger a $5,000 retainer fee to be paid upon signature. Dr. Weisenburger will charge hours against this retainer fee until such time as the retainer fee is completely used, at which time, Dr. Weisenburger may request another retainer of $5,000 as needed.

Signature below indicates understanding and acceptance of the terms and conditions stated herein.

8/12/15
Date

Dennis Dean Weisenburger, M.D

8/11/15
Date

Kathryn M. Forgie, Esq.
Andrus Wagstaff, PC

EXHIBIT
16-1

11/23/15

Re: Glyphosate / Roundup

Dear Ms. Forgie:

Enclosed is a bill for services rendered to date:

8/6/15	0.5 hr.	11/15	4.0 hr.
8/8	2.0	11/21	2.0
8/13	4.0	11/22	7.0
8/14	0.5	11/23	1.0
9/19	1.0	total	22 hrs. @

$500/hr. = $13,200.

retainer − 5,000.

Due $ 8,200.

Thanks & best wishes!

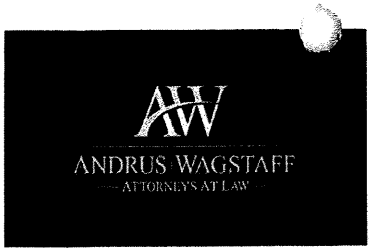
P.S. Please make the check out to me personally [redacted]

Dennis D. Weisenburger, M.D.

City of Hope

Dennis D. Weisenburger, M.D.
Chair, Department of Pathology
1500 East Duarte Road, Duarte, CA 91010-3000
[redacted]

ROUNDUP



Julie Kaye Wolf
Senior Staff Accountant
julie.wolf@andruswagstaff.com
AndrusWagstaff.com

7171 W Alaska Drive
Lakewood, Colorado 80226
Office: (303) 376-6360

Dr.Weisenburger,

Please find the enclosed check for your services in 2016. I added up the times for the dates written on your invoice. The hours on the invoice total 43 hours. Per Aimee Wagstaff's approval, I cut the check for the 43 hours instead of the 67.5 hours. If there are hours missing, please submit a second invoice. Thank you for your services. If you have any questions, please contact me at 303-376-6360.

Thank you,

Julie Kaye Wolf
Senior Staff Accountant

PER AIMEE 1/13/17

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12/11/16

Re. Glyphosate

Dear Ms. Fayre -

Enclosed is my bill for services rendered to date:

12/10/15	0.5 hr. ✓	9/23	0.5 hr. ✓
5/8/16	3.0 ✓	11/6	5.0 ✓
5/10	1.0 ✓	11/7	1.0 ✓
6/4	4.0 ✓	11/8	0.5 ✓
8/2	1.0 ✓	11/12	5.0 ✓
8/13	5.0 ✓	11/18	0.5 ✓
8/14	5.0 ✓	11/19	1.0 ✓
8/21	3.5 ✓	11/24	4.0 ✓
8/23	0.5 ✓	11/30	0.5 ✓
8/24	1.0 ✓	12/8	0.5 ✓

Total 67.5 hrs. @ $500. per hr. = $33,750. due

Please make the check payable to me personally [redacted].

Thanks & best wishes.

City of Hope

Dennis D. Weisenburger, M.D.
Chair, Department of Pathology
1500 East Duarte Road, Duarte, CA 91010-3000
[redacted]

12/11/16

Re. Glyphosate

Dear Ms. Fayne -

Enclosed is my bill for services rendered to date:

12/10/15	0.5 hr.	9/23	0.5 hr.
5/8/16	3.0	11/6	5.0
5/10	1.0	11/7	1.0
6/4	4.0	11/8	0.5
8/2	1.0	11/12	5.0
8/13	5.0	11/18	0.5
8/14	5.0	11/19	1.0
8/21	3.5	11/24	4.0
8/23	0.5	11/30	0.5
8/24	1.0	12/8	0.5

Total 67.5 hrs. @ $500. per hr. = $33,750. due

Please make the check payable to me personally [redacted].

Thanks & best wishes —

City of Hope

Dennis D. Weisenburger, M.D.
Chair, Department of Pathology
1500 East Duarte Road, Duarte, CA 91010-3000
[redacted]

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4/20/17

Dear Kathryn –

Enclosed is my final report, and bill for services to date = $68,750.

Please make the check out to me personally [redacted].

I look forward to continuing to work on this case with you.

Thanks

John Weisenburger M.D.

City of Hope

Dennis D. Weisenburger, M.D.
Chair, Department of Pathology

1500 East Duarte Road, Duarte, CA 91010-3000

[redacted]

Dennis D. Weisenburger, M.D. 4/20/17

Bill for Services:

1/14/17	5.0 hrs.	3/8	5.0 hrs.
1/15	6.0	3/9	1.0
1/18	1.0	3/17	2.0
1/19	1.0	3/18	1.0
1/20	3.0	3/20	1.5
1/21	4.5	3/25	8.5
1/24	1.5	3/26	8.0
1/25	1.0	3/27	1.0
1/28	1.5	3/28	1.5
2/3	0.5	3/30	1.0
2/5	7.5	3/31	1.0
2/6	1.5	4/1	8.0
2/7	3.0	4/2	3.0
2/8	0.5	4/3	1.5
2/9	1.0	4/4	1.0
2/10	3.0	4/6	1.5
2/11	10.0	4/8	2.0
2/12	5.0	4/11	1.5
2/18	7.0	4/13	2.5
2/19	2.0	4/17	1.5
2/25	7.5	4/18	0.5
2/26	4.0	4/9	1.0
3/3	1.0	Total hrs.	137.5
3/4	4.0		

Total hrs. 137.5 @ $500/hr. = $68,750.

UNITED STATES DISTRICT COURT

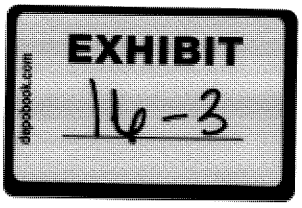
NORTHERN DISTRICT OF CALIFORNIA

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

IN RE: ROUNDUP PRODUCTS LIABILITY LITIGATION	MDL No. 2741 Case No. 16-md-02741-VC
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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

($p < 0.05$), but no significant dose-related trend and no increase in females. In another feeding study of Sprague-Dawley rats, IARC again found an increase in the incidence of pancreatic islet cell adenoma at all doses of glyphosate in males, with significant increases in the low-dose group ($p = 0.018$) and the high dose group ($p = 0.042$) but no significant dose-related trend, and no increase in females. In the same study, IARC also found a significant positive and dose-related trend in the incidence of hepatocellular adenoma in males ($p = 0.016$), and in thyroid follicular C-cell adenoma in females ($p = 0.031$).

In an industry-sponsored review (28) of industry studies in rodents, which were not available for review by IARC but were reviewed by EPA, the authors also found a significant increase in hepatocellular adenoma in male Wistar rats ($p = 0.028$) at the highest feeding dose in one study (study 7), and a significant dose-related trend in the incidence of these tumors ($p = 0.01$). In this same review, the authors also reported increases in malignant lymphoma (NHL), the same cancer seen in the human epidemiologic studies, in four mouse feeding studies. In study 13, they found a significant increase in lymphoma in the high-dose groups in both male and female Swiss albino mice compared to controls ($p < 0.05$). In study 14, a dose-related increase ($p = 0.01$) was seen in male but not female CD1 mice, whereas increases were seen in female CD1 mice (study 10) and in male ICD-CD-1 mice (study 12) at the highest feeding doses in the other two studies (p values not given).

In the EPA review of unpublished industry studies (18), the EPA found a significant increase in testicular interstitial cell tumors in male Sprague-Dawley rats at the highest dose ($p = 0.013$) in one study (study 1), with a significant dose-related trend ($p = 0.001$). In another study (study 8), they reported a significant increase ($p = 0.046$) in mammary gland tumors (adenoma and adenocarcinoma combined) at the highest dose in female Wistar rats, with a significant dose-related trend ($p = 0.01$). In a study of male CD1 mice (study 14), the EPA found an increase in lung adenocarcinoma with a significant dose-related trend ($p = 0.05$). In another study of SPF-ICR-CD-1 mice (study 12), they also reported a significant increase in hemangiomas in females at the highest dose ($p = 0.028$), with a dose-related trend ($p = 0.01$). I have read the three animal studies that were made available to me, and I concur with the above findings.

Despite these positive findings of carcinogenicity for glyphosate in multiple animal studies, industry and the EPA have continued to argue that glyphosate has no carcinogenic

potential based on other negative studies, and various methodologic, statistical and other issues (11, 14, 18, 28). However, the positive studies listed above cannot be dismissed, and provide sufficient evidence for the carcinogenicity of glyphosate in experimental animals despite these arguments.

Mechanisms of Carcinogenesis

The IARC Working Group (4) concluded that glyphosate and GBFs were genotoxic in various systems. They found that the mechanistic data overall provided strong evidence for genotoxicity and for oxidative stress induced by glyphosate, with evidence that these effects can also operate in humans.

Two studies of individuals living or working in areas sprayed with GBFs (29, 30) are particularly informative with regard to the genotoxicity of these chemicals in humans. In the first study (29), the authors used the comet assay to evaluate DNA damage in 24 persons exposed to aerial spray of a GBF, some of whom had symptoms of toxicity after several exposures, but who did not use other pesticides. The comet assay is a rapid and sensitive method for the detection of DNA damage induced in blood leukocytes *in vivo*. They found that the exposed group had a significant increase in DNA damage (DNA strand breaks) in blood leukocytes collected two weeks to two months after exposure compared to the unexposed controls ($p < 0.001$). In the other study (30), the authors used the blood lymphocyte micronucleus test as an index of chromosomal damage in 274 persons living in five regions of Columbia. This test is an appropriate biomarker for monitoring the effects of cumulative exposures to genotoxic agents. In the three regions with exposures to GBFs from aerial spraying, blood samples were taken from the same individuals at three time-points, before spraying (baseline), up to five days after spraying, and four months after spraying. The baseline frequency of binucleated cells with micronuclei was significantly higher in subjects from the three regions where there had been aerial spraying of GBFs, and in a fourth region with exposures due only to manual spraying of multiple pesticides, compared to the reference region without the use of pesticides ($p \leq 0.05$). The frequency of micronucleus formation in blood lymphocytes was further increased in the same individuals shortly after the aerial spraying of GBFs compared with the baseline levels in the same individuals ($p < 0.001$), and

remained significantly elevated in individuals from one of the three regions four months later. These two studies provide compelling evidence of genotoxic damage to blood cells (lymphocytes) in individuals exposed to GBFs in the immediate environment due to aerial spraying. These same assays have been used by others to monitor genetic damage in persons exposed to pesticides (31-33).

In vitro studies demonstrating the genotoxicity of glyphosate and GBFs in human blood lymphocytes using various assays have also been reported (34-40). Lioi et al (34) showed a significant dose-dependent increase in aberrant cells ($p < 0.05$) and chromosome aberrations ($p < 0.01$), as well as sister chromatid exchange frequencies per cell ($p < 0.05$), compared to controls, most likely due to oxidative stress and the generation of reactive oxygen species. In two studies, Mladinic et al (35, 36) demonstrated a significant increase in DNA strand breaks ($p < 0.01$) and chromosomal damage ($p < 0.01$), respectively, at the higher doses tested. Alvarez-Moya et al (37) also demonstrated a significant increase in DNA strand breaks ($p < 0.01$), even at very low concentrations. Manas et al (38) have also shown a significant increase in chromosomal aberrations ($p < 0.05$) with exposure to AMPA, an environmental metabolite of glyphosate. A significant increase in sister chromatid exchange frequency was also demonstrated for glyphosate and for Roundup ($p < 0.05$) by Bolognesi et al (39), with a dose-response effect seen for glyphosate, and 10-fold greater genotoxicity of Roundup compared to glyphosate. Vigfusson and Vyse (40) also found a significant increase in sister chromatid exchange frequency in human lymphocytes upon exposure to high concentrations of Roundup ($p < 0.001$).

Similar genotoxic effects have also been reported in other types of human cells tested *in vitro* with glyphosate, AMPA, or GBFs (4, 18). Genotoxic effects have also been reported in numerous studies of these chemicals in non-human mammalian cells *in vivo* and *in vitro*, including mouse bone marrow cells and bovine lymphocytes, as well as non-mammalian systems *in vivo* and *in vitro* (reviewed in 4, 18, 41). Thus, there is extensive evidence that glyphosate and GBFs are genotoxic to human and animal cells in numerous studies. IARC concluded that glyphosate and GBFs are genotoxic (4), and I concur with the IARC findings. However, industry-sponsored reviews (11, 15, 42, 43) and the EPA (18) have concluded that glyphosate and GBFs do not pose a genotoxic hazard, and explain away the positive findings in

the IARC assessment and their own analyses as due to technical or methodologic issues, or cytotoxicity rather than genotoxicity. The EPA and industry-sponsored studies also place undue weight on assays performed in bacteria, and on industry studies that were not available for review by IARC. I have placed greater weight on the two human biomonitoring studies (29, 30) and the many positive studies performed in mammalian systems, particularly human blood lymphocytes which are the cells from which NHL arises as a result of genetic damage.

Recent studies have shown that glyphosate and GBFs can have toxic effects on cells at doses below the regulatory limits (44, 45). For example, glyphosate provokes oxidative stress and cell damage in rat liver and kidneys by disrupting mitochondrial metabolism at exposure levels currently considered safe and acceptable by regulatory agencies (44, 45). Glyphosate and GBFs can also disrupt endocrine signaling in cells at low doses (44-46), induce human breast cancer cells to grow via estrogen receptors *in vitro* (47), and also induce breast tumors in female rats (48). GBFs can also alter the levels of xenobiotic-metabolizing enzymes (49) and affect cell cycle regulation (50, 51) at low doses, which are effects that can also contribute to carcinogenesis. Thus, these findings indicate that even low doses of these chemicals can have significant biological effects on living cells.

General Causation

In the evaluation of whether a specific exposure (glyphosate and GBFs in this case) is a cause of a specific disease (NHL in this case), experts follow a scientific method in the review and evaluation of evidence, and consider and weigh this evidence based on the guidelines set forth by Bradford Hill (52, 53). These guidelines or criteria for the evaluation of general causation are listed below along with my comments concerning this case.

1. **Temporal Relationship.** If an exposure causes a disease, the exposure must occur before the disease develops. This criteria was met by all of the epidemiologic and animal studies cited in this report.
2. **Strength of Association.** Relative risk is one of the cornerstones of causal inference. The higher the relative risk, the greater the likelihood that an exposure is causal. In the

epidemiologic case-control studies, relative risks of greater than 2.0 were seen in five of the six studies and were statistically significant in four of these studies (Table 1).

3. **Dose-response Relationship.** Generally, higher exposures should increase the frequency of disease, and a dose-response effect is considered strong evidence for a causal relationship. The two case-control studies in which a dose-response effect was evaluated (19, 22) showed significantly increased risks with an increased number of days that glyphosate was used. A dose-response effect was also seen in most of the positive animal studies.
4. **Replication of Results.** It is important that epidemiologic study results be replicated in different populations and by different investigators. Consistency of the findings in different studies is an important factor in making a judgement about causation. Five of the six case-control studies had positive findings for NHL, and these were performed by different investigators in the USA, Canada, Sweden, and six other countries in Europe. Only one study (23) with limited statistical power was negative. Animal studies have also replicated the findings for pancreatic islet cell adenoma, hepatocellular adenoma, hemangioma/hemangiosarcoma, and for malignant lymphoma (NHL).
5. **Biological Plausibility.** The association of an exposure with a disease should be consistent with existing knowledge and be biologically plausible. Human NHL is a disease characterized by genetic abnormalities. The occurrence of NHL in people exposed to GBFs is consistent with the genotoxic effects of these chemicals observed in exposed individuals, as well as in human and animal lymphocytes (the precursor cells of NHL), and in other animal and cell models. The fact that mice exposed to glyphosate also develop malignant lymphoma (NHL) contributes to biological plausibility.
6. **Alternative Explanations.** In assessing causation, experts should also consider alternative explanations for an association, such bias or confounding factors in epidemiologic studies. However, the case-control studies of NHL were performed by experienced epidemiologists using widely-accepted study designs and methods, were published in peer-reviewed journals, and were found acceptable for review and consideration by IARC and the EPA. In three of the five positive studies (20-22), the risk estimates for glyphosate were adjusted for the use of other pesticides but remained

elevated, suggesting that confounding due to the use of other pesticides does not fully explain the increased risk estimates for glyphosate. Also, in general, case-response bias tends to bias risk estimates toward the null and not create false-positive findings (54, 55). Thus, 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 possible methodological issues or the negative results of the immature Agricultural Health Study.

7. **Disease Specificity.** The only disease linked to glyphosate exposure to date is NHL, with negative findings for other hematopoietic malignancies including Hodgkin lymphoma, leukemia, and multiple myeloma, as well as negative findings for multiple other cancer types. Thus, glyphosate exposure causes a specific disease, namely NHL.
8. **Coherence.** The evidence described above is consistent with other relevant knowledge concerning similar pesticides as a cause of NHL. Glyphosate is an organophosphate herbicide, and other organophosphate pesticides have also been implicated as causes of NHL by similar mechanisms (8, 27, 56).

In summary, based on my expertise, and my review and evaluation of the literature on this subject, I conclude with a reasonable degree of medical certainty that glyphosate and GBFs (including Roundup) can cause NHL in humans exposed to these chemicals in the workplace or environment.

Dennis D. Weisenburger, M.D.
Professor and Chairman
Department of Pathology

Date: 4/21/17

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12. Solomon, K.R., *Glyphosate in the General Population and in Applicators: A Critical Review of Studies on Exposures.* Crit Rev Toxicol, 2016. 46(sup1): p. 21-27.
13. Acquavella, J., Garabrant, D., Marsh, G., Sorahan, T., and Weed, D.L., *Glyphosate Epidemiology Expert Panel Review: A Weight of Evidence Systematic Review of the Relationship between Glyphosate Exposure and Non-Hodgkin's Lymphoma or Multiple Myeloma.* Crit Rev Toxicol, 2016. 46(sup1): p. 28-43.
14. Williams, G.M., Berry, C., Burns, M., de Camargo, J.L., and Greim, H., *Glyphosate Rodent Carcinogenicity Bioassay Expert Panel Review.* Crit Rev Toxicol, 2016. 46(sup1): p. 44-55.

15. Brusick, D., Aardema, M., Kier, L., Kirkland, D., and Williams, G., *Genotoxicity Expert Panel Review: Weight of Evidence Evaluation of the Genotoxicity of Glyphosate, Glyphosate-Based Formulations, and Aminomethylphosphonic Acid.* Crit Rev Toxicol, 2016. 46(sup1): p. 56-74.

16. European Food Safety Authority (EFSA). *Conclusion on the Peer Review of the Pesticide Risk Assessment of the Active Substance Glyphosate.* EFSA Journal, 2015. 13(11): 4302, p. 1-107.

17. Rapporteur Member State (Germany). *Assessment of the IARC Monographics Volume 112 (2015): Glyphosate. Glyphosate Addendum I to Renewal Assessment Reprint, August 31, 2015.*

18. *Glyphosate Issue Paper: Evaluation of Carcinogenic Potential*, Environmental Protection Agency Office of Pesticide Programs, Editor September 12, 2016.

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31. Bolognesi, C., *Genotoxicity of Pesticides: A Review of Human Biomonitoring Studies.* Mutat Res, 2003. 543(3): p. 251-272.

32. Benedetti, D., Nunes, E., Sarmento, M., Porto, C., Dos Santos, C.E., Dias, J.F., and da Silva, J., *Genetic Damage in Soybean Workers Exposed to Pesticides: Evaluation with the Comet and Buccal Micronucleus Cytome Assays.* Mutat Res, 2013. 752(1-2): p. 28-33.

33. Bolognesi, C. and Holland, N., *The Use of the Lymphocyte Cytokinesis-Block Micronucleus Assay for Monitoring Pesticide-Exposed Populations.* Mutat Res, 2016. 770(Pt A): p. 183-203.

34. Lioi, M.B., Scarfi, M.R., Santoro, A., Barbieri, R., Zeni, O., Salvemini, F., Di Berardino, D., and Ursini, M.V., *Cytogenetic Damage and Induction of Pro-Oxidant State in Human Lymphocytes Exposed in Vitro to Gliphosate, Vinclozolin, Atrazine, and Dpx-E9636.* Environ Mol Mutagen, 1998. 32(1): p. 39-46.

35. Mladinic, M., Berend, S., Vrdoljak, A.L., Kopjar, N., Radic, B., and Zeljezic, D., *Evaluation of Genome Damage and Its Relation to Oxidative Stress Induced by Glyphosate in Human Lymphocytes in Vitro.* Environ Mol Mutagen, 2009. 50(9): p. 800-807.

36. Mladinic, M., Perkovic, P., and Zeljezic, D., *Characterization of Chromatin Instabilities Induced by Glyphosate, Terbuthylazine and Carbofuran Using Cytome Fish Assay.* Toxicol Lett, 2009. 189(2): p. 130-137.

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39. Bolognesi, C., Bonatti, S., Degan, P., Gallerani, E., Peluso, M., Rabboni, R., Roggieri, P., and Abbondandolo, A., *Genotoxic Activity of Glyphosate and Its Technical Formulation Roundup.* Journal of Agricultural and Food Chemistry, 1997. 45(5): p. 1957-1962.

40. Vigfusson, N.V. and Vyse, E.R., *The Effect of the Pesticides, Dexon, Captan and Roundup, on Sister-Chromatid Exchanges in Human Lymphocytes in Vitro.* Mutat Res, 1980. 79(1): p. 53-57.

41. Ghisi, N.d.C., Oliveira, E.C.d., and Prioli, A.J., *Does Exposure to Glyphosate Lead to an Increase in the Micronuclei Frequency? A Systematic and Meta-Analytic Review.* Chemosphere, 2016. 145: p. 42-54.

42. Kier, L.D. and Kirkland, D.J., *Review of Genotoxicity Studies of Glyphosate and Glyphosate-Based Formulations.* Crit Rev Toxicol, 2013. 43(4): p. 283-315.

43. Kier, L.D., *Review of Genotoxicity Biomonitoring Studies of Glyphosate-Based Formulations.* Crit Rev Toxicol, 2015. 45(3): p. 209-218.

44. Mesnage, R., Defarge, N., Spiroux de Vendomois, J., and Seralini, G.E., *Potential Toxic Effects of Glyphosate and Its Commercial Formulations Below Regulatory Limits.* Food Chem Toxicol, 2015. 84: p. 133-153.

45. Myers, J.P., Antoniou, M.N., Blumberg, B., Carroll, L., Colborn, T., Everett, L.G., Hansen, M., Landrigan, P.J., Lanphear, B.P., Mesnage, R., Vandenberg, L.N., Vom Saal, F.S., Welshons, W.V., and Benbrook, C.M., *Concerns over Use of Glyphosate-Based Herbicides and Risks Associated with Exposures: A Consensus Statement.* Environ Health, 2016. 15: p. 19.

46. Gasnier, C., Dumont, C., Benachour, N., Clair, E., Chagnon, M.C., and Seralini, G.E., *Glyphosate-Based Herbicides Are Toxic and Endocrine Disruptors in Human Cell Lines.* Toxicology, 2009. 262(3): p. 184-191.

47. Thongprakaisang, S., Thiantanawat, A., Rangkadilok, N., Suriyo, T., and Satayavivad, J., *Glyphosate Induces Human Breast Cancer Cells Growth Via Estrogen Receptors.* Food Chem Toxicol, 2013. 59(1): p. 129-136.

48. Seralini, G.E., Clair, E., Mesnage, R., Gress, S., Defarge, N., Malatesta, M., Hennequin, D., and de Vendomois, J.S., *Republished Study: Long-Term Toxicity of a Roundup Herbicide and a Roundup-Tolerant Genetically Modified Maize.* Environ Sci Eur, 2014. 26(1): p. 14.

49. Larsen, K., Najle, R., Lifschitz, A., Mate, M.L., Lanusse, C., and Virkel, G.L., *Effects of Sublethal Exposure to a Glyphosate-Based Herbicide Formulation on Metabolic Activities of Different Xenobiotic-Metabolizing Enzymes in Rats.* Int J Toxicol, 2014. 33(4): p. 307-318.

50. Marc, J., Mulner-Lorillon, O., and Belle, R., *Glyphosate-Based Pesticides Affect Cell Cycle Regulation.* Biol Cell, 2004. 96(3): p. 245-249.

51. Marc, J., Belle, R., Morales, J., Cormier, P., and Mulner-Lorillon, O., *Formulated Glyphosate Activates the DNA-Response Checkpoint of the Cell Cycle Leading to the Prevention of G2/M Transition.* Toxicol Sci, 2004. 82(2): p. 436-442.

52. Hill, A.B., *The Environment and Disease: Association or Causation?* Proceedings of the Royal Society of Medicine, 1965. 58(5): p. 295-300.

53. Green, M.D., Freedman, D.M., and Gordis, L., *Reference Guide on Epidemiology In: Reference Manual on Scientific Evidence: Third Edition.* The National Academies Press, 2011: p. 597-606.

54. Blair, A. and Zahm, S.H., *Patterns of Pesticide Use among Farmers: Implications for Epidemiologic Research.* Epidemiology, 1993. 4(1): p. 55-62.

55. Blair, A., Tarone, R., Sandler, D., Lynch, C.F., Rowland, A., Wintersteen, W., Steen, W.C., Samanic, C., Dosemeci, M., and Alavanja, M.C., *Reliability of Reporting on Life-Style and Agricultural Factors by a Sample of Participants in the Agricultural Health Study from Iowa.* Epidemiology, 2002. 13(1): p. 94-99.

56. Lukaszewicz-Hussain, A., *Role of Oxidative Stress in Organophosphate Insecticide Toxicity – Short Review.* Pesticide Biochemistry and Physiology, 2010. 98(2): p. 145-150.

EXHIBIT A

Dennis Weisenburger, MD - MC

CURRICULUM VITAE

DENNIS D. WEISENBURGER, MD

Professor and Chairman, Department of Pathology
City of Hope National Medical Center
1500 E. Duarte Road
Duarte, CA 91010
[redacted]

Date Prepared: April 2017

I. EDUCATION

University	University of North Dakota, Grand Forks, ND, BA (General), Honors, 1970
University	University of North Dakota, Grand Forks, ND, BS (Medicine), Honor, 1972
Medical School	University of Minnesota, Minneapolis, MN, MD, 1974

II. POST GRADUATE EDUCATION AND TRAINING

Internship	Ohio State University Hospitals (Internal Medicine), Columbus, OH, 07/74-06/75
Residency	University of Iowa Hospitals (Anatomic and Clinical Pathology), Iowa City, IA, 07/75-12/78
Fellowship	City of Hope National Medical Center (Hematopathology), Duarte, CA, 01/79-12/80

CERTIFICATIONS

- National Board of Medical Examiners, 1977
- Anatomic and Clinical Pathology, American Board of Pathology, 1979

MEDICAL LICENSURES

- MD-20612, Iowa, 1977, Active
- 16584, Nebraska, 1984, Active
- G38421, California, 2012, Active

III. PROFESSIONAL EXPERIENCE, POSITIONS & EMPLOYMENT Separate faculty appointments from other administrative, hospital or industry appointments and program affiliations

Hospital Appointments

Assistant Pathologist, City of Hope National Medical Center, Duarte, CA, 1981
Staff Pathologist, Mercy San Juan and American River Hospitals, Carmichael, CA, 1981-1984

Academic Appointments

Assistant Clinical Professor of Pathology, University of California at Davis Medical Center, 1981-1984

(Submitted: April, 14, 2017)

Associate Professor of Pathology & Microbiology, University of Nebraska Medical Center, 1984-1988
Director of Hematopathology
Chief Pathologist, Nebraska Lymphoma Study Group
Director of Hematopathology Fellowship Program, 1984-1988
Director of University Hospital Clinical Laboratories, 1986-1988
Director of Bone Marrow Culture Laboratory, 1984-1989
Director of University Hospital Regional Reference Laboratory, 1984-1987
Professor of Pathology & Microbiology, University of Nebraska Medical Center, 1988-2012
Director of Hematopathology
Chief Pathologist, Nebraska Lymphoma Study Group
Director of Hematopathology Fellowship Program, 1988-2011
Director of University Hospital Clinical Laboratories, 1988-1996
Professor and Chairman, Department of Pathology, City of Hope National Medical Center, 2012-present
Program Member, Hematologic Malignancies, City of Hope Comprehensive Cancer Center

Clinical Administrative Appointments

- See above

Other Professional Activities

Associate Professor Courtesy, Eppley Institute for Research in Cancer and Allied Diseases, 1985-1988
Graduate College Faculty Fellow, University of Nebraska Medical Center, 1985-2012
Consulting Pathologist, Omaha Veterans Administration Hospital, 1985-1993, 1997-2000
Consulting Pathologist, Nebraska Department of Health Laboratory, 1987-1989
Professor Courtesy, Eppley Institute for Research in Cancer and Allied Diseases, 1988-2012
Consulting Pathologist, North American Autologous Blood and Bone Marrow Transplant Registry, 1994-2012
Consulting Pathologist, Cancer and Leukemia Study Group B, 1996-1999
Member, Lymphoma and Pathology Core Committees, 1996-1999
Co-chair, Correlative Sciences Core Committee for Leukemia/Lymphoma, 1997-1998
Member, Center for Environmental Health and Toxicology, University of Nebraska, 1998-2012
NCI Leukemia, Lymphoma, and Myeloma Progress Review Group, 2000
NCI AIDS-related Malignancy Tissue Bank Review Group, 2000-2010
Lymphoma Foundation of America Scientific Review Panel, 2000-present
International Consortium of Investigators Working on Lymphoma Epidemiologic Studies, 2001-present (InterLymph); Chair, Pathology Working Group, 2001-2014
Member, Center for Research in Leukemia and Lymphoma, University of Nebraska, 2004-2012
Member, Center for Molecular Genetics and Genomics, University of Nebraska, 2007-2012
Advisory Board, Lugano International Conference on Malignant Lymphoma, 2009-2013

IV. National Honors, Scholarships and Awards Honors and Awards

1970	Phi Beta Kappa, University of North Dakota
1970	Grey Gown Award, University of North Dakota
1972	Pathology Award, University of North Dakota Medical School
1985	Alexander von Humbolt Fellowship
1994	Groundwater Foundation Special Recognition Award for Research
1996-1998	Best Doctors in America, Central Region
2000-present	America's Top Doctors/Medical Specialists
2001-present	Best Doctors in America
2004	Alpha Omega Alpha, University of Nebraska

2005-2008	Visiting Professor, China Three Gorges University
2005-2008	Visiting Professor, Hubei Province Cancer Hospital
2006	Milton R. Hales Lecture in Pathology, West Virginia University School of Medicine
2006-present	Who's Who in Science and Engineering
2006-present	American Men and Women of Science
2008	UNeMED Research Innovation Award
2008	UNMC Distinguished Scientist
2011	John J. Kepes Lectures in Pathology, Kansas City Society of Pathologists
2012, 2016	UNMC Innovation Award for Patent
2016	Distinguished Lecturer, Sylvester Comprehensive Cancer Center, University of Miami

V. CLINICAL ACTIVITIES

- See above

VI. SERVICE TO INSTITUTION

Administrative Service

Committee Assignments at University of Nebraska Medical Center:

1984-1985	Departmental Education Committee
1985-1987	Departmental Laboratory Computer Committee
1985-1987	University Hospital Computer Committee
1985-1998	Departmental Administrative Committee
1986-1996	Chairman, Clinical Laboratory Quality Assurance Committee
1985-1989	Deans Scholastic Evaluation Committee
1986	Deans Ad Hoc Committee on Tenure
1986-1987	Deans Ad Hoc Committee for selection of Obstetrics/Gynecology Chairman
1988-1989	Deans Ad Hoc Committee for selection of Biostatistics/Epidemiology Chairman
1988-1990	Intercampus Water Quality Advisory Committee for Governor's Research Initiatives
1988-1992	Chairman (1989), Departmental Promotion and Tenure Committee
1988-1989	Chancellors Ad Hoc Committee for selection of Director of Eppley Institute
1989-1990	Nursing Staffing Patterns Task Force
1988-1996	University Medical Associates (UMA) Ambulatory Affairs Committee
1988-1992	Chairman, UMA Ancillary Diagnostic Standards Committee
1989-1991	UMA Clinic Policies and Procedures Committee
1989-1992	Board of Directors, Professional Fees Office, Nebraska Clinicians Group
1990-1993	Chairman, Clinical Laboratory Service Excellence Committee
1991	Chancellor's Ad Hoc Subcommittee on Total Quality Management
1991	Chairman, Deans Ad Hoc Committee for selection of Water Center Toxicologist
1991-1992	American Board of Pathology, Hematology Committee
1991-1999	A. Ross McIntyre Awards Selection Committee
1992-1996	Chairman, Hospital Quality Assurance Committee for Ancillary Laboratory Testing
1993-1996	Hospital Quality Assurance and Improvement Committee
1993-1994	Clinical Laboratory Quality Monitoring Team
1994	University of Nebraska Medical Center Leadership Institute
1994-1995	University Hospital Consortium Laboratory Strategic Benchmarking Committee

1996-1997	Chairman, Departmental Promotion and Tenure Committee
1996-1997	Campus Committee for Selection of Director of Molecular Genetics
1997-2003	Cancer Center Membership Committee
1997-2012	Associate Director, Cancer Center Tissue Procurement Core Facility Committee
2002-2003	Campus Comprehensive Space Planning and Analysis Group
2002-2003	Campus Research Development Board
2002-2004	Departmental Promotion and Tenure Committee, Chairman 2002-2003,
2003-2011	College of Medicine Graduate Medical Education Committee
2004-2007	Chairman, Departmental Grand Rounds Committee
2004-2012	Executive Committee, Center for Research in Leukemia and Lymphoma
2008	Chairman, Departmental Workload Committee

Committee Assignments at City of Hope Medical Center:

2012-present	Committee of Chairs
2012-present	Medical Group Board of Directors
2012-present	Cancer Center Leadership Council
2012-2013	Chairman, Tissue Biorepository Initiative
2013-present	Chairman, City of Hope Biorepository Committee
2014-present	Director, Cancer Center Pathology Core Cluster Shared Resource
2015	Committee for Selection of Chair of Medical Oncology
2015-2016	Laboratory Information System Steering Committee
2015-present	Lymphoma Clinical Database Committee
2015-present	Lymphoma Center Investigator Committee
2015-present	ORIEN Steering Committee
2016-present	Clinical Laboratory Test Utilization Committee
2016-present	Precision Medicine Working Group

Teaching Service

- Director of Hematopathology Fellowship Program, University of Nebraska Medical Center, 1984-2011
- Hematopathology and general pathology for medical students, residents, and fellows, University of Nebraska Medical Center, 1984-2011

Other Research Mentoring Activities/Committees

- N/A

VII. SERVICE TO PROFESSION

Professional Organizations

National/International
American Association for Cancer Research, 1984-present
American Society of Clinical Pathologists, 1984-present
Member, Council on Hematology, 1994-2000
American Society for Hematology, 1984-present
College of American Pathologists, 1984-present
European Association for Haematopathology, 1984-present
Society for Hematopathology, 1984-present

	Member, Executive Committee, 1995-1999
	United States and Canadian Academy of Pathology, 1984-present
Regional/Local	Los Angeles Society of Pathologists, 2012-present
Government Activities	N/A
NIH Study Section	N/A
Editorships	N/A
Editorial Boards	Modern Pathology, 1990-2007 Clinical Lymphoma, Myeloma, and Leukemia, 2000-present Journal of Oncology 2008-2009 The European Journal of Clinical and Medical Oncology, 2009-present World Journal of Clinical Oncology, 2010-present Blood and Lymphatic Cancer: Targets and Therapy, 2010- present Journal of Epidemiology and Public Health, 2016-present Clinics in Oncology, 2016-present
Journal Reviews	American Journal of Clinical Pathology; American Journal of Gastroenterology; American Journal of Hematology; American Journal of Pathology; Annals of Hematology; Annals of Internal Medicine; Annals of Oncology; Blood; Bone Marrow Transplantation; Cancer; Cancer Causes and Control; Digestive Diseases; Environmental Health Perspectives; European Journal of Cancer; Human Pathology; International Journal of Cancer; Journal of Clinical Oncology; Laboratory Investigation; Leukemia; Leukemia and Lymphoma; Leukemia Research; New England Journal of Medicine.
Grant Reviews	N/A
Community Service	Nebraska Environmental Control Council (Governor's appointment), 1987-1989 Professional Education Committee, American Cancer Society, Nebraska Division, 1986-1989 Advisory Committee on Cancer Prevention and Control, Nebraska Department of Health, 1987-1995 Nebraska Cancer Registry Advisory Committee, Nebraska Department of Health, 1989-2011 Board of Directors, American Cancer Society, Nebraska Division, 1990-1992 Board of Directors, AAA Center for Pregnancy Counseling, 2004-2012

Other:

Symposia	N/A
Sessions Chaired	N/A
Consultantships	N/A

VIII. Grants/Research Support

ACTIVE GRANTS

- N/A

PENDING GRANTS/RESEARCH SUPPORT

- N/A

(Submitted: April, 14, 2017)

COMPLETED GRANTS/RESEARCH SUPPORT

- N/A

IX. Publications

Publications (peer-reviewed), 425 Total

1. Weisenburger, D.D., O'Conner, M.L., and Hart, M.N., Thrombotic Thrombocytopenic Purpura with C'3 Vascular Deposits: Report of a Case. Am J Clin Pathol, 1977. 67(1): p. 61-63.

2. Rankin, W.E., Hart, M.N., and Weisenburger, D.D., Thrombotic Thrombocytopenic Purpura in a Child with Alexander's Disease. Arch Pathol Lab Med, 1977. 101(12): p. 655-657.

3. Weisenburger, D., Armitage, J., and Dick, F., Immunoblastic Lymphadenopathy with Pulmonary Infiltrates, Hypocomplementemia and Vasculitis. A Hyperimmune Syndrome. Am J Med, 1977. 63(6): p. 849-854.

4. Weisenburger, D.D., Interstitial Pneumonitis Associated with Azathioprine Therapy. Am J Clin Pathol, 1978. 69(2): p. 181-185.

5. Weisenburger, D.D., Immunoblastic Lymphadenopathy Associated with Methyldopa Therapy: A Case Report. Cancer, 1978. 42(5): p. 2322-2327.

6. Seibert JJ, Seibert RW, Weisenburger DD, Alsbrook W. Multiple Congenital Hemangiopericytomas of the Head and Neck. Laryngoscope 88:1006-1011, 1978.

7. Helms, C.M., Sturm, R.H., Viner, J.P., Weisenburger, D., Renner, E., and Rose, E., Legionnaires' Disease: A Case from Iowa. J Iowa Med Soc, 1978. 68(9): p. 311-317.

8. Weisenburger, D.D., DeGowin, R.L., Gibson, P., and Armitage, J.O., Remission of Giant Lymph Node Hyperplasia with Anemia after Radiotherapy. Cancer, 1979. 44(2): p. 457-462.

9. Weisenburger, D.D., Membranous Nephropathy. Its Association with Multicentric Angiofollicular Lymph Node Hyperplasia. Arch Pathol Lab Med, 1979. 103(11): p. 591-594.

10. Hunsicker, L.G., Shearer, T.P., Plattner, S.B., and Weisenburger, D., The Role of Monocytes in Serum Sickness Nephritis. J Exp Med, 1979. 150(3): p. 413-425.

11. Weisenburger, D.D., Acute Myelofibrosis Terminating as Acute Myeloblastic Leukemia. Am J Clin Pathol, 1980. 73(1): p. 128-132.

12. Weisenburger, D.D., Rappaport, H., Ahluwalia, M.S., Melvani, R., and Renner, E.D., Legionnaires' Disease. Am J Med, 1980. 69(3): p. 476-482.

13. Diamond, L.W., Bearman, R.M., Berry, P.K., Mills, B.J., Nathwani, B.N., Weisenburger, D.D., Winberg, C.D., Teplitz, R.L., and Rappaport, H., Prolymphocytic Leukemia: Flow Microfluorometric, Immunologic, and Cytogenetic Observations. Am J Hematol, 1980. 9(3): p. 319-330.

14. Helms, C.M., Viner, J.P., Renner, E.D., Chiu, L.C., and Weisenburger, D.D., Legionnaires' Disease among Pneumonias in Iowa (Fy 1972-1978). Epidemiologic and Clinical Features of 30 Sporadic Cases of L. Pneumophila Infection. Am J Med Sci, 1981. 281(1): p. 2-13.

(Submitted: April, 14, 2017)

15. Weisenburger, D.D., Helms, C.M., and Renner, E.D., Sporadic Legionnaires' Disease. A Pathologic Study of 23 Fatal Cases. Arch Pathol Lab Med, 1981. 105(3): p. 130-137.

16. Weisenburger, D.D., Nathwani, B.N., Diamond, L.W., Winberg, C.D., and Rappaport, H., Malignant Lymphoma, Intermediate Lymphocytic Type: A Clinicopathologic Study of 42 Cases. Cancer, 1981. 48(6): p. 1415-1425.

17. Diamond, L.W., Weisenburger, D.D., and Rappaport, H., The Relationship between Lymphocyte Nuclear Morphology and Cell Cycle Stage in Lymphoid Neoplasia. Am J Hematol, 1981. 11(2): p. 165-173.

18. Weisenburger, D.D., Kim, H., and Rappaport, H., Mantle-Zone Lymphoma: A Follicular Variant of Intermediate Lymphocytic Lymphoma. Cancer, 1982. 49(7): p. 1429-1438.

19. Weisenburger, D.D., Nathwani, B.N., Forman, S.J., and Rappaport, H., Noncutaneous Peripheral T-Cell Lymphoma Histologically Resembling Mycosis Fungoides. Cancer, 1982. 49(9): p. 1839-1847.

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569. Siddiqi T, Scuto A, Beumer JH, Song JY, Frankel P, Ruel C, Cobb J, Kiesel BF, Weisenburger DD, Kelly KR, Tuscano J, Popplewell L, Forman SJ, Piekarz R, and Newman EM, Results From a Phase 1 Study and Expanded Cohort of an Interrupted Dosing Schedule of the Aurora Kinase A Inhibitor MLN8237 Combined with Vorinostat in Lymphoid Malignancies. 57th ASH Annual Meeting, 2015.

570. Perry AM, Diebold J, MacLennan KA, Müller-Hermelink HK, Nathwani BN, Boilesen E, Bast M, Armitage JO, Weisenburger DD. Classification of Non-Hodgkin Lymphoma in Seven Geographic Regions Around the World: Review of 4539 Cases from the International Non-Hodgkin Lymphoma Classification Project. 57th ASH Annual Meeting, 2015.

571. Perry AM, Diebold J, MacLennan KA, Müller-Hermelink HK, Nathwani BN, Boilesen E, Bast M, Armitage JO, Weisenburger DD. Classification of Non-Hodgkin Lymphoma (NHL) in the Developing World: The International NHL Classification Project. Mod Pathol 29: 368A, 2016.

572. Low L, Song JY, Chen YY, Valle M, Weisenburger DD, Kim YS. Coexpression of MYC and BCL2 Proteins Identifies a Subset of Follicular Lymphoma that Undergoes Transformation to Diffuse Large B-cell Lymphoma and Correlates with Poor Survival. Mod Pathol 29: 360A, 2016.

573. Ameri MD, Wong JT, Low L, Chen YY, Weisenburger DD, Pillai R, Kim YS, Song JY. CXCR4 Expression in Follicular Lymphoma. Mod Pathol 29: 334A, 2016.

574. Mohanty A, Sandoval N, Das M, Amin H, Marcucci G, Pillai R, Weisenburger DD, Rosen ST, Pham LV, Ngo VN. Cyclin D1 Mutations Increase Protein Stability and Promote Ibrutinib Resistance in Mantle Cell Lymphoma. ASH Lymphoma Biology Meeting, 2016.

575. Perry AM, Diebold J, Nathwani BN, MacLennan KA, Müller-Hermelink HK, Bast M, Boilesen E, Armitage JO, Weisenburger DD. Classification of Non-Hodgkin Lymphoma in Seven Geographic Regions Around the World: Review of 4539 Cases from the International Non-Hodgkin Lymphoma Classification Project. InterLymph Annual Conference, 2016.

576. Herrera AF, Low A, Griffin GK, Mei M, Merryman R, Song J, Bedell V, Sun H, Paris T, Stiller T, Alyea E, Brown J, Budde E, Chen R, Chen YB, Chan WC, Cutler C, Davids M, Freeman A, Fisher D, Ho V, Jacobsen E, Jacobson C, Koreth J, LaCasce A, Murata-Collins J, Nademanee A, Nikiforow S, Palmer J, Pihan G, Pillai R, Siddiqi T, Sohani A, Popplewell L, Zain J, Kwak L, Weinstock D, Soiffer R, Antin J, Forman S, Weisenburger DD, Rodig S, Kim Y, Krishnan A, Armand P. Outcomes after Autologous and Allogenic Stem Cell Transplantation (SCT) in Diffuse Large B-cell Lymphoma (DLBCL) Patients with MYC/BCL2 Co-expression, Double-hit Lymphoma, or MYC Copy Gain. European Hematology Association Annual Meeting, 2016.

577. Harris SA, Presutti R, Kachuri L, Spinelli JJ, Pahwa M, Blair A, Zham SH, Cantor KP, Weisenburger DD, Pahwa P, McLaughlin JR, Dosman JA, Freeman LB. Pesticide Exposures and the Risk of Multiple Myeloma in Men: An Analysis of the North American Pooled Project (NAPP). 50th IARC Global Cancer Occurance, Causes and Avenues to Prevention Conference, 2016.

578. Pahwa M, Freeman LEB, Spinelli JJ, Blair A, Zahm SH, Cantor KP, Pahwa P, Dosman JA, McLaughlin JR, Weisenburger DD, Demers PA, Harris SA. A Detailed Assessment of Glyphosate Use and the Risks of Non-Hodgkin Lymphoma Overall and by Major Histological Subtypes: Findings from the North American Pooled Project (NAPP). 50th IARC Global Cancer Occurance, Causes and Avenues to Prevention Conference, 2016.

579. Harris SA, Musa R, Pahwa M, Kachuri L, Spinelli JJ, Blair A, Pahwa P, McLaughlin JR, Dosman JA, Zahm SH, Cantor KP, Weisenburger DD, Freeman LEB. An Evaluation of Potentially Carcinogenic Pesticides and the Risks of Non-Hodgkin Lymphoma and its Histological Subtypes: An Analysis of the North American Pooled Project (NAPP). 50th IARC Global Cancer Occurance, Causes and Avenues to Prevention Conference, 2016.

580. Kachuri L, Harris SA, Spinelli JJ, Blair A, Pahwa M, Zahm SH, Cantor KP, Weisenburger DD, Pahwa P, Dosman JA, McLaughlin JR, Demers PA, Freeman LEB. An Investigation of Organochlorine Insecticide Use and the Risks of Non-Hodgkin Lymphoma Subtypes: Findings from the North American Pooled Project (NAPP). 50th IARC Global Cancer Occurance, Causes and Avenues to Prevention Conference, 2016.

581. Latifovic L, Freeman LB, Spinelli JJ, Pahwa M, Blair A, Pahwa P, McLaughlin JR, Dosman JA, Zahm SH, Cantor KP, Weisenburger DD, Demers PA, Harris SA. Pesticide Use and the Risk of Hodgkin Lymphoma: Results from the North American Pooled Project (NAPP). 50th IARC Global Cancer Occurance, Causes and Avenues to Prevention Conference, 2016.

582. Perry A, Diebold J, Nathwani B, MacLennan K, Müller-Hermelink HK, Bast M, Boilesen E, Armitage J, Weisenburger D. Non-Hodgkin Lymphoma in the Developing World: Review of 4539 Cases from the International Non-Hodgkin Classification Project. 18th Meeting of the European Association for Haematopathology, 2016.

583. Gonzalez BR, Song J, Weisenburger D, Palmer J, Zain J, Rosen ST, Querfeld C. The Immune Checkpoint Receptors ICOS and PD1 in Mycosis Fungoides and Sezary Syndrome: Correlation with Disease and Outcome. 3rd World Congress of Cutaneous Lymphomas, 2016.

584. Mohanty A, Sandoval N, Das M, Amin HM, Marcucci G, Pillai R, Weisenburger DD, Rosen ST, Pham LV, Ngo VN. CCND1 Mutations Increase Protein Stability and Promote Ibrutinib Resistance in Mantle Cell Lymphoma. 58th ASH Annual Meeting, 2016.

585. Herrera AF, Song JY, Griffin GK, Nikolaenko L, Mei M, Bedell V, Dal Cin P, Pak C, Stiller T, Sun H, Alyea EP, Budde LE, Chen RW, Chen Y-B, Chan WC, Cutler CS, Ho VT, Koreth J, Krishnan A, Murata-Collins JL, Nikiforow S, Palmer JM, Pihan GA, Pillai R, Popplewell L, Rosen ST, Siddiqi T, Sohani AR, Zain J, Kwak LW, Weisenburger DD, Nademanee AP, Weinstock DM, Soiffer RJ, Antin JH, Kim Y, Rodig SJ, Forman SJ, and Armand P, Double-Hit and Double-Expressor Lymphomas Are Not Associated with an Adverse Outcome after Allogeneic Stem Cell Transplantation. 58th ASH Annual Meeting, 2016.

586. Bouska A, Bi C, Lone W, Zhang W, Kedwaii A, Heavican TB, Lachel CM, Yu J, Fu K, Ferro RA, Eldorghamy N, Greiner TC, Vose JM, Weisenburger DD, Gascoyne RD, Rosenwald A, Ott G, Campo E, Rimsza LM, Jaffe ES, Braziel RM, Siebert R, Miles RR, Dave S, Reddy A, McKeithan TW, Staudt LM, Green MR, Chan WC, and Iqbal J, Comprehensive Genomic Analysis of Adult Burkitt Lymphoma Identifies the B-Cell Receptor Signaling Pathway as a Potential Therapeutic Target. 58th ASH Annual Meeting, 2016.

587. Heavican TB, Yu J, Bouska A, Greiner TC, Lachel CM, Wang C, Dave BJ, Amador CC, Fu K, Vose JM, Weisenburger DD, Gascoyne RD, Hartmann S, Pedersen MB, Wilcox R, Teh BT, Lim ST, Ong CK, Seto M, Berger F, Rosenwald A, Ott G, Campo E, Rimsza LM, Jaffe ES, Braziel RM, d'Amore FA, Inghirami G, Bertoni F, Staudt L, McKeithan TW, Pileri SA, Chan WC, and Iqbal J, Molecular Subgroups of Peripheral T-Cell Lymphoma Evolve by Distinct Genetic Pathways. 58th ASH Annual Meeting, 2016.

588. Song J, Perry A, Pillai R, Herrera A, Ottensen R, Nikowitz J, Skrabek P, Goldstein L, McCarthy C, Najera L, Zain J, Wang J, Wu X, Nademanee A, Niland J, Chan WC, Weisenburger DD. Evaluation of de novo Diffuse Large B-cell Lymphoma Using a Targeted Next Generation Sequencing Assay. Mod Pathol 30: 1519A, 2017.

589. Perry AM, Skrabek P, Ahsanuddin A, Schroedter I, Menard C, Lambert P, Song J, Weisenburger DD, Nasr M. Prognostic Significance of Telomere Length in Diffuse Large B-cell Lymphoma. Mod Pathol 30: 1483A, 2017.

590. Siaghani P, Song JY, Wong J, Chen YY, Weisenburger DD, Kim YS. Tumor-associated Macrophages do Not Predict Survival in Relapsed/refractory Hodgkin Lymphoma Treated with Autologous Stem Cell Transplantation. Mod Pathol 30: 1515A, 2017.

591. Song JY, Kim YS, Siaghani P, Cantu D, Chen YY, Pillai R, Chan WC, Weisenburger DD. CTLA-4 Expression in Hodgkin Lymphoma Confers a Worse Overall Survival in Relapsed/refractory Patients. Mod Pathol 30: 1518A, 2017.

592. Wong JT, Ameri MD, Cantu D, Siaghani P, Song J, Weisenburger DD, Kim Y. Defining True Cellularity in Age-matched Marrows. Mod Pathol 30: 2102A, 2017.

593. Wong JT, Ameri MD, Siaghani P, Cantu D, Chen YY, Song J, Weisenburger DD, Kim Y. Programmed Cell Death Ligand1 (PD-L1) Expression in the Follicular Lymphoma Microenvironment. Mod Pathol 30: 1545A, 2017.

594. Sibon D, Nguyen DP, Schmitz N, Suzuki R, Feldman AL, Gressin R, Lamant L, Weisenburger DD, Nakamura S, Ziepert M, Maurer MJ, Bast M, Armitage JO, Vose JM, Jais JP, Savage KJ. Prognostic Factors and Impact of Etoposide in Adults with Systemic ALK-Positive Anaplastic Large Cell Lymphoma: a Pooled Analysis of Six Studies. (submitted)

595. Weisenburger DD, El Behery R, Laurini JA, Smith LM, Dave BJ, Yuan J, Fu K, Chan WC, Nathwani BN, Bierman PJ, Bociek RG, Vose JM, Armitage JO, Greiner TC, Aoun P. Follicular Large Cleaved Cell (Centrocytic) Lymphoma: a Distinctive but Unrecognized Variant of Follicular Lymphoma. (submitted)

596. Moltok A, Wright G, Rosewald A, Ott G, Ramsower C, Campo E, Braziel RM, Delabie J, Weisenburger DD, Song J, Chan WC, Cook J, Fu K, Greiner T, Smeland E, Holte H, Glinsmann-Gibson BJ, Gascoyne RD, Staudt LM, Jaffe E, Conners JM, Scott DW, Steidl C, Rimsza LM. Molecular Classification of Primary Mediastinal Large B-Cell Lymphoma Using Formalin-Fixed, Paraffin-Embedded Tissue Specimens – an LLMPP Project. (submitted)

597. Cantu D, Siaghani P, Aoun P, Weisenburger DD, Pillai R. Molecular Profiling in Chronic Myelomocytic Leukemia. (submitted)

X. Invited Seminars/Lectures/Forums, 203 Total

1. "Malignant Lymphoma, Intermediate Lymphocytic Type: A Clinicopathologic Study of 42 Cases." International Academy of Pathology Meeting, 1981.

2. "Mantle-Zone Lymphoma." International Academy of Pathology Meeting, 1982.

3. "Multicentric Angiofollicular Lymph Node Hyperplasia: A Clinicopathologic Study of 16 Cases." International Academy of Pathology Meeting, 1984.

4. "Intermediate Lymphocytic Lymphoma: An Immunohistologic Study with Comparison to Other Lymphocytic Lymphomas." International Academy of Pathology Meeting, 1985.

5. "Immunologic Studies of Multicentric and Unicentric Angiofollicular Lymphoid Hyperplasia." International Academy of Pathology Meeting, 1986.

6. "Induction of B-Cell Lymphoma/Leukemia in Wistar Rats by 2-Hydroxyethylnitrosourea." Proceedings of the American Association for Cancer Research, 1986.

7. "Peripheral T-Cell Lymphoma: A Clinicopathologic Study of 42 Cases." Proceedings of the American Association for Cancer Research, 1986.

8. "Intermediate Lymphocytic Lymphoma: An Immunologic and Cytogenetic Study." International Congress of the International Academy of Pathology, 1986.

9. "Castleman's Disease: A Unified Concept." Eleventh Annual AFIP Course on Pathology of Lymph Nodes, 1987.

10. "B-Cell Neoplasia Recapitulates the Normal Humoral Immune Response." Third International Conference on Malignant Lymphoma, 1987.

11. "Detection of Occult Lymphoma Cells in Bone Marrow Harvested for Autologous Transplantation." International Academy of Pathology Meeting, 1988.

12. "Castleman's Disease: A Unified Concept." Twelfth Annual AFIP Course on Pathology of Lymph Nodes, 1988.

13. "Intermediate Lymphocytic and Mantle-Zone Lymphomas: Evolving Concepts." Twelfth Annual AFIP Course on Pathology of Lymph Nodes, 1988.

14. "Mantle-Zone Lymphoma: A Systematic Approach." ASCP Course on Lymph Node Pathology, 1988.

15. "Benign Diseases of Lymph Nodes: A Systematic Approach." ASCP Course on Lymph Node Pathology, 1988.

16. "Environmental Epidemiology of Non-Hodgkin's Lymphoma in Eastern Nebraska." Iowa Symposium on Agricultural Occupational and Environmental Health, 1988.

17. "Lymphoid Malignancies and Agricultural Practices." NIEHS Workshop on the Quantification of Risk in Immunotoxicology, 1988.

18. "Lymphoid Malignancies and Agricultural Practices." Symposium on Agricultural Impacts on Groundwater, American Association for the Advancement of Science Meeting, 1989.

19. "Castleman's Disease: A Unified Concept." Thirteenth Annual AFIP Course on Pathology of Lymph Nodes, 1989.

20. "Intermediate Lymphocytic and Mantle-Zone Lymphomas: Evolving Concepts." Thirteenth Annual AFIP Course on Pathology of Lymph Nodes, 1989.

21. "Benign Diseases of Lymph Nodes: A Systematic Approach." ASCP Course on Lymph Node Pathology, 1989.

22. "Hematopoietic Neoplasia: A Conceptual Understanding." Environmental Epidemiology Branch, National Cancer Institute, 1989.

23. "Benign Diseases of Lymph Nodes: A Pattern Approach." Short Course for American Society of Clinical Pathologists Meeting, 1989.

24. "Lymphoma Pathology in Epidemiologic Studies." Workshop on Cancer in Rural Areas, University of Saskatchewan, 1989.

25. "Non-Hodgkin's Lymphoma Associated with the Agricultural Use of Herbicides: Analysis by Histologic type." International Academy of Pathology Meeting, 1990.

26. "Benign Diseases of Lymph Nodes: A Systematic Approach." ASCP Course on Lymph Node Pathology, 1990.

27. "Benign Diseases of Lymph Nodes: A Pattern Approach." Short Course for American Society of Clinical Pathologists Meeting, 1990.

28. "Potential Health Consequences of Groundwater Contamination by Agrichemicals in Nebraska." NATO Advanced Research Workshop on Nitrate Contamination: Exposure, Consequences, and Control, 1990.

29. "Non-Hodgkin's Lymphoma Associated with the Agricultural Use of Herbicides: Analysis by Histologic type." Third Meeting of the European Association for Haematopathology, 1990.

30. "Non-Hodgkin's Lymphoma Associated with the Agricultural Use of Herbicides: Analysis by Histologic Type." Klein Symposium on Causes, Consequences, and Cures Lymphoproliferative Diseases, 1991.

31. "Mantle Zone Lymphoma." International Academy of Pathology Meeting, 1991.

32. "Non-Hodgkin's Lymphomas of Primary Follicle/Mantle Zone Origin." 2nd Vicenza International Workshop of Hematology, 1991.

33. "Cancers of the Lymphohematopoietic System in Humans Exposed to 1,3-Butadiene." Occupational Safety and Health Administration, 1991.

34. "Benign Diseases of Lymph Nodes: A Systematic Approach." ASCP Course on Lymph Node Pathology, 1991.

35. "Benign Diseases of Lymph Nodes: A Pattern Approach." Short Course for American Society of Clinical Pathologist Meeting, 1991.

36. "Intermediate Cell Lymphoma - Current Controversies." Society for Hematopathology Symposium, American Society of Clinical Pathologists Meeting, 1991.

37. "Human Health Effects of Agrichemical Use." Environmental and Occupational Disease - A State-of-the-Art Conference for Pathology Educators, 1991.

38. "Lymphoma Pathology in Epidemiologic Studies." National Cancer Institute Workshop on the Time Trends in Non-Hodgkin's Lymphoma - Current Knowledge and Recommendations for Research, 1991.

39. "Pesticides/Chemicals and Their Association with Non-Hodgkin's Lymphoma." National Cancer Institute Workshop on Mechanisms in B-Cell Neoplasia, 1992.

40. "Birth Defects and Well Water Contamination by Agrichemicals." Third International Symposium on Issues in Health, Agriculture and the Environment, 1992.

41. "Benign Diseases of Lymph Nodes: A Systemic Approach". ASCP Course on Lymph Node Pathology, 1992.

42. "Strategies for Service Excellence in the Clinical Laboratory." Short Course for American Society of Clinical Pathologists Meeting, 1992.

43. "Benign Diseases of Lymph Nodes: A Pattern Approach." Short Course for American Society of Clinical Pathologists Meeting, 1992.

44. "Is the 2;5 Chromosomal Translocation Specific for CD30-Positive Anaplastic Large Cell Lymphoma? US/Canadian Academy of Pathology Meeting, 1993.

45. "Epidemiology of Non-Hodgkin's Lymphoma." Keystone Symposium on B- and T-Cell Lymphomas, 1993.

46. "Epidemiology of Non-Hodgkin's Lymphoma." Fifth International Conference on Malignant Lymphoma, 1993.

47. "Benign Diseases of Lymph Nodes: A Systematic Approach." ASCP Course on Lymph Node Pathology, 1993.

48. "Strategies for Service Excellence in the Clinical Laboratory." Short Course for American Society of Clinical Pathologists Meeting, 1993.

49. "Benign Diseases of Lymph Nodes: A Pattern Approach." Short Course for American Society of Clinical Pathologists Meeting, 1993.

50. "Mantle Cell Lymphoma - Pathologic Features". Society for Hematopathology Workshop on Disorders of Small B-Lymphocytes, 1993.

51. "Mantle Cell Lymphoma". Department of Pathology, Northwestern University Medical Center, 1993.

52. Lymphoma Slide Seminar, Kansas City Society of Pathologists Meeting, 1993.

53. "Mantle Cell Lymphoma - Clinical Features". European Task Force on Lymphoma Workshop on Mantle Cell Lymphoma, 1994.

54. "Epidemiology of Hodgkin's Disease". International Symposium on Hodgkin's Disease, 1994.

55. "Pathology of Hodgkin's Disease". International Symposium on Hodgkin's Disease, 1994.

56. "Benign Diseases of Lymph Nodes: A Systematic Approach". ASCP Course on Lymph Node Pathology, 1994.

57. "Epidemiology of Non-Hodgkin's Lymphoma". Cancer Center, University of Virginia Medical Center, 1994.

58. "New Views on Non-Hodgkin's Lymphoma Classification". Pan Pacific Lymphoma Conference, 1994.

59. "New Concepts in the Pathology of Hodgkin's Disease". Pan Pacific Lymphoma Conference, 1994.

60. "Health Effects of Contaminated Groundwater". Fall Symposium of the Groundwater Foundation, 1994.

61. "Strategies for Service Excellence in the Clinical Laboratory." Short Course for American Society of Clinical Pathologists Meeting, 1994.

62. "Classification of Non-Hodgkin's Lymphoma", Colorado Springs Memorial Hospital, 8th Annual Oncology Conference, 1995.

63. "Benign Diseases of Lymph Nodes: A Systematic Approach". ASCP Course on Lymph Node Pathology, 1995.

64. "Benign Disorders of Lymph Nodes: A Pattern Approach". Society for Hematopathology Symposium on Diagnostic Issues and Advances in Hematopathology, 1995.

65. "International Non-Hodgkin's Lymphoma Classification Project", Department of Pathology Seminar, University of Hong Kong, 1995.

66. "Benign Diseases of Lymph Nodes: A Systematic Approach". ASCP Course on Lymph Node Pathology, 1996.

67. "Clinical Significance of the t(14;18)(q32;q21) in Follicular Large Cell Lymphoma". US and Canadian Academy of Pathology Meeting, 1996.

68. "Application of the International Lymphoma Study Group (ILSG) Classification of Non-Hodgkin's Lymphoma (NHL). Study Design, Methods, and Pathology Results". Lugano Workshop on New Lymphoma Classification, 1996.

69. "The International Non-Hodgkin's Lymphoma Classification Project - Preliminary Findings". CALGB Lymphoma Committee Meeting, 1996.

70. "A Prospective Study of the International Lymphoma Study Group (ILSG) Classification of Non-Hodgkin's Lymphoma: Pathology Findings". AACR/ASCO Joint Conference on Basic and Clinical Aspects of Lymphoma, 1997.

71. "The International Lymphoma Study Group (ILSG) Classification of Non-Hodgkin's Lymphoma: Pathology Findings from a Large Multicenter Study". US/Canadian Academy of Pathology Meeting, 1997.

72. "The International Lymphoma Study Group (ILSG) Classification of Non-Hodgkin's Lymphoma: Clinical Findings from a Large Multicenter Study". US/Canadian Academy of Pathology Meeting, 1997.

73. "Non-Hodgkin's Lymphoma: A Practical and Cost-effective Approach to Diagnosis". US/Canadian Academy of Pathology Course, 1997.

74. "Non-Hodgkin's Lymphoma: A Practical and Cost-Effective Approach to Diagnosis". ASCP Short Course, 1997.

75. "Overview of the Non-Hodgkin's Lymphoma Classification Project". Pan Pacific Lymphoma Conference, 1997.

76. "Mantle Cell Lymphoma - Pathology". Pan Pacific Lymphoma Conference, 1997.

77. "Follicular Lymphoma", International Non-Hodgkin's Lymphoma Classification Project Workshop, 1997.

78. "Grading of Follicular Lymphoma", WHO Clinical Advisory Committee Meeting on the Classification of Neoplastic Diseases of the Hematopoietic and Lymphoid Systems, 1997.

79. "Benign Diseases of Lymph Nodes: A Systematic Approach". ASCP Course on Lymph Node Pathology, 1997.

80. "Non-Hodgkin's Lymphoma: A Practical and Cost-effective Approach to Diagnosis". US/Canadian Academy of Pathology Course, 1998.

81. "Benign Diseases of Lymph Nodes: A Systematic Approach". ASCP Course on Lymph Node Pathology, 1998.

82. "New Classification for Non-Hodgkin's Lymphoma". Fifth Seminar on New Trends in Treatment for Acute Leukemia, 1998.

83. "Mantle Cell Lymphoma - Biological Characterization". 2nd International Symposium on Malignant Lymphomas, 1998.

84. "Evaluation of the New Lymphoma Classification". Medical College of Ohio, 1998.

85. "Benign Diseases of Lymph Nodes: A Systematic Approach". ASCP Course on Lymph Node Pathology, 1999.

86. "Results of the Non-Hodgkin's Lymphoma Classification Project". University of the Witwaterstrand, 1999.

87. "Burkitt-like Lymphoma". Pan Pacific Lymphoma Conference, 1999.

88. "Mantle Cell Lymphoma". ASCO-PANARAB Conference on Malignant Lymphoma, 1999.

89. "The Non-Hodgkin's Lymphoma Classification Project". ASCO-PANARAB Conference on Malignant Lymphoma, 1999.

90. "Histologic Type Predicts Survival in Adults with Diffuse Aggressive B-cell Lymphoma". US and Canadian Academy of Pathology Meeting, 2000.

91. "Gene Expression in Lymphoid Malignancies Using cDNA Microarray Technology". Workshop on the Comparative Pathology of HIV- and SIV-associated Lymphoma, 2000.

92. "Grading of Follicular Lymphoma: Diagnostic Accuracy, Reproducibility, and Clinical Relevance". Meeting of the European Association for Haematopathology, 2000.

93. "The Non-Hodgkin's Lymphoma Classification Project". University of Texas M.D. Anderson Hospital, 2000.

94. "Benign Diseases of Lymph Nodes: A Systematic Approach". ASCP Course on Lymph Node Pathology, 2000.

95. "Classification and Staging of Non-Hodgkin's Lymphoma". 23rd Annual Nebraska Tumor Registry Workshop, 2000.

96. "The Non-Hodgkin's Lymphoma Classification – Clinical Relevance". International Symposium on New Trends in the Management of Lymphoma, 2000.

97. "Mantle Cell Lymphoma". International Symposium on New Trends in the Management of Lymphoma, 2000.

98. "The Non-Hodgkin's Lymphoma Classification Project". Thai Society of Pathologists, 2001.

99. "The Non-Hodgkin's Lymphoma Classification Project". Tata Memorial Hospital Lymphoma Study Group, 2001.

100. "Benign Diseases of Lymph Nodes: A Systematic Approach." ASCP Course on Lymph Node Pathology, 2001.

101. "The Non-Hodgkin's Lymphoma Classification Project." Beijing International Lymphoma Symposium, 2001.

102. "Mantle Cell Lymphoma." Beijing International Lymphoma Symposium, 2001.

103. "Low-Grade B-cell Lymphoma Slide Seminar." Beijing International Lymphoma Symposium, 2001.

104. "Incorporating Pathology into Epidemiologic Studies." International Consortium of Investigators Working on Lymphoma Epidemiologic Studies (InterLymph), 2001.

105. "Benign Diseases of Lymph Nodes: A Systematic Approach." ASCP Course on Lymph Node Pathology, 2002.

106. "Molecular Classification of Lymphoma – A Work in Progress." Roswell Park Cancer Institute, 2002.

107. "The REALity of Lymphoma Classification – Pathology Perspectives." Conference on Lymphoma & Myeloma, 2002.

108. "Benign Diseases of Lymph Nodes: A Systematic Approach." ASCP Course on Lymph Node Pathology, 2003.

109. "Update on Lymphoma Classification." Pan-Pacific Lymphoma Conference, 2003.

110. "Mantle Cell Lymphoma: From Discovery to 2003." Department of Pathology and Microbiology Grand Rounds, University of Nebraska Medical Center, 2003.

111. "Cyclin DI-negative Mantle Cell Lymphoma." United States and Canadian Academy of Pathology Meeting, 2004.

112. "Follicular Lymphoma, Grade 3. Clinical and Biological Features." Lymphoma . . . the Next Questions International Conference, 2004.

113. "Benign Diseases of Lymph Nodes: A Systematic Approach." ASCP Course on Lymph Node Pathology, 2004.

114. "Follicular Lymphomas: Are They All the Same?" Conference in Lymphoma and Myeloma, 2004.

115. "Peripheral T-cell Lymphoma: a Clinicopathologic Analysis with Comparison to Diffuse Large B-cell Lymphoma." United States and Canadian Academy of Pathology Meeting, 2005.

116. "Peripheral T-cell Lymphoma: How Many Separate Disease Entities?" Lugano Workshop on T-cell Lymphoma, 2005.

117. "Non-Hodgkin Lymphoma (NHL) Around the World: Distribution of Major Subtypes Differs by Geographic Region." 9th International Conference on Malignant Lymphoma, 2005.

118. "Peripheral T-cell Lymphoma: the American View." Institute of Medical Hematology and Oncology, University of Bolongna, 2005.

119. "Peripheral T-cell Lymphoma – International Classification and Clinical Project." Pan-Pacific Lymphoma Conference, 2005.

120. "Classification and Outcome in Peripheral T-cell Lymphoma." Society for Hematopathology Workshop on Progress in T-cell and NK-cell Malignancies, 2005.

121. "WHO Classification of Malignant Lymphoma." Wuhan First International Cancer Symposium, 2005.

122. "Mantle Cell Lymphoma." Wuhan First International Cancer Symposium, 2005.

123. "Peripheral T-cell Lymphoma – International Classification and Clinical Project." Wuhan First International Cancer Symposium, 2005.

124. "WHO Classification of Haematopoietic Malignancy – Clinical Relevance." Egyptian Society of Haematology Congress, 2005.

125. "T-cell Lymphoma." Egyptian Society of Haematology Congress, 2005.

126. "Mantle Cell Lymphoma." 2nd Annual Egyptian Oncology and Hematology Meeting, 2005.

127. "Classification and Outcome in Peripheral T-cell Lymphoma." Milton R. Hales Lecture in Pathology, West Virginia University School of Medicine, 2006.

128. "Peripheral T-cell and NK/T-cell Lymphomas: an International Study of 1320 Cases." United States and Canadian Academy of Pathology Meeting, 2006.

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129. "Classification and Outcome in Peripheral T-cell Lymphoma." 46th Annual Meeting of the Japanese Society of Lymphoreticular Tissue Research, 2006.

130. "Peripheral T-cell Lymphomas." Neoplastic Hematopathology Update: New Insights into Old Questions, 2006.

131. "Peripheral T-cell Lymphoma: Prognostic Factors." Bologna Workshop on T-cell Lymphomas, 2006.

132. "Non-Hodgkin Lymphoma Around the World." 13th Hong Kong International Cancer Congress, 2006.

133. "Peripheral T-cell Lymphoma, Unspecified." International T-cell Lymphoma Project Meeting, 2006.

134. "Peripheral T-cell Lymphoma – New Findings." Asia-Pacific T-cell Advisory Board Meeting, 2007.

135. "Geographic Variation in Non-Hodgkin Lymphoma Incidence." 7th International Network for Cancer Treatment and Research (INCTR) Meeting, 2007.

136. "Peripheral T-cell Lymphoma – New Findings." Department of Pathology, Fluminense Federal University of Brazil, 2007.

137. "Peripheral T-cell Lymphoma – New Findings." Hospital do Cancer, Sao Paulo, Brazil, 2007.

138. "Non-Hodgkin Lymphoma Around the World." International Non-Hodgkin Lymphoma Symposium, Society of Hematology in Chile, 2007.

139. "Pathology and Pathogenesis of B-cell Chronic Lymphocytic Leukemia." Monoclonal B-cell Lymphocytosis and Chronic Lymphocytic Leukemia: Environmental and Genetic Risk Factors Workshop, 2007.

140. "What Pathologic Prognostic Markers Can Be Helpful in Mantle Cell Lymphoma?" First Global Workshop on Mantle Cell Lymphoma, 2007.

141. "WHO Classification of Lymphoid Neoplasms: Update in 2008." Japanese Malignant Lymphoma Academy, 2008.

142. "How I Diagnose Lymphoma in Routine Practice and Consultation." Japanese Malignant Lymphoma Academy, 2008.

143. "Histopathologic and Molecular Diagnosis of Diffuse Large B-cell Lymphoma." Japanese Malignant Lymphoma Academy, 2008.

144. "Peripheral T-cell Lymphoma, Not Otherwise Specified: a Clinicopathologic Study of 340 Cases from the International Peripheral T-cell Project. 10th International Conference on Malignant Lymphoma, 2008.

145. "WHO Classification of Non-Hodgkin Lymphoma in Developing Countries." Workshop in Epidemiology and Management of Lymphoma in Developing Countries: Challenges and Opportunities for International Collaborations. 10th International Conference on Malignant Lymphoma, 2008.

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151. "Update on Mantle Cell Lymphoma." 27th International Congress of the International Academy of Pathology, 2008.

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154. "Non-Hodgkin Lymphoma Around the World". Lymphoma Symposium in Argentina, 2009.

155. "Update on Mantle Cell Lymphoma". 22nd European Congress of Pathology, 2009.

156. "Non-Hodgkin Lymphoma Around the World". The 11th National Symposium on Lymphoma in China, 2009.

157. "Mantle Cell Lymphoma - Update and New Perspectives". Department of Pathology, Fudan University Shanghai Cancer Center, 2010.

158. "Non-Hodgkin Lymphoma in Relation to Environmental Contaminants In Nebraska." UNMC Center for Environmental Health and Toxicology, 2010.

159. "Epidemiology of Non-Hodgkin Lymphoma in Nebraska and Around the World". UNMC Center for Research in Leukemia and Lymphoma, 2010.

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163. "Epidemiology of Non-Hodgkin Lymphoma in Nebraska and Around the World." Chinese Lymphoma Study Group, 2010.

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166. "Epidemiology of Non-Hodgkin Lymphoma Around the World". Peru National Institute of Cancer, 2011.

167. "Epidemiology of Non-Hodgkin Lymphoma Around the World". Pan Pacific Lymphoma Conference, 2011.

168. "CD30 Expression in Lymphoma". Seattle Genetics Advisory Board, 2011.

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171. "Peripheral T-cell Lymphomas". City of Hope Medical Center, 2011.

172. "Epidemiology of Lymphomas". 8th Russian Conference on Malignant Lymphomas, 2011.

173. "Epidemiology of Non-Hodgkin Lymphoma in Nebraska and Around the World". Kansas City Society of Pathologists, 2011.

174. "Mantle Cell Lymphoma: Update and New Perspectives". Kansas City Society of Pathologists, 2011.

175. "Peripheral T-cell Lymphoma". Kansas City Society of Pathologists, 2011.

176. "CD30 Expression in Lymphoma". Seattle Genetics Pathology Round Table, 2011.

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180. "Follicular Lymphoma: Does Grading Really Predict Outcome?" Pan-Pacific Lymphoma Conference, 2012.

181. "Peripheral T-cell Lymphoma." Neoplastic Hematopathology Update, 2012.

182. "Peripheral T-cell Lymphoma - an Update." Kaiser Pathology Group of Southern California, 2012.

183. "Molecular Prognostic Factors in Peripheral T-cell Lymphoma." 5th Annual T-cell Lymphoma Forum, 2013.

184. "Malignant Lymphomas Around the World with Special Regard to Lymphomas in South-East Europe." 1st Macedonian Inter-Congress Meeting, 2013.

185. "Peripheral T-cell Lymphoma." University of Macedonia School of Medicine, 2013.

186. "Nanostring Technology for Molecular Epidemiology Research." Pathology Working Group, 12th InterLymph Meeting, 2013.

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188. "Follicular Lymphoma Around the World." News Around Follicular Lymphoma Symposium, University of Munich, 2013.

189. "Non-Hodgkin Lymphoma Around the World." Ohio State University Pathology Update Course, 2013.

190. "Peripheral T-cell Lymphomas." Ohio State University Pathology Update Course, 2013.

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192. "Follicular Lymphoma: Environment and Lifestyle". 13th InterLymph Meeting, 2014.

193. "Peripheral T-cell Lymphoma". San Diego Society of Hematopathology Meeting, 2014.

194. "Peripheral T-cell Lymphoma". Department of Pathology Grand Rounds, Harbor-UCLA Medical Center, 2015.

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196. "Mantle Cell Lymphoma – Pathology and Biology". Postgraduate Athens Lymphoma Seminar, 2015.

197. "Considerations for Future Modifications of the WHO Classification of T-cell Lymphoma". Postgraduate Athens Lymphoma Seminar, 2015.

198. "Peripheral T-cell Lymphoma". Hematology Grand Rounds, University of Southern California, 2016.

199. "New Insights into Peripheral T-cell Lymphoma". Pan Pacific Lymphoma Conference, 2016.

200. "Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma – Same Disease? Same Approach?" Pan Pacific Lymphoma Conference, 2016.

(Submitted: April, 14, 2017)

201. "Plasmablastic Lymphoma Arising in a Background of Small Lymphocytic Lymphoma". 18th Meeting of the European Association of Haematopathology, 2016.

202. "New Insights into Peripheral T-cell Lymphoma", University of Miami Medical Center, 2016.

203. "Mantle Cell Lymphoma – Pathology and Biology", Nebraska Association of Pathologists, 2016.

XI. PATENTS, INVENTIONS AND COPYRIGHTS

PATENTS

- No. 8,131,475 Methods for Identifying, Diagnosing, and Predicting Survival of Lymphomas
- No. 14/540,302 Survival Predictor for Diffuse Large B-Cell Lymphoma
- No. 61900553 Method for Selecting and Treating Lymphoma Types
- No. PCT/US14/64161 Methods for Selecting and Treating Lymphoma Patients
- No. 62/325,213 Evaluation of Mantle Cell Lymphoma and Methods Related Thereto
- No. 14803288.1 – 1403/3066215 Method for Subtyping Lymphoma Types by Means of Expression Profiling

TECHNOLOGIES LICENSED

1. Methods for Identifying, Diagnosing, and Predicting Survival of Lymphomas, Nanostring

EXHIBIT B

Dennis D. Weisenburger, MD – Case Testimony in last 4 years

1. Wendell vs. Johnson & Johnson, et al. United States District Court, Northern District of California, Oakland Division, 2014. Case No. 4:09-cv-04124-CW

Dennis D. Weisenburger, MD – Fees

$500 per hour for work and $5000 per day for deposition and trial, plus travel expenses.

EXHIBIT C

Other Literature Reviewed

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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	**MONSANTO COMPANY'S NOTICE TO TAKE ORAL AND VIDEOTAPED DEPOSITION OF DR. DENNIS D. WEISENBURGER**

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. Dennis D. Weisenburger on September 11, 2017** before a person duly authorized to administer oaths. The deposition shall commence at **9:00 a.m. PDT at Courtyard by Marriott, 700 Huntington Drive, Monrovia, CA.** 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. Weisenburger shall produce any documents identified in Schedule A attached to his Document Subpoena, at least 10 days prior to the deposition. *See* August 21, 2017 Document Subpoena for Dr. Dennis D. Weisenburger.

DATED: August 21, 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-CV

SUBPOENA TO PRODUCE DOCUMENTS, INFORMATION, OR OBJECTS OR TO PERMIT INSPECTION OF PREMISES IN A CIVIL ACTION

To: Dr. Dennis D. Weisenburger

(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:	Date and Time:
Hollingsworth LLP, 1350 I Street, N.W., Washington D.C. 20005	09/01/2017 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: 08/21/2017

CLERK OF COURT

OR

Signature of Clerk or Deputy Clerk *Attorney's signature*

The name, address, e-mail address, and telephone number of the attorney representing *(name of party)* _____, who issues or requests this subpoena, are:

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-CV

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; Alfred Neugut; Charles Jameson; Chadi Nabhan; 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.

13. All communications and documents relating to the North American Pooled Project ("NAPP"), including, but not limited to, all communications and documents with Shelley A. Harris, Laura Beane-Freeman, John Spinelli, Aaron Blair, Manisha Pahwa, Linda Kachuri, Paul Demers, Stella Koutros, Lidija Latifovic, Shelia Hoar Zahm, Kenneth P. Cantor, John McLaughlin, Punam Pahwa, and James A. Dosman regarding glyphosate and/or Roundup®, which are not publicly or otherwise available.

14. All communications and documents with individual plaintiffs in the Roundup®/ glyphosate litigation at City of Hope regarding recruitment of plaintiffs for the Roundup®/ glyphosate litigation, which are not publicly or otherwise available.

15. All communications and documents with plaintiffs' counsel relating to any drafts of publications concerning glyphosate and/or Roundup® that you have authored or co-authored after being retained by plaintiffs' counsel for the Roundup®/ glyphosate litigation, which are not publicly or otherwise available.

16. All communications and documents you have with Aaron Blair, Laura Beane-Freeman, Jonathan Hofmann, Jane Hoppin, Dale Sandler, Michael Alavanja, Stella Koutros, Charles F. Lynch, Kathryn Hughes Barry, Cynthia J. Hines, Kent Thomas, Joe Barker, Gabriella Andreotti, and Anneclaire J. DeRoos regarding the Agricultural Health Study and glyphosate from the last five (5) years, which are not publicly or otherwise available.

DATED: August 21, 2017

Respectfully submitted,

/s/ Heather A. Pigman
Heather A. Pigman (*pro hac vice*)
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Attorneys for Defendant
MONSANTO COMPANY

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

IN RE ROUNDUP PRODUCTS LIABILITY LITIGATION	MDL No. 2741 Case No. 16-md-02741
This Document Relates To All Actions	**PLAINTIFFS' OBJECTIONS AND RESPONSES TO MONSANTO COMPANY'S SCHEDULE "A" TO NOTICE OF DEPOSITION OF DR. DENNIS D. WEISENBURGER**

Plaintiffs hereby respond and object to Monsanto Company's "Notice to Take Oral and Videotaped Deposition of Dr. Dennis D. Weisenburger" (the "Notice") and "Schedule A" to the same.

The responses and objections contained herein are made without in any way waiving or intending to waive–but on the contrary reserving and intending to reserve–the right at any time to revise, supplement, correct, or add to these objections and responses. Plaintiffs' further note that no documents have been withheld from production on the basis of the objections set forth in these Responses unless expressly stated. Plaintiffs respond to Requests for Production as follows;

GENERAL OBJECTIONS TO SCHEDULE "A"

Plaintiffs object to Definition No. 6 to the extent it seeks documents unrelated to the instant multidistrict litigation, MDL 2741.

SPECIFIC OBJECTIONS AND RESPONSES TO DOCUMENT REQUESTS

1. All documents provided to you, or that you have, related to the Roundup®/glyphosate litigation that are not publicly or otherwise available.

RESPONSE: Plaintiffs object to this Request as overly broad, vague, unduly burdensome, and seeking documents that are privileged and otherwise not related to the issues of general causation. Plaintiffs further object to the extent this Request seeks documents or

information protected by the attorney work product doctrine and/or outside the scope of expert discovery permitted by the Federal Rules of Civil Procedure. Plaintiffs further object to this request to the extent it seeks communications between Dr. Weisenburger and other physicians or parties relating to the peer review process associated with scientific journals. Such information is protected by rights of privacy and the burden imposed on the peer review process by such discoveyr outweighs the benefits of such discovery. *Volkswagen of America v. Superior Court*, 139 Cal.App.4th 1481, 1492 (2006); *In re Bextra and Celebrex Marketing Sales Practices and Prods. Liab. Litig.*, 249 F.R.D. 8,13 (D. Mass 2008); *Humane Society of the United States v. Superior Court*, 214 Cal. App. 4th 1233 (2013). The term "otherwise available" is undefined, and its meaning is unknown. Without waiving these objections, Dr. Weisenburger will produce any other documents upon which he relied or considered in connection with his expert report in MDL 2741 to the extent they are responsive, properly discoverable, non-privileged and are not publicly available and/or produced by Monsanto in MDL 2741. Plaintiffs further refer Defendant to Dr. Weisenburger's materials reliance list, which was provided with his expert report in this matter.

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.

RESPONSE: Plaintiffs object to this Request as overly broad, vague, unduly burdensome, and seeking documents that are privileged and otherwise not related to the issues of general causation. Plaintiffs further object to the extent this Request seeks documents or information protected by the attorney work product doctrine and/or outside the scope of expert discovery permitted by the Federal Rules of Civil Procedure. Plaintiffs further object to this request to the extent it seeks communications between Dr. Weisenburger and other physicians or parties relating to the peer review process associated with scientific journals. Such information is

protected by rights of privacy and the burden imposed on the peer review process by such discoveyr outweighs the benefits of such discovery. *Volkswagen of America v. Superior Court*, 139 Cal.App.4th 1481, 1492 (2006); *In re Bextra and Celebrex Marketing Sales Practices and Prods. Liab. Litig.*, 249 F.R.D. 8,13 (D. Mass 2008); *Humane Society of the United States v. Superior Court*, 214 Cal. App. 4th 1233 (2013). The term "otherwise available" is undefined, and its meaning is unknown. Without waiving these objections, Dr. Weisenburger will produce any other documents upon which he relied or considered in connection with his expert report in MDL 2741 to the extent they are responsive, properly discoverable, non-privileged and are not publicly available and/or produced by Monsanto in MDL 2741. Plaintiffs further refer Defendant to Dr. Weisenburger's materials reliance list, which was provided with his expert report in this matter.

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.

RESPONSE: Plaintiffs object to this Request as overly broad, vague, unduly burdensome, and seeking documents that are privileged and otherwise not related to the issues of general causation. Plaintiffs further object to the extent this Request seeks documents or information protected by the attorney work product doctrine and/or outside the scope of expert discovery permitted by the Federal Rules of Civil Procedure. Plaintiffs further object to this request to the extent it seeks communications between Dr. Weisenburger and other physicians or parties relating to the peer review process associated with scientific journals. Such information is protected by rights of privacy and the burden imposed on the peer review process by such discoveyr outweighs the benefits of such discovery. *Volkswagen of America v. Superior Court*, 139 Cal.App.4th 1481, 1492 (2006); *In re Bextra and Celebrex Marketing Sales Practices and*

Prods. Liab. Litig., 249 F.R.D. 8,13 (D. Mass 2008); *Humane Society of the United States v. Superior Court*, 214 Cal. App. 4th 1233 (2013). The term "otherwise available" is undefined, and its meaning is unknown. Without waiving these objections, Dr. Weisenburger will produce any other documents upon which he relied or considered in connection with his expert report in MDL 2741 to the extent they are responsive, properly discoverable, non-privileged and are not publicly available and/or produced by Monsanto in MDL 2741. Plaintiffs further refer Defendant to Dr. Weisenburger's materials reliance list, which was provided with his expert report in this matter.

4. Your most recent curriculum vitae.

RESPONSE: Dr. Weisenburger will produce his 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.

RESPONSE: Plaintiffs object to this Request as overly broad. Without waiving these objections, Dr. Weisenburger will provide any responsive documents to the extent they are responsive, properly discoverable, non-privileged and are not publicly available and/or produced by Monsanto in MDL 2741.

6. Any retainer letter, contract, agreement, or other document setting forth the retention of you to work in the Roundup®/glyphosate litigation.

RESPONSE: Plaintiffs object to this Request as overly broad. Without waiving these objections, Dr. Weisenburger will provide any responsive documents to the extent they are responsive, properly discoverable, non-privileged and are not publicly available and/or produced by Monsanto in MDL 2741.

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.

RESPONSE: Plaintiffs object to this Request as overly broad, vague, unduly burdensome, and seeking documents that are privileged and otherwise not related to the issues of general causation. Dr. Weisenburger, as Monsanto is aware, has worked for over 30 years on hematopoietic malignancies and the causes of such malignancies, including pesticides, not all of which are related to glyphosate and/ or Roundup® or the issues of general causation. Monsanto's request is not proportional to the needs of the case as it demands over three decades worth of potentially irrelevant documents. Plaintiffs further object to this request to the extent it seeks communications between Dr. Weisenburger and other physicians or parties relating to the peer review process associated with scientific journals. Such information is protected by rights of privacy and the burden imposed on the peer review process by such discoveyr outweighs the benefits of such discovery. *Volkswagen of America v. Superior Court*, 139 Cal.App.4th 1481, 1492 (2006); *In re Bextra and Celebrex Marketing Sales Practices and Prods. Liab. Litig.*, 249 F.R.D. 8,13 (D. Mass 2008); *Humane Society of the United States v. Superior Court*, 214 Cal. App. 4th 1233 (2013). The term "otherwise available" is undefined, and its meaning is unknown. Without waiving these objections, Dr. Weisenburger will provide any responsive documents to the extent they are related to Roundup® and NHL, are responsive, properly discoverable, non-privileged and are not publicly available and/or produced by Monsanto in MDL 2741. Plaintiffs further refer Defendant to Dr. Weisenburger's materials reliance list, which was provided with his expert report in this matter.

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.

RESPONSE: Plaintiffs object to this Request as overly broad, vague, unduly burdensome, and seeking documents that are privileged and otherwise not related to the issues of general causation. The term "otherwise available" is undefined, and its meaning is unknown. Without waiving these objections, Dr. Weisenburger will provide any responsive documents to the extent they are related to Roundup® and NHL, are responsive, properly discoverable, non-privileged and are not publicly available and/or produced by Monsanto in MDL 2741. Plaintiffs further refer Defendant to Dr. Weisenburger's materials reliance list, which was provided with his expert report in this matter.

9. A copy of all handouts, power points or other documents used by you at any lecture you have given on pesticides, including but not limited to glyphosate and/or Roundup®, that are not publicly or otherwise available.

RESPONSE: Plaintiffs object to this Request as overly broad, vague, unduly burdensome, and seeking documents that are privileged and otherwise not related to the issues of general causation. The term "otherwise available" is undefined, and its meaning is unknown. Without waiving these objections, Dr. Weisenburger will provide any other responsive documents to the extent they are related to Roundup® and NHL, are responsive, properly discoverable, non-privileged and are not publicly available and/or produced by Monsanto in MDL 2741. Plaintiffs further refer Defendant to Dr. Weisenburger's materials reliance list, which was provided with his expert report in this matter.

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 assessments and hazard assessments. This request is limited to documents that are not publicly or otherwise available.

RESPONSE: Plaintiffs object to this Request as overly broad, vague, unduly burdensome, and seeking documents that are privileged and otherwise not related to the issues of general causation. The term "otherwise available" is undefined, and its meaning is unknown. Without waiving these objections, Dr. Weisenburger will provide any other responsive documents to the extent they are related to Roundup® and NHL, are responsive, properly discoverable, non-privileged and are not publicly available and/or produced by Monsanto in MDL 2741. Plaintiffs further refer Defendant to Dr. Weisenburger's materials reliance list, which was provided with his expert report in this matter.

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, Alfred Neugut, Charles Jameson, Chadi Nabhan, Aaron Blair, and/or Matthew Ross.

RESPONSE: Plaintiffs object to this Request as overly broad, vague, unduly burdensome, and seeking documents that are privileged and otherwise not related to the issues of general causation. Plaintiffs further object to this request to the extent it seeks communications between Dr. Weisenburger and other physicians or parties relating to the peer review process associated with scientific journals. Such information is protected by rights of privacy and the burden imposed on the peer review process by such discoveyr outweighs the benefits of such discovery. *Volkswagen of America v. Superior Court*, 139 Cal.App.4th 1481, 1492 (2006); *In re Bextra and Celebrex Marketing Sales Practices and Prods. Liab. Litig.*, 249 F.R.D. 8,13 (D. Mass 2008); *Humane Society of the United States v. Superior Court*, 214 Cal. App. 4th 1233 (2013). Without waiving these objections, Dr. Weisenburger will produce any documents to the

extent they are related to Roundup® and NHL, are responsive, properly discoverable, non-privileged and are not publicly available and/or produced by Monsanto in MDL 2741. Plaintiffs further refer Defendant to Dr. Weisenburger's materials reliance list, which was provided with his expert report in this matter.

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.

RESPONSE: Plaintiffs object to this Request as overly broad, vague, unduly burdensome, and seeking documents that are privileged and otherwise not related to the issues of general causation. Without waiving these objections, Dr. Weisenburger will produce any documents to the extent they are related to Roundup® and NHL, are responsive, properly discoverable, non-privileged and are not publicly available and/or produced by Monsanto in MDL 2741. Plaintiffs further refer Defendant to Dr. Weisenburger's materials reliance list, which was provided with his expert report in this matter.

13. All communications and documents relating to the North American Pooled Project ("NAPP"), including, but not limited to, all communications and documents with Shelley A. Harris, Laura Beane-Freeman, John Spinelli, Aaron Blair, Manisha Pahwa, Linda Kachuri, Paul Demers, Stella Koutros, Lidija Latifovic, Shelia Hoar Zahm, Kenneth P. Cantor, John McLaughlin, Punam Pahwa, and James A. Dosman regarding glyphosate and/or Roundup®, which are not publicly or otherwise available.

RESPONSE: Plaintiffs object to this Request as overly broad, vague, unduly burdensome, and seeking documents that are privileged and otherwise not related to the issues of general causation. Plaintiffs further object to this request to the extent it seeks communications between Dr. Weisenburger and other physicians or parties relating to the peer review process associated with scientific journals. Such information is protected by rights of privacy and the burden imposed on the peer review process by such discoveyr outweighs the benefits of such

discovery. *Volkswagen of America v. Superior Court*, 139 Cal.App.4th 1481, 1492 (2006); *In re Bextra and Celebrex Marketing Sales Practices and Prods. Liab. Litig.*, 249 F.R.D. 8,13 (D. Mass 2008); *Humane Society of the United States v. Superior Court*, 214 Cal. App. 4th 1233 (2013). Without waiving these objections, Dr. Weisenburger will produce any documents to the extent they are related to Roundup® and NHL, are responsive, properly discoverable, non-privileged and are not publicly available and/or produced by Monsanto in MDL 2741. Plaintiffs further refer Defendant to Dr. Weisenburger's materials reliance list, which was provided with his expert report in this matter.

14. All communications and documents with individual plaintiffs in the Roundup®/ glyphosate litigation at City of Hope regarding recruitment of plaintiffs for the Roundup®/ glyphosate litigation, which are not publicly or otherwise available.

RESPONSE: Plaintiffs object to this Request as overly broad, vague, unduly burdensome, and seeking documents that are privileged and otherwise not related to the issues of general causation. Without waiving these objections, Dr. Weisenburger will produce any documents to the extent they are responsive, properly discoverable, non-privileged and are not publicly available and/or produced by Monsanto in MDL 2741.

15. All communications and documents with plaintiffs' counsel relating to any drafts of publications concerning glyphosate and/or Roundup® that you have authored or co-authored after being retained by plaintiffs' counsel for the Roundup®/ glyphosate litigation, which are not publicly or otherwise available.

RESPONSE: Plaintiffs object to this Request as overly broad, vague, unduly burdensome, and seeking documents that are privileged and otherwise not related to the issues of general causation. Plaintiffs further object to this request to the extent it seeks communications between Dr. Weisenburger and other physicians or parties relating to the peer review process associated with scientific journals. Such information is protected by rights of privacy and the burden imposed on the peer review process by such discoveyr outweighs the benefits of such

discovery. *Volkswagen of America v. Superior Court*, 139 Cal.App.4th 1481, 1492 (2006); *In re Bextra and Celebrex Marketing Sales Practices and Prods. Liab. Litig.*, 249 F.R.D. 8,13 (D. Mass 2008); *Humane Society of the United States v. Superior Court*, 214 Cal. App. 4th 1233 (2013). Without waiving these objections, Dr. Weisenburger will produce any documents to the extent they are related to Roundup® and NHL, are responsive, properly discoverable, non-privileged and are not publicly available and/or produced by Monsanto in MDL 2741. Plaintiffs further refer Defendant to Dr. Weisenburger's materials reliance list, which was provided with his expert report in this matter.

16. All communications and documents you have with Aaron Blair, Laura Beane- Freeman, Jonathan Hofmann, Jane Hoppin, Dale Sandler, Michael Alavanja, Stella Koutros, Charles F. Lynch, Kathryn Hughes Barry, Cynthia J. Hines, Kent Thomas, Joe Barker, Gabriella Andreotti, and Anneclaire J. DeRoos regarding the Agricultural Health Study and glyphosate from the last five (5) years, which are not publicly or otherwise available.

RESPONSE: Plaintiffs object to this Request as overly broad, vague, unduly burdensome, and seeking documents that are privileged and otherwise not related to the issues of general causation. Plaintiffs further object to this request to the extent it seeks communications between Dr. Weisenburger and other physicians or parties relating to the peer review process associated with scientific journals. Such information is protected by rights of privacy and the burden imposed on the peer review process by such discoveyr outweighs the benefits of such discovery. *Volkswagen of America v. Superior Court*, 139 Cal.App.4th 1481, 1492 (2006); *In re Bextra and Celebrex Marketing Sales Practices and Prods. Liab. Litig.*, 249 F.R.D. 8,13 (D. Mass 2008); *Humane Society of the United States v. Superior Court*, 214 Cal. App. 4th 1233 (2013). Without waiving these objections, Dr. Weisenburger will produce any documents to the extent they are related to Roundup® and NHL, are responsive, properly discoverable, non-privileged and are not publicly available and/or produced by Monsanto in MDL 2741. Plaintiffs

further refer Defendant to Dr. Weisenburger's materials reliance list, which was provided with his expert report in this matter.

DATED: September 2, 2017

/s/ Kathryn M. Forgie, Esq.
ANDRUS WAGSTAFF, PC
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Lakewood, CO 80226
Tel: (303) 376-6360
Fax: (303) 376-6361
kathryn.forgie@andruswagstaff.com

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing document was electronically served on Defendant via email.

DATED: September 2, 2017

/s/ Kathryn M. Forgie, Esq.
ANDRUS WAGSTAFF, PC
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Lakewood, CO 80226
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Glyphosate Factsheet

Part 1 of 2

[Part 1 | Part 2]

Caroline Cox / Journal of Pesticide Reform v.108, n.3 Fall98 rev.Oct00

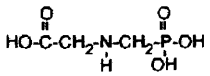
[More on **Monsanto** and its products]

Caroline Cox is JPR's editor.

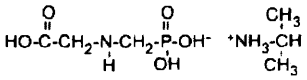
Glyphosate is a broad-spectrum herbicide widely used to kill unwanted plants both in agriculture and in nonagricultural landscapes. Estimated use in the U.S. is between 38 and 48 million pounds per year. Most glyphosate-containing products are either made or used with a surfactant, chemicals that help glyphosate to penetrate plant cells.

Glyphosate-containing products are acutely toxic to animals, including humans. Symptoms include eye and skin irritation, headache, nausea, numbness, elevated blood pressure, and heart palpitations. The surfactant used in a common glyphosate product (Roundup) is more acutely toxic than glyphosate itself the combination of the two is yet more toxic.

Figure 1
Glyphosate



glyphosate
N-(phosphonomethyl)glycine

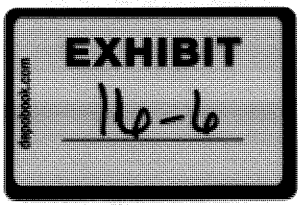


isopropylamine salt of glyphosate

Given the marketing of glyphosate herbicides as benign, it is striking that laboratory studies have found adverse effects in all standard categories of laboratory toxicology testing. These include medium-term toxicity (salivary gland lesions), long-term toxicity (inflamed stomach linings), genetic damage (in human blood cells), effects on reproduction (reduced sperm counts in rats; increased frequency of abnormal sperm in rabbits), and carcinogenicity (increased frequency of liver tumors in male rats and thyroid cancer in female rats).

In studies of people (mostly farmers) exposed to glyphosate herbicides, exposure is associated with an increased risk of miscarriages, premature birth, and the cancer non-Hodgkin's lymphoma.

Glyphosate has been called "extremely persistent" by the U.S. Environmental Protection



Agency, and half lives of over 100 days have been measured in field tests in Iowa and New York. Glyphosate has been found in streams following agricultural, urban, and forestry applications.

Glyphosate treatment has reduced populations of beneficial insects, birds, and small mammals by destroying vegetation on which they depend for food and shelter.

In laboratory tests, glyphosate increased plants' susceptibility to disease and reduced the growth of nitrogen-fixing bacteria.

Described by their manufacturer as pesticides of "low toxicity and environmental friendliness,"[1] glyphosate-based herbicides can seem like a silver bullet when dealing with unwanted vegetation. However, glyphosate poses a variety of health and environmental hazards. The following article is a summary of those hazards.

Glyphosate, N-(phosphonomethyl) glycine (Figure 1), is a systemic and nonselective herbicide used to kill broadleaved, grass, and sedge species.[2] It has been registered in the U.S. since 1974 and is used to control weeds in a wide variety of agricultural, urban, lawn and garden, aquatic, and forestry situations.[3] Most glyphosate herbicides contain the isopropylamine salt of glyphosate.[4]

Glyphosate products are manufactured by Monsanto Company worldwide. They are marketed under a variety of trade names: Roundup, Rodeo, and Accord are the most common names in the US.[2]

Unlike most other herbicides, chemicals which are closely related to glyphosate are not effective herbicides.'

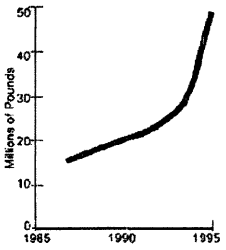
Use

Glyphosate is the seventh most commonly used pesticide in U.S. agriculture, the third most commonly used pesticide on industrial and commercial land, and the second most commonly used home and garden pesticide. Estimated annual use according to the U.S. Environmental Protection Agency (EPA) is between 38 and 48 million pounds.[6] The largest agricultural uses are in the production of soybeans, corn, hay and pasture, and on fallow land.[7] Glyphosate use is currently (1998) growing at a rate of about 20 percent annually, primarily because of the recent introduction of crops which are genetically engineered to be tolerant of the herbicide.[8] (See Figure 2.)

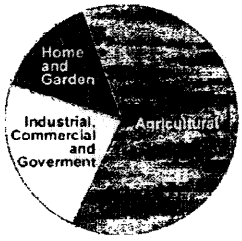
In the U.S., 25 million applications are made yearly on lawns and in yards. [9]

Figure 2
Glyphosate Use in the U.S.

Increase Since 1987



Types of Use



Aspelin, A. 1. 1990; 1994; 1997. *Pesticide industry sales and usage: 1988 market estimates; 1992 and 1993 market estimates; 1994 and 1995 market estimates. U.S.* EPA. Office of Prevention, Pesticides and Toxic Substances. Office of Pesticide Programs. Biological and Economic Analysis Division. Washington, D.C.

Mode of Action

Glyphosate's mode of action is "not known at this time," [4] according to EPA. However, considerable research has established that glyphosate inhibits an enzyme pathway, the shikimic acid pathway, preventing plants from synthesizing three aromatic amino acids. These amino acids are essential for growth and survival of most plants. The key enzyme inhibited by glyphosate is called EPSP synthese.[10] Glyphosate also "may inhibitor repress" [4] two other enzymes, involved in the synthesis of the same amino acids.[4] These enzymes are present in higher plants and microorganisms but not in animals.[10]

Two of the three aromatic amino acids are essential amino acids in the human diet because humans, like all higher animals, lack the shikimic acid pathway, cannot synthesize these amino

TOXICOLOGY OF "INERT" INGREDIENTS IN GLYPHOSATE CONTAINING PRODUCTS

Three glyphosate products contain ammonium sulfate.[29, 30, 32] It causes eye irritation, nausea and diarrhea, and may cause allergic respiratory reactions. Prolonged exposure can cause permanent eye damage.[46] One glyphosate product contains benzisothiazolone.[47] It causes eczema, skin irritation,[48] and a light-induced allergic reaction in sensitive people.[49,50] Four glyphosate products contain 3-iodo-2-propynyl butylcarbamate (IPBC).[39-41, 47] It is severely irritating to eyes and increases the incidence of miscarriages in laboratory tests.[51] It also can cause allergic skin

acids, and rely on their foods to provide these compounds. One is synthesized in animals through another pathway.[11]

Glyphosate can affect plant enzymes not connected with the shikimic acid pathway. In sugar cane, it reduces the activity of one of the enzymes involved in sugar metabolism.[12] It also inhibits a major detoxification enzyme in plants.[13]

Roundup affects enzymes found in mammals. In rats, Roundup decreased the activity of two detoxification enzymes in the liver and an intestinal enzyme.[14]

"Inert" Ingredients in Glyphosate-containing Products

Virtually every pesticide product contains ingredients other than what is called the "active" ingredient(s), the one designed to provide killing action. These ingredients are misleadingly called "inert." The purpose of these "inerts" is to make the product easier to use or more efficient. In general, they are not identified on the labels of pesticide products.

In the case of glyphosate products, many "inerts" have been identified. See "Toxicology of `Inert' Ingredients of Glyphosate-containing Products," (at right), for basic information about these "inerts."

Many of the toxicology studies that will be summarized in this factsheet have been conducted using glyphosate, the active ingredient, alone. Some have been conducted with commercial products containing glyphosate and "inert" ingredients. When no testing is done with the product as it is actually used, it is impossible to accurately assess its hazards.

reactions.[52] One glyphosate product contains isobutane.[30] It causes nausea, nervous system depression, and difficulty breathing. It is a severe fire hazard.[53] One glyphosate product contains methyl pyrrolidinone.[20] It causes severe eye irritation.[54] It has caused fetal loss and reduced fetal weights in laboratory animals.[55] Three glyphosate products contain pelargonic acid.[29, 30, 32] It causes severe eye and skin irritation and may cause respiratory tract irritation.[56] Nine glyphosate products contain polyethoxylated tallowamine (POEA).[21-24, 31, 35-38] It causes eye burns; skin redness, swelling, and blistering; nausea; and diarrhea.[23, 45] Three glyphosate products contain potassium hydroxide.[29, 30, 32] It causes irreversible eye injury, deep skin ulcers, severe digestive tract burns, and severe irritation of the respiratory tract.[57] One glyphosate product contains sodium sulfite.[34] It may cause eye and skin irritation with vomiting and diarrhea's as well as skin allergies.[59] Exposure to small amounts can cause severe allergic reactions.[60] Three glyphosate products contain sorbic acid.[35, 36, 37] It may cause severe skin irritation, nausea, vomiting, chemical pneumonitis, and sore throat.[61] It also causes allergic reactions.[62, 63] Isopropylamine is used in some Roundup products.[47,64] It is "extremely destructive to tissue of the mucous membranes and upper respiratory tract."[65] Symptoms of exposure are wheezing, laryngitis, headache, and nausea.[65]

We will discuss both types of studies, and will identify insofar as is possible what material was used in each study.

Acute Toxicity to Laboratory Animals

Glyphosate's acute oral median lethal dose (the dose that causes death in 50 percent of a population of test animals; LD_{50} in rats is greater than 4,320 milligrams per kilogram (mg/kg) of body weight. This places the herbicide in Toxicity Category III (Caution)[4] Its acute dermal toxicity (dermal LD_{50}) in rabbits is greater than 2,000 mg/kg of body weight, also Toxicity Category III.[4]

Commercial glyphosate herbicides are more acutely toxic than glyphosate. The amount of Roundup (containing glyphosate and the surfactant POEA) required to kill rats is about 1/3 the amount of glyphosate alone.' Roundup is also more acutely toxic than POEA.[15]

Glyphosate-containing products are more toxic via inhalation than orally. Inhalation of Roundup by rats caused "signs of toxicity in all test groups," [16] even at the lowest concentration tested. These signs included gasping, congested eyes, reduced activity," and body weight loss.[16] Lungs were red or blood-congested.[17] The dose required to cause lung damage and mortality following pulmonary administration of two Roundup products and POEA (when forced into the trachea, the tube carrying air into the lungs) was only 1/10 the dose causing damage orally.[15, 18]

Effects on the Circulatory System: When dogs were given intravenous injections of glyphosate, POEA, or Roundup so that blood concentrations were approximately those found in humans who ingested glyphosate, glyphosate increased the ability of the heart muscle to contract. POEA reduced the output of the heart and the pressure in the arteries. Roundup caused cardiac depression.[19]

Eye Irritation: NCAP surveyed eye hazards listed on material safety data sheets for 25 glyphosate-containing products. One of the products is "severely irritating," [20] four cause "substantial but temporary eye injury," [21-24] eight "cause eye irritation," [25-32] five "may cause eye irritation," [33-37] one is "moderately irritating," [38] and three are "slightly irritating." [39-41] The other three products require addition of a surfactant (wetting agent) before use,[42-44] and the surfactant sold by glyphosate's manufacturer for this purpose "causes eye burns." [45]

Skin Irritation: Glyphosate is classified as a slightly irritating to skin. Roundup is a "moderate skin irritant," and recovery can take over two weeks.[16]

Table 1
Symptoms Following Unintentional Exposure to Glyphosate Herbicides

eye irritation	blisters	chest pains	facial numbness
painful eyes	skin rash	congestion	burning sensation

burning eyes	rapid heartbeat	coughing	on skin
blurred vision	heart palpitations	headache	itchy skin
swollen eye, face, joints	elevated blood pressure	nausea	tingling skin recurrent eczema

Temple, W.A. and N.A. Smith. 1992. Glyphosate herbicide poisoning experience in New Zealand. N.Z. *Med. J.* 105:173-174.
Calif. EPA. Dept. of Pesticide Regulation. 1998. Case reports received by the California Pesticide Illness Surveillance Program in which health effects were attributed to glyphosate, 1993-1995. Unpublished report.

Acute Toxicity to Humans

The acute toxicity of glyphosate products to humans was first publicized by physicians in Japan who studied [56] suicide attempts; nine cases were fatal. Symptoms included intestinal pain, vomiting, excess fluid in the lungs, pneumonia, clouding of consciousness, and destruction of red blood cells.[66] They calculated that the fatal cases ingested on average about 200 milliliters (3/4 of a cup). They believed that POEA was the cause of Roundup's toxicity.[66] More recent reviews of poisoning incidents have found similar symptoms, as well as lung dysfunction,[67-69] erosion of the gastrointestinal tract,[67, 69] abnormal electrocardiograms,[69] low blood pressure,[67, 69] kidney damage,[67, 68, 70] and damage to the larynx.[71]

Smaller amounts of Roundup cause adverse effects, usually skin or eye irritation as well as some of the symptoms listed above. (See Table 1.) For example, rubbing of Roundup in an eye caused eye and lid swelling, rapid heartbeat and elevated blood pressure. Wiping the face after touching leaky spray equipment caused swelling of the face. Accidental drenching with horticultural Roundup caused eczema of the hands and arms lasting two months.[63] A spill resulted in dizziness, fever, nausea, palpitations, and sore throat.[72]

Toxicology Overview

Glyphosate is often portrayed as toxicologically benign: "extensive investigations strongly support the conclusion that glyphosate has a very low level of toxicity...[73] NCAP's review of glyphosate's toxicology comes to a different conclusion. Adverse effects have been identified in each standard category of testing (subchronic, chronic, carcinogenicity, mutagenicity, and reproduction). NCAP's review has been challenged by the assertion that these effects were found because standard test protocols *require* finding adverse effects at the highest dose tested. However, the following five sections of this article summarize adverse effects did *not* result from this requirement: they were all found at less than the highest dose tested. (The few exceptions are clearly identified.)

Subchronic Toxicity

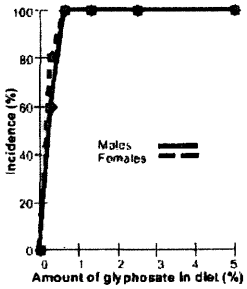
In subchronic (medium term) studies of rats and mice done by the National Toxicology Program (NTP), microscopic salivary gland lesions were found in all doses tested in rats (200 - 3400 mg/kg per day) and in all but the lowest dose tested in mice (1,000-12,000 mg/kg per day). (See Figure 3.) A follow-up study by NTP found that the mechanism by which glyphosate caused these lesions involved the hormone adrenalin.[74]

The NTP study also found increases in two liver enzymes at all but the two lowest doses tested. Other effects found in at least two doses in this study were reduced weight gain in rats and mice; diarrhea in rats; and changes in kidney and liver weights in male rats and mice.[74]

Another subchronic laboratory test found that blood levels of potassium and phosphorus in rats increased at all doses tested (60-1600 mg/kg/day).[4]

Glyphosate-containing products are more toxic than glyphosate in subchronic tests. In a 7 day study with calves, 790 mg/kg per day of Roundup caused pneumonia, and death of 1/3 of the animals tested. At lower doses decreased food intake and diarrhea were observed.[2]

Figure 3
Salivary Gland Lesions in Rats Fed Glyphosate



U.S. Dept. of Health and Human Services. Public Health Service. National Institutes of Health. 1992. NTP technical report on toxicity studies of glyphosate (CAS No. 1071-83-6) administered in dosed feed to F344/N rats and B6C3FI mice. Research Triangle Park, NC: National Toxicology Program.

Glyphosate causes salivary gland lesions in rats, mediated by the hormone adrenalin.

Chronic Toxicity

Glyphosate is also toxic in long-term studies. At all but the lowest dose tested, excessive cell division in the urinary bladder occurred in male mice[2] and inflammation of the stomach lining occurred in both sexes of rats.[2]

Carcinogenicity

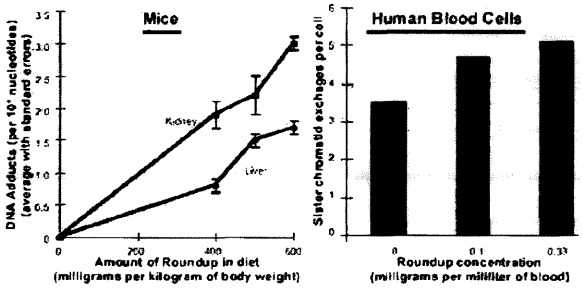
A recent Swedish study of hairy cell leukemia (HCE), a form of the cancer non-Hodgkin's lymphoma, found that people who were occupationally exposed to glyphosate herbicides had a threefold higher risk of HCE. A similar study of people with non-Hodgkin's lymphoma found exposure to glyphosate herbicides was associated with an increase in risk of about the same size.[74ab]

The publicly available laboratory studies of glyphosate's ability to cause cancer were all

conducted by or for its manufacturer.[2] The first carcinogenicity study submitted to EPA (1981) found an increase in testicular tumors in male rats at the highest dose tested as well as an increase in the frequency of a thyroid cancer in females. Both results occurred at the highest dose tested (30 mg/kg of body weight per day). [75, 76] The second study (1983) found an increasing trend in the frequency of a rare kidney tumor in male mice.[77] The most recent study (1990) found an increase in pancreas and liver tumors in male rats together with an increase of the same thyroid cancer found in the 1983 study in females.[78]

All of these increases in tumor or cancer incidence are "not considered compound-related" [78] according to EPA (This means that EPA did not consider glyphosate the cause of the tumors.) For the testicular tumors, EPA accepted the interpretation of an industry pathologist who said that the incidence in treated groups (12 percent) was similar to those observed (4.5 percent) in other rats not fed glyphosate.[78] For the thyroid cancer, EPA stated that it was not possible to distinguish between cancers and tumors of this type, so that the two should be considered together. The combined data are not statistically significant.[76] For the kidney tumors, the manufacturer reexamined the tissue and found an additional tumor in untreated mice so that statistical significance was lost. This was despite the opinion of EPA's pathologist that the lesion in question was not really a tumor.[77] For the pancreatic tumors, EPA stated that there was no dose-related trend. For the liver and thyroid tumors, EPA stated that pairwise comparisons between treated and untreated animals were not statistically significant.[78]

Figure 4
Genetic Damage Caused by Roundup



Peluso, M. et al. 1998. 32P-Postlabeling detection of DNA adducts in mice treated with the herbicide Roundup. Environ. Molec. Mutag.31:55-59.

Bolognesi, C. et al. 1997. Genotoxic activity of glyphosate and its technical formulation Roundup. J. Agric. *Food* Chem. 45:1957-1962.

Roundup causes genetic damage in laboratory animals and in human blood cells.

EPA concluded that glyphosate should be classified as Group E, "evidence of non-carcinogenicity for humans.[78] They added that this classification "should not be interpreted as a definitive conclusion."" The cancer tests leave many questions unanswered. Concerning one of the carcinogenicity studies, an EPA statistician wrote, "Viewpoint is a key issue. Our viewpoint is one of protecting the public health when we see suspicious data. Unfortunately, EPA has not taken that viewpoint in its assessment of glyphosate's cancer-causing potential.

There are no publicly available laboratory studies of the carcinogenicity of Roundup or other glyphosate-containing products.

Mutagenicity

Although glyphosate's manufacturer describes "a large battery of assays"[80] showing that glyphosate does not cause genetic damage,[80] other studies have shown that both glyphosate and glyphosate products are mutagenic. Glyphosate-containing products are more potent mutagens than glyphosate.[81] The studies include the following:

In fruit flies, Roundup and Pondmaster (an aquatic herbicide consisting of glyphosate and a trade secret surfactant[82]) both increased the frequency of sex-linked, recessive lethal mutations. (These are mutations that are usually visible only in males. Only a single concentration was tested in this study .[83]

A study of human lymphocytes (a type of white blood cell showed an increase in the frequency of sister chromatid exchanges following exposure to the lowest dose tested of Roundup.[84] (Sister chromatid exchanges are exchanges of genetic material during cell division between members of a chromosome pair. They result from point mutations.) A 1997 study of human lymphocytes (see Figure 4) found similar results with Roundup (at both doses tested and with glyphosate (at all but the lowest dose tested).[81]

In *Salmonella* bacteria, Roundup was weakly mutagenic at two concentrations. In onion root cells, Roundup caused an increase in chromosome aberrations, also at two concentrations. [85]

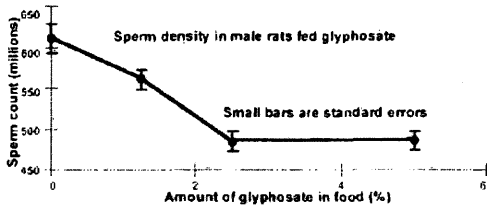
In mice injected with Roundup, the frequency of DNA adducts (the binding to genetic material of reactive molecules that lead to mutations) in the liver and kidney increased at all three doses tested.[86] (See Figure 4.)

In another study of mice injected with glyphosate and Roundup, the frequency of chromosome damage and DNA damage increased in bone marrow, liver, and kidney. (Only a single concentration was tested in this study.) [81]

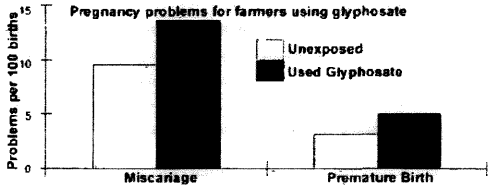
Reproductive Effects

Glyphosate exposure has been linked to reproductive problems in humans. A study in Ontario, Canada, found that fathers' use of glyphosate was associated with an increase in miscarriages and premature births in farm families.[87] (See Figure 5.) In addition, a case report from the University of California discussed a student athlete who suffered abnormally frequent menstruation when she competed at tracks where glyphosate had been used.[88]

Figure 5
Effects of Glyphosate on Male Reproductive Success



U.S. Dept. of Health and Human Services. Public Health Serv. National Inst. Health. 1992. NTP technical report on toxicity studies of glyphosate (CAS No. 1071-83-6) administered in dosed feed to F344/N rats and B6C3Fl mice. Research Triangle Park, NC: National Toxicology Program.



Savitz, D.A. et al. 1997. Male pesticide exposure and pregnancy outcome. *Am. J. Epidemiol.* 146:1025-1036.

Glyphosate exposure is associated with reproductive problems in both laboratory animals and farmers.

Laboratory studies have also demonstrated a number of effects of glyphosate on reproduction.

In rats, glyphosate reduced sperm counts at the two highest doses tested. (See Figure 5.) In male rabbits, glyphosate at doses of 1/10 and 1/100 of the LD_{50} increased the frequency of abnormal and dead sperm.[89]

Using cells taken from Leydig cell testicular tumors in mice, researchers from Texas Tech University showed that exposure to Roundup (but not glyphosate alone caused a decrease in the production of sex hormones. Specifically, Roundup inhibited the expression of a protein that carries cholesterol (the molecule from which sex hormones are made to the site where these hormones are synthesized. Lacking necessary amounts of cholesterol, the testicle cells' production of sex hormones decreased about 90 percent.[89a]

In a study of female rabbits, glyphosate caused a decrease in fetal weight in all treated groups.[90]

Toxicology of Glyphosate's Major Metabolite

In general, studies of the breakdown of glyphosate find only one metabolite, aminomethylphosphonic acid (AMPA).[2] Although AMPA has low acute toxicity (its LD_{50} is 8,300 mg/kg of body weight in rats),[16] it causes a variety of toxicological problems. In subchronic tests on rats, AMPA caused an increase in the activity of an enzyme, lactic dehydrogenase, in both sexes; a decrease in liver weights in males at all doses tested; and excessive cell division in the lining of the urinary bladder in both sexes.[16] AMPA is more persistent than glyphosate; studies in eight states found that the half-life in soil (the time required for half of the original concentration of a compound to break down or dissipate) was between 119 and 958 days.[2] AMPA has been found in lettuce and barley planted a year after glyphosate treatment.[90a]

Quality of Laboratory Testing

Tests done on glyphosate to meet registration requirements have been associated with fraudulent practices.

Laboratory fraud first made headlines in 1983 when EPA publicly announced that a 1976 audit had discovered "serious deficiencies and improprieties" in studies conducted by Industrial Biotest Laboratories (IBT)." Problems included "countless deaths of rats and mice" and "routine falsification of data."[91]

IBT was one of the largest laboratories performing tests in support of pesticide registrations.[91] About 30 tests on glyphosate and glyphosate-containing products were performed by IBT, including 11 of the 19 chronic toxicology studies.[92] A compelling example of the poor quality of IBT data comes from an EPA toxicologist who wrote, "It is also somewhat difficult not to doubt the scientific integrity of a study when the IBT stated that it took specimens from the uteri (of male rabbits for histopathological examination."[93] (Emphasis added.)

In 1991, EPA alleged that Craven Laboratories, a company that performed studies for 262

pesticide companies including Monsanto, had falsified tests.[94] "Tricks" employed by Craven Labs included "falsifying laboratory notebook entries" and "manually manipulating scientific equipment to produce false reports."[95] Roundup residue studies on plums, potatoes, grapes, and sugarbeets were among the tests in question.[96]

The following year, the owner of Craven Labs and three employees were indicted on 20 felony counts.[97] The owner was sentenced to five years in prison and fined $50,000; Craven Labs was fined 15.5 million dollars, and ordered to pay 3.7 million dollars in restitution.[95]

Although the tests of glyphosate identified as fraudulent have been replaced, this fraud casts shadows on the entire pesticide registration process.

Illegal Advertising

In 1996, Monsanto Co. negotiated an agreement with the New York attorney general that required Monsanto to stop making certain health and environmental claims in ads for glyphosate products and pay the attorney general $50,000 in costs." Claims that glyphosate products are "safer than table salt,"98 safe for people, pets, and the environment, and degrade "soon after application "[98] were challenged by the attorney general because they are in violation of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), the national pesticide law.[98] According to the attorney-general, Monsanto had engaged in "false and misleading" advertising.[98]

In 1998, Monsanto Co. negotiated a similar agreement with the New York attorney-general about a different advertisement. The attorney general found that the advertisement featuring a horticulturist from the San Diego Zoo also was "false and misleading" because it implied to consumers that Roundup could be used (contrary to label directions) in and around water.[98a] Monsanto paid $75,000 in costs.[98a]

EPA made a similar determination about Roundup ads in 1998, finding that they contained "false and misleading"[98] claims and were in violation of FIFRA. However, EPA took no action and did not even notify Monsanto Co. about the determination because two years had elapsed between the time that the ads were submitted to EPA and the time that EPA made the determination[99]

Human Exposure

People are exposed to glyphosate through workplace exposure (for people who use glyphosate products on the job), eating of contaminated food, exposure caused by off target movement following application (drift), contact with contaminated soil, and drinking or bathing in contaminated water. The next five sections of this factsheet summarize information about these five routes of exposure. The third section, discussing drift, also covers impacts on plants.

Contamination of Food

Analysis of glyphosate residues is "in general laborious, complex, and costly.[2]

" Glyphosate's manufacturer reported that drift from a ground application in Minnesota damaged 25 acres of corn, and the Washington Department of Agriculture reported damage to 30 acres of onions from a ground application of a glyphosate herbicide."

For this reason, it is not included in government monitoring of pesticide residues in food.[2] The only information available about contamination of food comes from research studies.

Monsanto's studies of residues in food crops found glyphosate in lettuce over five months after treatment (the lettuce was planted four months after treatment). Monsanto also found glyphosate in barley over four months after treatment (the barley was planted one month after treatment) .[90a]

"Significant residues,"[2] according to the World Health Organization, have been identified from pre-harvest use of glyphosate on wheat (to dry out the grain). Bran contains between 2 and 4 times the amount on whole grains. Residues are not lost during baking.[2]

Occupational Exposure

In California, the state with the most comprehensive program for reporting of pesticide-caused illness, glyphosate-containing herbicides were the third most commonly-reported cause of pesticide illness among agricultural workers.[100] Among landscape maintenance workers, glyphosate herbicides were the most commonly reported cause.[101] (Both these statistics come from illness reports collected between 1984 and 1990.) Even when glyphosate's extensive use in California is considered, and the illness statistics presented as "number of acute illnesses reported per million pounds used in California," glyphosate ranked twelfth.[100]

While many of the California reports involve "irritant effects," [102] mostly to the eyes and skin, NCAP's survey of about 100 reports made in 1993, 1994, and 1995 found that over half of them involved more serious effects: burning of eyes or skin, blurred vision, peeling of skin, nausea, headache, vomiting, diarrhea, chest pain, dizziness, numbness, burning of the genitals, and wheezing.[103]

Other occupational symptoms were observed in a flax milling operation in Great Britain. A study compared the effects of breathing dust from flax treated with Roundup with the effects of dust from untreated flax. Treated dust caused a decrease in lung function and an increase in coughing, and breathlessness. [104]

Drift

In general, movement of a pesticide through unwanted drift is "unavoidable."[105] Drift of glyphosate is no exception. Glyphosate drift, however, is particularly significant because drift

"damage is likely to be much more extensive and more persistent than with many other herbicides." [106] This is because glyphosate moves readily within plants so that even unexposed parts of a plant can be damaged. Damage to perennial plants (when not exposed to enough glyphosate to kill them) is persistent, with some symptoms lasting several years.[106] In addition, plant susceptibility varies widely. Some wildflowers are almost a hundred times more sensitive than others; drift in amounts equal to 1/1000 of typical application rates will damage these species.[107]

A simple answer to the question, "How far can I expect glyphosate to travel off site?" is difficult, since drift is "notoriously variable."[108] However, extensive drift of glyphosate has been measured since the 1970s when a California study found glyphosate 800 m (2600 feet) from aerial and ground applications. Similar drift distances were found for the 8 different spray systems tested in this study.[109]

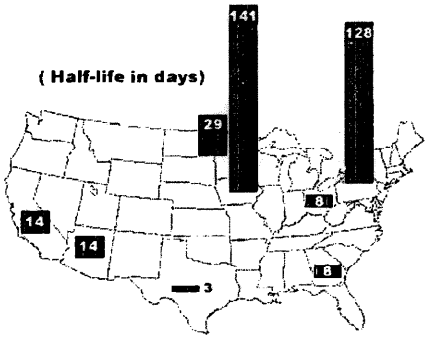
Drift distances that have been measured more recently for the major application techniques include the following:

Ground Applications: A study of 15 noncrop plants found seedling mortality (killing about 10 percent of seedlings) for most of the species tested at 20 meters (66 feet) downwind when using a tractor-mounted sprayer. Seedlings of some sensitive species were killed at 40 meters (131 feet).110 A drift model predicted some native species would be damaged at distances of 80 meters (262 feet).[107] Glyphosate's manufacturer reported that drift from a ground application in Minnesota damaged 25 acres of corn,[111] and the Washington Department of Agriculture reported damage to 30 acres of onions from a ground application of a glyphosate herbicide.[112]

Helicopter applications: A study done in Canada[113] measured glyphosate residues 200 meters (656 feet) from target areas following helicopter applications to forest sites. In this study, 200 meters was the farthest distance at which samples were taken, so the longest distance glyphosate traveled is not known.

Fixed-wing aircraft: Long drift distances occur following applications of glyphosate made from airplanes. Two studies on forested sites conducted by Agriculture Canada (the Canadian agricultural ministry) showed that glyphosate was found at the farthest distance from the target areas that measurements were made (300 and 400 meters, or 984 and 1312 feet).[114, 115] One of these studies[115] calculated that buffer zones of between 75 and 1200 meters (246 feet - 0.75 miles) would be required to protect nontarget vegetation. According to Monsanto, drift from single aerial applications of glyphosate has been extensive enough to damage 1000 trees in one case,[116] 250 acres of corn in another,[117] and 155 acres of tomatoes in a third incident.[118]

Figure 6 Persistence or Glyphosate in U.S. Agricultural Soils



Note: Numbers, as well as the length of the columns, give the half-life, in days, of glyphosate in soil. Half-life is the length of time required for half the applied glyphosate to break down or move out of the test site.

Source: U.S. EPA. Environmental Fate and Effects Division. 1993. Pesticide environmental fate one line summary; Glyphosate. Washington, D.C., May 6.

Glyphosate's persistence in soil varies widely, but its half-life in agricultural soil can be over 4 months.

Persistence and Movement in Soil

Glyphosate's persistence in soil varies widely, so giving a simple answer to the question "How long does glyphosate persist in soil?" is not possible. Half-lives (the time required for half of the amount of glyphosate applied to break down or move away) as low as 3 days (in Texas) and as long as 141 days (in Iowa) have been measured by glyphosate's manufacturer.[119] (See Figure 6.) Initial degradation (breakdown) is faster than the subsequent degradation of what remains.[120] Long persistence has been measured in the following studies: 55 days on an Oregon Coast Range forestry site[121]; 249 days on Finnish agricultural soils[122]; between 259 and 296 days on eight Finnish forestry sites[120]; 335 days on an Ontario (Canada) forestry site[123]; 360 days on 3 British Columbia forestry sites[124]; and, from 1 to 3 years on eleven Swedish forestry sites.[125] EPA's Ecological Effect's Branch wrote, "In summary, this herbicide is extremely persistent under typical application conditions. "[126]

Glyphosate is thought to be "tightly complexed [bound] by most soils"[127] and therefore "in most soils, glyphosate is essentially immobile."[127] This means that the glyphosate will be unlikely to contaminate water or soil away from the application site. However, this binding to soil is "reversible." For example, one study found that glyphosate bound readily to four different soils. However, desorption, when glyphosate unbinds from soil particles, also

occurred readily. In one soil, 80 percent of the added glyphosate desorbed in a two hour period. The study concluded that "this herbicide can be extensively mobile in the soil ...." [123]

Water Contamination

When glyphosate binds readily to soil particles, it does not have the chemical characteristics of a pesticide that is likely to leach into water.[2] (When it readily desorbs, as described above, this changes. However, glyphosate can move into sur face water when the soil particles to which it is bound are washed into streams or rivers.[4] How often this happens is not known, because routine monitoring for glyphosate in water is infrequent.[2]

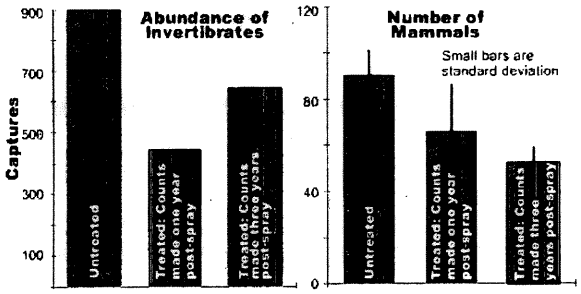
Glyphosate has been found in both ground and surface water. Examples include farm ponds in Ontario, Canada, contaminated by runoff from an agricultural treatment and a spill[129]; the runoff from a watersheds treated with Roundup during production of no-till corn and fescue[130]; contaminated surface water in the Netherlands'; seven U.S. wells (one in Texas, six in Virginia contaminated with glyphosate [131]; contaminated forest streams in Oregon and Washington[132, 133]; contaminated streams near Puget Sound, Washington [134]; and contaminated wells under electrical substations treated with glyphosate.[135]

Glyphosate's persistence in water is shorter than its persistence in soils. Two Canadian studies found glyphosate persisted 12 to 60 days in pond water.[136.137] Glyphosate persists longer in pond sediments (mud at the bottom of a pond). For example, the half-life in pond sediments in a Missouri study was 120 days; persistence was over a year in pond sediments in Michigan and Oregon.[4]

Ecological Effects

Glyphosate can impact many organisms not intended as targets of the herbicide. The next two sections describe both direct mortality and indirect effects, through destruction of food or shelter.

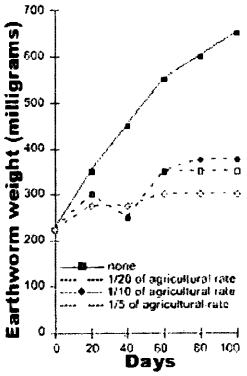
Figure 7 Impacts or Glyphosate on Nontarget Animals on Maine Clear-cuts



Santillo, D.J., D.M. Leslie, and P.W. Brown. 1989. Responses of small mammals and habitat to glyphosate application on clearcuts. J. Wildl. Manage. 53(1):164-172.

Glyphosate treatment reduced invertebrate and small mammal populations for up to 3 years.

Figure 8 Effect or Glyphosate on the Growth or Earthworms



Springer, J.A. and R.A.J. Gray. 1992. Effect of repeated low doses of biocides on the earthworm Aporrectodea caliginosa in laboratory culture. Soil Biol. *Biochem.* 24(12):1739-1744.

Repeated applications of glyphosate reduce the growth of earthworms.

[**Part 1** | **Part 2**]

Glyphosate Factsheet

Part 2 of 2

[Part 1 | Part 2]

Caroline Cox / Journal of Pesticide Reform v.108, n.3 Fall98 rev.Oct00

[More on **Monsanto** and its products]

Effects on Nontarget Animals

Beneficial insects: Beneficial insects kill other species that are agricultural pests. The International Organization for Biological Control found that exposure to freshly dried Roundup killed over 50 percent of three species of beneficial insects: a parasitic wasp, a lacewing, and a ladybug. Over 80 percent of a fourth species, a predatory beetle, was killed.[138] Impacts on beneficial insects have also been shown in field studies, probably due to destruction of their habitat by the herbicide. In North Carolina wheat fields, populations of large carabid beetles declined after treatment with a glyphosate product and did not recover for 28 days.[139] A study of Roundup treatment of hedgerows in the United Kingdom also showed a decline in carabid beetles.[140]

Other insects: Roundup treatment of a Maine clear-cut caused an *89* percent decline in the number of herbivorous (plant-eating insects because of the destruction of the vegetation on which they live and feed. (See Figure 7.) These insects serve as food resources for birds and insect-eating small mammals.[141]

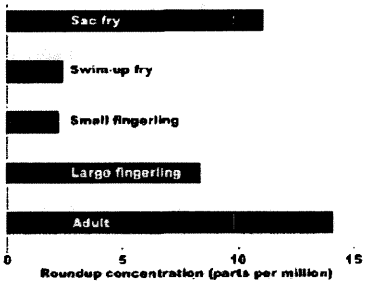
The U.S. Fish and Wildlife Service has identified one endangered insect, a longhorn beetle, that would be jeopardized by use of glyphosate herbicides.[142]

Other arthropods: Glyphosate and glyphosate-containing products kill a variety of other arthropods. For example, over 50 percent of test populations of a beneficial predatory mite were killed by exposure to Roundup.[138] In another laboratory study, Roundup exposure caused a decrease in survival and a decrease in body weight of woodlice. These arthropods are important in humus production and soil aeration.[143] Roundup treatment of hedgerows reduced the number of spiders, probably by killing the plants they preferred for web-spinning.[140] The water flea *Daphnia pulex* is killed by concentrations of Roundup between 3 and 25 ppm.[144-141] Young *Daphnia* are more susceptible than mature individuals.[145] The red swamp crawfish, a commercial species, was killed by 47 ppm of Roundup.[147]

Earthworms: A study of the most common earthworm found in agricultural soils in New Zealand showed that repeated applications of glyphosate significantly affect growth and survival of earthworms. Biweekly applications of low rates of glyphosate *(1/20* of typical rates caused a reduction in growth (see Figure 8), an increase in the time to maturity, and an increase

in mortality.[148]

Figure 9
Toxicity or Roundup to Rainbow Trout or Different Ages



Folmar, L.C., H.O. Sanders, and A.M. John. 1979. Toxicity of the herbicide glyphosate and several of its formulations to fish and aquatic invertebrates. Arch. Environ. Contam. Toxicol. 8269-278.

Young rainbow trout (swim-up fry and small fingerlings) are more susceptible to Roundup than adult rainbow trout.

Fish: Both glyphosate and the commercial products that contain glyphosate are acutely toxic to fish. In general, glyphosate alone is less toxic than the common glyphosate product, Roundup, and other glyphosate products have intermediate toxicity. Part of these differences can be explained by the toxicity of the surfactant (detergent-like ingredient) in Roundup. It is 20 to 70 times more toxic to fish than glyphosate itself.[144]

Acute toxicities of glyphosate vary widely: median lethal concentrations (LC_{50}s; the concentrations killing 50 percent of a population of test animals from 10 ppm to over 200 ppm have been reported depending on the species of fish and test conditions.[2]

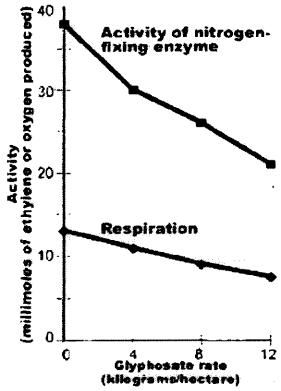
Acute toxicities (LC_{50}) of Roundup to fish range from 2 ppm to 55 ppm.[2] Part of this variability is due to age: young fish are more sensitive to Roundup than are older fish.144 (See Figure 9.) Acute toxicities of Rodeo (used with the surfactant X-77 per label recommendations) vary from 120 to 290 ppm.[149]

In soft water there is little difference between the toxicities of glyphosate and Roundup.[150] Also, if fish have not recently eaten, the toxicity of glyphosate (LC_{50} = 2.9 ppm) is similar to that of Roundup.[151]

Roundup toxicity increases with increased water temperature. In both rainbow trout and bluegills, toxicity about doubled between 7 and 17°C (45 and 63°F).[144] Treatment of riparian areas with glyphosate causes water temperatures to increase for several years following treatment [152] because the herbicide kills shading vegetation. This means that use of glyphosate could cause increased toxicity to fish. In addition, the temperature increase could be critical for fish, like juvenile salmon, that thrive in cold water.

Sublethal effects of glyphosate occur at low concentrations. In rainbow trout and *Tilapia* concentrations of about 1/2 and 1/3 of the LC_{50} (respectively) caused erratic swimming.[153, 154] The trout also exhibited labored breathing.[153] These effects can increase the risk that the fish will be eaten, as well as affecting feeding, migration, and reproduction.[154] Less than 1 percent of the LC_{50} caused gill damage in carp and less than 2 percent caused changes in liver structure.[155]

Figure 10
Effect or Glyphosate on a Nitrogen-Fixing Bacteria



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Birds: Glyphosate has indirect impacts on birds. Because glyphosate kills plants, its use can create a dramatic change in the structure of the plant community. This affects bird populations, since the birds depend on the plants for food, shelter, and nest support.

For example, a study of four glyphosate -treated clear-cuts (and an unsprayed control plot) in Nova Scotia found that the densities of the two most common species of birds (whitethroated

sparrow and common yellowthroat) decreased for two years after treatment. By the fourth year post-spray, densities had returned to normal for these two species. By then the unsprayed plot had been colonized by new species of birds (warblers, vireos, and a hummingbird) which were not found on the sprayed plots.[156]

An earlier three year study of songbird abundance following glyphosate treatment of clear-cuts in Maine forests showed similar results. Abundances of the total number of birds and three common species decreased. The decrease in bird abundance was correlated with decrease in the diversity of the habitat.[157]

Black grouse avoided glyphosate-treated clearcuts in Norway for several years after treatment.[158] Researchers recommended that the herbicide not be used near grouse courtship areas.

Small mammals: In field studies, small mammals have been indirectly affected when glyphosate kills the vegetation they (or their prey) use for food or shelter. On clear-cuts in Maine,[141] insect-eating shrews declined for three years post-treatment; plant-eating voles declined for two. (See Figure 7.) A second study in Maine after a Roundup treatment [159] found similar results for voles. In British Columbia, deer mice populations were 83 percent lower following glyphosate treatment.[160] Another study from British Columbia found declines in chipmunk populations after Roundup treatment.[161] In Norway, there was a "strong reduction" in use of sprayed clear-cuts by mountain hare.[162] Other studies have not found impacts on small mammals,[163] suggesting that the particular characteristics of the site and the herbicide application are significant.

Wildlife: Canadian research has documented that plants serving as important food sources for wildlife are significantly damaged by glyphosate. "Severe" or "very severe damage" was recorded for 46 percent of the important food species eaten by moose, between 34 and 40 percent of the species eaten by elk, and 36 percent of the species eaten by mule deer.[164]

Effects on Nontarget Plants

As a broad-spectrum herbicide, glyphosate has potent acutely toxic effects on most plant species. There are also other kinds of serious effects. These include effects on endangered species, reduced seed quality, reduction in the ability to fix nitrogen, increased susceptibility to plant diseases, and reduction in the activity of mycorrhizal fungi.

Endangered species: Because many plants are susceptible to glyphosate, it can seriously impact endangered plant species. The U.S. Fish and Wildlife Service has identified *74* endangered plant species that it believes could be jeopardized by glyphosate. This list is based on the use of glyphosate on 9 crops, and does not include over 50 other uses.**142**

Seed Quality: Sublethal treatment of cotton with Roundup "severely affects seed germination, vigor and stand establishment under field conditions." At the lowest glyphosate rate tested, seed germination was reduced between 24 and 85 percent and seedling weight was reduced

between 19 and 83 percent.[165]

Nitrogen fixation: Most living things cannot use nitrogen in its common form and instead use ammonia and nitrates, much rarer compounds. Ammonia and nitrates are created by processes called nitrogen fixation and nitrification. They are carried out by bacteria which can be found in soil and in nodules on roots of legumes and certain other plants.[166]

Studies showing effects of glyphosate on nitrogen fixation include the following: At a concentration corresponding to typical application rates, glyphosate reduced by 70 percent the number of nitrogen-fixing nodules on clover planted 120 days after treatment[167]; a similar concentration of a glyphosate herbicide reduced by 27 percent the number of nodules on hydroponically grown clover[168]; a similar concentration of glyphosate reduced by 20 percent nitrogen-fixation by a soil bacteria[169] (see Figure 10); a concentration of glyphosate approximately that expected in soybean roots following treatment inhibited the growth of soybean's nitrogen-fixing bacteria between 10 and 40 percent [170]; and treatment with a glyphosate herbicide at the lowest concentration tested (10 times typical application rates) reduced the number of nodules on clover between 68 and 95 percent.[171]

All of the studies summarized above were done in the laboratory. In the field, such effects have been difficult to observe. However, use of genetically-engineered glyphosate-tolerant crop plants means that nitrogen-fixing bacteria in field situations "could be affected by repeated applications of glyphosate." [170]

Glyphosate also impacts other parts of the nitrogen cycle. A Canadian study found that treatment of a grass field with Roundup increased nitrate loss up to 7 weeks after treatment. The increase was probably caused by the nutrients released into the soil by dying vegetation.[172]

Mycorrhizal fungi: Mycorrhizal fungi are beneficial fungi that live in and around plant roots. They help plants absorb nutrients and water and can protect them from cold and drought.[173] Roundup is toxic to mycorrhizal fungi in laboratory studies. Effects on some species associated with conifers have been observed at concentrations of 1 part per million (ppm), lower than those found in soil following typical applications.[174, 175] In orchids, treatment with glyphosate changed the mutually beneficial interaction between the orchid and its mycorrhizae into a parasitic interaction (one that does not benefit the plant).[176]

Plant diseases: Glyphosate treatment increases the susceptibility of crop plants to a number of diseases. For example, glyphosate increased the susceptibility of tomatoes to crown and root disease[177]; reduced the ability of bean plants to defend themselves against the disease anthracnose[178]; increased the growth of take-all disease in soil from a wheat field and decreased the proportion of soil fungi which was antagonistic to the take-all fungus[179]; and increased soil populations of two important root pathogens of peas.[180] In addition, Roundup injection of lodgepole pine inhibited the defensive response of the tree to blue stain fungus.[181]

Both the inhibition of mycorrhizae and the increased susceptibility to disease have been observed in laboratory, not field, studies. Given the serious consequences these kinds of effects could have, more research is crucial.

Plant Resistance

Plants that are resistant to glyphosate are able to tolerate treatment without showing signs of toxicity. Although many weed scientists argue that "it is nearly impossible for glyphosate resistance to evolve in weeds,"[182] others argue that "there are few constraints to weeds evolving resistance." The second group of scientists appears to be correct. In 1996 an Australian researcher reported that a population of annual ryegrass had developed resistance and tolerated five times the recommended field application rate.[183]

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mindfully.org note: hyperlinks within references have not been checked for accuracy.

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[**Part 1** | **Part 2**]

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The Environment and Disease: Association or Causation?

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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

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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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Etiologic Heterogeneity Among Non-Hodgkin Lymphoma Subtypes: The InterLymph Non-Hodgkin Lymphoma Subtypes Project

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Background Non-Hodgkin lymphoma (NHL) comprises biologically and clinically heterogeneous subtypes. Previously, study size has limited the ability to compare and contrast the risk factor profiles among these heterogeneous subtypes.

Methods We pooled individual-level data from 17 471 NHL cases and 23 096 controls in 20 case–control studies from the International Lymphoma Epidemiology Consortium (InterLymph). We estimated the associations, measured as odds ratios, between each of 11 NHL subtypes and self-reported medical history, family history of hematologic malignancy, lifestyle factors, and occupation. We then assessed the heterogeneity of associations by evaluating the variability (*Q* value) of the estimated odds ratios for a given exposure among subtypes. Finally, we organized the subtypes into a hierarchical tree to identify groups that had similar risk factor profiles. Statistical significance of tree partitions was estimated by permutation-based *P* values (P_{NODE}).

Results Risks differed statistically significantly among NHL subtypes for medical history factors (autoimmune diseases, hepatitis C virus seropositivity, eczema, and blood transfusion), family history of leukemia and multiple myeloma, alcohol consumption, cigarette smoking, and certain occupations, whereas generally homogeneous risks among subtypes were observed for family history of NHL, recreational sun exposure, hay fever, allergy, and socioeconomic status. Overall, the greatest difference in risk factors occurred between T-cell and B-cell lymphomas ($P_{NODE} < 1.0 \times 10^{-4}$), with increased risks generally restricted to T-cell lymphomas for eczema, T-cell-activating autoimmune diseases, family history of multiple myeloma, and occupation as a painter. We further observed substantial heterogeneity among B-cell lymphomas ($P_{NODE} < 1.0 \times 10^{-4}$). Increased risks for B-cell-activating autoimmune disease and hepatitis C virus seropositivity and decreased risks for alcohol consumption and occupation as a teacher generally were restricted to marginal zone lymphoma, Burkitt/Burkitt-like lymphoma/leukemia, diffuse large B-cell lymphoma, and/or lymphoplasmacytic lymphoma/Waldenström macroglobulinemia.

Conclusions Using a novel approach to investigate etiologic heterogeneity among NHL subtypes, we identified risk factors that were common among subtypes as well as risk factors that appeared to be distinct among individual or a few subtypes, suggesting both subtype-specific and shared underlying mechanisms. Further research is needed to test putative mechanisms, investigate other risk factors (eg, other infections, environmental exposures, and diet), and evaluate potential joint effects with genetic susceptibility.

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Non-Hodgkin lymphoma (NHL) is the most common hematologic malignancy and the fifth most common type of cancer in more developed regions of the world (1). Numerous NHL subtypes with distinct combinations of morphologic, immunophenotypic, genetic, and clinical features are currently recognized (2,3). The incidence of NHL subtypes varies substantially by age, sex, and race/ethnicity (4–7). However, the etiological implications of this biological, clinical, and epidemiological diversity are incompletely understood.

The importance of investigating etiology by NHL subtype is clearly supported by research on immunosuppression, infections, and autoimmune diseases, which are the strongest and most established risk factors for NHL. Studies of solid organ transplant recipients and individuals infected with HIV demonstrate that risks are markedly increased for several—but not all—NHL subtypes (8–13). Some infections and autoimmune diseases are associated with a single specific subtype [eg, human T-cell lymphotropic virus, type I (HTLV-I) with adult T-cell leukemia/lymphoma (14), celiac disease with enteropathy-type peripheral T-cell lymphoma (PTCL) (15–17)], whereas others [eg, Epstein–Barr virus, hepatitis C virus (HCV), Sjögren's syndrome (18–21)] have been associated with multiple subtypes.

In the last two decades, reports from individual epidemiological studies of NHL have suggested differences in risks among NHL subtypes for a wide range of risk factors, but most studies have lacked the statistical power to assess any differences quantitatively and have not systematically evaluated combinations of subtypes. One study assessed multiple risk factors and found support for both etiologic commonality and heterogeneity for NHL subtypes, with risk factor patterns suggesting that immune dysfunction is of greater etiologic importance for diffuse large B-cell lymphoma (DLBCL) and marginal zone lymphoma than for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and follicular lymphoma (22). However, that analysis was limited to approximately 1300 NHL cases and considered only the four most common NHL subtypes. Pooling data from multiple studies through the International Lymphoma Epidemiology Consortium (InterLymph) have provided substantial insight into associations between specific risk factors and NHL subtypes, with evidence that family history of hematologic malignancy, autoimmune diseases, atopic conditions, lifestyle factors (smoking, alcohol, anthropometric measures, and hair dye use), and sun exposure are associated with NHL risk (19,21,23–32). However, no previous study has compared patterns of risk for a range of exposures for both common and rarer NHL subtypes.

We undertook the InterLymph NHL Subtypes Project, a pooled analysis of 20 case–control studies including 17 471 NHL cases and 23 096 controls, to advance understanding of NHL etiology by investigating NHL subtype-specific risks associated with medical history, family history of hematologic malignancy, lifestyle factors, and occupation. The detailed risk factor profiles for each of 11 NHL subtypes appear in this issue (15–17,33–40). In this report, we assess risk factor heterogeneity among the NHL subtypes and identify subtypes that have similar risk factor profiles.

Methods

Study Population and Data Harmonization

Detailed methodology for the InterLymph NHL Subtypes Project is provided elsewhere in this issue (41). Briefly, the 20 studies included in this pooled analysis fulfilled the following criteria: 1) case–control design with incident, histologically confirmed cases of NHL and 2) availability of individual-level data by December 31, 2011. Contributing studies were approved by local ethics review committees, and all participants provided informed consent before interview.

NHL subtypes were defined according to the World Health Organization (WHO) classification (2,3), and guidelines from the InterLymph Pathology Working Group were used to harmonize NHL subtypes classified using other methods (42,43). Consistent with the WHO, lymphoid leukemias were included in this analysis; however, plasma cell neoplasms were excluded because few studies collected data for these cases. Overall, 70% of cases were originally classified using the WHO classification, with the percentage ranging from 54% for Burkitt/Burkitt-like lymphoma/leukemia (BL) to 100% for marginal zone lymphoma, mantle cell lymphoma, and lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM; Table 1).

Each study collected data in a standardized, structured format by in-person or telephone interviews and/or self-administered questionnaires. In some studies, participants also provided a venous blood sample at the time of interview. We centrally harmonized individual-level, de-identified data for medical history, family history of hematologic malignancy, lifestyle factors, and occupation from each study when data on that factor were available from at least four studies. All of these risk factors were included in this analysis regardless of the subtype-specific results presented elsewhere (15–17,33–40).

Statistical Analysis

We first assessed the overall association between each exposure and NHL using odds ratios (ORs) from unconditional fixed effects logistic regression, adjusting for age, race/ethnicity, sex, and study. Because studies selectively focused on specific NHL subtypes and the resulting distribution of cases was not representative of NHL in the general population, our analysis weighted subtypes (using the R function svyglm) to reflect their prevalence among US adults, which is approximately comparable to NHL subtype distributions in Europe and Australia (Supplementary Table 1, available online). For all analyses, categorical and ordinal variables were transformed into a single continuous covariate by ordering the categories and assigning them to equally spaced values between 0 and 1, as listed in Supplementary Table 2 (available online). Therefore, for binary exposures the OR is the increase in the odds of cancer among exposed individuals, while for categorical and ordinal variables, OR is a summary value approximating the increase in odds among individuals in the highest category, compared to those in the lowest category.

We then assessed the association between each exposure and each NHL subtype, estimating ORs from fixed effects logistic regression, adjusting for age, race/ethnicity, sex, and study. The estimated ORs are presented in a colored array (Figure 1) for statistically significantly associated exposures (described below) and in Supplementary Table 2 (available online) for all exposures. We used these estimated ORs to 1) assess whether the exposure was associated with at least one NHL subtype, 2) evaluate risk factor heterogeneity among NHL subtypes, and 3) cluster the subtypes into groups with similar risk factor profiles.

Table 1. Characteristics of 17 471 non-Hodgkin lymphoma cases and 23 096 controls included in the InterLymph NHL Subtypes Project*

Characteristics	Controls	Total NHL cases	Specified NHL subtypes†										
			DLBCL	FL	CLL/SLL	MZL	PTCL	MCL	LPL/WM	MF/SS	BL	HCL	ALL
Total No.	23 096	17 471	4667	3530	2440	1052	584	557	374	324	295	154	152
No. contributing studies	20	20	19	19	13	13	15	13	11	14	18	5	16
Population-based design, %	77.3	80.2	81.4	82.4	67.9	80.5	80.8	78.1	77.8	86.4	83.7	70.8	68.4
By region, %													
North America	49.6	45.9	44.1	52.5	36.1	53.3	40.6	45.4	41.7	61.4	62.4	0.0	36.8
Northern Europe	28.3	31.6	34.8	31.2	45.7	32.6	41.6	47.4	41.7	20.1	19.7	72.7	38.8
Southern Europe	19.0	18.4	16.2	9.2	17.0	8.3	15.1	3.2	9.4	17.3	16.6	20.8	21.1
Australia	3.0	4.0	4.9	7.1	1.2	5.8	2.7	3.9	7.2	1.2	1.4	6.5	3.3
Cases classified by WHO, %	N/A	68.6	71.1	73.2	81.2	100	90.4	100	100	77.8	53.9	80.5	60.5
Male, %	58.4	57.4	55.2	50.6	66.1	46.8	59.4	74.0	60.7	56.8	70.2	78.6	60.5
Non-Hispanic white, %	93.4	91.5	90.4	91.5	95.7	87.2	87.7	93.9	94.1	83.6	84.4	96.1	86.8
Median age, y‡ (range)	59 (16–98)	60 (17–96)	59 (18–96)	58 (18–91)	64 (28–93)	61 (19–91)	56 (18–88)	62 (22–88)	64 (27–89)	56 (22–84)	53 (18–84)	55 (29–79)	41 (18–91)

* ALL = acute lymphoblastic leukemia/lymphoma; BL = Burkitt/Burkitt-like lymphoma/leukemia; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HCL = hairy cell leukemia; InterLymph = International Lymphoma Epidemiology Consortium; LPL/WM = lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; MCL = mantle cell lymphoma; MF/SS = mycosis fungoides/Sézary syndrome; MZL = marginal zone lymphoma; N/A = not applicable; NHL = non-Hodgkin lymphoma; PTCL = peripheral T-cell lymphoma; WHO = World Health Organization.

† We grouped cases into NHL subtypes according to the WHO classification (2,3) using guidelines from the InterLymph Pathology Working Group (42,43). Total also includes rare subtypes with less than 100 cases (N = 50) and poorly specified subtypes (N = 3292). Most studies had some form of centralized pathology review by at least one expert hematopathologist to confirm the diagnoses. All NHL subtypes were not included in each study, either by design or because that subtype could not be reliably identified based on the available pathology data.

‡ Median age at diagnosis (cases) or interview (controls).

Exposure Category[A]	Specific Exposure	Prevalence (%) Cases	Cntls	P_{ASSET}	P_H	Overall NHL OR (95% CI)
Family history of hematologic malignancy[B]	Any	9.1	5.2	1.6×10^{-22}	3.5×10^{-2}	1.72 (1.54 - 1.93)
	NHL	4.0	2.0	1.7×10^{-13}	5.2×10^{-1}	1.79 (1.51 - 2.13)
	Leukemia	4.2	2.8	1.3×10^{-11}	3.9×10^{-5}	1.51 (1.29 - 1.77)
	Multiple myeloma	0.7	0.4	7.5×10^{-4}	2.2×10^{-2}	1.77 (1.15 - 2.72)
	Hodgkin lymphoma	1.1	0.6	2.0×10^{-3}	4.7×10^{-1}	1.65 (1.18 - 2.29)
Autoimmune disease[C]	Any B-cell activating disease	0.9	0.8	3.8×10^{-22}	9.8×10^{-10}	1.96 (1.60 - 2.40)
	Sjögren's syndrome	0.6	0.1	6.3×10^{-18}	7.3×10^{-9}	7.52 (3.68 - 15.4)
	Systemic lupus erythematosus	0.5	0.2	1.9×10^{-9}	1.8×10^{-1}	2.83 (1.82 - 4.41)
	Any T-cell activating disease	3.4	3.3	5.3×10^{-3}	1.2×10^{-2}	1.07 (0.95 - 1.21)
	Celiac disease	0.4	0.2	5.2×10^{-11}	5.1×10^{-8}	1.77 (1.05 - 2.99)
	Systemic sclerosis/scleroderma	0.1	0.1	5.1×10^{-3}	6.5×10^{-2}	1.03 (0.41 - 2.58)
HCV seropositivity[D]		2.3	2.2	2.3×10^{-8}	2.1×10^{-3}	1.81 (1.39 - 2.37)
Atopic disease[E]	Hay fever	18.2	20.1	9.1×10^{-9}	1.2×10^{-1}	0.82 (0.77 - 0.88)
	Eczema	9.8	9.8	5.0×10^{-5}	2.6×10^{-5}	1.01 (0.93 - 1.10)
	Allergy	22.0	24.4	5.9×10^{-5}	2.4×10^{-1}	0.86 (0.81 - 0.92)
Blood transfusion[F]	Transfusion occurring <1990	14.2	15.5	5.0×10^{-5}	1.3×10^{-2}	0.76 (0.67 - 0.87)
Anthropometric factors[G]	Body mass index as a young adult	21.1	17.9	4.2×10^{-9}	2.8×10^{-1}	1.95 (1.51 - 2.53)
	Height	53.2	52.0	1.7×10^{-3}	2.4×10^{-2}	1.20 (1.08 - 1.32)
Alcohol consumption (≥1 drink per month)	Any alcohol	69.3	72.1	8.9×10^{-9}	6.2×10^{-2}	0.87 (0.81 - 0.93)
	Wine	56.8	57.5	4.9×10^{-9}	1.4×10^{-2}	0.85 (0.79 - 0.91)
	Liquor	37.0	39.9	4.1×10^{-6}	6.6×10^{-1}	0.84 (0.78 - 0.91)
	Beer	44.9	47.2	9.3×10^{-4}	1.4×10^{-1}	0.90 (0.84 - 0.97)
Cigarette smoking[G]	Duration of smoking	57.0	56.7	2.2×10^{-5}	3.2×10^{-9}	1.06 (0.99 - 1.14)
Recreational sun exposure[G]		49.9	53.0	2.7×10^{-6}	7.9×10^{-1}	0.74 (0.66 - 0.83)
Socioeconomic status[G]		43.8	41.1	3.4×10^{-5}	6.1×10^{-2}	0.88 (0.83 - 0.93)
Occupational history[H]	Teacher	8.6	10.0	5.6×10^{-4}	6.2×10^{-3}	0.86 (0.77 - 0.95)
	Painter	2.0	1.8	4.8×10^{-3}	8.6×10^{-2}	1.22 (0.99 - 1.51)
	General farm worker	4.3	3.4	8.2×10^{-3}	3.4×10^{-1}	1.28 (1.10 - 1.50)

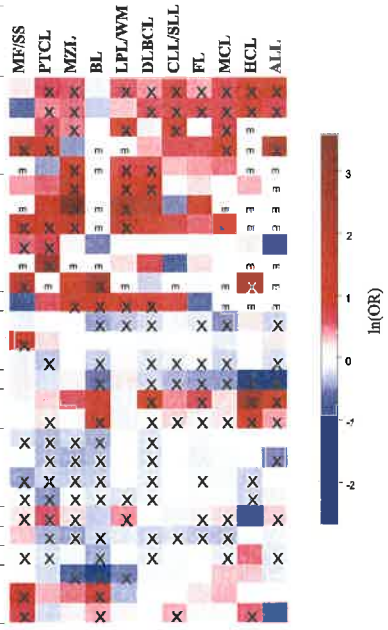


Figure 1. The table lists the overall odds ratio (OR) (95% confidence interval) for all risk factors affecting one or more non-Hodgkin lymphoma NHL subtypes (P_{ASSET} < 0.01), adjusting for age, race/ethnicity, sex, and study. For binary variables, OR compares exposed vs unexposed, and for ordinal variables[G], OR compares highest vs lowest category. The columns list the exposure category, specific exposure, prevalence (all variables dichotomized) in cases and controls, p-value for association (P_{ASSET}), p-value for effect homogeneity (PH), and the OR. The colored grid indicates the log odds ratio associated with the exposure for each subtype separately. **Red (blue)** indicates the exposure increases (decreases) risk. **X** indicates ASSET analysis identified a statistically significant association, whereas **m** indicates missing due to lack of data. For groups of highly correlated exposures (e.g., duration, pack-years smoking), only a single representative variable is listed here. Results for all risk factors are available in Supplementary Table 2 (available online). Subtypes include Burkitt/Burkitt-like lymphoma/leukemia (BL); chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM); mantle cell lymphoma (MCL); marginal zone lymphoma (MZL); mycosis fungoides/Sézary syndrome (MF/SS); peripheral T-cell lymphoma (PTCL). [A] In total, the family history category included 5 variables; autoimmune disease – 16; atopic disease – 5; blood transfusion – 5; anthropometric factors – 5; alcohol – 19, smoking – 7, sun – 2, occupation – 33; hair-dye – 8; reproductive and hormone – 5. [B] Type of hematologic malignancy was coded according to International Classification of Diseases (ICD) as non-Hodgkin lymphoma (NHL) (ICD-9: 200, 202.0-202.2, 202.8-202.9; ICD-10: C82-C85, C96.3), Hodgkin lymphoma (ICD-9: 201, ICD-10: C81), leukemia (ICD-9: 202.4, 203.1, 204-208; ICD-10: C90.1, C91-C95), or multiple myeloma (ICD-9: 203, ICD-10: C90.0, C90.2)). Note that leukemia includes both lymphoid and myeloid leukemias, and lymphoid leukemias and plasma cell neoplasms are not considered part of NHL in ICD, in contrast to the World Health Organization (WHO) classification (2,3) and InterLymph guidelines (42,43). [C] Includes self-reported history of specific autoimmune diseases occurring ≥2 years prior to diagnosis/interview (except the New South Wales study, which did not ascertain date of onset). Autoimmune diseases were classified according to whether they are primary mediated by B-cell or T-cell responses (21,54-57). B-cell activating diseases include Hashimoto thyroiditis, hemolytic anemia, myasthenia gravis, pernicious anemia, rheumatoid arthritis, Sjögren's syndrome, and systemic lupus erythematosus. T-cell activating disease include celiac disease, Immune thrombocytopenic purpura, inflammatory bowel disorder (Crohn's disease, ulcerative colitis), multiple sclerosis, polymyositis or dermatomyositis, psoriasis, sarcoidosis, systemic sclerosis or scleroderma, and type 1 diabetes. [D] Serum antibodies to HCV were evaluated using a third generation enzyme-linked immunosorbent assay (58). [E] Includes self-reported history of atopic conditions occurring ≥2 years prior to diagnosis/interview. Any allergy included plant, food, animal, dust, insect, or mold, but excluded drug allergies. [F] Includes self-reported history of blood transfusions occurring ≥1 year prior to diagnosis/interview. [G] OR represents risk per increasing category of an ordinal variable with categories assigned to equally spaced values between 0 and 1 for body-mass index as a young adult (<18.5, 18.5-22.4, 22.5-24.9, 25.0-29.9, ≥30 kg/m2), height (sex-specific quartiles, males: <172.0, 172.0-177.7, 177.8-181.9, ≥182.0 cm; females: <159.0, 159.0-162.9, 163.0-167.9, ≥168.0 cm), duration of cigarette smoking (0, 1-19, 20-29, 30-39, ≥40 years), recreational sun exposure (hours per week, study-specific quartiles available upon request), and socioeconomic status (low, medium, high; measured by years of education for studies in North America or by dividing measures of education or socioeconomic status into tertiles for studies in Europe or Australia). [H] Occupations (ascertained by complete work history in 8 studies and longest held occupation in 2 studies) were coded according to the International Standard Classification of Occupations (ISCO), Revised Edition 1968 (59).

Specifically, we tested whether the exposure was associated with at least one subtype using ASSET, a subset-based statistical approach (44). ASSET is designed for studies evaluating exposures with multiple related outcomes, such as multiple NHL subtypes. The method has increased statistical power when the exposure is only associated with a subset of outcomes. ASSET gains this advantage by testing for an association with each subset of outcomes. For a given exposure, our first step in this analysis was to collect the Z-statistics ($\hat{\beta}_k / \sqrt{\hat{\sigma}_k^2}$) from the logistic regressions performed separately for each NHL subtype. We then calculated $Z_M = \max_S \left(\left| \sum_{k \in S} w_k Z_k \right| \right)$, where the weights ($w_k$) depended on the number of subjects and S was a set of subtypes. We identified those subtypes in S^*, where $S^* = \text{argmax}_S \left(\left| \sum_{k \in S} w_k Z_k \right| \right)$, as being putatively associated with the exposure and then calculated a P value, P_{ASSET}, for the significance of Z_M by permutation. Exposures with $P_{ASSET} < .01$ are included in Figure 1, and the NHL subtype(s) putatively associated with the exposure are marked with an "X".

We then measured the variability in the ORs among NHL subtypes by the Q value (45), $Q=\sum_k w_k(\hat{\beta}_k-\bar{\beta})^2$, where $\hat{\beta}_k$ and $\hat{\sigma}_k^2$ were the estimates of the log(OR) and its variance for subtype k, $\bar{\beta}=\sum_\kappa w_\kappa\hat{\beta}_\kappa$, and $w_k=\left(\sum_k(1/\hat{\sigma}_k^2)\right)^{-1}(1/\hat{\sigma}_k^2)$. We obtained a P value, $P_{HOMOGENEITY}$, by comparing Q to a χ^2 distribution with $K-1$ degrees of freedom, where K was the number of studies measuring that exposure.

Finally, we clustered subtypes into groups that shared similar associations with each putative risk factor, or with the total collection of risk factors, using a divisive or "top-down" hierarchical clustering method specifically designed for this study. Again, let S be a set of subtypes and S^c be its complement. Let $Y_s=1$ and $Y_s=0$ if a case was diagnosed with a subtype in sets S and S^c, respectively, with Y_s set to missing for all controls. Let p_s be the P value from a case-only logistic regression of Y_s on the risk factor of interest, adjusting for age, race/ethnicity, sex, and study. Let $P_M=\min_S(p_s)$. Then we clustered the subtypes into two groups, S^* and S^{c*}, where $S^*=\text{argmin}_S(p_s)$. We defined P_{NODE} to be the probability that P_M was below the observed value under the null hypothesis and calculated it by 10 000 permutations of subtype assignment. We repeated this clustering procedure on S^* and S^{c*} to continue building the tree. Because the rare subtypes ALL and hairy cell leukemia (N ~ 150 cases) could not be assigned reliably to clusters, we omitted them from this analysis.

When clustering subtypes according to all risk factors (Figure 6), we used a different method for calculating p_s. Had each study included all NHL subtypes and exposures, we could have used the P value from a Wald statistic produced by a single logistic regression. Instead, we used a pseudo-Wald statistic where the log(OR) for each exposure was estimated from a separate analysis. Let $\hat{\beta}_{skj}$ be the parameter from a logistic regression of Y_S on exposure j (adjusting for age, race/ethnicity, sex, and study) in study k, $\hat{\sigma}^2_{skij}$ estimate the covariance between $\hat{\beta}_{ski}$ and $\hat{\beta}_{skj}$, and $\delta_{kj}=1$ if study k includes exposure j. Then we defined

$$\hat{\beta}_{sj}=\sum_{k:\delta_{kj}=1} w_{skj}\hat{\beta}_{skj}$$

where the weights (w_{skj}) were inversely proportional to the estimated variance

$$w_{skj}=\frac{1/\hat{\sigma}^2_{skjj}}{\sum_{k:\delta_{kj}=1}1/\hat{\sigma}^2_{skjj}}$$

and we estimated the covariance of $\hat{\beta}'_s=\{\hat{\beta}_{s1},\ldots,\hat{\beta}_{sN}\}$ by the $N\times N$ matrix $\hat{\Sigma}$ with the i,jth entry defined as

$$\hat{\Sigma}_s[i,j]=\sum_{k:\delta_{ki}\cdot\delta_{kj}=1} w_{ski}w_{skj}\hat{\sigma}^2_{skij}$$

The resulting test statistic, $\hat{\beta}'_s\hat{\Sigma}_s^{-1}\hat{\beta}_s$, was our pseudo-Wald statistic, which was compared to a χ^2 distribution with N degrees of freedom to obtain p_s.

Results

The pooled study population included 17 471 NHL cases and 23 096 controls derived from 14 population-based and six hospital/clinic-based case–control studies. The study population was predominantly male (58%) and non-Hispanic white (93%, Table 1). DLBCL (N = 4667) was the most common and acute lymphoblastic leukemia/lymphoma (ALL, N = 152) was the least common NHL subtype included in this analysis. Hairy cell leukemia cases had the most striking male predominance (79%), whereas marginal zone lymphoma cases had the least (47%). The median age at diagnosis ranged from 41 years for ALL cases to 64 years for CLL/SLL and LPL/WM cases.

Risk Factors for One or More NHL Subtypes

We identified family history, medical history, lifestyle, and occupational risk factors that were associated with one or more NHL subtypes ($P_{ASSET}<.01$, Figure 1; Supplementary Table 2, available online, contains results for all risk factors). For highly correlated variables ($r>0.8$; eg, duration and pack-years of smoking), we selected the variable with the smaller P_{ASSET}. The total number of variables we analyzed and the correlation among variables within each risk factor category are provided in Figure 1.

Family history of any hematologic malignancy in a first-degree relative was the most statistically significant risk factor ($P_{ASSET}=1.6\times10^{-22}$), with associations observed for family history of NHL ($P_{ASSET}=1.7\times10^{-13}$), leukemia ($P_{ASSET}=1.3\times10^{-11}$), multiple myeloma ($P_{ASSET}=7.5\times10^{-4}$), and Hodgkin lymphoma ($P_{ASSET}=.0020$). Some autoimmune diseases also were strongly associated with one or more NHL subtypes. The association for B-cell-activating autoimmune disease ($P_{ASSET}=3.8\times10^{-22}$) was driven by Sjögren's syndrome ($P_{ASSET}=6.3\times10^{-18}$) and systemic lupus erythematosus ($P_{ASSET}=1.9\times10^{-8}$), whereas the association for T-cell-activating autoimmune disease ($P_{ASSET}=.0053$) was driven mainly by celiac disease ($P_{ASSET}=5.2\times10^{-11}$) and also by systemic sclerosis/scleroderma ($P_{ASSET}=.0051$). Other medical history factors associated with one or more NHL subtypes included HCV seropositivity ($P_{ASSET}=2.3\times10^{-8}$), hay fever ($P_{ASSET}=9.1\times10^{-9}$), eczema ($P_{ASSET}=5.0\times10^{-5}$), allergy ($P_{ASSET}=5.9\times10^{-5}$), and blood transfusion before 1990 ($P_{ASSET}=5.0\times10^{-5}$).

Among the lifestyle factors we examined, associations with one or more NHL subtypes were observed for body mass index as a young adult ($P_{ASSET}=4.2\times10^{-9}$); height ($P_{ASSET}=.0017$); alcohol consumption ($P_{ASSET}=8.9\times10^{-8}$), including wine ($P_{ASSET}=4.9\times10^{-9}$), liquor ($P_{ASSET}=4.1\times10^{-6}$), and beer ($P_{ASSET}=9.3\times10^{-4}$); duration of cigarette smoking ($P_{ASSET}=2.2\times10^{-5}$); recreational sun exposure ($P_{ASSET}=2.7\times10^{-6}$); and socioeconomic status ($P_{ASSET}=3.4\times10^{-5}$). Certain occupations also were associated with one or more NHL subtypes, specifically occupation as a teacher ($P_{ASSET}=5.6\times10^{-4}$), painter ($P_{ASSET}=.0048$), or general farm worker ($P_{ASSET}=.0082$).

Effect of Heterogeneity Among NHL Subtypes for Specific Risk Factors

Among family history variables, the greatest heterogeneity among NHL subtypes was observed for family history of leukemia ($P_{HOMOGENEITY}=3.9\times10^{-5}$), which increased risk 2.41-fold for CLL/SLL, 2.19 for LPL/WM, 1.98 for mantle cell, and 1.84 for PTCL

(P_{NODE} = 4.0×10^{-4}), versus weaker (OR = 1.66 for marginal zone lymphoma) or null associations for the other subtypes (Figure 2A). Risk associated with family history of multiple myeloma also was statistically significantly different among NHL subtypes ($P_{HOMOGENEITY}$ = .022), with particularly elevated risks for MF/SS (OR = 6.11, P_{NODE} = .027) compared with weaker or null associations (OR ≤ 3.10) for the other subtypes that were not statistically significantly heterogeneous (Figure 2B). In contrast, family history of NHL or HL increased risk for NHL overall by 1.79- and 1.65-fold, respectively, with no statistically significant heterogeneity in risks among NHL subtypes (NHL: $P_{HOMOGENEITY}$ = .52, P_{NODE} = .94; HL: $P_{HOMOGENEITY}$ = .47, P_{NODE} = .74; Supplementary Table 3, available online, provides the results of the clustering analysis for all risk factors with P_{ASSET} < .01 as listed in Figure 1).

Autoimmune diseases were relatively rare but were associated with the highest ORs for specific NHL subtypes. B-cell-activating autoimmune disease ($P_{HOMOGENEITY}$ = 9.8×10^{-10}) increased risk 5.46-fold for marginal zone lymphoma (P_{NODE} = 1.0×10^{-4}) and 2.61- and 2.45-fold for LPL/WM and DLBCL, respectively (P_{NODE} = .011, Figure 3A). Analyses of specific B-cell-activating autoimmune diseases revealed strikingly increased risk for marginal zone lymphoma associated with Sjögren's syndrome (OR = 38.07, $P_{HOMOGENEITY}$ = 7.3×10^{-9}, P_{NODE} < 1.0×10^{-4}), with weaker associations for LPL/WM (OR = 12.14) and the other subtypes (Figure 3B). ORs for systemic lupus erythematosus ranged from 1.81 to 8.41, but these differences did not reach statistical significance ($P_{HOMOGENEITY}$ = .18, P_{NODE} = .24). T-cell-activating autoimmune disease increased risk for PTCL and MF/SS (OR = 1.95 and 1.66, respectively, $P_{HOMOGENEITY}$ = .012, P_{NODE} = .0054, Figure 3C), with particularly elevated risk for PTCL associated with celiac disease (OR = 14.82, $P_{HOMOGENEITY}$ = 5.1×10^{-8}, P_{NODE} < 1.0×10^{-4}, Figure 3D). ORs for systemic sclerosis/scleroderma ranged from 0.71 to 20.16, but these differences did not reach statistical significance ($P_{HOMOGENEITY}$ = .065, P_{NODE} = .28).

Among the other medical history factors we evaluated, HCV-associated risks differed by NHL subtype ($P_{HOMOGENEITY}$ = .0021), with 3.05-fold increased risk for BL, 3.04 for marginal zone lymphoma, 2.70 for LPL/WM, and 2.33 for DLBCL (P_{NODE} = .010); 2.08-fold increased risk for CLL/SLL (P_{NODE} = .032); and no associations for other subtypes (Figure 4A). Eczema was associated with statistically significantly increased risk for MF/SS (OR = 2.31, $P_{HOMOGENEITY}$ = 2.6×10^{-5}, P_{NODE} < 1.0×10^{-4}) but no other NHL

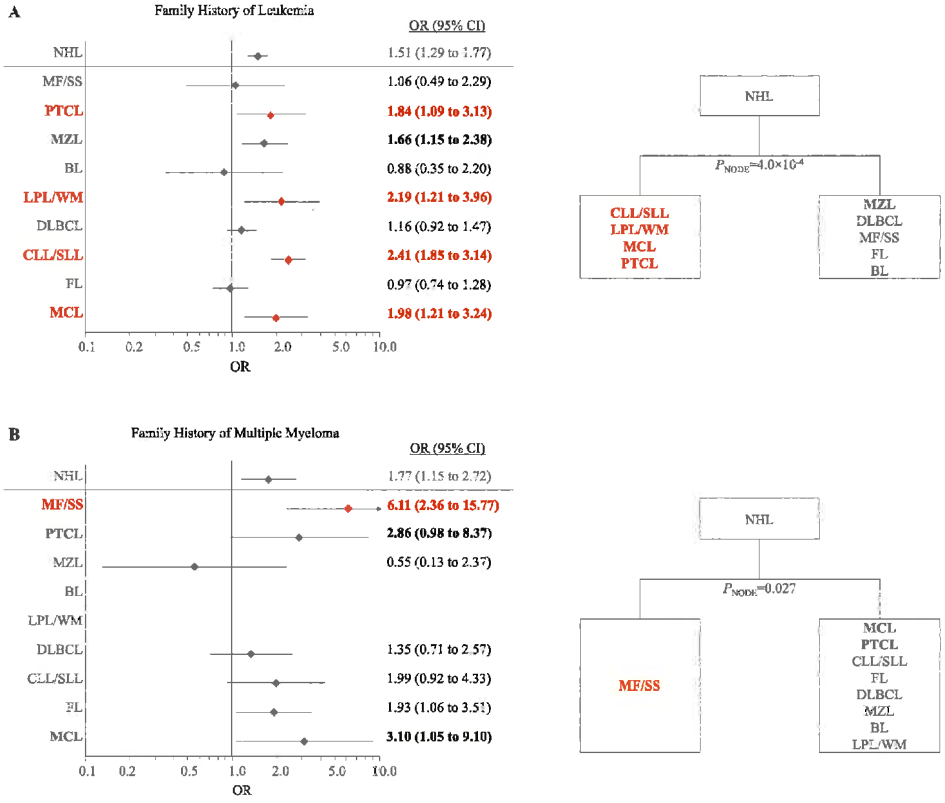


Figure 2. Forest plots list the odds ratio (OR) and 95% confidence interval (CI) for being diagnosed with non-Hodgkin lymphoma (NHL), or its specific subtypes, for individuals with a **(A)** family history of leukemia or **(B)** family history of multiple myeloma, compared to individuals without a family history. ORs were adjusted for age, ethnicity, sex, and study. **Bold font** indicates associated subtypes in ASSET and **colors** represent distinct tree nodes. The trees on the right of the figure split the NHL subtypes into groups of subtypes that were similarly affected by the given exposure. Hairy cell leukemia (HCL) and acute lymphoblastic leukemia/lymphoma (ALL) were excluded from trees because small sample sizes prevented reliable clustering. P_{NODE} is the *P*-value for creation of that node during hierarchical clustering. Subtypes include Burkitt/Burkitt-like lymphoma/leukemia (BL); chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM); mantle cell lymphoma (MCL); marginal zone lymphoma (MZL); mycosis fungoides/Sézary syndrome (MF/SS); peripheral T-cell lymphoma (PTCL).

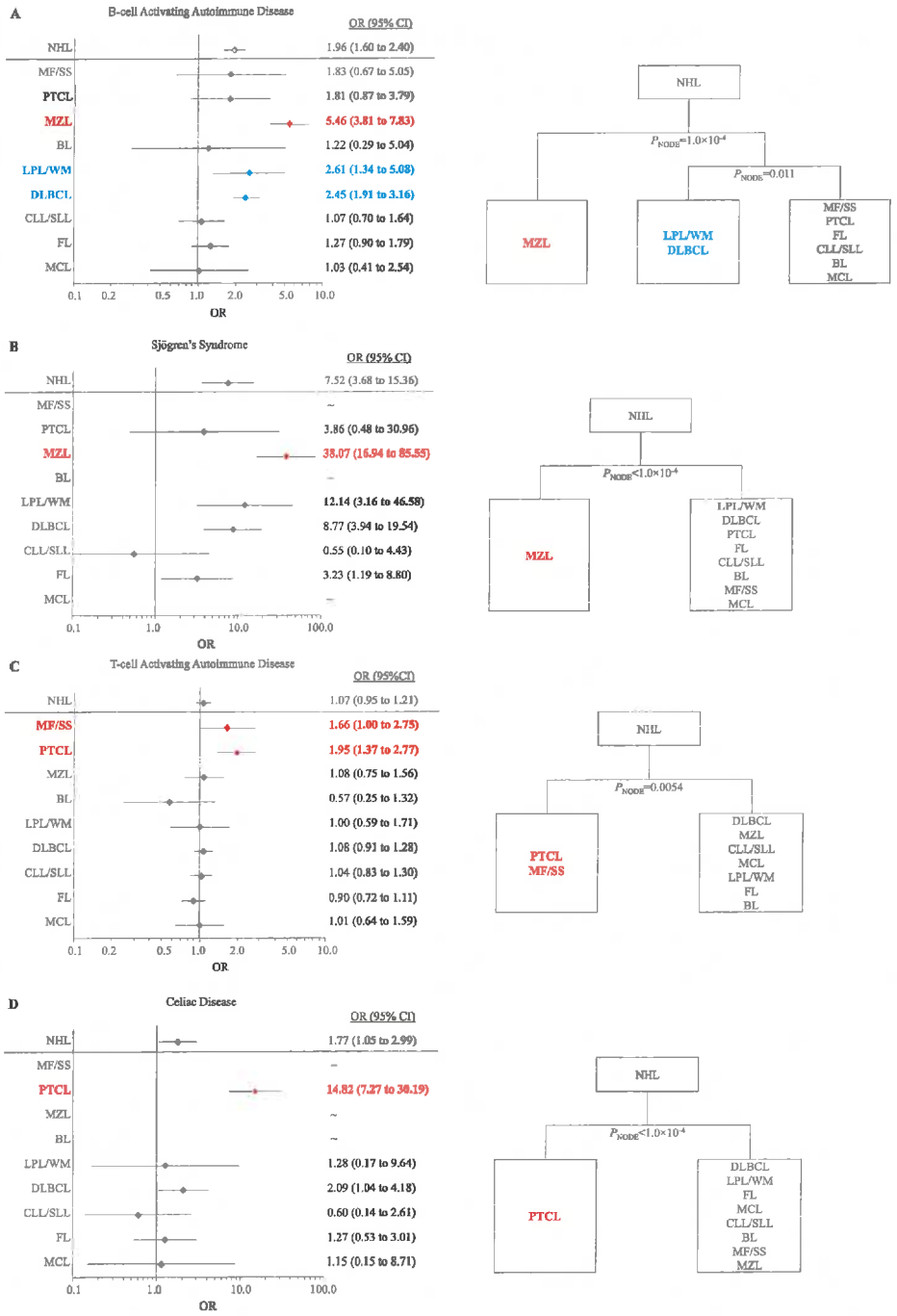


Figure 3. Forest plots list the odds ratio (OR) and 95% confidence interval (CI) for being diagnosed with non-Hodgkin lymphoma (NHL), or its specific subtypes, for individuals with a history of **(A)** B-cell-activating autoimmune disease, **(B)** Sjögren's syndrome, **(C)** T-cell-activating autoimmune disease, and **(D)** celiac disease, compared to individuals without a family history. ORs were adjusted for age, ethnicity, sex, and study. **Bold font** indicates associated subtypes in ASSET and **colors** represent distinct tree nodes. The trees on the right of the figure split the NHL subtypes into groups of subtypes that were similarly affected by the given exposure. Hairy cell leukemia (HCL) and acute lymphoblastic leukemia/lymphoma (ALL) were excluded from trees because small sample sizes prevented reliable clustering. P_{NODE} is the *P*-value for creation of that node during hierarchical clustering. Subtypes include Burkitt/Burkitt-like lymphoma/leukemia (BL); chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM); mantle cell lymphoma (MCL); marginal zone lymphoma (MZL); mycosis fungoides/Sézary syndrome (MF/SS); peripheral T-cell lymphoma (PTCL).

subtype (Figure 4B). The ORs for receipt of a blood transfusion before 1990 ranged from 0.57 to 0.84 for PTCL, DLBCL, CLL/SLL, follicular lymphoma, mantle cell lymphoma, and BL ($P_{HOMOGENEITY}$ = .013, P_{NODE} = .025), whereas the OR was nonsignificantly greater than 1 for MF/SS, LPL/WM, and marginal zone lymphoma (Figure 4C). In contrast, the inverse associations observed for NHL overall did not differ statistically significantly among NHL subtypes for hay fever (OR = 0.82, $P_{HOMOGENEITY}$ = .12, P_{NODE} = .36) and allergy (OR = 0.86, $P_{HOMOGENEITY}$ = .24, P_{NODE} = .084). In analyses of other putative medical history risk factors for NHL, peptic ulcer did not reach the threshold for significance in ASSET but demonstrated evidence for heterogeneity, with risk statistically significantly increased 1.55-fold for marginal zone lymphoma and no association observed for any other NHL subtype (P_{ASSET} = .058, $P_{HOMOGENEITY}$ = .034, P_{NODE} = .0057).

Lifestyle factors and occupations generally exhibited smaller ORs and less heterogeneity among NHL subtypes than medical history and family history factors although some differences were observed. The inverse association between alcohol consumption and NHL showed weak evidence of heterogeneity, with slightly stronger associations for DLBCL, BL, PTCL, and marginal zone lymphoma than other subtypes, particularly for wine consumption

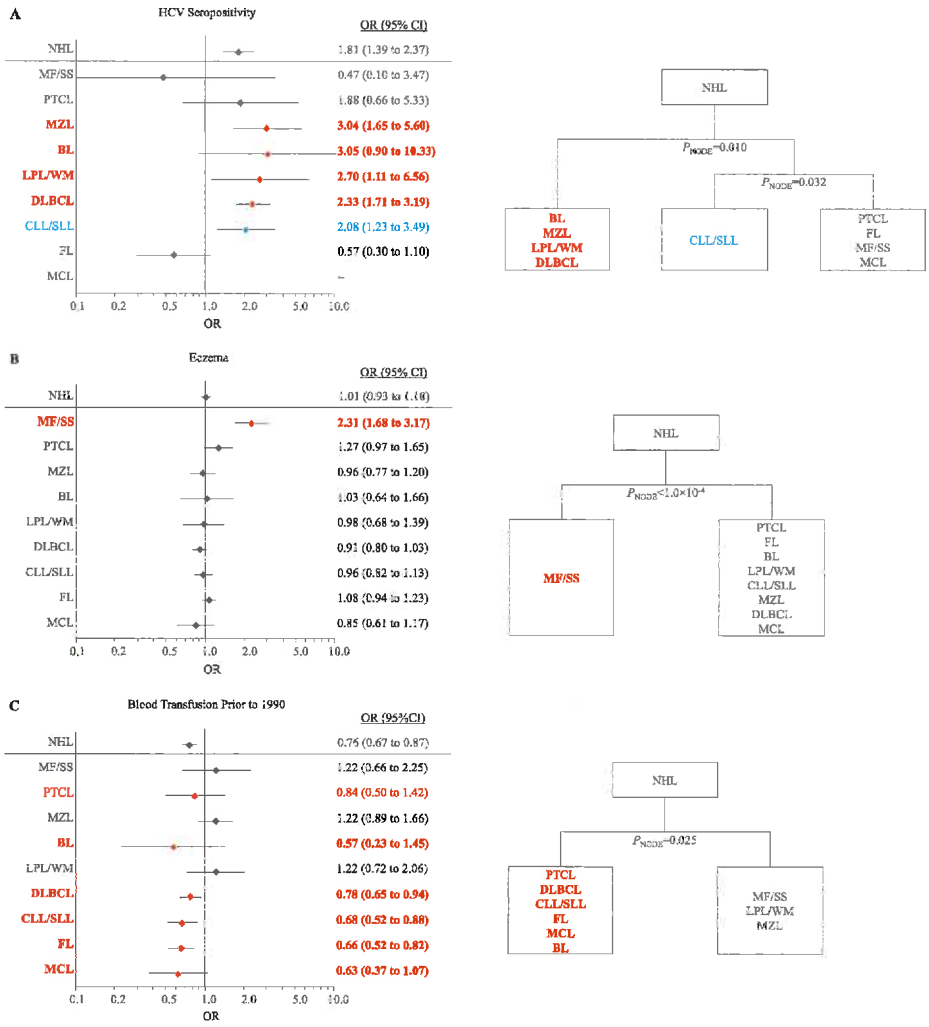


Figure 4. Forest plots list the odds ratio (OR) for being diagnosed with non-Hodgkin lymphoma (NHL), or its specific subtypes, for individuals with **(A)** hepatitis c virus (HCV) seropositivity, **(B)** eczema, and **(C)** blood transfusion prior to 1990, compared to individuals without that condition. ORs were adjusted for age, ethnicity, sex, and study. **Bold font** indicates associated subtypes in ASSET and **colors** represent distinct tree nodes. The trees on the right of the figure split the NHL subtypes into groups of subtypes that were similarly affected by the given exposure. Hairy cell leukemia (HCL) and acute lymphoblastic leukemia/lymphoma (ALL) were excluded from trees because small sample sizes prevented reliable clustering. P_{NODE} is the *P*-value for creation of that node during hierarchical clustering. Subtypes include Burkitt/Burkitt-like lymphoma/leukemia (BL); chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM); mantle cell lymphoma (MCL); marginal zone lymphoma (MZL); mycosis fungoides/Sézary syndrome (MF/SS); peripheral T-cell lymphoma (PTCL).

(ORs = 0.64–0.81, $P_{HOMOGENEITY}$ = .014, P_{NODE} = .098, Figure 5A). Increased duration of cigarette smoking was associated with the greatest increased risk for PTCL and LPL/WM (OR = 1.75 and 1.50, respectively, per increasing category of duration) and more modest increases for marginal zone lymphoma, mantle cell lymphoma, MF/SS, and follicular lymphoma (ORs = 1.19–1.27, $P_{HOMOGENEITY} = 3.2\times10^{-9}$, $P_{NODE} = 1.0\times10^{-4}$), whereas the OR was 1.02 for DLBCL, 0.84 for CLL/SLL, and 0.77 for BL (Figure 5B). Occupation as a teacher was inversely associated with LPL/WM, marginal zone lymphoma, and BL (ORs = 0.27–0.59, $P_{HOMOGENEITY}$ = .0062, P_{NODE} = .035, Figure 5C) but not other subtypes, whereas occupation as a painter increased risk for MF/SS and BL (ORs = 3.42 and 2.28, respectively, $P_{HOMOGENEITY}$ = .085, P_{NODE} = .023, Figure 5D). Usual adult body mass index did not reach the threshold for significance in ASSET but demonstrated some evidence for heterogeneity, with risk statistically significantly increased 1.95- and 1.32-fold for MF/SS and DLBCL, respectively, per increasing WHO category (P_{ASSET} = .018, $P_{HOMOGENEITY} = 3.1\times10^{-4}$, P_{NODE} = .015). For height, risks were statistically nonsignificantly higher for BL than other subtypes (OR = 2.43 per increasing sex-specific quartile versus OR = 1.20 for overall NHL, $P_{HOMOGENEITY}$ = .024, P_{NODE} = .26). In contrast, statistically significant variability among NHL subtypes was not observed for the positive associations for body mass index as a young adult (OR = 1.95 per increasing category of body mass index, $P_{HOMOGENEITY}$ = .28, P_{NODE} = .15) and occupation as a general farm worker (OR = 1.28, $P_{HOMOGENEITY}$ = .085, P_{NODE} = .20) or for the negative associations for recreational sun exposure (OR = 0.74 per increasing quartile of hours per week, $P_{HOMOGENEITY}$ = .79, P_{NODE} = .70) and socioeconomic status (OR = 0.88 per increasing tertile, $P_{HOMOGENEITY}$ = .061, P_{NODE} = .45).

Other putative NHL risk factors that we evaluated, including measures of history of living and/or working on a farm, personal, and/or occupational exposure to hair dye, hormonal/reproductive factors, and occupations other than those listed above, did not reach the threshold for significance in ASSET (P_{ASSET} < .01) and showed no clear evidence of heterogeneity among the NHL subtypes (Supplementary Table 2, available online).

Overall Risk Factor Pattern Among NHL Subtypes

Although the specific patterns of association among NHL subtypes varied by exposure, when all risk factors were taken into account, we observed statistically significant clustering among subtypes. The greatest difference in risk factor patterns was between T-cell and B-cell lymphomas ($P_{NODE} < 1.0\times10^{-4}$, Figure 6). Eczema, occupation as a painter, T-cell-activating autoimmune diseases, family history of multiple myeloma, and cigarette smoking were all more strongly associated with risk for T-cell than B-cell lymphomas although some of these factors were not exclusively associated with T-cell lymphomas. MF/SS and PTCL also were different from one another due to the striking association of eczema with MF/SS (P_{NODE} = .058). Additionally, substantial heterogeneity was observed among B-cell lymphomas for the risk factors that we evaluated, with the tree first separating marginal zone lymphoma and BL ($P_{NODE} < 1.0\times10^{-4}$), then follicular lymphoma and mantle cell lymphoma (P_{NODE} = .017), and finally DLBCL and LPL/WM suggestively separating from CLL/SLL (P_{NODE} = .062). Key risk factors differentiating B-cell NHL subtypes included B-cell-activating autoimmune diseases, hay fever, allergy, alcohol consumption, HCV seropositivity, cigarette smoking, and occupation as a teacher or general farm worker.

Discussion

In this large-scale, international collaborative study, we provide the first comprehensive effort to quantitatively compare similarities and differences in postulated risk factors among both common and rarer NHL subtypes. Based on a novel methodological approach to cluster NHL subtypes according to a broad spectrum of risk factors, the majority of risk factors showed differences in risk among NHL subtypes, whereas fewer factors showed consistent risks among subtypes. Overall, this approach most strongly distinguished T-cell from B-cell lymphomas, with additional heterogeneity among specific types of B-cell lymphoma, although the patterns of effect heterogeneity varied substantially for the different risk factors. These results synthesize the highly detailed analyses of risk factors for individual subtypes discussed elsewhere in this issue (15–17,33–40) and expand previous InterLymph pooled analyses by including data from additional studies and/or reporting risks for rarer NHL subtypes (19,21,24–32).

Our clustering results support the relatively greater importance of immune perturbation in the etiologies of PTCL, marginal zone lymphoma, BL, DLBCL, and LPL/WM compared with MF/SS, CLL/SLL, follicular lymphoma, and mantle cell lymphoma. We found that HCV, autoimmune diseases, and peptic ulcer (a proxy for *Helicobacter pylori* infection), which have previously been reported as NHL risk factors and are thought to increase lymphoma risk through chronic antigenic stimulation (18,46,47), were predominantly associated with PTCL, marginal zone lymphoma, BL, DLBCL, and/or LPL/WM. The importance of immune perturbation is further supported by 1) the patterns of association for autoimmune diseases, whereby B-cell-activating autoimmune diseases were most strongly associated with certain B-cell NHLs and T-cell-activating autoimmune diseases with T-cell NHLs and 2) the particularly elevated site-specific risks associated with autoimmune diseases localized to specific organs, as reported in the analyses for marginal zone lymphoma, PTCL, and DLBCL [eg, celiac disease with enteropathy-type PTCL (15–17)]. Intriguingly, our finding that alcohol consumption and occupation as a teacher were most closely associated with some of these same NHL subtypes raises the hypothesis that these factors also may influence lymphoma risk via an immune-related mechanism. Our observations are consistent with the NHL subtype-specific risks observed in solid organ transplant recipients and individuals with HIV/AIDS, where lymphoma risk is thought to be related to reduced control of lymphomagenic viruses such as Epstein–Barr virus, decreased immunosurveillance capability, and immune activation (8–13,48–51). However, variability in the specific immune-related risk factor associations within this group of NHL subtypes suggests that further research is needed to better understand the specific immune perturbations that contribute to each subtype.

Other risk factors that we evaluated—including family history of leukemia or multiple myeloma, cigarette smoking, some anthropometric measures, blood transfusions, and certain

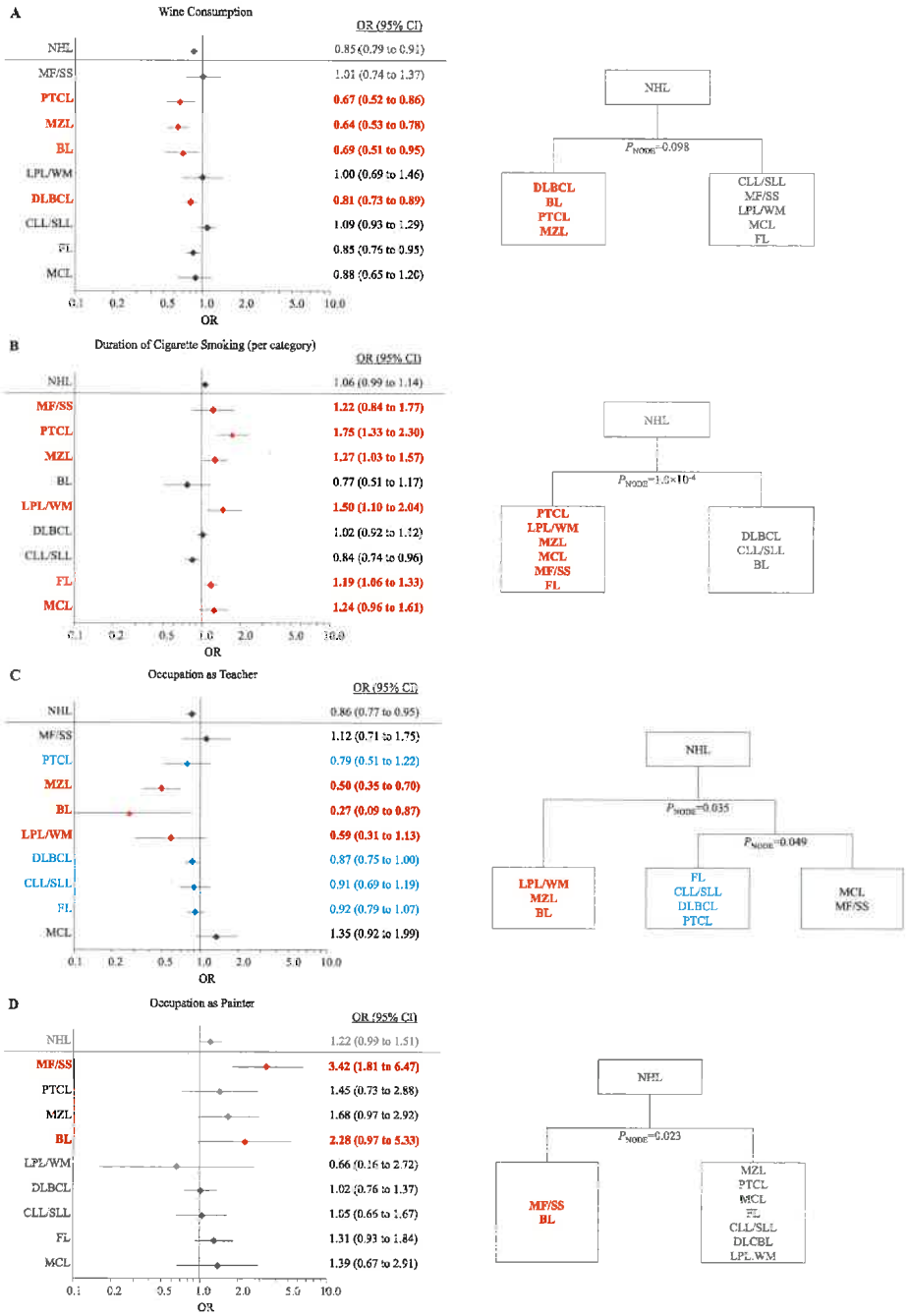
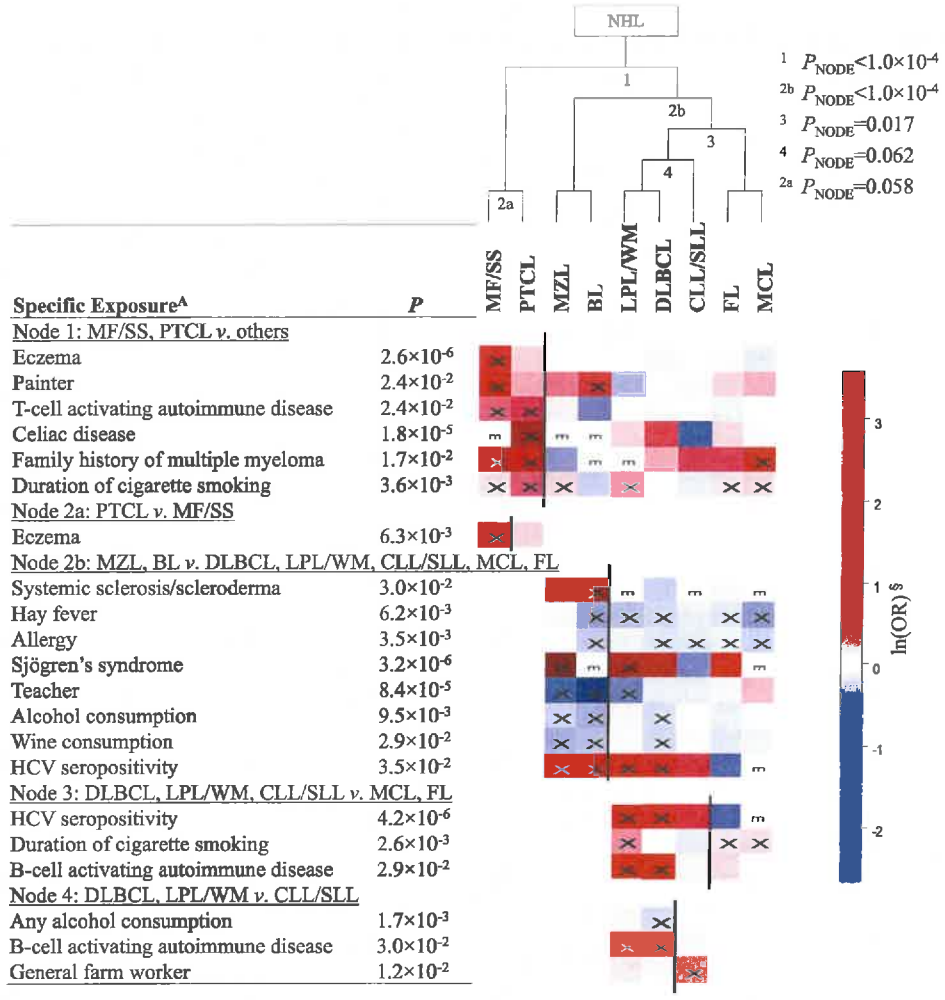


Figure 5. Forest plots list the odds ratio (OR) for being diagnosed with non-Hodgkin lymphoma (NHL), or its specific subtypes, for individuals **(A)** consuming ≥ 1 serving of wine/month; **(B)** smoking longer, smoking duration categorized into groupings of 0, 1–19, 20–29, 30–39, and ≥40 years, with assigned values of 0, 1/4, 2/4, 3/4, and 1 for calculating OR; **(C)** occupation as teacher; and **(D)** occupation as Painter. ORs were adjusted for age, ethnicity, sex, and study. **Bold font** indicates associated subtypes in ASSET and **colors** represent distinct tree nodes. The trees on the right of the figure split the NHL subtypes into groups of subtypes that were similarly affected by the given exposure. Hairy cell leukemia (HCL) and acute lymphoblastic leukemia/lymphoma (ALL) were excluded from trees because small sample sizes prevented reliable clustering. P_{NODE} is the *P*-value for creation of that node during hierarchical clustering. Subtypes include Burkitt/Burkitt-like lymphoma/leukemia (BL); chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM); mantle cell lymphoma (MCL); marginal zone lymphoma (MZL); mycosis fungoides/Sézary syndrome (MF/SS); peripheral T-cell lymphoma (PTCL).



Specific Exposure[A]	P
Node 1: MF/SS, PTCL *v.* others	
Eczema	2.6×10⁻⁶
Painter	2.4×10⁻²
T-cell activating autoimmune disease	2.4×10⁻²
Celiac disease	1.8×10⁻⁵
Family history of multiple myeloma	1.7×10⁻²
Duration of cigarette smoking	3.6×10⁻³
Node 2a: PTCL *v.* MF/SS	
Eczema	6.3×10⁻³
Node 2b: MZL, BL *v.* DLBCL, LPL/WM, CLL/SLL, MCL, FL	
Systemic sclerosis/scleroderma	3.0×10⁻²
Hay fever	6.2×10⁻³
Allergy	3.5×10⁻³
Sjögren's syndrome	3.2×10⁻⁶
Teacher	8.4×10⁻⁵
Alcohol consumption	9.5×10⁻³
Wine consumption	2.9×10⁻²
HCV seropositivity	3.5×10⁻²
Node 3: DLBCL, LPL/WM, CLL/SLL *v.* MCL, FL	
HCV seropositivity	4.2×10⁻⁶
Duration of cigarette smoking	2.6×10⁻³
B-cell activating autoimmune disease	2.9×10⁻²
Node 4: DLBCL, LPL/WM *v.* CLL/SLL	
Any alcohol consumption	1.7×10⁻³
B-cell activating autoimmune disease	3.0×10⁻²
General farm worker	1.2×10⁻²

Figure 6. Top-down heierarchical clustering identified groups of subtypes that had similar risk profiles among significant exposures (P_{ASSET} < 0.01). The tree at the top of the figure illustrates that the first split separated MF/SS and PTCL from the remaining seven subtypes, the second split further divided that larger group, separating MZL and BL from the remaining five subtypes, and so forth. For each split, the table lists the risk factors that distinguish the subtypes in the two resulting nodes at a statistically significant level (p < .05) and the colored grid (similar to Figure 1) indicates the odds ratios for the relevant subtype/risk factor pairings. P_{NODE} is the *P*-value for creation of that node during hierarchical clustering. Hairy cell leukemia (HCL) and acute lymphoblastic leukemia/lymphoma (ALL) were excluded from the tree because small sample sizes prevented reliable clustering. Subtypes include Burkitt/Burkitt-like lymphoma/leukemia (BL); chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM); mantle cell lymphoma (MCL); marginal zone lymphoma (MZL); mycosis fungoides/Sézary syndrome (MF/SS); peripheral T-cell lymphoma (PTCL). [A] Details regarding specific risk factors are provided in the footnote for Figure 1.

occupations—demonstrated heterogeneity among NHL subtypes but no consistent patterns emerged. Detailed consideration of these observed associations and potential biological mechanisms are presented in the NHL subtype-specific analyses in this issue (15–17,33–40). By conducting this analysis among subtypes, two key observations arose. First, our results clearly demonstrated that there is etiologic heterogeneity among NHL subtypes for numerous, but not all, risk factors. However, the inconsistency of some of the patterns suggests that further research is needed to identify the characteristics that may lead to shared etiology among NHL subtypes defined by the WHO classification. Investigation of molecular characteristics is a particularly promising avenue. Molecular characterization of lymphomas has revealed distinct subtypes within existing entities (eg, activated vs germinal center B-cell DLBCL), as well as certain molecular characteristics that may cut across existing entities [eg, Epstein–Barr virus infection, t(14;18) translocations, double-hit lymphomas (52)]. Future research on NHL etiology should explore the potential for relating specific exposures to molecular subtypes of disease. Second, we observed relatively modest associations for many of the risk factors evaluated herein, particularly for lifestyle factors and occupation. Future studies should refine exposure assessment, such as considering relevant periods of exposure, gene–environment interaction, and biomarkers rather than self-reported exposures, and expand research to include other factors not assessed here, such as dietary factors or specific chemicals.

This analysis exemplifies the benefits of international consortial collaboration. Inclusion of more than 17 000 NHL cases provided sufficient statistical power to investigate the etiology of common and rarer NHL subtypes. Across the broad range of exposures we considered in this analysis, we provide the strongest evidence to date of the importance of family history of hematologic malignancy and certain medical conditions, environmental and lifestyle factors, and occupations in lymphoma etiology. Centralized data harmonization with rigorous quality control ensured standardized NHL subtype definitions and exposure variables among studies. Three complementary statistical approaches were used to identify risk factors that were robustly associated with one or more NHL subtypes, quantify the magnitude of the associations, and identify NHL subtypes with similar risk factor patterns. These approaches accounted for the complex pattern of missing data among studies and different sample sizes among NHL subtypes and used permutation-based *P* values to reduce the chance of false positive results. Subtype-specific reports published elsewhere in this issue (15–17,33–40) demonstrate that individual risk factors associated with each subtype generally were independent of one another and that, on the whole, interstudy heterogeneity in risks was not evident despite some differences in exposure prevalence among studies (Supplementary Table 4, available online).

Several key limitations of this project should be considered in the interpretation of our results. It was not feasible to centrally review original pathology reports and materials for all cases, and 30% of the cases were not originally classified according to the WHO. However, each participating study's pathology review procedures, rules for NHL subtype classification, and NHL subtype distribution were reviewed by an interdisciplinary team of pathologists and epidemiologists to ensure that subtype definitions were as consistent as possible among studies and with the WHO classification. Also, the subtype-specific reports confirmed that findings were consistent when restricted to cases classified by the WHO. Despite the large sample size, risk estimates were still unstable for rarer exposures, and the numbers of cases for HCL and ALL were too small to include in the clustering analysis. As with all pooled analyses, data harmonization necessitated broadening of certain exposure categorizations and reduced ability to evaluate detailed exposure characteristics, which might have attenuated risk estimates, and we only considered potential risk factors that were available in at least four contributing studies. Additionally, widely varying sample size among exposures because of variability in data availability among studies may have affected our ability to detect heterogeneity for certain risk factors. Additional limitations inherent to case–control studies include potential for biased risk estimates due to biased study population selection, inaccurate recall of exposures and/or differential recall by cases and controls (53), and reverse causality because exposures were ascertained after disease onset.

In conclusion, we have demonstrated that the etiology of NHL is complex and multifactorial, with substantial heterogeneity among NHL subtypes. Of the risk factors considered in this analysis, most were associated with several subtypes, some were associated with nearly all subtypes, and very few were associated with only a single subtype. Our analysis supports the importance of pooling carefully harmonized data as well as utilizing novel statistical methods to assess risks for specific disease subtypes. Additional research is needed to investigate potential associations with other factors not included in these analyses, such as infectious agents other than HCV, specific environmental and occupational exposures, dietary factors, medications, and genetic susceptibility, particularly for CLL/SLL, follicular lymphoma, and mantle cell lymphoma, which were associated with relatively few risk factors in this analysis. The insights provided by the risk factor patterns that we observed should motivate future research into mechanisms of lymphomagenesis, particularly in understanding the specific immune perturbations that lead to risk of marginal zone lymphoma, BL, LPL/WM, DLBCL, and PTCL. Replication of our results in prospective studies will provide support for the causality of the associations we identified. Further research also is needed to evaluate potential differences in risks for population subgroups, such as by sex or race/ethnicity, and to consider heterogeneity within NHL subtypes, such as by anatomical site or molecular subtype, which is particularly important as our understanding of NHL subtypes continues to evolve. Finally, it will be important to evaluate potential joint effects of risk factors with genetic susceptibility.

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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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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 ≥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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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	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

Agent	Time span, last exposure-diagnosis, years			
	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

Agent	Univariate		Multivariate	
	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 $\approx ((\ln(10))/3.92)^2 \cong 0.35$), 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 14] 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.[37 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.[12 52] Some recent studies have reported excess risk among

manufacturers[53] and farmers,[8] while others have not.[51] 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.[54] Furthermore, a study of professional 2,4-D applicators in Kansas observed an increase in the lymphocyte replication index following application.[55]

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.[55] 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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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

Manisha Pahwa, John J. Spinelli, Laura Beane Freeman, Paul A. Demers, Aaron Blair, Punam Pahwa, James A. Dosman, John R. McLaughlin, Shelia Hoar Zahm, Kenneth P. Cantor, Dennis D. Weisenburger, Shelley A. Harris

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#868 (Pesticides and Other POPs)

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.[6] In mice, malathion increased hepatocellular adenoma or carcinoma (combined).[1c] 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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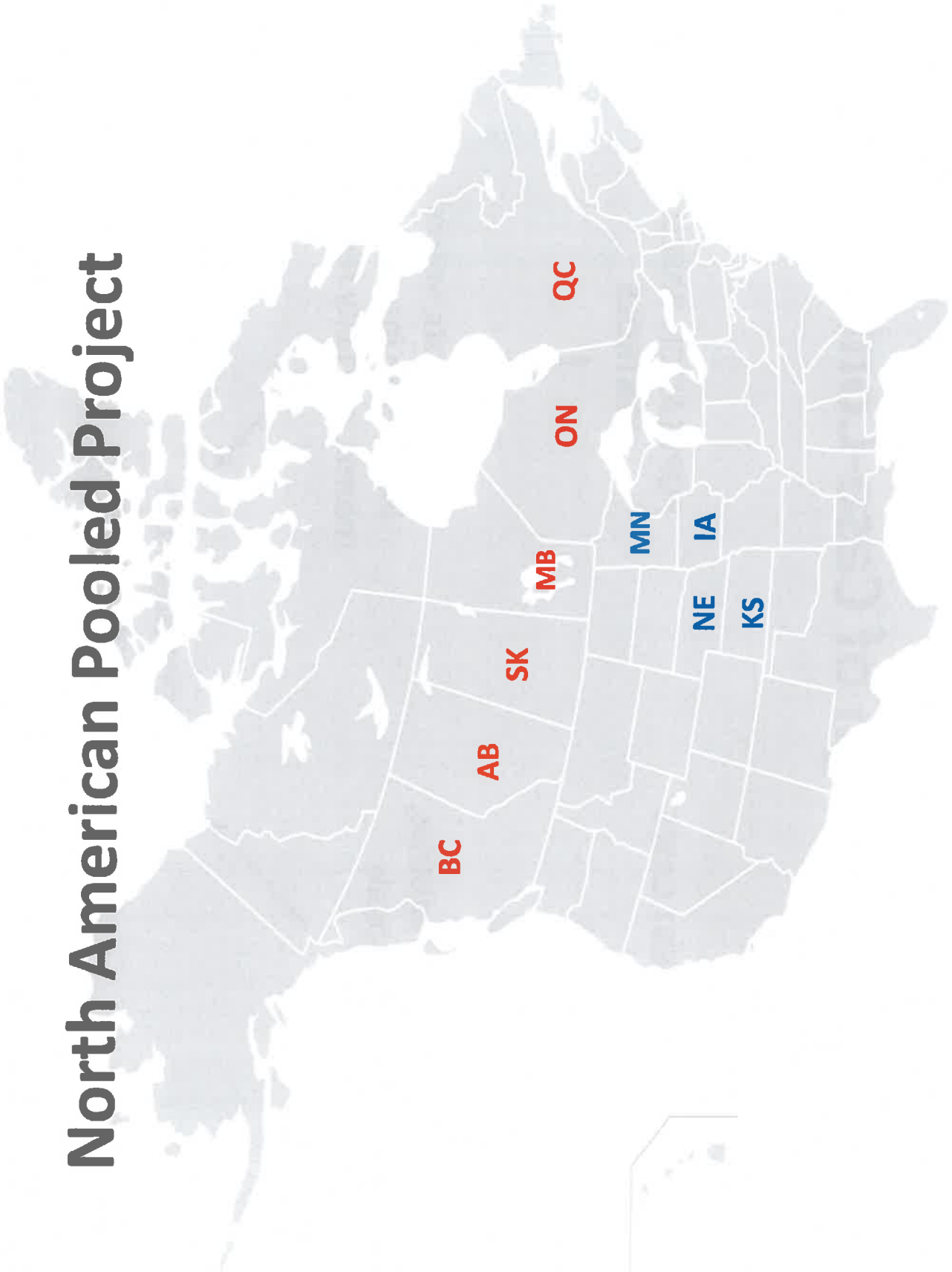
International Survey of Herbicide Resistant Weeds: http://weedscience.org/graphs/geochart.aspx


North American Pooled Project
QC
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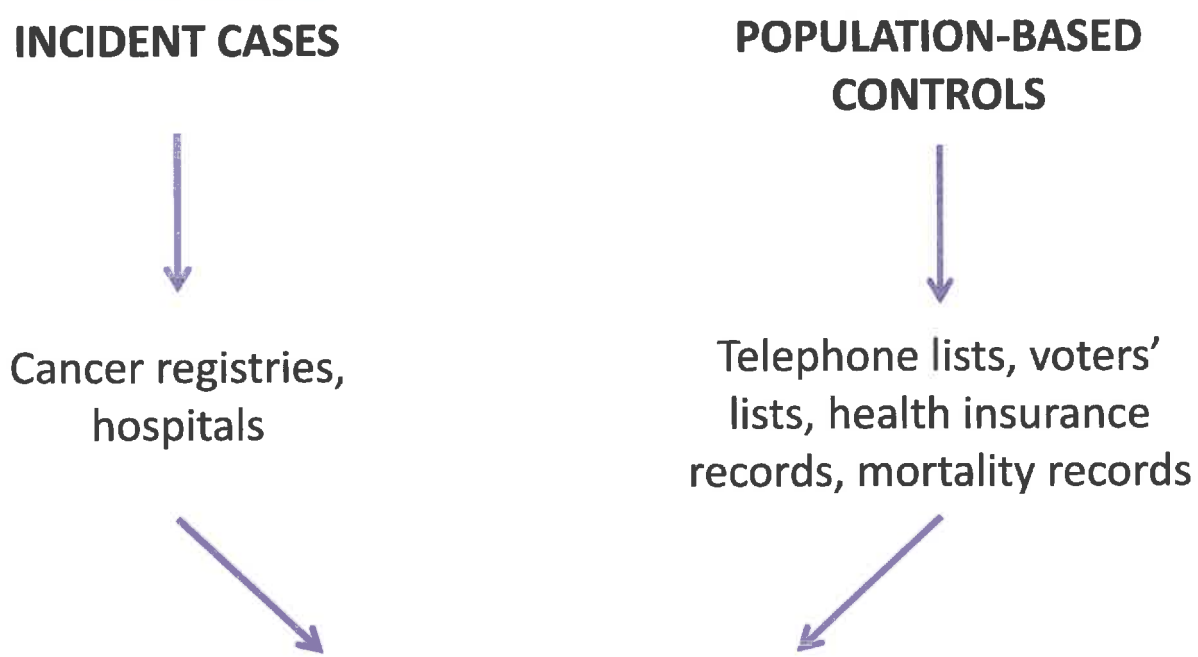
General Design of Case-Control Studies



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

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About NHL and Glyphosate

NHL

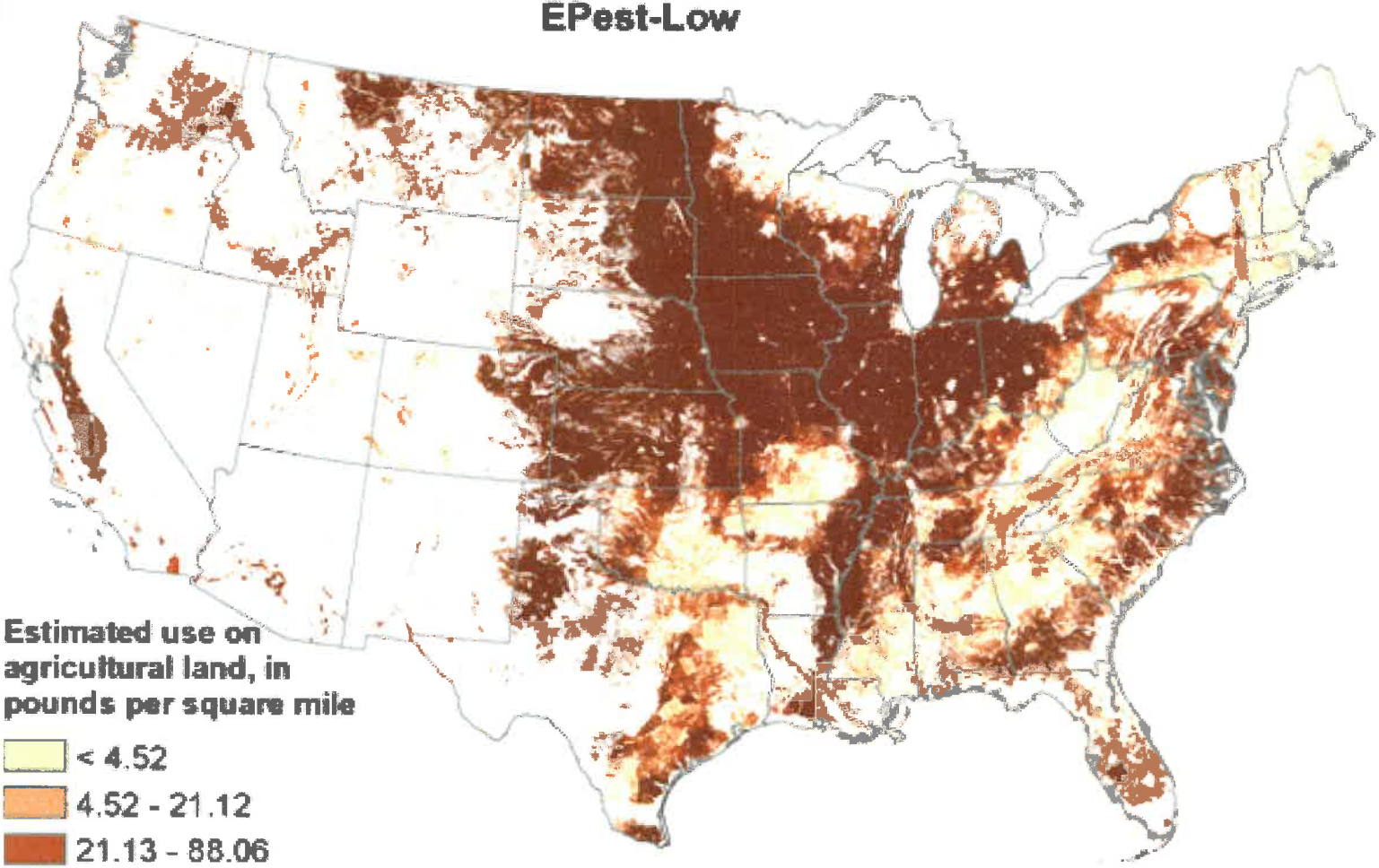
- A cancer that starts in the lymphocytes
- Heterogeneous, according to type of cell affected

Glyphosate

- A broad-spectrum herbicide
- Commonly known as "Roundup"
- The most frequently used herbicide in the world

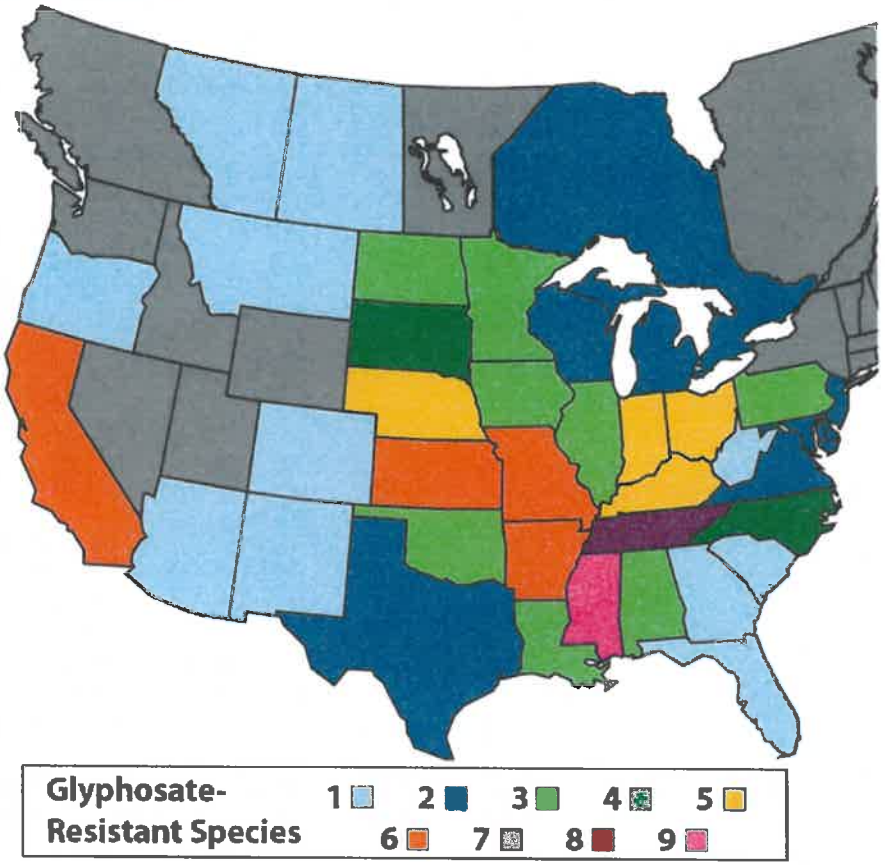
Estimated Agricultural Use for Glyphosate, 2012

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

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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

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- Dennis D. Weisenburger

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TITLE

An evaluation of glyphosate use and the risk of non-Hodgkin lymphoma major histological sub-types in the North American Pooled Project (NAPP)

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WHAT THIS PAPER ADDS

- Exposure to glyphosate, a broad-spectrum and frequently used herbicide, may be associated with non-Hodgkin lymphoma (NHL). Little is known about how risks may differ by glyphosate exposure levels and NHL sub-types.
- To address this research gap, this analysis integrated detailed, self-reported glyphosate use information with assessments of NHL risk overall and by major histological sub-type using pooled data from 1690 NHL cases and 5131 controls from the U.S. Midwest and Canada.
- Subjects who ever used glyphosate had elevated odds ratios for NHL overall and for all subtypes except follicular lymphoma. Significant or nearly significant risks of NHL overall were observed for >2 days per year (OR=2.42, 95% CI: 1.48, 3.96) and >7 lifetime days (OR=1.55, 95% CI: 0.99, 2.44) of glyphosate use, with some differences in risk by sub-type.
- Glyphosate use may be associated with elevated NHL risk. Although the pattern of risks was not clear across exposure categories, these findings from a large dataset offer more precision than results from previous studies.

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ABSTRACT (249)

Objectives: Glyphosate is the most frequently used herbicide worldwide. Some epidemiological studies have found positive associations between glyphosate exposure and non-Hodgkin lymphoma (NHL). This study aimed to evaluate NHL risk overall and by major histological sub-type using detailed glyphosate use metrics.

Methods: The NAPP, composed of pooled case-control studies from the U.S. and Canada, includes NHL cases (N=1690) and controls (N=5131) who provided information on pesticide use. Cases (follicular lymphoma [FL], diffuse large B-cell lymphoma [DLBCL], small lymphocytic lymphoma [SLL], other) from cancer registries and hospitals were frequency-matched to population-based controls. Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) by ever/never, duration, frequency, and lifetime days of glyphosate use. Models were adjusted for age, sex, location, proxy respondent, family history of lymphohematopoietic cancer, and personal protective equipment.

Results: Cases who ever used glyphosate (N=133) had a significantly elevated risk of NHL overall (OR=1.43, 95% CI: 1.11, 1.83). Subjects who used glyphosate for >3.5 years had increased SLL risk (OR=1.98, 95% CI: 0.89, 4.39) and those who handled glyphosate for >2 days/year had significantly elevated odds of NHL overall (OR=2.42, 95% CI: 1.48, 3.96) and DLBCL (OR=2.83, 95% CI: 1.48, 5.41). There were suggestive increases (p-trend ≤0.02) in risk of NHL overall, FL, and SLL with more days/year of glyphosate use.

Conclusions: Glyphosate use may be associated with increased NHL risk. Although risk differences by histological sub-type were not consistent across glyphosate use metrics, the NAPP's large sample size yielded more precise results than possible in previous studies.

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INTRODUCTION

Glyphosate [N-(phosphonomethyl)glycine] is a broad-spectrum herbicide that is one of the most frequently applied pesticides in the world. First developed commercially for agricultural use in the early 1970s, glyphosate quickly became a popular chemical; as of 2012, it was used in more than 750 products with an annual global production volume exceeding 600,000 tonnes (1). In the U.S., the highest levels of agricultural use occur in the mid-west on crops such as corn, soybeans, and wheat (2). These crops are also examples of the many different types of plants that have been genetically engineered to be resistant to glyphosate.

Comment [AB1]: Check to make sure all these crops have genetically modified seed on the market. I do not think that is the case for wheat yet. I think rice was to be available this year.

Glyphosate has been examined as a potential risk factor for lymphatic and hematopoietic cancers including non-Hodgkin lymphoma (NHL). In Canada, NHL ranks as the fifth most incident cancer in males following neoplasms of the prostate, colorectum, lung, and bladder (3). In the American mid-west NHL accounts for an unusually large number of cancers in agricultural areas where populations tend to have lower cancer rates overall (4). The causes of NHL are largely unknown (Hartge P, Wang SS, Bracci PM, Devesa SS, Holly EA. Non-Hodgkin Lymphoma. In Cancer epidemiology and Prevention, 3rd Edition. Shottenfeld D, Fraumeni JF, Jr. (Eds.). Oxford University Press, NY, Ny, 2006), pp. 898-918.). ~~Male~~ NHL has been associated with farming (Blair et al., 1992)~~gender, advanced age, and immune suppression are the best-known risk factors. Agricultural exposures are hypothesized to be involved in the development of NHL~~ and this has prompted studies focused on pesticides.

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In the 1980s and 1990s Four~~four~~ population-based case-control studies were conducted in the U.S. mid-west and six Canadian provinces to examine putative associations between agricultural exposures and pesticides and the risk of NHL. Individual study results showed positive associations between self-reported glyphosate use and NHL risk, although there was variation in the magnitude and statistical significance of risks between studies. In an analysis of the Canadian study the odds ratio [OR] for NHL was 1.26 (95% confidence interval [CI]: 0.87, 1.80) for the use of glyphosate with adjustment for age and province (N=51 exposed cases) (5). The OR was slightly higher from~~A similar risk estimate was found in a separate analysis of men who reportedly ever handled glyphosate in Iowa and Minnesota (6) and higher odds were calculated in~~ a pooled analysis that included 36 exposed male cases from Iowa, Minnesota, Kansas, and Nebraska (logistic regression OR=2.1, 95% CI: 1.1, 4.0 adjusted for age, study site, and other pesticides) (7).

Other studies involving glyphosate exposure and NHL risk have been conducted and many were included in a systematic literature review and meta-analysis of epidemiological studies of pesticide exposure and NHL risk (8). This meta-analysis found~~demonstrated~~ that glyphosate exposure was significantly associated with ~~elevated risks of~~ NHL ~~overall~~ (meta risk ratio [mRR]=1.5, 95% CI: 1.1-2.0, 6 papers). The OR for ~~and~~ B cell lymphoma, ~~(mRR=2.0, 95% CI: 1.1-3.6, 2 papers),~~ a commonly diagnosed NHL sub-type in the regions from which included studies were drawn, was (mRR=2.0, 95% CI: 1.1-3.6, 2 papers). ~~However, meta-analyses were based on a small number of included papers and each study contained low numbers of exposed subjects. Only one included study (9) reported risks by NHL sub-type and only three (5, 9, 10) reported risks by glyphosate exposure level.~~

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A comprehensive evaluation of glyphosate carcinogenicity was recently undertaken by the International Agency for Research on Cancer (IARC) (11). This review of mechanistic, animal, and epidemiological evidence classifiedled to the evaluation of glyphosate as a "probable" (group 2A) carcinogen for NHL based on limited evidence in humans and sufficient evidence in experimental animals. The assessment of limited evidence from epidemiological studies was based on case-control studiesprimarily focused on evidence from case-control studies of occupational glyphosate exposure in the U.S., Canada, and Sweden that reported increased risks of NHL that persisted after adjustment for other pesticides. No association between NHL and use of glyphosate was seend in the Agricultural Health Study (AHS), a large prospective study of farmers and commercial pesticide applicators in the U.S.(11). In bioassays, gGlyphosate was was associated with renal tubule carcinoma, pancreatic islet-cell adenoma, and skin tumors (11). able to cause different cancers in mice, postulated to occur through initiation and promotion. Mechanistic and other data supported the "probable" carcinogen conclusion by providing strong evidence for genotoxicity and oxidative stress, both of which are mechanisms of action that can take place in humans (11).

There are several research gaps that need to be addressed in order to better understand the role and impact of glyphosate exposure on the development ofcancer risk, specifically NHL. Individual studies often have limited power for glyphosate exposure, lack evaluation of NHL by sub-type, and do not adjust risk estimates for other pesticides and other exposures (8, 11). MAdditionally, most studies do not have quantitative exposure data needed to perform more sensitive epidemiological analyses and few have addressed potential effect modifiers to identify if glyphosate exposure has a different impact on NHL risk under certain circumstances. Schinasi and Leon (8) have suggested pooling studies as an attempt to overcome some of these limitations. ; AGRICOH, a consortium of agricultural cohorts, is a global effort of this kind (12). Other existing studies can be similarly leveraged for enhancing our knowledge and understanding about glyphosate exposure and NHL risk.

The North American Pooled Project (NAPP) is a pooled resource of population-based case-control studies previously conducted in the U.S. and Canada. The primary objective of this effortstudy was to provide larger numbers for more detailed analyses of possible relationships between NHL and pesticide use. In this paper we evaluate the association between glyphosate use and the risk of NHL among men and women In the NAPP. In the North American Pooled Project (NAPP), a pooled resource of population-based case-control studies previously conducted in the U.S. and Canada. NHL risk was assessed overall and by histological sub-type using detailed self-reported glyphosate use information and adjustment for other pesticides and possible risk factors. The secondary aim of this study was to examine the effects of personal protective equipment (PPE) on the association between glyphosate use and NHL risk overall.

METHODS

Study population

The NAPP is a large and newly established resource of pooling ofed data from four previously conducted case-control studies of men and women who were diagnosed with soft tissue sarcoma and lymphatic

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and hematopoietic cancers, including NHL, in the U.S. and Canada. NHL cases were recruited from cancer registries and hospitals during the 1980s in four states (Iowa, Minnesota, Kansas, and Nebraska) and between 1991 and 1994 in six provinces (Quebec, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia). Cases were 19 years of age or older in all jurisdictions (I think the 19 age cut is correct, just check each study to make sure). Controls were selected from the general population in each state or province. Selection procedures varied by study but included ~~by~~ random digit dialing, voters' lists, health insurance records, Medicare listings for those older than 65 years, and from state mortality files for deceased cases. Controls were matched to NHL cases in each state/province on the basis of age (±2 or 5 years). In some states, cases and controls were matched on the additional variables of sex (Nebraska), race (Nebraska), and vital status and year of death for deceased cases (Iowa, Minnesota, Nebraska, Kansas). All states and provinces included men; women were only included in Nebraska. Deceased cases and controls were eligible for inclusion in the U.S. ~~case-control~~ studies. The Canadian study only considered alive cases and controls. The present analysis used data from both men and women and from alive and deceased NHL cases (N=1690) and controls (N=5131).

Data collection

Participants, or surrogates, provided detailed information about demographic characteristics, pesticide use, agricultural exposures, and exposure to other known or suspected NHL risk factors including lifestyle, medical and occupational history. Interviewer-administered questionnaires were conducted by telephone (Kansas and Nebraska) or in person (Iowa and Minnesota) with cases and controls or their surrogates if subjects were deceased or too ill to respond themselves. In Canada, all cases and controls were mailed a questionnaire to complete themselves (or by their surrogates). Participants who indicated that they had used pesticides were subsequently interviewed over the telephone for details about their pesticide exposure. The Canadian questionnaire was modified from the telephone interview questionnaires that were used in Kansas and Nebraska. The questionnaires from all case-control studies were very similar since they shared a common research objective, involved overlapping groups of principal investigators, and were developed during the same time period. This made the data highly amenable to pooling ~~at present~~. The complete methodologies of each case-control study have been described by Cantor et al., 1992 (Iowa and Minnesota) (6), Hoar et al., 1986 (Kansas) (13), Zahm et al., 1990 (Nebraska) (14), and McDuffie et al., 2001 (Canada) (5).

The NAPP contains extensive information about pesticide use and agricultural exposures reported by cases and controls. In general, pesticide classifications are available from ~~data were collected beginning with the~~ broad ~~est~~ categories (e.g. occupations with potential pesticide exposure), to ~~followed by~~ major chemical classes (e.g. herbicides), to chemical groups (e.g. phenoxy herbicides), and finally individual compounds (e.g. 2,4-D). For each individual compound reported, information was collected for dichotomous use (ever/never), duration of use (number of years), and frequency of personal handling (number of days/year). Duration data were not collected in Kansas and frequency information was not collected in Iowa, Minnesota, and Kansas ~~and Kansas~~. In Kansas participants were asked to open-endedly recall the details of their pesticide use whereas in all other jurisdictions subjects were prompted by a list of chemicals and their trade names. Participants were also asked to report if they had used any

type of PPE in general (Nebraska and Canada) and with herbicides (Iowa, Minnesota, and Kansas) and specific individual pesticides (Iowa and Minnesota).

Assessment of glyphosate use

Self-reported glyphosate use was examined using several different metrics: dichotomous, duration, frequency, and lifetime days (derived by multiplying number of years used with number of days/year handled). Ordinal categories were created for duration, frequency, and lifetime days analyses based on the median of glyphosate used/handled in controls. Since information about duration of glyphosate use was not collected in Kansas, cases and controls from Kansas were omitted from duration analyses. Similarly, cases and controls from Iowa, Minnesota, and Kansas were excluded from frequency and lifetime days analyses owing to the lack of frequency data collected in these states. Participants who had missing or unknown glyphosate use information, but who were from jurisdictions where glyphosate use information was collected, were coded as "never used" in dichotomous analyses. ; fFor duration and frequency analyses, missing values were assigned based on the median duration or frequency by state/province, age, and NHL sub-type (simple imputation, rounded to the nearest whole number). Subjects who reported that they used glyphosate were coded as "ever used" or used/handled for the number of years and days/year that they had reported. Continuous analyses were also conducted in order to determine possible trends and changes in risk for every 5 years, 5 days/year, and 10 lifetime days of glyphosate use.

NHL classification

NHL cases in these s tudies were diagnosed ~~at different time periods~~ during the 1980s and 1990s. NHL cases were classified in Iowa, Minnesota, and Nebraska according to the Working Formulation (15, 16); in Kansas and Quebec by the International Classification of Diseases for Oncology First Edition (ICD-O-1) (1976) (17); and in Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia by ICD-O-2 (1990) (18). The original histology codes used in each study were revisited to classify NHL cases using a single or similar scheme for the NAPP. We used ICD-O-1 to code NHL overall and sub-types in the NAPP since histological sub-types were classified in all jurisdictions according to ICD-O-1. These sub-types were follicular lymphoma (FL), diffuse large B cell lymphoma (DLBCL), small lymphocytic lymphoma (SLL), and other. The "other" sub-type included all cases whose histologies were unknown or not FL, DLBCL, or SLL. Pathology reviews were conducted on 84% of Canadian cases (5), 87% of Kansas cases (13), and for all interviewed cases in Iowa and Minnesota (6) and Nebraska (14) in order to validate NHL diagnoses.

~~Power and sample size~~

A power and sample size analysis was conducted using the U.S. National Cancer Institute's (NCI) Power Version 3.0 program (19, 20) by inputting the following parameters: number of controls = 5131; number of cases = 1690; control:case ratio = 3; type I error (two-sided) = 0.05; type II error = 0.2; probability of NHL at baseline = 0.04 (21).

Of all 5131 controls available in the NAPP, 244 (4.76%) reported that they ever used glyphosate. A 5% prevalence of pesticide exposure in controls corresponds to a~~perfect~~ power of ~~(~~1.00~~)~~ to detect ORs of

2.00 or higher and a ~~, but lower~~ power of (0.4~~5~~) to detect an OR of 1.25. Given that approximately 5% of controls reported ever being exposed to glyphosate, at a power level of 0.80, a total of 1103 NHL cases would be required to detect an OR of 1.50 (Appendix 1). The numbers of NHL cases and controls in the NAPP appear to be suitable to ~~for~~ detecting low to moderate relative risks associated with glyphosate exposure in this population.

Statistical analyses

Descriptive statistics were used to characterize the study population and identify potentially confounding variables. Based on previously published literature, a priori possible confounders included age, sex, state/province, use of a proxy respondent (5, 6, 22), lymphatic or hematopoietic cancer in a first-degree relative (23), and diagnosis with select medical conditions related to immune suppression (any allergies, food allergies, drug allergies, asthma, hay fever, mononucleosis, arthritis, or tuberculosis; ever received chemotherapy or radiation) (24-26). History of living or working on a farm or ranch was also evaluated as a potential confounder.

It was possible that the use of other pesticides in the NAPP may confound the relationship between glyphosate use and NHL risk. A two-pronged approach was used to identify potentially confounding by other pesticides. First, a correlation matrix of pooled data was produced to determine the presence and extent of correlation between glyphosate and each individual herbicide, insecticide, and fungicide reportedly used by NAPP subjects. Second, previously published articles based on the individual case-control studies comprising the NAPP were searched to identify any positive or significant relationships between individual pesticides and NHL risk, as would be required for confounding to occur. Pesticides that were most strongly correlated with glyphosate (defined in this study as Spearman coefficients ≥0.35 and Cohen's Kappa value ≥0.30) and that were significantly or strongly associated with NHL in previous studies were evaluated as confounders. These were the herbicides 2,4-D (2,4-dichlorophenoxyacetic acid) (5, 6) and dicamba (5, 7), as well as the insecticide malathion (5, 7).

The use of PPE with glyphosate could theoretically modify NHL risk by reducing subjects' exposure to glyphosate. Although such information was sought in some studies, data were on a sizable ~~There was a large~~ proportion of the study subjects ~~missing data for the more specific variables of PPE used for herbicides and glyphosate~~ and. ~~Therefore,~~ effect modification analyses could only be conducted using ~~involving any lifetime PPE use were conducted using data reported by~~ cases and controls from ~~in~~ Nebraska and Canada. Any lifetime PPE usage was also included as a confounding variable in models where it was not evaluated as a possible effect modifier.

Unconditional multiple logistic regression was performed using the LOGISTIC procedure of ~~on~~ the SAS 9.2 statistical software package (SAS Institute, Cary, North Carolina) to calculate pooled ORs and 95% CIs for associations between glyphosate exposure (dichotomous, duration, frequency, lifetime days, and as a continuous variable) and the risk of NHL overall and by histological sub-type (FL, DLBCL, SLL, and other). Primary logistic regression models (OR^a) contained the following variables as confounders: age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, and use of any PPE. Secondary logistic regression models (OR^b) contained the covariates in the primary

model plus reported use of the pesticides 2,4-D, dicamba, and malathion. Medical conditions and history of living or working on a farm or ranch were found not to ~~did not appear to play a role in~~ confounding the relationship between glyphosate use and NHL risk and were not included in the models. Use-response trends for duration, frequency, and lifetime days analyses were deemed to be statistically significant if the two-sided p-value for the ordinal glyphosate use category was ≤0.05. The reference group for all analyses was subjects who never used glyphosate. There was a small proportion of subjects (N=175, 2.57% of all participants) with missing age values; these were imputed based on state/province- and case/control-specific means rounded to the nearest whole number.

Sensitivity tests were conducted by excluding proxy respondents from the main analyses. Proxy respondents were excluded from the analyses of PPE as a potential effect modifier in order to minimize the possibility of bias. For the effect modification analyses, glyphosate use was classified dichotomously and by duration, frequency, and lifetime days and overall NHL risks were calculated using logistic regression models adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, and use of 2,4-D, dicamba, and malathion.

Ethics approval

Approval to conduct this analysis was obtained from the University of Toronto Health Sciences Research Ethics Board (#25166) and an ethics exemption was obtained from the U.S. NCI Office of Human Subjects Research (#11351). Individual studies had obtained human subjects approval prior to collection of the data and aAll participants provided informed consent before taking part in the studies included in the NAPP analyses.

RESULTS

Characteristics of NHL cases and controls

A total of 1690 NHL cases and 5131 controls were available in the NAPP for analysis. All participants were included in analyses that encompassed proxy respondents. For assessments involving the duration of glyphosate use, 1520 cases and 4183 controls were available; in frequency and lifetime days analyses, 898 cases and 2938 controls were included. The numbers of cases and controls available for the sensitivity analyses excluding proxy respondents were smallerlower (Figure 1).

The most frequently diagnosed histological sub-type was DLBCL (38.28%), followed by FL (27.69%), other (23.91%), and SLL (10.12%) (Table 1). Nebraska yielded the highest proportion of cases (22.78%) and controls (27.91%) compared to other states and provinces. The average ages of cases and controls were 62.72 and 61.66 years, respectively. The majority of subjects were male. A similar proportion of proxy respondents were used by cases and controls. Cases were more than twice as likely to report that a first-degree relative was diagnosed with lymphatic or hematopoietic cancer compared to controls (OR=2.13, 95% CI: 1.69, 2.67). Medical history variables were evaluated as potential confounders but they did not have an appreciable impact on adjusted ORs in the main analyses (OR^a and OR^b) and were thus excluded from logistic regression models.

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Missing glyphosate use data

There were 7 cases with missing values for the number of years of glyphosate used and 13 cases with missing values for the number of days/year of glyphosate handled in the jurisdictions where duration and frequency of glyphosate use data were collected. The median values for the number of years of glyphosate use in cases all subjects with missing values ranged from 0-2 based on jurisdiction, NHL sub-type, and age. The median value for days/year for subjects with missing information was 0 (zero).

Glyphosate use and NHL risks overall and by major histological sub-type

Overall, 113/1690 cases (6.69%) and 244/5131 (4.76%) controls reported that they had used glyphosate at any point in their lifetime. There was a significant association between glyphosate use and the risk of NHL overall (OR^a=1.43, 95% CI: 1.11, 1.83) (Table 2). Risks were elevated for most NHL sub-types but the magnitude of risk differed by sub-type. The greatest risk was observed in SLL cases (OR^a=1.77, 95% CI: 0.98, 3.22) and the lowest risk was found for FL (OR^a=1.00, 95% CI: 0.65, 1.54). Similar and significant excesses were observed for DLBCL (OR^a=1.60, 95% CI: 1.12, 2.29) and other (OR^a=1.66, 95% CI: 1.04, 2.63) sub-types. Associations were attenuated and no longer statistically significant when the model represented by OR^a was further adjusted for ever use of 2,4-D, dicamba, and malathion (OR^b). The odds of SLL did not change even after adjusting risk estimates for these three pesticides.

When glyphosate use was examined by duration (Table 2), there was a general inverse trend in risks except for cases of SLL, where the odds increased with longer duration of glyphosate use (OR^a=1.98, 95% CI: 0.89, 4.39 for >3.5 years versus OR^a=1.49, 95% CI: 0.63, 3.58 for >0 and ≤3.5 years) and this trend was of borderline statistical significance (p-trend for OR^a=0.08). Additional adjustment for the chemicals 2,4-D, dicamba, and malathion generally resulted in attenuated risk estimates (OR^b) compared to models unadjusted for these pesticides (OR^a) except for SLL, for which the addition of these agents in logistic regression models had no substantial effect on risk (e.g. for >3.5 years of glyphosate use, OR^b=1.94, 95% CI: 0.79, 4.80).

In contrast to duration of glyphosate use, a more consistent pattern of NHL risk emerged in association with frequency of glyphosate personally handled (Table 2). Subjects who handled glyphosate for >2 days/year had NHL risks that were approximately two times the odds observed in participants who handled glyphosate for >0 and ≤2 days/year. This finding was consistent for NHL overall and all sub-types. Elevated risks in the highest category (>2 days/year) were significant for NHL overall (OR^a=2.42, 95% CI: 1.48, 3.96) and DLBCL (OR^a=2.83, 95% CI: 1.48, 5.41) compared to subjects who did not handle glyphosate at all. Significant trends in risk were also found for NHL overall (p-trend for OR^a=0.02) and DLBCL (p-trend for OR^a=0.04). For NHL overall and DLBCL, ORs associated with handling glyphosate for >2 days/year were attenuated but remained statistically significant even after adjusting for the use of 2,4-D, dicamba, and malathion. The pattern of increased risks with more frequent glyphosate handling was still apparent for NHL overall and all sub-types although trends were no longer statistically significant upon adjusting for these three pesticides.

The analysis of lifetime days, derived from the product of number of years used and days/year handled, generally showed risk increases for NHL overall and most sub-types (except "other") in association with

a greater number of lifetime days of glyphosate use (Table 2). These trends were significant for NHL overall (p-trend for OR^a=0.02), FL (p-trend for OR^a=0.02), and SLL (p-trend for OR^a=0.01). There were elevated risks of NHL among participants who had used glyphosate for >7 lifetime days; this was most pronounced for SLL (OR^a=2.13, 95% CI: 0.76, 5.96). Adjusting for 2,4-D, dicamba, and malathion attenuated risks compared to odds that were unadjusted for these chemicals; however, the general pattern of increased risks remained intact and in some cases (i.e. SLL), was still statistically significant (p-trend for OR^b=0.03).

Sensitivity analysis

Proxy respondents were used for deceased cases and controls and for alive cases who were too ill to respond to the case-control study questionnaires themselves. The use of proxy respondents might have introduced misclassification of glyphosate use. To account for this possibility, glyphosate use data provided by proxy respondents were excluded from the main analysis presented in Table 2. This generally resulted in reduced ORs compared to risks that included data provided by both self- and proxy respondents, with little effect on the width of confidence intervals and the same general patterns of risks for dichotomous, duration, frequency, and lifetime days analyses (Table 3). For instance, there were significant trends for lifetime days of glyphosate use and the risks of NHL overall (p-trend for OR^a=0.04), FL (p-trend for OR^a=0.03), and SLL (p-trend for OR^a=0.01) (Table 3) that paralleled the trends found in the analysis of data provided by both self- and proxy respondents (Table 2).

However, there were some exceptions to this overall observation. Odds ratios for SLL mostly strengthened with the exclusion of proxy respondents in models both unadjusted for 2,4-D, dicamba, and malathion and models adjusted for these chemicals. For instance, among subjects who ever used glyphosate the risk of SLL excluding data from proxy respondents was 1.89 (OR^a, 95% CI: 1.03, 3.49) which was slightly greater than the risk of SLL based on data provided by self- and proxy respondents (OR^a=1.77, 95% CI: 0.98, 3.22). Trends of increasing risk of SLL in association with longer duration, greater frequency and lifetime days of glyphosate use were also marginally stronger when data from proxy respondents were excluded.

Effect of PPE

Potential effect modification by PPE usage was evaluated based on data pooled from Canadian and Nebraskan participants. The association between ever glyphosate use and NHL risk overall was generally higher among subjects who reportedly used any type of PPE in their lifetime (OR=0.83, 95% CI: 0.40, 1.73) compared to subjects who never used any type of PPE (OR=0.65, 95% CI: 0.31, 1.35) (Table 4). This pattern of elevated NHL risks in subjects who ever used PPE compared to subjects who never used PPE persisted when glyphosate use was also evaluated by duration, frequency, and lifetime days. Similar to the results in Tables 2 and 3, there were inverse associations between the duration of glyphosate use and NHL risk and positive (increasing) associations between frequency and lifetime days of glyphosate use and NHL risk, regardless of PPE use status. There were many subjects with unknown or missing PPE use information and they were separately modeled in order to reduce the possibility of analyzing

misclassified PPE use data. Risks were high and unstable in this latter group due to the small number of subjects in each glyphosate usage category.

DISCUSSION

The objective of this study was to evaluate potential associations between glyphosate use and NHL risk in the NAPP, a large pooled dataset with detailed information about glyphosate use reported by 1690 NHL cases and 5131 controls. Glyphosate use was associated with elevated NHL risk, a finding that was consistent with previous analyses. Odds somewhat differed by histological sub-type, although there wasn't a consistent pattern across glyphosate use metrics. The novelty of this analysis and increased precision of risk estimates compared to smaller individual studies were major strengths. Yet, the limitations of this study illustrate the need for more research that can better characterize the relationship between glyphosate exposure and the development of NHL.

This report confirms previous analyses indicating increased risks of NHL in association with glyphosate exposure. The odds of NHL for glyphosate use was 1.43 (OR[a], 95% CI: 1.11, 1.83), a value that was situated approximately in between the risks observed in earlier analyses of the Canadian study (OR=1.26, 95% CI: 0.87, 1.80, adjusted for age and province, N=51 exposed cases) (5) and the three pooled U.S. studies (logistic regression OR=2.1, 95% CI: 1.1, 4.0, adjusted for age, study site, and other pesticides, N=36 exposed cases) (7). Further adjusting OR[a] for the pesticides 2,4-D, dicamba, and malathion resulted in an attenuated risk of NHL overall in the NAPP (OR[b]=1.13, 95% CI: 0.84, 1.51). De Roos et al. (2003) (7) used a more conservative approach, a hierarchical regression model, for assessing NHL risk in the three U.S. pooled case-control studies and found that this reduced the odds of NHL overall (OR=1.6, 95% CI: 0.9, 2.8, adjusted for age, study site, and other pesticides). A statistically significant excess of NHL was found in association with more than 2 days per year of use (OR=2.12, 95% CI: 1.20, 3.73) (5) in the Canadian study, a finding that was in agreement with our analogous pooled risk estimate for NHL (OR[a]=2.42, 95% CI: 1.48, 3.96).

Our results are also aligned with findings from epidemiological studies of other populations that found an elevated risk of NHL for glyphosate exposure and with a greater number of days/year of glyphosate use (9), as well as a meta-analysis of glyphosate use and NHL risk (8). From an epidemiological perspective, our results were supportive of the IARC evaluation of glyphosate as a probable (group 2A) carcinogen for NHL (11).

The large sample size of the NAPP was conducive to analyzing NHL risks with different metrics of glyphosate use. Evaluations of dichotomous glyphosate use showed nearly universal increases in risks of NHL overall and by sub-type, but results were more varied upon further examination by duration, frequency, and lifetime days. The odds of NHL, overall and by sub-type, were higher among subjects who reportedly used glyphosate more often in a year or who had greater cumulative use in their lifetime compared to unexposed subjects. Subjects who used glyphosate reported mostly initiating its use in the year 1980. Glyphosate was used by cases and controls for an average of 5 years and handled for an average of 5 days/year. The short duration of use made it challenging to calculate risks associated with longer-term usage, although the mean frequency of handling was typical of how often farmers

reportedly apply glyphosate to agricultural crops (27). For the days/year and lifetime days analyses some trends and risks were statistically significant while others were not, likely due to the lack of sufficient numbers of exposed cases for some sub-types.

There were some differences in risks by sub-type but these were not consistent between the different glyphosate use metrics and were unlikely to be statistically significant. For example, the significant trends observed for lifetime days of glyphosate use and the risks of NHL overall, FL, and SLL were not present for the frequency analysis, where significant trends were only found for NHL overall and DLBCL. In the duration analysis an upward trend was observed for SLL but not for any of the other sub-types or for NHL overall. Despite these uneven results the risks of FL were consistently lower than other sub-types in association with any of the glyphosate use metrics. There was a relatively large number of FL cases in this analysis compared to the numbers available for other sub-types, lessening the likelihood that findings for FL were primarily due to chance. FL is a type of B-cell lymphoma that is the second most common type of NHL, accounting for 22% of all NHLs (28). The observation of lowered FL risks for glyphosate use in this study was a lead for further evaluation. Additionally, the classification of NHL has changed since the case-control studies in the NAPP were conducted. Multiple myeloma is now considered a sub-type of NHL but was not evaluated in this analysis.

A fairly consistent decrease in NHL risk was found when ORs were further adjusted for the pesticides 2,4-D, dicamba, and malathion. This observation suggested that elevated risks of NHL may be attributed, in part, to pesticides other than glyphosate. Formulations of glyphosate reported by NAPP subjects may have contained other active ingredients. In addition or alternatively, glyphosate may have been used in combination with other pesticide active ingredients at the time of application or in the same growing season or year. It is relatively unknown how combinations of pesticides might interact, and we were not able to evaluate this in our analysis. There is a need to further investigate other individual compounds with respect to NHL risk, such as the herbicide 2,4-D, which IARC recently assessed as possibly carcinogenic to humans based on inadequate evidence in humans and limited evidence in animals for NHL (29).

Glyphosate and covariate data provided by self-respondents generally resulted in attenuated risks compared to odds derived from information provided by both self- and proxy respondents. The proportion of proxy respondents used for cases and controls was similar (about one third). Excluding proxies appreciably reduced the numbers of subjects in the sensitivity analysis which might have partly explained differences in risks. There was also the possibility of exposure misclassification by proxy respondents due to inaccurate recall of glyphosate use, which was likely non-differential (27, 30). Non-differential pesticide exposure misclassification was also an issue amongst self-respondents (31). There was less agreement between self-respondents and surrogates for detailed glyphosate use metrics (years and days/year) compared to the dichotomous variable (32). Nevertheless, significant trends of increasing risks in association with greater lifetime days of glyphosate use persisted for NHL overall, FL, and SLL, even when the analysis was limited to self-respondents.

The evaluation of PPE as an effect modifier of the relationship between glyphosate use and overall NHL risk raised some interesting observations. We expected that the use of any PPE such as masks, gloves,

clothing and/or other equipment may confer a protective effect on the development of NHL from glyphosate use by reducing the probability and degree of dermal, respiratory, and oral contact with glyphosate. However, in this study PPE was found to have no effect on the association between glyphosate use and NHL risk overall. This analysis was limited because PPE usage was not specific to glyphosate use or the type or timing of PPE worn. It was also based on pooled data from Canada and Nebraska only and there was a large proportion of missing data. This hypothesis warrants further investigation in larger studies with more information about PPE used with glyphosate in particular.

The exact causes of lymphatic and hematopoietic cancers are not yet known. A suppressed immune system is the most well established risk factor for NHL. It has been hypothesized that pesticides may play a role in modifying immune function (24-26), but there is little evidence to support this hypothesis for glyphosate specifically (11, 25). An alternative or additional explanation is that pesticides may influence the risk of lymphatic and hematopoietic cancers through pathways involving oxidative stress and receptor-mediated mechanisms. The pathway that glyphosate affects in plants is not present in mammals, but there is strong evidence from mechanistic studies that glyphosate causes genotoxicity and the production of reactive oxygen species (11).

The limitations of this study were primarily related to statistical power for some analyses and the possibility of biases and unmeasured confounding. We endeavoured to use data from all subjects for this analysis as reflected by the inclusion of both men and women and alive and deceased subjects. In Canada alone, 50 NHL cases and 133 controls reported ever using glyphosate; pooling resulted in an additional 63 NHL cases and 111 controls who ever used glyphosate in Iowa, Minnesota, Kansas, and Nebraska. Nevertheless, there were small numbers for some categories of duration, frequency, and lifetime days by NHL sub-type due to the absence of duration data collected in Kansas and frequency and lifetime days information from Iowa, Minnesota, and Kansas. Risk estimates based on small numbers may be unstable and could represent chance findings.

To evaluate possible recall bias of self-reported pesticide use, in the study in Kansas, pesticide suppliers were asked to provide information on crops and pesticide purchases for a sample of 130 subjects with farming experience (13, 27). In the Iowa and Nebraska studies, case recall bias was assessed by comparing information on pesticides used that was volunteered versus information that required probing by the interviewer (14, 27, 33). In the Iowa and Minnesota study, interviews were conducted with both farmers and their wives for a sample of subjects (32). There was a moderate level of correspondence between pesticide use information reported by farmers and their pesticide suppliers in Kansas (13, 27). In Iowa and Nebraska, the number of insecticides and herbicides voluntarily identified was similar and suggested the absence of case-response bias, but probing increased the number of positive responses for individual agents (14, 27, 33). In Iowa and Minnesota, surrogate responders were generally a poorer source of information compared to farmers as they had reported a smaller number of pesticides ever used and a greater proportion of "I don't know" answers (32). No similar analysis of recall bias has been conducted in the Canadian case-control study, but the similarity of study designs between the U.S. and Canada make it likely that recall bias is not a major concern in the Canadian study and NAPP as a whole.

Adjusting for several pesticides (2,4-D, dicamba, and malathion) was a useful way to attempt to disentangle the effect of glyphosate from other pesticides on NHL risk. These agents have been shown to be independently associated with NHL in individual case-control studies (5-7). However, they are somewhat correlated with glyphosate exposure in the NAPP and thus their inclusion as confounders may have introduced some degree of collinearity. Unmeasured confounding by other pesticides, agricultural exposures, or unknown factors cannot be ruled out.

While these results are not independent from previous studies, the evaluations by histological sub-type and for detailed glyphosate use metrics are a new and important contribution to the epidemiological literature. NHL is a constellation of heterogeneous cancers that each has its own causes, risk factors, and etiologies. Pesticides, including individual agents such as glyphosate, may exert different effects on these sub-types, and the large size of the NAPP made it possible to parse this out.

The large sample size also resulted in more precise results than possible in previous smaller studies that only had sufficient power to assess risks for dichotomous glyphosate exposure. We were able to model different glyphosate use categories and identify potential trends in NHL risk by sub-type with increasing duration, frequency, and lifetime days of glyphosate use. This made it possible to characterize possible dose-response relationships between glyphosate exposure and lymphoma risk. The effect modification analysis by PPE further allowed an examination of factors that might modify glyphosate exposure (and risk). Both agricultural and non-agricultural uses of glyphosate were reported by cases and controls in this population-based, pooled case-control study, making this evaluation externally valid.

The results of this analysis may be considered in future scientific and regulatory reviews of glyphosate in North America and globally. Stakeholders may also use these results as part of future approaches that communicate the health risks of pesticides using information directly ascertained from the North American population. This will help to inform efforts aimed at mitigating occupational and environmental exposure to pesticides. It will also provide high-quality risk estimates that can be used in future estimations of the burden of cancer from pesticide exposure.

ACKNOLWEDGEMENTS

The authors thank Mr. Joe Barker at IMS, Inc., for his computer programming services to pool the case-control datasets. The authors also thank all of the principal investigators of the individual case-control studies for allowing the data to be pooled.

COMPETING INTERESTS

The authors declare no competing interests.

FUNDING

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Date of last revision: September 21, 2015

AUTHORS' CONTRIBUTION

MP designed and conducted this analysis and wrote this manuscript. SAH, JJS, and LBF collectively form the NAPP Executive Committee and approved the proposal for this analysis and provided scientific input during the analytic and manuscript preparation phases. AB, SHZ, DDW, and KPC led the original case-control studies in the U.S. JJS, JAM, and JAD were among the principal investigators of the CCSPH in Canada. All co-authors reviewed and approved this manuscript for submission.

DATA SHARING

Unpublished NAPP data is available upon formal request to the NAPP Executive Committee (SAH, JJS, LBF).

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Message

From: Blair, Aaron (NIH/NCI) [V] [redacted]
Sent: 8/26/2015 10:18:52 AM
To: John Spinelli [redacted]; Beane-Freeman, Laura (NIH/NCI) [E] [redacted] 'Pahwa, Manisha' [redacted]; Weisenburger, Dennis [redacted]; Cantor, Kenneth (NIH/NCI) [C] [redacted] Zahm, Shelia (NIH/NCI) [C] [redacted]
CC: Harris, Shelley [redacted] Demers, Paul [redacted]
Subject: RE: Glyphosate and NHL presentation [ISEE Conference]

Attached are the slides with my comments in the Notes at the bottom of each slide.

We need to get prepared for "press" activities. I am sure there is going to be a lot of it after the presentation. I would suggest that that Manisha not deal with the press at the meeting, but wait until back at work where there would be support to consider what to do. I would start developing "talking" points for interviews that we all can look at. Questions would be:
- What do these data say about the IARC evaluation?
- How strong to these findings point to specific histologic types?
- Adjustment for a few pesticides tended to reduce risks from glyphosate, would adjustment for more reduce relative risks further?
Others should add there thoughts.

I think we should notify IARC that this presentation is coming. If the meeting abstract appears on the ISEE website, send that to IARC now. Send them the slides the day of the presentation.

Make modifications to the slides suggested by the coauthors and send us the new version. Do this as quickly as possible, so we can share the slides with others at NCI so they know what is coming.

Aaorn

From: John Spinelli [redacted]
Sent: Tuesday, August 25, 2015 7:50 PM
To: Beane-Freeman, Laura (NIH/NCI) [E]; 'Pahwa, Manisha'; Blair, Aaron (NIH/NCI) [V]; [redacted] Weisenburger, Dennis; Cantor, Kenneth (NIH/NCI) [C]; Zahm, Shelia (NIH/NCI) [C]
Cc: Harris, Shelley; Demers, Paul
Subject: RE: Glyphosate and NHL presentation [ISEE Conference]

Hi Manisha,

I don't have much to add to Laura's comments. I was also very confused about the relevance of the weed-resistance. Is the "Other" category, "Other and NOS", or were the lymphoma NOS discarded?

Do you have any thoughts why duration and frequency are both significant for DLBCL only, but lifetime is significant for FL and SLL, but not DLBCL?

Enjoy Brazil.

John

From: Beane-Freeman, Laura (NIH/NCI) [E] [redacted]
Sent: Tuesday, August 25, 2015 3:19 PM
To: 'Pahwa, Manisha'; Blair, Aaron (NIH/NCI) [V]; [redacted]; John Spinelli; [redacted] Weisenburger, Dennis; Cantor, Kenneth (NIH/NCI) [C]; Zahm, Shelia (NIH/NCI) [C]
Cc: Harris, Shelley; Demers, Paul
Subject: RE: Glyphosate and NHL presentation [ISEE Conference]

Thanks for sharing, Manisha. This has come together nicely. I had a few comments/questions for you.

I do think that you need to acknowledge the previous findings from the individual case-control studies somewhere. IARC cited the results from these studies in their classification, and they provide most of the epi evidence for NHL (Aaron can correct me if I'm wrong on that point). You make the point in the conclusions that these provide more precise effect estimates, but that's hard to evaluate without the individual study results.

It also wasn't clear to me what you meant in the strengths about results not presented when controlled for other pesticides—do you mean other than 2,4-D, dicamba and malathion? It wasn't clear in the presentation why these chemicals were selected—you should probably make that clear.

I also think that for the paper at a minimum, but also a consideration for the presentation, is some test of heterogeneity for the NHL sub-types. Based on the small number of exposed cases, it's unlikely to be significant, but I do think that it's important to consider since you do make a point in the conclusions about sub-type differences.

Finally, this may just be me, but I'm not sure that I understand the rationale for so much focus on weed-resistance. If weeds are becoming resistant and you're rather implying that glyphosate is the most commonly used herbicide so likely to be a chemical that weeds are becoming resistant to, doesn't this imply that use would go down?

I look forward to seeing you in Brazil.

Laura

From: Pahwa, Manisha [redacted]
Sent: Tuesday, August 25, 2015 4:30 PM
To: Beane-Freeman, Laura (NIH/NCI) [E]; Blair, Aaron (NIH/NCI) [V]; [redacted] Weisenburger, Dennis; Cantor, Kenneth (NIH/NCI) [C]; Zahm, Shelia (NIH/NCI) [C]
Cc: Harris, Shelley; Demers, Paul
Subject: Glyphosate and NHL presentation [ISEE Conference]

Dear all,

Next week Monday, August 31 I will be presenting the results of my analysis of glyphosate use and NHL risk in the NAPP at the International Society for Environmental Epidemiology (ISEE) Conference in Sao Paulo. My slide deck is attached and I thought it would be best to share this with you given the sensitivity of the topic. Please feel free to send me your feedback, ideally by Saturday evening.

Thank you, and please let me know if you have any questions or would like additional information.

Manisha

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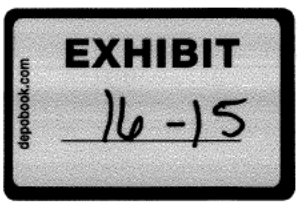
From: "Pahwa, Manisha" <[redacted]
Date: August 27, 2015 3:45:28 PM EDT
[redacted]
Cc: "Harris, Shelley" <[redacted], "Demers, Paul"
[redacted]
Subject: RE: Revised slides and responses to your comments

Hello all,

Here are responses to a few questions that may arise from the media. Do you think that a question might arise about the differences in risk found in the sensitivity analysis of proxy/self-respondents, or would that be too specific? Please add to the list of questions if you think of anything else.

Thanks very much,
Manisha

From: [redacted] **Sent:** Wednesday, August 26, 2015 7:58 PM **To:** Pahwa, Manisha



[redacted]
[redacted] **Cc:** Harris, Shelley
[redacted] Demers, Paul
Subject: Re: Revised slides and responses to your comments

Manisha and coauthors,

Below is a start of thinking about talking points to questions about IARC and your study by the audience. I though these could be used to start the discussion to help Manisha.

Please make suggestions.

Aaron

1) These studies were all considered for the IARC Monograph on glyphosate. These combined data show an excess for NHL as did the U.S. and Canadian studies separately.
2) Pooling provided larger numbers and opportunities to perform analyses not possible in the individual studies, e.g., by histologic type.
3) A positive trend for NHL occurred with days per year and cumulative days of use of glyphosate, but not for duration (years) of use.
4) There were hints of differences for these use metrics among the histologic types, although they were not statistically different across the histologic types.
5) Adjustment for use of 2,4-D, dicamba, and malathion reduced the ORs. Although excesses still occurred, they

were no longer statistically significant.
6) These data, although far from conclusive, suggest that the association between glyphosate and NHL might differ by histologic type. FL was not linked to glyphosate at all.

-----Original Message----- From: Pahwa, Manisha
[redacted]
[redacted] Cc: Harris, Shelley
Demers, Paul
Sent: Wed, Aug 26, 2015 6:25 pm Subject: Revised slides and responses to your comments

Hi all,

Thank you again for providing your rapid and useful comments on my ISEE presentation slides. I have revised them according to your feedback (attached). Below are specific comments from John M., John S., Laura, and Aaron (in that order) and my responses to them in **bold red**. Apologies for the lengthy e-mail! Please let me know if further edits need to be made.

From John M.:
Hi Manisha (and Aaron et al.),

Thanks for the opportunity to review and comment.

The slides and results look excellent, are important, and will surely draw interest. I agree too with the need to be ready for media interests – which may be intense (based on my many interviews about the IARC

you trust.

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From: British Airways <[redacted]>
Date: November 27, 2014 9:52:58 AM EST
To: [redacted]
Cc: [redacted]
Subject: Receipt for paid seat selection for booking: [redacted]

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From: British Airways <[redacted]>
Date: January 13, 2015 6:30:40 PM EST
To: [redacted]
Subject: Your Departure [redacted]

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From: "Cantor, Kenneth (NIH/NCI) [C]" <[redacted]>
Date: January 14, 2016 4:33:23 PM EST
To: "Harris, Shelley" <[redacted]>, "Beane-Freeman, Laura (NIH/NCI) [E]" <[redacted]> John Spinelli [redacted] "John McLaughlin [redacted]" <[redacted]>, "'James Dosman' [redacted] "Punam Pahwa [redacted] "Blair, Aaron (NIH/NCI) [V]" <[redacted]> "Weisenburger, Dennis" [redacted] "Zahm, Shelia (NIH/NCI) [C]" <[redacted]>, "Demers, Paul" <[redacted]>
Cc: "Pahwa, Manisha" <[redacted]>, "Latifovic, Lidija" [redacted], "Kachuri, Linda" [redacted]
Subject: RE: 5 NAPP abstracts attached for review - short deadline Jan 14th 2016

Shelley –

Attached are the 5 abstracts for the IARC meeting with a few comments in the text. I've indicated very minor typo or editorial suggestions on most. Results in the 2nd abstract (glyphosphate) are less than convincing, given that control for other pesticides results in attenuated OR, which aren't

in the abstract. Given this, I suggest that the last sentence be removed (I've done this on the attached). The published paper will present all relevant information.

My best,

Ken Cantor

From: Harris, Shelley [redacted] **Sent:** Monday, January 11, 2016 5:43 PM **To:** Beane-Freeman, Laura (NIH/NCI) [E]; John Spinelli; John McLaughlin [redacted] 'James Dosman' [redacted] Punam Pahwa [redacted] Blair, Aaron (NIH/NCI) [V]; [redacted] Weisenburger, Dennis; Cantor, Kenneth (NIH/NCI) [C]; Zahm, Shelia (NIH/NCI) [C]; Demers, Paul **Cc:** Pahwa, Manisha; Latifovic, Lidija; Kachuri, Linda; [redacted] **Subject:** 5 NAPP abstracts attached for review - short deadline Jan 14th 2016 **Importance:** High

Hello NAPP colleagues and Happy New Year!

I have enclosed a word document containing 5 abstracts that we hope to submit this Friday January 15th for the IARC 2016 conference: Global Cancer, Occurrence, Causes and Avenues to Prevention which takes place June 7-10, 2016 in Lyon France (http://www.iarc-conference2016.com/index.php?langue=en&onglet=3&acces=&idUser=&emailUser=).

You have all seen (a shorter version) of the first two abstracts, the multiple myeloma manuscript which has been submitted to the International Journal of Cancer, and the Glyphosate/NHL manuscript which is under NCI review. The third abstract is from a NHL manuscript (carcinogenicity scores) that is currently under revision at CCO and we will send that manuscript out for the group to review in the near future.

I have included two additional abstracts authored by Linda Kachuri and Lidija Latifovic that describe some preliminary analyses we have conducted in the

past month. Linda's abstract describes results for an analysis of organochlorine pesticides and NHL risk and Lidija has conducted an analysis on all pesticides and HL risk. Admittedly, these are preliminary results and a more detailed analysis will be conducted, but I wanted to give them both the opportunity to draft an abstract and submit to IARC for review, so they could attend this meeting. I have asked them to report/focus on only those results that had clear dose-response relationships (using duration data) and were statistically significant. We can send supporting tables to any of you who wish to review. At the time of the conference, we should have draft manuscripts prepared for both of these analyses.

I have attempted to suggest author orders for these papers, and these can be modified as necessary.

Please send me your comments/revisions by January 14th so that we can revise and submit by the 15th. I'll assume that if I don't hear back from you, we can include you as an author and that you have no required revisions. My apologies for the short turn-around time.

Thanks everyone and hope to see you in France!

Shelley

Shelley Harris, PhD **Scientist Population Health and Prevention, Prevention and Cancer Control**

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Message

From: Weisenburger, Dennis [redacted]
Sent: 8/22/2016 3:09:05 PM
To: Blair, Aaron (NIH/NCI) [V] [redacted]
Subject: FW: EU glyphosate review

It seems important to get our US/Canadian paper on this submitted soon so it could be considered in this review.

Dennis D. Weisenburger, M.D.
Professor/Chair, Department of Pathology
City of Hope Medical Center
1500 East Duarte Road
Duarte, CA 91010
Phone: 626-218-3584
Fax: 626-301-8842
[redacted]

Pathology Dept.: 626-256-4673 x 62456

-----Original Message
From: Chris Portier [redacted]
Sent: Monday, August 22, 2016 5:40 AM
To: Weisenburger, Dennis [redacted]
Subject: Re: EU glyphosate review

Denis,

I am sorry I have not answered before now, but I have been ill.

The EU approved the use of Glyphosate for 18 months while the European Chemical Agency reviews all of the data.

C.

> On Aug 14, 2016, at 7:23 PM, Weisenburger, Dennis [redacted] wrote:
>
> Chris - what is the status of this review? has it been approved for use? restrictions? Thanks - DW
>
> Sent from my iPad
>
> ---
> *SECURITY/CONFIDENTIALITY WARNING:
> This message and any attachments are intended solely for the individual or entity to which they are addressed. This communication may contain information that is privileged, confidential, or exempt from disclosure under applicable law (e.g., personal health information, research data, financial information). Because this e-mail has been sent without encryption, individuals other than the intended recipient may be able to view the information, forward it to others or tamper with the information without the knowledge or consent of the sender. If you are not the intended recipient, or the employee or person responsible for delivering the message to the intended recipient, any dissemination, distribution or copying of the communication is strictly prohibited. If you received the communication in error, please notify the sender immediately by replying to this message and deleting the message and any accompanying files from your system. If, due to the security risks, you do not wish to receive further communications via e-mail, please reply to this message and inform the sender that you do not wish to receive further e-mail from the sender. (fpc5p)
> ---
>

Message

From: Weisenburger, Dennis [redacted]
Sent: 5/5/2016 11:03:18 PM
To: Blair, Aaron (NIH/NCI) [V] [redacted]
Subject: FW: EPA and glyphosate

fyi

Dennis D. Weisenburger, M.D.
Professor/Chair, Department of Pathology
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From: Kathryn M. Forgie [mailto:kathryn.forgie@andruswagstaff.com]
Sent: Thursday, May 05, 2016 3:03 PM
To: Weisenburger, Dennis <[redacted]
Subject: Re: EPA and glyphosate

Would sometime next Tuesday work for you, please?

Sent from my iPad

On May 5, 2016, at 5:59 PM, Weisenburger, Dennis <[redacted]> wrote:

> When do you want to discuss your first case?
>
> Dennis D. Weisenburger, M.D.
> Professor/Chair, Department of Pathology
> City of Hope Medical Center
> 1500 East Duarte Road
> Duarte, CA 91010
> Phone: 626-218-3584
> Fax: 626-301-8842
> [redacted]
>
> Pathology Dept.: 626-256-4673 x 62456
>
> **From:** Kathryn M. Forgie [mailto:kathryn.forgie@andruswagstaff.com]
> **Sent:** Thursday, May 05, 2016 1:33 PM
> **To:** Weisenburger, Dennis [redacted]
> **Subject:** EPA and glyphosate
>
> FYI..Kathryn
>
> http://www.reuters.com/article/us-usa-glyphosate-epa-idUSKCN0XU01K

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Fwd: Dr. Weisenburger

Pigman, Heather
Sent: Sunday, September 10, 2017 1:28 PM
To: Monsantosci
Attachments: Dr. Weisenburger Additiona~1.pdf (100 KB) ; ATT00001.htm (232 B)

Begin forwarded message:

From: "Greenwald, Robin" <RGreenwald@weitzlux.com>
Date: September 10, 2017 at 12:56:09 PM EDT
To: "Pigman, Heather" <HPigman@Hollingsworthllp.com>
Cc: Kathryn Forgie <kathryn.forgie@andruswagstaff.com>, "Trembour, Rosa S." <rstrembour@locklaw.com>
Subject: Dr. Weisenburger

Heather:
Attached is a list of Dr. Weisenburger's Additional Materials.
Regards,
Robin
Please visit us at http://www.weitzlux.com

****

All e-mail to W & L or any individuals at W & L should be followed up by hard copy including attachment(s), as specific file types may be blocked at any time without notice being provided to sender or recipient.

****

Dr. Weisenburger's Additional Materials

1. Depositions of Drs. Nabhan, Neugut, and Ross

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Int. J. Cancer: **123,** 1657–1663 (2008)

Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis

Mikael Eriksson[1]*, Lennart Hardell[2], Michael Carlberg[2] and Måns Åkerman[3]

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[2]*Department of Oncology, University Hospital, Örebro, Sweden*
[3]*Department of Pathology, University Hospital, Lund, Sweden*

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-

Grant sponsor: FAS; Grant number: 2001-0224; Grant sponsors: Cancer- och Allergifonden, Nyckelfonden, Örebro University Hospital Cancer Fund.
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Received 4 November 2007; Accepted after revision 20 February 2008
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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 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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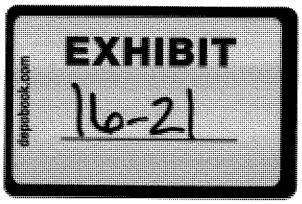

and lifestyle factors. Applicators who completed this questionnaire were given a self-administered take-home questionnaire, which contained additional questions on occupational exposures and lifestyle factors. The questionnaires are available from the AHS website (National Institutes of Health 2004).

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	7,296 (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 ($n = 54,315$)[b]	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	38	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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The Agricultural Health Study

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The Agricultural Health Study, a large prospective cohort study, has been initiated in North Carolina and Iowa. The objectives of this study are to: 1) identify and quantify cancer risks among men, women, whites, and minorities associated with direct exposure to pesticides and other agricultural agents; 2) evaluate noncancer health risks including neurotoxicity, reproductive effects, immunologic effects, nonmalignant respiratory disease, kidney disease, and growth and development among children; 3) evaluate disease risks among spouses and children of farmers that may arise from direct contact with pesticides and agricultural chemicals used in the home, lawns and gardens, and from indirect contact, such as spray drift, laundering work clothes, or contaminated food or water; 4) assess current and past occupational and nonoccupational agricultural exposures using periodic interviews and environmental and biologic monitoring; 5) study the relationship between agricultural exposures, biomarkers of exposure, biologic effect, and genetic susceptibility factors relevant to carcinogenesis; and 6) identify and quantify cancer and other disease risks associated with lifestyle factors such as diet, cooking practices, physical activity, smoking and alcohol consumption, and hair dye use. In the first year of a 3-year enrollment period, 26,235 people have been enrolled in the study, including 19,776 registered pesticide applicators and 6,459 spouses of registered farmer applicators. It is estimated that when the total cohort is assembled in 1997 it will include approximately 75,000 adult study subjects. Farmers, the largest group of registered pesticide applicators, comprise 77% of the target population enrolled in the study. This experience compares favorably with enrollment rates of previous prospective studies. *Key words:* cancers, exposure assessment, farmers, lymphoma, noncancer toxicity, pesticides, prospective cohort. *Environ Health Perspect* 104:362–369 (1996)

Farming is a demanding occupation requiring individuals to carry out a variety of tasks. Farmers, farm workers, and farm family members may operate agricultural machinery, apply pesticides and fertilizers, build and repair equipment, and handle livestock which may put them at risk of injury and disease. Farmers and farm workers have long been recognized as being at high risk of injury, nonmalignant respiratory disease (e.g., farmers' lung), and some types of dermatitis (e.g., cattle ringworm, chemical burns, and irritant dermatitis) (*1*). On the other hand, studies from North America, Europe, Australia, and New Zealand have established that farmers have a lower overall mortality rate, a lower heart disease mortality rate, and lower mortality rates for cancers of the lung, esophagus, bladder, and colon than the general population (*2–5*). Low mortality rates from these cancers and for heart disease have been attributed to lower smoking rates among farmers (*2,6–9*), with possible additional contributions from diet and a physically active lifestyle (*2*).

Despite an excellent overall mortality experience, farmers in many countries appear to have higher rates than the general population for Hodgkin's disease, leukemia, multiple myeloma, non-Hodgkin's lymphoma, and cancers of the lip, stomach, prostate, skin (melanotic, nonmelanotic), brain, and connective tissue (*2–5*). While each cancer is not elevated in every study of agricultural workers, the tendency toward excess is intriguing given the diversity in agricultural practices within and between countries. These cancers do not initially appear to have much in common. They vary in frequency, histology, and prognosis. On more careful reflection, however, two factors of commonality stand out (*2*). First, they are not strongly associated with tobacco use. Second, several of these tumors (e.g., non-Hodgkin's lymphoma, leukemia, soft-tissue sarcoma, and cancers of the skin, stomach, brain, and lip) are excessive among persons with naturally occurring or medically induced immunodeficiencies. This latter connection suggests that agricultural exposures or other factors in the rural environment may contribute to cancer among farmers through immunologic perturbations.

Specific factors that may contribute to cancer incidence excess among farmers include prolonged occupational exposure to sunlight, diet, contaminated drinking water, and occupational exposure to a variety of potentially hazardous chemicals and biological agents (*2,10–14*). Agricultural workers and their families may have exposure to pesticides, animal viruses, mycotoxins, dust, fuels, oils, engine exhaust, and fertilizers. Cancer patterns in related agricultural groups, including flour millers (*15*), agricultural extension agents (*16*), soil and forest conservationists (*17*), commercial pesticide appliers (*18*), slaughterhouse workers (*3*), and veterinarians (*3,5*), also suggest that agricultural exposures deserve attention. To date, however, the strongest links of exposures and malignancies have been with pesticides (*4,19*).

Potential noncancer health outcomes that may be influenced by agents found in the farm environment, particularly pesticides, include deleterious effects on the nervous, renal, respiratory, and reproductive systems of both men and women (*20,21*). Much of the evidence for such effects comes from experimental studies and case reports. Other than studies of potentially increased cancer risk among agricultural workers, few population studies of health outcomes have been conducted. Health effects in children and women living on farms are also of potential concern, yet few studies have focused on health risks to these groups.

Studies evaluating chronic disease risks from agricultural exposures have typically been of a case–control design where recollection of exposures of many years in the

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past may result in misclassification, or cohort studies where few details regarding exposure were available. In case–control studies nondifferential misclassification due to inaccurate recall of exposure history would be expected to underestimate the true risk, while better recall on the part of cases (i.e., case recall bias) could bias estimates in either direction. In cohort studies done to date, such as the studies conducted on farmers in Sweden (*22,23*), Iceland (*24*), and in New York (*25*), little detail on specific agricultural exposures were available. Even in the few studies with some exposure data, such as a large Canadian study, information was available on the use of categories of pesticides in general but not on specific chemicals, and little information was available on potential confounding factors such as smoking and diet (*19,26–29*).

We have initiated a large prospective cohort study in North Carolina and Iowa called the Agricultural Health Study (Fig. 1) in order to: 1) identify and quantify cancer risks among men and women as well as whites and minorities associated with direct exposure to pesticides and to other agricultural agents; 2) evaluate noncancer health risks including neurotoxicity, reproductive effects, immunologic effects, nonmalignant respiratory disease, kidney disease, and growth and development; 3) evaluate disease risks among spouses and children of farmers that may arise from direct contact with pesticides and agricultural chemicals used in the home, lawns and gardens, and from indirect contact, such as spray drift, laundering work clothes, or contaminated food or water; 4) assess current and past occupational and nonoccupational agricultural exposures using periodic interviews and environmental and biologic monitoring; 5) study the relationship between agricultural exposures, the occurrence of biomarkers of exposure, biologic effect, and genetic susceptibility factors relevant to carcinogenesis; and 6) identify and quantify cancer and other disease risks associated with lifestyle factors such as diet, cooking practices, physical activity, smoking and alcohol consumption, and hair dye use.

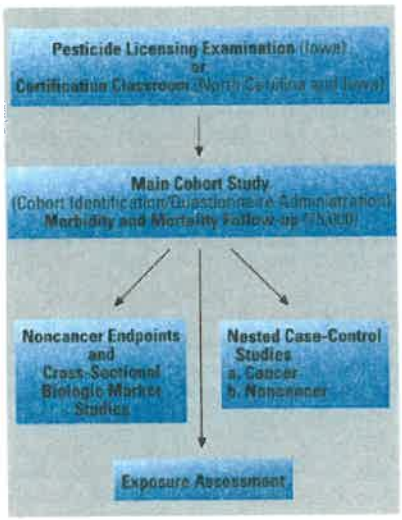

Figure 1. Agricultural health study.

Methods

The Agricultural Health Study is a collaborative effort involving the National Cancer Institute (NCI), the National Institute of Environmental Health Sciences (NIEHS), and the U.S. Environmental Protection Agency (EPA). It is being conducted in Iowa and North Carolina through field stations at the University of Iowa and Battelle/Survey Research Associates. The study has four major components including the main prospective cohort study, noncancer endpoints and cross-sectional biologic marker studies, nested case-control studies, and exposure assessment.

Prospective Cohort Study

A prospective cohort approach offers two distinct advantages over other study designs including the opportunity to evaluate a number of diseases simultaneously, and to perform periodic assessments of agricultural and other exposures. Periodic assessment of recent exposures should improve recall and reduce nondifferential misclassification. Determining exposure prior to onset of disease will eliminate case-recall bias, an issue sometimes raised regarding weaknesses of case-control studies.

Farmers and pesticide applicators are identified when they seek a restricted-use pesticide license from the state Cooperative Extension Services or Departments of Agriculture. All persons in Iowa and North Carolina who wish to apply restricted-use pesticides must obtain a pesticide applicator license by undergoing training or testing in the safe handling of pesticides; the license is valid for three years. There are two licensing categories: "private" applicators (i.e., farmers), are estimated to be 70% of licensed applicators and "commercial" applicators comprise the remaining 30% and include persons employed by pest control companies or by businesses that use pesticides but whose primary function is not pesticide application, such as grain millers and warehouse operators.

At the licensing facility, each pesticide applicator is asked to complete a 21-page, optically scannable enrollment questionnaire. In Iowa, both commercial and farmer applicators attend some of the same sessions and are invited to participate in the study. In North Carolina, farmers and commercial applicators attend separate training sessions; only farmer applicators from North Carolina are enrolled. Since the enrollment questionnaire includes exposure data on 50 pesticides, crops grown and livestock raised, protective clothing/equipment used, smoking and alcohol consumption, fruit and vegetable intake, medical conditions as well as basic demographic data, the enrollment questionnaire will be the basis for a large number of cohort analyses. In addition, the enrollment questionnaire asks applicators to identify their spouse and whether or not they have young children living at home; this provides the opportunity to enroll the spouses of farmers and obtain information about their children.

Farmer applicators completing the enrollment questionnaire are given three take-home questionnaires—the applicator, spouse, and female and family health questionnaires—which are also optically scannable. Commercial applicators receive the applicator questionnaire and, if female, the female and family health questionnaire. They are not given the spouse questionnaire since the work site of commercial applicators is generally not proximate to their home; the possibility of accidental exposure to pesticides by a commercial applicator's spouse is therefore less than for a spouse of a farmer applicator. The take-home questionnaires are designed to supplement information in the enrollment questionnaire (see Appendix A).

Before 1994, all Iowa applicators were tested every three years. In October 1993, an option to acquire a license through three consecutive years of training was initiated. Classes since 1994 consist of a mix of applicators who have already attended one or more sessions (and had multiple opportunities to enroll in the study), as well as persons beginning their application process (who would be new to the study). Thus, the second and third years of the study provide an opportunity to re-interview a sample of the cohort to assess the reliability of information provided in the enrollment questionnaire. Applicators returning for their second training class are asked to fill out a shortened version of the enrollment questionnaire which requests information on pesticide use, work practices, and smoking history. These responses will be compared to the responses obtained in the prior year to obtain estimates of reliability. It is expected that approximately 3000 follow-up questionnaires will be obtained in the second year.

In both states, response rates for the supplemental take-home questionnaires have been about 50% during the first year. The low response rate raises potential questions regarding the quality and generalizability of studies based on the supplemental data. One would like to pursue nonresponders through telephone interviews and structured "refusal conversion" procedures. The large size of the Agricultural Health Study and accompanying cost of such activities, however, precludes such an effort. Alternatively, a series of smaller efforts have been developed to evaluate whether responders and nonresponders differ in any way that might affect the interpretation of study results. In one such effort, farmer applicators enrolled in the Agricultural Health Study who had completed the supplemental take-home questionnaire were compared to those who did not complete the take-home questionnaire. Although a number of differences were found, all the differences were small and etiologically insignificant (Tarone et al., under review), suggesting that any bias resulting from using data from the supplemental questionnaires would be minimal. Additional efforts have been undertaken to obtain information from nonresponders. Three random samples of 1000 persons have been selected: women 30–39 years old, women 40–64 years old, and men 40–64 years old. Nonrespondents in each sample will be contacted for a brief telephone interview covering selected questions from either the farmer applicator or the spouse and family health questionnaires. These samples will provide data to compare responders to initial nonresponders for information that is not covered on the enrollment questionnaire and for which it is important to assess possible bias or lack of generalizability such as the etiology of spontaneous abortion (i.e., women 30–39 years old) and neurologic and immunologic disease for women 40–64 years old and men 40–64 years old.

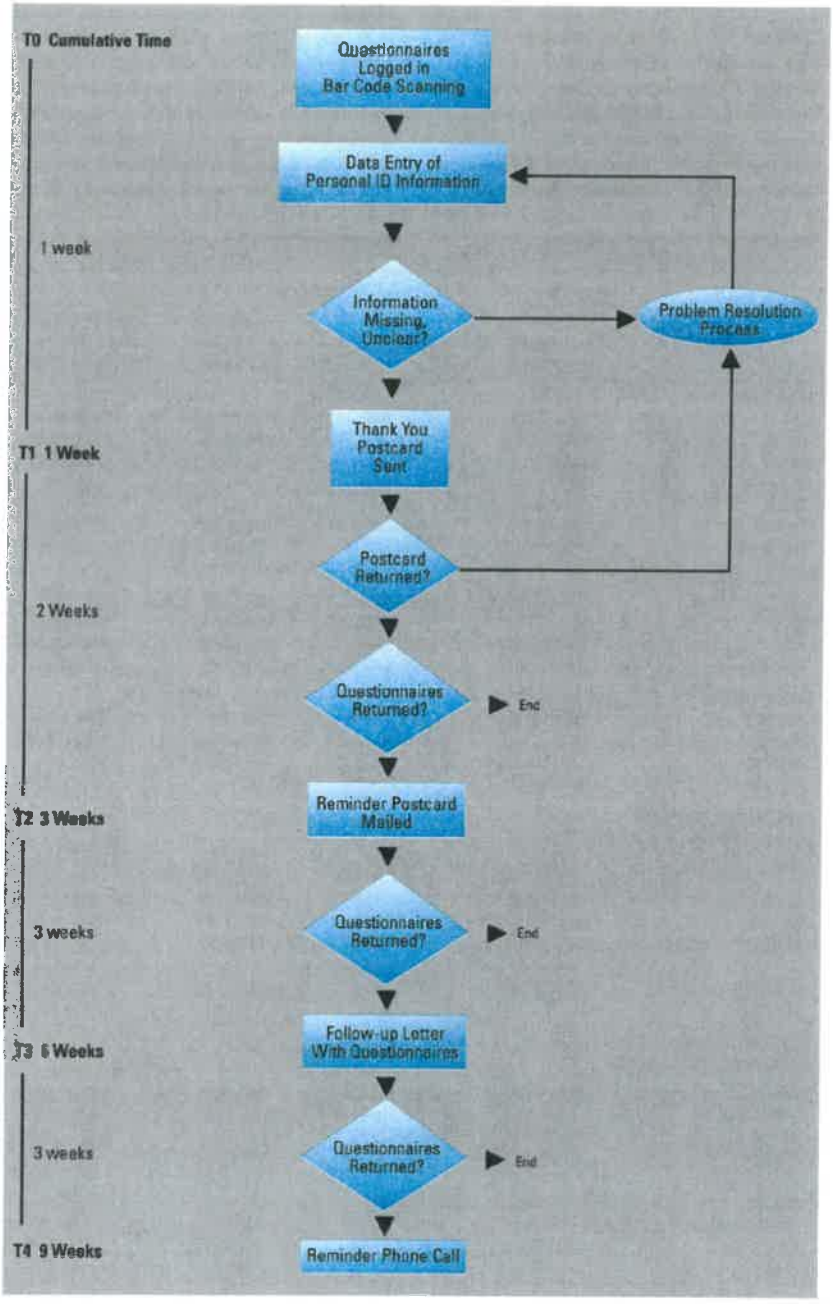

Figure 2. Field station follow-up procedure.

The field stations administer and collect enrollment questionnaires. Follow-up procedures for obtaining subsequent mailed questionnaires include reminder cards, phone calls, and remailing take-home questionnaires (Fig. 2). The cohort will be linked annually with the state cancer registries to obtain information on cancer incidence and periodically to the National Death Index to determine mortality.

Noncancer Endpoints and Cross-Sectional Biologic Marker Studies

Noncancer endpoints will be studied in a variety of ways. For example, the United States Renal Data Survey will be used to periodically update the incidence of end-stage renal disease in the cohort. The health information on selected noncancer outcomes (i.e., renal, neurological, reproductive, developmental, and immunological endpoints) obtained from questionnaires of applicators and their families will be compared with that of a national sample obtained using data from the National Health and Nutrition Examination Survey. In addition, the incidence and prevalence of diseases and symptoms will be contrasted between persons exposed and unexposed to specific pesticides or other factors of interest. The cross-sectional data may also be used to identify groups of particular interest for investigating health endpoints (e.g., childhood development, immunologic or neurologic dysfunction, and asthma) where biologic markers of exposure or early disease would enhance the study.

Nested Case–Control Studies

Over the course of the study, a series of nested case–control studies on a variety of diseases is anticipated. For cancer, rapid ascertainment procedures will be used to identify cases as soon as possible after diagnosis, usually within 1–6 months. Controls will be selected from the nondiseased cohort members. This design is an efficient method to obtain additional information for use in evaluating the risk of specific selected diseases. Cases and controls will be interviewed to obtain more detailed information on known nonfarm, nonpesticide related risk factors than was possible to collect at enrollment. In addition, they will be asked to provide a blood sample, which can be analyzed for genetic susceptibility biomarkers to explore the interaction between exogenous exposures and genetic risk. Tumor tissue will be obtained from all cases for pathologic review. Initial plans call for case–control studies of non-Hodgkin's lymphoma, leukemia, skin melanoma, and cancers of the prostate, brain, ovary, breast, lung, colon, stomach, testis, and pancreas. Pilot efforts regarding breast cancer are underway.

A similar methodology will be used to look at noncancer endpoints; the specific details will be dependent upon the disease endpoint being studied and have not yet been finalized.

Exposure Assessment

Interviews will serve as the primary source of information on agricultural, environmental, and lifestyle exposures. Questionnaire information on pesticide exposures will be supplemented and enhanced with detailed monitoring conducted on a small sample of the cohort and with data on pesticide exposures from the Pesticide Handlers Exposure Database (*30,31*). Pesticide exposure will be directly assessed by environmental and biologic monitoring for approximately 200 families in the cohort. Monitoring will include family members as well as the applicator to evaluate direct and indirect exposure. Food and water samples will also be collected and analyzed.

The questionnaires seek information on the frequency and duration of pesticide use, type of application methods, protective equipment used, and personal hygiene practices. The monitoring effort among the 200 families obtains actual measurements so that pesticide exposures can be related to factors thought to influence exposure. This comparison will provide a quantitative indication of the relative importance of work practices and occupational exposure. With monitoring data on specific pesticides, it will be possible to relate biomarkers of internal dose, target dose and biological effect, application procedures, and protective practices.

The monitoring component of the project, although extremely valuable, will be limited to only a sample of the cohort. These monitoring data and exposure information from the questionnaire will, therefore, be supplemented with information from the Pesticide Handlers Exposure Database. This database, developed by the EPA in conjunction with Health and Welfare Canada and the American Crop Protection Association, includes best-case scenario data from approximately 120 registrant-submitted monitoring studies which can be pooled to estimate pesticide exposure to different parts of the body while engaged in mixing, loading, and applying pesticides and when using various protective practices. The monitoring data in this resource, although not on farmers in our cohort, can be used to provide a relative ranking of exposures from different application patterns reported by our subjects and aid in the development of pesticide exposure scores.

Although the Pesticide Handlers Exposure Database contains more records than any published study, some applicator exposure scenarios encountered in the Agricultural Health Study may not be included. In addition, this database lacks information on specific pesticides and no information on nonoccupational exposures experienced by family members of the

Table 1. Demographic characteristics of agricultural health study cohort: year 1 enrollment[a]

	Number (%)			
	Total applicators (n = 20,235)	Farmer applicators (n = 16,535)	Commercial applicators (n = 3,700)	Spouse of farmer applicators (n = 6,459)
Age (years)				
<40	6585 (32.6)	4702 (28.4)	1883 (51.0)	1683 (26.1)
40–60	8384 (41.4)	7054 (42.7)	1330 (35.9)	3269 (50.6)
>60	3188 (15.7)	2971 (18.0)	209 (5.6)	1349 (20.9)
Unknown	2086 (10.3)	1808 (10.9)	278 (7.5)	158 (2.4)
Mean	45.3	46.7	39.2	48.4
Female	594 (2.9)	454 (2.8)	140 (3.8)	5979 (92.6)
Nonwhite	586 (2.9)	573 (3.5)	13 (0.3)	134 (2.1)
Highest grade completed				
<12	1846 (9.1)	1739 (10.5)	107 (2.9)	459 (7.1)
12	8514 (42.1)	7076 (42.8)	1438 (38.9)	2575 (39.8)
>12	8167 (40.4)	6287 (38.0)	1880 (50.8)	3240 (50.2)
Unknown	1708 (8.4)	1433 (8.7)	275 (7.4)	185 (2.9)
Smoking status				
Never	9373 (46.3)	7730 (46.8)	1643 (44.4)	4586 (70.7)
Former	5693 (28.1)	4733 (28.6)	960 (25.9)	1119 (17.3)
Current	3358 (16.6)	2509 (15.2)	849 (22.3)	627 (9.7)
No answer	1811 (8.9)	1563 (9.4)	248 (6.7)	147 (2.3)
Years personally mixed/ applied pesticide				
<1	660 (3.3)	382 (2.3)	278 (7.5)	273 (4.2)
2–5	2600 (12.8)	1761 (10.7)	839 (22.7)	541 (8.4)
6–10	3015 (14.9)	2358 (14.3)	657 (17.7)	401 (6.2)
11–20	5641 (27.9)	4814 (29.1)	827 (22.4)	569 (8.8)
21–30	3437 (17.0)	3097 (18.7)	340 (9.2)	315 (4.9)
>30	1851 (9.1)	1754 (10.6)	97 (2.6)	265 (4.1)
Unknown	3031 (15.0)	2369 (14.3)	662 (17.9)	4095 (63.4)
Median	15.4	16.4	10.8	12.8
Days per year personally mixed or applied pesticide[b]				
<5	2731 (13.5)	2389 (14.4)	342 (9.2)	969 (15.0)
5–9	3472 (17.2)	3139 (19.0)	333 (9.0)	608 (9.4)
10–19	4586 (22.7)	4065 (24.6)	521 (14.1)	475 (7.4)
20–39	3577 (17.7)	2930 (17.7)	647 (17.5)	222 (3.4)
40–59	1167 (5.8)	732 (4.4)	435 (11.8)	48 (0.7)
60–150	1112 (5.5)	533 (3.2)	579 (15.7)	30 (0.5)
>150	273 (1.3)	123 (0.7)	150 (4.1)	14 (0.2)
Unknown	3317 (16.4)	2624 (15.9)	693 (18.7)	4093 (63.4)
Median	23.3	20.4	44.7	11.7

[a]Subject enrollment will take 3 years. These data represent subjects enrolled in year 1.
[b]During years applied.

applicants. These omissions underscore the need for the monitoring project. Thus, the monitoring component and the Pesticide Handlers Exposure Database make important as well as complementary contributions to the exposure assessment effort. Together they can be used to develop a comprehensive assessment of exposure, which exceeds previous exposure assessments of the agricultural environment conducted in the context of an epidemiologic study.

Advisory Groups

An Advisory Panel composed of epidemiologists, biostatisticians, agricultural exposure experts, and farmers has been assembled to provide advice and oversight to the collaborating agencies during the development and conduct of the project. The Advisory Panel meets annually to review study protocols, evaluate study progress, and comment on analyses and reports. In addition, advisory panels were also established in each state by the Field Stations working with the state departments of agriculture and the cooperative extension services. These state panels provide insight into specific state agricultural issues and act as liaisons to state agencies and agricultural associations.

Results and Discussion

Recruitment

Data are currently available from the first year of enrollment, but should reflect the proportionate distribution of the ultimate cohort. During the first year, we enrolled 16,535 farmers, 3,700 commercial applicators, and 6,459 spouses of farmers for a total of 26,694 subjects (Table 1). These data are being analyzed to evaluate the enrollment process and to characterize the anticipated cohort.

Based on enrollment figures for the first year, we estimate the total cohort will include approximately 49,000 farmer applicators (62% of the cohort), 20,000 spouses of farmer applicators (24%), and 7,000 commercial pesticide applicators (14%).

During the first year, 77% of the eligible farmer applicators completed the enrollment questionnaire (74% in Iowa and 82% in North Carolina). This response rate compares very favorably with the response rates achieved by other recent prospective cohort studies which generally have enrollment rates below 70% (Tarone, et al., under review). Response rates for return of the take-home questionnaires were approximately 50% (i.e., 50% of those completing the enrollment questionnaire completed the take-home questionnaires).

Currently about 3% of the applicators enrolling are women and 3% are minorities. In addition to the female applicators, 93% of the spouses are females. With the current enrollment rate of spouses (i.e., a spouse questionnaire is completed) at approximately 50% and with a married rate of about 80%, we expect to enroll over 19,000 females by the end of the study. Approximately 15,000 additional female spouses will be registered through information provided by the applicator on the enrollment questionnaire. Although a completed spouse questionnaire is not available for these individuals, they are considered eligible for inclusion in the nested case–control studies. When enrollment is complete this study will be the largest cohort available to study the effect of agricultural exposures on women's health.

A supplemental minority recruitment effort conducted through African-American churches has been implemented through the North Carolina Field Station because of the small number of African-Americans eligible to enter into the study through the normal enrollment process. Over the past several decades the number of minorities farming in North Carolina as well as the rest of the United States declined even more precipitously than for white farmers (*32*). This supplemental recruitment cohort will differ from the main cohort in that it will include nonlicensed farmers, retired farmers, and their spouses in addition to currently licensed applicators. The special recruitment effort will draw respondents from several eastern North Carolina counties, the historic locus of African-American farming in North Carolina. Approximately 1,800 minority subjects will be enrolled through the normal recruitment process and 1,400 more will result from the supplemental minority recruitment effort in North Carolina for a total of 3,200.

Demographics

The mean ages of the farmer applicator and his/her spouse are 46.7 and 48.4 years of age, respectively, while commercial applicators are significantly younger, with a mean age of 39.2 (Table 1). (Preliminary analysis of responders versus nonresponders to the take-home questionnaires indicates older applicants are more likely to return these questionnaires; this accounts for the slightly higher mean age of the spouses). Although the mean age of minorities enrolled through standard procedures is 45.9 years old, pilot data suggest the mean age will be substantially older for those enrolled through the special recruitment effort. We therefore expect minorities will make a disproportionate contribution to the total number of chronic disease cases coming from the cohort because of their more advanced age.

The cohort is overwhelmingly white (97%), reflecting the general proportions of racial groups seeking licenses in the study areas. Nearly all of the nonwhite applicators (82%) are African-American and most (98%) live in North Carolina.

About 90% of the applicators and 93% of the farmers' spouses have graduated from high school and approximately 40% have completed some college. A larger proportion of commercial applicators and farmers' spouses have attended college than farmer applicators. Because we used self-completion questionnaires, there was some concern about illiteracy. This has not been a significant problem for enrollment. In the small number of cases where the applicator was illiterate, anecdotal evidence from the field indicates a literate spouse usually assisted with the completion of the enrollment questionnaire. However, literacy may be a barrier with the take-home questionnaires and may account for some of the nonresponse. Special supplemental surveys designed to evaluate nonresponse will be informative in this regard as these interviews will be conducted by telephone.

Overall, 17% of the applicators and 10% of the spouses of farmer applicators are current smokers (Table 1). These rates are lower than the rate for the United States as a whole (28% for males and 23% for females) (*33*). More commercial applicators (22%) are current smokers than are farmers (15%), and more North Carolina farmers smoke (20%) than do Iowa farmers (10%).

Commercial pesticide applicators in the study are a diverse group; 45% of the commercial applicators applied herbicides to crops, 37% applied pesticides to lawns and gardens, 25% applied insecticides to crops, 13% applied pesticides to homes, and 4% were engaged in forestry applications. Although they are younger and had somewhat fewer years of experience applying pesticides, commercial applicators tend to mix or apply pesticides more frequently than the farmer applicators (Table 1). This younger group of heavier users may therefore be particularly useful for studying noncancer endpoints with relatively short latency periods such as certain reproductive and neurological disorders.

Farm Characteristics

Agriculture in Iowa and North Carolina differs considerably. Consequently, agricultural exposures experienced by this cohort will be more diverse than in many previous studies. In Iowa, the major crops are corn, soybeans,

oats, hay, and alfalfa. North Carolina agriculture is more varied (Fig. 3). Corn, soybeans, and hay are major crops, but North Carolina farmers also grow tobacco, peanuts, cotton, sweet corn, and cucumbers.

Farms in North Carolina are generally smaller than Iowa farms (Fig. 4). More than half of the farms in North Carolina are under 200 acres; only 19% of the Iowa farms are 200 acres or less. At the other end of the scale, 17% of Iowa respondents report farm sizes of over 1,000 acres; only 9% of North Carolina farmers reported farms of that magnitude.

In Iowa, 47% of the farmers report that they raise hogs and 44% raise beef, while only about 5% report sheep or dairy operations. In North Carolina, raising beef is reported by about 23% of farmers while raising sheep is reported by less than 1%. Hogs are raised by 9%, and dairy cattle and poultry are reported by 3–5% of the North Carolina farmers. Raising poultry is more prevalent in North Carolina than in Iowa.

Pesticide Use

The average farmer applicator in this cohort has mixed or applied pesticides for 16 years while the average commercial applicator has mixed or applied pesticides for approximately 11 years (Table 2). Although commercial pesticide applicators tended to mix or apply pesticides for fewer years than the farmer applicators, they mixed or applied pesticides more days per year (a median of 45 days per year for commercial versus 20 days per year for farmer applicators). Approximately one-third of the spouses of farmers also apply pesticides. The average spouse has applied pesticides for approximately 13 years at a median frequency of 12 days per year.

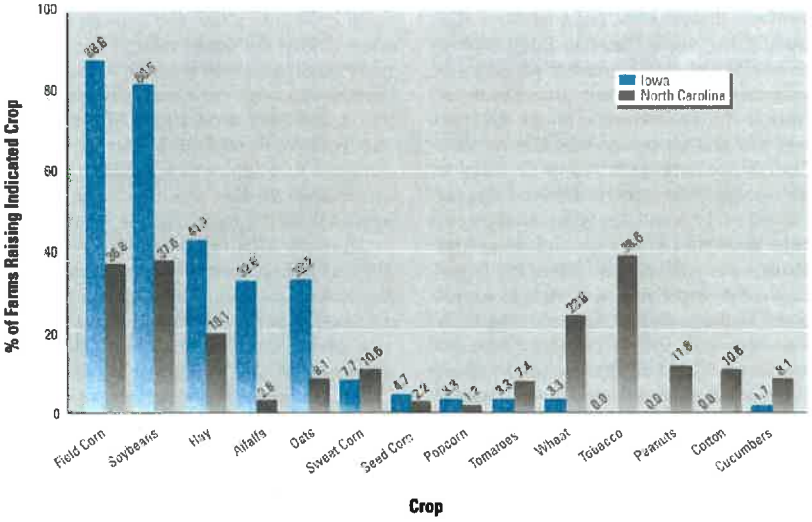

Figure 3. Top crops in Iowa and North Carolina.

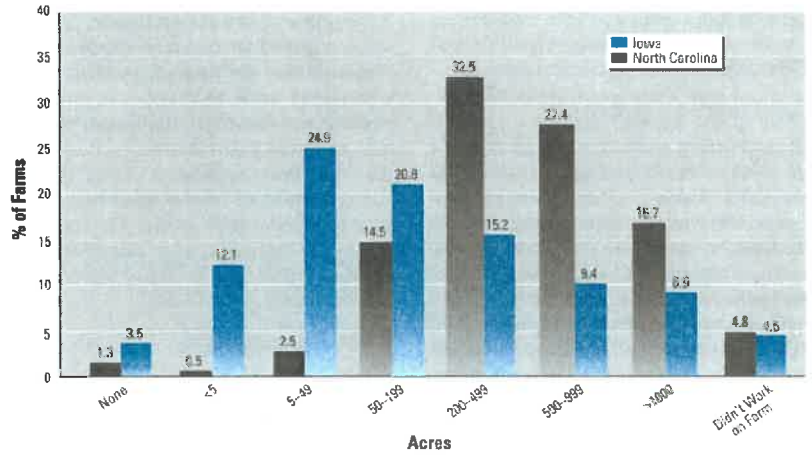

Figure 4. Distribution of farm size in Iowa and North Carolina.

The contribution of women to farm operations is often overlooked, yet a survey of farm women found 47% ran farm errands, 37% took care of animals, 22% harvested crops, and 5% applied fertilizers and pesticides (*34*). Our own early data confirm these observations.

Agricultural Activities and Exposures

The questionnaires provided information on a variety of activities and exposures. A substantial percentage of farmer applicators weld (60%), grind metal (63%), and repair engines (39%). Less than 4% of the spouses perform any of these particular activities. Grinding animal feed at least monthly is performed by 36% of the farmers and 6% of the spouses, while butchering animals or providing veterinary services to livestock on a monthly or more frequent basis is performed by 33% of the farmers and 11% of the spouses.

For farmer applicators who have held nonfarm jobs, the most prevalent exposures reported on these jobs were engine exhaust (20%), solvents (16%), welding fumes (15%), and gasoline (15%). Commercial applicators report an even wider variety of other significant exposures on nonfarm jobs, including exposure to gasoline (42%), engine exhaust (40%), grain dust (31%), welding fumes (31%), and solvents (28%). Spouses report fewer exposures to additional agents than either farmer or commercial groups, with exposure most frequently occurring to solvents (7%), X-ray radiation (5%), and engine exhaust (4%).

Studies of the chronic disease rates among women who do not engage in mixing or application but who, nonetheless, may be exposed because they live on a farm will be important in their own right. Their exposures are likely to exceed those experienced by most of the general population. Data being collected on household activities, including laundry, vacuuming, and pesticide storage, and location of the house or well in relation to areas where pesticides are mixed or applied, will aid in this evaluation of household exposure (*35*).

Exposure Assessment

Although environmental and biological monitoring among pesticide-exposed workers have been conducted to characterize exposure, pesticide exposure monitoring is virtually nonexistent in previous epidemiologic studies of cancer and other chronic diseases (*19,36*). Improving exposure assessment in the context of a prospective epidemiologic study is a key objective of the Agricultural Health Study. When finalized the exposure monitoring component will be designed to provide information

Table 2. Types of pesticide applications performed by private and commercial applicators in the Agricultural Health Study

Type of pesticide application	% Applicators with indicated exposure	
	Private applicator (n = 16,535)	Commercial applicator (n = 3,700)
Termite control	3.1	2.0
Rodent control	21.9	11.1
Lawn and garden	27.7	37.1
Greenhouse	4.0	2.9
Stored grain	13.4	10.1
Highway weed control	6.4	9.1
Forestry	1.6	3.5
Aerial spraying	0.9	0.9
Herbicide, crop	70.1	45.1
Herbicide, other	0.5	2.4
Insecticide, farm crop	54.7	24.6
Insecticide, farm animal	24.2	7.6
Insecticide, pets	13.1	7.8
Insecticide, home	11.7	13.2
Insecticide, commercial buildings	1.8	4.6
Fungicide	14.1	7.0
Fumigant	9.3	4.1

regarding the total exposure to pesticides from all routes (i.e., food and water ingestion, air inhalation, and skin exposure) and from environmental and occupational sources. It will also provide monitoring data that can be used to complement information obtained by interview and create relative exposure rankings for all individuals in the cohort.

The epidemiologic analyses in this study will be based primarily on exposure information obtained from the questionnaires because this information is obtained on all participants. The proposed monitoring effort will provide additional data to develop a more reliable exposure classification. No existing database contains information combining use of specific pesticides by application methods, formulation types, and work practices, yet these factors are all important exposure determinants. For example, monitoring studies have indicated that most dermal exposure to pesticides occurs from hand contact (*37*). A logical analysis would be to compare disease rates among persons who reported use of protective gloves with rates of those who did not, while controlling for pesticide formulation type, application method, and other work practices. Such a comparison, however, would be deceptive if there was no actual difference in exposure between the two groups. Monitoring will improve our confidence in exposure groupings based on interview data. Integrating environmental monitoring with questionnaire data on exposure determinants will enhance the validity of exposure assessment in the etiologic analysis.

Because of practical limitations and costs, however, it will not be possible to monitor all possible factors that influence exposure. The Pesticide Handlers Exposure Database will be used to fill some of these gaps, particularly regarding application techniques and types of protection. This well-validated database will provide an extremely valuable source of occupational exposure information. On the other hand, the Pesticide Handlers Exposure Database does not include nonoccupational pesticide exposures. This may represent an especially important source of exposure for dependents. The EPA (*38,39*) found that nonoccupational exposures to many pesticides occur at detectable levels in residential air and Starr et al. (*40*) found that house dust in 28 homes of farmers and pesticide formulators in Colorado contained organochlorine pesticides in all environmental media (air, water, food, and house dust/soil). By linking questionnaire data on nonoccupational opportunities for pesticide exposure through household storage or handling of soiled clothes and biomonitoring data, the Agricultural Health Study has an opportunity to make a substantial contribution to our understanding of sources and effects of household exposure to pesticides.

Collaborative Agreements

The sponsoring agencies recognize that the full value of this cohort can be maximized only if it is seen as a national resource available to the scientific community through collaborative agreements with federal investigators. Proposals for such collaborative arrangements to answer specific etiologic and methodologic questions are welcome and will be encouraged for the duration of the study. While the opportunities for collaborative research are many and varied, some examples of potential collaborative research include: chemical analysis and biomarker analysis of blood, DNA, and urine from nested case–control studies, development of economical exposure measures on specific subgroups, intervention studies of good work practices, birth defect surveillance, developmental testing of children, and assessment of nonpesticide exposures on farms (e.g., aflatoxins, dusts, solvents, viruses, and allergies).

Appendix A. Content of Cohort Questionnaires

Enrollment Questionnaire

a. Demographic data
b. Pesticides used (50 pesticides), other pesticide-related questions
c. Lifestyle (i.e., smoking, alcohol, vegetable, and fruit consumption)
d. Brief medical history
e. Family history of cancer, kidney failure, diabetes, and heart disease
f. Farm exposures other than pesticides (not in commercial pesticide applicator version)
g. Personal identifiers, spouse identifiers, children identifiers

Farmer Applicator Questionnaire/ Commercial Applicator Questionnaire

a. Farm exposures (comprehensive)
b. Pesticide use information (i.e., methods of application, additional pesticides used)
c. Work practices used currently versus those used 10 years ago
d. Other occupational exposures
e. Leisure and work physical activity, physical attributes (e.g., height, weight, eye color, skin pigmentation category)
f. Dietary and cooking practices
g. Medical history (comprehensive)
f. Personal identifiers

Spouse Questionnaire

a. Demographic data
b. Pesticide use
c. Agricultural/other occupational exposures
d. Alcohol and smoking history
e. Physical activity, hair dye use
f. Medical history (comprehensive)
g. Personal identifier

Female and Family Health Questionnaire

a. Reproductive history
b. Pregnancy history
c. Information about children
d. Personal identifiers

Appendix B. Additional Data Gathered

Spontaneous Abortions

a. Basic demographic information
b. Smoking history
c. Pesticide exposures
d. Residential history/water consumption history
e. Pesticide treatment of gardens,

homes, and pets
f. Ionizing radiation exposure
g. Occupational exposures
h. Menstrual/pregnancy/reproductive history
i. Personal identifiers

Neurologic and Immunologic Disease
a. Basic demographic information
b. Agricultural/other occupational exposures
c. Pesticide exposure
d. Pesticide application work practices
e. Other occupational exposures
f. Medical history
g. Neurologic/immunologic symptoms
h. Personal identifier

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DRAFT-
Lymphoma risk and pesticide use in the Agricultural Health Study

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March 15, 2013

Saved as: AlavanjaNHL March(15) 2013

ABBREVIATIONS

Agricultural Health Study (AHS)

Rate ratios (RR)

95% confidence intervals (CI)

Organochlorine insecticides (OC)

Organophosphate insecticides (OP)

United States Environmental Protection Agency (U.S. EPA)

International Agency for Research on Cancer (IARC)

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Running Title: Pesticides and Non-Hodgkin Lymphoma

Abstract: 247 words: 250 word limit for EHP.

Manuscript, references and tables 1-5: 8,162 including title page etc.. [narrative (abstract & main manuscript 3,717, references 1,411, tables 2942] 7000 word limit for EHP.

Comment [a1]: If we have the message and analyses right we have to cut 1,200 words for EHP. We may want to go to another journal.

Comment [AB2]: I suggest go to another journal

ABSTRACT

Background: Farming and eExposure to pesticides haves been linked to non-Hodgkin lymphoma (NHL) in a number of previous studies. **Objective**: To evaluate specific pesticides for associations with NHL and NHL subtypes in a prospective cohort of farmers and commercial pesticide applicatorsregistered pesticide applicators. **Methods**: We examined NHL incidence in a prospective cohort of 57,310 licensed pesticide applicators in Iowa and North Carolina from 1993- 2008. Information on pesticide and other agricultural eExposure, information lifestyle and medical historyhealth histories waseere obtained from a self-administered questionnaires administered at enrollment (1993-1997) and in a telephone follow-up questionnaire administered approximately five years later (1998-2004). Poisson regression modeling was used to evaluate the association between use of specific pesticides and the rate ratios of NHL and NHL subtypes while adjusting for age and other potential confounding variables. **Results**: A statistically significant monotonic increase in the risk of overall NHL with increasing life-time exposure-days for lindane (organochlorine insecticide) was observed and a significant positive non-monotonic trend was observed for butylate (thiocarbamate herbicide), among 50 pesticides evaluated. Significantly increasing risk of specific NHL subtypes with increasing life-time exposure-days of use were observed for lindane, butylate, dicamba, terbufos, alachlor, EPTC, imazethapyr and trifluralin. The total number of different pesticides used was not associated with NHL risk overall, but the number of different triazine/triazone herbicides was significantly associated NHL. Chlorinated and organophosphate insecticide and triazine/triazone herbicides used, was related to risk in specific NHL subtypes. **Conclusions**: A wide variety of chemically-distinct herbicides and insecticides were significantly associated with different NHL subtypes. Most pesticides are associated with only one NHL subtype.

Comment [AB3]: Need to indicate which subtypes were associated with which pesticides.

Comment [AB4]: Mention the chemical class – subtype associations before the specific pesticide associations. Go from the general to the specific.

Comment [AB5]: I am not sure we want to deliver this message. As written it says we believe we found a number of meaningful pesticide – subtype links and that the links were specific. This implies we believe these findings are probably "real." I think the message should be – this is one of the few studies (and the only prospective study I think) that has looked at specific pesticide – subtype associations. Since different subtypes may have different etiologies these findings provide leads for future evaluations.

Keywords: Cohort Study, Farming, Pesticide Exposure, Non-Hodgkin Lymphoma.

INTRODUCTION

Non-Hodgkin lymphomas (NHLs) are a heterogeneous group of over 20 different B and T-cell neoplasms affecting the immune system/ lymphatic system arising primarily in the lymph nodes (Swerlow et al. 2008; Shankland et al., 2012). MNumerous eta-analyses (Blair et al., 1985; Blair et al., 1993; Beane Freeman, 2009) studies relate lymphohaematopoietic cancers with farming (Blair A et al., 1993; Blair and Beane Freeman, 2009), with exposure to pesticides being a hypothesized etiologic agent. Since the 1980s a number of studies have been conducted to evaluate possible links between specific pesticides and NHL. A meta-analysis of 13 case-control studies published between1993-2005 observed an overall significant meta-odds ratio between occupational exposure to pesticides and NHL (OR=1.35; 95% CI: 1.2-1.5). When observations were limited to those that had more than 10 years of exposure the risk increased (OR=1.65; 95% CI: 1.08-1.95) (Merhi M, et al., 2007). While the meta-analysis supports the hypothesis that pesticides are associated with NHL, it did notthey lack sufficient detail about evaluate exposure to specific pesticide exposure and other information on risk factors for hematopoietic cancers to identify specific causes (Merhi M, et al., 2007). In individual studies of NHL have reported links a number of specific pesticides including phenoxy acid herbicides (Dich et al 1997; Hardell L et al., 1981; Hoar SK et al., 1986; Zahm et al, 1990, Miligi et al, 2006, McDuffie et al, 2001Eriksson M et al., 2008; Burns et al., 2011; 8), and chlorinated pesticides (McDuffie et al, 2001, Colt et al., 2006; Spinelli JJ et al 2007, Purdue et al, 2007, Brauner EV, et al., 2012; Quintana et al., 2004; Coco et al., 2004), organophosphates (Waddell et al., 2001; Hohenadel et al., 2011)dicamba (McDuffie et al., 2001; nitro-derivaties (Miligi et al., 2003); and triazole fungicides and urea herbicides (Orsi et al., 2009)have been suggested as causes of NHL, , but the evidence has been inconsistent. Little evidence of an association between phenoxy acid herbicides and NHL was observed in New Zealand (Pearce NE et al 1987), Washington state (USA) (Woods JS, et al 1987), or Minnesota and Iowa (USA) (Cantor KP et al, 1992) and little evidence for chlorinated pesticides was observed in a European study that measure pesticide metabolites in plasma samples (Cocco P et al, 2008). A variety of other pesticides have also been associated with NHL but the evidence available to date does not conclusively link a specific pesticide to NHL (Alavanja M et al., 2012; Cocco P et al., 2013). In a study from the six Canadian provinces case-control study, the risk of NHL increased with the number of different pesticides used (Hohenadel K et al., 2011).(I think the flow of this first

Comment [AB6]: References are numbered in the reference list, but not in the text.

Comment [AB7]: Is the Beane Freeman article cited here Laura's livestock article? It is the only one in the references.

Comment [a8]: Moved the Merhi study up to mention the general association first and later the pesticide class specific-Done

Comment [a9]: Added reference

Comment [a10]: Added reference

Comment [a11]: Added reference

Comment [a12]: Added Purdue

Comment [a13]: Sentence added in reference to Laura's comment to mention other chemical associations by way of citing a review article.-Done We are >8,100 words, EHP limit 7,000

Comment [a14]: Cindy suggests cutting down the introduction. --Done

paragraph can be modified to make it clearer. Start with farming, then list pesticides that have been linked to NHL in some studies. This should cover the different pesticides that have been linked to NHL. Then list your review and Cocco (2013) to indicate that the evidence is not conclusive for any pesticide).

In the Agricultural Health Study (AHS) we had the opportunity to evaluate the risk of NHL overall and by cell type by ~~both the association of~~ lifetime use of individual pesticides obtained from enrollment and follow-up questionnaires ~~and the number of different pesticides used and NHL incidence overall and by cell type~~ in a prospective cohort study of licensed pesticide applicators in Iowa and North Carolina.

~~We evaluated potential confounders including a previous history of malignant disease (Wang et al., 2007), different immunosuppressive states (Simard JF, et al., 2012), and body mass index (BMI) (Patel et al., 2013) and other factors observed to be associated with NHL in the AHS cohort.~~

MATERIALS & METHODS

Study Population

The AHS is a prospective cohort study of 52,394 licensed private pesticide applicators in Iowa and North Carolina and 4,916 licensed commercial applicators from Iowa. The cohort has been described in detail (Alavanja et al., 1996). Briefly, the cohort included individuals seeking licenses for restricted use pesticides from December 1993 through December 1997 (82% of the target population enrolled). The protocol was approved by relevant institutional review boards. We obtained cancer incidence information by regular linkage to cancer registry files in Iowa and North Carolina. In addition, we matched cohort members to state residential mortality registries and the National Death Index to identify vital status, and to address records of the Internal Revenue Service, motor vehicle registration files, and pesticide license registries of state

Comment [a15]: Infor about cancer registries deleted as suggested by Laura.

agricultural departments to determine residence in Iowa or North Carolina. The current analysis included all incident primary non-Hodgkin lymphomas (*n*=333) diagnosed from enrollment (1993-1997) through December 31, 2008. We censored follow-up at diagnosis of NHL or any other cancer, date of death, movement out of state, or December 31, 2008, whichever was earlier. Person-years of follow-up summed to 714,770.

Tumor Characteristics

Information on tumor characteristics was obtained from state cancer registries. Cases were classified into 5 groups of cell types according to the Surveillance Epidemiology and END Result (SEER) coding scheme (http://seer.cancer.gov/lymphomarecode) SEER recodes of cell type are listed in appendix 1. The first group (n=117) includes chronic B-cell lymphocytic lymphomas (CLL) /small B-cell lympocytic lymphomas (SLL) [n=101], and mantle-cell lymphomas (MCL) (n=16). The second group includes 94 diffuse large B-cell lymphomas; the third group includes 53 follicular lymphomas. There were 34 'other B-cell lymphomas' consisting of a diverse set of B-cell lymphomas including precursor acute lymphoblastic leukemia/lymphoma (n=4), Waldenstrom macro globulinemia (n=2), lymphoplasmacytic lymphoma (n=2), hairy-cell leukemia (n=6), B-cell non-Hodgkin lymphoma not otherwise specified(n=6), Burkitt lymphoma/leukemia (n=1), and extra-nodal Marginal Zone Lymphomas (MZL)/ MALT type/ Nodal MZL(n=13). The fifth grouping included 35 cases consisting of T-cell lymphomas (n=12) and non-Hodgkin lymphoma of unknown lineage (n=23). The fifth grouping was excluded from cell type-specific analyses because of small numbers of cases with identified cell types. Although multiple myeloma (MM) (n=77) and plasmacytomas (n=6) are

Comment [lbf16]: Did you remove prevalent cancers? Does this mean that you also included second cancers if they were NHL? Eg. If someone had an incident prostate cancer and then was diagnosed with an NHL, do you consider them to be an NHL case? Or, did you censor them at their diagnosis of prostate cancer? I would remove all prevalent cancers (n=1,074) and only include first primary NHL diagnoses, censoring at diagnosis of any cancer.

Comment [a17]: Yes, we removed all prevalent cancers and included only primary NHL cases.-clarification made in sentence.-no other change necessary.

Comment [a18]: Cindy would like the 5 groups to be named. They do not have names so it is may be inappropriate to give them non-standard names. I gave the SEER recode number in the table as a means of identification.

Comment [lbf19]: Since you present them in the appendix, I would suggest taking them out of the text here—it'shard to read with all these numbers. You could also add them to the relevant tables under the specific sub-types.

Comment [a20]: SEER recodes deleted as recommended by Laura.

now classified as a type of non-Hodgkin lymphoma (Morton LM et al., 2007), the pesticide literature prior to 2008 (including the AHS) examined multiple myeloma (and plasmacytomas) separately. (AB - I wonder if the decision not to include myeloma might seem inconsistent with our decision to go with the new definition of NHL. We say we are changing the cancers we characterize as NHL to fit the new definition, but then we promptly say we are not going to follow the new definition for all of the new inclusions, i.e., myeloma will not be included. It is inconsistent and seems gerrymandered. The reason given also does not seem adequate (myeloma has been analyzed separately for pesticides) because there have also been studies that looked a pesticides and chronic lymphocytic leukemia, yet it is included as NHL here. Not sure what to do but the whole thing just seems messy. We need to talk about this on an EC call.) We continue to examine MM separately to facilitate comparisons to the previous literature. We provide supplemental table 7 which shows NHL risk (previous definition, ICD-O-3) and lifetime use of individual pesticides (AB - I think to make clear the possible the impact, or lack of it, of changing the NHL definition, Table 7 needs to include ORs from both definitions of NHL for the same length of follow up. This would make it clear that any difference regarding specific pesticides would be due to differences in disease classification.) A comparison of cell types in the previous (ICD-O-3) and recent Inter Lymph hierarchical classification of NHL is provided in appendix 2.

Comment [a21]: We added the phrase 'prior to 2008" to avoid a large increase in citations which would contribute an additional 90 words or more (approximately).

Comment [lbf22]: You will need to cite these papers in the discussion.

Exposure Assessment

Information on lifetime use of 50 pesticides was captured in two self-administered questionnaires (http://aghealth.org/questionnaires.html) completed during cohort enrollment (Phase 1). All 57,310 applicators completed the first enrollment questionnaire, which inquired about ever/never use of the 50 pesticides, as well as duration (years) and frequency (average days/year) of use for a subset of 22 pesticides. In addition, 25,291 (44.1%) of the applicators returned the second (take-home) questionnaire, which inquired about duration and frequency of use for the remaining 28 pesticides.

A follow-up questionnaire, which ascertained pesticide use since enrollment, was administered about five~~5~~ years after enrollment (1998-2003, Phase 2) and completed by 36,342 (63%) of the original participants. For participants who did not complete a Phase 2 questionnaire (20,968 applicators~~, 37%~~), a data-driven multiple imputation procedure based on logistic regression and stratified sampling was employed to impute likely use of specific pesticides in Phase 2 (Heltshe et al.,2012) ~~which used logistic regression and stratified sampling to impute the use of specific pesticides in phase 2.~~

Comment [a23]: Description of imputation procedure shortened considerable per suggestion.- Done

Information on pesticide use obtained from Phase 1 and Phase 2 interviews was used to construct two individual pesticide exposure metrics~~We used 2 exposure metrics to assess cumulative exposure to each pesticide~~: (i) lifetime days of pesticide use, i.e. the product of years of use of a specific pesticide and the number of days used per year; and (ii) intensity-weighted lifetime days of use, i.e. the product of lifetime days of use and a measure of exposure intensity. Intensity of exposure was derived from an algorithm using questionnaire data on mixing status, application method, equipment repair and use of personal protective equipment (Coble et al. 2011).

Comment [a24]: Dropped Dosemeci as suggested. Dosemeci is referenced in Coble et al. No additional changes made to this section.

We analyzed total NHL risk and specific cell type NHL by pesticide classes, individual pesticides ~~use~~, and by the number of different pesticides used within a chemical/functional class and the total number of different pesticides used in a working lifetime.

Comment [a25]: Analysis requested by Aaron.

Statistical Analyses

We used Poisson regression to calculate rate ratios (RR) and 95% confidence intervals (95% CI) for overall NHL and four NHL subtypes in relation to pesticide use. Data were obtained from AHS data release versions P1REL201005.00 (for Phase 1) and P2REL201007.00 (for Phase 2). We evaluated pesticides with 15 or more exposed cases of total NHL, thereby excluding aldicarb, aluminum phosphide, carbon tetrachloride/carbon disulfide, dieldrin, (Might look specifically at dieldrin even though it is below your cutpoint because it has been linked to NHL in the past.) ethylene dibromide, maneb, parathion, 2,4,5-TP, trichlorofon, and ziram (This list is different than that provided in the first draft. Why the change?). For each pesticide analyzed, we categorized exposure into non-exposed and tertiles of exposure based on the distribution of exposed cases. A first set of rate ratios were adjusted for age and a second set of rate ratios were adjusted for age and other statistically significant (α=0.05) predictors of NHL in the AHS. We evaluated several lifestyle and demographic measures and identified the following as potential confounding variables: age at enrollment (<40, 40-49, 50-59, 60-70, ≥70), race (White, Black, other, missing), state (Iowa, North Carolina), family history of lymphoma in first-degree relatives (yes, no, missing), body mass index (BMI <25, 25-<30, ≥30), cigarette smoking history (never, former, current, missing), alcohol consumption per week (none, < once per week, ≥ once

Comment [a26]: Correction suggested by Cindy.

Comment [a27]: We analyzed BMI and it was not a confounder. We added to table 1.

We examined available pack-years and there was no confounding.

per week) and several occupational exposures (i.e., number of livestock, poultry, acres planted, welding, diesel use, number of different pesticides used, and pesticides shown to be associated with NHL in the current analysis)(So all of these factors all significantly associated with risk of NHL here? From Table 1 it looked like most of the other adjustment factors were not significantly associated with NHL.). Tests for trend used the midpoint value of each exposure category, and the Likelihood Ratio tests were used to assess differences between strata (p-interaction). All tests were two-sided and conducted at the α=0.05 level. (I do not quite understand the rationale for the tables. The above indicates ORs were adjusted for several factors. The first set of tables say they are "age adjusted." The supplemental tables have more extensive adjustment. If it is important to adjust for factors other than age, why are these analyses in supplemental tables. If they are not important, why are they done at all. In any case I am not sure you need two tables. Often you see age adjusted and more extensively adjusted ORs in the same table. That would be better because it allows the reader to see if the additional adjusment made any difference in the ORs.)

We also conducted various sensitivity analyses. We analyzed Phase 1 data alone to assess the impact of the additional information collected or imputed from Phase 2. We also explored the effect of lagging exposure data 5 and 15 years since ~~recent these~~ recent exposures may not have had an impact on the development of cancer. Reported results show un-lagged exposure data from Phase 1 and Phase 2 combined for cumulative intensity-weighted and un-weighted days of use. (AB - I think we should start doing some analyses by type of protective equipment used. I know it is supposedly taken into account in the intensity score, but it would be informative if there were differences in OR by different protective approaches. It could be used with number

Comment [AB28]: Probably need to add you chose to show these data because the other analyses had not impact.

of days of pesticide use where it has not been taken into account. It provides information that is useful to farmers and extension agents.)

RESULTS

The risk of NHL increased significantly and in a near monotonic fashion with age in the AHS cohort (Table 1). The age-adjusted risk of NHL is significantly lower in NC compared to IA and among current smokers compared to nonsmokers. Other demographic factors including gender, license type, educational level, alcohol consumption, BMI, and a family history of lymphomas were not significant risk factors of NHL in this cohort. We evaluated whether other occupational factors were associated with NHL. Of those evaluated, the number of livestock on the farm and whether cohort members drove farm equipment with diesel engines significantly increased risk of NHL.

The age-adjusted risk of NHL and NHL subtypes from possible exposure to~~associated with~~ 16 insecticides and herbicides ~~associated with NHL or NHL subtypes or~~ previously associated with NHL are listed in Table 2 (age-adjusted risk of NHL for all other evaluated pesticides in the AHS may be found in supplemental table 1 and fully-adjusted risk of NHL in supplemental table 2). Lindane, an organochlorine insecticide, is the only pesticide showing a monotonic rise in overall NHL risk with increasing life-time days of use (p trend=0.003) and intensity-weighted lifetime days of use (p trend=0.05). Butylate, a thiocarbamate herbicide, showed a significant increasing trend in life-time days of use (p trend=0.004) and intensity-weighted lifetime days of

Comment [lbf29]: I think that you can cut down on reporting the results that are presented in the tables, but I would like to see some more results in the text that aren't in the tables. E.g., what happens when you put both lindane and butylate in the model? What is frequency of use of chemicals, etc.?

Comment [a30]: Narrative now mentions that there is no apparent confounding between lindane and butylate. Only pesticides with 15 or more exposed cases are listed in the tables for analysis. Space limits more extensive discussion of frequency of pesticide use in the AHS, although this can be ascertained from use in controls.

Comment [AB31]: The Methods says they were significant risk factors.

Comment [a32]: Previous table 2 deleted and discussion of potential confounding variables shortened as suggested by Laura.

Comment [t33]: It's not clear why you are showing these 22 pesticides

Comment [AB34]: I think it would help the reader if you presented ever/never results for all pesticides analyzed. This would set the stage for the exposure response analyses. You would largely include only those pesticides with some excess in the ever category in the trend analyses. Now it is not clear why some are listed and others are not. As of now the Results just sort of jump into detailed exposure-response analyses.

Comment [t35]: If there's not a big difference between age and fully adjusted models I would delete fully adjusted

use (p trend=0.04) but the associations were not monotonic. Some other pesticides had individual point estimates that were significant but did not show a significant pattern of increasing risk with increasing exposure. Lindane and butylate did not ~~show~~ confound~~ing with~~ each other when they were put in the same model. The significant increasing trend of NHL risk with exposure to lindane and butylate was also not changed with the adjustment days of all other pesticide use, nor with adjustment for days of use of organophosphate insecticides, carbamate insecticides, other insecticides, triazine/triazone herbicides, other herbicides, fungicides, or fumigants. The results from fully adjusted risk of NHL (i.e., Age [<45,45-49,50-54,55-59,60-64,65-69,≥70], smoking status(current, former, never), number of livestock (0,,<100,100-999,>999), drove diesel tractor (<weekly,≥weekly, state (NC, IA) [data not shown were comparable to the age-adjusted risk]. Also, these unlagged results were comparable (not shown) to 5 year and 15 year lagged exposures, therefore we present RRs for unlagged exposure only.

Comment [lbf36]: I find these lists of RR and 95% CI throughout to be a bit hard to read, plus they take up a lot of words. I think it would be better to provide more information in the text about results that aren't presented in the tables. E.g., for lindane,, how many people reported using it in Phase 1 vs. Phase 2 as it was approaching phase out. This will help to set the stage for putting the results in context later in the discussion.

Comment [a37]: Point estimates deleted to reduce word count as recommended.

Comment [a38]: Need to define the pesticides included in each group appendix 2-done

Comment [AB39]: Supplement Table 2 does show the fully adjusted model, right?

We also analyzed Phase 1 data only to assess the impact of the additional information collected or imputed from Phase 2, although there was an increase in precession including phase 2 estimates, no meaningful change was observed in the risk estimates.

Comment [lbf40]: I don't think you mention this in the results.

Comment [lbf41]: How did you choose the 22 pesticides in this table? Why not 28 as in table 2? Regardless, need to explain rationale/criteria for presenting some and not others

The risk of the four major categories of B cell lymphomas by number of days of use of individual pesticide is shown in Table 3. For the CLL/SLL/MCL group of lymphomas, dicamba, a carbamate herbicide (p trend=0.03) and butylate, a thiocarbamate herbicide (p trend=0.04), and

lindane, a chlorinated insecticide, (p trend=0.005) were observed to have a significant increased trend of risk with increasing lifetime-days of use. Metribuzin, a triazone herbicide, (p trend=0.06) had a near significant relationship with this group of lymphomas. Carbaryl, a carbamate insecticide, was observed to have a significant inverse relationship (p trend=0.007).

Comment [a42]: Metribuzin, is a triazone herbicide not a triazine herbicide.-corrected

A significant increase in the risk of Other B-cell Lymphomas was associated with the number of life-time days of use of six herbicides and one insecticide: alachlor (p trend=0.02); butylate, (p trend=0.0499); dicamba (p trend=0.02); EPTC use (p trend=0.01): imazethapyr (p trend=0.03); trifluralin use (p trend=0.01); and terbufos (p trend=0.01) (Table 3). Risk of other B-cell lymphomas was also associated with a non-significant elevated risk for the low and medium exposure categories and was significantly associated with the highest category of exposure for atrazine use (RR=3.6 [95% CI: 1.2-10.8]; p trend=0.06).

Comment [AB43]: Since insecticides come before the herbicides in the table discuss terbufos before the herbicides here in the text.

No pesticide had a significant exposure response pattern with either diffuse large B-cell lymphomas or follicular B-cell lymphomas, although significant point estimates of risk were identified for butylate, terbufos, and methyl bromide.

Comment [AB44]: Glyphosate had a significant trend for diffuse and chlordane and malathion were borderline EPTC and butylate had borderline trends for follicular.

The number of different triazine/triazone herbicides used, adjusted for age and lifetime days of use of triazine/triazone herbicides was associated with a significant increasing trend with total NHL risk (p trend=0.04) (Table 4). No other chemical/functional class showed a significant pattern of NHL risk. The association between the age-adjusted risk of the four NHL B-cell sub-types and the total number of different pesticides by chemical class used is presented in Table 5. For the CLL/SLL/MCL group of lymphomas, the number of different chlorinated insecticides (p

Comment [AB45]: Not sure what is meant here. Triazine/triazones adjusted for triazine/triazone?

trend=0.02) and the number of different organophosphate insecticides (p trend= 0.03) showed a significant trend of increase risk with increasing number of insecticides from these chemical/functional classes. Similar trends were observed for the number of different triazine/triazone herbicides (p trend=0.07), other herbicides (p trend=0.06) and fungicides (p trend=0.11) but the trends were not statistically significant.

Comment [a46]: Typo corrected as suggested.

For either diffuse large B-cell lymphomas or follicular B-cell lymphomas, no pesticide class had a significant pattern of increasing risk with number of pesticides used, although a significant decreased risk with increasing number of pesticides used was observed for chlorinated pesticides (p trend=0.05) and other insecticides (p trend= 0.04) with the diffuse large B-cell lymphoma group.

For the other B-cell lymphoma group, the number of different triazine/triazone herbicides (p trend=0.006) and the number of different acetamide herbicides (p trend= 0.009) both were observed to have a significant trend of increasing risk with increasing days of use. Similar trends were observed for the number of different carbamate herbicides (p trend=0.11) and 'other herbicides' (p trend=0.06) but these trends were not statistically significant.

Comment [a47]: These will be adjusted for total number of exposure days to chemicals in this class.- Done

DISCUSSION

AB – I think we need to start with the big picture comparisons first. I suggest the order for the discussion should be: (1) Ever/never comparisons for NHL overall, (2) Then move to trends for NHL overall, (3) Then trends for subtypes. (4) Next have a discussion of how the change in

Comment [lbf48]: Throughout , you need to reference the previous analyses of AHS data and specific chemicals. You reference Mark Purdue's paper in the intro, but no others

Comment [a49]: See changes made throughout to address these points.

Comment [lbf50]: *This paper just came out and used the most recent definitions of NHL. Actually supportive of these AHS findings.*
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Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study

NHL definition might affect comparison of our results with those from the literature. (5) Comparison of these results with literature pesticide by pesticide (or pesticide group). (6) Strengths and limitations. (7) Conclusions.

In this analysis, we observed a significant increase in the risk of overall NHL with two pesticides, lindane an organochlorine insecticide no longer registered for use in the U.S and butylate a thio-carbamate herbicide widely used in the United States and other countries. Our findings for total NHL are inconsistent with a number of other studies which found increased risks with a variety of chlorinated and organophosphate insecticides and triazine and phenoxy acid herbicides (Dich et al 1997; Hardell L et al., 1981; Hoar SK et al., 1986; Zahm et al, 1990). However, we did find significantly increasing risk of specific NHL subtypes with increasing life-time exposure days of individual pesticides use. Butylate and dicamba, carbamate herbicides, and lindane, a chlorinated insecticide, were observed to have a significant increasing risk of the CLL/SLL/ MCL lymphomas sub-types with increasing lifetime-days of use. (This first paragraph just sort of jumps into the subtype/specific pesticide links. I think a smoother opening paragraph would be to comment on ever/never for specific pesticides, then exposure trends by specific pesticide, and finally exposure trends by NHL subtypes. This summary of the findings should then be followed by a discussion of the effects, or lack of them, from the change in the definition of NHL. Then the findings from this analysis can be compared to the previous literature.)

Comment [lbf51]: What was percentage of use in P1 vs. P2? If people aren't still using, but we still have excess then we need to explore this further. Do we see stronger effects in earlier time periods? Do we expect this to not be aproblem since lindane is no longer on the market? Or, is this going to be a persistent problem? We also need to say something about when lindane was taken off the market.

Comment [AB52]: There is a bit of an inconsistency here. Says there is an excess for lindane, but these findings differ from earlier work that saw excesses for a variety of chlorinated insecticides. Lindane is a chlorinated insecticide.

Comment [lbf53]: This sounds like all the other studies are positive, which isn't actually true. I think that you need to have a more in-depth discussion of specific pesticides and findings.

Comment [AB54]: I do not think we can make this statement of differences with past studies without immediately including a discussion of the difference in disease definition and whether or not this might account for the differences/or similarities with past research. Probably need to start the discussion with comparison of results of analyses for the two different definitions to orient the reader regarding what changes occurred simply because of the change in definition. Then this should be followed with a discussion of findings from an ever/never comparison. Then you go to trends.

Other B-cell lymphomas are a varied group including 8 different cell types of lymphomas. Excess risks of other B-cell lymphomas were observed for several widely-used pesticides including: the organophosphorous insecticide terbufos, for alachlor, an acetanilide-herbicide, imazethapyr, an imidazoline-herbicides, and trifluralin, a dinitroaniline-herbicide, and for

butylate, dicamba, and, EPTC which all belong to the family of carbamate herbicides. The triazine herbicides atrazine and cyanazine had specific point estimates that were elevated but the trends of risk were neither significant nor monotonic. ~~Metribuzin, a triazone herbicide. had too few other B-cell lymphomas to evaluate.~~ The wide array of functional groups and chemical classes that are associated with an increased risk of Other B-cell lymphomas does not suggest a single known mechanism of action. Multiple pathways seem to be involved.

Comment [AB55]: I am not sure you want to talk about pathways. This assumes that the links observed here are real. Perhaps the wide array of function groups and chemical classes is just noise. You might try to dissect the individual histologies in this "Other B-cell" to see if any one stands out with a particular pesticide.

In a Swedish case-control study a significant excess risk of NHL was associated with the phenoxy herbicide MCPA and glyphosate (Ericksson et al., 2008). 2,4-D and 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) have been banned from Sweden and could not be evaluated (Eriksson M et al.,2008). In our study we could not evaluate MCPA but found no excess risk of NHL or its subtypes with the use of glyphospate, 2,4-D or 2,4,5-T.

Comment [AB56]: Check to make sure 2,4-D was banned during the time of pesticide use by people in Eriksson's study. My impression is that it just was not used much in Scandinavia, but was not banned until later.

In a population-based case-control study conducted in six Canadian provinces increased risk to NHL was associated with a positive family history of cancer both with and without pesticide exposure [OR=1.72 (95% CI 1.21-2.45) and OR=1.43 (95% CI: 1.12-1.83), respectively] (McDuffie HH, et.al, 2009). In this same case-control study six pesticides/pesticide analytes also showed a significant association with NHL [beta-hexachlorocyclohexane, *p, p'*- dichloro-diphenyl-dichloroethylene (DDE), hexachlorobenzene, mirex, oxychlordane and trans-nonachlor] (Spinelli et al., 2007). The strongest association was found for oxychlordane, a metabolite of the pesticide chlordane (highest vs. lowest quartile OR=2.68, 95% CI 1.69-4.2). These finding were not confirmed in a recent analysis of plasma samples from 174 NHL cases and 203 controls from France, Germany and Spain. The risk of NHL did not increase with

Comment [AB57]: Not sure we need this sentence. Certainly should not lead with it because family history was not evaluate our NHL study.

plasma levels of hexachlorobenzene, beta-hexachlorobenzene or DDE (Cocco P et al., 2008). In our study NHL was associated with lindane but no excess risk was observed for chlordane and no excess risk was observed among those with a family history of lymphoma. ~~The other chemicals evaluated in the Canadian six province study were not evaluated in the AHS cohort.~~

New evidence linking NHL with chlorinated pesticide use (Brauner EV, et al., 2012) and a study linking the number of different pesticides used with NHL (Hohenadel K et al., 2011) are somewhat supported by our findings in the AHS cohort. While the number of different pesticides used overall was not associated with NHL risk in the AHS, a significant increase in the CLL/SLL/MCL sub-group of NHL was observed with the number of different chlorinated pesticides used and the number of different organophosphate chemicals used. A similar pattern of increase risk was observed in the other B-cell lymphoma subgroup of NHL with an increasing number of triazine/triazone pesticides used.

Comment [lbf58]: Expand to discuss what these actually show—similar to ours? Not similar to ours?

Comment [a59]: Modified sentence in response to comment

Comment [AB60]: I have a hard time following the discussion. I wonder if it might not be clearing if the link to previous literature is done pesticide by pesticide. Then you could indicate what is found here and follow that with findings for that pesticide in the literature. This means previous studies could be cited numerous times, but it would be easier to see the relationship between our findings and those from other studies for individual pesticides.

A strength of this investigation is that a relatively large population of licensed pesticide applicators provided reliable information regarding their pesticide application history (Blair et al. 2002; Coble et al. 2011, should cite Jane's paper on reliability also). In the AHS, a priori derived algorithm scores that incorporated several exposure determinants were found to be able to ~~used to~~ predict urinary pesticide levels (Thomas et al., Coble 2011). Few? studies of pesticide use with a prospective design have been large enough or had sufficiently detailed exposure information, to evaluate the potential link between NHL, NHL subtypes and specific pesticide exposures (Are there any other prospective studies that could look at specific pesticides?). Also, because occupational pesticide users are seldom exposed to a single agent, we controlled for the total pesticide exposure days and total pesticide exposure days by chemical/functional class and found

no meaningful change in the associations. Additionally, potential confounding of pesticides by other occupational exposures was reported to be minimal in the AHS (Coble et al., 2002) and adjustment for various agricultural exposures did not fundamentally change calculated RR for NHL from various pesticide exposures. – (Mention ability to control of possible non-occupational confounders, use of incidence rather than mortality)

Comment [AB61]: I have a real problem with this approach and the interpretation of the findings from it. Is total pesticide exposure days associated with NHL? If not, then it clearly does not control from individual pesticides because some individual pesticides are associated with NHL. This would work if most pesticides were associated with NHL, but most are not Thus, this total pesticide scale is so water down that it cannot control for anything. This said, I doubt that there is confounding among the pesticides, but we cannot us this approach as evidence for no confounding. The most straightforward, and usual approach, is to adjust the RR for one pesticide by each individual pesticide thought to be a potential confounder.

Although this is a large prospective study, there are limitations~~limitations should be acknowledged~~. Cell-type information in the AHS was obtained from the cancer registry database and did not involve pathologic re-review of diagnostic slides. Other limitations including a small number of exposed cases for certain chemical of interest.

Comment [AB62]: I do not think I would list this. These are data that are used to establish cancer patterns by the NCI. I think the reliability/validity of the diagnosis from tumor registries is well accepted.

Need to add a paragraph of exposure assessment. Discuss the information on our exposure scale in relation to the monitoring work. Discuss the likely magnitude of misclassification and its likely impact on the estimates of RR. Might also want to say something about multiple exposures. Cannot look only at a single exposure. This is an issue raised by critics. Just as well address it here.

AB – This next paragraph seems part of the conclusions. I would try to merge it with the conclusions paragraph.

In our study no pesticide had a significant exposure response pattern with either diffuse large B-cell lymphoma or follicular B-cell lymphoma, although significant relative~~point estimates of~~ risks were identified for butylate (a carbamate herbicide), terbufos (an organophosphate insecticide), and methyl bromide (an organic halide)(Not clear what you are trying to say here – No exposure-response pattern, but significant RRs.). Previously, NHL subtypes with t (14;18) translocations were associated with the chlorinated insecticides dieldrin, lindane, and toxaphene

Comment [AB63]: But there were borderline trends for these subtypes

and the triazine herbicide atrazine (chiu BCH et al., 2006 and Chiu BCH and Blair A 2009). We were unable to evaluate translocations in this analysis. Although it is possible that t (14;18) translocations are an initiating event of a causative cascade leading to an NHL subtype, follicular lymphoma (FL), much more work needs to be done to establish this etiologic pathway. (Not sure mentioning t(14;18) is worthwhile here. This study sheds no light on this issue. This point might be combined in a paragraph that discusses future research, but it does not fit by itself)—.

Conclusion:

(I do not think you should start the conclusion with comments about subtypes. Start with NHL overall. In summary, our results suggest that there is subtype specificity in associations between NHL and pesticides exposures. The varying etiology of NHL sub-types may have masked real associations between pesticides and NHL in previous studies where NHL sub-type information was not available (Not sure how varying etiology by subtype would mask associations with NHL overall. If each study had all the subtypes then either the subtype links power through to overall NHL or they do not. The reverse is true. Looking only at NHL overall would hide associations with specific subtypes.). Although the epidemiological evidence for associations between specific pesticides and specific cell types is growing (probably should cite the other papers that have information on specific pesticides and subtypes), the observation that pesticides of different chemical and functional classes and different known toxicological properties are associated with the same cell type (Is it know that different pesticides are associated with the same cell type?) indicates that relatively little is known about the biological/toxicological mechanisms by which these compounds may be contributing to this disease. Cautious interpretation of these results is advised since the number of exposed-cases for

each subgroup of NHL in the AHS is still relatively small. (Overall I think the conclusion is too strong. It seems to say that the links between specific pesticides and certain NHL subtypes observed in this study are real and this is why we do not understand the mechanisms for pesticides causing cancer. The findings here are interesting, but they are leads to be confirmed. I do not think they are strong enough to be making statements about what this says about mechanisms. I think the tone should be – few studies have been able to look at specific pesticides and NHL subtypes. What we found is interesting. Need to see if other studies will have similar findings. I may be in a minority about this, but I would like to have a discussion about this on an EC call.)

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Comment [AB64]: This affiliation does not cover ally coauthors. Don't we usually put some comment of appreciation to the participants in the AHS in the acknowledgements?

Comment [a65]: Get correct contract numbers here.

The authors have no conflicts of interest in connection with this manuscript.

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Table 1. Baseline characteristics of AHS study participants in the NHL incidence analysis from 1993 through 2008				
	All NHL cases	Cohort Person-years.	RR[1]	95% CI
Age at Enrollment				
<45	51	368,766.80	1.0 (ref)	
45-49	34	88,648.48	2.8	1.8-4.3
50-54	51	75,781.37	4.9	3.3-7.2
55-59	59	67,981.37	6.3	4.3-9.1
60-64	46	53,346.73	6.2	4.2-9.3
65-69	46	34,532.71	9.6	6.5-14.4
≥70	46	25,713.12	12.9	8.7-19.3
Gender				
Male	328 (ref)	695,190.90	1.0 (ref)	
Female	5	19,579.34	0.5	0.2-1.3
State				
IA	213 (ref)	461,697.24	1.0 (ref)	
NC	120	253,072.27	0.8	0.6-0.97
License type				
Private	318	652,562.25	1.0 (ref)	
Commercial	15	62,207.89	0.9	0.5-1.5
Education				
<12 yrs.	57	61,656.39	1.0 (ref)	
HS/GED	143	326,344.92	0.8	0.6-1.1
>12 yrs.	121	297,437.85	1.0	0.7-1.4
Smoking Status				

Never	165	371,929.66	1.0 (ref)	
Former	127	203,445.28	0.93	0.7-1.2
Current	29	116,254.87	0.6	0.4-0.9
Body Mass Index (BMI)				
<25	58		1.0 (ref)	
25-<30	138		1.1	0.8-1.5
≥30	61		0.94	0.7-1.4
Alcohol consumption per week				
None	128	212,928.70	1.0 (ref)	
<once a week	89	217,015.35	1.0	0.8-1.4
≥once a week	89	240,745.51	1.0	0.8-1.4
First degree relative with lymphoma				
No	291	639,748.82	1 (ref)	
Yes	7	12,606.85	1.1	0.5-2.4

[1] All variables except age are age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)

[2] Numbers do not sum to totals (333 cases, 714,770 person-years) due to missing data.

Table 2. Pesticide exposure (Lifetime Days [LD] & intensity weighted Lifetime Days [IWLD]) and the age-adjusted risk of NHL incidence (1993 through 2008)

Insecticides				
Pesticide (chemical-functional class) [median days of lifetime exposure for each category]	NHL Cases	RR[1] (95%) by Total Days of Exposure	NHL Cases	RR[1] (95% CI) Intensity-weighted days of exposure
Carbaryl (carbamate-insecticide)				
None	81	1.0 (ref)	81	1.0 (ref)
Low [8.75]	31	0.9 (0.5-1.5)	27	0.9 (0.5-1.5)
Medium [56]	23	0.7 (0.4-1.1)	26	0.8 (0.5-1.4)
High [124.5]	25	0.9 (0.6-1.5)	26	0.8 (0.5-1.3)
		P trend=0.86		P trend=0.47
Malathion (organophosphorous-insecticide)				
None	55	1.0 (ref)	55	1.0 (ref)
Low [8.75]	46	1.0 (0.7-1.5)	37	1.0 (0.7-1.6)
Medium [42.75]	28	0.7 (0.4-1.2)	38	0.8 (0.5-1.3)
High [103.75]	36	1.0 (0.7-1.6)	35	0.91 (0.6-1.4)
		P trend=0.74		P trend=0.71
Terbufos (organophosphorous-insecticide)				
None	157	1.0 (ref)	157	1.0 (ref)
Low [24.5]	58	1.4 (1.1-1.9)	43	1.3 (0.92-1.8)
Medium [56]	38	2.0 (1.4-2.8)	43	2.0 (1.4-2.8)
High [116]	34	1.2 (0.8-1.7)	42	1.2 (0.9-1.8)

		P trend=0.23		P trend=0.19
Chlorinated Insecticide				
Chlordane (Chlorinated Insecticide)				
None	223	1.0 (ref)	223	1.0 (ref)
Low [8.75]	23	0.9 (0.6-1.4)	13	1.1 (0.7-2.0)
Medium [20]	6	1.7 (0.8-3.8)	13	0.9 (0.5-1.6)
High [38.75]	9	0.8 (0.4-1.6)	12	0.9 (0.5-1.6)
		P trend=0.89		P trend=0.77
DDT (Chlorinated Insecticide)				
None	194	1.0 (ref)	194	1.0 (ref)
Low [8.75]	20	0.8 (0.5-1.3)	19	0.9 (0.6-1.5)
Medium [56]	18	0.9 (0.6-1.6)	18	0.8 (0.5-1.4)
High [116]	17	1.5 (0.9-2.5)	18	1.4 (0.8-2.2)
		P trend=0.14		P trend=0.28
Lindane (Chlorinated Insecticide)				
None	209	1.0 (ref)	209	1.0 (ref)
Low [17.75]	11	1.0(0.5-2.0)	10	1.1(0.6-2.0)
Medium [56]	10	1.2(0.6-2.3)	11	1.4(0.7-2.6)
High [116]	10	2.7(1.4-5.1)	9	1.9(0.95-3.7)
		P trend=0.003		P trend=0.04
Herbicides				
Alachlor (acetamide-herbicide)				
None	138	1.0 (ref)	138	1.0 (ref)

Comment [lbf66]: I like this heading—suggest using them throughout the tables and then deleting the chemical class in parentheses

Low [24.5]	65	1.0 (0.7-1.3)	53	1.0 (0.7-1.3)
Medium [116]	49	0.9(0.6-1.2)	50	0.9 (0.6-1.2)
High [224.75]	43	1.3(0.9-1.9)	51	1.2 (0.9-1.7)
		P trend=0.12		P trend=0.19
Atrazine (triazine-herbicide)				
None	85	1.0 (ref)	85	1.0 (ref)
Low [38.75]	88	1.2(0.8-1.7)	79	1.1(0.8-1.6)
Medium [114.5]	72	1.3(0.96-1.9)	78	1.4(1.0-2.0)
High [224.75]	77	1.2(0.9-1.6)	78	1.2(0.8-1.6)
		P trend=0.56		P trend=0.68
Butylate (thiocarbamate-herbicide)				
None	107	1.0 (ref)	107	1.0 (ref)
Low [24.5]	22	1.0(0.6-1.5)	16	0.9(0.5-1.5)
Medium [56]	18	2.8(1.7-4.7)	16	2.1(1.2-3.5)
High [56]	7	1.1(0.5-2.4)	15	1.5(0.9-2.6)
		P trend=0.004		P trend=0.04
Dicamba (benzoic-herbicide)				
None	121	1.0 (ref)	121	1.0 (ref)
Low [20]	66	1.3(0.94-1.8)	56	1.2(0.9-1.8)
Medium [56]	52	1.5(1.1-2.1)	54	1.5(1.1-2.1)
High [128.5]	47	1.2(0.9-1.7)	55	1.3(0.9-1.8)
		P trend=0.38	P trend=0.23	
2,4-D (phenoxy-herbicide)				

None	71	1.0 (ref)	71	1.0 (ref)
Low [46.75]	83	1.0(0.7-1.4)	82	1.0(0.7-1.4)
Medium [133.35]	83	1.2(0.8-1.6)	83	1.1(0.8-1.6)
High [371.75]	82	1.0(0.7-1.4)	81	1.0(0.7-1.4)
		P trend=0.96		P trend=0.94
EPTC (thiocarbamate-herbicide)				
None	229	1.0 (ref)	229	1.0 (ref)
Low [8.75]	28	1.3(0.9-2.0)	20	1.3(0.8-2.1)
Medium [50.75]	14	1.0(0.6-1.7)	20	1.2(0.7-1.8)
High [108.5]	18	1.3(0.8-2.0)	19	1.1(0.7-1.8)
		P trend=0.35		P trend=0.54
Glyphosate (phosphinic acid-herbicide)				
None	70	1.0 (ref)	70	1.0 (ref)
Low [20]	89	0.8(0.6-1.2)	83	0.9(0.6-1.3)
Medium [65.75]	78	0.8(0.6-1.2)	84	0.8(0.5-1.1)
High [173.25]	83	1.0(0.7-1.4)	82	1.0(0.7-1.3)
		P trend=0.58		P trend=0.81
Imazethapyr (imidazolinone-herbicide)				
None	181	1.0 (ref)	181	1.0 (ref)
Low [8.75]	39	0.9(0.6-1.3)	36	1.0(0.7-1.4)
Medium [28.75]	34	0.9(0.6-1.4)	37	0.9(0.6-1.3)
High [56]	35	1.2(0.8-1.7)	35	1.2(0.8-1.7)
		P trend=0.54		P trend=0.55
Metribuzin				

(triazine-herbicide)				
None	94	1.0 (ref)	94	1.0 (ref)
Low [8.75]	28	1.0 (0.7-1.7)	21	1.2(0.7-2.0)
Medium [50.75]	15	0.9(0.5-1.6)	23	1.1(0.7-1.7)
High [56]	20	1.7(1.0-2.7)	19	1.3(0.8-2.2)
		P trend=0.06		P trend=0.28
Trifluralin (dinitroaniline-herbicide)				
None	140	1.0 (ref)	140	1.0 (ref)
Low [25]	51	1.0 (0.7-1.4)	50	1.0(0.7-1.4)
Medium [108.5]	58	1.1(0.8-1.5)	52	1.1(0.8-1.5)
High [224.75]	43	1.0(0.7-1.3)	48	0.9(0.7-1.3)
		P trend=0.81		P trend=0.65

[1]Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)

[2] Numbers do not sum to total number of NHL cases (n=333) due to missing data.

Table 3. Pesticides exposure (Lifetime-days and the age-adjusted risk of NHL by cell type (1993-2008).

	CLL, SLL, MCL		Diffuse Large B-cell		Follicular B-cell		Other B-cell types	
	Insecticides, fungicide and fumigant							
	RR[1] (95% CI)	**n**	**RR[1] (95% CI)**	**n**	**RR[1] (95% CI)**	**n**	**RR[1] (95% CI)**	**N**
Carbaryl								
None	1.0 (ref)	32	1.0 (ref)	23	1.0 (ref)	9	1.0 (ref)	9
Low	1.1(0.5-2.2)	15	0.7(0.3-1.5)	10	1.1(0.3-4.0)	5	Xxx	6
Medium	1.0(0.2-4.2)	2	1.3(0.6-3.0)	8	1.8(0.6-5.9)	4	Xxx	0
High	0.4(0.2-0.8)	8	1.5(0.7-3.5)	8	1.3(0.4-4.1)	4	xxx-	1
	P trend=0.007		P trend=0.19		P trend=0.66		P trend=xxx	
Malathion								
None	1.0 (ref)	21	1.0 (ref)	16	1.0 (ref)	5	1.0 (ref)	6
Low	0.94(0.5-1.8)	17	0.8(0.4-1.7)	16	1.0(0.3-3.6)	6	xxx-	8
Medium	0.8(0.4-1.7)	11	0.9(0.4-2.1)	8	1.2(0.3-4.3)	5	-xxx	0
High	0.8(0.4-1.7)	11	1.7(0.8-3.8)	11	1.5(0.4-4.9)	5	-xxx	3
	P trend=0.52		P trend=0.07		P trend=0.48		P trend=xxx	
Terbufos								
None	1.0 (ref)	53	1.0 (ref)	47	1.0 (ref)	26	1.0 (ref)	10
Low	1.8(1.0-3.1)	17	0.9(0.4-1.7)	12	2.5(1.1-5.4)	8	2.3 (0.8-6.6)	6
Medium	2.2(1.3-3.6)	21	2.2(1.2-4.2)	12	1.8(0.7-4.3)	7	3.1(1.1-9.2)	5
High	1.4(0.8-2.6)	13	1.1(0.5-2.3)	10	0.7(0.3-1.8)	6	4.1(1.4-11.9)	5
	P trend=0.16		P trend=0.34		P trend=0.54		P trend=0.01	
	Chlorinated pesticides							
Chlordane								
None	1.0 (ref)	74	1.0 (ref)	68	1.0 (ref)	35	1.0 (ref)	21

Comment [lbf67]: Insert the codes here and then you can remove them from the text.

Comment [lbf68]: Would suggest using the headings as suggest in Table 2 to orient people to chemical class.

Low	1.4 (0.7-2.7)	10	0.8 (0.4-2.0)	6	1.6 (0.4-6.9)	2	Xxx	1
Medium	2.8 (0.9-9.0)	3	1.8 (0.6-5.1)	4	0.8 (0.2-3.4)	2	Xxx	2
High	0.8 (0.3-2.7)	3	1.0 (0.2-4.1)	2	0.7 (0.1-5.1)	1	Xxx	0
	P trend=0.56		P trend=0.09		P trend=0.92		P trend=xxx	
DDT								
None	1.0 (ref)	62	1.0 (ref)	53	1.0 (ref)	36	1.0 (ref)	22
Low	0.91 (0.4-2.0)	8	1.1 (0.5-2.6)	7	1.1 (0.4-3.4)	4	0.4 (0.1-1.9)	2
Medium	1.1 (0.5-2.4)	8	2.3 (1.0-5.4)	7	0.3 (0.1-2.6)	1	1.4 (0.3-6.2)	2
High	2.3 (1.0-5.3)	7	1.2 (0.5-2.9)	6	0.7 (0.1-5.0)	1	0.9 (0.1-6.7)	1
	P trend=0.45		P trend=0.31		P trend=0.72		P trend=0.77	
Lindane								
None	1.0 (ref)	41	1.0 (ref)	39	1.0 (ref)	14	1.0 (ref)	14
Low	1.6(0.7-3.6)	8	0.7(0.2-3.0)	9	2.7(0.8-9.4)	3	Xxx	1
Medium	1.1(0.3-4.8)	3	1.1(0.3-3.7)	6	3.6(0.8-15.9)	2	Xxx	0
High	3.8(1.5-9.6)	5	1.3(0.2-9.7)	5	2.4(0.5-10.4)	2	Xxx	0
	P trend=0.005		P trend=0.25		P trend=0.25		P trend=xxx	
Herbicides								
Alachlor (acetanilide)								
None	1.0 (ref)	53	1.0 (ref)	42	1.0 (ref)	22	1.0 (ref)	9
Low	0.9(0.6-1.5)	23	0.9(0.5-1.6)	13	1.3(0.6-2.6)	10	1.6 (0.6-4.4)	7
Medium	0.8(0.5-1.4)	18	0.7(0.4-1.3)	14	0.8(0.3-1.6)	9	2.1 (0.8-5.3)	10
High	1.1(0.6-2.1)	14	0.8(0.4-1.6)	10	1.1(0.4-2.7)	6	4.0 (1.2-13.0)	4
	P =0.67		P trend=0.52		P trend=0.99		P trend=0.02	
Atrazine (triazine)								
None	1.0 (ref)	34	1.0 (ref)	26	1.0 (ref)	12	1.0 (ref)	5

Low	1.0 (0.6-1.7)	29	1.1(0.6-2.0)	21	1.7(0.7-3.9)	17	2.4 (0.9-6.8)	13
Medium	1.2 (0.7-2.0)	25	1.1(0.6-2.2)	23	1.3(0.5-3.4)	10	1.7(0.5-5.9)	6
High	1.0 (0.6-1.7)	26	0.9(0.5-1.7)	19	1.4(0.6-3.4)	13	3.6 (1.2-10.8)	9
	P trend=0.90		P trend=0.62		P trend=0.83		P trend=0.06	
Butylate (thio-carbamate-)								
None	1.0 (ref)	40	1.0 (ref)	33	1.0 (ref)	14	1.0 (ref)	8
Low	0.8(0.4-1.9)	7	1.1(0.4-3.0)	4	0.8(0.2-2.9)	3	3.0 (0.8-11.3)	3
Medium	3.5(1.6-7.6)	8	1.2(0.4-3.5)	4	6.3(2.1-19.3)	4	4.0(1.2-13.7)	4
High	1.3(0.4-4.3)	3	0.8(0.2-2.5)	3	1.0(0.1-7.9)	1	2.4 (0.3-19.7)	1
	P trend=0.04		P trend=0.69		P trend=0.07		P trend=0.0499	
2,4-D (Chlorinated Phenoxy)								
None	1.0 (ref)	25	1.0 (ref)	23	1.0 (ref)	9	1.0 (ref)	5
Low	0.90(0.5-1.5)	31	0.9(0.5-1.7)	23	1.8(0.8-4.4)	14	1.9 (0.6-6.2)	10
Medium	1.2(0.7-2.0)	29	1.0(0.6-1.9)	21	1.0(0.4-2.4)	14	1.7 (0.5-5.6)	9
High	1.3(0.7-2.2)	29	0.7(0.4-1.3)	21	1.4(0.6-3.4)	12	2.2 (0.7-7.2)	9
	P trend=0.20		P trend=0.23		P trend=0.84		P trend=0.35	
Dicamba (benzoic acid)								
None	1.0 (ref)	39	1.0 (ref)	40	1.0 (ref)	22	1.0 (ref)	6
Low	1.5 (0.9-2.6)	23	1.1 (0.6-2.1)	12	1.5(0.7-3.4)	9	3.2 (1.0-9.9)	8
Medium	1.5 (0.9-3.4)	20	1.1 (0.6-2.1)	13	1.8(0.90-4.0)	10	5.2(1.6-16.6)	7
High	2.0 (1.1-3.4)	20	0.7 (0.4-1.4)	11	0.7(0.3-1.5)	8	5.1(1.6-16.1)	7
	P trend=0.03		P trend=0.26		P trend=0.32		P trend=0.02	

EPTC (thio-carbamate)								
None	1.0 (ref)	86	1.0 (ref)	62	1.0 (ref)	40	1.0 (ref)	19
Low	1,2(0.6-2.3)	9	1.2(0.6-2.7)	7	xxx	3	2.1 (0.7-6.0)	4
Medium	1.2(0.6-2.5)	8	1.7(0.7-4.2)	5	xxx	0	2.1 (0.6-7.1)	3
High	1.4(0.6-3.4)	5	0.8(0.3-2.3)	4	xxx	1	4.9 (1.4-16.7)	3
	P trend= 0.41		P trend=0.98		P trend=0.10		P trend=0.01	
Glyphosate (isopropyl-amine)								
None	1.0 (ref)	25	1.0 (ref)	19	1.0 (ref)	13	1.0 (ref)	10
Low	0.6(0.4-1.1)	32	1.3(0.7-2.6)	23	0.7(0.3-1.7)	15	0.4 (0.1-1.2)	9
Medium	1.1(0.6-1.9)	29	1.1(0.5-2.1)	23	0.6(0.2-1.4)	11	0.6 (0.2-1.6)	7
High	1.1(0.6-1.8)	29	0.7(0.4-1.3)	22	0.7(0.3-1.8)	12	0.6 (0.2-1.8)	7
	P trend=0.21		P trend=0.05		P trend=0.66		P trend=0.98	
Imazethapyr (imid-azolinone)								
None	1.0 (ref)	68	1.0 (ref)	57	1.0 (ref)	29	1.0 (ref)	12
Low	1.0(0.6-1.8)	16	0.7(0.3-1.4)	10	0.7(0.3-1.7)	6	1.6 (0.6-3.8)	8
Medium	0.8(0.4-1.6)	11	0.6(0.3-1.4)	6	1.1(0.3-3.5)	6	5.2 (1.6-16.6)	4
High	1.2(0.6-2.2)	12	0.5(0.2-1.2)	5	1.0(0.4-2.8)	5	3.2 (1.0-10.0)	4
	P trend=0.71		P trend=0.16		P trend=0.90		P trend=0.03	
Metribuzin (Triazone)								
None	1.0 (ref)	30	1.0 (ref)	35	1.0 (ref)	13	1.0 (ref)	9
Low	1.5(0.7-2.9)	11	0.5(0.2-1.4)	5	1.4(0.5-3.9)	5	1.0 (0.2-4.9)	3

Medium	2.1(1.1-4.0)	13	0.5(0.1-2.0)	3	0.8(0.2-2.9)	3	2.8 (0.9-8.9)	5
High	1.8(0.6-5.2)	4	0.4(0.1-1.6)	2	1.3(0.2-9.8)	1	-	0
	P trend=0.06		P trend=0.13		P trend=0.88		P trend=0.60	
Trifluralin (dinitro-aniline)								
None	1.0 (ref)	45	1.0 (ref)	43	1.0 (ref)	25	1.0 (ref)	10
Low	1.1(0.7-1.9)	23	0.9(0.5-1.7)	14	0.9(0.4-1.9)	8	1.2 (0.4-3.2)	7
Medium	1.6(0.9-2.6)	21	0.8(0.4-1.7)	11	0.8(0.4-1.8)	8	2.7 (1.0-7.0)	7
High	1.1(0.6-1.9)	15	0.6(0.3-1.2)	11	0.8(0.3-1.9)	7	3.3 (1.2-9.1)	6
	P trend= 0.81		P trend=0.13		P trend=0.62		P trend=0.01	

[1] Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)
[2] Numbers do not sum to NHL subtype totals due to missing data.

Table 4: The number of different pesticides in a pesticide class used and the risk of NHL (95% CI)

Number pesticides in a pesticide class	All NHL Cases[1]	Cohort Person-Years	RR[2]	95% CI
All pesticide				
0-4	36	46,624	1.0 (ref)	
5-8	58	62,304	1.2	(0.8-1.9)
9-11	50	56,373	1.2	(0.8-2.0)
12-16	65	93,714	0.9	(0.5-1.4)
17-20	48	57,874	1.1	(0.7-1.8)
>20	75	71,281	1.1	(0.7-1.8)
			P trend=0.53	
Chlorinated Insecticides				
0	111	344,026	1.0 (ref)	
1	63	131,439	1.1	(0.6-1.9)
2	42	77,989	1.1	(0.6-2.0)
≥3	89	122,276	0.9	(0.5-1.7)
			P trend=0.45	
Organophosphate insecticides				
0	38	90,621	1.0 (ref)	
1	59	128,694	1.2	(0.7-1.8)
2	69	146,183	1.3	(0.8-2.0)
3	56	133,273	1.1	(0.6-1.8)
≥4	107	208,634	1.2	(0.7-2.1)
			P trend=0.59	
Carbamate insecticide				
0	104	231,849	1 (ref)	
1	126	294,727	0.7	(0.5-1.0)
≥2	89	163,706	0.9	(0.6-1.4)
			P trend=0.64	
Other insecticides				
0	251	532,835	1.0 (ref)	
>1	43	112,489	1.1	(0.6-1.8)
			P trend=0.36	
Triazine herbicides				
0	67	161,040	1.0	
1	92	187,057	1.2	(0.6-2.4)
2	78	185,777	1.0	(0.5-2.1)
3	92	173,920	1.4	(0.7-3.0)
			P trend=0.04	
Acetamide herbicides				
0	90	206,537	1.0	
1	115	236,407	1.6	(0.8-3.4)
2	102	219,200	1.7	(0.7-3.7)

			P trend=0.10	
Carbamate herbicides				
0	193	414,729	1.0 (ref)	
1	79	179,871	0.8	(0.5-1.2)
2	40	84,589	0.8	0.8 (0.4-1.4)
			P trend=0.80	
Other herbicides				
0	13	25,880	1.0 (ref)	
1-2	67	131,595	1.1	(0.5-2.7)
3-4	76	162,359	1.0	(0.4-2.4)
5-6	78	185,337	1.0	(0.4-2.5)
≥7	97	205,915	1.1	(0.4-2.6)
			P trend=0.19	
Fungicides				
0	203	442,307	1.0 (ref)	
1	73	152,882	1.1	(0.8-1.5)
≥2	52	110,590	1.5	(0.99-2.3)
			P trend=0.31	
Fumigants				
0	240	538,867	1.0 (ref)	
1	73	123,473	1.4	(0.9-2.1)
≥2	15	42,165	0.9	(0.4-1.9)
			P trend=0.24	

[1] Numbers do not sum to totals (333 cases, 714,770 person-years) due to missing data
[2] NHL risks are age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)and adjusted for lifetime days of use of pesticides in the specific pesticide class

Table 5. Number of different pesticides used by pesticide type (in the NHL incidence analysis from 1993 through 2008) for B cell sub-types.[1,2]

	CLL, SLL, PLL, MCL		Diffuse Large B-cell		Follicular B-cell		Other B-cell types	
	RR[1] (95% CI)	n	RR[1] (95% CI)	n	RR[1] (95% CI)	n	RR[1] (95% CI)	n
Insecticides								
Carbamate insecticides[3]								
0	1.0 (ref)	34	1.0(ref)	33	1.0(ref)	12	1.0 (ref)	13
1	0.8 (0.5-1.3)	45	0.7(0.4-1.2)	36	1.5(0.8-3.0)	26	0.3 (0.1-0.8)	7
2-3	1.1 (0.7-1.7)	32	0.7(0.4-1.2)	20	1.2(0.5-2.7)	12	1.2 (0.5-2.5)	13
	P trend= 0.82		P trend=0.21		P trend=0.63		P trend= 0.75	
Chlorinated insecticides[4]								
None	1.0 (ref)	8	1.0(ref)	16	1.0(ref)	3	1.0 (ref0	6
1	1.6 (0.7-3.8)	17	0.9 (04-1.7)	18	4.1(1.2-14.1)	15	0.9 (0.3-2.7)	7
2	2.2 (0.95-5.0)	19	0.6(0.3-1.3)	10	2.5(0.6-9.6)	7	0.5 (0.1-1.9)	3
3	2.4 (1.2-5.2)	41	0.5(0.3-1.0)	17	1.7(0.5-6.5)	9	0.8 (0.3-2.3)	10
	P trend=0.02		P trend=0.05		P trend=0.73		P trend= 0.48	
Organophosphate Insecticides[5]								
0	1.0 (ref)	13	1.0 (ref)	14	1.0(ref)	5	1.0	5
1	0.93(0.4-2.0)	15	1.2(0.6-2.4)	21	1.3(0.4-3.9)	8	0.8 (0.2-2.8)	5
2	1.4 (0.7-2.7)	25	1.0(0.5-2.0)	20	1.7(0.6-4.7)	12	1.3 (0.4-4.0)	9
3	1.3 (0.6-2.5)	20	0.8(0.4-1.7)	14	1.4(0.5-4.1)	9	0.5 (0.1-2.1)	3
>4	1.7 (0.92-3.2)	42	0.8(0.4-1.6)	23	1.6(0.6-4.4)	17	1.3 (0.5-3.7)	12

Comment [lbf69]: Interesting results

	P trend =0.03		P trend= 0.28		P trend=0.38		P trend=0.67	
Other Insecticides[6]								
0	1.0 (ref)	86	1.0 (ref)	71	1.0(ref)	35	1.0 (ref)	22
1	0.94 (0.6-1.6)	19	0.5(0.2-1.0)	9	1.3(0.6-2.4)	12	1.1 (0.5-2.8)	6
	P trend=0.78		P trend= .04		P trend=0.49	6	P trend=0.82	
Herbicides								
Acetamide Herbicide[7]								
0	1.0 (ref)	37	1.0(ref)	32	1.0(ref)	14	1.0	6
1	0.97 (0.6-1.5)	35	1.0(0.6-1.6)	32	1.3(0.7-2.6)	19	1.4 (0.5-4.0)	8
2	1.2 (0.8-2.0)	39	0.6(0.4-1.1)	18	1.2(0.6-2.4)	15	3.9 (1.2-8.2)	16
	P trend=0.35		P trend=0.16		P trend=0.72		P trend= 0.009	
Carbamate Herbicide[8]								
0	1.0 (ref)	67	1.0(ref)	58	1.0(ref)	27	1.0	16
1	0.98 (0.6-1.5)	27	0.7(0.4-1.2)	17	1.3(0.7-2.5)	16	1.5 (0.7-3.4)	10
2	1.5 (0.9-2.5)	17	0.9(0.4-1.7)	9	0.6(0.2-1.8)	3	2.2 (0.9-5.7)	6
	P trend=0.29		P trend=0.33		P trend=0.71		P trend=0.11	
Other herbicides[9]								
0	1.0 (ref)	6	1.0(ref)	6	1.0(ref)	1	1.0	2
1-2	1.2(0.5-2.8)	25	1.0(0.4-2.5)	22	3.2(0.5-27.0)	13	0.6 (0.1-3.1)	4
2-4	0.9 (0.4-2.2)	20	1.4(0.6-3.4)	33	2.5(0.3-19.2)	10	0.94(0.2-4.6)	7
5-6	1.2 (0.5-2.8)	26	0.7(0.3-1.7)	16	4.0(0.5-29.8)	17	1.2(0.3-5.7)	9
≥7	1.7 (0.7-4.1)	38	0.7(0.3-1.7)	16	2.5(0.3-19.3)	11	1.7(0.4-7.6)	12
	P trend=0.06		P trend=0.08		P trend=0.84		P trend= 0.06	
Triazine/Triazone herbicides[10]								
0	1.0	29	1.0 (ref)	22	1.0(ref)	6	1.0 (ref)	4
1	0.8 (0.5-1.4)	24	1.5(0.9-2.6)	34	3.2(1.3-8.0)	20	2.0 (0.6-6.6)	8

Comment [lbf70]: Interesting results

2	1.0(0.6-1.7)	27	0.8(0.4-1.5)	17	2.1(0.8-6.7)	13	2.5 (0.8-8.3)	9
3	1.5 (0.91-2.5)	35	1.1(0.6-2.0)	20	2.3(0.9-6.1)	13	4.2 (1.4-13.1)	13
	P trend=0.07		P trend=0.64		P trend=0.30		P trend=.006	
Fungicides and Fumigants								
Fungicides[11]								
0	1.0 (ref)	4	1.0 (ref)	6	1.0(ref)	3	1.0	2
1	1.3 (0.4-3.6)	29	0.7(0.3-1.8)	28	1.1(0.3-3.6)	23	1.2 (0.3-5.6)	14
2	1.7 (0.6-4.6)	81	0.8(0.3-1.8)	58	0.6(0.2-2.1)	26	0.8 (0.2-3.4)	18
	P trend=0.11		P trend=0.75		P trend=0.10		P trend=0.29	
Fumigants[12]								
0	1.0 (ref)	43	1.0 (ref)	30	1.0(ref)	25	1.0	9
1	1.0 (0.6-1.9)	13	2.0(1.1-3.7)	17	0.6(0.2-1.7)	4	2.8 (1.0-7.4)	7
≥2	0.95(0.6-1.4)	58	1.1(0.7-1.8)	45	0.7(0.4-1.2)	22	1.5(0.7-3.3)	18
	P trend=0.81		P trend=0.75		Ptrend=0.20		P trend=0.43	

[1]Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70 [2] Numbers do not sum to NHL subtype totals due to missing data [3]Carbamate insecticides: carbofuran, aldicarb, carbaryl [4]Chlorinated insecticides: aldrin, chlordane, dieldrin, DDT, heptachlor, lindane, toxaphene [5]Organophosphate insecticides: Chlorpyrifos, coumaphos, diazinon, dichlorvos, fonofos, malathion, parathion, phorate, terbufos, [6]Other insecticides: permethrin [7]Acetamide: metolachlor, alachlor [8]Carbamate herbicide: Butylate: EPTC [9]Other herbicides: Glyphosate, imazethapyr, herbicide oil, paraquat, chlorimuron ethyl, dicamba, pendimethalin, trifluralin, 2,4-D, 2,4,5-T, 2,4-TP[10]Triazine herbicides: Atrazine, cyanazine, metribuzin [11]Fungicides: Benomyl, chlorthalonil, captan, maneb/macozeb, metalaxyl, ziram [12]Fumigants: methyl bromide, aluminum phosphate, ethylene dibromide, carbon tetra chloride/carbon disulfide

Supplemental Table 1 Other pesticide exposures (lifetime days [LD} and intensity weighted total days) and age-adjusted risk of NHL incidence (1993 through 2008).

Pesticide (chemical-functional class) [median days of lifetime exposure for each category]	NHL Cases	RR (95%) by Lifetime- Days of Exposure	NHL Cases	RR (95% CI) Intensity weighted Lifetime-Days of exposure
Benomyl (carbamate-fungicide)				
None	134	1.0 (ref)	134	1.0 (ref)
Low [0.5]	6	5.6 (2.4-12.6)	6	4.1(1.8-9.3)
Medium [12.25]	5	1.0 (0.4-2.6)	5	1.0 (0.4-2.6)
High [108.5]	5	0.8 (0.3-1.9)	5	0.8 (0.3-1.9)
		P for trend=0.50		P for trend=0.57
Captan (dicarboximide-fungicide)				
None	258	1.0 (ref)	258	1.0 (ref)
Low [4]	8	0.6 (0.3-1.3)	8	0.7 (0.4-1.5)
Medium [12.25]	8	1.6 (0.6-4.1)	7	1.2 (0.5-2.9)
High [124]	7	0.6 (0.3-1.5)	7	0.5 (0.2-1.3)
		P for trend=0.33		P for trend=0.20
Carbofuran (carbamate-insecticide)				
None	199	1.0 (ref)	199	1.0 (ref)
Low [8.75]	35	1.1 (0.8-1.6)	29	1.2 (0.8-1.8)
Medium [38.75]	25	1.0 (0.7-1.6)	29	0.9 (0.6-1.3)
High [56]	28	1.0 (0.7-1.5)	28	1.1 (0.8-1.7)

Comment [lbf71]: I think that you need to put number of days for each pesticide. Low/Med/High is not the same for each pesticide under study and this leaves the impression that they are.

Comment [a72]: Lifetime days added as suggested.

		P trend=0.81		P trend=0.74
Chlorpyrifos (organophosphate-insecticide)				
None	189	1.0 (ref)	189	1.0 (ref)
Low [14.75]	44	1.1 (0.7-1.5)	40	1.1 (0.8-1.5)
Medium [38.75]	45	1.3(0.9-1.8)	41	1.0 (0.7-1.5)
High [116]	43	0.9 (0.7-1.3)	39	1.1 (0.8-1.5)
		P trend=0.57		P trend=0.67
Chlorthalonil (thalonitrile-fungicide)				
None	301	1.0 (ref)	301	1.0 (ref)
Low [8]	7	1.3 (0.6-2.7)	7	1.1 (0.5-2.4)
Medium [54.25]	6	0.6 (0.2-1.6)	6	0.6 (0.2-1.5)
High [79]	6	0.6 (0.2-1.2)	6	0.7 (0.3-1.5)
		P for trend=0.12		P for trend=0.23
Coumaphos (0rganophosphate-insecticide)				
None	258	1.0(ref)	258	1.0 (ref)
Low [8.75]	12	1.2 (0.7-2.2)	10	1.6 (0.8-2.9)
Medium [38.75]	10	1.4 (0.8-2.7)	11	1.2 (0.6-2.1)
High [63.75]	8	1.2 (0.6-2.4)	9	1.2 (0.6-2.3)
		P for trend=0.41		P for trend=0.55
DDVP (dimethyl phosphate-insecticide)				
None	261	1.0 (ref)	261	1.0 (ref)

Low [8.75]	10	1.2 (0.6-2.2)	10	1.2 (0.7-2.3)
Medium [108.5]	11	1.1 (0.6-2.0)	9	0.8 (0.4-1.6)
High [457.25]	7	0.7 (0.3-1.5)	9	1.0 (0.5-1.9)
		P for trend=0.42		P for trend=0.95
Diazinon (organophosphosphorous-insecticide)				
None	113	1.0 (ref)	113	1.0 (ref)
Low [8.75]	19	1.2 (0.7-2.0)	14	1.3 (0.7-2.2)
Medium [30]	10	0.7 (0.3-1.7)	15	0.9 (0.5-1.7)
High [56]	13	1.1 (0.6-2.1)	13	1.1 (0.6-1.9)
		P trend=0.73		P trend=0.92
Fonofos (phosphonothioate-insecticide)				
None	220	1.0 (ref)	220	1.0 (ref)
Low [20]	28	1.3 (0.9-1.9)	23	1.2 (0.8-1.9)
Medium [50.75]	19	1.2 (0.8-2.0)	23	1.4 (0.93-2.2)
High [108.5]	22	1.1 (0.7-1.7)	22	1.0 (0.6-1.5)
		P for trend=0.67		P for trend=0.98
Matalaxyl (analine methyl ester-fungicide)				
None	126	1.0 (ref)	126	1.0 (ref)
Low [3.5]	10	1.2 (0.6-2.2)	10	1.8 (0.95-3.4)
Medium [24.5]	11	0.9 (0.5-1.7)	11	0.7 (0.4-1.4)
High [50]	9	0.8 (0.4-1.5)	9	0.8 (0.4-1.5)

		P for trend=0.43		P for trend=028
Methyl bromide (methyl halide-fumigant)				
None	268	1.0 (ref)	268	1.0 (ref)
Low [8]	25	1.9 (1.2-2.8)	17	1.9 (1.2-3.1)
Medium [15.5]	9	0.9 (0.4-1.7)	16	1.3 (0.8-2.1)
High [28]	16	0.6 (0.3-0.9)	16	0.5 (0.3-0.9)
		P for trend=0.03		P for trend=0.02
Permethrin Animals (pyrethroid-insecticide)				
None	263	1.0 (ref)	263	1.0 (ref)
Low [8.75]	15	1.3 (0.8-2.3)	10	1.3 (0.7-2.5)
Medium [24]	5	0.8 (0.3-2.5)	10	0.8 (0.4-1.7)
High [56]	9	0.6 (0.3-1.2)	9	0.8 (0.4-1.5)
		P trend= 0.18		P trend=0.43
Permethrin Crops (pyrethroid-insecticide)				
None	249	1.0 (ref)	249	1.0 (ref)
Low [8.75]]	17	1.0 (0.6-1.7)	12	1.1 (0.5-2.2)
Medium [24.5]	9	1.1 (0.5-2.3)	12	1.2 (0.7-2.2)
High [59]	10	0.7 (0.4-1.4)	11	0.6 (0.3-1.1)
		P for trend=0.36		P for trend=0.15
Phorate (organophosphate-insecticide)				
None	102	1.0 (ref)	102	1.0 (ref)
Low [20]	20	1. (0.6-1.6)	17	0.9(0.5-1.5)

Comment [lbf73]: Do you show permethrin on crops anywhere?

Medium [24.5]	20	2.2 (1.4-3.5)	17	1.9 (1.1-3.1)
High [56]	10	0.7 (0.4-1.3)	16	1.0(0.6-1.7)
		P for trend=0.80		P for trend=0.67
Herbicide exposures				
	Life-time days of Exposure		Intensity weighted days of exposure*	
	NHL Cases	RR (95%)	NHL Cases	RR (95% CI)
Chlorimuron-ethyl (benzoic acid ester-herbicide)				
None	105	1.0 (ref)	105	1.0 (ref)
Low [8.75]	28	1.2(0.9-1.8)	18	1.1(0.6-1.9)
Medium [24.5]	18	1.9(1.2-3.2)	18	1.5(0.9-2.5)
High [24.5]	7	0.7(0.3-1.5)	17	1.1(0.7-1.9)
		P for trend=0.83		P for trend=0.60
Cyanazine (triazine-herbicide)				
None	162	1.0 (ref)	162	1.0 (ref)
Low [20]	58	1.4(0.9-1.9)	45	1.3(0.8-1.7)
Medium [56]	43	1.2(0.8-1.7)	45	1.4(1.0-1.9)
High [116]	35	1.1(0.8-1.6)	44	1.1(0.8-1.5)
		P for trend=0.81		P for trend=0.67
Herbicide Oil (Petroleum oils-herbicide)				
None	120	1.0 (ref)	120	1.0 (ref)
Low [20]	14	1.0(0.6-1.9)	13	1.3(0.7-2.3)
Medium [56]	13	1.8(1.0-1.1)	12	1.1(0.6-1.9)

High [173.25]	10	1.0(0.5-2.0)	12	1.3(0.7-2.4)
		P for trend=0.84		P for trend=0.36
Metolachlor (acetamide-herbicide)				
None	145	1.0 (ref)	145	1.0 (ref)
Low [20]	50	1.2(0.9-1.7)	49	1.2(0.8-1.6)
Medium [56]	54	1.3(0.94-1.5)	49	1.4(1.0-2.0)
High [116]	44	1.1(0.8-1.5)	48	1.1(0.8-1.5)
		P for trend=0.67		P for trend=0.28
Paraquat				
None	127	1.0 (ref)	127	1.0 (ref)
Low [7]	10	1.5(0.8-2.8)	10	1.9(1.0-3.7)
Medium [24.5]	10	0.8(0.4-1.5)	9	0.5(0.3-1.1)
High [116]	8	1.0(0.5-2.0)	9	1.5(0.8-3.0)
		P for trend= 0.88		P for trend=0.26
Pendimethalin				
None	96	1.0 (ref)	96	1.0 (ref)
Low [8.75]	32	1.1(0.7-1.6)	25	1.1(0.6-1.8)
Medium [24.5]	23	1.2(0.7-2.0)	26	1.0(0.7-1.6)
High [56]	20	1.0(0.6-1.6)	24	1.2(0.7-1.8)
		P for trend=0.87		P for trend=0.52
2,4,5 T (phenoxyacetic acid)				
None	71	1.0 (ref)	71	1.0 (ref)
Low [8.75]	30	1.7(1.1-2.5)	17	1.6(0.9-2.8)
Medium [8.75]	4	1.2(0.4-3.3)	16	1.9(1.1-3.2)
High [20]	15	1.2(0.7-2.2)	16	1.0(0.6-1.7)

		P for trend=0.52		P for trend=0.51

[1]Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)

Supplemental Table 2. Pesticide exposures (total days and intensity weight total days) fully adjusted risks of NHL incidence (1993 through 2008).				
	NHL Cases	RR (95%) by Total Days of Exposure	NHL Cases	RR (95% CI) Intensity weighted days of exposure
Benomyl				
none	134	1.0 (ref)	134	1.0 (ref)
Low	6	6.1(2.7-13.8)	6	4.6 (2.0-10.6)
medium	5	1.0(0.4-2.6)	5	1.4 (0.6-3.5)
High	5	1.0(0.4-2.6)	5	1.1 (0.4-2.8)
		P trend (full)=0.98		P trend (full)=0.94
Captan				
none	258	1.0 (ref)	258	1.0 (ref)
Low	8	0.6(0.3-1.2)	8	0.7 (0.3-1.4)
medium	8	1.7(0.7-4.3)	7	1.2 (0.5-2.0)
High	7	0.7(0.3-1.6)	7	0.6 (0.2-1.4)
		P trend (full)=0.45		P trend (full)=0.28
Carbaryl				
none	81	1.0(ref)	81	1.0 (ref)
Low	31	0.96(0.6-1.6)	27	0.91 (0.6-1.5)
medium	23	0.8(0.5-1.4)	26	0.99 (0.6-1.6)
High	25	1.3(0.8-2.2)	26	1.1 (0.7-1.9)
		P trend (full)=0.26		P trend (full)=0.54
Carbofuran				
none	199	1.0 (ref)	199	1.0 (ref)
Low	35	1.0(0.7-1.5)	29	1.1(0.8-1.6)
medium	25	0.97(0.6-1.5)	29	0.8(0.5-1.2)
High	28	0.96(0.6-1.4)	28	1.1(0.7-1.6)

		P trend (full)=0.83		P trend (full)=0.95
Chlorthalonil				
none	301	1.0 (ref)	301	1.0 (ref)
Low	7	1.4(0.7-3.0)	7	1.2 (0.6-2.6)
Medium	6	0.7(0.3-1.8)	6	0.6 (0.2-1.9)
High	6	0.6 (0.3-1.4)	6	0.7 (0.3-1.6)
		P trend (full)=0.21		P trend (full)=0.37
Chlorpyrifos				
None	189	1.0 (ref)	189	1.0 (ref)
Low	44	1.0(0.7-1.5)	40	1.0 (0.7-1.5)
Medium	45	1.2(0.9-1.7)	41	0.94 (0.7-1.3)
High	43	0.8(0.6-1.2)	39	1.0 (0.7-1.4)
		P trend (full)=0.31		P trend (full)=0.99
Coumaphos				
none	258	1.0 (ref)	258	1.0 (ref)
Low	12	1.1(0.6-2.0)	10	1.4 (0.8-2.7)
medium	10	1.3 (0.7-2.5)	11	1.1 (0.6-2.0)
High	8	1.1(0.5-2.2)	9	1.1 (0.6-2.1)
		P trend (full)=0.62		P trend (full)=0.75
Diazinon				
None	113	1.0 (ref)	113	1.0 (ref)
Low	19	1.3(0.8-2.1)	14	1.3 (0.7-2.2)
medium	10	0.8(0.3-1.8)	15	0.9 (0.5-1.7)
High	13	1.3(0.7-2.5)	13	1.3 (0.7-2.3)
		P trend (full)=0.41		P trend (full)=0.50

DDVP				
none	261	1.0 (ref)	261	1.0 (ref)
Low	10	1.0 (0.5-1.9)	10	1.1 (0.6-2.1)
medium	11	0.92 (0.5-1.7)	9	0.7 (0.4-1.4)
High	7	0.6 (0.3-1.3)	9	0.9 (0.4-1.7)
		P trend (full)=0.22		P trend (full)=0.61
Fonofos				
None	220	1.0 (ref)	220	1.0 (ref)
Low	28	1.2(0.8-1.7)	23	1.1(0.7-1.7)
medium	19	1.1(0.7-1.7)	23	1.2(0.8-1.9)
High	22	0.9 (0.6-1.5)	22	0.9(0.5-1.3)
		P trend (full)=0.76		P trend (full)=0.51
Lindane				
None	122	1.0 (ref)	122	1.0 (ref)
Low	11	0.9(0.5-1.8)	10	1.0(0.5-1.8)
medium	10	1.0(0.5-2.0)	11	1.2(0.6-2.3)
High	10	2.3(1.2-4.5)	9	1.7(0.9-3.3)
		P trend (full)=0.01		P trend (full)=0.12
Malathion				
none	55	1.0 (ref)	55	1.0 (ref)
Low	46	0.9(0.6-1.3)	37	0.9 (0.6-1.4)
medium	28	0.7(0.4-1.1)	38	0.8 (0.5-1.1)
High	36	1.0(0.7-1.5)	35	0.9 (0.6-1.4)
		P trend (full)=0.68		P trend (full)=0.91
Metalaxyl				
none	126	1.0 (ref)	126	1.0 (ref)
Low	10	1.2(0.6-2.4)	10	1.7 (0.9-3.4)

medium	11	1.1(0.6-2.2)	11	0.9 (0.4-1.7)
High	9	1.1(0.5-2.3)	9	1.0 (0.5-2.2)
		P trend (full)=0.89		P trend (full)=0.93
Methyl bromide				
none	268	1.0 (ref)	268	1.0 (ref)
Low	25	2.2 (1.4-3.4)	17	2.3 (1.4-3.8)
medium	9	1.1 (0.5-2.1)	16	1.5 (0.9-2.6)
High	16	0.7 (0.4-1.2)	16	0.7 (0.4-1.1)
		P trend (full)=0.13		P trend (full)=0.07
Permethrin Animals				
None	263	1.0 (ref)	263	1.0 (ref)
Low	15	1.1(0.7-1.9)	10	1.1(0.6-2.1)
medium	5	0.7(0.2-2.1)	10	0.7(0.3-1.4)
High	9	0.5(0.3-1.0)	9	0.6(0.3-1.2)
		P trend (full)=0.055		P trend (full)=0.15
Permethrin Crops				
None	249	1.0 (ref)	249	1.0 (ref)
Low	17	0.9(0.5-1.6)	12	1.0(0.5-2.0)
medium	9	1.1(0.5-2.2)	12	1.2(0.7-2.2)
High	10	0.8(0.4-1.5)	11	0.6(0.3-1.2)
		P trend (full)=0.44		P trend (full)=0.18
Phorate				
none	102	1.0 (ref)	102	1.0 (ref)
Low	20	0.8(0.5-1.3)	17	0.7 (0.4-1.2)
medium	20	1.7(1.0-2.8)	17	1.5 (0.9-2.5)
High	10	0.6(0.3-1.0)	16	0.8 (0.5-1.4)
		P trend (full)=0.26		P trend (full)=0.70

Terbufos				
None	157	1.0 (ref)	157	1.0 (ref)
Low	58	1.3(0.9-1.8)	43	1.2(0.8-1.7)
medium	38	1.7(1.2-2.5)	43	1.7(1.2-2.4)
High	34	1.0(0.7-1.5)	42	1.1(0.8-1.6)
		P trend (full)=0.78		P trend (full)=0.65
Herbicide exposures				
	Life-time days of Exposure		Intensity weighted days of exposure*	
	NHL Cases	RR (95%)	NHL Cases	RR (95% CI)
Alachlor				
None	138	1.0 (ref)	138	1.0 (ref)
Low	65	0.9 (0.7-1.2)	53	0.9(0.7-1.2)
medium	49	0.8((0.6-1.1)	50	0.8 (0.6-1.1)
High	43	1.2((0.9-1.8)	51	1.2 (0.8-1.6)
		P trend (full)=0.20		P trend (full)=0.27
Atrazine				
None	85	1.0 (ref)	85	1.0 (ref)
Low	88	1.1(0.8-1.5)	79	1.0(0.7-1.4)
medium	72	1.2 (0.8-1.6)	78	1.2(0.9-1.7)
High	77	1.0 (0.7-1.4)	78	0.98(0.7-1.4)
		P trend (full)= 0.72		P trend (full)=0.73
Butylate				
None	107	1.0 (ref)	107	1.0 (ref)
Low	22	0.9(0.5-1.4)	16	0.8 (0.5-1.3)
medium	18	2.4(1.4-4.0)	16	1.8 (1.0-3.0)
High	7	1.0(0.4-2.1)	15	1.3 (0.8-2.3)

		P trend (full)=0.03		P trend (full)=0.14
Chlorimuron-ethyl				
None	105	1.0 (ref)	105	1.0 (ref)
Low	28	1.1 (0.7-1.7)	18	1.0 (0.6-1.7)
medium	18	1.7 (1.0-2.9)	18	1.3(0.8-2.2)
High	7	0.7 (0.3-1.5)	17	1.1(0.6-1.8)
		P trend (full)=0.69		P trend (full)=0.68
Cyanazine				
None	162	1.0 (ref)	162	1.0 (ref)
Low	58	1.3(0.94-1.8)	45	1.2(0.8-1.7)
medium	43	1.1(0.8-1.6)	45	1.3(0.9-1.8)
High	35	1.0(0.7-1.4)	44	1.0(0.7-1.4)
		P trend (full)=0.65		P trend (full)=0.76
Dicamba				
None	121	1.0 (ref)	121	1.0 (ref)
Low	66	1.2 (0.8-1.7)	24	1.1(0.7-1.6)
medium	52	1.3 (0.9-1.9)	54	1.3(0.9-1.9)
High	47	1.1 (0.7-1.6)	55	1.1(0.8-1.6)
		P trend (full)=0.99		P trend (full)=0.76
2,4-D				
None	71	1.0 (ref)	71	1.0 (ref)
Low	83	0.9(0.6-1.3)	82	0.9 (0.6-1.2)
medium	83	1.0(0.7-1.4)	83	0.97 (0.7-1.4)
High	82	0.8(0.6-1.2)	81	0.9 (0.6-1.2)
		P trend (full)=0.35		P trend (full)=0.46
EPTC				
None	229	1.0 (ref)	229	1.0 (ref)

Low	28	1.2(0.8-1.8)	20	1.2 (0.8-2.0)
medium	14	0.9(0.7-1.9)	20	1.1 (0.7-1.7)
High	18	1.2(0.7-1.9)	19	1.0 (0.6-1.7)
		P trend (full)=0.56		P trend (full)=0.85
Glyphosate				
None	70	1.0 (ref)	70	1.0 (ref)
Low	89	0.8(0.6-1.2)	83	0.91 (0.6-1.3)
medium	78	0.8(0.6-1.2)	84	0.8 (0.5-1.1)
High	83	1.0(0.7-1.4)	82	0.97 (0.7-1.4)
		P trend (full)=0.63		P trend (full)=0.69
Herbicide Oil				
None	120	1.0 (ref)	120	1.0 (ref)
Low	14	1.0(0.6-1.7)	13	1.2 (0.6-2.1)
medium	13	1.7(0.93-2.9)	12	1.0 (0.5-1.8)
High	10	0.9((0.5-1.8)	12	1.2 (0.7-2.2)
		P for trend (full)=0.88		P for trend (full)=0.56
Imazethapyr				
None	181	1.0 (ref)	181	1.0 (ref)
Low	39	0.8(0.5-1.2)	36	0.8 (0.6-1.2)
medium	34	0.8(0.5-1.2)	37	0.7 (0.5-1.1)
High	35	1.0(0.7-1.5)	35	0.99 (0.7-1.5)
		P trend (full)=0.90		P trend (full)=0.92
Metolachlor				
None	145	1.0 (ref)	145	1.0 (ref)
Low	50	1.2 (0.8-1.6)	49	1.1(0.8-1.5)
medium	54	1.2 (0.8-1.7)	49	1.3(0.9-1.9)
High	44	1.0 (0.7-1.4)	48	0.98(0.7-1.4)

		P trend (full)=0.90		P trend (full)=0.81
Metribuzin				
None	94	1.0 (ref)	94	1.0 (ref)
Low	28	1.0(0.6-1.5)	21	1.0 (0.6-1.7)
medium	15	0.8(0.4-1.3)	23	0.91 (0.6-1.5)
High	20	1.4(0.8-2.3)	19	1.1 (0.7-1.9)
		P trend (full)=0.29		P trend (full)=0.66
Paraquat				
None	127	1.0 (ref)	127	1.0 (ref)
Low	10	1.6(0.8-3.0)	10	2.0 (1.0-3.7)
medium	10	0.9(0.5-1.7)	9	0.6 (0.3-1.3)
High	8	1.2(0.6-2.5)	9	1.9 (0.9-3.9)
		P trend (full)=0.72		P trend (full)=0.08
Pendimethalin				
None	96	1.0 (ref)	96	1.0 (ref)
Low	32	1.0(0.6-1.5)	25	0.9 (0.5-1.6)
medium	23	1.0(0.6-1.8)	26	0.9 (0.6-1.4)
High	20	1.0(0.6-1.5)	24	1.1 (0.7-1.8)
		P trend (full)=0.72		P trend (full)=0.60
Trifluralin				
None	140	1.0 (ref)	140	1.0 (ref)
Low	51	0.9(0.7-1.3)	50	0.9 (0.6-1.2)
medium	58	1.0(0.7-1.3)	52	1.0 (0.7-1.4)
High	43	0.8(0.6-1.2)	48	0.8 (0.6-1.1)
		P trend (full)=0.41		P trend (full)=0.30
2,4,5 T				
None	71	1.0 (ref)	71	1.0 (ref)

Low	30	1.6(1.0-2.4)	17	1.6 (0.9-2.6)
medium	4	1.1(0.4-3.0)	16	1.7 (1.0-2.9)
High	15	1.1(0.7-2.0)	16	1.0 (0.6-1.7)
		P trend (full)=0.78		P trend (full)=0.23

[1]Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70), smoking status(current, former, never), number of livestock (0,<100,100-999,>999), drove diesel tractor(<weekly,≥weekly), state (NC, IA)

Supplemental Table 1A. Chlorinated Insecticide exposure (in total days and intensity weighted days) and NHL age-adjusted relative risk(1993 through 2008).				
	Total exposure days		Intensity weight exposure days	
	NHL cases	RR (95% CI)[1]	NHL cases	RR (95% CI)
Aldrin (Chlorinated Insecticide)				
None	232	1.0 (ref)	232	1.0 (ref)
Low [8.75]	14	0.8 (0.5-1.6)	12	0.9(0.5-1.6)
Medium [56]	14	0.8(0.5-1.4)	12	0.8(0.4-1.4)
High [116]	7	1.6(0.7-3.4)	11	1.0(0.6-1.9)
		P trend=0.70		P trend=0.86
Aldrin				
None	232	1.0 (ref)	232	1.0 (ref)
Low	14	0.8 (0.5-1.4)	12	0.9 (0.5-1.6)
medium	14	1.6 (0.8-3.4)	12	1.0 (0.6-1.9)
high	7	0.9 (0.7-1.2)	11	0.9 (0.7-1.2)
		P for trend=0.42		P for trend=0.95
		P for trend (full)=0.34		P for trend (full)=0.60
Heptachlor (Chlorinated Insecticide)				
None	240	1.0 (ref)	240	1.0 (ref)
Low [8.75]	11	2.1 (1.3-3.6)	10	2.8 (1.5-5.3)
Medium [24.5]	15	0.9 (0.3-2.1)	10	1.0 (0.5-1.9)
High [24.5]	5	1.0 (0.7-1.3)	10	1.0 (0.7-1.30
		P trend=0.26		P trend=0.42

Heptachlor				
None	240	1.0 (ref)	240	1.0 (ref)
Low	11	0.9 (0.5-1.6)	11	0.9 (0.5-1.7)
medium	15	2.1 (1.3-3.6)	10	2.8 (1.5-5.3)
high	5	0.9 (0.4-2.1)	10	1.0 (0.5-1.9)
		P for trend=0.11		P for trend=0.41
		P for trend (full)=0.19		P for trend (full)=0.16
2,4,5 TP				
None	276	1.0 (ref)	276	1.0 (ref)
Low	8	1.8 (0.9-3.7)	4	1.6 (0.6-4.3)
medium	0	0.6 (0.2-1.9)	4	1.4 (0.5-3.8)
high	3	0.9 (0.6-1.2)	3	0.8 (0.2-2.4)
		P for trend=0.40		P for trend=0.75
		P for trend (full)=0.27		P for trend (full)=0.74
Toxaphene (Chlorinated Insecticide)				
None	250	1 .0 (ref)	250	1.0 (ref)
Low [8.75]	10	3.4(1.4-8.3)	7	0.8(0.4-1.6)
Medium [20]	5	0.6(0.3-1.3)	8	0.7(0.3-1.6)
High [50.75]	6	1.0(0.7-1.3)	6	1.0(0.7-1.3)
	P trend=0.66		P trend=0.83	
Toxaphene				
None	250	1.0 (ref)	250	1.0 (ref)
Low	10	3.4 (1.4-8.3)	7	1.6 (0.8-3.5)
medium	5	0.6 (0.3-1.3)	8	0.8 (0.4-1.6)
high	6	1.0 (0.7-1.3)	6	0.7 (0.3-1.6)

	P for trend=0.33		P for trend=0.31
	P for trend (full)= 0.12		P for trend (full)=0.69

[1]Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)

Supplemental Table 2A. Chlorinated Insecticide exposure (in total days and intensity weighted days) and NHL fully adjusted relative risk (1993 through 2008).				
	Life-time exposure days		Intensity weight exposure days	
	NHL cases	RR (95% CI)[1]	NHL cases	RR (95% CI)
Aldrin				
None	232	1.0 (ref)	232	1.0 (ref)
Low	14	0.7 (0.4-1.3)	12	0.8 (0.5-1.5)
medium	14	0.7 (0.4-1.2)	12	0.7 (0.4-1.3)
high	7	1.4 (0.7)	11	0.9 (0.5-1.7)
		P for trend (full)=0.34		P for trend (full)=0.60
Chlordane				
None	223	1.0 (ref)	223	1.0 (ref)
Low	23	1.0 (0.6-1.6)	13	1.2 (0.7-2.2)
medium	6	1.8 (0.8-4.2)	13	0.9 (0.5-1.7)
high	9	0.4 (0.4-1.7)	12	1.0 (0.6-1.8)
		P for trend (full)=0.63		P for trend (full)=0.90
DDT				
None	194	1.0 (ref)	194	1.0 (ref)
Low	20	0.8 (0.5-1.3)	19	0.9 (0.6-1.5)

medium	18	1.0 (0.6-1.6)	18	0.9 (0.5-1.4)
high	17	1.5 (0.9-2.5)	18	1.4 (0.9-2.4)
		P for trend (full)=0.48		P for trend (full)=0.61
Heptachlor				
None	240	1.0 (ref)	240	1.0 (ref)
Low	11	0.8 (0.4-1.5)	11	0.8 (0.5-1.6)
medium	15	1.9 (1.1-3.3)	10	2.4 (1.3-4.7)
high	5	0.8 (0.3-1.9)	10	0.9 (0.5-1.8)
		P for trend (full)=0.19		P for trend (full)=0.16
Lindane				
None	122	1.0 (ref)	122	1.0 (ref)
Low	11	0.9 (0.5-1.8)	10	1.0(0.5-1.8)
medium	10	1.0 (0.5-2.0)	11	1.2(0.6-2.3)
high	10	2.4 (1.2-4.5)	9	1.7(0.9-3.3)
		P for trend (full)=0.01		P for trend (full)=0.12
Toxaphene				
None	250	1.0 (ref)	250	1.0 (ref)
Low	10	0.91 (0.5-1.7)	7	1.6 (0.7-3.3)
medium	5	3.4 (1.4-8.3)	8	0.8 (0.4-1.6)
high	6	0.6 (0.3-1.3)	6	0.7 (0.3-1.7)
		P for trend (full)= 0.12		P for trend (full)=0.69

Supplemental Table 3. Herbicide exposures (Life-time days) and age-adjusted NHL risk by cell type (1993 through 2008).

Pesticide (chemical class)	CLL, SLL, PLL, MCL		Diffuse Large B-cell		Follicular B-cell		Other B-cell types	
	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n
Alachlor (acetanilide)								
None	1.0 (ref)	53	1.0 (ref)	43	1.0 (ref)	22	1.0 (ref)	9
low	0.9(0.6-1.5)	23	0.9(0.5-1.6)	13	1.3(0.6-2.6)	10	1.6 (0.6-4.4)	7
medium	0.8(0.5-1.4)	18	0.7(0.4-1.3)	14	0.8(0.3-1.6)	9	2.1 (0.8-5.3)	10
high	1.1(0.6-2.1)	14	0.8(0.4-1.6)	10	1.1(0.4-2.7)	6	4.0 (1.2-13.0)	4
	LD P =0.67		LD P trend=0.52		LD P trend=0.99		LD P trend=0.02	
	IWLD P=0.49		IWLD P trend=0.092		IWLD P trend=0.97		IWLD P trend= 0.20	
Atrazine (triazine)								
None	1.0 (ref)	34	1.0 (ref)	26	1.0 (ref)	12	1.0 (ref)	5
low	1.0 (0.6-1.7)	29	1.1(0.6-2.0)	21	1.7(0.7-3.9)	17	2.4 (0.9-6.8)	13
medium	1.2 (0.7-2.0)	25	1.1(0.6-2.2)	23	1.3(0.5-3.4)	10	1.7(0.5-5.9)	6
high	1.0 (0.6-1.7)	26	0.9(0.5-1.7)	19	1.4(0.6-3.4)	13	3.6 (1.2-10.8)	9
	LD P trend=0.90		LD P trend=0.62		LD P trend=0.83		LD P trend=0.06	
	IWLD P trend=0.75		IWLD P trend=0.87		IWLD P trend=0.76		IWLD P trend=0.22	

Butylate (thio-carbamate-)								
None	1.0 (ref)	40	1.0 (ref)	33	1.0 (ref)	14	1.0 (ref)	8
low	0.8(0.4-1.9)	7	1.1(0.4-3.0)	4	0.8(0.2-2.9)	3	3.0 (0.8-11.3)	3
medium	3.5(1.6-7.6)	8	1.2(0.4-3.5)	4	6.3(2.1-19.3)	4	4.0(1.2-13.7)	4
high	1.3(0.4-4.3)	3	0.8(0.2-2.5)	3	1.0(0.1-7.9)	1	2.4 (0.3-19.7)	1
	LD P trend=0.04		LD P trend=0.69		LD P trend=0.07		LD P trend=0.05	
	IWLD P trend=0.19		IWLD P trend=0.89		IWLD P trend=0.12		IWLD P trend=0.13	
Chlorimuron-ethyl (Sulfonylurea)								
None	1.0 (ref)	38	1.0 (ref)	29	1.0 (ref)	14	1.0 (ref)	14
low	1.3(0.7-2.6)	11	1.4(0.7-3.0)	9	0.9(0.3-3.1)	3	-	1
medium	2.9(1.4-6.6)	9	1.2(0.4-4.0)	3	2.8(0.9-8.7)	4	-	1
high	0.3(0.1-2.5)	1	1.4(0.5-3.9)	4	0.7(0.9-5.1)	1	-	0
	LD P for trend=0.91		LD P trend=0.21		LD P trend=0.56		LD P for trend=xx	
	IWLD P trend=0.56		IWLD P trend=0.92		IWLD P trend=0.62		IWLD P trend=	
Cyanazine (triazine)								
None	1.0 (ref)	65	1.0 (ref)	46	1.0 (ref)	24	1.0 (ref)	10
low	1.2 (0.7-2.2)	15	1.4 (0.8-2.4)	16	1.9(0.9-3.8)	12	3.7(1.4-9.7)	7
medium	0.9 (0.5-1.6)	16	0.8 (0.4-1.8)	8	1.7(0.8-3.6)	9	2.9 (1.5-7.5)	8
high	1.1(0.6-2.0)	14	1.0 (0.5-2.1)	8	0.8(0.3-2.2)	4	2.6(0.9-7.5)	5
	LD P trend=0.93		LD P trend=0.93		LD P trend=0.87		LD P trend=0.17	

	IWLD P trend=0.35		IWLD P trend=0.47		IWLD P trend=0.68		IWLD P trend=0.15	
2,4-D (Chlorinated Phenoxy)								
None	1.0 (ref)	25	1.0 (ref)	23	1.0 (ref)	9	1.0 (ref)	5
low	0.90(0.5-1.5)	31	0.9(0.5-1.7)	23	1.8(0.8-4.4)	14	1.9 (0.6-6.2)	10
medium	1.2(0.7-2.0)	29	1.0(0.6-1.9)	21	1.0(0.4-2.4)	14	1.7 (0.5-5.6)	9
high	1.3(0.7-2.2)	29	0.7(0.4-1.3)	21	1.4(0.6-3.4)	12	2.2 (0.7-7.2)	9
	LD P trend=0.20		LD P trend=0.23		LD P trend=0.84		LD P trend=0.35	
	IWLD P trend=0.83		IWLD P trend=0.41		IWLD P trend=0.22		IWLD P trend=0.75	
Dicamba (benzoic acid)								
None	1.0 (ref)	39	1.0 (ref)	40	1.0 (ref)	22	1.0 (ref)	6
low	1.5 (0.9-2.6)	23	1.1 (0.6-2.1)	12	1.5(0.7-3.4)	9	3.2 (1.0-9.9)	8
medium	1.5 (0.9-3.4)	20	1.1 (0.6-2.1)	13	1.8(0.90-4.0)	10	5.2(1.6-16.6)	7
high	2.0 (1.1-3.4)	20	0.7 (0.4-1.4)	11	0.7(0.3-1.5)	8	5.1(1.6-16.1)	7
	LD P trend=0.03		LD P trend=0.26		LD P trend=0.32		LD P trend=0.02	
	IWLD P trend=0.04		IWLD P trend=0.35		IWLD P trend=0.22		IWLD P trend=0.02	
EPTC (thio-carbamate)								
None	1.0 (ref)	86	1.0 (ref)	62	1.0 (ref)	40	1.0 (ref)	19
low	1,2(0.6-2.3)	9	1.2(0.6-2.7)	7	-	3	2.1 (0.7-6.0)	4
medium	1.2(0.6-2.5)	8	1.7(0.7-4.2)	5	-	0	2.1 (0.6-7.1)	3
high	1.4(0.6-3.4)	5	0.8(0.3-2.3)	4	-	1	4.9 (1.4-16.7)	3
	LD P trend= 0.41		LD P trend=0.98		LD P trend=0.10		LD P trend=0.01	
	IWLD P trend=0.43		IWLD P trend=0.59		IWLD P trend=0.14		IWLD P trend=0.15	

Glyphosate (isopropyl-amine)								
None	1.0 (ref)	25	1.0 (ref)	19	1.0 (ref)	13	1.0 (ref)	10
low	0.6(0.4-1.1)	32	1.3(0.7-2.6)	23	0.7(0.3-1.7)	15	0.4 (0.1-1.2)	9
medium	1.1(0.6-1.9)	29	1.1(0.5-2.1)	23	0.6(0.2-1.4)	11	0.6 (0.2-1.6)	7
high	1.1(0.6-1.8)	29	0.7(0.4-1.3)	22	0.7(0.3-1.8)	12	0.6 (0.2-1.8)	7
	LD P trend=0.21		LD P trend=0.05		LD P trend=0.66		LD P trend=0.98	
	IWLD P trend=0.18		IWLD P trend=0.19		IWLD P trend=0.83		IWLD P trend=0.75	
Herbicide Oil (petroleum oil)								
None	1.0 (ref)	42	1.0 (ref)	35	1.0 (ref)	17	1.0 (ref)	14
low	1.8(0.8-4.3)	7	1.0(0.4-2.5)	6	1.4(0.3-5.9)	2	-	1
medium	2.6(1.0-6.7)	5	2.8(0.7-11.9)	2	1.1(0.1-8.4)	1	-	1
high	1.0(0.4-2.6)	5	1.4(0.4-4.5)	3	0.5(0.1-3.6)	1	0	0
	LD P trend=0.76		LD P trend=0.55		LD P trend=0.46		LD P trend=xxx	
	IWLD P trend=0.88		IWLD P trend=0.16		IWLD P trend=0.40		IWLD P trend=xxx	
Imazethapyr (imid-azolinone)								
None	1.0 (ref)	68	1.0 (ref)	57	1.0 (ref)	29	1.0 (ref)	12
low	1.0(0.6-1.8)	16	0.7(0.3-1.4)	10	0.7(0.3-1.7)	6	1.6 (0.6-3.8)	8
medium	0.8(0.4-1.6)	11	0.6(0.3-1.4)	6	1.1(0.3-3.5)	6	5.2 (1.6-16.6)	4
high	1.2(0.6-2.2)	12	0.5(0.2-1.2)	3	1.0(0.4-2.8)	5	3.2 (1.0-10.0)	4
	LD P trend=0.71		Ld P trend=0.16		LD P trend=0.90		LD P trend=0.03	
	IWLD P trend=0.95		IWLD P trend=0.34		IWLD P trend=0.83		IWLD P trend=0.03	

Metolachlor (chlor-acetanilide)								
None	1.0 (ref)	52	1.0 (ref)	48	1.0 (ref)	20	1.0 (ref)	10
low	1.2(0.7-2.0)	23	0.9(0.4-2.1)	11	1.4(0.6-3.2)	9	2.7 (1.0-7.0)	9
medium	1.7(0.95-3.2)	17	1.3(0.7-2.4)	12	1.4(0.6-3.7)	9	2.1 (0.6-7.7)	4
high	1.3(0.8-2.3)	18	0.4(0.2-0.9)	9	1.5(0.7-3.6)	8	2.6 (0.9-7.2)	6
	LD P trend=0.19		LD P trend=0.07		LD P trend=0.43		LD P trend=0.19	
	IWLD P trend=0.20		IWLD P trend=0.23		IWLD P trend=0.33		IWLD P trend=0.64	
Metribuzin (Triazinone)								
None	1.0 (ref)	30	1.0 (ref)	35	1.0 (ref)	13	1.0 (ref)	9
low	1.5(0.7-2.9)	11	0.5(0.2-1.4)	5	1.4(0.5-3.9)	5	1.0 (0.2-4.9)	3
medium	2.1(1.1-4.0)	13	0.5(0.1-2.0)	3	0.8(0.2-2.9)	3	2.8 (0.9-8.9)	5
high	1.8(0.6-5.2)	4	0.4(0.1-1.6)	2	1.3(0.2-9.8)	1	-	0
	LD P trend=0.06		LD P trend=0.13		LD P trend=0.88		LD P trend=0.60	
	IWLD P trend=0.03		IWLD P trend=0.21		IWLD P trend=0.10		IWLD P trend=0.43	
Paraquat (bi-pyridylium)								
None	1.0 (ref)	48	1.0 (ref)	37	1.0 (ref)	15	1.0 (ref)	14
low	1.0(0.4-2.4)	5	2.4(0.9-6.7)	4	2.9(0.7-12.7)	2	-	1
medium	1.0(0.2-4.0)	2	0.7-0.2-2.3)	3	1.2(0.3-5.3)	2	-	1
high	1.0(0.3-3.2)	3	0.8(0.2-3.4)	2	1.0(0.1-7.6)	1	-	0
	Ld P trend=0.99		LD P trend=0.23		LD P trend=0.94		LD P trend=xxx	
	IWLD P trend=0.44		IWLD P trend=0.78		IWLD P trend=0.75		IWLD P trend=xxx	

Pendi-methalin (dinitro-aniline)								
None	1.0 (ref)	38	1.0 (ref)	28	1.0 (ref)	11	1.0 (ref)	8
low	1.2(0.6-2.2)	12	1.0(0.4-2.2)	9	1.4(0.5-4.2)	6	1.8 (0.5-6.2)	5
medium	1.2(0.6-2.7)	8	0.92(0.3-2.6)	6	1.5(0.4-5.4)	4	2.3 (0.6-8.9)	4
high	0.8(0.3-1.9)	6	0.8(0.3-2.1)	5	1.4(0.5-4.5)	4	1.8 (0.5-6.9)	3
	LD P trend=0.66		LD P trend=0.66		LD P trend=0.57		LD P trend=0.42	
	IWLD P trend=0.44		IWLD P trend= 0.88		IWLD P trend=0.49		IWLD P trend=0.70	
Trifluralin (dinitro-aniline)								
None	1.0 (ref)	45	1.0 (ref)	43	1.0 (ref)	25	1.0 (ref)	10
low	1.1(0.7-1.9)	23	0.9(0.5-1.7)	14	0.9(0.4-1.9)	8	1.2 (0.4-3.2)	7
medium	1.6(0.9-2.6)	21	0.8(0.4-1.7)	11	0.8(0.4-1.8)	8	2.7 (1.0-7.0)	7
high	1.1(0.6-1.9)	15	0.6(0.3-1.2)	11	0.8(0.3-1.9)	7	3.3 (1.2-9.1)	6
	LD P trend= 0.08		LD P trend=0.13		LD P trend=0.62		LD P trend=0.01	
	IWLD P trend=0.80		IWLD P trend=0.11		IWLD P trend=0.65		IWLD P trend=0.08	
2,4,5 T								
None	1.0 (ref)	37	1.0 (ref)	33	1.0 (ref)	14	1.0 (ref)	12
low	2.1(1.1-3.9)	14	1.3(0.6-3.0)	7	4.6(1.3-16.1)	3	-	3
medium	2.4(0.7-7.00	3	0.9(0.2-3.7)	2	2.1(0.6-7.2)	3	-	0
high	1.1(0.4-2.8)	5	1.3(0.4-4.3)	3	1.1(0.2-4.8)	2	-	1
	LD P trend= 0.33		LD P trend=0.71		LD P trend=0.73		LD P trend=xxx	
	IWLD P trend=0.83		IWLD P trend=0.90		IWLD P trend=0.80		IWLD P trend=0.97	

[1]Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)

[2] Numbers do not sum to NHL subtype totals due to missing data

Supplemental Table 4. Insecticides, fungicide and fumigant exposure (life-time days) and age-adjusted risk of NHL by cell type (1993 through 2008).

	CLL, SLL, PLL, MCL		Diffuse Large B-cell		Follicular B-cell		Other B-cell types	
	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n
Aldicarb								
None	1.0 (ref)	51	1.0 (ref)	40	1.0 (ref)	19	1.0 (ref)	15
low	1.9(0.3-13.4)	1	1.7(0.4-7.2)	2	6.1(0.8-45.7)	1	-	1
medium	0.95(0.1-6.9))	1	4.8(1.2-19.8)	2	1.2(0.2-9.4)	2	-	1
high	-	0	0.5(0.1-4.1)	1	-	0	-	0
	LD P trend=0.15		LD P trend=0.72		LD P trend=0.63		LD P trend=xxx	
	IWLD P trend=0.14		IWLD P trend=0.89		IWLD P trend=0.64		IWLD P trend=xxx	
Carbaryl								
None	1.0 (ref)	32	1.0 (ref)	23	1.0 (ref)	9	1.0 (ref)	9
low	1.1(0.5-2.2)	15	0.7(0.3-1.5)	10	1.1(0.3-4.0)	5	xxx-	6
medium	1.0(0.2-4.2)	2	1.3(0.6-3.0)	8	1.8(0.6-5.9)	4	xxx-	0
high	0.4(0.2-0.8)	8	1.5(0.7-3.5)	8	1.3(0.4-4.1)	4	xxx-	1
	LD P trend=0.007		LD P trend=0.19		LD P trend=0.66		LD P trend=xxx	
	IWLD P trend=0.02		IWLD P trend=0.27		IWLD P trend=0.81		IWLD P trend=xxx	
Carbofuran								
None	1.0 (ref)	67	1.0 (ref)	58	1.0 (ref)	33	1.0 (ref)	19
low	1.4(0.8-2.5)	15	0.9(0.4-1.9)	8	0.96(0.4-2.5)	5	1.0 (0.4-2.7)	5

Comment [lbf74]: It looks like in the main tables you have restricted presenting results when there aren't 5 cases in a cell. You should use the same rules in the supplemtnal tables.

medium	1.2(0.6-2.4)	10	0.9(0.4-1.8)	9	1.6(0.7-3.9)	6	1.4(0.2-10.7)	1
high	1.3(0.7-2.4)	12	1.1(0.5-2.9)	5	0.6(0.2-2.0)	3	0.94(0.2-4.1)	2
	LD P trend=0.36		LD P trend=0.81		LD P trend=0.79		LD P trend=0.99	
	IWLD P trend=0.79		IWLD P trend=0.71		IWLD P trend=0.72		IWLD P trend=xxx	
Chlorpyrifos								
None	1.0 (ref)	69	1.0 (ref)	55	1.0 (ref)	26	1.0 (ref)	18
low	0.9(0.5-1.7)	15	1.2(0.6-2.1)	13	1.4(0.7-3.1)	10	0.9(0.3-2.6)	5
medium	1.1(0.7-2.0)	16	1.0(0.5-1.7)	15	1.2(0.5-2.9)	7	4.2(1.7-10.6)	6
high	1.0(0.5-1.7)	14	0.9(0.6-4.0)	7	1.4(0.6-3.4)	6	0.8(0.3-2.3)	4
	LD P trend=0.99		LD P trend=0.66		LD P trend=0.56		LD P trend=0.97	
	IWLD P trend=0.88		IWLD P trend=0.67		IWLD P trend=0.22		IWLD P trend=	
Chlorthalonil								
None	1.0 (ref)	107	1.0 (ref)	84	1.0 (ref)	45	1.0 (ref)	32
low	0.9(0.3-2.9)	3	1.6(0.4-6.6)	2	3.1(0.7-12.6)	2	-	1
medium	0.7(0.2-2.7)	2	1.4(0.3-5.6)	2	1.2(0.3-4.8)	2	-	0
high	0.7(0.2-2.7)	2	0.2(0.1-1.4)	1	0.6(0.1-4.4)	1	-	0
	LD P trend=0.46		LD P trend=0.11		LD P trend=0.61		LD P trend=xxx	
	IWLD P trend=0.96		IWLD P trend=0.17		IWLD P trend=0.41		IWLD P trend=xxx	
Coumaphos								
None	1.0 (ref)	92	1.0 (ref)	72	1.0 (ref)	42	1.0 (ref)	22
low	1.1(0.4-3.1)	4	0.7(0.2-2.3)	3	1.9(0.6-6.0)	3	xxx-	4
medium	2.0(0.8-4.9)	5	2.1(0.5-8.5)	2	0.5(0.1-4.0)	1	xxx-	0

high	1.3(0.4-4.0)	3	1.5(0.4-5.9)	2	2.2(0.3-16.3)	1	-	1
	LD P trend=0.36		LD P trend=0.47		LD P trend=0.43		LD P trend=xxx	
	IWLD P trend=0.53		IWLD P trend=0.74		IWLD P trend=0.82		IWLD P trend=xxx	
Diazinon								
None	1.0 (ref)	40	1.0 (ref)	33	1.0 (ref)	13	1.0 (ref)	12
low	1.5(0.7-3.1)	9	1.2(0.4-3.1)	5	1.6(0.4-5.5)	3	xxx-	2
medium	1.2(0.4-3.6)	5	0.9(0.3-2.8)	4	1.6(0.4-7.4)	3	xxx-	1
high	1.2(0.5-3.0)	5	1.2(0.4-3.8)	3	2.0(0.4-10.0)	2	xxx-	0
	LD P trend=0.72		LD P trend=0.84		LD P trend=0.35		LD P trend=xxx	
	IWLD P trend=0.60		IWLD P trend=0.84		IWLD P trend=0.53		IWLD P trend=xxx	
DDVP								
None	1.0 (ref)	95	1.0 (ref)	74	1.0 (ref)	43	1.0 (ref)	24
low	1.3(0.5-3.5)	4	4.1(1.0-16.9)	2	0.7(0.2-3.1)	2	xxx-	1
medium	1.4(0.6-3.4)	5	0.5(0.1-1.9)	2	2.2(0.3-16.1)	1	xxx-	2
high	0.3(0.1-2.1)	3	0.3(0.1-2.2)	1	0.5(0.1-3.9)	1	-xxx	0
	LD P trend=0.46		LD P trend=0.25		LD P trend=0.54		LD P trend=xxx	
	IWLD P trend=0.85		IWLD P trend=0.54		IWLD P trend=0.53		IWLD P trend=xxx	
Fonofos								
None	1.0 (ref)	79	1.0 (ref)	61	1.0 (ref)	40	1.0 (ref)	17
low	1.6(.8-2.9)	12	1.5(0.8-3.1)	9	-	5	2.2(0.8-5.9)	5
medium	1.2(0.5-2.9)	5	1.0(0.4-2.3)	6	-	0	2.0(0.6-6.7)	3
high	0.9(0.5-2.0)	8	1.3(0.5-3.2)	5	-	2	2.3(0.3-17.0)	1
	LD P trend=0.88		LD P trend=0.62		LD P trend=0.20		LD P trend=0.19	

	IWLD P trend=0.94		IWLD P trend=0.77		IWLD P trend=0.18		IWLD P trend=xxx	
Lindane								
None	1.0 (ref)	41	1.0 (ref)	39	1.0 (ref)	14	1.0 (ref)	14
low	1.6(0.7-3.6)	8	0.7(0.2-3.0)	9	2.7(0.8-9.4)	3	xxx-	1
medium	1.1(0.3-4.8)	3	1.1(0.3-3.7)	6	3.6(0.8-15.9)	2	xxx-	0
high	3.8(1.5-9.6)	5	1.3(0.2-9.7)	5	2.4(0.5-10.4)	2	xxx-	0
	LD P trend=0.005		LD P trend=0.25		LD P trend=0.25		LD P trend=xxx	
	IWLD P trend=0.04		IWLD P trend=0.29		IWLD P trend=0.18		IWLD P trend=xxx	
Malathion								
None	1.0 (ref)	21	1.0 (ref)	16	1.0 (ref)	5	1.0 (ref)	6
low	0.94(0.5-1.8)	17	0.8(0.4-1.7)	16	1.0(0.3-3.6)	6	-xxx	8
medium	0.8(0.4-1.7)	11	0.9(0.4-2.1)	8	1.2(0.3-4.3)	5	-xxx	0
high	0.8(0.4-1.7)	11	1.7(0.8-3.8)	11	1.5(0.4-4.9)	5	-xxx	3
	LD P trend=0.52		LD P trend=0.07		LD P trend=0.48		LD P trend=xxx	
	IWLD P trend=0.24		IWLD P trend=0.33		IWLD P trend=0.56		IWLD P trend=xxx	
Maneb								
None	1.0 (ref)	52	1.0 (ref)	37	1.0 (ref)	19	1.0 (ref)	16
low	2.9(0.9-9.4)	3	2.6(0.6-10.9)	2	2.6(0.4-19.8)	1	-xxx	0
medium	1.6(0.4-6.6)	2	1.3(0.4-4.2)	3	1.1(0.1-8.0)	1	-xxx	0
high	0.3(0.1-2.4)	1	3.5(0.5-25.4)	1	-	0	-xxx	0
	LD P trend=0.43		LD P trend=0.19		LD P trend=0.55		LD P trend=xxx	
	IWLD P trend=0.49		IWLD P trend=0.17		IWLD P trend=0.66		IWLD P trend=xxx	

Metalaxyl								
None	1.0 (ref)	46	1.0 (ref)	34	1.0 (ref)	18	1.0 (ref)	
Low	3.9(1.7-9.3)	6	1.1(0.3-3.6)	4	0.8(0.2-3.4)	2	-xxx	
medium	1.3(0.3-5.4)	2	1.4(0.5-3.9)	5	2.1(0.5-9.2)	2	-xxx	
high	0.4(0.1-1.2)	3	0.9(0.2-4.0)	2	0.9(0.1-6.4)	1	-xxx	
	LD P trend=0.08		LD P trend=0.92		LD P trend=0.81		LD P trend=xxx	
	IWLD P trend=0.04		IWLD P trend=0.85		IWLD P trend=0.83		IWLD P trend=xxx	
Methylbromide								
None	1.0 (ref)	101	1.0 (ref)	65	1.0 (ref)	45	1.0 (ref)	14
low	0.8(0.3-2.1)	4	4.8(2.5-9.3)	10	1.4(0.3-5.8)	2	-xxx	1
medium	0.7(0.3-1.6)	5	1.3(0.6-3.1)	6	1.2(0.4-4.0)	3	-xxx	1
high	0.4(0.1-1.3)	3	1.2(0.5-2.6)	7	-	0	-xxx	0
	LD P trend=0.09		LD P trend=0.71		LD P trend=0.08		LD P trend=xxx	
	IWLD P trend=0.02		IWLD P trend=0.57		IWLD P trend=0.09		IWLD P trend=xxx	
Permethrin animals								
None	1.0 (ref)	95	1.0 (ref)	78	1.0 (ref)	38	1.0 (ref)	25
low	1.3(0.5-3.3)	5	0.2(0.1-1.3)	1	2.8(1.1-7.0)	5	-xxx	1
medium	0.9(0.2-3.7)	3	0.5(0.1-3.4)	1	2.9(0.7-12.0)	2	-xxx	2
high	0.8(0.3-2.5)	3	-	0	0.8(0.2-3.5)	2	-xxx	0
	LD P trend=0.75		LD P trend=0.19		LD P trend=0.93		LD P trend=0.87	
	IWLD P trend=0.70		IWLD P trend=0.29		IWLD P trend=0.73		IWLD P trend=xxx	
Permethrin crops								

None	1.0 (ref)	86	1.0 (ref)	72	1.0 (ref)	39	1.0 (ref)	23
low	1.9(0.6-5.4)	6	0.6(0.1-2.2)	3	1.1(0.3-3.5)	3	-xxx	4
medium	0.8(0.4-1.9)	6	2.7(0.7-10.6)	2	1.5(0.4-6.4)	2	-xxx	0
high	1.2(0.4-4.0)	4	0.4(0.1-1.8)	2	0.5(0.1-3.9)	2	-xxx	0
	LD P trend=0.76		LD P trend=0.28		LD P trend=0.57		LD P trend=0.37	
	IWLD P trend=0.70		IWLD P trend=0.33		IWLD P trend=0.45		IWLD P trend=xxx	
Phorate								
None	1.0 (ref)	36	1.0 (ref)	29	1.0 (ref)	15	1.0 (ref)	10
low	1.4(0.7-3.0)	9	1.0(0.4-2.6)	5	0.6(0.1-2.7)	2	1.4 (0.4-4.6)	4
medium	1.4(0.6-3.2)	6	2.0(0.9-4.7)	7	2.9(0.96-8.7)	4	1.5 (0.2-11.6)	1
high	0.94(0.4-2.4)	5	0.7(0.2-2.4)	3	-	0	1.4 (0.2-11.2)	1
	LD P trend=0.90		LD P trend=0.92		LD P trend=0.82		LD P trend=XXX	
	IWLD P trend=0.53		IWLD P trend=0.98		IWLD P trend=0.33		IWLD P trend=xxx	
Terbufos								
None	1.0 (ref)	53	1.0 (ref)	47	1.0 (ref)	26	1.0 (ref)	10
low	1.8(1.0-3.1)	17	0.9(0.4-1.7)	12	2.5(1.1-5.4)	8	2.3 (0.8-6.6)	6
medium	2.2(1.3-3.6)	21	2.2(1.2-4.2)	12	1.8(0.7-4.3)	7	3.1(1.1-9.2)	5
high	1.4(0.8-2.6)	13	1.1(0.5-2.3)	10	0.7(0.3-1.8)	6	4.1(1.4-11.9)	5
	LD P trend=0.16		LD P trend=0.34		LD P trend=0.54		LD P trend=0.01	
	IWLD P trend=0.14		IWLD P trend=0.40		IWLD P trend=0.18		IWLD P trend=xxx	

[1]Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)

Supplemental Table 5. Estimated individual and joint effects of pesticide combinations and age-adjusted risk of NHL

Comment [a75]: Need to delete. No really interesting findings, no space. Timing of pesticides not possible.

Individual and joint pesticide exposures	Exposed cases	Poisson Regression RR (95% CI)[1]
Chlordane and DDT		
--Neither	174	1.0 (reference)
--Chlordane only	19	0.6 (0.4-1.0)
--DDT only	49	0.8(0.6-1.2)
--Both	56	0.9 (0.7-1.3)
Chlordane and Lindane		
--Neither	200	1.0 (reference)
--Chlordane only	47	0.8(0.6-1.2)
--Lindane only	23	1.0(0.6-1.5)
--both	28	1.0(0.7-1.6)
Lindane and dicamba		
--Neither	113	1.0 (reference)
--Lindane only	15	1.0 (0.6-1.7)
--dicamba only	120	1.3 (0.98-1.6)
--both	32	1.2 (0.8-1.8)
Atrazine and Chlordane		
--Neither	58	1.0 (reference)
--atrazine only	162	1.3(0.97-1.8)
--Chlordane only	19	1.0(0.6-1.7)
--Both	57	1.1(0.8-1.6)
2,4,5 t and Lindane		
--Neither	190	1.0 (reference)
--2,4,5-t only	57	1.1(0.9-1.6)

--Lindane only	27	1.1(0.7-1.6)
--Both	25	1.2 (0.8-1.8)
Atrazine and Lindane		
--Neither	73	1.0 (reference)
--Atrazine only	173	1.1 (0.9-1.5)
--Lindane only	4	0.5 (0.2-1.3)
--both	47	1.3 (0.9-1.9)
Atrazine and Dicamba		
--Neither	61	1.0 (reference)
--Atrazine only	72	1.0 (0.7-1.4)
--Dicamba only	17	1.0 (0.6-1.7)
--both	140	1.3 (0.97-1.8)
Atrazine and Carbofuran		
--Neither	68	1.0 (reference)
--Atrazine only	132	1.1 (0.9-1.5)
--Carbofuran only	9	0.9 (0.4-1.8)
--Both	81	1.2 (0.9-1.6)
Atrazine and Diazinon		
--Neither	58	1.0 (reference)
--atrazine only	163	1.2 (0.9-1.7)
--Diazinon only	20	0.9 (0.5-1.5)
--Both	59	1.1 (0.8-1.6)
Atrazine and alachlor		
--Neither	65	1.0 (reference)
--atrazine only	73	1.1 (0.8-1.5)

--alachlor only	16	0.8 (0.5-1.4)
--Both	146	1.1 (0.8-1.5)
2,4, 5 t and dicamba		
--Neither	94	1.0 (reference)
--2,4,5-t only	32	1.3 (0.9-1.9)
--dicamba only	107	1.4 (1.0-1.8)
--Both	45	1.3 (0.9-1.8)
2,4-D and Chlordane		
--Neither	55	1.0 (reference)
--2,4-D only	164	1.1(0.8-1.5)
--Chlordane only	7	0.7(0.3-1.5)
--Both	70	1.0 (0.7-1.5)
Glyphosate and atrazine		
--Neither	30	1.0 (reference)
--Glyphosate only	60	0.96(0.6-1.5)
--atrazine only	63	1.4(0.9-2.1)
--Both	171	1.1(0.7-1.6)
Glyphosate and 2,4-D		
--Neither	32	1.0 (reference)
--Glyphosate only	44	1.1(0.7-1.7)
--2,4-D only	61	1.4(0.9-2.1)
--Both	188	1.1(0.7-1.5)
Glyphosate and Chlordane		
--Neither	72	1.0 (reference)
--Glyphosate only	147	0.9 (0.7-1.2)

--chlordane only	13	1.0 (0.5-1.7)
--Both	64	0.8 (0.6-1.1)
2,4-D and Lindane		
---Neither	60	1.0 (reference)
---only 2,4-D	180	1.1(0.8-1.4)
---only lindane	3	0.6(0.2-1.8)
---both	48	1.2(0.8-1.7)
2,4-D and atrazine		
---Neither	41	1.0 (reference)
---only 2,4-D	49	1.0(0.7-1.5)
---only atrazine	35	1.2(0.8-1.9)
---both	199	1.2(0.8-1.7)
2,4-D and dicamba		
---Neither	51	1.0 (reference)
---only 2,4-D	81	0.9(0.6-1.3)
---only dicamba	13	1.2(0.7-2.2)
---both	144	1.2(0.9-1.7)
2,4-D and cyanazine		
---Neither	58	1.0 (reference)
---only 2,4-D	104	0.9(0.6-1.2)
---only cyanazine	11	0.9(0.5-1.7)
---both	130	1.2(0.9-1.6)
2,4-D and terbufos		
---Neither	48	1.0 (reference)
---only 2,4-D	113	1.0(0.7-1.5)

---only terbufos	16	1.7(0.97-3.0)
---both	115	1.5(1.0-2.0)
Cyanazine and atrazine		
---Neither	72	1.0 (reference)
---only cyanazine	11	1.3(0.7-2.4)
---only atrazine	90	1.0(0.8-1.4)
---both	130	1.3(0.97-1.7)

[1]Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)

Appendix 1. **Frequency of NHL in Agricultural Health Study applying New (InterLymp hierarchial classification of lymphoid neoplasms) and Older Definitions (ICD-O-3)**			
Lymphoma category and type (ICD-O-3 codes)[1]	**Number NHL cases, new definition (InterLymph hierarchical classification)[1]**	**Number cases NHL, older definition (ICD-O-3)[2]**	**SEER Recode[1]**
CLL/SLL/PLL/MCL (Mature NHL, B-cell)			
Small lymphocytic lymphoma (9670)	27	27	08
Chronic lymphocytic leukemia/small lymphocytic lymphoma (9823)	74	0	08
Mantle -cell lymphoma (9673)	16	16	10
Diffuse Large B-cell Lymphoma (Mature NHL, B-cell)			
DLBCL (9680)	94	94	13
Follicular Lymphoma (Mature NHL, B-cell)			
Follicular lymphoma (9690, 9691,9695,9698)	53	53	21
Other B-cell Types			
Precursor acute lymphoblastic leukemia/lymphoma (9835(B), 9836)	4	0	07
Waldenstrom macroglobulinemia (9761)	2	0	12
Lymphoplasmacytic lymphoma (9671)	2	2	11
Hairy-cell leukemia (9940)	6	0	22
NHL, NOS (9591(B), 9675(B))	6	6	26
Burkitt lymphoma/leukemia (9687)	1	1	17
Extranodal marginal zone lymphoma (MZL), Malt type & Nodal MZL (9699)	13	13	19, 20
Plasma cell neoplasms			
Plasmacytoma (9734, 9731)	6	0	23
Multiple myeloma (9732)	77	0	24
Other NHL Types			
Precursor acute lymphoblastic leukemia/lymphoma (9835(T), 9837)	1	0	27
Mycosis fungoides (9700)	6	6	28
Peripheral T-cell lymphoma, NOS (9702)	2	2	30
Anaplastic large cell lymphoma, T or null cell (9714)	2	2	33
Enteropathy type T-cell lymphoma (9717)	1	1	35
Primary cutaneous anaplastic large cell lymphoma (9718)	1	1	37
T-cell lymph, nasal-type/aggressive NK leukemia (9719)	1	1	39
NHL, NOS (9591(T))	1	1	42
Lymphoid leukemia, NOS (9820(U))	1	0	
Precursor acute lymphoblastic leukemia/lymphoma (9727(U), 9835(U))	3	1	43
NHL, NOS (9591(U), 9675(U))	6	6	45
Lymphoid neoplasm, NOS (9590(U))	10	10	47
Total	416	243	

Lineage: B=B-cell, T=T-cell, U=Unknown

[1] http://seer.cancer.gov/lymphomarecode based on Morton LM et al. Blood, 2007;110:695-708.

[2] Percy C. et al., Lyon, France: IARC Press: 2001.

Comment [CL76]: This was originally coded as 9713, which is an ICD-O-2 code, which becomes 9719 in ICD-O-3. Since we are presenting ICD-O-3 codes in this table, I have changed this code to 9719.

Comment [CL77]: Since IA and NC cancer registries are not yet using 2008 WHO codes, the reference for this table should be the Morton LM et al. publication noted here. This reference should also be noted in the text. Reference to the 2010 blood paper should not be noted in regard to the NHL classification used in this paper.

Appendix 2. Pesticide Classification by Chemical/Functional Class	
Chemical/functional class	**Pesticide**
Acetamide herbicide	Metolachlor, alachlor
Carbamate herbicde	Butlylate, EPTC
Other herbicides	Chloromuron ethyl, 2,4-D, dicamba, glyphosate, herbicide oil, imazethapyr. Paraquat, pendimethalin, 2,4,5-T, 2,4,5TP, trifluralin
Triazine/triazinone herbicides	Atrazine, cyanazine, metribuzin
Carbamate insecticides	Carbofuran, aldicarb, carbaryl
Chlorinated insecticides	Aldrin, chlordane, DDT, dieldrin, heptachlor, lindane, toxaphine
Organophosphate insecticides	Chlorpyrifos, coumaphos, diazinon, dichlorvos, fonofos, malathion, parathion, phorate, terbufos
Other insecticides	Permethrin (crops & animals), trichlorfon
Fungicides	Benomyl, chlorthalonil, captan, maneb/mancozeb, methylaxyl, ziram
Fumigants	Methyl bromide, aluminum phosphate, ethylene dibromide, carbon tetra chloride/carbondisulfide

Supplemental table 7: Pesticide exposures (total days and intensity weight total days) age- adjusted risks of NHL incidence (1993 through 2008)[old nhl definition; n=243].

	NHL Cases	RR[1] (95%) by Total Days of Exposure	NHL Cases	RR[1] (95% CI) Intensity-weighted days of exposure
Insecticides, Fungicides and Fumigants				
		P trend=		
Carbaryl (carbamate-insecticide)				
None	56	1.0 (ref)	56	1.0 (ref)
Low	19	0.8 (0.5-1.3)	19	0.9(0.6-1.6)
Medium	20	0.9(0.5-1.5)	20	0.7(0.4-1.2)
High	18	1.1(0.6-1.8)	18	1.2(0.7-2.0)
		P trend=0.64		P trend=0.42
Carbofuran (carbamate-insecticide)				
None	140	1.0 (ref)	140	1.0 (ref)

Low	26	1.2(0.8-1.8)	22	1.0(0.7-1.7)
Medium	18	1.1 (0.7-1.7)	21	1.0 (0.6-1.6)
High	21	1.1(0.7-1.7)	21	1.3(0.8-2.0)
		P trend=0.70		P trend=0.37
Chlorpyrifos (organophosphate-insecticide)				
None	134	1.0 (ref)	134	1.0 (ref)
Low	33	1.2(0.8-1.8)	30	1.2(0.8-1.8)
Medium	33	1.2(0.8-1.8)	30	0.9 (0.6-1.3)
High	32	0.9(0.6-1.3)	29	1.2 (0.8-1.7)
		P trend=0.50		P trend=0.56
Coumaphos				
None	186	1.0(ref)	186	1.0 (ref)
Low	9	1.3(0.7-2.5)	7	1.6(0.7-3.3)
Medium	7	1.1(0.5-2.3)	8	1.1(0.5-2.2)
High	5	1.4(0.6-3.4)	6	1.2(0.5-2.7)
		P trend=0.45		P trend=0.65
Diazinon (organophosphosphorous-insecticide)				
None	80	1.0 (ref)	80	1.0 (ref)
Low	12	1.0(0.6-1.9)	10	1.0(0.5-2.0)
Medium	8	0.9(0.4-1.9)	10	1.1(0.6-2.1)
High	9	1.2(0.6-2.4)	9	1.1(0.5-2.1)
		P trend=0.66		P trend=0.82
DDVP				
None	190	1.0(ref)	190	1.0 (ref)
Low	6	1.0(0.4-2.1)	6	1.1 (0.5-2.5)
Medium	6	0.9(0.4-2.0)	6	0.6(0.3-1.3)

High	5	0.6(0.3-1.6)	5	1.0(0.4-2.4)
		P trend=0.30		P trend=0.99
Fonofos				
None	163	1.0(ref)	163	1.0 (ref)
Low	18	1.1(0.7-1.8)	15	1.3(0.8-2.2)
Medium	13	1.1(0.6-2.0)	15	1.3(0.8-2.2)
Low	13	0.9(0.5-1.5)	14	0.7(0.4-1.2)
		P trend=0.		P trend=0.19
Malathion (organophosphorous-insecticide)				
None	39	1.0 (ref)	39	1.0 (ref)
Low	32	1.0(0.6-1.6)	26	1.1(0.7-1.8)
Medium	23	0.8(0.5-1.3)	27	0.7(0.4-1.2)
High	23	1.0 (0.6-1.7)	25	1.0(0.6-1.7)
		P trend=0.70		P trend=0.79
Metalaxyl				
None	91	1.0 (ref)	91	1.0 (ref)
Low	12	1.0 (0.5-1.8)	7	0.8(0.4-1.7)
Medium	3	0.7 (0.2-2.1)	7	1.1(0.5-2.4)
High	5	0.8 (0.3-2.0)	6	0.8(0.3-1.7)
		P trend=0.56		P trend=0.62
Methylbromide				
None	189	1.0 (ref)	189	1.0 (ref)
Low	16	2.7(1.6-4.5)	15	2.6 (1.6-4.5)
Medium	13	1.3(0.7-2.2)	13	1.5(0.8-2.6)
High	13	0.7(0.4-1.2)	13	0.6(0.4-1.1)
		P trend=0.24		P trend=0.07
Permethrin Animals				

(pyrethroid-insecticide)				
None	189	1.0 (ref)	189	1.0 (ref)
Low	9	1.1(0.6-2.2)	7	1.3(0.6-2.8)
Medium	5	0.9(0.4-2.1)	7	0.7(0.3-1.6)
High	6	0.7(0.3-1.5)	6	0.7(0.3-1.7)
		P trend= 0.27		P trend=0.04
Phorate (organophosphate-insecticide)				
None	72	1.0 (ref)	72	1.0 (ref)
low	15	1.0(0.6-1.8)	12	1.3(0.7-2.5)
medium	15	2.3(1.3-4.1)	12	1.2(0.7-2.3)
high	5	0.5(0.2-1.2)	11	0.9(0.5-1.6)
		P for trend=0.53		P for trend=00.86.
Terbufos (organophosphorous-insecticide)				
None	114	1.0 (ref)	114	1.0 (ref)
Low	40	1.4(0.94-1.9)	31-	1.3(0.9-1.9)
Medium	26	1.9(1.2-2.8)	31	1.7(1.2-2.6)
High	26	1.2(0.8-1.9)	30	1.3(0.9-2.0)
		P trend=0.24		P trend=0.16
Chlorinated insecticides				
Aldrin				
None	86	1.0 (ref)	86	1.0 (ref)
Low	9	0.8(0.4-1.6)	9	1.0(0.5-1.9)
Medium	8	0.7(0.4-1.5)	7	0.7(0.3-1.5)
High	6	2.4(1.0-5.4)	7	1.3(0.6-2.9)
		P trend=0.21		P trend=0.86
Chlordane				

None	78	1.0 (ref)	78	1.0 (ref)
Low	10	1.2(0.7-2.0)	10	1.5(0.8-2.9)
Medium	8	1.3(0.7-2.4)	9	1.0(0.4-2.3)
High	10	1.0(0.9-1.1)	9	1.1(0.6-2.1)
		P trend=0.89		P trend=0.77
DDT				
None	71	1.0 (ref)	71	1.0 (ref)
Low	14	0.9(0.5-1.7)	13	1.1(0.6-2.2)
Medium	12	1.4(0.7-2.6)	12	1.0(0.5-1.8)
High	11	1.1(0.6-2.2)	12	1.3(0.7-2.4)
		P trend=0.61		P trend=0.47
Dieldrin				
None	101	1.0 (ref)	101	1.0 (ref)
Low	3	0.9(0.3-2.9)	3	1.9(0.6-5.9)
Medium	3	2.9(0.9-9.2)	2	1.3(0.3-5.2)
High	1	1.1(0.1-7.7)	2	0.9(0.2-3.8)
		P trend=0.47		P trend=0.97
Heptachlor				
None	88	1.0 (ref)	88	1.0 (ref)
Low	8	0.9(0.7-2.6)	7	1.2(0.6-2.4)
Medium	8	1.4(0.7-2.6)	8	1.7(0.7-3.8)
High	5	1.1(0.6-2.2)	6	1.4(0.6-3.3)
		P trend=0.26		P trend=0.42
Lindane				
None	86	1.0 (ref)	86	1.0 (ref)
Low	7	1.0(0.5-2.1)	7	1.1(0.5-2.3)
Medium	8	1.2(0.6-2.4)	7	1.0(0.5-2.2)
High	6	3.7(1.6-8.4)	6	2.8(1.2-6.4)

		P trend=0.0.01		P trend=0.04
Toxaphene				
None	90	1.0 (ref)	90	1.0 (ref)
Low	8	1.2(0.6-2.5)	6	1.6(0.7-3.5)
Medium	4	4.4(1.6-12.1	7	1.3(0.6-3.0)
High	6	0.9(0.4-2.0)	5	0.9(0.4-2.3)
		P trend=0.66		P trend=0.83
Herbicides				
Alachlor (acetamide-herbicide)				
None	96	1.0 (ref)	96	1.0 (ref)
Low	39	1.1(0.8-1.6)	38	1.1(0.7-1.6)
Medium	45	0.9(0.6-1.2)	40	0.8 (0.6-1.2)
High	31	1.4(0.9-2.0)	36	1.4(0.96-2.1)
		P trend=0.22		P trend=0.09
Atrazine (triazine-herbicide)				
None	59	1.0 (ref)	59	1.0 (ref)
Low	64	1.1(0.8-1.6)	58	1.1(0.8-1.6)
Medium	56	1.3(0.9-1.9)	59	1.2(0.9-1.8)
High	55	1.2(0.8-1.7)	57	1.3(0.9-1.8)
		P trend=0.52		P trend=0.27
Butylate (thiocarbamate-herbicide)				
None	75	1.0 (ref)	75	1.0 (ref)
Low	14	0.9 (0.5-1.6)	12	0.9(0.5-1.6)
Medium	15	3.4(1.9-5.9)	11	2.7(1.4-5.0)
High	5	1.1(0.4-2.7)	11	1.6(0.9-3.0)

		P trend=0.005		P trend=0.049
Chlorimuron-ethyl (benzoic acid ester-herbicide)				
None	75	1.0 (ref)	75	1.0 (ref)
low	20	1.1(0.7-1.9)	13	1.1(0.6-2.0)
medium	11	1.5(0.8-2.9)	12	1.3(0.7-2.4))
high	6	0.7(0.3-1.7)	12	1.0(0.5-1.9)
		P for trend=0.73		P for trend=0.94
Cyanazine (triazine-herbicide)				
None	114	1.0 (ref)	114	1.0 (ref)
Low	41	1.4(0.95-1.9))	33	1.2(0.8-1.7)
Medium	32	1.3(0.9-1.9)	32	1.3(0.9-1.9)
High	25	1.1(0.7-1.6)	32	1.2(0.8-1.8)
		P for trend=0.0.89		P for trend=0.34
Dicamba (benzoic-herbicide)				
None	92	1.0 (ref)	92	1.0 (ref)
Low	39	1.5(1.0-2.2)	38	1.2(0.8-1.8)
Medium	38	1.2(0.8-1.8)	39	1.4(0.9-2.0)
High	38	1.0(0.7-1.5)	37	1.0(0.7-1.5)
		P trend=0.64		P trend=0.95
2,4-D (phenoxy-herbicide)				
None	53	1.0 (ref)	53	1.0 (ref)
Low	60	0.9(0.6-1.3)	59	0.9(0.6-1.4)
Medium	59	1.0(0.7-1.5)	60	1.0(0.7-1.4)
High	59	0.9(0.6-1.3)	58	0.9(0.6-1.3)

		P trend=0.61		P trend=0.69
EPTC (thiocarbamate-herbicide)				
None	164	1.0 (ref)	164	1.0 (ref)
Low	21	1.3(0.9-2.1)	15	1.4(0.8-2.4)
Medium	9	1.1(0.6-2.2)	12	1.1(0.6-2.0)
High	10	0.8(0.4-1.5)	13	0.8(0.5-1.5)
		P trend=0.39		P trend=0.61
Glyphosate (phosphinic acid-herbicide)				
None	48	1.0 (ref)	48	1.0 (ref)
Low	72	1.0(0.7-1.4)	61	1.1(0.7-1.6)
Medium	51	0.7(0.5-1.0)	61	0.7(0.5-1.0)
High	60	1.0(0.7-1.4)	60	0.9(0.6-1.4)
		P trend=0.79		P trend=0.0.99
Herbicide Oil				
None	84	1.0 (ref)	84	1.0 (ref)
Low	9	1.0(0.5-1.9)	9	1.2(0.6-2.4)
Medium	10	1.8(0.95-3.6)	10	1.1(0.6-2.1)
High	8	1.1(0.6-2.6)	8	1.5(0.7-3.1)
		P trend=0.62		P trend=0.29
Imazethapyr (imidazolinone-herbicide)				
None	132	1.0 (ref)	132	1.0 (ref)
Low	30	0.9(0.6-1.3)	25	1.0(0.6-1.5)
Medium	20	0.8(0.5-1.2)	25	0.8(0.5-1.3)
High	24	0.9(0.6-1.4)	24	0.8(0.5-1.2)
		P trend=0.50		P trend=0.64

Metolachlor				
None	101	1.0 (ref)	101	1.0(ref)
Low	36	1.2(0.8-1.8)	35	1.1(0.8-1.7)
Medium	36	1.3(0.9-1.9)	36	1.4(0.9-2.0)
High	34	1.1(0.7-1.6)	34	1.1(0.8-1.6)
		P trend=0.73		P trend=0.71
Metribuzin (triazine-herbicide)				
None	70	1.0 (ref)	70	1.0 (ref)
Low	15	0.8 (0.5-1.5)	14	0.9(0.5-1.6)
Medium	20	1.2(0.7-2.0)	14	1.1(0.6-2.0)
High	6	1.1 (0.5-2.5)	13	1.2(0.6-2.1)
		P trend=0.0.59		P trend=0.55
Paraquat				
None	88	1.0 (ref)	88	1.0(ref)
Low	8	2.1(1.0-4.3)	8	4.8(2.3-9.9)
Medium	8	0.8(0.4-1.7)	7	0.7(0.3-1.5)
High	6	1.0(0.4-2.3)	7	0.9(0.4-2.0)
		P trend=0.91		P trend=0.73
Pendimethalin				
None	63	1.0 (ref)	63	1.0(ref)
Low	22	1.3(0.8-2.0)	19	1.5(0.9-2.5)
Medium	17	1.3(0.8-2.3)	19	1.0(0.6-1.7)
High	17	1.1(0.6-1.9)	18	1.3(0.8-2.2)
		P trend=0.68		Ptrend=0.43
Permethrin (Crop)				
None	179	1.0 (ref)	179	1.0 (ref)
Low	12	1.0(0.6-1.9)	9	1.4(0.7-2.7)

Medium	6	2.2(1.0-5.1)	9	1.2(0.6-2.4)
High	8	0.6(0.3-1.2)	8	0.6(0.3-1.2)
		P trend=0.18		P trend=0.15
Trifluralin (dinitroaniline-herbicide)				
None	104	1.0 (ref)	104	1.0 (ref)
Low	39	1.0 (0.7-1.5)	37	1.0(0.7-1.4)
Medium	40	1.0(0.7-1.4)	36	1.0(0.7-1.4)
High	29	0.8(0.6-1.3)	34	0.9(0.6-1.3)
		P trend=0.0.36		P trend=0.44
2,4,5 T (phenoxyacetic acid)				
None	73	1.0 (ref)	73	1.0 (ref)
low	22	1.9(1.2-3.1)	13	2.0(1.1-3.6)
medium	3	1.3(0.4-4.3)	12	1.8(0.99-3.4)
high	12	1.5(0.8-4.3)	12	1.4(0.7-2.5)
		P for trend=0.0.27		P for trend=0.94

Carbofuran								
None	1.0(ref)	67	1.0(ref)	58	1.0(ref)	33	1.0(ref)	19
Low	1.4 (0.8-2.5)	15	0.9 (0.4-1.9)	8	0.96(0.4-2.5)	5	1.0(04-2.7)	5
Medium	1.2 (0.6-2.4)	10	0.9 (0.4-1.8)	9	1.6(0.7-3.9)	6	1.4(0.2-10.7)	1
High	1.3 (0.7-2.4)	12	1.1 (0.5-2.9)	5	0.6(0.2-2.0)	3	0.94(0.2-4.1)	2
	P trend=0.36		P trend=0.81		P trend=0.79		P trend=0.99	
Chlorpyrifos								
None	1.0 (ref)	69	1.0 (ref)	55	1.0 (ref)	26	1.0 (ref)	18
Low	0.9(0.5-1.7)	15	1.2(0.6-2.1)	13	1.4(0.7-3.1)	10	0.9(0.3-2.6)	5
Medium	1.1(0.7-2.0)	16	1.0(0.5-1.7)	15	1.2(0.5-2.9)	7	4.2(1.7-10.6)	6
High	1.0(0.5-1.7)	14	0.9(0.6-4.0)	7	1.4(0.6-3.4)	6	0.8(0.3-2.3)	4
	P trend=0.99		P trend=0.66		P trend=0.56		P trend=0.97	
Diazinon								
None	1.0 (ref)	40	1.0 (ref)	33	1.0 (ref)	13	1.0 (ref)	12
Low	1.5(0.7-3.1)	9	1.2(0.4-3.1)	5	1.6(0.4-5.5)	3	xxx	2
Medium	1.2(0.4-3.6)	5	0.9(0.3-2.8)	4	1.6(0.4-7.4)	3	xxx-	1
High	1.2(0.5-3.0)	5	1.2(0.4-3.8)	3	2.0(0.4-10.0)	2	xxx	0
	P trend=0.72		P trend=0.84		P trend=0.35		P trend=xxx	
Permethrin animals								
None	1.0 (ref)	95	1.0 (ref)	78	1.0 (ref)	38	1.0 (ref)	25
Low	1.3(0.5-3.3)	5	Xxx	1	2.8(1.1-7.0)	5	xxx-	1
Medium	0.9(0.2-3.7)	3	xxx	1	2.9(0.7-12.0)	2	-xxx	2
High	0.8(0.3-2.5)	3	-xxx	0	0.8(0.2-3.5)	2	-xxx	0
	P trend=0.75		P trend=xxx		P trend=0.93		P trend=xxx	
Cyanazine								

(triazine)								
None	1.0 (ref)	65	1.0 (ref)	46	1.0 (ref)	24	1.0 (ref)	10
Low	1.2 (0.7-2.2)	15	1.4 (0.8-2.4)	16	1.9(0.9-3.8)	12	3.7(1.4-9.7)	7
Medium	0.9 (0.5-1.6)	16	0.8 (0.4-1.8)	8	1.7(0.8-3.6)	9	2.9 (1.5-7.5)	8
High	1.1(0.6-2.0)	14	1.0 (0.5-2.1)	8	0.8(0.3-2.2)	4	2.6(0.9-7.5)	5
	P trend=0.93		P trend=0.93		P trend=0.87		P trend=0.17	

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Short Communication

Evaluation of DNA damage in an Ecuadorian population exposed to glyphosate

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Abstract

We analyzed the consequences of aerial spraying with glyphosate added to a surfactant solution in the northern part of Ecuador. A total of 24 exposed and 21 unexposed control individuals were investigated using the comet assay. The results showed a higher degree of DNA damage in the exposed group (comet length = 35.5 μm) compared to the control group (comet length = 25.94 μm). These results suggest that in the formulation used during aerial spraying glyphosate had a genotoxic effect on the exposed individuals.

Key words: comet assay, DNA damage, Ecuador, genotoxicity, glyphosate.

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Glyphosate is a non-selective herbicide which is the main chemical component in many systemic herbicides used to control most annual and perennial plants. It controls weeds by inhibiting the synthesis of aromatic amino acids necessary for protein formation, which link primary and secondary metabolism in susceptible plants (Carlisle and Trevors, 1988; U.S. Forest Service, 1997).

According to some reports glyphosate shows no adverse effects on soil microorganisms, it is relatively non-toxic to fish (U.S. Forest Service, 1997) and is of relatively low toxicity to birds and mammals, including humans (Batt *et al.*, 1980; Evans and Batty, Williams *et al.*, 2000; Goldstein *et al.*, 2002). However, Lioi *et al.*, (1998) reported de induction of oxidative stress and mutagenic effects for some pesticides, including glyphosate, in bovines and Paz-y-Miño *et al.*, (2002a) reported that some pesticides were associated with genetic damage in human populations subjected to high pesticide exposure levels due intensive use, misuse or failure of control measures.

Since January 2001, the northern area of Ecuador (mainly Sucumbíos district) has been subjected to aerial spraying by the Colombian Government with Roundup-Ultra, a herbicide formulation containing glyphosate, polyethoxylated tallowamine surfactant (POEA) and the adjuvant Cosmoflux 411F which is a propriety Colombian component probably included to aid the adherence or absorption of the herbicide (Ministerio de Relaciones Exteriores, Ecuador (MREE), 2003). According to the National Narcotic Council for air spraying of illicit cultures the load of the airplane was 1137 to 1705 liters and the effective unloading with Roundup Ultra (43.9% of glyphosate) was 23.4 liters ha^{-1} equivalent to 10.3 L ha^{-1} of glyphosate (Acción Ecológica, 2003, Nivia, 2001). The main purpose of spraying glyphosate in this formulation is to eradicate illicit crops grown in this area, and several research projects have been carried out to investigate the consequences of the use of this formulation in Ecuador (MRE, Ecuador, 2003; Acción Ecológica, 2003).

The comet assay can be used to evaluate DNA damage and provides a useful tool for estimating the genetic risk from exposure to complex mixtures of chemicals (Paz-y-Miño *et al.*, 2002b), this assay having been widely applied in genotoxicity studies of factors such as X-rays and pesticides (Singh *et al.*, 1988; Tice *et al.*, 1990; Scarpato *et al.*, 1996; Slamenová *et al.*, 1999; Blasiak *et al*; 1999; Garaj-Vrhovac and Zeljezic, 2000; Paz-y-Miño *et al.*, 2002a; Paz-y-Miño *et al.*, 2002b; Acción Ecológica, 2003).

The aim of the study described in this paper was to determine the possible influence of the formulation of

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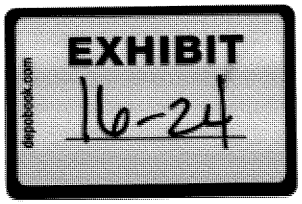

glyphosate used during aerial spraying in northern Ecuador on the genetic material of exposed individuals.

The exposed (E) group consisted of 24 randomly selected individuals (Table 1) who lived 3 km or less from an area on the border between Ecuador and Colombia where aerial spraying with a glyphosate-based herbicide had occurred continuously during three days between December 2000 and March 2001, sporadic aerial spraying continuing for three weeks following continuous spraying (MREE, 2003, Acción Ecológica 2004). Exposed group individuals manifested symptoms of toxicity after several exposures to aerial spraying, with half of the individuals in this group having received spraying directly over their houses and the other half living within 200m to 3 km from the sprayed areas.

A clinical history was completed for each of the exposed individuals and a wide-range of reactions were noted, including intestinal pain and vomiting, diarrhea, fever, heart palpitations, headaches, dizziness, numbness, insomnia, sadness, burning of eyes or skin, blurred vision, difficulty in breathing and blisters or rash (MREE, 2003; Acción Ecológica 2003).

Venous blood (5 mL) was taken from the exposed individuals between two weeks and two months after their exposure to aerial spraying and processed immediately after collection.

The blood samples analyzed in this study were provided by Dr. Adolfo Maldonado, a specialist in tropical medicine and a member of the Ecological Action foundation and part of the group of investigators of the International Commission on the Impact on Ecuadorian Territory of Aerial Fumigations in Colombia. This study was approved by the Bioethics Committee of the Pontifical Catholic University of Ecuador, according to the international guidelines. Each individual completed a personal and biomedical survey and gave their informed consent to be part of this study. In the case of the adolescents involved in the study (14-17 year-olds) their legal guardians, as well as themselves, gave their informed consent.

All of the individuals included in this study combine their activities mainly in the house and sometimes cultivating and harvesting. This persons neither used herbicides, pesticides nor similar substances in the named activities (Acción Ecológica, 2004).

Table 1 - DNA damage assessed by the comet assay in individuals exposed (E) to glyphosate and unexposed (U) control individuals. Note that the same numbers (1, 2, 3 etc.) for the individuals does not indicate that the exposed and control individuals were matched.

Exposed to glyphosate								Unexposed controls							
Individual (gender, age)[a]	Number of cells scored in each group					DNA migration (μm)		Individual (gender, age)[a]	Number of cells scored in each group					DNA migration (μm)	
	A	B	C	D	E	Mean	Median		A	B	C	D	E	Mean	Median
1E (F, 53)	2	120	76	5	3	39.5	32.5	1U (F, 17)	150	59	3	0	0	26.2	25.0
2E (F, 37)	13	92	82	14	0	44.1	32.5	2U (F, 40)	164	43	4	0	0	25.4	25.0
3E (F, 40)	2	64	62	77	4	56.6	52.5	3U (F, 26)	165	40	2	0	0	25.7	25.0
4E (M, 27)	8	75	64	47	8	49.2	37.5	4U (M, 14)	111	96	6	0	0	27.3	26.5
5E (F, 44)	9	138	63	3	0	34.6	30.0	5U (M, 32)	165	38	3	0	0	25.9	25.0
6E (F, 50)	51	113	30	3	0	30.8	27.5	6U (M, 21)	171	35	1	0	0	25.7	25.0
7E (F, 38)	21	139	48	3	0	33.2	30.0	7U (M, 16)	177	25	6	0	0	25.8	25.0
8E (F, 46)	21	116	72	4	0	35.2	30.0	8U (F, 47)	176	25	3	0	0	25.7	25.0
9E (F, 55)	26	100	84	1	0	32.8	30.0	9U (F, 15)	190	14	1	0	0	25.2	25.0
10E (F, 50)	26	100	84	1	0	34.2	30.0	10U (F, 36)	179	25	1	0	0	25.4	25.0
11E (F, 22)	28	123	60	0	0	32.0	27.5	11U (F, 21)	150	46	9	0	0	26.3	25.0
12E (F, 27)	11	130	63	6	0	33.7	30.0	12U (F, 43)	148	49	15	0	0	26.8	25.0
13E (F, 28)	40	132	40	2	0	31.0	30.0	13U (F, 53)	161	27	10	0	0	26.1	25.0
14E (F, 59)	10	96	99	1	0	36.4	32.5	14U (F, 35)	164	23	21	0	0	27.0	25.0
15E (F, 55)	35	110	62	1	0	32.7	30.0	15U (F, 38)	169	28	11	0	0	26.4	25.0
16E (F, 17)	60	101	44	1	0	31.3	37.5	16U (F, 22)	183	15	8	0	0	25.1	25.0
17E (F, 34)	7	114	57	2	0	33.4	30.0	17U (F, 71)	191	8	5	0	0	25.0	25.0
18E (F, 45)	10	150	50	4	0	33.0	30.0	18U (F, 39)	195	13	6	0	0	25.5	25.0
19E (F, 28)	13	160	44	0	0	31.1	27.5	19U (F, 21)	179	20	8	0	0	25.9	25.0
20E (F, 21)	1	153	47	3	0	33.2	30.0	20U (F, 50)	190	14	2	0	0	25.3	25.0
21E (F, 34)	2	130	25	1	0	31.8	30.0	21U (F, 43)	150	56	9	0	0	26.4	25.0
22E (F, 23)	0	29	173	2	0	39.3	37.5								
23E (F, 34)	2	88	115	1	0	35.5	37.5								
24E (F, 42)	93	103	9	0	0	27.6	27.5								
Mean age = 38 ± 12.2[b]						35.5 ± 6.4[c]	30 ± 5.4[d]	Mean age = 33 + 15 [b]						25.94 ± 0.6[c]	25 ± 0.3[d]

[a]F = female; M = male, [b,c]Mean ± standard deviation (SD), [d]Mean median value ± SD.

The unexposed (U) control group consisted of 21 unrelated healthy individuals living 80 km away from the spraying area. They were similar to the exposed group regarding their demographic characteristics and occupation but were not matched controls. Blood samples were collected and processed as for the exposed group, but not concomitantly.

None of the individuals analyzed in this study (neither the exposed group nor the control group) smoked tobacco, drank alcohol, took non-prescription drugs or had been exposed to pesticides during the course of their normal daily lives. All of the individuals included in this study mainly worked at home, sometimes cultivating and harvesting crops without the use of herbicides, pesticides or similar substances in the named activities and their windowed houses did not contain asbestos in the ceilings or roofs (Acción Ecológica, 2004).

The Comet assay is a rapid and sensitive method for the detection of DNA damage induced *in vivo* (Singh *et al.*, 1988, McKelvey-Martin *et al.*, 1993, Monroy *et al.*, 2005) or after environmental and occupational exposures (Albertini *et al.*, 1996, Leroy *et al.*, 1996).

The blood samples were assayed using the alkaline comet assay as described by Singh *et al.*, (Singh *et al.*, 1988) with the modifications implemented in our laboratory (Paz-y-Miño *et al.*, 2002). The comet assay slides were analyzed at 400x magnification using a Zeiss fluorescence microscope equipped with a calibrated ocular micrometer and a 50 W mercury lamp with and excitation filter of 515-560nm and a 590nm barrier filter.

Cells were visually allocated to classified one o five predefined categories (A-E) according to the amount of DNA in the comet's tail, tail and a rank-number of from 0 (A) to 400 (E) was assigned to quantify the damage in each cell and calculate a mean of the amount of DNA damage (Anderson *et al.*, 1994).

To measure the head-to-tail comet length randomly-selected cells from the center of the gel were measured using a calibrated scale and DNA migration was determined by measuring the nuclear DNA and the migrating DNA (Singh *et al.*, 1988).

An average of 200 cells per individual was scored and the mean and median comet length from each individual was used for statistical analysis by the Mann-Whitney U test, which was applied to determine the differences between exposed and control group in the comet assay.

We found that individuals in the group which had been exposed to spraying with the glyphosate-containing herbicide showed higher DNA migration levels than controls ($p < 0.001$), the exposed group having a mean total migration level of 35.50 µm as compared with 25.94 µm for the control group (Table 1). Comet types D and E were not observed in the control group (Table 1).

This work reports the results of the cytogenetic monitoring and DNA damage assessment of individuals exposed to aerial spraying of glyphosate in the northern part of Ecuador. A study of the genotoxicity of chemicals, such as glyphosate is important because of their possible consequences on human health and their association with cancer, as has been published in similar studies with pesticides (Paz-y-Miño *et al.*, 2002a). The Alaska Community Action on Toxics (ACAT, 1998) factshhet, other studies like Arbuckle *et al.*, (2001) and Richard *et al.*, (2005) reported that when people ingest or absorb glyphosate through their skin or bathe or drink in water contaminated with this herbicide a wide range of symptoms can occur, such as headaches or reactions which affect the eyes, skin, lungs, heart, blood cells and genitals and gonads. Ecuadorian governmental data confirms the existence of health problems associate with such symptoms in the spraying zone (MREE, 2003).

Published data showed that chromosomal damage induced by pesticides appears to be transient transient in acute or discontinuous exposure but cumulative in continuous exposure to complex agrochemical mixtures (Bolognesi, 2003).

Formulated herbicides containing glyphosate are more potent mutagens to animals and humans than pure glyphosate, most probably due to the concomitant effects of additional toxic components, such as surfactants (ACAT, 1998). The aerial spraying on the border between Ecuador and Colombia used 44% of Roundup-Ultra (see above) but the recommended application rate of this formulation in the USA is 1.6% to 7.7% up to a maximum concentration of 29% (MREE, 2003) and according to Acción Ecológica (2003) the application rate of the formulated product must not exceed 0.95 L ha^{-1}. In the area of our study the application rate was 23.4 L ha-1 (10.3 L ha^{-1} with respect to glyphosate) and therefore more than 20 times the maximum recommended application rate for the formulated product, which may explain our comet assay results (Table 1) (Acción Ecológica, 2003, Nivia, 2001).

The analysis of genes implicated in the process of DNA detoxification, would be useful to understand the genetic influence of some chemicals like glyphosate. In our study factors such us age and DNA damage were not found to be related and because most members of the exposed and control groups were female we cannot conclude anything regarding the influence of sex on the results of the comet assay. Similar results have been reported in other investigations, which report that in general terms sex and age seem to have little, if any, effect in pesticide exposed populations (Carbonell *et al.*, 1993, Steenland *et al.*, 1986).

However, we did find a higher degree of DNA damage in the exposed group compared to the control group (Table 1). The significant increase in DNA damage levels observed seem to reflect a general response to the formulation used during aerial spraying, since none of the individuals in the exposed group smoked tobacco or drank alcohol

or had been exposed to other pesticides when the samples were taken.

Our findings suggest the existence of a genotoxic risk for glyphosate exposure in the formulation used during the aerial sprayings and indicate the need for further studies on individuals exposed to glyphosate to determine its possible influence on genetic material.

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We are grateful to Dr. Adolfo Maldonado, specialized in tropical medicine, for providing us the blood samples analyzed in this study. He is member of Ecological Action Foundation and part of the group of investigators of the "International Commission of Impact over Ecuadorian territory of Aerial Fumigations in Colombia" FUNDACYT-PUCE PIC 015 Project.

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Baseline determination in social, health, and genetic areas in communities affected by glyphosate aerial spraying on the northeastern Ecuadorian border

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Abstract

The northeastern Ecuadorian border has undergone aerial spraying with an herbicide mix that contains surfactants and adjuvants, executed by the Colombian Government. The purpose of this study was to diagnose social, health, and genetic aspects of the people affected by glyphosate. For this objective to be achieved, 144 people were interviewed, and 521 medical diagnoses and 182 peripheral blood samples were obtained. Genotyping of GSTP1 Ile105Val, GPX-1 Pro198Leu, and XRCC1 Arg399Gln polymorphisms were analyzed, using PCR-RFLP technique. The assessment of chromosomal aberrations was performed, obtaining 182 karyotypes. Malnutrition in children was 3%. Of the total population, 7.7% had children with malformations, and the percentage of abortions was 12.7%. Concerning genotyping, individuals with GSTP1 Val/Val obtained an odds ratio of 4.88 ($p<0.001$), and Ile/Val individuals, together with Val/Val individuals, had an odds ratio of 2.6 ($p<0.05$). In addition, GPX-1 Leu/Leu individuals presented an odds ratio (OR) of 8.5 ($p<0.05$). Regarding karyotyping, the 182 individuals had normal karyotypes. In conclusion, the study population did not present significant chromosomal and DNA alterations. The most important social impact was fear. We recommend future prospective studies to assess the communities.

Keywords: Arg399Gln; GPX-1; GSTP1; Ile105Val; Pro198Leu; XRCC1.

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Introduction

Glyphosate (N-phosphonometyl glycine) is a nonselective, broad spectrum, postmergence organophosphorus herbicide effective in controlling annual, biennial, and perennial herb species, pastures, and broadleaf weeds (1). Glyphosate is one of the world's most widely used herbicides with 20,000 tons year used in Europe and 51,000 tons year in the USA (2, 3). The glyphosate activity is primarily due to the inhibition of 5-enolpyruvylshikimate-3-phosphate synthase, resulting in a retardation of the shikimate pathway that is involved in the synthesis of aromatic amino acids in plants and microorganisms (4, 5). The herbicide is commonly formulated with surfactants that decrease the surface tension of the solution and increase penetration into the tissues (6). Roundup® (Monsanto, St. Louis, MO, USA) is an aqueous solution of the isopropylamine salt of glyphosate with a polyethoxylated tallowamine surfactant (POEA) and the adjuvant Cosmoflux 411F (Monsanto, St. Louis, MO, USA) (7, 8).

Several research studies worldwide demonstrated that the use of glyphosate formulations develops high and low levels of toxicity in different organisms. Glyphosate can interfere with certain enzymatic functions in animals, but the symptoms of poisoning depend on the dose and exposure time. In humans, Roundup® is toxic in placental and embryonic cells and sexual steroid biosynthesis (9). This pesticide mixed with adjuvants was cytotoxic through alteration of succinate dehydrogenase and was toxic to human peripheral blood mononuclear cells (10). The results of four case-control studies suggested an association between glyphosate and the risk of non-Hodgkin's lymphoma (11–14). In amphibians, *Rana pipiens* Schreber tadpoles showed decreased snout-vent length at metamorphosis and increased time for metamorphosis to occur, tail damage, and gonadal abnormalities. Pesticide toxicity is often proposed as a contributing factor to the worldwide decline of amphibian populations (15, 16). In sea urchin eggs development, glyphosate prevents the hatching enzyme transcription synergistically and activates the DNA damage checkpoint CDK1/cycline B of the first cell cycle of development for commitment to cell death by apoptosis (9, 17, 18). In rabbits, glyphosate treatment resulted in a decline in body weight, sperm concentration, and semen osmolality (19). In isolated rat liver mitochondria, Roundup® depresses the mitochondrial complexes II, III and is able to induce a dose-dependent formation of DNA adducts in the kidney and the liver (20).

Among the research studies showing a low toxicity of glyphosate, an outstanding study conducted by Bolognesi

et al. (8) executed a cytogenetic analysis of agricultural workers from five Colombian regions; a study conducted by Sanin et al. (21) proved a non-association between glyphosate and the prolongation of pregnancy in women; and another study proved the genotoxicity of glyphosate at a low-risk level in the environment, compared with the harmful products used during cocaine production in Colombia (22).

During the period 2000–2007, the Ecuadorian northern border suffered from repeated aerial spraying with an herbicide mix composed of high doses of glyphosate, the surfactant polyethoxylated tallowamine (POEA), and the adjuvant Cosmoflux 411F. After analyses were conducted in 2004 and 2006, in which an increase in DNA damage and genetic risk was detected, biomonitoring established a baseline for social, health, genetic, and environmental areas in the Ecuadorian communities bordering Colombia, to determine what occurred at the biological level once aerial spraying with a broad spectrum herbicide was suspended two years after the last aerial spraying with a herbicide mix with glyphosate.

Experimental

Area of study

This research was carried out in the province of Sucumbíos located in the Ecuadorian Amazon basin bordering Colombia. Baseline determination in social, health, and genetic areas was performed in the following communities: Chone-2, Yanamarum, Playera Oriental, Fuerzas Unidas, Puerto Escondido, Corazon Orense, Santa Marianita, San Francisco, and Las Salinas 5 de Agosto in the province of Sucumbíos (Figure 1).

Biological samples and field data collection

Subjects (n=144) were interviewed, and 521 medical diagnoses of men (47.8%) and women (52.2%) were obtained. The origin of the population from the study area corresponds to 53.4% of those born in the Amazonian region, 46.6% come from other Ecuadorian regions, and 16.1% are Colombian immigrants; the presence of immigrants from said country has increased over the last 10 years, when aerial spraying of illegal crops in Colombia started. Psychological assessment in children from different schools belonging to the study communities consisted of

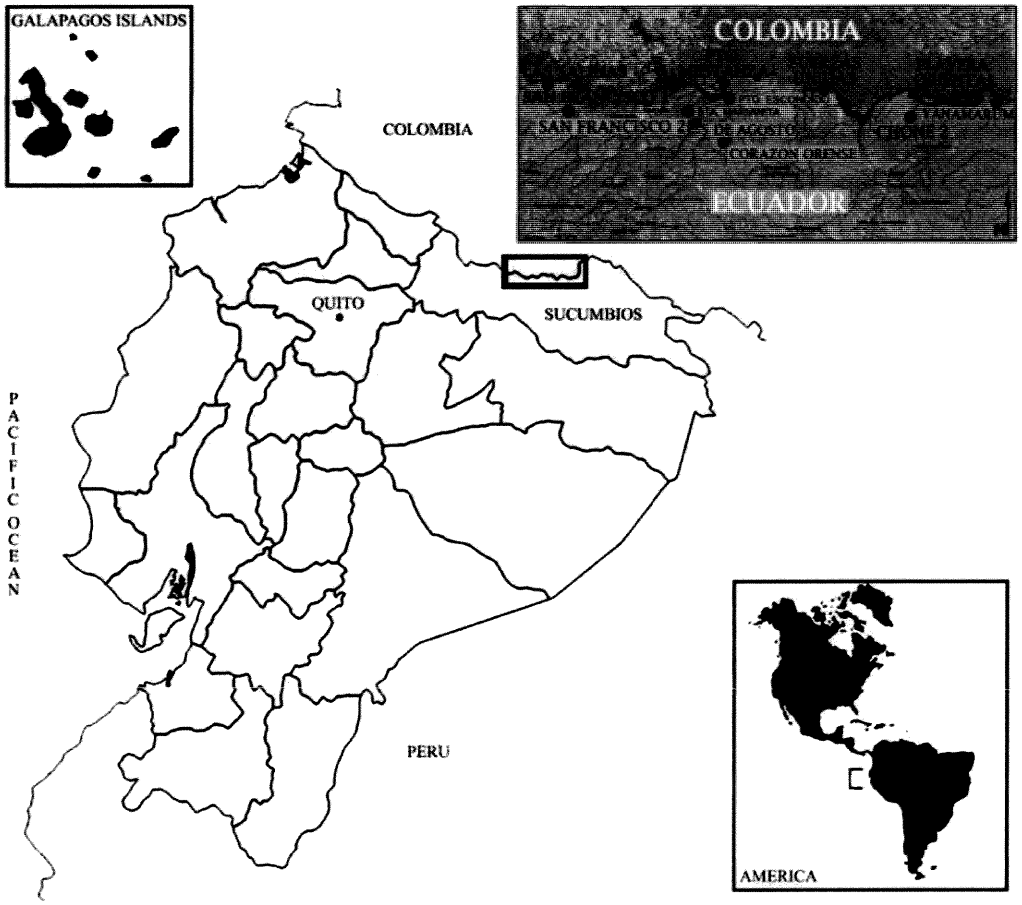

Figure 1 Studied communities in Ecuador.

the analysis of drawings made by the children, for which the following formal features were considered – transparency, contrast, proportionality, symmetry, support base, concealment, confusion, motion, rigidity, lines, presentation, chromatic expression, outline, and texture.

For the analysis of chromosomal aberrations and the study of GSTP1 (glutathione S-transferase pi 1), GPX-1 (glutathione peroxidase 1), and XRCC1 (X-ray repair cross-complementing group 1) genes, 92 peripheral blood samples in vacutainer tubes with heparin and EDTA were obtained from individuals exposed to the aerial spraying of an herbicide mix with glyphosate. The genetic study also required the analysis of 90 DNA samples from healthy individuals who belonged to several provinces of the country who did not have a background of smoking or exposure to genotoxic substances, such as hydrocarbons, X-rays, or pesticides. Each one of these study individuals signed their corresponding informed consent.

Genotyping

DNA from individuals exposed to an herbicide mix with glyphosate and that of healthy individuals, stored in the nucleic acid data bank of the Biomedical Research Institute at the Universidad de las Américas, was extracted from peripheral blood samples using PureLink™ Genomic DNA Kit (Invitrogen). The mean concentration of the DNA samples was 100 ng mL^{-1} measured in a Qubit® Fluorometer (Invitrogen). Because the affected communities had a background involving spraying with an herbicide mix with glyphosate, we proceeded to study single nucleotide polymorphisms (SNPs) in the GSTP1 (Ile105Val), GPX-1 (Pro198Leu), and XRCC1 (Arg399Gln) genes. Genotyping was performed through the polymerase chain reaction–restriction fragment length polymorphism technique (PCR-RFLP). For GSTP1, GPX-1, and XRCC1 genes amplification, a PCR final volume of 50 µL was prepared, containing 4 µL of DNA template, 34 µL H_2O Milli-Q, 0.4 µM of forward and reverse primers, 1.5 mM $MgCl_2$, 5 µL 10× buffer (200 mM Tris-HCl pH 8.4, 500 mM KCl), 0.2 µM each deoxynucleotide triphosphate (dNTPs), and 2.5 U Taq DNA polymerase (Invitrogen). For the 177 bp fragment amplification and the analysis of the Ile105Val polymorphism found in chromosome 11, codon 105, exon 5, we used the following primers: FW 5′-ACCCCAGGGCTCTATGGGAA-3′ and RV 5′-TGAGGGCACAAGAAGCCCCT-3′. Once the PCR reaction was obtained, the samples were placed in the MultiGene Thermal Cycler TC9600-G for amplification (Labnet, Edison, NJ, USA). The initial denaturation lasted 5 min at 95°C, followed by 35 cycles of 45 s at 94°C, 30 s at 62°C, 30 s at 72°C, and 1 min at 72°C. Digestion of the amplified fragment was performed during 2 h at 37°C with 5 U of the Alw26I (Promega, Madison, WI, USA) restriction enzyme. Electrophoresis analysis revealed homozygous individuals (Ile/Ile), (Val/Val) or heterozygous (Ile/Val) (23). For a 191 bp fragment amplification and the analysis of the Pro198Leu polymorphism found in chromosome 3, we used FW 5′-AAGGTGTTCCTCCCTCGTAGGT-3′ and RV 5′-CTACGCAGGTACAGCCGCCGCT-3′ primers (24, 25). In the thermal cycler, the initial denaturation step lasted 10 min at 95°C, then 35 cycles of 30 s at 56°C, 30 s at 56°C, 45 s at 72°C and 3 min at 72°C were needed. Digestion of PCR product was carried out during 2 h at 37°C with the ApaI (Promega) restriction enzyme. The PCR-RFLP test revealed homozygous individuals (Pro/Pro), (Leu/Leu) or heterozygous (Pro/Leu) (25, 26), whereas for a 242 bp fragment amplification and the analysis of the Arg399Gln polymorphism found in chromosome 19, codon 399, exon 10, the following primers FW 5′-CCCCAAGTACAGCCAGGTC-3′ and RV 5′-TGCCCCCGCTCCTCTCAGTAG-3′ were used (27). The initial denaturation step lasted 5 min at 95°C, then 35 cycles of 45 s at 94°C, 1 min at 59°C, 30 s at 72°C and 3 min at 72°C. Digestion of amplicon was performed during 2 h at 37°C with the MspI (Promega) restriction enzyme. The analysis revealed homozygote individuals (Arg/Arg), (Gln/Gln), or heterozygote individuals (Arg/Gln) (27).

Karyotyping

For the cytogenetic analysis, we used techniques that we modified in our laboratory from previously standardized protocols (28, 29). The 92 individuals belonging to the 10 communities in the study area in Ecuador's northern border area were karyotyped to assess the existence of chromosomal alterations, according to the 'An International System for Human Cytogenetic Nomenclature' (30). Peripheral blood (5 mL) in vacutainer tubes with heparin was extracted, the samples were cultured at 37°C using RPMI 1640 medium (Gibco Laboratories, Grand Island, NY, USA), complemented with 10% phytohemagglutinin, 15% fetal bovine serum, 0.5 mL L-glutamine, 1.5 mL penicillin-streptomycin, and 1.5 mL HEPES buffer for the stimulation of cell division. After 48 h, 200 µL of colcemid was placed in the culture medium to collect metaphase cells. For harvesting the cells: we used hypotonic solutions (KCl) to increase cell volume, which spreads apart the chromosomes, and methanol-acetic acid to fix them for study. The fixed cells were dropped onto slides, stained with Giemsa 8% diluted with buffer solution (KH_2PO_4 0.025 M, pH 6.8) and ready to be observed with an Olympus BX51 microscope at 100×. The CytoVision® System (Applied Imaging, Santa Clara, CA, USA) allowed us to order the chromosomes in homologous pairs to obtain the karyotyping of the individuals.

Statistical analysis

The allelic and genotypic frequencies of each single nucleotide polymorphism were calculated from the information provided by the genotypes, and the Hardy-Weinberg equilibrium was determined by using software available on the Internet (http://www.genes.org.uk/software/hardy-weinberg.shtml). All the information obtained from the individuals studied was compiled in a database, and the statistical analysis was carried out using PASW Statistical 17 for Windows (SPSS, Chicago, IL, USA). The allelic and genotypic frequencies of the GSTP1, GPX-1, and XRCC1 genes were calculated. The chi-square (χ^2) analysis was performed to determine significant differences between the presence of Ile105Val, Pro198Leu, and Arg399Gln polymorphisms and the studied population. The relative risk of dysfunction in the DNA detoxification or repair process, in the presence of the polymorphisms in individuals exposed and non-exposed to the aerial spraying with glyphosate, was determined using the odds ratio test (OR). The data were analyzed using a 2×2 contingency table.

Results

Social and health analysis

A descriptive study was conducted to determine the population baseline in the social and health areas. The health and housing general conditions in the communities studied here are not very appropriate for the environment found in the Amazon Basin. Houses are built with zinc roofs, 73.9% of the houses are barely open to the air, and 43.3% have no awning that protects them from vectors. The population consumes water that comes mainly from such natural sources as rivers, marshes, or springs (38.8%), whereas 25.2% of water comes

from rain, 21.58% from open wells, and drinking water consumption represents only 14.42%. Of the families, 38.4% have facilities for the elimination of feces, whereas 61.4% eliminate feces in the open land.

As for the global nutritional status (weight-for-age), 2 years after the last aerial spraying with pesticide (2007), we observed that the global malnutrition status of children aged between 6 and 17 years old decreased from 10.3% to 3%, and the risk of slight malnutrition diminished from 36.3% to 23.2%. The group of children under 6 years old had the largest percentage of malnutrition (14.9% in boys and 13.6% in girls); the percentage of malnutrition decreased markedly in the group of children between 6 and 11 years old (2% boys and 1.8% girls); whereas the percentage of malnutrition in the group between 12 and 17 years old increased to 3.8% in boys and 6.7% in girls. Concerning chronic malnutrition (height-for-age), we found numbers very similar to those obtained in young people between the ages of 6 and 17 years old in 2006, when the percentage of chronic malnutrition decreased from 29% to 28%. The most malnourished group is the one between the ages of 12 and 17 years old (41%), in comparison with the group of children under 6 years old (30%), and the group of children between 6 and 11 years old (22%). Regarding acute malnutrition (weight-for-height), a slight change is seen now if we compare the data obtained in 2006, in which the percentage of acute malnutrition decreased from 1.87% to 1% and the risk went down from 7.17% to 5.8%. The body mass index (BMI) in adults demonstrates that, after 2 years without aerial spraying, no malnutrition occurred in adults over 18 years old, but rather a surge in the tendency to obesity in women (29.7%) and in men (7.8%). As for family health, we observed that during the aerial spraying the percentage of abortions rose from 8.4% to 12.7%, whereas in the same period the percentage of child mortality decreased from 12% to 9.1%. The main causes of child mortality were diseases (40%), unknown reasons (17%), labor (13%), violence (9%), malaria (6%), aerial spraying with glyphosate (5%), cancer (4%), traffic accidents and congenital malformations (2%), and finally, pesticides and snakebites (1%).

Concerning the health conditions caused by aerial spraying with glyphosate, we found that in 84.7% of families, an individual fell ill during the spraying, and the symptoms were respiratory, digestive, and ophthalmological problems, cephalea, and skin conditions, whereas a little after the spraying, the latter became the most important problem. Psychological tests determined that 84.86% of the population had psychological manifestations, with fear being the most frequent reaction (51.3%). After the spraying, fear diminished and concern about the future of the crops rose (18.6%), as well as depression (16.7%).

Genotyping

Table 1 shows the Hardy-Weinberg equilibrium and the genotypic and allelic frequency of the studied polymorphisms. Table 2 shows the statistical analysis through χ^2 and OR tests. The study population was found in Hardy-Weinberg equilibrium. Regarding the GSTP1 Ile105Val polymorphism, we observed that the frequency of the Val allele was higher in exposed individuals (0.48) than in control individuals (0.28) (Table 1). The presence of the Val/Val variant was associated with a 4.88-fold risk of acquiring detoxification problems (OR=4.88, 95% CI, 2.0–11.8, $p<0.001$), whereas the combination of the Ile/Val and Val/Val alleles was associated with a 2.6-fold risk of presenting a GSTP1 gene dysfunction (OR=2.6, 95% CI, 1.4–4.8, $p<0.05$) (Table 2). As for the GPX-1 Pro198Leu polymorphism, we observed that the Leu allele had a higher frequency in exposed individuals (0.41), unlike control individuals (0.32) (Table 1). The presence of the Leu/Leu variant was associated with an 8.5-fold risk of having problems in the function of the GPX-1 gene (OR=8.5, 95% CI, 1.8–39.9, $p<0.05$) (Table 2). Concerning the XRCC1 Arg399Gln polymorphism, we observed that the frequency of the Gln allele was higher in control individuals (0.98), unlike the population exposed to glyphosate (0.54) (Table 1). None of the variables of the Arg399Gln polymorphism presented a significant OR (Table 2).

Chromosomal analysis

After analyzing the metaphases and karyotyping the 92 individuals who belonged to the different communities of the province of Sucumbios located in Ecuador's northeastern border, we observed that all the analyzed women obtained a normal karyotype (46, XX). We also observed that 33% of the 92 individuals with normal karyotype had a low percentage of chromosomal fragility (<5%), whereas 67% of the individuals did not present this feature. All the studied population came within the normal parameters considered for studies of chromosomal fragility (30) (Table 3).

Discussion

During the years 2000–2007, the communities located in the Ecuadorian northern area bordering Colombia suffered from involuntary exposure to aerial spraying with a broad spectrum herbicide mix containing high doses of glyphosate (main herbicide), as well as surfactants and adjuvants to strengthen its power. The aerial spraying with this herbicide mix is part of a program provided by the Colombian National Police (DIRAN-CNP) to eliminate cocaine production (*Erythroxyum coca*) in Colombia. Involuntary exposure to this herbicide mix with high doses of glyphosate has triggered a political, social, and economic conflict between the two countries. Therefore, the Instituto de Investigaciones Biomédicas at the Universidad de las Américas has conducted a descriptive study to determine the baseline on the aerial spraying system and its impact on the social, health, genetic, and environmental areas in the communities located along Ecuador's northeastern border, affected by the aerial spraying with an herbicide mix containing high doses of glyphosate.

The communities studied here do not have health and housing general conditions appropriate for the environment found in the Amazon basin because many lack ventilation systems, as well as protection systems against vectors. The

Table 1 Genotype distribution and allelic frequency of GSTP1 Ile105Val, GPX-1 Pro198Leu and XRCC1 Arg399Gln polymorphism.

Genes	Genotype	Genotypic frequency			Allelic frequency			HWE (χ^2)
		Case	Control	All	Case	Control	All	
GSTP1 Ile105Val	Ile/Ile	0.32	0.54	0.43	0.52	0.72	0.62	0.04^{NS}
	Ile/Val	0.40	0.36	0.38				
	Val/Val	0.28	0.10	0.19	0.48	0.28	0.38	
GPX-1 Pro198Leu	Pro/Pro	0.35	0.38	0.36	0.59	0.68	0.63	0.03^{NS}
	Pro/Leu	0.48	0.6	0.54				
	Leu/Leu	0.17	0.02	0.1	0.41	0.32	0.37	
XRCC1 Arg399Gln	Arg/Arg	0.07	0.01	0.04	0.46	0.02	0.25	0.01^{NS}
	Arg/Gln	0.79	0.01	0.41				
	Gln/Gln	0.14	0.98	0.55	0.54	0.98	0.75	

HWE, Hardy-Weinberg equilibrium of all study population; NS, no significant difference.

Table 2 Statistical analysis of case and control individuals.

Genes	Genotype	Cases (n=92) No. (%)	No. (%) of control (n=90)	OR	95% CI	p-Value
GSTP1 Ile105Val	Ile/Ile	29 (32)	49 (54)	1.0 (reference)		
	Ile/Val	37 (40)	32 (36)	1.95	1.0–3.8	0.07^{NS}
	Val/Val	26 (28)	9 (10)	4.88	2.0–11.8	<0.001[a]
	Ile/Val+Val/Val	63 (58)	41 (37)	2.6	1.4–4.8	<0.05[a]
GPX-1 Pro198Leu	Pro/Pro	32 (35)	34 (38)	1.0 (reference)		
	Pro/Leu	44 (48)	54 (60)	0.87	0.5–1.6	0.77^{NS}
	Leu/Leu	16 (17)	2 (2)	8.5	1.8–39.9	<0.05[a]
	Pro/Leu+Leu/Leu	60 (55)	56 (50)	1.14	0.6–2.1	0.79^{NS}
XRCC1 Arg399Gln	Arg/Arg	6 (7)	1 (1)	1.0 (reference)		
	Arg/Gln	73 (79)	1 (1)	12.2	0.7–219.8	0.4^{NS}
	Gln/Gln	13 (14)	88 (98)	0.03	0.003–0.2	<0.001[a]
	Arg/Gln+Gln/Gln	86 (79)	89 (80)	0.2	0.02–1.4	0.1^{NS}

[a]Significant difference. NS, no significant difference.

water consumed by the population comes mainly from natural sources, such as rivers, marshes or springs that are highly prone to be polluted by chemical substances.

Concerning nutritional status, 2 years after the last aerial spraying with an herbicide mix, we observed that the global malnutrition status of children aged between 6 and 17 years decreased from 10.3% to 3%, whereas the risk of slight malnutrition diminished from 36.3% to 23.2%. As for chronic malnutrition, we observed that this percentage decreased from 29% to 28%, and acute malnutrition diminished from 1.87% to 1%, in comparison with the studies carried out by Acción Ecológica in 2006 (31). Likewise, the body mass index in adults demonstrated no malnutrition in adults over 18 years old; yet, with a tendency to obesity in women (29.7%) and in men (7.8%). This information clearly indicates that during the aerial spraying, the population had nutritional problems due to the broad spectrum herbicides that caused harm in the agricultural products essential for the population feeding, whereas the analyses obtained 2 years after the last aerial spraying confirmed improvement in the general nutritional status of the population.

Regarding family health, we noticed that the percentage of abortions rose during the aerial spraying with an herbicide mix with glyphosate, whereas child mortality decreased. According to the data compiled in the communities bordering Colombia, 5% of child mortality was caused by health complications due to exposure to the aerial spraying with an herbicide mix. Of the interviewed families, 84.7% had an ill relative during the spraying who presented the following symptoms: respiratory, digestive, ophthalmological problems, cephalea, or skin conditions. Regarding the psychological study, one of the most important impacts developed by the aerial spraying was fear. Fear is a feeling that has lasted until now, and 7.7% of the interviewed subjects manifested their fear as nightmares, abnormal behavior, developmental disorders, and stuttering. In the psychological study consisting of drawings made by the children, the pictures reflected sensitivity, creativity, expression capability, adaptation to environmental demands, and in turn, anguish, caution, and paranoid tendencies, where the need for protection and safety was evident.

Genetic assessment consisted of the analysis of DNA damage through the presence of chromosomal aberrations or

Table 3 Chromosomal fragmentation and karyotypes.

Individuals (n=92)	62	2	14	1	2	1	7	1	1	1
Percentage	0	1	1.2	1.4	1.5	1.9	2	2.4	2.5	2.8
Karyotype	46, XX			n=92				100%		

DNA variation through the presence of polymorphisms in the GSTP1, XRCC1, and GPX-1 genes in women of different ages who present a major susceptibility to hepatic toxins due to the variety of physiological processes. In 2006, DNA damage in 24 Ecuadorian individuals exposed to the aerial spraying with an herbicide mix with glyphosate was assessed by means of the comet assay technique, which has a high use in studies with genotoxic substances, such as hydrocarbons, X-rays, and pesticides (32–34). The results showed that DNA in the exposed individuals was highly damaged (comet length=35.5 μm), in comparison with the control group (comet length=25.94 μm). Thus, the results suggest that the individuals exposed to the broadspectrum herbicide suffered a genotoxic effect (35). Two years after the last aerial spraying, none of the studied population had any type of chromosomal alteration, being their normal karyotype (46, XX), and the percentage of chromosomal fragility was within normal parameters. Regarding genetics, the GSTP1 gene encodes proteins that are believed to function in xenobiotic metabolism and play the role as regulator of apoptosis (36–38). We observed a higher frequency of the valine allele in exposed individuals (0.48) than in healthy ones (0.28). Glutathione peroxidase (GPX-1), one of the most important antioxidant enzymes in humans, is responsible for the detoxification of hydrogen peroxide and is part of the enzymatic antioxidant defense system preventing oxidative DNA damage (38). A Pro198Leu polymorphism has been associated with the risk of developing lung, breast, and bladder cancer (23, 25, 39, 40). We observed a higher frequency of the leucine allele in exposed individuals (0.41) than in healthy ones (0.32). Those individuals presenting the GSTP1 Val/Val and GPX-1 Leu/Leu variables may have a higher risk of acquiring problems in the detoxification functions as in the case of the Ecuadorian population with bladder cancer (25). The protein encoded by the XRCC1 gene is involved in the maintenance of the structural integrity of DNA in the face of damage arising from environmental abuse, as well as from normal metabolic processes (41). The Arg allele was found mainly in the population exposed to the glyphosate. The OR test determined no significant risk in the population bearing the Arg399Gln polymorphism. The genetic analyses, carried out during the aerial spraying with an herbicide mix containing glyphosate, showed that the population had suffered DNA fragmentation (35), whereas the cytogenetic assessment executed 2 years after the last aerial spraying with the same herbicide proved that the studied population had no chromosomal alterations.

Several research studies related to glyphosate exposure have been conducted in Colombia by Bolognesi et al. (8), Sanin et al. (21), and Solomon et al. (22), which state that the studied populations have low genotoxic risk associated with glyphosate. Regarding our study, we obtained results showing no chromosomal alterations in the analyzed individuals. Nevertheless, the aerial spraying had a socially and psychologically negative impact on the Ecuadorian communities. Carrying out studies in the short and long term is very important for taking control of population health and for monitoring possible disease development in the coming future.

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Biomonitoring of Genotoxic Risk in Agricultural Workers from Five Colombian Regions: Association to Occupational Exposure to Glyphosate

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In order to assess possible human effects associated with glyphosate formulations used in the Colombian aerial spray program for control of illicit crops, a cytogenetic biomonitoring study was carried out in subjects from five Colombian regions, characterized by different exposure to glyphosate and other pesticides. Women of reproductive age (137 persons 15–49 yr old) and their spouses (137 persons) were interviewed to obtain data on current health status, history, lifestyle, including past and current occupational exposure to pesticides, and factors including those known to be associated with increased frequency of micronuclei (MN). In regions where glyphosate was being sprayed, blood samples were taken prior to spraying (indicative of baseline exposure), 5 d after spraying, and 4 mo after spraying. Lymphocytes were cultured and a cytokinesis-block micronucleus cytome assay was applied to evaluate chromosomal damage and cytotoxicity. Compared with Santa Marta, where organic coffee is grown without pesticides, the baseline frequency of binucleated cells with micronuclei (BNMN) was significantly greater in subjects from the other four regions. The highest frequency of BNMN was in Boyacá, where no aerial eradication spraying of glyphosate was conducted, and in Valle del Cauca, where glyphosate was used for maturation of sugar cane. Region, gender, and older age (≥35 yr) were the only variables associated with the frequency of BNMN measured before spraying. A significant increase in frequency of BNMN between first and second sampling was observed in Nariño, Putumayo, and Valle immediately (<5 d) after spraying. In the post-spray sample, those who reported direct contact with the eradication spray showed a higher quantitative frequency of BNMN compared to those without glyphosate exposure. The increase in frequency of BNMN observed immediately after the glyphosate spraying was not consistent with the rates of application used in the regions and there was no association between self-reported direct contact with eradication sprays and frequency of BNMN. Four months after spraying, a statistically significant decrease in the mean frequency of BNMN compared with the second sampling was observed in Nariño, but not in Putumayo and Valle del Cauca. Overall, data suggest that genotoxic damage associated with glyphosate spraying for control of illicit crops as evidenced by MN test is small and appears to be transient. Evidence indicates that the genotoxic risk potentially associated with exposure to glyphosate in the areas where the herbicide is applied for coca and poppy eradication is low.

Glyphosate (*N*-phosphonomethyl glycine), a nonselective herbicide, is the active ingredient of a number of herbicide formulations and one of the most widely used pesticides on a global basis (Baylis, 2000; Woodburn, 2000; Duke & Powles, 2008). It is a postemergence herbicide, effective for the control of annual, biennial, and perennial species of grasses, sedges, and broadleaf weeds. The relatively high water solubility and the ionic nature of glyphosate retard penetration through plant hydrophobic cuticular waxes. For this reason, glyphosate is commonly formulated with surfactants that decrease the surface tension of the solution and increase penetration into the tissues of plants (World Health Organization International Program on Chemical Safety, 1994; Giesy et al., 2000).

A large number of glyphosate-based formulations are registered in more than 100 countries and are available under different brand names. One of the most commonly applied glyphosate-based products is Roundup, containing glyphosate as the active ingredient (AI) and polyethoxylated tallowamine

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(POEA) as a surfactant. Glyphosate and its formulations have been extensively investigated for potential adverse effects in humans (Williams et al., 2000). This pesticide was reported to exert a low acute toxicity to different animal species. Experimental evidence showed that glyphosate did not bioaccumulate in any animal tissues (Williams et al., 2000). Chronic feeding studies in rodents did not find evidence of carcinogenic activity or any other relevant chronic effects (U.S. EPA, 1993; World Health Organization International Program on Chemical Safety, 1994).

With in vitro studies with tissue cultures or aquatic organisms, several of the formulated products are more toxic than glyphosate AI (Giesy et al., 2000; Williams et al., 2000). Differences in the response of test organisms to the AI and the commercial formulation, e.g., Roundup, are likely due to the toxicity of different formulants and surfactants contained in commercial products. There is a general agreement that adjuvants may be more toxic for animals than glyphosate itself (Giesy et al., 2000; Williams et al., 2000; Richard et al., 2005). Cytotoxicity of the commercial formulation Roundup to human peripheral mononuclear cells was 30-fold higher (LC_{50} = 56 mg/L) than for the AI (LC_{50} = 1640 mg/L) (Martinez et al., 2007). Several in vitro and in vivo studies with parallel testing of glyphosate AI and Roundup showed that only the commercial formulation was genotoxic (Rank et al., 1993; Bolognesi et al., 1997b; Gebel et al., 1997; Grisolia 2002). Cytotoxic and genotoxic effects were observed with Roundup and other formulations of glyphosate, but not with glyphosate AI alone in comparative studies involving different experimental systems (Peluso et al., 1998; Richard et al., 2005; Dimitrov et al., 2006). The observed differences were attributed to some ingredients of Roundup, mainly surfactants, and/or to a synergic effect of glyphosate and components of the formulation (Sirisattha et al., 2004; Peixoto 2005).

Epidemiological studies generally showed no consistent or strong relationships between human exposure to glyphosate or glyphosate-containing products and health outcomes in human populations. No statistically significant association in humans was found with spontaneous abortion, fetal deaths, preterm birth, neural tube defects (Rull et al., 2006), and cancer incidence overall, although a suggested association between cumulative exposure to glyphosate and the risk of multiple myeloma was reported (De Roos et al., 2005).The epidemiologic evidence is insufficient to verify a cause–effect relationship for childhood cancer (Wigle et al., 2008). Four case-control studies suggested an association between reported glyphosate use and the risk of non-Hodgkin's lymphoma (NHL) in age groups from 20 to 70 yr (Hardell & Eriksson, 1999; McDuffie et al., 2001; Hardell et al., 2002; De Roos et al., 2003; Eriksson et al., 2008).

Glyphosate AI and Roundup were extensively tested for genotoxicity in a wide range of in vitro and in vivo systems evaluating different genetic endpoints (gene mutation, chromosome mutation, DNA damage and repair) using bacteria and mammalian somatic cells (Williams et al., 2000). The active ingredient did not induce any relevant genotoxic effects such as gene mutations in a variety of in vitro bacterial assays including the *Salmonella typhimurium* reversion assay, with and without metabolic activation (Wildeman & Nazar 1982; Moriya et al., 1983; Li & Long, 1988) and *Escherichia coli* WP-2 (Moriya et al., 1983; Li & Long, 1988). The active ingredient was also negative in the Chinese hamster ovary cell HGPRT gene mutation assay and in primary hepatocyte DNA repair assay (Li & Long, 1988). The genotoxic potential of the formulation Roundup was investigated in a number of studies evaluating various genetic endpoints in different biological systems and was (1) negative in the *S. typhimurium* reversion assay (Kier et al., 1997), (2) negative in the sex-linked recessive lethal assay with *Drosophila melanogaster* (Gopalan & Njagi, 1981), and (3) negative for in vivo micronucleus (MN) induction in mouse bone marrow (Rank et al., 1993; Kier et al., 1997; Dimitrov et al., 2006). The Roundup formulation was reported in a number of studies to exert weak genotoxic effects in short-term assays.

Differences in the response of test organisms to the active ingredient glyphosate and the commercial formulation Roundup might be due to the toxicity of different co-formulants and surfactants contained in commercial products. Several studies with parallel testing of glyphosate and Roundup showed that only the commercial formulation was genotoxic (Rank et al., 1993; Bolognesi et al., 1997b; Gebel et al., 1997; Grisolia 2002). A recent study on the genotoxic potential of glyphosate formulations found that in some cases the genotoxic effects were obtained under exposure conditions that are not relevant for humans (Heydens et al., 2008).

An in vitro study described a concentration-dependent increase of DNA single-strand breaks (SSB), evaluated by comet assay, in two different human cell lines treated with glyphosate at sublethal concentrations (Monroy et al., 2005). Roundup formulations were shown to affect the cell cycle by inhibiting the G2/M transition and DNA synthesis leading to a genomic instability (Marc et al., 2004a, 2004b). Evidence of DNA damage in peripheral lymphocytes from a small group of subjects potentially exposed to glyphosate was reported in a recent paper (Paz-y-Miño et al., 2007). The number of subjects (21 control and 24 exposed) was small and there were 23 females and only 1 male in the exposed group, making interpretation of the results difficult.

Frequency of MN in human lymphocytes has been widely used for biomonitoring exposure to pesticides (Bolognesi, 2003; Costa et al., 2006; Montero et al., 2006). The MN test, an index of chromosomal damage, is one of the most appropriate biomarkers for monitoring a cumulative exposure to genotoxic agents. Chromosomal damage, as a result of inefficient or incorrect DNA repair, is expressed during the cell

division and represents an index of accumulated genotoxic effects. The cytokinesis-block micronucleus (CBMN) methodology (Fenech & Morley, 1985) allows a distinction to be made between a mononucleated cell that did not divide and a binucleated cell that has divided once, expressing any genomic damage associated to recent exposure. The test in its comprehensive application, as was proposed by Fenech (2007) including a set of markers of gene amplification, cellular necrosis, and apoptosis, allows evaluation of genotoxic and cytotoxic effects induced by exposure to a genotoxic agent.

Colombia's anti-drugs strategy includes a number of measures ranging from aerial spraying of a mixture of a commercial formulation of glyphosate (Glyphos) and an adjuvant, Cosmo-Flux (Solomon et al., 2007b), to manual eradication, including alternative development and crop substitution programs (UNODC, 2007). In order to assess the potential genotoxic risk associated with the aerial spraying program with the glyphosate mixture, a cytogenetic biomonitoring study was carried out in subjects from five Colombian regions, characterized by different exposure to glyphosate formulations and other pesticides.

MATERIALS AND METHODS

The study was carried out in five regions of Colombia, with different potential exposure to glyphosate as reported by Sanin et al. (2009). Briefly, the characteristics of the study areas are described here:

Sierra Nevada de Santa Marta—where organic coffee is grown without use of pesticides.

Boyacá—an area of illicit crops, where manual eradication is performed and the use of pesticides and other chemical agents is common.

Putumayo and Nariño—where aerial spraying of glyphosate is performed for coca and poppy eradication. The aerial application rate for eradication of coca is 3.69 kg glyphosate a.e. (acid equivalents)/ha (Solomon et al., 2007b). In order to maximize penetration and effectiveness of the spray formulation, Glyphos is tank-mixed with an adjuvant (Cosmo-Flux® 411F; Cosmoagro, Bogotá).

Valle del Cauca—where glyphosate is applied through aerial spraying for sugar cane maturation. Roundup 747 is the most commonly used product and is applied at a rate of 1 kg a.e./ha, and has no additional adjuvant (personal communication, ASOCAÑA, the Colombian Association for Sugar Growers, December 2008).

Study Population

Two hundred and seventy-four individuals were included in the study. The objective was to sample 30 couples of reproductive age in each area and, where possible, the same couples in the study conducted by Sanin et al. (2009) were sampled. In Putumayo, Nariño, and Valle del Cauca, the population was selected based on the scheduled aerial spraying of glyphosate. This schedule was confidential and provided exclusively for the purpose of the study by the Antinarcotics Police (Putumayo and Nariño) or ASOCAÑA (Valle del Cauca). In Valle del Cauca, a sample size of 30 couples could not be achieved because spraying was not carried out in populated areas of the study region. Most spraying during the study period was carried out on sugar cane crops where no inhabitants were found. All reported areas to be sprayed in Valle del Cauca were visited to search for couples; however, only 14 could be included.

In Sierra Nevada de Santa Marta and Boyacá, the same areas investigated in a previous study (Sanin et al., 2009) were identified, although, due to the instability of the population and high migration, most couples from the previous study were not located. In all regions, the same strategy as described before (Sanin et al., 2009) was followed, visiting household by household until completing 30 couples who fulfilled the inclusion criteria, women of reproductive age (15–49 yr of age) and their spouses, who voluntarily accepted to participate in the study.

Field Data Collection

Field data collection was carried out between October 2006 and December 2007. Epidemiologists and interviewers in the five regions who participated in the Sanin et al. (2009) study were informed about the objectives of the study and trained for data collection. The Ethical Committee of Fundacion Santa Fe de Bogotá approved the study protocol and the informed consent forms used for the study. All the subjects were informed about the aims of the study. All of them gave their informed consent and volunteered to donate blood for sampling. They did not self-report illness at the time of blood sampling and interviews. Every volunteer was interviewed with a standardized questionnaire, designed to obtain relevant details about the current health status, history, and lifestyle. This included information about possible confounding factors for chromosomal damage: smoking, use of medicinal products, severe infections or viral diseases during the last 6 mo, recent vaccinations, presence of known indoor/outdoor pollutants, exposure to diagnostic x-rays, and previous radio- or chemotherapy. A simplified food frequency questionnaire that had already been used in other regions of Colombia was also applied, in order to evaluate dietary folic acid intake. Folic acid intake was characterized because of the role of folic acid deficiency in baseline genetic damage in human lymphocytes (Fenech & Rinaldi, 1994). Specific information about exposure at the time of aerial spraying in Putumayo, Nariño, and Valle del Cauca was addressed in the questionnaire.

Blood Sampling and Cell Culture

Blood samples were collected twice in Boyacá, at the beginning of the study and 1 mo after the first survey, and at 3 different times in Nariño, Putumayo, and Valle del Cauca: immediately before spraying, within 5 d after spraying, and 4 mo later. A sample of 10 ml whole blood was collected from each subject, by venipuncture, using heparinized Vacutainer tubes kept at room temperature and sent within 24 h for the establishment of the lymphocyte cultures. The samples were coded before culturing. The modified cytokinesis-blocked method of Fenech and Morley (1985) was used to determine frequency of MN in lymphocytes. Whole blood cultures were set up for cytogenetic analysis in Bogotá (Colombia) by personnel specifically trained by cytogeneticists from Environmental Carcinogenesis Unit of the National Cancer Research Institute (Genoa, Italy).

Three sterile cultures of lymphocytes were prepared. A 0.4-ml aliquot of whole blood was incubated at 37°C in duplicate in 4.6 ml RPMI 1640 (Life Technologies, Milano, Italy) supplemented with 10% fetal bovine serum (Gibco BRL, Life Technologies SrL, Milano, Italy), 1.5% phytohemoagglutinin (Murex Biotech, Dartford, UK), 100 units/ml penicillin, and 100 µg/ml streptomycin. After 44 h, cytochalasin B (Sigma, Milano, Italy) was added at a concentration of 6 µg/ml. At the end of incubation at 37°C for 72 h, cells were centrifuged (800 × g, 10 min), then treated with 5 ml of 0.075 m*M* KCl for 3 min at room temperature to lyse erythrocytes. The samples were then treated with pre-fixative (methanol:acetic acid 3:1) and centrifuged . The cellular pellets were resuspended in 1 ml methanol. At this step the samples were sent to the Environmental Carcinogenesis Unit (National Cancer Research Institute, Genoa, Italy). All the samples were centrifuged in methanol. Treatment with fixative (methanol:acetic acid, 5:1) followed by centrifugation was repeated twice for 20 min. Lymphocytes in fresh fixative were dropped onto clean iced slides, air-dried, and stained in 2% Giemsa (Sigma, Milano, Italy). MN analysis was performed blind only on lymphocytes with preserved cytoplasm. On average, 2000 cells were analyzed for each subject. Cells were scored cytologically using the cytome approach to evaluate viability status (necrosis, apoptosis), mitotic status (mononucleated, binucleated, multinucleated) and chromosomal damage or instability status (presence of micronuclei, nucleoplasmic bridges, nucleoplasmic buds) (Fenech 2007). The proliferation index (PI) was calculated as follows:

$$\begin{aligned} PI = &(\text{number of mononucleated cells} + 2 \\ &\times \text{number of binucleated cells} + 3 \\ &\times \text{number of polynucleated cells})/ \text{total number of cells.} \end{aligned}$$

Statistical Analysis

Continuous variables were characterized using mean and standard deviation, while categorical variables were expressed as proportions. Dependent variables, micronuclei per binucleated cell (BNMN), and differences in MN between sampling were square-root transformed where required to comply with the required assumptions of normal distribution and equal variances. Comparison of MN between areas was made by one-way analysis of variance (ANOVA). A significance level at 5% was used to assess differences among areas. For multiple comparisons, the Bonferroni test was applied ($\alpha = .05$). Significance of differences in frequency of BNMN between first and second, and second and third sampling were tested by the unpaired *t*-test with equal variances. Difference and 95% confidence interval were used to compare between samplings.

Bivariate analysis between dependent variables and putative risk factors was performed by one-way ANOVA, comparing exposed and nonexposed subjects. In cases where risk factor was continuous, such as age, folic acid intake, alcohol consumption, and coffee consumption, the correlation coefficient was used.

A multiple linear regression was conducted to assess association with BNMN at the first sampling with different variables: region, age (as continuous variable as well as categorical age), ethnicity as a dichotomous variable, exposure to genotoxic products as defined earlier, gender (female vs. male), and intake of folic acid (categorized in quartiles). Regression analysis was conducted with transformed variables, with square root transformation of BNMN and natural logarithm of age, to obtain a normal distribution.

RESULTS

Demographic characteristics and habits of the study groups are described in Table 1. The study population comprised 274 subjects (137 female and 137 male; average age 30.4 ± 7.8 yr). The mean age of the subjects was similar in the different regions. A large part of the studied population was mestizo, with the exception of the Nariño area consisting of individuals of African origin. In the total population, 38% of interviewees had not completed primary education. Putumayo had the largest proportion with education and Valle del Cauca the lowest as shown in Table 1. Only 10% of all subjects were smokers, (20% in Putumayo); a large majority of subjects were drinkers of beer or liquor with a consistent consumption of guarapo (traditional alcoholic beverage prepared by fermentation of maize) in Santa Marta and Boyacá. No statistically significant differences of folic acid intake were observed between different regions (the mean values ranged from 750 and 1189 µg/wk).

One hundred and nine (39.8%) of 274 participants reported current use of pesticides in their occupation or other activities. Nariño (76.6%) and Putumayo (61.7%) were the two regions where prevalence of use of genotoxic pesticides was higher; Boyacá (24.2%) and Valle del Cauca (28.6%) reported lower use. None of the study subjects in Santa Marta reported use of pesticides. No data regarding quantity of pesticide used were available. Fifty (18.3%) out of 273 who gave information

TABLE 1
Demographic Characteristics and Possible Confounding Exposures in the Study Populations

Area	Santa Marta	Boyacá	Putumayo	Nariño	Valle del Cauca
Number of subjects	60	62	60	64	28
Age (mean (SD))	27.0 (5.6)	29.1 (8.8)	31.4 (7.2)	32.5 (7.4)	33.4 (8.7)
Ethnicity (%)					
Mestizo	100	100	88.3	3.1	60.7
African			6.7	96.9	39.3
Indian			5.0		
Education (%)					
None		4.8	1.7		
Primary incomplete	26.7	38.7	53.3	42.2	21.4
Primary complete	21.7	29.0	20.0	23.4	32.1
High school incomplete	25.0	8.1	20.0	25.0	28.6
High school complete	26.7	19.4	3.3	9.4	17.9
Technical			1.7		
Occupation (%)					
Agriculture	10.0	41.9	60.0	62.5	7.1
Housewife	40.0	50.0	38.3	34.4	50.0
Other	50.0	8.1	1.7	3.1	42.9
Health insurance (%)					
Uninsured	50.0	9.7	36.7	71.9	7.1
Subsidized	38.3	83.9	60.0	18.7	50.0
Insured	11.7	6.4	3.3	9.4	42.9
Coffee consumption (cups/day)					
Mean (SD)	1.8 (2.3)	1.7 (0.8)	2.3 (4.1)	1.3 (0.4)	1.7 (1.2)
Percent of population	80.0	67.7	88.3	76.6	82.1
Smoking (%)					
Nonsmokers	91.7	95.2	80.0	87.5	92.9
Alcohol (%)					
Liquor	28.3	25.8	53.3	78.1	78.6
Beer	51.6	67.7	63.1	82.8	64.3
Guarapo	6.7	59.7	1.7	3.2	10.7
Users of illicit drugs (%)	6.7	0	5.0	7.8	0
Diet					
Folic acid intake (μg/wk)	1189	873	750	1160	812

about x-ray examination reported to having been exposed at some time; however, only 21 out of 46 who gave information on dates of x-ray reported exposure in the last 6 mo before the interview and first blood sample. Sixty-one percent of population reported viral infections, the highest prevalence in Nariño (89.5%) and the lowest in Putumayo (49.2%). However, 89.3% of viral infections were the common cold and 6.1% dengue fever. Hepatitis was reported by six interviewees without any specification of the type of the infection.

The means and standard deviations of frequency of MN and related parameters according to regions are shown in Table 2 and presented graphically in Figure 1. Compared with Santa Marta, where people grow organic coffee without the use of pesticides and which is considered as a reference area, the baseline frequency of BNMN was significantly greater in subjects from the other four regions. The highest frequency of BNMN was in Boyacá, where no aerial eradication spraying of glyphosate was carried out, and Valle del Cauca, where aerial spraying was for maturation of sugar cane. There was no significant difference between mean frequency of BNMN in Boyacá and Valle del Cauca. There was no significant difference in frequency of BNMN between Putumayo and Nariño,

TABLE 2

Mean (SD) Frequency of Binucleated Cells with Micronuclei (BNMN), Total Micronuclei (MNL) per 1000 Binucleated Peripheral Lymphocytes, Frequency of Mononucleated Cells per 1000 Lymphocytes (MNMO), and Proliferation Index (PI) by Region before the Exposure (Phase 1), 5 d after Spraying (Phase 2) and 4 mo Later (Phase 3)

Region	Santa Marta	Boyacá	Putumayo	Nariño	Valle del Cauca
Phase 1					
Number of subjects	60	62	58	63	28
BNMN	1.83 (0.97)	5.64 (1.72)	3.61 (1.51)	4.12 (1.65)	5.75 (2.48)
MNL	1.97 (1.05)	6.16 (1.91)	3.90 (1.66)	4.36 (1.85)	6.02 (2.50)
MNMO	0.41 (0.44)	0.99 (0.64)	0.47 (0.51)	0.51 (0.39)	1.12 (0.88)
PI	1.54 (0.14)	1.45 (0.14)	1.68 (0.15)	1.47 (0.12)	1.51 (0.15)
Phase 2					
Number of subjects	ND	55	53	55	27
BNMN		4.96 (2.00)	4.64 (2.45)	5.98 (2.03)	8.64 (2.81)
MNL		5.41 (2.25)	5.02 (2.95)	6.35 (2.18)	8.98 (2.93)
MNMO		0.87 (0.65)	0.44 (0.46)	0.70 (0.45)	1.65 (0.62)
PI		1.72 (0.14)	1.66 (0.20)	1.40 (0.18)	1.51 (0.14)
Phase 3					
Number of subjects	ND	ND	50	56	26
BNMN			5.61(3.08)	3.91 (1.99)	7.38 (2.41)
MNL			5.96 (3.23)	4.13 (2.20)	8.17 (2.72)
MNMO			0.82 (0.54)	0.55 (0.42)	0.98 (0.60)
PI			1.43 (0.17)	1.41 (0.14)	1.45 (0.20)

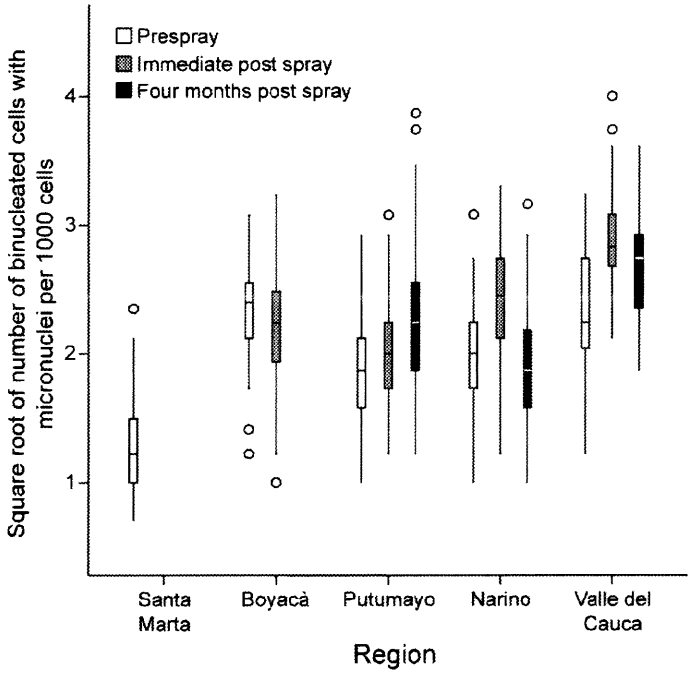

FIG. 1. Box plot of frequency of BNMN in the five study regions with samples taken prespray, 4–5 d post-spray, and 4 mo post-spray. Box plots: The center horizontal line marks the median of the sample. The length of each box shows the range within which the central 50% of the values fall, with the top and bottom of the box at the first and third quartiles. The vertical T-lines represent intervals in which 90% of the values fall. The O symbols show outliers. See text for description of statistically significant differences.

although Boyacá and Valle del Cauca showed a significantly higher frequency than Nariño and Putumayo. A higher frequency of BNMN in Boyacá was also observed in a second sampling 1 mo later.

There were differences in frequency of BNMN between sampling periods. A statistically significant difference in frequency of BNMN between first and second sampling was observed in Valle, Putumayo, and Nariño immediately (<5 d) after spraying. Four months after spraying in Nariño, there was a statistically significant decrease in the mean frequency of BNMN compared with the second sampling, but in Valle del Cauca the decrease was not significant nor was the increase observed in Putumayo significant (Figure 1 and Table 2).

The frequency of mononucleated cells with micronuclei (MOMN) was used as an index of background level of chromosomal damage accumulated in vivo (Table 2). The lowest frequency of MOMN for the first sampling was observed in Santa Marta; however, there was no marked difference in frequency of MOMN in Santa Marta, Putumayo, and Nariño and no statistically significant difference between Valle and Boyacá. However, Valle and Boyacá had a significantly higher frequency of MOMN than Putumayo, Nariño, and Santa Marta at first sampling. Immediately after spraying, Valle showed a significantly higher frequency of MOMN compared to Putumayo and Nariño, and Nariño was also higher than Putumayo. Between first and second sampling, the increase in frequency of MOMN in Nariño and Valle was statistically significant, but there was no difference in Putumayo nor in Boyacá 4 mo after the first sampling. Data suggest greater exposure to genotoxic agents in these populations is independent of the exposure to glyphosate products.

The proliferation index (PI) in all the studied groups was in the range of normal values described in the literature. No significant reduction of PI was observed in association with environmental exposures in groups of subjects from the different regions. A statistically significant correlation coefficient (0.288) between PI values from the first and the second samplings was observed, confirming the association with individual characteristics and not with any toxicity related to the exposure or to the culture techniques. Due to the low frequency observed, data with respect to other nuclear alterations, including in cytome analysis (Fenech, 2007), are not described in Table 2: the mean frequency of nucleoplasmic bridges (NPB) for all subjects was 0.010 per 1000 cells, that of nuclear buds was 0.022 per 1000 cells, and only rare necrotic and apoptotic cells were found in some samples.

Gender was the most important demographic variable affecting the BNMN index. Frequencies of BNMN in females were greater than those in males (mean 4.43 ± 2.36 vs. 3.61 ± 1.82, respectively, in total population) (Table 3). The groups of subjects were evenly matched for gender by including only couples in the study. No association was found between frequency of MN and age as a categorical variable, nor was there an association with smoking, but prevalence of smoking was low (~10% in the total population). A higher baseline frequency of MN was observed in subjects of African origin, suggesting greater susceptibility. Other lifestyle factors such as alcohol, coffee consumption, or illicit drug intake were not associated with initial measures of BNMN and MOMN.

One hundred and thirty-four of the 152 subjects in Nariño, Putumayo, and Valle reported information on contact with Glyphos and Cosmo-Flux after eradication spraying. The other 18 did not provide information in the second survey or blood samples were inadequate for testing micronuclei. Sixty-six (49.2.0%) reported no contact with the spray and 68 (50.8%) reported coming into contact with the spray because they entered sprayed fields or reported contact with the spray droplets. The mean BNMN in Nariño and Putumayo was greater in respondents who self-reported exposure, but differences were not statistically significant (Table 4). In Valle, only one respondent reported contact with glyphosate.

Region, gender, and older age (≥35 yr) were the only variables associated with the frequency of BNMN before spraying (Table 5). In fact, using Santa Martha, where no use of pesticides was reported, as reference, Boyacá, Valle del Cauca, Putumayo, and Nariño showed a statistically significant higher mean frequency of BNMN. There were also significant differences between Boyacá and Valle and Putumayo and Nariño. Females had a statistically higher mean frequency of BNMN than males after adjusting for all other variables. Greater age was also associated with greater frequency of BNMN. Neither exposure to genotoxic products, nor ethnicity, nor intake of folic acid was associated with frequency of BMMN at the first sampling. The multiple linear regression analysis of difference between second and first sampling only demonstrated statistically significant association with region after adjusting for all other variables, indicating that Putumayo, Nariño, and Valle had significantly greater differences between second and first sampling than Boyacá.

DISCUSSION

The main objective of this study was to test whether there was an association between aerial spraying of glyphosate and cytogenetic alterations, evaluated as frequency of MN in peripheral leukocytes. Biomonitoring was carried out in three regions of Colombia in populations exposed to aerial spraying of glyphosate: Putumayo and Nariño, where the application was performed for eradication of coca and poppy, and Valle del Cauca where the herbicide was used for maturation of sugar cane. Two control populations not exposed to aerial spraying of glyphosate were also selected: the first one from Sierra Nevada de Santa Marta, where organic coffee is grown without the use of any pesticides, and the other from Boyacá, with a region of illicit crops, where manual eradication is performed and subjects were potentially exposed to several pesticides but not glyphosate for aerial eradication. The ex vivo analysis of leukocytes in the presence of cytochalasin B, added 44 h after the

TABLE 3
Association of Mean (SD) Frequency of Binucleated Cells (First Sampling) with Micronuclei (BNMN/1000 Binucleated Lymphocytes) and Demographic Variables

Variable	Santa Marta	Boyacá	Putumayo	Nariño	Valle del Cauca	Total
Sex						
Females	1.98 (1.03)	6.22 (1.79)	3.91 (1.71)	4.57(1.77)	6.45 (2.82)	4.43 (2.36)
Males	1.68 (0.90)	5.06 (1.46)	3.31 (1.25)	3.66 (1.39)	5.05 (1.94)	3.61 (1.82)
p	.236	.007	.131	.028	.138	.002
Age						
18–24 yr	2.00 (1.14)	5.50 (1.96)	3.32 (1.25)	3.64 (1.72)	6.19 (2.15)	3.67 (2.16)
25–34 yr	1.66 (0.87)	5.70 (1.66)	3.53 (1.17)	4.20 (1.77)	4.20 (0.76)	3.97 (2.08)
35 yr and older	1.93 (0.67)	5.62 (1.73)	3.84 (1.86)	4.25 (1.52)	6.04 (2.84)	4.41 (2.19)
p	.438	.929	.574	.564	.313	.093
Ethnicity						
Mestizo	1.83 (0.97)	5.64 (1.72)	3.72 (1.52)	4.75 (1.06)	5.82 (2.44)	3.94(2.24)
Africa and Indian	0	0	2.86 (1.31)	4.10 (1.66)	5.64 (2.65)	4.20(1.90)
p			.162	.588	.850	.368
Smoking						
Yes	2.00 (1.06)	5.33 (0.76)	3.31 (1.00)	4.77 (1.51)	4.50 (1.41)	3.83 (1.60)
No	1.82 (0.97)	5.65 (1.76)	3.80 (1.56)	4.03 (1.66)	5.90 (2.57)	4.07 (2.20)
p	.693	.756	.395	.233	.459	.592
Folic acid intake (quartiles)						
1	1.92 (0.99)	6.11 (1.95)	3.23 (1.12)	4.50 (1.75)	5.86 (2.34)	3.89 (2.23)
2	1.64 (0.66)	5.70 (1.75)	3.47 (1.49)	3.80 (1.47)	5.86 (2.74)	3.97 (2.21)
3	1.69 (0.92)	5.69 (1.82)	4.00 (1.37)	3.85 (2.04)	6.58 (2.84)	4.47 (2.22)
4	1.94 (1.20)	4.94 (1.13)	3.69 (2.429)	4.28 (1.51)	4.63 (2.05)	3.75 (1.89)
p	.779	.399	.515	.645	.612	.220

TABLE 4
Mean Frequency of Binucleated Cells with Micronuclei (BNMN) at the Second Sampling per 1000 Binucleated Lymphocytes and Self-Reported Exposures to the Glyphosate Spray in Three Areas Where Aerial Application Had Occurred

	Nariño (*n* = 55)		Putumayo (*n* = 53)		Valle del Cauca (*n* = 26)	
Route of exposure	*n*	Mean BNMN (SD)	*n*	Mean BNMN (SD)	*n*	Mean BNMN (SD)
No exposure	28	5.81 (1.85)	13	3.84 (1.30)	25	8.56 (2.90)
Spray in air	5	7.30 (0.57)	1	5.50 (0)		
Spray on skin	8	5.62 (1.60)	15	4.90 (1.87)	1	9.50 (0)
Entered sprayed field	14	6.06 (2.77)	24	4.87 (3.18)		
p Value (ANOVA)		0.472		0.612		0.760
Any exposure	27	6.16 (2.22)	40	4.90 (2.69)	1	9.50 (0)
p Value (no exposure vs. any exposure)		0.525		0.181		0.760

Note. The data comprise respondents in the second survey from which blood samples were obtained.

TABLE 5
Multiple Linear Regression Analysis Adjusted for Region, Age, Gender, Ethnicity, and Folic Acid Intake

Variable	Coefficient	*p*	95% CI
Region			
Boyacá	3.75	≤.0001	3.19, 4.31
Putumayo	1.58	≤.0001	1.00, 2.16
Nariño	2.06	≤.0001	1.49, 2.64
Valle del Cauca	3.65	≤.0001	2.92, 4.39
Age (yr)			
25–34	0.28	.250	–0.20, 0.76
35 and older	0.75	.008	0.20, 1.31
Gender			
Females	1.00	≤.0001	0.60, 1.40

start of cultivation, made it possible to distinguish between non-dividing mononucleated cells—as an index of accumulated chromosomal damage—and binucleated cells, which had completed one nuclear division during in vitro culture and expressed MN associated with recent exposure to genotoxic agents.

The baseline level of chromosomal damage, evaluated as frequency of BNMN, was associated with the different regions considered in our study. The frequency of BNMN before spraying was also associated with region, gender, and age. Gender difference in the background incidence of MN in peripheral leukocytes, with the frequency being consistently higher in females, and a strong correlation between MN frequency and increasing age are well documented (Bonassi et al., 1995, 2001; Bolognesi et al., 1997a).

Data demonstrated no significant effect of smoking, confirming findings from the literature (Bonassi et al., 2003) although prevalence of smoking in our study population was small (7–20%, Table 1). No association with alcohol consumption was observed. A higher susceptibility of people of African origin compared to the mestizo group was suggested by a greater baseline frequency of BNMN and increased frequency at the second sampling period.

There was some indication of an association between BNMN and exposure to pesticides in general. The lowest frequency of BNMN was observed in Sierra Nevada de Santa Marta, where people self-reported that they did not use pesticides. The mean frequency of BNMN in this group of subjects (1.83 ± 0.97) was similar to that observed in healthy unexposed subjects for the same range of age (Bolognesi et al., personal communication). The higher mean frequency of BNMN observed in Boyacá and Valle del Cauca (5.64 ± 1.72 and 5.75 ± 2.48, respectively) and that in Nariño and Putumayo (4.12 ± 1.65 and 3.65 ± 1.51, respectively), compared to Santa Marta, are in agreement with similar biomonitoring studies carried out in subjects exposed to pesticides using the MN test or other genetic endpoints (Bolognesi, 2003; Bull et al., 2006).

There was no clear relationship between BNMN and the reported use of pesticides classified as genotoxic. Participants in Boyacá and Valle del Cauca showed higher frequency of BNMN than those in Putumayo and Nariño. However, a greater proportion of participants in the latter regions self-reported the use genotoxic pesticides (76.6% in Nariño and 61.7% in Putumayo). There is no information available on other relevant factors such as frequency of use, rate applied, time of exposure, and protective measures used, and we could therefore not characterize exposures to explain the differences. There were further inconsistencies; for example, in Boyacá, where more frequent use of pesticides was expected, only 24.2% of participants self-reported use, compared with the greater values in Nariño and Putumayo. However, it is possible that in areas such as Boyacá, individuals might be potentially exposed to persistent pesticides applied in the past and still present in the environment.

There was no evidence of an association between BNMN and folic acid deficiency. An assessment of folic acid intake from the semiquantitative food frequency questionnaire showed that, according to accepted recommendations (Herbert, 1987), the diet of the study populations was not deficient in folic acid and there were only small differences between regions. Consistent with these data, no association was found between MN and folic acid intake, either as a continuous variable or by quartiles.

The frequency of BNMN increased after spraying with glyphosate but not consistently. The results obtained with a second sampling, carried out immediately after the glyphosate spraying, showed a statistically significant increase in frequency of BNMN in the three regions where glyphosate was sprayed. However, this was not consistent with the rates of application use in the regions. The increase in frequency of BNMN in Valle (application rate = 1 kg a.e. glyphosate/ha) was greater than that in Nariño and Putumayo (3.69 kg a.e. glyphosate/ha).

There was no significant association between self-reported direct contact with eradication sprays and frequency of BNMN. The frequency of BNMN in participants who self-reported that they were exposed to glyphosate because they entered the field immediately after spraying (to pick the coca leaves), felt spray drops in their skin, or they thought they were exposed because they had contact with the chemical in the air, was not significantly greater than in subjects living in the same areas but who were not present during spraying. Decreases in frequency of BNMN in the recovery period after glyphosate spraying were not consistent. The third sampling, 4 mo after spraying, demonstrated a statistically significant decrease in frequency of BNMN only in Nariño.

Overall, these results suggest that genotoxic damage associated with glyphosate spraying, as evidenced by the MN test, is small and appears to be transient. The frequencies of BNMN in Nariño and Putumayo during the second and the third sampling fell within the range of values observed in Boyacá, an area

where people were exposed to a complex mixture of different pesticides (including glyphosate). A greater increase in frequency of BNMN was observed in Valle del Cauca, but it cannot be attributed only to the glyphosate exposure, because the application rate of the herbicide in this area was one-third compared with that in Nariño and Putumayo. This conclusion is further supported by the frequency of MN in mononucleated cells (MOMN), which provides an indication of the background level of chromosome/genome mutations accumulated in vivo (Manteuca et al., 2006). A statistically significant increase of MOMN was observed in Boyacá and Valle del Cauca before and after the aerial spraying, suggesting exposure to other genotoxic compounds in these populations was independent of the exposure to glyphosate. Evidence indicates that the genotoxic risk potentially associated with exposure to glyphosate in the areas where the herbicide is applied for eradication of coca and poppy is of low biological relevance. One of the strengths of our study was the detection of a transient chromosomal damage, evaluated as MN frequency in peripheral blood of the exposed subjects, since it was possible to compare the baseline before spraying with the effects detected immediately after spraying. Glyphosate persists in the environment for only a short time (half-life for biological availability in soil and sediments is hours, and 1-3 d in water; Giesy et al., 2000), is rapidly excreted by mammals and other vertebrates (Williams et al., 2000; Acquavella et al., 2004) and chronic effects, if any, would not be expected.

One of the major drawbacks of environmental epidemiology studies is the characterization of exposures to the agents being investigated. In this study two approaches were used to characterize exposures to glyphosate: ecological and self-reported. In the ecological study design, frequency of BNMN in participants was compared from regions with different patterns of pesticide use. As previously discussed (Sanin et al., 2009), this ecological design may result in misclassification of exposures (Arbuckle et al., 2004), but as an exploratory assessment of exposure it is useful (Ritter et al., 2006).

Others have attempted to improve assessment of exposure to pesticides in epidemiological studies. One study used a self-administered questionnaire for the assessment of exposure to glyphosate, which 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 times days/year); and (c) intensity-weighted cumulative exposure days (years of use times days/year times estimated intensity level) (De Roos et al., 2005). A pesticide exposure score based on self-reported work practices was recently developed to estimate annual exposure level (Firth et al., 2007). Based on an algorithm to estimate lifetime exposure to glyphosate from questionnaire information, a moderate correlation was found with concentrations of glyphosate in urine and no significant correlation with self-reported exposure (Acquavella et al., 2004).

In our study, questions related to whether there was direct contact with the spray were used but this did not consider area of skin exposed, region of skin exposed, differences in rates of penetration, or personal hygiene.

Given the situation, the best approach possible, a prospective cohort, was used but the need to use better procedures to estimate the exposure is acknowledged. Based on the applicable Bradford–Hill guidelines (Hill, 1965), it is not possible to assign causality to the increases in frequency of BNMN observed in our study. There was a smaller frequency of BNMN and MOMN in the region of no pesticide use compared with the regions where pesticides (including glyphosate) were used, which is consistent with other reports in the literature. Although temporality was satisfied in the increase in frequency of BNMN after spraying, this response did not show strength as it was not consistently correlated with the rate of application. Recovery was also inconsistent with decreases in frequency of BNMN in the areas of eradication spraying but not in the area where lower rates were applied on sugar cane.

Further studies are needed to better characterize the potential genotoxic risk associated with the application of glyphosate for sugar cane maturation. The smaller number of subjects recruited in this study and small amount of information about the exposure precluded any conclusions. Many pesticides are used in conventional agriculture in Colombia and many pesticides are used in the production of coca (Solomon et al., 2007a, 2007b); however, there is not sufficient information to correlate the frequency of MN to the pesticide exposure.

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