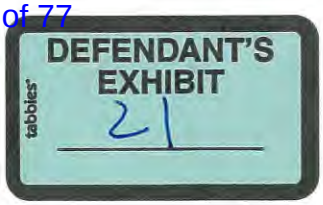


From: Alavanja, Michael (NIH/NCI) [E]
To: Sandler, Dale (NIH/NIEHS) [E]
Cc: Beane-Freeman, Laura (NIH/NCI) [E]; Hofmann, Jonathan (NIH/NCI) [E]; Lynch, Charles F.; Hines, Cynthia (CDC/NIOSH/DSHEFS); Barry, Kathryn Hughes (NIH/NCI) [F]; Barker, Joe (IMS); Buckman, Dennis (NIH/NCI) [C]; "Thomas, Kent"; Koutros, Stella (NIH/NCI) [E]; Andreotti, Gabriella (NIH/NCI) [E]; Lubin, Jay (NIH/NCI) [V]; Blair, Aaron (NIH/NCI) [V]; Hoppin, Jane (NIH/NIEHS) [V]; Alavanja, Michael (NIH/NCI) [E]
Subject: FW: A second thought about the IJC rejection of the NHL manuscript
Date: Friday, February 28, 2014 3:44:55 PM

Hi Dale,

Although initially surprised by the decision of IJC concerning our NHL paper, upon reflection I think I can understand their decision. We have been cautious in our conclusions. Our Abstract states " *However, tests of homogeneity* ***did not show significant*** *differences in exposure-response among NHL-subtypes for any chemical. These findings are* ***among*** *the first to* ***suggest*** *links between DDT, lindane, permethrin, diazinon and terbufos with NHL subtypes.* " In our conclusion we say "The epidemiologic literature on NHL and these pesticides is inconsistent and "*although the findings from this large, prospective cohort add important information,* ***additional studies that focus on NHL and its subtypes and specific pesticides are needed."*** In other words, we conclude that the paper does not present conclusive evidence. While the paper is important to science, public health, IARC and EPA, it is certainly not conclusive. I think we should take great pride in the very careful wording of our report, since it doesn't overstate the data. We have spent a great deal of time insuring that the manuscript reflects the opinion of all the authors and the federal agencies they represent. I strongly believe that It would be unethical to change the content, scope or tone of the paper merely for publication in a journal with a high impact factor.

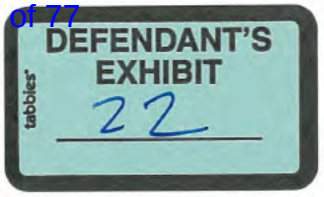
At the current time IARC is making plans for a new monograph on pesticides. Considering IARCs timetable for selecting candidate pesticide for the monograph, it would be irresponsible if we didn't seek publication of our NHL manuscript in time to influence IARCs decision. Since all authors and every federal agencies involved has signed off on the current content of the paper, we should be ready to submit very shortly and we should change the current manuscript as little as possible, if at all.

.

Your help is always appreciated, thank you,

Michael

Michael C.R. Alavanja, Dr.P.H.
Senior Investigator,
USPHS Captain (retired).
Division of Cancer Epidemiology and Genetics,
National Cancer Institute,
9609 Medical Center Drive, Rm 6E602
Rockville, Maryland 20892, USA
[redacted]



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From: "Sandler, Dale (NIH/NIEHS) [E]" [redacted]>
Date: September 16, 2016 4:59:59 PM EDT
To: [redacted]
Subject: **Re: Subpoiena Aaron Received**

These are the same AHS papers and request for all dat that came recently through a third party FOIA. Have you spoken with Laura and DEBORAH? We were hoping to make the FOIA go away by offering dat through a data sharing agreement. Now it is clearer what was behind it. The subpoena seems ridiculously broad from IARC deliberations to our data. Probably time to seek protection from NIH lawyers?

Get Outlook for iOS

On Fri, Sep 16, 2016 at 4:49 PM -0400, [redacted]" [redacted]> wrote:

Dale,

Attached is a copy of the subpoena that I received from an attorney representing Monsanto. It asks for some AHS documents.

Aaron

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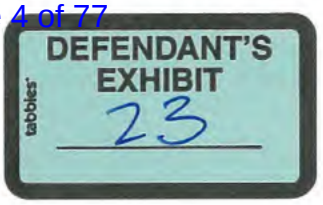
From: Stacy Rollins [redacted]
Date: March 30, 2015 11:06:58 AM EDT
To: "blairkansas@aol.com" [redacted]
Subject: **Interview- The Dr. Oz Show**

Hi Dr. Blair,



From: Kathryn Guyton
To: Blair, Aaron (NIH/NCI) [V]; Straif Kurt [redacted]; Dana Loomis; GuadinN@iarc.fr
Subject: Re: Interview with Betsy Jibben and the Farm Journal
Date: Wednesday, March 25, 2015 10:08:12 AM

Dear Aaron,

Thanks for your efforts. With regard to the WHO report, below is some background information. However I believe it may be too technical. It may be easier to say that the Working Group made an independent judgement of the data provided in WHO and other government reports. According to the IARC monograph published procedures, results in rats and mice were judged "positive" if they were statistically significant.

Hope this helps, and good luck with the further interviews. I will likely speak with the NY Times later today, but hope to save the German and South American inquiries for the German-speaking Kurt and Spanish-speaking Dana. Here's an article in Le Monde: http://www.lemonde.fr/planete/article/2015/03/25/le-desherbant-roundup-classe-cancerogene_4600906_3244.html

Best,
Kate

The WHO-JMPR report is available here:
http://whqlibdoc.who.int/publications/2006/9241665203_eng.pdf?ua=1

According to published procedures, the IARC Working Group made an independent assessment of the data provided in the WHO-JMPR report. Specifically, the Working Group determined that there was a statistically significant positive trend in the incidence of haemangiosarcoma in male mice. Based on this statistically significant finding, the Working Group reached the conclusion that this study provided positive evidence of carcinogenicity in experimental animals. This Working Group conclusion, and not the conclusion of the JMPR, is presented in the Lancet Oncology summary.

From: <Blair>, "Aaron [V] (NIH/NCI)" <[redacted]
Date: Wednesday 25 March 2015 14:54
To: Kate Guyton [redacted], "Straif Kurt [redacted] Dana Loomis [redacted], "Loukissas, Jennifer (NIH/NCI) [E]" [redacted]
Subject: Interview with Betsy Jibben and the Farm Journal

She asked several times why the IARC findings differed for other reviews. I pointed out that

new studies become available and reviews are for different purposes. She asked why the IARC evaluation was different from other parts of WHO. I was not sure what this was about, but indicated that IARC was the organized that WHO specifically tasks with developing hazard assessments.

I have one other person who wants to talk to me. Charles Benbrook at Washington State University. I will talk to him today.

Aaron

From: Kathryn Guyton [redacted]
Sent: Monday, March 23, 2015 5:40 PM
To: Blair, Aaron (NIH/NCI) [V]; Straif Kurt [redacted] Dana Loomis
Cc [redacted]
Subject: Re: Pesticide interviews

Dear Aaron,

Thanks so much for all your efforts.

With regard to the different evaluations, it is of note that a key human study on genotoxicity cited in the Lancet Oncology summary (Bolognesi et al., 2009; http://www.ncbi.nlm.nih.gov/pubmed/19672767/) is NOT cited in the German BfR draft report (http://dar.efsa.europa.eu/dar-web/provision). This is somewhat at odds with the statement "Each of the studies considered by IARC have been previously reviewed and considered by regulatory agencies – most recently by the German government on behalf of the European Union."— http://news.monsanto.com/news/monsanto-disagrees-iarc-classification-glyphosate

Keep up the good work!
Kate

From: <Blair>, "Aaron [V] (NIH/NCI)"
[redacted]
Date: Monday 23 March 2015 22:24
To: "Straif Kurt [redacted]
Dana Loomis [redacted]>>, Kate Guyton
[redacted]
Cc: [redacted]
[redacted]

Subject: FW: Pesticide interviews

Dear All,

Below is a listing of press contacts today. I have talked with everyone below except Betsy Jibben. I expect her to call me.I also talked with the German report (whose name I have forgotten) that Nicolas arranged.

Nothing special about any of the calls or questions. I made sure they understood the Working Process and how the evaluations were made. They were interested in why the IARC evaluations were different that those done earlier elsewhere. I pointed out the new information becomes available over time.

Aaron

From: Loukissas, Jennifer (NIH/NCI) [E]
Sent: Monday, March 23, 2015 4:01 PM
To: Blair, Aaron (NIH/NCI) [V]
Cc: Fisher, Victoria (NIH/NCI) [E]; Loukissas, Jennifer (NIH/NCI) [E]
Subject: Pesticide interviews

Dan Charles, NPR National Ag reporter – [redacted] 5:30 PM Deadline

Laura Dattaro VICE news video news channel/site
(http://news.vice.com)/<UrlBlockedError.aspx><UrlBlockedError.aspx>
[redacted]

Reporter: Betsy Jibben
Outlet: Farm Journal Media (will capture material for radio as well)
[redacted]

Reporter: Durrie Bouscaren, Health & Science Desk
St. Louis Public Radio | 90.7 KWMU
University of Missouri-St. Louis
[redacted]

Jennifer K. Loukissas, M.P.P.
Communication Manager
Division of Cancer Epidemiology and Genetics
National Cancer Institute
9609 Medical Center Drive, Room 7E-434
[redacted]
[redacted]
[redacted]>

Follow on Twitter @NCIEpiTraining<https://twitter.com/NCIEpiTraining>
[redacted]
Join us on LinkedIn NCI Cancer Epidemiology and Genetics<https://www.linkedin.com/groups?home=&gid=8205837&trk=anet_ug_hm>

From: Carey Gillam
To: Blair, Aaron (NIH/NCI) [V]
Subject: Re: quick question from Carey Gillam
Date: Thursday, September 29, 2016 2:36:24 PM

Thanks so much for the lovely chat. You helped me understand the situation so much better.
Bests,
Carey

On Thu, Sep 29, 2016 at 9:27 AM, Blair, Aaron (NIH/NCI) [V] <[redacted] wrote:

> You can reach me at [redacted]
>
> Aaron Blair
>
> ---
>
> **From:** Carey Gillam [redacted]
> **Sent:** Wednesday, September 21, 2016 10:51 AM
> **To:** Blair, Aaron (NIH/NCI) [V]
> **Subject:** Re: quick question from Carey Gillam
>
> Hello again. I'd like to check with you on a couple of matters. I just got off the phone with Chris Poirer who was quite helpful, so I don't need much of your time at all. Could you provide me with a number? Or call me at [redacted]
> Bests,
> Carey
>
> On Fri, Sep 16, 2016 at 3:02 PM, Blair, Aaron (NIH/NCI) [V] <[redacted] wrote:
>
> > Carey,
> >
> > I actually do not remember much of a discussion in the IARC Working Group to classify glyphosate as Group 1 rather than 2A. It might have been raised, but it is not something that stuck with me. Any documentation would be in the actual IARC Monograph.
> >
> > Regarding aftermath effects, you should know that my email and other records are under court subpoena by lawyers representing Monsanto. So your email and my response will be included in the transfer I will make in a few weeks.
> >
> > Aaron Blair
> >
> > ---
> >
> > **From:** Carey Gillam [redacted]
> > **Sent:** Friday, September 16, 2016 2:02 PM
> > **To:** Blair, Aaron (NIH/NCI) [V]
> > **Subject:** quick question from Carey Gillam

Dr. Blair -- I interviewed you a couple of times in the last year and a half regarding the IARC/Glyphosate finding, and I'm now writing a book about glyphosate and other pesticides and the assorted controversies. Someone I spoke with today said that the IARC group that you chaired actually had several members who thought glyphosate should be classified as a Group 1, rather than a Group 2A. I feel like I've heard that perhaps before, but I'm not sure if I have ever seen that confirmed anywhere. Can you tell me if it is true, and if so, if it is documented in the record anywhere that I might access? I'd like to at least mention that in the part of the book that talks about IARC's work.
Additionally, if you would consider talking with me about the aftermath, the efforts to invalidate or contradict the committee's work, for the book I would be most grateful. I could speak to you on background if you were comfortable with that, or for quotation if you be good with that. Please let me know!

--

Best regards,

Carey Gillam

[redacted]

[redacted]

www.careygillam.com

https://twitter.com/careygillam

--

Best regards,

Carey Gillam

[redacted]

www.careygillam.com

https://twitter.com/careygillam

--

Best regards,

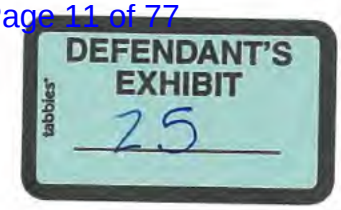
[redacted]

[redacted]

careygillamNewsNow@gmail.com

www.careygillam.com

https://twitter.com/careygillam



From: Marie-Monique Robin
To: Blair, Aaron (NIH/NCI) [V]
Subject: From Marie-Monique Robin/ On behalf of Kathleen Guyton
Date: Friday, August 19, 2016 9:50:17 PM

Dear Mr. Blair,
I'd be very thankful if you could confirm that you received my e mail from 8/8.
Best regards,
Marie-Monique Robin

---------- Forwarded message ----------
From: **Marie-Monique Robin** <[redacted]
Date: 2016-08-08 18:51 GMT+02:00
Subject: From Marie-Monique Robin/ On behalf of Kathleen Guyton
To: [redacted]

Dear Aron Blair,

I am writing to you on Dr. Guyton's behalf.
As a french filmmaker and writer, I am the author of the documentaries and books "The World according to Monsanto", "Our Daily Poison", "Crops of the Future" and "Good Old Growth", which are available in english (see below the links).
Now I am preparing a new investigation (film and book) on glyphosate for which I recently interviewed Kathleen Guyton and Kurt Straif at the IARC.
In my documentary I will include parts of the Monsanto International Tribunal, which will be held in the Hague on October 14-16. This very unique event aims to contribute to an evolution of the international law so that it includes a new criminal figure which is ecocide. Ecocide designs a crime against environment and ecosystems. According to the many studies, reports and observations made all over the world, glyphosate could be considered - this is what the judges will evaluate- as being responsible for an ecocide: it affects soils, plants, animals and humans. According to their verdict , the eminent judges who accepted to seat int he Tribunal will make recommendations to the International Criminal Court in the Hague to recognize the crime of ecocide. You can find more informations on the MIT at this link: http://www.monsanto-tribunal.org/how/
As member of the steering committee, I suggested to invite Dr. Guyton as an expert to be heart by the judges. Unfortunately Dr. Guyton didn't receive the authorization to participate from the WHO. She recommended to contact you, as the chairman of the IARC Working Group on glyphosate.
I really think it is important that you come to The Hague. Kathleen told me that you are now retired and enjoying your family somewhere in Florida. As you know, our planet and the living organisms living on it (and from it) are facing a great danger. It is hard time to find new tools to stop the destructive machine so that our chidren and grandchildren can keep living in decent conditions. The MIT will contribute to that...
Of course, all the expenses for your trip to the Hague will be paid by the MIT Foundation (flights, hotel, etc).
If you need more information, don't hesitate to ask me!

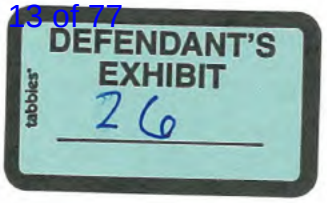
With my best regards,
Marie-Monique Robin

www.m2rfilms.com
Links:
http://www.amazon.com/World-According-Monsanto/dp/B001KWB0L0/ref=sr_1_1?ie=UTF8&qid=1440667908&sr=8-1&keywords=The+World+according+to+Monsanto+DVD
http://thenewpress.com/books/world-according-monsanto

http://icarusfilms.com/new2011/pois.html
thenewpress.com/books/our-daily-poison

http://www.harmonywithnatureun.org/index.php?page=view&type=12&nr=30&menu=195&str=&pub_year=0&language=0&librarytype=16

http://frenchculture.org/film-tv-and-new-media/events/screening-good-old-growth-and-qa-marie-monique-robin-un



From: Kurt Straif
To: Blair, Aaron (NIH/NCI) [V]; Kathryn Guyton
Cc: Dana Loomis; Nicolas Gaudin; Véronique Terrasse
Subject: RE: IARC
Date: Friday, March 25, 2016 6:04:00 AM

Aaron,

There are 2 potential issues that come to my mind, but both are based on assumptions and analogies with other criticisms, ad are not based on reading industry criticisms about you

- the issue about the "negative" AHS study "outweighing" the positive studies on NHL
- experts reviewing their own work

After the latest invitation to the European Parliament, we have posted additional material on our website (Kate's ppt from Brussels, extended Q&A responding to some criticism (including the AHS issue), see upper right hand corner "Featured News" on IARC's homepage http://www.iarc.fr/

I have also copied Kate, Dana, Nicolas and Veronique, if they are aware of any specific criticism about you.

Please keep us posted,
Kurt

-----Original Message-----
From: Blair, Aaron (NIH/NCI) [V] [redacted]
Sent: 25 March 2016 05:40
To: Kathryn Guyton <[redacted]; Straif Kurt ([redacted]
Subject: FW: IARC

Any idea what criticism he is referring to? Any advice?

Aaron

From: Andrew Martin (BLOOMBERG/ NEWSROOM:) [redacted]
Sent: Thursday, March 24, 2016 5:51 PM
To: Blair, Aaron (NIH/NCI) [V]
Subject: RE: IARC

Dr. Blair,This is Andrew Martin from Bloomberg again. I wonder if you would be willing to talk about the pesticide industry's response to the IARC report on glyphosate, in particular criticism that was specific to you. If so, is there a time and a number I can reach you? Thanks! Andrew

---

Andrew Martin
Bloomberg News
731 Lexington Ave.
New York, NY 10022
[redacted]

----- Original Message -----
From: [redacted]
To: Andrew Martin (BLOOMBERG/ NEWSROOM:)
At: Mar 8 2016 10:53:27

Andrew,

I suggest that you contact IARC directly. You should try:

Kate Guyton - [redacted]
or
Kurt Straif - [redacted]

From: Andrew Martin (BLOOMBERG/ NEWSROOM:) [redacted]
Sent: Thursday, March 03, 2016 2:09 PM
To: Blair, Aaron (NIH/NCI) [V]
Subject: IARC

Hi professor, This is Andy Martin at Bloomberg Businessweek. I wondered if you were available for a brief chat about your work for the IARC. If so, can you tell me when and where I can reach you? Thanks, Andy Martin

---

Andrew Martin
Bloomberg News
731 Lexington Ave.
New York, NY 10022
[redacted]

International Agency for Research on Cancer

World Health Organization

1 March 2016

Q&A on Glyphosate

In March 2015, IARC classified glyphosate as "probably carcinogenic to humans" (Group 2A).

This was based on "limited" evidence of cancer in humans (from real-world exposures that actually occurred) and "sufficient" evidence of cancer in experimental animals (from studies of "pure" glyphosate).

IARC also concluded that there was "strong" evidence for genotoxicity, both for "pure" glyphosate and for glyphosate formulations.

The IARC Monographs evaluation is based on the systematic assembly and review of all publicly available and pertinent studies, by independent experts, free from vested interests. It follows strict scientific criteria, and the classification system is recognized and used as a reference all around the world. This is because IARC evaluations are based on independent scientific review and rigorous criteria and procedures.

To reach these conclusions, IARC reviewed about 1000 studies. Some of the studies looked at people exposed through their jobs, such as farmers. Others were experimental studies on cancer and cancer-related effects in experimental systems.

Could the carcinogenic effects of glyphosate be related to the other chemicals in the formulations?

No. The IARC Monographs evaluation is based on the systematic assembly and review of all publicly available evidence relevant to the carcinogenicity of glyphosate. Most people's exposure to glyphosate concerns commercial formulations that include glyphosate and other ingredients. The Monograph included these studies of real-world exposures to humans. It also included experimental studies of "pure" glyphosate and of glyphosate-based formulations.

For the experimental studies of "pure" glyphosate, the Monograph concluded that the evidence for causing cancer in experimental animals was "sufficient'' and the evidence for causing genotoxicity was "strong". The real-world exposures experienced by human populations are to a variety of formulations of glyphosate with other chemicals, because this is how glyphosate is mainly sold and used. Similar results were reported in studies of different formulations used in different geographical regions at different times.

Taking all of this evidence together, the IARC Working Group classified glyphosate as "probably carcinogenic to humans" (Group 2A). Following the criteria in the Preamble to the IARC Monographs, the classification of glyphosate is based on "limited" evidence of cancer in humans (from exposures that actually occurred) and "sufficient" evidence of cancer in experimental animals (from studies of "pure" glyphosate). This classification is further supported by "strong" evidence for genotoxicity, both for "pure" glyphosate and for glyphosate formulations.

IARC, 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France - Tel: +33 (0)4 72 73 84 85 - Fax: +33 (0)4 72 73 85 75

Q&A on Glyphosate

Could the co-formulants be the cause of the genotoxic effects reported in the IARC Monograph?

With regard to genotoxicity, the IARC Working Group evaluated studies of "pure" glyphosate as well as studies of glyphosate-based formulations. The Working Group reached the same hazard conclusion for glyphosate and for its formulations: they concluded that the evidence for genotoxicity was "strong" for glyphosate and "strong" for glyphosate formulations.

Several of the epidemiological studies considered by the IARC expert Working Group showed increased cancer rates in occupational settings after exposure to glyphosate herbicides. Can this be attributed to glyphosate as a single ingredient or could it be due to other chemicals in the formulations?

Real-world exposures that people experience are to glyphosate in formulated products. Studies of humans exposed to different formulations in different regions at different times reported similar increases in the same type of cancer, non-Hodgkin lymphoma. Data on "pure" glyphosate from animal and other experimental studies, including on human cells, support the conclusion from the studies of exposed people. For the studies of "pure" glyphosate, the Monograph concluded that the evidence for cancer in experimental animals was "sufficient" and the evidence for genotoxicity was "strong".

One of the key studies evaluated in the Monograph was the United States Agricultural Health Study (AHS). This study did not find an association between non-Hodgkin lymphoma and glyphosate. Can this study alone outweigh the positive associations found in other epidemiological studies?

The Agricultural Health Study (AHS) has been described as the "most powerful" study, but this is not correct. The AHS collected data on cancer and pesticide use in more than 50 000 farmers and pesticide applicators in two states in the USA. The weakness of the study is that people were followed up for a short period of time, which means fewer cases of cancer would have had time to appear. This factor can limit the ability of a study to detect an association if one truly exists. Therefore, although the AHS is a large, well-conducted study, its results on glyphosate and non-Hodgkin lymphoma risk do not outweigh those of other studies.

The IARC Working Group also conducted an objective statistical analysis of the results of all of the available studies on glyphosate and non-Hodgkin lymphoma, which included the AHS and all of the case–control studies. The data from all of the studies combined show a statistically significant association between non-Hodgkin lymphoma and exposure to glyphosate.

In the studies IARC evaluated, were there cancers only seen in animals exposed to the toxic doses of glyphosate?

No. The IARC Working Group identified statistically significant trends of higher numbers of cancers with higher doses of "pure" glyphosate in studies of mice, suggesting increasing response with dose. Cancers were seen in the absence of toxicity.

An important consideration in the IARC Working Group's evaluation was that glyphosate caused unusual types of tumours, which are very rarely seen in untreated animals. Rare tumours can provide important evidence of a cause-and-effect relationship, but may only be seen at high doses. The IARC Working Group's evaluation of these tumours was in line with accepted principles and gave highly significant results.

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Q&A on Glyphosate

Regulatory agencies have reviewed the key studies examined by IARC – and more – and concluded that glyphosate poses no unreasonable risks to humans. What did IARC do differently?

Many regulatory agencies rely primarily on industry data from toxicological studies that are not available in the public domain. In contrast, IARC systematically assembles and evaluates all relevant evidence available in the public domain for independent scientific review.

For the IARC Monograph on glyphosate, the total volume of publications and other information sources considered by the Working Group was about 1000 citations. All citations were then screened for relevance, following the principles in the Preamble to the IARC Monographs.

After this screening process, the Monograph sections on cancer epidemiology and cancer bioassays in laboratory animals cited every included study. The sections on exposure and mechanisms of carcinogenesis consider representative studies and therefore do not necessarily cite every identified study. Once published, the IARC Monograph on glyphosate cited 269 references.

In the interests of transparency, IARC evaluations rely only on data that are in the public domain and available for independent scientific review. The IARC Working Group's evaluation of glyphosate included any industry studies that met these criteria. However, they did not include data from summary tables in online supplements to published articles, which did not provide enough detail for independent assessment. This was the case with some of the industry studies of cancer in experimental animals.

With the material reviewed by the Working Group, there was enough evidence to conclude that glyphosate is probably carcinogenic to humans.

What does IARC's classification mean in terms of the probability of developing a cancer?

The IARC Working Group's classification of glyphosate as "probably carcinogenic to humans" (Group 2A) is based on "limited" evidence of cancer in humans (from real-world exposures that actually occurred) and "sufficient" evidence of cancer in experimental animals (from studies of "pure" glyphosate). This classification is further supported by "strong" evidence for genotoxicity, both for "pure" glyphosate and for glyphosate formulations.

The IARC Monographs evaluation is a hazard classification. It indicates the strength of evidence that glyphosate can cause cancer. The probability of developing a cancer will depend on factors such as the type and extent of exposure and the strength of the effect of the agent.

IARC, 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France - Tel: +33 (0)4 72 73 84 85 - Fax: +33 (0)4 72 73 85 75

May 13, 2016 8:56 AM **To:** Henry, Natasha <[redacted]
Subject: Re: Meeting on Glyphosate, 05/16/16 at 10am

Natasha,

Thanks for the questions.

Attached is my c.v. for your information. You may share with you colleagues if you wish.

Aaron

-----Original Message----- From: Henry, Natasha <[redacted] To: blairkansas [redacted] Cc: Joseph, Lauretta [redacted]>; Fekete, Gabrielle [redacted]>; Harris, Jeffrey [redacted] Sent: Thu, May 12, 2016 4:03 pm
Subject: Meeting on Glyphosate, 05/16/16 at 10am

Good Afternoon Dr. Blair,

We are looking forward to speaking with you on **Monday, May 16 at 10 am EST.** I have attached some questions to help guide our conversation.

As a reminder, please call into the following conference line for our meeting**:**
[redacted]

Thank you so much!
Natasha

Natasha-A. Henry
Health Scientist | US EPA - Office of Inspector General
Office of Program Evaluation:
Toxics, Chemical Management, and Pollution Prevention
290 Broadway | Suite 1520 | New York, NY 10007-1866
[redacted]

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From: "Henry, Natasha" <[redacted]
Date: May 13, 2016 12:17:41 PM EDT
To: [redacted]
Subject: **RE: Meeting on Glyphosate, 05/16/16 at 10am**

Hi Aaron,

Though our conversation will most focus on glyphosate and health, I have attached our OIG team's notification memo that explains a bit more of our overall research objectives.

We are looking forward to learning from you on Monday!
Natasha

Natasha-A. Henry
Health Scientist | US EPA - Office of Inspector General
Office of Program Evaluation:
Toxics, Chemical Management, and Pollution Prevention
290 Broadway | Suite 1520 | New York, NY 10007-1866
[redacted]

From: [redacted] **Sent:** Friday, May 13, 2016 8:56 AM **To:** Henry, Natasha [redacted]
Subject: Re: Meeting on Glyphosate, 05/16/16 at 10am

Natasha,

Thanks for the questions.

Attached is my c.v. for your information. You may share with you colleagues if you wish.

Aaron

-----Original Message----- From: Henry, Natasha [redacted] To: [redacted] > Cc: Joseph, Lauretta [redacted]; Fekete, Gabrielle [redacted]; Harris, Jeffrey [redacted] Sent: Thu, May 12, 2016 4:03 pm
Subject: Meeting on Glyphosate, 05/16/16 at 10am

Good Afternoon Dr. Blair,

We are looking forward to speaking with you on **Monday, May 16 at 10 am EST.** I have attached some questions to help guide our conversation.

As a reminder, please call into the following conference line for our meeting**:**
[redacted]

Thank you so much!
Natasha

Natasha-A. Henry
Health Scientist | US EPA - Office of Inspector General
Office of Program Evaluation:
Toxics, Chemical Management, and Pollution Prevention
290 Broadway | Suite 1520 | New York, NY 10007-1866
(: [redacted]

Notification of the OIG Evaluation of Herbicide Resistance Management.pdf ¬
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From: "Henry, Natasha" [redacted]
Date: May 16, 2016 10:02:41 AM EDT
To: [redacted]>
Subject: **Available for our 10am?**

Good Morning Aaron,

Are you still able to dial into this morning's call?
Teleconference: [redacted]

If not, please let me know if you would like to reschedule.

Thank you!

Natasha-A. Henry
Health Scientist | US EPA - Office of Inspector General
Office of Program Evaluation:

Toxics, Chemical Management, and Pollution Prevention
290 Broadway | Suite 1520 | New York, NY 10007-1866
[redacted]

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From: "Henry, Natasha" [redacted]
Date: May 16, 2016 11:58:34 AM EDT
To: [redacted]
Subject: **Follow-up to today's call.**

Dr. Blair,

Please forgive my abrupt ending of our call and us running out of time. Once again, we appreciate your time and were happy to learn from you.

I had two additional questions:

1. As a follow-up to your final thoughts—do you think an interdisciplinary approach is useful for EPA pesticide review process?

2. Based on our conversation, are there any people or organizations that you would recommend we contact?

Thanks so much!
Natasha

Natasha-A. Henry
Health Scientist | US EPA - Office of Inspector General
Office of Program Evaluation:
Toxics, Chemical Management, and Pollution Prevention
290 Broadway | Suite 1520 | New York, NY 10007-1866
[redacted]

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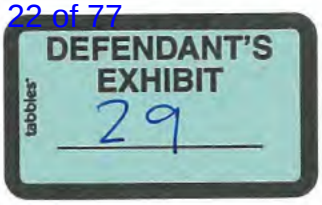


From: Kathryn Forgie
To: Blair, Aaron (NIH/NCI) [V]
Subject: Re: Pesticide Exposure and Cancer
Date: Monday, December 07, 2015 8:34:47 PM

Perfect. See you Wednesday. Kathryn

On Mon, Dec 7, 2015 at 2:56 PM, Blair, Aaron (NIH/NCI) [V] <[redacted] wrote:

> 9:30 am on Wed is fine. See you then.
>
> Aaron

From: Kathryn Forgie [redacted]
Sent: Monday, December 07, 2015 12:44 PM
To: Blair, Aaron (NIH/NCI) [V]
Subject: Re: Pesticide Exposure and Cancer

Aaron, I will be at the [redacted] at 9:30 on Wednesday. Looking forward to meeting you. Regards. Kathryn

On Friday, December 4, 2015, Blair, Aaron (NIH/NCI) [V] [redacted] wrote:

> Kathryn,
>
> I would be able to meet with you on Wednesday, Dec. 9. I would prefer to meet at my home at:
>
> [redacted]
>
> I would prefer that we meet in the morning, but actually anytime during the day would be okay, if necessary to fit your schedule.
>
> Aaron

From: Kathryn M. Forgie [redacted]
Sent: Thursday, December 03, 2015 4:00 PM
To: Blair, Aaron (NIH/NCI) [V]
Subject: Re: Pesticide Exposure and Cancer

Aaron: Thank you, I would appreciate meeting with you. Trying to finalize my arrangements, but looks like I will be in DC next week. Would it be possible to meet with you on Wednesday, the 9th for a few hours? If so, what time would work best for you, and could we meet at your office, or would you prefer to meet somewhere else? I look forward to meeting you. Best. Kathryn

Sent from my iPad

On Nov 30, 2015, at 9:14 AM, Blair, Aaron (NIH/NCI) [V] [redacted] wrote:

Kathryn,

I could meet with you during your trip to DC. I would generally be available about any day and any time. I am at the National Cancer Institute in my emeritus position on Monday and Tuesday. I usually have many meetings on those days, so Wed through Friday would be better for me.

Aaron

From: Kathryn Forgie [redacted]
Sent: Wednesday, November 18, 2015 3:44 PM
To: Blair, Aaron (NIH/NCI) [V]
Subject: Re: Pesticide Exposure and Cancer

Greetings Dr. Blair. I got deeply involved in some other matters, and never got a chance to pursue the opportunity to meet with you. I hope all has been well in the meantime. In any event, it looks like I will be in the DC area sometime in the first two weeks of December. Is there any chance that you would be available to meet with me for a few hours? I would like to discuss the epidemiology of pesticides and NHL, and the studies you have been involved with. Thank you for your time and attention in this matter, and I hope i have the opportunity to meet with you. Happy Thanksgiving. Kathryn M. Forgie [redacted]

On Thu, Aug 20, 2015 at 3:10 PM, Blair, Aaron (NIH/NCI) [V] [redacted] > wrote:

Kathryn,

Could you give me an idea of what sort of information you would like to discuss with me? Is it about studies I have been involved in, overall background about this type of work, or something else?

Aaron

From: Kathryn M. Forgie [redacted]

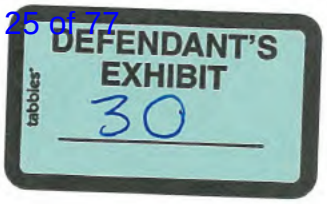
Sent: Thursday, August 20, 2015 11:14 AM
To: Blair, Aaron (NIH/NCI) [V]
Subject: Pesticide Exposure and Cancer

Dear Dr. Blair: I hope you remember me. I have spoken to you twice with regard to pesticide exposure and cancer which developed in several of my clients. (I am an attorney - spoke with you the first time with my partner Aimee Wagstaff, and the second time just the two of us).

It looks like I am going to be in the Washington DC area the week of August 31 - September 4, and I am wondering if it would be possible to meet with you in person for an hour or so to discuss your studies further. Dr. Weisenberger is also helping me with regard to these issues. He explained to me your early work with him in Nebraska, and suggested that you were the guru/leader of it all, and that I would learn a lot from meeting with you.

Please let me know if you are available to meet with me some time that week. I could probably move my schedule around to accommodate almost any time. Best regards. Kathryn [redacted]

Sent from my iPad



From: Weisenburger, Dennis
To: Blair, Aaron (NIH/NCI) [V]
Subject: FW: EPA and glyphosate
Date: Thursday, May 05, 2016 7:03:24 PM

fyi

Dennis D. Weisenburger, M.D.
Professor/Chair, Department of Pathology
City of Hope Medical Center
1500 East Duarte Road
Duarte, CA 91010
[redacted]

From: Kathryn M. Forgie [redacted]
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
> [redacted]
>
> **From:** Kathryn M. Forgie [redacted]
> **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

From: Blair, Aaron (NIH/NCI) [V]
To: Beane-Freeman, Laura (NIH/NCI) [E]
Subject: RE: Glyphosate and NHL presentation [ISEE Conference]
Date: Wednesday, August 26, 2015 10:02:10 AM

Bummer.

From: Beane-Freeman, Laura (NIH/NCI) [E]
Sent: Wednesday, August 26, 2015 9:56 AM
To: Blair, Aaron (NIH/NCI) [V]
Subject: RE: Glyphosate and NHL presentation [ISEE Conference]

I don't know for sure now that I'm going to be able to go. The Russian Embassy has my passport issuing a visa for my trip to Siberia. The guy from Fogarty is not sure that I will get it back in time to leave on Friday. I'd rather go to Brazil than to Siberia…

From: Blair, Aaron (NIH/NCI) [V]
Sent: Wednesday, August 26, 2015 9:55 AM
To: Beane-Freeman, Laura (NIH/NCI) [E]
Subject: RE: Glyphosate and NHL presentation [ISEE Conference]

You have probably been to more ISEE meetings than I have. I just suspect Monsanto has someone scanning programs of meetings like ISEE and would want to get press if they can.

From: Beane-Freeman, Laura (NIH/NCI) [E]
Sent: Wednesday, August 26, 2015 9:13 AM
To: Blair, Aaron (NIH/NCI) [V]; Zahm, Shelia (NIH/NCI) [C]
Subject: RE: Glyphosate and NHL presentation [ISEE Conference]

You probably have more experience than about the press coverage at ISEE, but my general sense was that there wasn't too much press, particularly when it's in a foreign country. But, maybe I'm wrong. Regardless, good to be prepared.

From: Blair, Aaron (NIH/NCI) [V]
Sent: Wednesday, August 26, 2015 6:57 AM
To: Zahm, Shelia (NIH/NCI) [C]; Beane-Freeman, Laura (NIH/NCI) [E]
Subject: RE: Glyphosate and NHL presentation [ISEE Conference]

I think we should wait for the next version. I just sent comments out to Manisha and all coauthors.

The abstract is on an ISEE website, right? If so, I would be there is going to be some considerable press. I think we should start getting prepared. I suggested in the email to all coauthors that Manisha not deal with the press at ISEE, but wait until back in Toronto where there is some support.

Laura perhaps you can talk to Manisha at the meeting before her presentation regarding how to handle questions after the presentation and press issues.

I think the question is going to be "Do these data indicate the IARC evaluation was wrong?" We need to be able to deal with it clearly.

I thought IARC should be alerted also.

Aaron

From: Zahm, Shelia (NIH/NCI) [C]
Sent: Tuesday, August 25, 2015 6:19 PM
To: Beane-Freeman, Laura (NIH/NCI) [E]; Blair, Aaron (NIH/NCI) [V]
Subject: RE: Glyphosate and NHL presentation [ISEE Conference]

If she revises and sends the final version, that's great. If not, I think even sending the penultimate before she presents is a good idea. I don't expect press attention in Sao Paolo, but you never know.... I can wait until next week.

From: Beane-Freeman, Laura (NIH/NCI) [E]
Sent: Tuesday, August 25, 2015 5:57 PM
To: Zahm, Shelia (NIH/NCI) [C]; Blair, Aaron (NIH/NCI) [V]
Subject: RE: Glyphosate and NHL presentation [ISEE Conference]

I'm ok philosophically with sharing, but I have a few comments/ questions back to Manisha. Do you want to wait for the final version to share? Or, more important to share in advance?

Laura

From: Zahm, Shelia (NIH/NCI) [C]
Sent: Tuesday, August 25, 2015 5:26 PM
To: Beane-Freeman, Laura (NIH/NCI) [E]; Blair, Aaron (NIH/NCI) [V]
Subject: FW: Glyphosate and NHL presentation [ISEE Conference]

Is it okay with you two if I forward this to Stephen and Bob just as an FYI?

Shelia

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], Dennis; Cantor, Kenneth (NIH/NCI) [C]; Zahm, Shelia (NIH/NCI) [C]
Cc: Harris, Shelley; Demers, Paul
Subject: Glyphosate and NHL presentation [ISEE Conference]

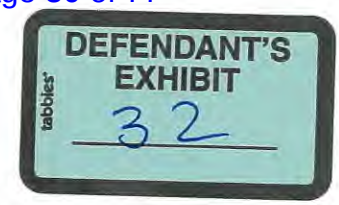
Dear all,

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

Manisha Pahwa, Research Associate
Occupational Cancer Research Centre, Cancer Care Ontario
620 University Avenue, Toronto, Ontario, M5G 2L7
[redacted]
www.occupationalcancer.ca



From: Blair, Aaron (NIH/NCI) [V]
To: Beane-Freeman, Laura (NIH/NCI) [E]; Zahm, Shelia (NIH/NCI) [C]
Subject: RE: Glyphosate and NHL presentation [ISEE Conference]
Date: Wednesday, August 26, 2015 5:03:09 PM

Sorry, I remember now. Should I do something, is it okay as is.

I think we also also to provide some suggested talking points about how these findings relate to the IARC evaluation in case Manisha gets asked questions at her presentation. Here is what I am thinking. What do you think. Once we agree, Laura can suggest this to Manisha and the rest of the group.

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.
3) Adjustment for use of 2,4-D, dicamba, and malathion reduced the ORs. Although excesses still occurred, they were no longer statistically significant.
4) 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.

From: Beane-Freeman, Laura (NIH/NCI) [E]
Sent: Wednesday, August 26, 2015 4:35 PM
To: Zahm, Shelia (NIH/NCI) [C]; Blair, Aaron (NIH/NCI) [V]
Subject: RE: Glyphosate and NHL presentation [ISEE Conference]

Ok.

From: Zahm, Shelia (NIH/NCI) [C]
Sent: Wednesday, August 26, 2015 4:34 PM
To: Beane-Freeman, Laura (NIH/NCI) [E]; Blair, Aaron (NIH/NCI) [V]
Subject: RE: Glyphosate and NHL presentation [ISEE Conference]

Manisha can send to Kurt, and Jennifer can send to her IARC press contact.

From: Beane-Freeman, Laura (NIH/NCI) [E]
Sent: Wednesday, August 26, 2015 4:33 PM
To: Blair, Aaron (NIH/NCI) [V]
Cc: Zahm, Shelia (NIH/NCI) [C]
Subject: RE: Glyphosate and NHL presentation [ISEE Conference]

I thought that we were going to do that here through Jennifer L and her contact with the IARC communications person?

From: Blair, Aaron (NIH/NCI) [V]
Sent: Wednesday, August 26, 2015 4:33 PM
To: Pahwa, Manisha; Beane-Freeman, Laura (NIH/NCI) [E]; [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]

Manisha,

Thanks. Have any of the other coauthors weighed in about notifiying IARC in advance?

I think sending them the abstract you submitted and the final slides before the ISEE meeting just for their information might be useful. They should probably go to Kurt Straif, who is head of the Monograph program.

Aaron

From: Pahwa, Manisha [redacted]
Sent: Wednesday, August 26, 2015 4:22 PM
To: Blair, Aaron (NIH/NCI) [V]; Beane-Freeman, Laura (NIH/NCI) [E]; [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 Aaron,

Yes, absolutely! I'm now revising the slides according to the comments that I have received so far from you, John S., John M., and Laura. A few others have responded but with no comments. I will send everyone a revised slide deck this evening. Hopefully, this will allow enough time to share the slides with others at NCI. If any further changes need to be made, I will address them right away and send the final slides to our co-authors prior to my presentation. Does that sound like a good plan?

To address the questions in your earlier e-mail, the abstract does not appear on the ISEE website or in the conference program. I can prepare a final version of the slides for IARC if you would like. I agree that it would be best for me to not deal with any potential press while at the conference, but I will develop "talking points" that could assist with responses to interviews that may arise following the meeting. I'll draft talking points today and disseminate to the group along with my revised slides.

Thanks to you and everyone for your rapid and helpful feedback!

Speak again soon,

Manisha

From: Blair, Aaron (NIH/NCI) [V] [redacted]
Sent: Wednesday, August 26, 2015 4:11 PM
To: Pahwa, Manisha [redacted]; Beane-Freeman, Laura (NIH/NCI) [E] [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]

Manisha,

Thanks for circulating the slides. You did a good job.

Will you be able to get a new set out for us to look at before you depart for ISEE?

Aaron

From: Pahwa, Manisha [redacted]
Sent: Tuesday, August 25, 2015 4:29 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

Manisha Pahwa, Research Associate
Occupational Cancer Research Centre, Cancer Care Ontario
620 University Avenue, Toronto, Ontario, M5G 2L7
[redacted]
www.occupationalcancer.ca

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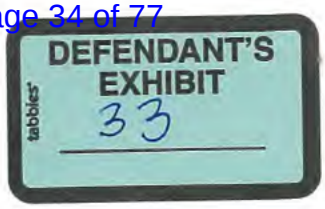

you trust.

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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 6ZHHOW: IAD-LHR 1 Mar 2015 18:30**

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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]>, "'James Dosman' [redacted], "Punam Pahwa [redacted])" [redacted]>, "Blair, Aaron (NIH/NCI) [V]" [redacted]>, [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

Occupational Cancer Research Centre

A detailed assessment of glyphosate use and the risks of non-Hodgkin lymphoma overall and by major histological sub-types: findings from the North American Pooled Project

Manisha Pahwa, Laura E. Beane Freeman, John J. Spinelli, Aaron Blair, Shelia Hoar Zahm, Kenneth P. Cantor, Punam Pahwa, James A. Dosman, John R. McLaughlin, Dennis D. Weisenburger, Paul A. Demers, Shelley A. Harris

June 10, 2016

Towards a cancer-free workplace

Glyphosate

- Broad-spectrum herbicide that is widely used in agriculture, forestry, and other settings
- Most frequently sold herbicide globally with sales >$6.5 billion in 2010
- IARC evaluation (2015): probable (group 2A) carcinogen, based on:
  - Limited evidence of NHL in humans
  - Sufficient evidence of cancer in animals
  - Mechanistic evidence of genotoxicity and oxidative stress

THE WALL STREET JOURNAL.

WORLD

EU to Propose Temporary Extension for Glyphosate Use

EU needs more time to assess whether the active ingredient in Monsanto's Roundup causes cancer

nature International weekly journal of science

NATURE | NEWS: EXPLAINER

Widely used herbicide linked to cancer

As the World Health Organization's research arm declares glyphosate a probable carcinogen, *Nature* looks at the evidence.

Daniel Cressey

24 March 2015

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SHARE

Popular herbicide doesn't cause cancer, European Union agency says

By Gretchen Vogel | Nov. 12, 2015 , 8:00 AM

Glyphosate, one of the world's most commonly used herbicides, is unlikely to increase the risk of cancer—at least in its pure form—according to **an assessment released today** by the European Food Safety Authority (EFSA) in Parma, Italy. The report will likely have a major influence on the European Union's upcoming decision whether to keep glyphosate, the active ingredient in widely used herbicides such as Roundup, on its list of approved chemical substances. Approval for the chemical expires at the end of 2015.

European Scientists Split Over Glyphosate Cancer Claims

European scientists are split on the safety of Monsanto's controversial herbicide glyphosate, which was previously linked to cancer by the World Health Organization.

By Derrick Broze - Jan 14, 2016

theguardian

Glyphosate unlikely to pose risk to humans, UN/WHO study says

Chemical used in Monsanto's Roundup weedkiller 'unlikely to pose carcinogenic risk from exposure through diet'

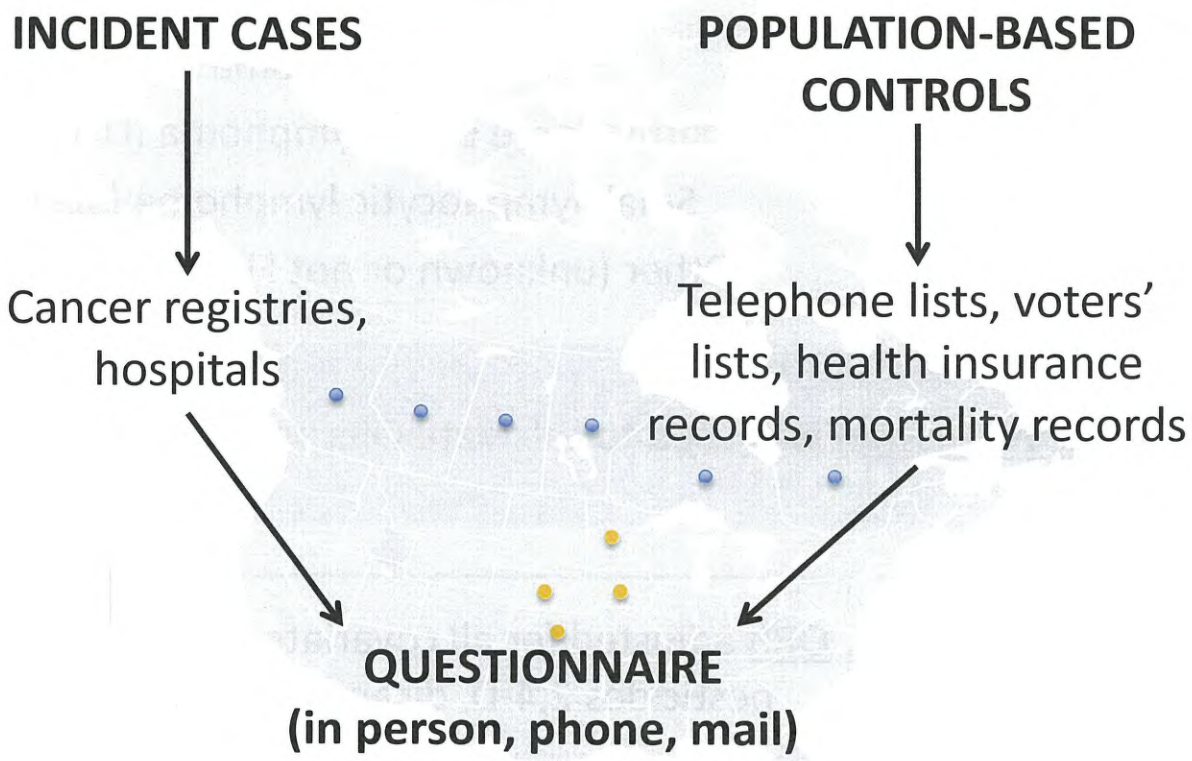
Objective and Rationale

- Most previous studies included in hazard and risk assessments of glyphosate had little power to detect significant risks, did not assess sub-types, and usually did not have quantitative exposure data

Objective

- **To evaluate the associations between different metrics of glyphosate use and the risk of non-Hodgkin lymphoma (NHL) and its sub-types using data from the North American Pooled Project (NAPP)**

North American Pooled Project



4 case-control studies

- 4 Midwestern U.S. states
- 6 Canadian provinces

Methods

Self-reported glyphosate use was categorized:

Ever/never

Duration (# years)

Frequency (# days/year)

Lifetime-days (# years * # days/year)

NHL cases were classified using ICD-O-1:

NHL overall

Follicular lymphoma (FL)

Diffuse large B-cell lymphoma (DLBCL)

Small lymphocytic lymphoma (SLL)

Other (unknown or not FL, DLBCL, SLL)

Unconditional multiple logistic regression was used to calculate ORs and 95% CIs

ORa adjusted for location, age, sex, familial lymphatic or hematopoietic cancer, proxy respondent, PPE

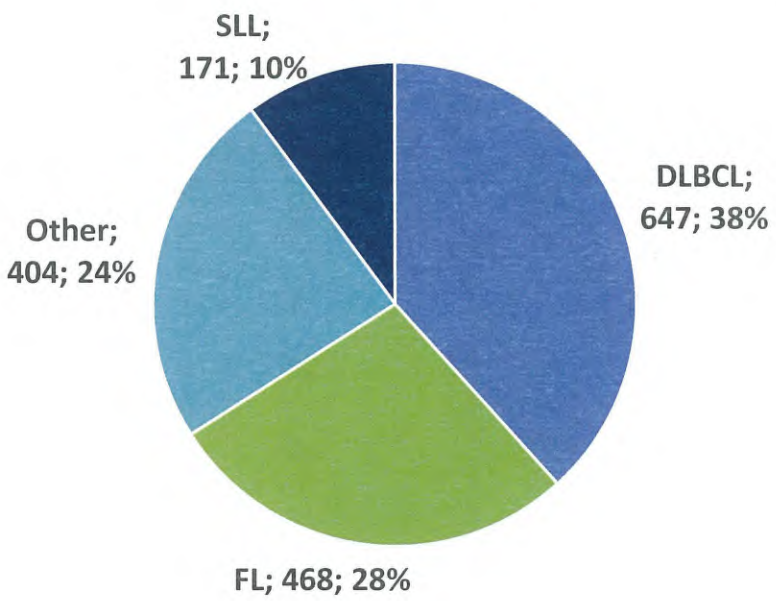
ORb adjusted for all covariates in ORa, plus the pesticides 2,4-D, dicamba, and malathion

Glyphosate Use Information

STUDY	EVER/NEVER	DURATION # Years	FREQUENCY # Days/Year	LIFETIME DAYS # Years x # Days/Year
Iowa/Minnesota	✓	✓	X	X
Kansas	✓	X	X	X
Nebraska	✓	✓	✓	✓
Canada	✓	✓	✓	✓

Selected Characteristics of NHL Cases & Controls

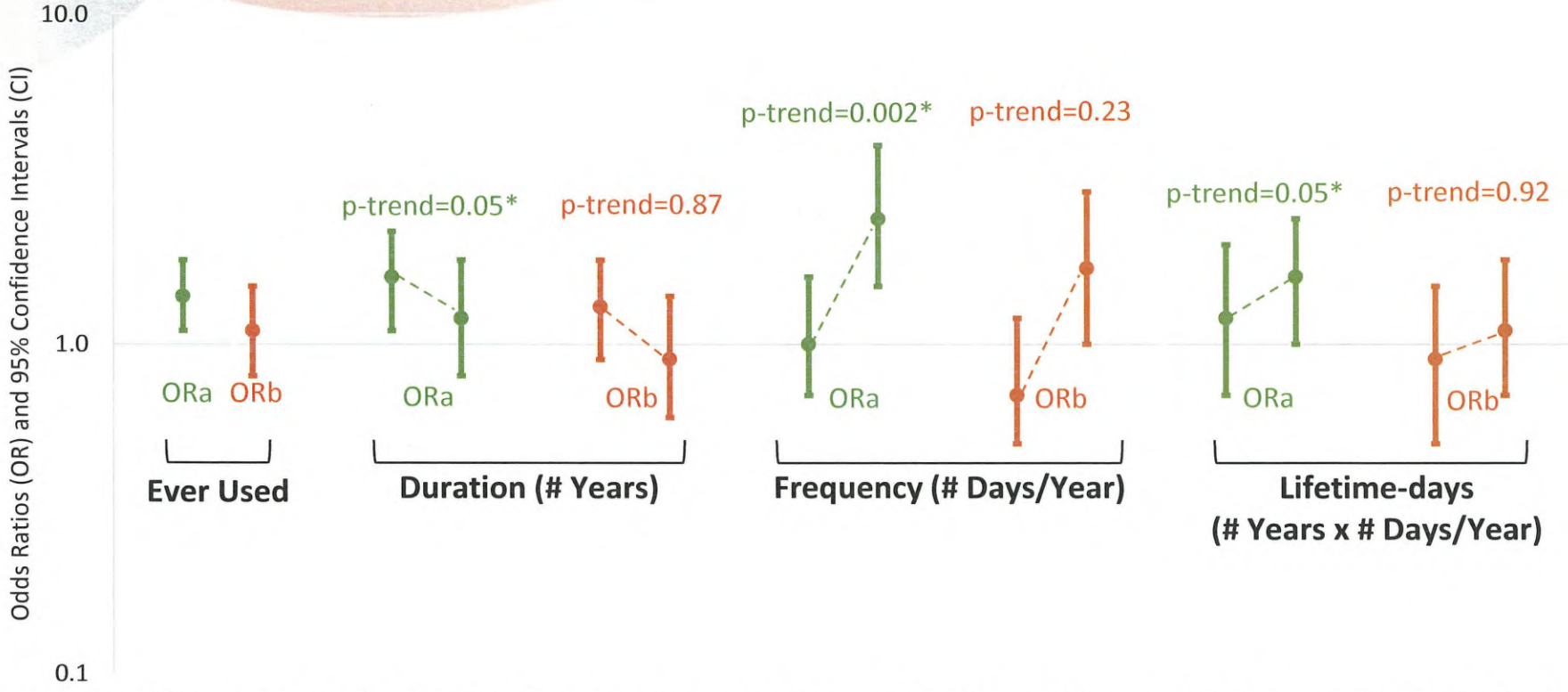
Histological sub-type



	Cases N=1690	Controls N=5131	OR* (95% CI)
Location			
U.S.	1177 (70%)	3625 (71%)	
Canada	513 (30%)	1506 (29%)	
Respondent type			
Self	1140 (68%)	3372 (66%)	1
Proxy	533 (32%)	1692 (33%)	1.0 (0.9, 1.2)
Lymphatic or hematopoietic cancer in a first-degree relative			
No	1493 (88%)	4790 (93%)	1
Yes	139 (8%)	202 (4%)	2.1 (1.7, 2.7)

*ORs adjusted for age and state/province of residence

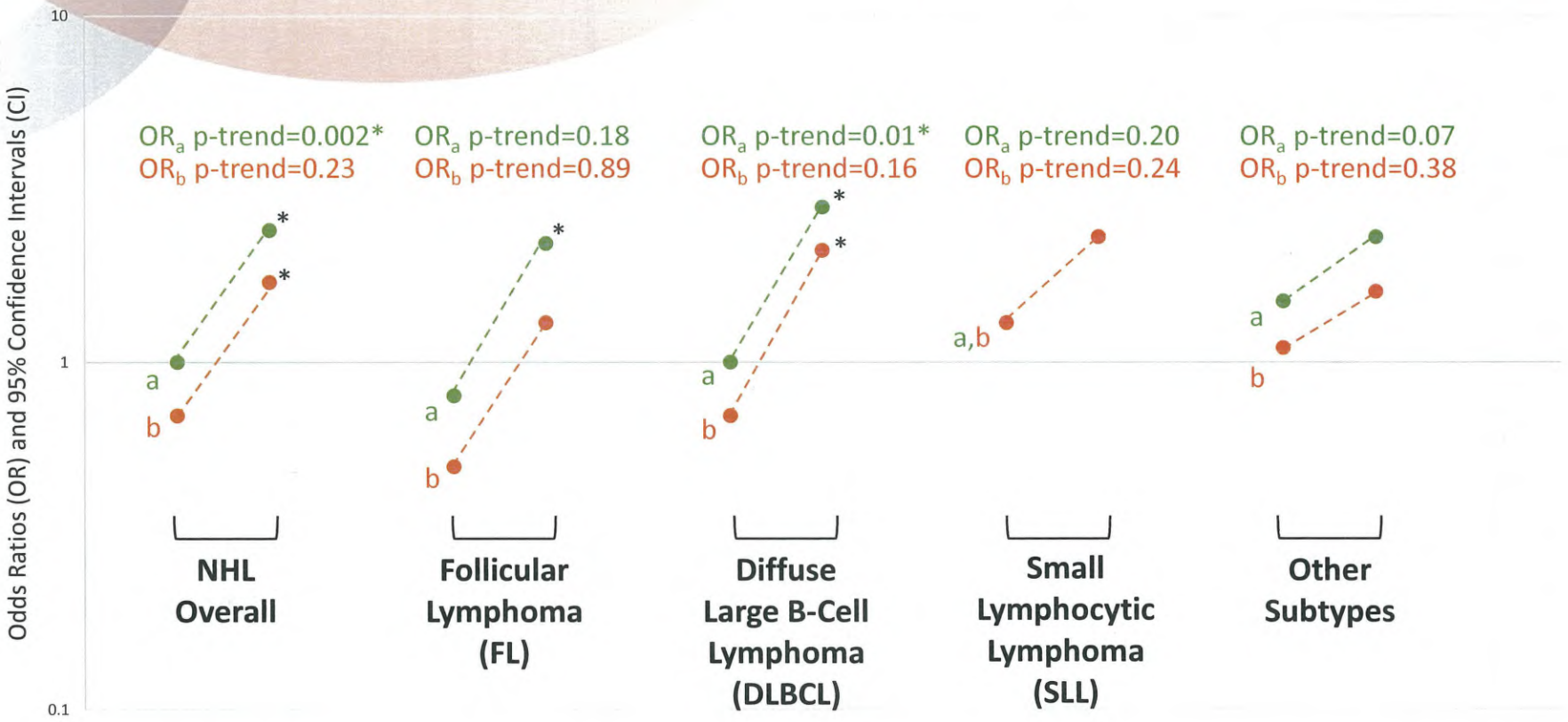
Glyphosate Uses and Risks of NHL Overall



OR_a adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, use of any PPE.

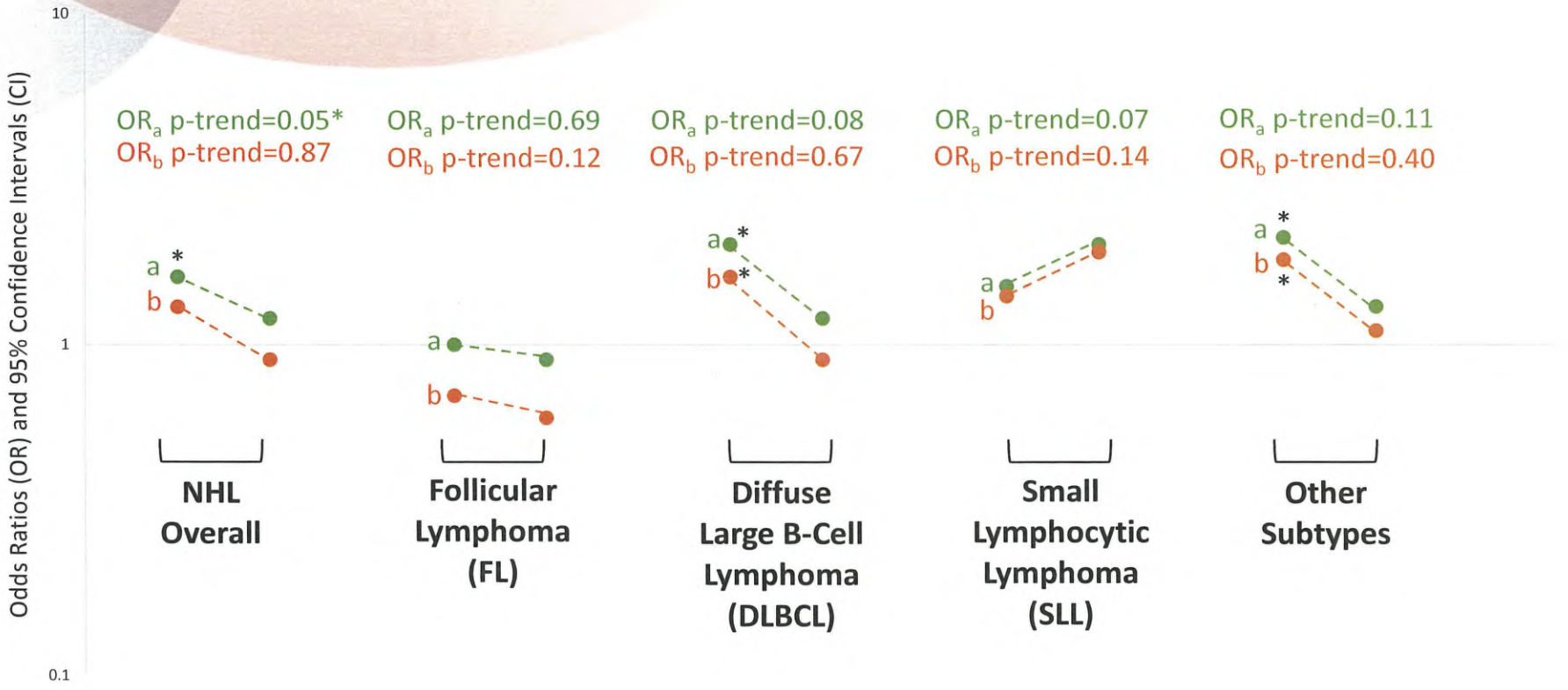
OR_b adjusted for variables in OR_a and use of 2,4-D, dicamba, and malathion.

Frequency of glyphosate use and NHL risks



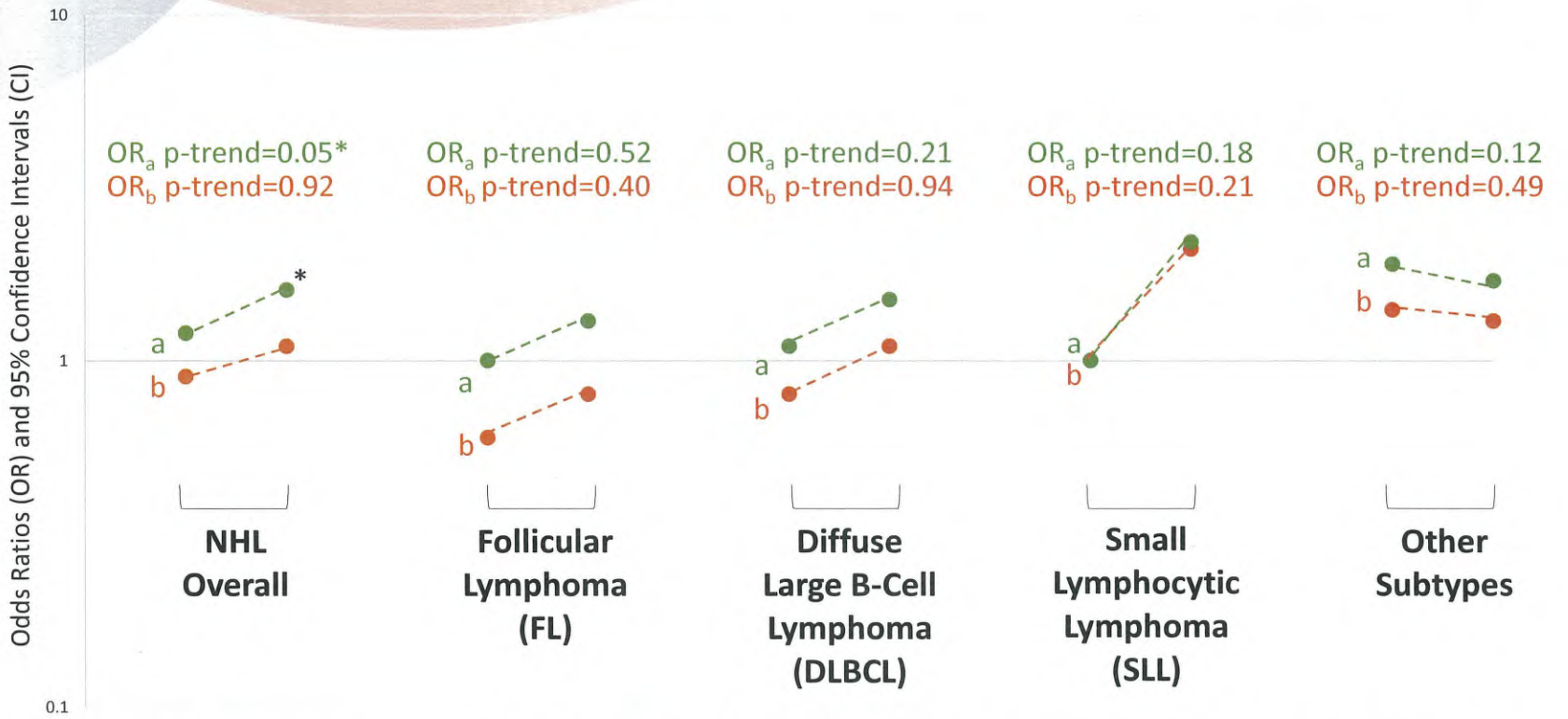
OR_a adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, use of any PPE.
OR_b adjusted for variables in OR_a and use of 2,4-D, dicamba, and malathion.

Duration of glyphosate use and NHL risks



OR_a adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, use of any PPE.
OR_b adjusted for variables in OR_a and use of 2,4-D, dicamba, and malathion.

Lifetime-days of glyphosate use and NHL risks



OR_a adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, use of any PPE.

OR_b adjusted for variables in OR_a and use of 2,4-D, dicamba, and malathion.

Discussion

Challenges

- Uncollected information about duration and frequency of glyphosate use in some locations
- Small numbers for certain stratified analyses
- Measurement error
- Potential recall bias

Strengths

- Sufficient statistical power to evaluate NHL sub-types with quantitative glyphosate use metrics
- Two different models used to obtain risk estimates, unadjusted and adjusted for other pesticides
- Conducted several sensitivity analyses, e.g. proxy respondents excluded

Conclusions

- Glyphosate use may be associated with ↑ risk of NHL overall
- Adjusting odds ratios for other pesticides generally attenuated risks
- Different exposure metrics yielded different results; however, there were consistent increases in the risk of SLL, even though these odds ratios and trends were not always statistically significant

Acknowledgements

- **Canadian investigators:** Drs. Shelley A. Harris, John J. Spinelli, Paul A. Demers, Punam Pahwa, James A. Dosman, John R. McLaughlin, Helen H. McDuffie (late)
- **U.S. investigators:** Drs. Laura Beane Freeman, Aaron Blair, Shelia Hoar Zahm, Kenneth P. Cantor, Dennis D. Weisenburger, Leon Burmeister (late)
- **NAPP Executive Committee:** Drs. Shelley A. Harris, Laura Beane Freeman, John J. Spinelli
- **Data pooling:** Mr. Joe Barker (IMS Inc.)

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CCO Cancer Care Ontario / Action Cancer Ontario

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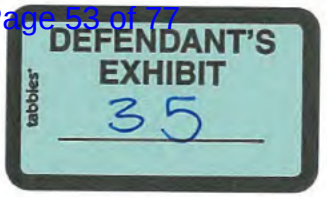

From: Weisenburger, Dennis
To: Blair, Aaron (NIH/NCI) [V]
Subject: FW: EU glyphosate review
Date: Monday, August 22, 2016 11:09:12 AM

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
[redacted]

-----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]org> 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)
> ---
>

Increased Cancer Burden Among Pesticide Applicators and Others Due to Pesticide Exposure

Michael C. R. Alavanja, DrPH[1]; Matthew K. Ross, PhD[2]; Matthew R. Bonner, PhD, MPH[3]

A growing number of well-designed epidemiological and molecular studies provide substantial evidence that the pesticides used in agricultural, commercial, and home and garden applications are associated with excess cancer risk. This risk is associated both with those applying the pesticide and, under some conditions, those who are simply bystanders to the application. In this article, the epidemiological, molecular biology, and toxicological evidence emerging from recent literature assessing the link between specific pesticides and several cancers including prostate cancer, non-Hodgkin lymphoma, leukemia, multiple myeloma, and breast cancer are integrated. Although the review is not exhaustive in its scope or depth, the literature does strongly suggest that the public health problem is real. If we are to avoid the introduction of harmful chemicals into the environment in the future, the integrated efforts of molecular biology, pesticide toxicology, and epidemiology are needed to help identify the human carcinogens and thereby improve our understanding of human carcinogenicity and reduce cancer risk. CA Cancer J Clin 2013;63:120–142. © 2013 American Cancer Society.*

Keywords: pesticides, cancer burden, carcinogen, risk, environmental cancer, public health

Introduction

A comprehensive and successful strategy for minimizing cancer risk from pesticide use should combine research initiatives aimed at identifying pesticides that are human carcinogens with policies that attempt to reduce these exposures to workers and the general public. In this discussion, pesticides are defined as a diverse group of chemical formulations used to control pests, including insects, molds, and unwanted plants.

Pest problems in public health (ie, vectors of disease), agriculture, and commerce are not static because pests develop resistance to widely used pesticides and are periodically introduced to new geographic areas without effective natural controls. Historically, the evolution of new pests has resulted in the development of new pesticides, followed shortly thereafter by new pesticide problems, such as pest resistance and unintended toxicities. In the United States and other developed countries, regulatory toxicity testing has kept many genotoxic chemicals and animal carcinogens out of the market place.[1] An incomplete understanding of human carcinogenicity, however, seems to have resulted in allowing some human carcinogens on to the worldwide market, resulting in excess cancer risk to those who are highly exposed and those who are particularly vulnerable.[2,3] For example, an International Agency for Research on Cancer (IARC) monograph published in 1991 stated, "occupational exposures in spraying and application of non-arsenical insecticides" as a group are classified as "probable human carcinogens" (category 2A),[2] yet the identification of specific pesticides as human carcinogens has not yet been made. If current regulatory toxicity testing has been inadequate, new data from toxicology and cancer biology will need to be used in conjunction with epidemiology to help improve our regulatory procedures and more reliably identify human carcinogens.

Rather than wait for human carcinogens to be identified, several European countries, including Sweden, Denmark, the Netherlands, and others, have initiated pesticide use reduction policies that have resulted in substantially diminished

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TABLE 1. Most Commonly Used Conventional Pesticide Active Ingredients, Agricultural Market Sector, 2007 Estimates, Ranked by Range in Millions of Pounds of Active Ingredient

ACTIVE INGREDIENT	FUNCTIONAL CLASS	CHEMICAL CLASS	RANK	RANGE
Glyphosate	Herbicide	Phosphinic acid	1	180-185
Atrazine	Herbicide	Triazine	2	73-78
Metam sodium	Fumigant	Dithiocarbamate	3	50-55
S-metolachlor	Herbicide	Acetamide	4	30-35
Acetochlor	Herbicide	Acetamide	5	28-33
1,3-dichloropropene	Fumigant	Organochlorine	6	27-32
2,4-D	Herbicide	Phenoxy acid	7	25-29
Methyl bromide	Fumigant	Methyl halide	8	11-15
Chloropicrin	Fumigant	Organochlorine	9	9-11
Pendimethalin	Herbicide	Dinitroaniline	10	7-9
Ethephon	Plant growth regulator	Ethylene generator	11	7-9
Chlorothalonil	Fungicide	Phthalamide	12	7-9
Metam potassium	Fumigant	Dithiocarbamate	13	7-9
Chlorpyrifos	Insecticide	Organophosphate	14	7-9
Copper hydroxide	Fungicide	Inorganic alkali	15	6-8
Simazine	Herbicide	Triazine	16	5-7
Trifluralin	Herbicide	Dinitroaniline	17	5-7
Propanil	Herbicide	Anilide	18	4-6
Mancozeb	Fungicide	Dithiocarbamate	19	4-6
Aldicarb	Insecticide	Carbamate	20	3-4
Acephate	Insecticide	Organophosphorus	21	2-4
Diuron	Herbicide	Urea	22	2-4
MCPA	Herbicide	Phenoxy acid	23	2-4
Paraquat (dipyridylium)	Herbicide	Bipyridal	24	2-4
Dimethenamid	Herbicide	Acetamide	25	2-4

2,4-D indicates 2,4-dichlorophenoxyacetic acid; MCPA, 2-methyl-4-chlorophenoxyacetic acid.

Source: US Environmental Protection Agency Office of Pesticide Programs. Pesticide Industry Sales and Usage. 2006 and 2007 Market Estimates. Washington, DC: US Environmental Protection Agency; 2007. Available from: epa.gov/pesticides/pestsales/07pestsales/usage2007_2.htm. Accessed November 27, 2012.

pesticide use overall.[4] In the United States, a nationwide use reduction policy has met with resistance politically because of disagreements about the net benefit to health and debate concerning the disproportionate economic impact of these policies on selected groups (eg, farmers, food processors, and pesticide manufacturers) and on food prices.[1] The information available for these policy debates on cost-benefit are not yet equal since identifying the impact of pesticides on cancer risk has been difficult and progress relatively slow, while estimating the immediate economic impact of pesticide use reduction policies on agriculture and commerce is more readily quantifiable. Since pesticides are pervasive in our environment, environmental health policy in the United States has instead focused on reducing human exposure to pesticides by controlling the methods and conditions of use.[1]

The active ingredients of pesticides are a very diverse array of chemical structures. Many pesticide structures are very complex and cannot be categorized simply. A convenient classification is based on the targeted pest (eg, herbicides, insecticides, fungicides, nematicides, and rodenticides). The classes may then be subdivided into smaller subclasses based on chemical structure. Herbicides account for the largest portion of total use, followed by other pesticides, insecticides, and fungicides. The amount of pesticide used in the US in both 2006 and 2007 exceeded 1.1 billion pounds.[5]

TABLE 2. Most Commonly Used Conventional Pesticide Active Ingredient in the Home and Garden Market Sector, 2007 and 2005 Estimates, Ranked by Range in Millions of Pounds of Active Ingredient

ACTIVE INGREDIENT	TYPE	CHEMICAL CLASS	RANK	RANGE
2,4-D	Herbicide	Phenoxy acid	1	8-11
Glyphosate	Herbicide	Phosphinic acid	2	5-8
Carbaryl	Insecticide	Carbamate	3	4-6
MCPP	Herbicide	Phenoxy_acid	4	4-6
Pendimethalin	Herbicide	Dinitroaniline	5	3-5
Pyrethroids	Insecticide	Pyrethroid	6	2-4
Malathion	Insecticide	Organophophorus	7	2-4
Dicamba	Herbicide	Benzoic_acid	8	1-3
Trifluralin	Herbicide	Dinitroaniline	9	1-3
Pelarganoc acid	Herbicide	Fatty acid	10	<1

2,4-D indicates 2,4-Dichlorophenoxyacetic acid; MCPP, methylchlorophenoxypropionic acid.

Does not include moth controls: paradichlorobenzene (30-35 million pounds per year) and naphthalene (2-4 million pounds per year). Also does not include insect repellent N,N-diethyl-meta-toluamide (5-7 millions pound per year).

Source: US Environmental Protection Agency Office of Pesticide Programs. Pesticide Industry Sales and Usage. 2006 and 2007 Market Estimates. Washington, DC: US Environmental Protection Agency; 2007. Available from: epa.gov/pesticides/pestsales/07pestsales/usage2007_2.htm. Accessed November 27, 2012.

The amount of pesticide used in the US accounted for 22% of the total world pesticide amount used, 25% of the world herbicide amount used, 10% of the world insecticide amount used, 14% of the world fungicide amount used, and more than 25% of other pesticide amounts used in both years.[6] The most highly used pesticides in agriculture, home and garden use, and government and commercial use are identified in Tables 1, 2, and 3.[5]

Pesticide Exposures and Control

Among members of the general public who are not applying pesticides, multiple routes of exposure are possible depending on whether the individual is an adult or a child, the location of their residence in relation to pesticide applications, whether a residence was treated with pesticides, the occupations of household members, the volatility of the compound, the persistence of the pesticides

TABLE 3. Most Commonly Used Conventional Pesticide Active Ingredients in the Industry/Commercial/Government Market Sector, 2007, 2005, 2003, and 2001 Estimates, Ranked by Range in Millions of Pounds of Active Ingredient

ACTIVE INGREDIENT	TYPE	CHEMICAL CLASS	RANK	RANGE
2,4-D	Herbicide	Phenoxy acid	1	19-22
Glyphosate	Herbicide	Phosphinic acid	2	13-15
Chlorothalonil	Fungicide	Phthalimide	3	3-5
MSMA	Herbicide	Organoarsenic	4	2-4
Diuron	Herbicide	Urea	5	2-4
Pendimethalin	Herbicide	Dinitroaniline	6	2-4
Triclopyr	Herbicide	Organochlorine	7	2-4
Copper sulfate	Fungicide	Inorganic sulfate	8	2-4
Malathion	Insecticide	Oganophosphorous	9	1-3
Sulfuryl fluoride	Insecticide	Inorganic fluoride	10	1-3

2,4-D indicates 2,4-dichlorophenoxyacetic acid; MSMA, monosodium methyl arsenate.

Includes applications to homes and gardens by professional applicators. Does not include sulfur or petroleum oil. Due to lack of data, the same estimate is used for both 2005 and 2007 in this report.

Source: US Environmental Protection Agency Office of Pesticide Programs. Pesticide Industry Sales and Usage. 2006 and 2007 Market Estimates. Washington, DC: US Environmental Protection Agency; 2007. Available from: epa.gov/pesticides/pestsales/07pestsales/usage2007_2.htm. Accessed November 27, 2012.

TABLE 4. Routes of Pesticide Exposure and Exposure Control Measures

SUBJECT	MAJOR ROUTES OF EXPOSURE	PREVENTIVE OR CORRECTIVE ACTION	REFERENCES
Pesticide applicator	Dermal	1. Use personal protective equipment including chemically resistant gloves. 2. Remove all pesticide-soiled clothing as soon as possible. 3. Wash or shower immediately following application. 4. Follow all pesticide label instructions.	14-18
	Ingestion	1. Do not eat, drink, or smoke during pesticide handling or application.	17
	Inhalation	1. Mix or load pesticides in a well-ventilated area. 2. Wear appropriate respiratory protective equipment according to pesticide label instructions.	14,17
Adult bystander and children's guardians	Dermal	1. Do not enter fields, lawns, or confined spaces where pesticides have been applied for the period specified on label instructions. Do not allow children to do so. 2. Interrupt take-home pathways: a. Encourage family members to remove shoes and other pesticide-soiled clothing outside the home if possible or as soon as possible after entering the home. b. Vacuum rug and/or clean floors if possibly soiled with pesticides. c. Do not store pesticides in living areas or anywhere within the reach of children. Keep all pesticides in a locked cabinet in a well-ventilated utility area or garden shed. 3. Keep children and pets away from areas where pesticides were applied. 4. Encourage family members exposed to pesticides to wash or shower as soon as possible after exposure. 5. Do not have pets enter the living areas of the home when soiled with pesticides until cleaned. 6. Wash clothing soiled with pesticides separately from other laundry.	6-13
	Ingestion	1. Never store pesticides in cabinets with or near food. 2. Always store pesticides in their original containers, complete with labels that list ingredients, directions for use, and first aid in case of accidental exposure. 3. Never transfer pesticides to soft drink bottles or other containers. 4. Rinse fruits and vegetables with water. Scrub with a brush and peel them if possible.	3,5,6,9,10,13
	Inhalation/general	1. Do not stockpile pesticides. Purchase only what you need for immediate application. 2. Follow the pesticide label directions for proper disposal. 3. Report any symptoms possibly related to pesticide exposure to your health care provider. When possible, report the name of the product, the ingredients, and the first aid instructions contained on the product label. 4. If a close neighbor or someone else is applying pesticides outdoors near your home, stay indoors with your children and pets. Keep windows and doors closed.	3,6,14,17
Regulatory agencies, scientific community, and chemical manufacturers	All	1. Identify human carcinogens and remove them from the market place or greatly curtail their use. 2. Identity the persistence and accumulation potential of pesticides and reduce the use of long-lived pesticides wherever possible. 3. Identify good pesticide work practices and educate the public in these practices. 4. Design more effective pesticide containers and application equipment that minimizes pesticide exposure to the applicator and to children who may come into contact with these containers.	3,5,6

in the environment, and several other chemical and physical properties of the pesticides (Table 4).[3,5-18] Pesticide applications to the home by a second party can result in both dermal and respiratory exposure. Other common routes of exposure to the general public include drinking water and dietary sources.[6] To minimize nonoccupational exposures to pesticides, EPA regulations have discouraged the use of the longer-lasting pesticides such as organophosphate (OP) insecticides in the home.[5] A trend toward the use of pyrethroids and other shorter-lived pesticides is resulting in lower OP exposures among the general public.[5]

The National Academy of Sciences[3] suggested that children may experience greater risk from pesticide exposure than adults because of the behavioral, dietary, and physiological characteristics associated with development. Among children, an important source of pesticide exposure results from diet[7]; for example, the consumption of organic produce is associated with a substantially lower concentration of urinary dialkylphosphate levels (which indicate organophosphorus pesticide exposure) than in those eating conventional foods,[7,8] but we do not have substantial evidence suggesting a cancer hazard associated with this exposure.[9] Another important source of pesticide

exposure results from the transfer of pesticides from a person who is occupationally exposed.[10] For example, urinary dialkylphosphate levels have been measured in studies of children and show parental occupation or their household proximity to farmland[7,8,10-12] and self-reported residential use of pesticides by parents[12,13] are important sources of childhood exposure (Table 4).[3,5-18]

Among adults applying liquid pesticides of low volatility, dermal exposures typically account for 90% of pesticide exposures.[14-16] The dermal penetration can vary between 2% and 20% if the pesticide is left on the skin for 8 hours or longer,[15] and therefore the use of proper protective equipment including chemical-resistant gloves and protective suits when handling the pesticide can substantially reduce exposure.[17] When the skin is immediately washed after pesticide use, a substantial additional reduction takes place.[14,18] A larger fraction of the exposure would be by the respiratory route among those applying more volatile pesticides (eg, flying insect spray) and other aerosols, and thus respiratory protection appropriate to the chemical being used is usually recommended (Table 4).[3-18]

To minimize nonoccupational exposures to pesticides, EPA regulations have discouraged the use of the longer-lasting and broad-spectrum pesticides. The lipophilic bioaccumulative organochlorine (OC) insecticides that were widely used in the mid-20th century were subsequently replaced by OPs, carbamates, and pyrethroids because these compounds were more environmentally labile and did not accumulate in the food chain to the same extent as the OCs. Moreover, compounds such as pyrethroids have become extremely attractive for pest control because they exhibit greater selective lethality toward insects compared with mammals.[19] Importantly, when humans are exposed to pyrethroids, OPs, and carbamates, the compounds are generally metabolized and eliminated from the body within 24 to 48 hours as water-soluble metabolites in urine. Physiologically based pharmacokinetic models that predict the internal dose of specific pesticides as a function of time are tools used to assess chemical dosimetry following exposures, although these models are more developed in animal studies than in humans.[20]

Since a total ban on the use of chemical pesticides is unlikely to happen in any country in the foreseeable future, ensuring cancer risk reduction from pesticides will depend on identifying pesticides that are human carcinogens. This review is not exhaustive, but rather it is focused on several cancers (ie, prostate cancer, non-Hodgkin lymphoma [NHL], adult and childhood leukemia, multiple myeloma, and breast cancer) where considerable progress has been made in identifying pesticides likely to be human carcinogens by synthesizing results from epidemiology, toxicology, and cancer biology. Although more than 800 active pesticide ingredients are currently on the market in the United States and other countries, only arsenical insecticides[2] and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (a contaminant of the phenoxy herbicide 2,4,5,-T) have been identified as human carcinogens by the IARC (category 1).[2] However, literature developed subsequent to publication of the IARC monograph suggests that chemicals in every major functional class of pesticides (ie, insecticides, herbicides, fungicides, and fumigants) are associated with human cancer. Table 5 presents a list of pesticides that have been carefully evaluated in well-designed epidemiological and/or toxicological/cancer biology studies for human carcinogenicity of the prostate, NHL, adult leukemia, and multiple myeloma.[21-68] While we discuss a potential link between pesticides and breast cancer and childhood leukemia because of widespread public anxiety about these cancers, no specific pesticide has yet been strongly linked to these cancers and therefore we do not include them in our table. The list is not exhaustive and considers only these 4 cancer sites because the literature is most developed for these sites. Other chemicals are likely to emerge as our understanding of pesticide-induced mechanisms of cancer etiology expands.

Mechanisms of Pesticide Toxicity

Pesticides have diverse chemical structures and exhibit a variety of biological modes of action in both target and nontarget organisms.[69] Following absorption into the body, pesticides are often biotransformed to water-soluble metabolites for the purpose of detoxification and elimination. Rates of biotransformation can be rapid (hours to days), as in the case of OP insecticides, or extremely slow (years to decades), as is noted for OC insecticides, which accounts for the bioaccumulation of these lipophilic compounds in adipose tissue. Multiple mechanisms are likely involved in pesticide-mediated carcinogenesis. Most of the published literature point toward oxidative stress and/or receptor-mediated mechanisms being important determinants, whereas inflammatory and aberrant epigenetic mechanisms caused by pesticide exposure are only in a preliminary stage of development and, consequently, there is not a lot of literature to support these mechanisms at this time. However, epigenetic modifications of tumor suppressor genes and oncogenes that alter their expression in tumors have been shown to be molecular drivers of cancer pathogenesis during the promotion and progression phases. Thus, this section will briefly focus on oxidative stress and receptor-mediated toxicities that are caused by pesticides.

TABLE 5. Epidemiological and Toxicological Evidence of Carcinogenicity for Selected Cancer Sites and Pesticides

CANCER SITE	PESTICIDE	CURRENT US EPA REGULATORY STATUS[a]	IARC CLASSIFICATION (YEAR)[b]	EXPOSURE SOURCE	EPIDEMIOLOGIC EVIDENCE	REFERENCE	TOXICOLOGICAL EVIDENCE	REFERENCE
Prostate	Fonofos (OP)	Not registered	Not evaluated	Occupational	1. Monotonic increase in risk of aggressive PC.	25	No direct evidence for PC.	—
					2. Significant interaction between exposure and genetic variants in 8q24, base excision repair, nucleotide excision repair.	23,24,91	Mutagenic in *S. typhimurium* and *S. cerevisae* genotoxicity assays.	26
	Terbufos (OP)	Registered	Not evaluated	Occupational	1. Monotonic increase in risk of aggressive PC.	25	No direct evidence for PC.	—
					2. Significant interaction between exposure and genetic variants in 8q24, base excision repair.	23,24	Mutagenic in *S. typhimurium* and *S. cerevisae* genotoxicity assays.	26
	Malathion (OP)	Registered	Group 3 (1987)	Occupational	1. Monotonic increase in risk of aggressive PC.	25	No direct evidence for PC.	—
					2. Positively associated with PC.	102		
	Permethrin (pyrethroid)	Registered	Not evaluated	Occupational	1. Significant interaction between exposure and genetic variants in 8q24.	24	No direct evidence for PC.	—
	Aldrin (OC)	Not registered	Group 3 (1987)	Occupational	1. Increased in risk of PC among men with a family history of PC.	25	No direct evidence for PCr;	—
							Hepatocarcinogenesis in mice through a nongenotoxic mode of action.	22
	Chlordecone (OC)	Not registered	Group 2B (1987)	Environmental	1. Increased risk of PC in highest exposure tertile.	29	Androgenic activity in cultured prostate cells.	28
	Lindane (HCH)	Not registered	Group 2B (1987)	Environmental	1. Serum concentrations positively associated with prevalence of PC.	32	Low levels of HCH alter androgen signaling in cultured prostate cells.	31
					2. Positively associated with PC.	102	Lindane induces micronuclei in cultured human prostate cells.	30
	DDT (OC)	Not registered	Group 2B (1991)	Occupational	1. Positively associated with PC.	102	DDE (environmental metabolite of DDT) can bind to androgen receptor in cultured prostate cells.	28
	Dieldrin (OC)	Not registered	Group 3 (1987)	Environmental	1. Serum concentrations positively association with prevalence of PC.	32	No direct evidence for PC.	—
							Induces oxidative stress and hepatocarcinogenic in mice through a nongenotoxic mode of action.	22
							Disrupt normal estrogen and androgen receptor function in cultured cells.	32
	Simazine (triazine)	Registered	Group 3 (1999)	Occupational	1. Positively associated with PC.	102	No direct evidence for PC.	—
	Atrazine (triazine)	Registered	Group 3 (1999)	Occupational	1. Not associated with PC.	105	No direct evidence for PC.	—
	Methyl bromide (methyl halide)	Registered	Group 3 (1999)	Environmental	1. Positively associated with PC.	35	Mutagenic in bacterial assays.	36
							DNA adducts (O^6-methylguanine) detected in rodent forestomach and liver.	36,37
	Oxychlordane (metabolite of chlordane, an OC)	Not registered	Group 2B (2001)	Environmental	1. No association with PC.	38-41	No direct evidence for PC.	—
	HCB (OC)	Not registered	Group 2B (2001)	Environmental	1. No association with PC.	40,113	Low levels of HCB enhance androgen signaling in cultured prostate cells and mouse prostate.	42
					2. Positively associated with PC.	39		
	Mirex (OC)	Not registered	Group 2B (1987)	Environmental	1. No association with PC.	40	No direct evidence for PC.	—
NHL	Lindane (HCH)	Not registered	Group 2B (1987)	Environmental	1. Positively associated with NHL with t(14:18).	43,52	No direct evidence for NHL.	—
					2. Positively associated with NHL.	44		
	Dieldrin (OC)	Not registered	Group 3 (1987)	Environmental	1. Positively associated with NHL with t(14:18).	43,52	No direct evidence for NHL.	—
					2. Positively associated with NHL.	54	Increased CYP1A and 1B expression in female rat liver, kidney, and mammary tissue.	50
					3. No association with NHL.	58,60,126		
	Toxaphene (OC)	Not registered	Group 2B (2001)	Environmental	1. Positively associated with NHL with t(14:18).	43,52	No direct evidence for NHL.	—

TABLE 5 (Continued)

CANCER SITE	PESTICIDE	CURRENT US EPA REGULATORY STATUS[a]	IARC CLASSIFICATION (YEAR)[b]	EXPOSURE SOURCE	EPIDEMIOLOGIC EVIDENCE	REFERENCE	TOXICOLOGICAL EVIDENCE	REFERENCE
	2,4-D (phenoxy herbicide)	Registered	Group 2B (1987)	Occupational	1. Positively associated with NHL. 2. No association with NHL.	121 62,123,124	No direct evidence for NHL. Increased CYP1A and 1B expression in female rat liver, kidney, and mammary tissue.	— 50
	MCPA (phenoxy herbicide)	Registered	Group 2B (1987)	Occupational	1. Positively associated with NHL. 2. Positively associated with NHL among those with asthma or hay fever.	47 61	No direct evidence for NHL.	—
	β-Hexachlorobenzene (a metabolite of HCB; chlorinated hydrocarbon)	Not registered	Group 2B (2001)	Environmental	1. Plasma concentrations positively associated with NHL.	127	No direct evidence for NHL.	—
	HCB (OC)	Not registered	Group 2B (2001)	Environmental	1. No association with NHL. 2. Plasma concentrations positively associated with NHL.	46,48,54,55 58,60,126 127	No direct evidence for NHL.	—
	TCDD (OC)	Not registered	Group 1 (2012)	Occupational	1. Positively associated with NHL mortality.	45	No direct evidence for NHL. Increased CYP1A and 1B expression in female rat liver, kidney, and mammary tissue.	— 50
	DDT (OC)	Not registered	Group 2B (1991)	Environmental	1. Positively associated with NHL. 2. No association with NHL.	48,55,60 126,127 46,54,56 59,131	No direct evidence for NHL.	—
	Chlordane/oxychlordane (OC)	Not registered	Group 2B (2001)	Environmental	1. Positively associated with NHL. 2. No association with NHL.	55,60,126,127 48,54,58	No direct evidence for NHL.	—
	Glyphosate (OP herbicide)	Registered	Not evaluated	Occupational	1. Positively associated with NHL.	47	No direct evidence for NHL.	—
	Atrazine (triazine)	Registered	Group 3 (1999)	Occupational	1. Superadditive effect in combination with alachlor, diazinon, and carbofuran 2. Positively associated with NHL with t(14:18).	128 52	No direct evidence for NHL.	—
	Mirex (OC)	Not registered	Group 2B (1987)	Environmental	1.Positively associated with NHL. 2. No association with NHL.	127 46	No direct evidence for NHL.	—
Adult leukemia	Fonofos (OP)	Not registered	Not evaluated	Occupational	1. Positively associated with leukemia.	148	No direct evidence for leukemia.	—
	Diazinon (OP)	Registered	Not evaluated	Occupational	1. Positively associated with leukemia.	149	No direct evidence for leukemia.	—
	Metribuzin (triazinone herbicide)	Registered	Not evaluated	Occupational	1. Positively associated with leukemia.	150	No direct evidence for leukemia.	—
	Alachlor (aniline herbicide)	Registered	Not evaluated	Occupational	1. Positively associated in the highest-exposure category only.	151	No direct evidence for leukemia.	—
	EPTC (thiocarbamate)	Registered	Not evaluated	Occupational	1. Positively associated in the highest-exposure category only.	65	No direct evidence for leukemia.	—
	Chlordane/heptachlor (OC)	Not registered	Group 2B (2001)	Occupational	1. Positively associated with leukemia.	44	No direct evidence for leukemia.	—
MM	Permethrin (pyrethroid insecticide)	Registered	Group 3 (1991)	Occupational	1. Positively associated with MM.	156	No direct evidence for MM.	—
	Captan (phthalimide fungicide)	Registered	Group 3 (1987)	Occupational	1. Positively associated with MM.	186	No direct evidence for MM.	—
	Carbaryl (carbamate insecticide)	Registered	Group 3 (1987)	Occupational	1. Positively associated with MM.	186	No direct evidence for MM.	—

EPA indicates Environmental Protection Agency; IARC, International Agency for Research on Cancer; OP, organophosphate; PC, prostate cancer; *S. typhimurium*; *Salmonella typhimurium*; *S. cerevisae*, *Saccharomyces cerevisiae*; OC, organochlorine; HCH, hexachlorocyclohexane; DDT, dichloro-diphenyl-trichloroethane; DDE, dichlorodiphenyldichloroethylene; HCB, hexachlorobenzene; NHL, non-Hodgkin lymphoma; CYP1A/1B, cytochrome P4501A/1B; 2,4-D, 2,4-dichlorophenoxyacetic acid; MCPA, 2-methyl-4-chlorophenoxyacetic acid; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; EPTC, S-ethyl-N,N-dipropylthiocarbamate; MM, multiple myeloma.

[a]Regulation status was obtained from the Pesticide Action Network Pesticides Database (pesticideinfo.org [accessed October 20, 2012]).

[b]IARC classifications are as follows: group 1: carcinogenic to humans; group 2A, probably carcinogenic to humans; group 2B, possibly carcinogenic to humans; group 3, not classifiable regarding its carcinogenicity to humans; and group 4: probably not carcinogenic to humans.

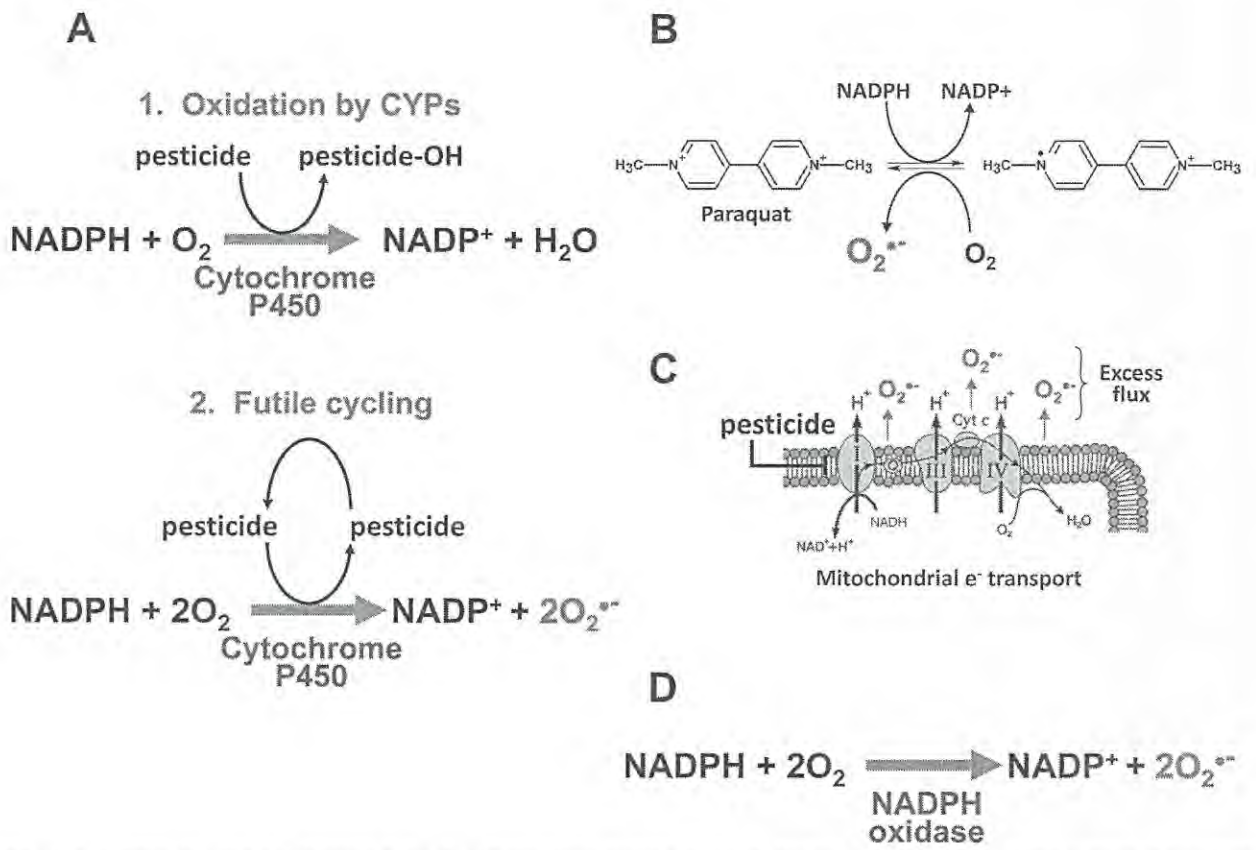

FIGURE 1. Summary of Potential Mechanisms by Which Pesticides Cause Oxidative Stress. (A) Mechanism 1 describes the normal oxidation of a pesticide catalyzed by cytochrome P450 (CYP), leading to a hydroxylated metabolite. Mechanism 2 describes futile oxidative metabolism of a pesticide by CYP450s, leading to reaction uncoupling and superoxide (O_2) production (eg, organochlorines, polychlorinated biphenyls cause futile cycling).[70] (B) Generation of redox-active pesticide metabolites, such as quinones or bipyridinium compounds, which undergo redox cycling leading to superoxide formation (paraquat redox cycling is shown as an example).[71] (C) Impairment of electron transport cascades in mitochondria, leading to excess superoxide flux (eg, rotenone is well known to inhibit complex I).[72] (D) Activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase by pesticides can liberate superoxide.[73] OH indicates hydroxyl radical; H_2O, water.

Oxidative Stress

Exposure to pesticides may cause the net production of reactive oxygen species (ROS) in tissues when antioxidant defense mechanisms are overwhelmed. ROS are often free radicals (ie, oxygen-containing species containing an unpaired electron, such as superoxide [$O_2^{\bullet-}$] and hydroxyl radical [OH]), which renders them highly unstable in a chemical sense. There are generally 4 mechanisms by which pesticides can increase the levels of ROS, such as superoxide (Fig. 1).[70-73] However, regardless of the mechanism by which ROS are produced, a consequence of their overproduction is that they can cause extensive DNA and protein damage in cells. Although the oxidative stress hypothesis of pesticide-induced cancers is attractive, several unanswered questions remain and many details need to be filled in. For example, are tumor suppressor genes or oncogenes specifically targeted by ROS generated by pesticide exposure, thus contributing to disease? Moreover, the identification of specific biomarkers that can distinguish between pesticide exposure, oxidative stress, and disease are needed to establish the links between pesticides and disease endpoints.

Steroid and Xenobiotic Receptors and Pesticides: Endocrine Disruption and Xenobiotic Metabolism

Although most pesticides on the market are not mutagenic in genotoxicity assays such as the Ames mutagenicity test, there is increasing epidemiological evidence of links between pesticide exposure and cancer. Therefore, it is logical to hypothesize alternative mechanisms of action by which pesticides might contribute to cancer beyond canonical DNA damage and mutagenic mechanisms. Endocrine disruptors are chemicals found in the environment (xenochemicals) that block or mimic hormone action, contributing to a wide range of pathologies. They are found in many products, including pesticides. Many xenochemicals can bind to and displace endogenous ligands for the steroid nuclear receptor family, which includes protein receptors that bind to the sex hormones estrogen

TABLE 6. Biomarkers of Exposure, Oxidative Stress, DNA Damage, and Genetic Susceptibility Relevant to Pesticide-Induced Cancers

BIOMARKER	ANALYTE OR ENZYME ACTIVITY ASSAYED	BIOLOGICAL FLUID/SAMPLE USED	REFERENCES
Pesticide exposure	Biomonitoring of pesticides and their metabolites	Urine, serum, plasma	76
	Blood cholinesterase activity and mass spectrometric detection of OP-adducted cholinesterases	Blood	77
Oxidative stress	Malondialdehyde, F2-isoprostanes, thiobarbituric acid-reactive substances	Urine, serum, plasma	78-81
	Catalase and SOD activities	RBCs	78
	8-oxo- or 8-OH-deoxyguanosine	Urine	82
DNA damage	Alkaline comet assay, micronuclei, chromosomal aberrations, sister chromatid exchange	Blood lymphocytes	83-85
	8-oxo- or 8-OH-deoxyguanosine	Urine	86,87
	Apurinic/apyrimidinic endonuclease activity	Blood lymphocytes	83
	"Challenge" assay (DNA repair phenotype)	Blood lymphocytes	88
Genetic susceptibility	Paraoxonase 1 polymorphism	Lipoproteins (HDL)	89,90
	Glutathione transferase, cytochrome P450 polymorphisms	Blood lymphocytes	23,90
	Base excision repair polymorphism	Blood lymphocytes	23
	Nucleotide excision repair polymorphism	Blood lymphocytes	91

OP indicates organophosphate; SOD, superoxide dismutase; RBCs, red blood cells; HDL, high-density lipoprotein.

and androgen, thus aberrantly activating receptor function and leading to changes in gene expression networks.[74,75] Inappropriate activation of androgen and estrogen receptors by pesticides is one hypothesis that might contribute to the excess cancer burden caused by pesticides, particularly the contribution of hydrophobic OCs to prostate and breast cancer risk. Therefore, although pesticides might not be genotoxic per se, their ability to bind steroid and xenobiotic receptors may cause significant alterations in gene expression programs that modulate the carcinogenic activities of common environmental pollutants.

Biomarkers Relevant to Pesticide-Induced Cancers

Biomarkers of exposure, genetic susceptibility, and biological effects such as oxidative stress and DNA damage relevant to pesticide-induced cancers are presented in Table 6.[23,76-91] This list is not exhaustive but highlights both established markers of pesticide exposure (such as cholinesterase activity) and emerging biomarkers (such as the "challenge assay," which assesses the DNA repair capacity of cells). It should be noted that most of these biomarkers are not used in the clinic at present; however, they have usefulness in research studies that aim to determine the etiology of cancers that have been linked to agrochemical exposure.

Cell-Based and Animal Studies to Establish Biomarkers of Pesticide Toxicity

The use of cultured animal and human cells allows high-throughput assays of pesticide toxicity to be assessed at much lower cost compared with whole-animal studies and without the ethical constraints that limit human studies. The purpose of these high-throughput cell-based assays is not to completely replace in vivo studies. Rather, it is a screening process to prioritize the environmental chemicals that will be tested in whole-animal studies. This approach has been embraced by the US EPA and National Institute of Environmental Health Sciences National Toxicology Program to establish the most important environmental chemicals to focus on and to conserve resources.[92] However, effective risk characterization of pesticides will require the integration of in vitro studies, in vivo studies, and epidemiological evidence in order to provide the best protection of public health.

In the US EPA's ToxCast research program, part of the phase 1 study examined 309 chemicals (mostly pesticides) in a high-throughput genotoxicity assay that measured the activity of the p53 transcription factor, which is activated upon DNA damage.[93] As expected, only a small fraction of the tested compounds gave positive hits (10%); a full listing of the chemicals found to be genotoxic can be found at the EPA ToxCast Web site (epa.gov/ncct/toxcast/ accessed November 27, 2012). A caveat to this study is that this high-throughput screen lacked a metabolic activation

system, which might have caused false-negative results to be reported, and positive hits were found at high concentrations of 12.5 μM or higher. With respect to the ability of pesticides to enhance ROS production in cells, high concentrations (approximately 50-100 μM) of organophosphorus pesticides were shown to induce oxidative stress and reduce the activity of antioxidant enzymes in cultured PC-12 cells, which is an in vitro model of dopaminergic neurons.[94] Evidence of DNA damage was also evident in this study. Moreover, these toxic effects could be ameliorated by vitamin E supplementation. However, except for deliberate poisoning episodes, it is highly unlikely that humans would ever be exposed to such high supraphysiological concentrations of pesticide. An earlier study, also using PC-12 cells treated with pesticides (endrin, chlordane, alachlor, fenthion, and chlorpyrifos) but at a much lower concentration (100 nM), demonstrated increased levels of DNA single-strand breaks compared with untreated cells when assessed by the alkaline elution method.[95] Cultured neuroblastoma cells (SH-SY5Y) exposed to fipronil, a phenylpyrazole insecticide, exhibited elevated amounts of ROS and were more likely to undergo apoptosis (cell suicide) compared with untreated cells.[96] Apoptosis was found to correlate with the extent of oxidative stress caused by the fipronil. Thus, these representative descriptive reports do suggest that pesticides can enhance levels of ROS in cultured cells. However, mechanistic information in this area is sparse and much more work is required.

In whole-animal studies, enhanced ROS production and lipid peroxidation in Sprague-Dawley rat liver and brain was found following treatments with the pesticides endrin, chlordane, alachlor, fenthion, or chlorpyrifos.[95,96] In addition, DNA single-strand breaks were also elevated in the livers and brains of pesticide-treated rats. Thus, oxidative stress can be elicited in cultured cells and intact animals by pesticides that have very different chemical structures. There is no chemical similarity between OPs (eg, chlorpyrifos) and OCs (eg, chlordane) and thus it is unlikely that these different classes of pesticides elicit toxicities through a common mode of action. This again highlights the complexity of studying the biological effects of pesticides and trying to find common mechanisms of action. Future studies will need to become more systematic in their approach to selecting pesticides for further mechanistic study. Moreover, animal studies occasionally give conflicting results, even for chemicals thought to exhibit well-defined mechanisms of toxicity. For example, paraquat is well known to induce oxidative stress in human lung, and an in vivo study using rats demonstrated that paraquat could significantly enhance the production of 8-OH-deoxyguanosine, particularly in the brain, lung, and heart.[97] However, in another study, no significant effects on the level of oxidized deoxyguanosine in rat liver, lung, or urine were found following a single intraperitoneal injection of 20 mg/kg of paraquat compared with untreated controls.[98] Therefore, these examples highlight the discordance that often exists between animal and human studies, and the challenge that epidemiologists and toxicologists face when trying to reconcile such conflicting reports.

Exposure to Pesticides and Select Cancer Sites

A growing body of epidemiological, molecular biology, and toxicological evidence assessing the link (or lack of a link) between specific pesticides and specific cancers is becoming available in the scientific literature. While space limitations prevent a comprehensive review of all cancers here, the emerging multidiscipline literature is well illustrated in the case of prostate cancer, NHL, leukemia, multiple myeloma, and breast cancer. In should be noted that tumor sites in rodents following treatment with pesticides almost never concord with human epidemiological findings, which is probably due to species differences and different exposure scenarios. An additional challenge is trying to estimate the degree of caution that should be exercised when using a compound if the specific pesticide can induce tumors in nontarget tissues in cancer bioassays. For example, risk assessors would be concerned with their risk estimates if a tested pesticide could cause liver tumors in a rodent, even though it is highly unlikely that the pesticide would cause liver tumors in human epidemiologic data.

Prostate Cancer

Prostate cancer is the most common cancer diagnosed among men in the United States, accounting for an estimated 28.5% of all cancers diagnosed in men in 2012.[99] Approximately 241,740 cases will be diagnosed in 2012, with an estimated 28,170 deaths occurring.[99] Prostate cancer ranks second after lung cancer as the underlying cause of death in men, accounting for an estimated 9.3% of all cancer deaths in men.[99] Prostate cancer risk associated with pesticides has been evaluated in over 100 occupational studies worldwide (mostly among farmers and other pesticide users). Results from meta-analyses based on these studies are consistent with a weak, positive association between farming and prostate cancer.[100] More recent epidemiologic evidence from a number of different studies now, more convincingly, shows that prostate cancer is related to pesticide use specifically.

In one of the largest prospective studies of pesticide exposures published to date, the Agricultural Health Study (AHS), which was conducted in Iowa and North Carolina, a small but significant excess prostate cancer risk was

observed among both farmers (19% excess) and commercial pesticide applicators (28% excess).[21] Among the 1962 incident prostate cancer cases that developed in the AHS cohort from 54,412 pesticide applicators that were cancer free at the start of the observation period,[21] 3 OP insecticides and an OC insecticide were significantly associated with a monotonic increase in the risk of aggressive prostate cancer as the metric of exposure increased. In this study, aggressive prostate cancer was defined as having one or more of the following tumor characteristics: distant stage, poorly differentiated grade, Gleason score of 7 or higher, or fatal prostate cancer (underlying-cause prostate cancer). The OP chemicals identified include fonofos, which is no longer registered for use in the United States, and 2 other OP insecticides currently used widely in the United States and worldwide: malathion and terbufos. However, the biological mechanisms by which these compounds might cause prostate cancer is uncertain. In vitro studies demonstrated that fonofos and terbufos were both genotoxic in *Salmonella typhimurium* and *Saccharomyces cerevisiae*,[26] although no studies have determined whether these 2 OPs can cause DNA damage in mammalian cells. In addition, the recent study by Koutros et al[25] demonstrated that a significantly increased risk of prostate cancer was observed among men with documented exposure to fonofos or aldrin and a family history of prostate cancer, whereas there was no increased risk among men without a family history. These results suggest an important genetic component contributes to the prostate cancer risk associated with selected pesticides.

Aldrin is an OC insecticide that was extensively used worldwide until 1970, when it was banned in the United States and most other countries. Animal studies suggest that OCs such as aldrin and dieldrin can induce hepatocarcinogenesis in mice through a nongenotoxic mode of action in which the slow oxidative metabolism of these compounds, or futile cycling leading to cytochrome P450 decoupling (Fig. 1A), is accompanied by increased levels of ROS, the depletion of hepatic antioxidant defenses (particularly α-tocopherol), and elevated lipid peroxidation.[22] It was also shown that dieldrin, which is structurally related to aldrin, can induce oxidative stress, resulting in the modulation of gene expression that favors the expansion of latent initiated preneoplastic cells in mouse liver.[22] However, the "tumor promoter-like" effects of OCs such as aldrin and dieldrin do not seem to occur in rat, dog, and monkey liver. Thus, because of the inconsistency in the induction of hepatocarcinomas caused by OC exposure in various species, it is unclear whether results from studies in mice can be translated to humans. Moreover, the organ specificity of cancer in the mouse model caused by OCs, such as dieldrin, does not concord with the human epidemiological findings. Furthermore, prostate tumors are not detected in mice following treatment with dieldrin.

In the AHS, significant interactions between terbufos and fonofos exposures and genetic variants on chromosome 8q24,[24] in the base excision repair pathway,[23] and in the nucleotide excision repair pathway[91] and prostate cancer risk were observed. Although more studies are needed to verify these reports, one interpretation of these findings is that DNA damage elicited by terbufos and fonofos is inefficiently repaired by individuals with DNA repair gene variants, which may contribute to disease development. An alternative explanation is that terbufos and fonofos (or their metabolites) do not directly damage DNA; however, these compounds may promote the growth of initiated cells found in genetic backgrounds of inefficient DNA repair.

In other analyses from the AHS project, occupational exposure to petroleum oil herbicides and the presence of single nucleotide polymorphisms (SNPs) in genes that encode xenobiotic metabolizing enzymes caused the risk of prostate cancer to be 3.7 times higher than in individuals who possess the same SNP but did not use petroleum oil herbicides.[101] One xenobiotic metabolizing enzymes identified with a variant allele linked to petroleum oil herbicide exposure and a higher prostate cancer risk was found in the gene that encodes microsomal epoxide hydrolase, which is an important detoxication enzyme of reactive epoxides.[27] Epoxides are chemicals that are formed via cytochrome P450-mediated monooxygenation of carcinogens, such as benzo(a)pyrene found in cigarette smoke and aflatoxin B1, which is produced by the mold *Aspergillus flavus*. Epoxides produced in vivo are often chemically unstable and can covalently modify DNA, thus forming DNA adducts with a propensity to cause mutation. Thus, components of petroleum oil herbicides may be bioactivated to reactive epoxides that can damage DNA, and this risk may be modified by SNPs in microsomal epoxide hydrolase.

In a case-control study of prostate cancer conducted on 709 consecutive cases of histologically confirmed prostate cancer identified between June 2004 and December 2007 in Guadeloupe, a French archipelago in the Caribbean, prostate cancer risk increased with increasing plasma chlordecone concentration (ie, Kepone [Allied Signal Company and LifeSciences Product Company, Hopewell, VA]).[29] Chlordecone is a chlorinated polycyclic ketone insecticide that was used extensively in the French West Indies for more than 30 years, but was banned in the United States in 1975 and worldwide in 2009. Chlordecone is an endocrine disruptor with estrogenic activity.[29] A 1.77-fold excess risk of prostate cancer was observed in individuals in the highest tertile of exposure compared with those not exposed (P for trend = .002).

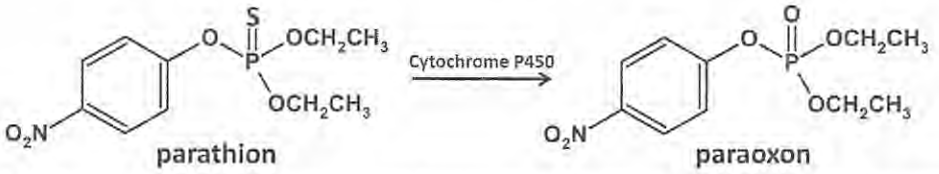

FIGURE 2. Oxidative Desulfuration of the Organophosphate Insecticide Parathion. Parathion is oxidized by cytochrome P450s to the reactive oxon metabolite paraoxon.

Stronger associations were observed among those with a positive family history of prostate cancer. Among subjects with plasma chlordecone concentrations above the limit of detection and 2 at-risk genetic polymorphisms, the risk of prostate cancer was 5.23-fold higher than for those without the exposure or the genetic polymorphism. OC pesticide exposure is often associated with an increased risk of hormone-related cancers, including prostate cancer. After adjustment for other covariates, analysis of National Health and Nutrition Examination Survey (NHANES) data showed that serum concentrations of lindane (P for trend = .02), transnonachlor (P for trend = .002), and dieldrin (P for trend = .04) were significantly associated with the risk of prostate cancer.[32] A popular hypothesis for the toxic mechanism of hydrophobic OCs and other chlorinated pesticides is that they disrupt normal estrogen and androgen receptor functions, thus causing altered gene expression programs to be induced in cells, paving the way for malignant cell development.[42] For example, in vivo and in vitro data from mice and cultured cells suggest that low levels of hexachlorobenzene (HCB) can weakly agonize androgen action and thus enhance androgen signaling, whereas high levels of HCB interfere with androgen signaling.[31] In addition, genotoxic mechanisms may also be in play for OCs. For instance, the OC lindane was found to induce micronuclei in cultured human prostate cells following treatment at very low concentrations (10^{-12}-10^{-10} M) for 24 hours.[30] Thus, both receptor- and genotoxic-mediated toxicities may be at work for OCs and prostate cancer.

Collectively, these studies seem to show that subpopulations with specific genetic characteristics may be particularly vulnerable to the carcinogenic effects of certain OC and OP insecticides. A recent study from Canada also found a significantly increased risk of prostate cancer caused by malathion,[102] and a recent study from the AHS found an excess risk of prostate cancer among occupational users of terbufos.[103] OPs, such as malathion, parathion, and terbufos, can be bioactivated by cytochrome P450-mediated monooxygenation reactions to yield the oxon metabolites (see Figure 2 for example of bioactivation of parathion). Oxons are exquisitely potent compounds that inhibit serine hydrolases via covalent modification of the catalytic serine residue in the enzyme active site.[104] Serine hydrolases participate in a wide variety of physiological and pathophysiological processes, including signal transduction in neural tissue, digestion, immune response, xenobiotic detoxification, and the clotting cascade. Thus, inhibition of these enzymes may lead to a variety of pathological effects. In contrast to most OP compounds, malathion is generally thought to be safe to humans because it contains 2 labile carboxylic acid ester bonds that are easily hydrolyzed by carboxylesterases, thus producing nontoxic products. Nevertheless, human are highly exposed to malathion and this compound can be converted to malaoxon in mammals, which can inhibit serine hydrolases and lead to unwanted toxicities.

A significant association between prostate cancer risk and exposure to dichlorodiphenyltrichlorethane (DDT), a chlorinated insecticide (1.68-fold excess risk for those highly exposed compared with those not exposed); simazine, a triazine herbicide (1.89-fold excess risk for those highly exposed compared with those not exposed); and lindane, a chlorinated insecticide (2.02-fold excess risk for those highly exposed compared with those not exposed) was observed among 1516 prostate cancer cases and 4994 age-matched controls in a population-based case-control study in British Columbia, Canada.[102] Atrazine, a triazine herbicide, was previously suspected of being associated with prostate cancer in a small study of pesticide manufacturing workers,[33] but was not associated with prostate cancer in a much larger evaluation done in the AHS study.[105] Atrazine is one of the most heavily used pesticides in the United States and concerns have been raised about the high levels detected in groundwater. Atrazine is rapidly metabolized to polar metabolites that are readily excreted in the urine of both rodents and humans.[106,107] However, its major quantitative metabolite, dialkylchlorotriazine, was recently shown to covalently modify proteins both in vitro and in vivo,[108] suggesting that dialkylchlorotriazine has the potential to alter protein and cellular function. In addition, there are concerns about the neuroendocrine-disrupting effects of this herbicide.[34]

In contrast to occupational settings, relatively little epidemiology has been conducted to characterize the role that environmental or residential exposures may have in the etiology of prostate cancer. The added complexity in assessing often unknown or poorly quantified environmental exposure to pesticides is a likely explanation.

While the greatest cancer risks from carcinogenic chemicals might be expected to occur among those with long-term occupational exposures, recently, male residents of California's intensely agricultural Central Valley who had ambient exposure to methyl bromide were observed to have a 1.62-fold excess risk of prostate cancer compared with those with no ambient exposure. Similar risks were not observed for simazine, maneb (a dicarbamate fungicide), or paraquat dichloride (a bipyridinium dichloride herbicide).[35] Similar to many methyl halides, methyl bromide was found to be positive in a battery of mutagenicity test systems.[36] Mutation formation is not dependent on the presence of an exogenous enzyme activation system, and thus methyl halides can directly modify DNA because of the relative ease of breaking the carbon-halide bond.[36] Indeed, methyl bromide can directly methylate calf thymus DNA in aqueous solution.[37] Moreover, methyl bromide causes aberrant DNA methylation in rats and mice in vivo,[109,110] and can generate the highly mutagenic O^6-methyl guanine lesion.[37,109] Glutathione conjugation of methyl bromide is the primary mechanism of its detoxification and this reaction is catalyzed by the glutathione S-transferase theta-1 (GSTT1) isoform.[111] The frequency of the GSTT1 null polymorphism in the human population is 20% for whites and 80% for Asians; these individuals do not express a functional GSTT1 enzyme.[112] Future studies that examine the null GSTT1 genotype, methyl bromide exposure, and prostate cancer risk might be worth pursuing because individuals who cannot express GSTT1 would be predicted to have a higher prostate cancer risk. However, it should be noted that methyl bromide is being phased out of use because of its ability to deplete atmospheric ozone.

It is also important to point out that prostate tissue has the ability to both activate and detoxify genotoxins and to repair any consequential DNA damage. The expression of mRNA transcripts for phase 1-activating enzymes such as cytochrome P450 1A2 (*CYP1A2*), *CYP1A1*, and *CYP1B1* has been demonstrated in human prostate.[38] This indicates that carcinogens can be metabolized in situ within the prostate tissue into reactive intermediates that damage macromolecules. Nevertheless, much more mechanistic toxicology studies need to be performed to determine whether occupational exposure to pesticides such as methyl bromide can cause prostate cancer. In light of the increasing epidemiological database linking specific pesticides with prostate cancer, it is reasonable to assume that much more will be learned in the future.

Nonoccupational exposure to OC insecticides was investigated in 4 case-control studies by measuring the concentrations of selected OC insecticides in serum,[41] adipose tissue,[39] or plasma.[40,113] Aronson et al[40] reviewed medical records for male participants aged 50 years to 80 years who visited one of 5 urology clinics in Kingston, Ontario, Canada between 1997 and 1999. Of the 7 OC insecticides assayed (*p,p'*-dichlorodiphenyldichloroethylene [DDE], *p,p'*-DDT, *trans*-nonachlor, oxychlordane, HBC, β-hexachlorocyclohexane, and mirex), none was associated with prostate cancer.[40]

Ritchie and Vial[41] also examined concentrations of OC insecticides in serum from a case-control study of men with prostate cancer in Iowa. Of the 8 analytes reported, only 3 (*p,p'*-DDE [100% cases, 99% controls], *trans*-nonachlor [98% cases, 88% controls], and oxychlordane [91% cases, 82% controls]) had detectable concentrations above 50% for both the cases and controls, but none of these 3 pesticides was clearly associated with prostate cancer. In a case-control study nested in the Japan Public Health Center-based Prospective Study,[113] 201 incident prostate cancer cases were identified through December 31, 2005. Nine analytes were assayed, including *o,p'*-DDT, *p,p'*-DDT, *p,p'*-DDE, trans-nonachlor, cis-nonachlor, oxychlordane, HCB, mirex, and β-HCH. However, none of these analytes was associated with prostate cancer.

In a small case-control study comprised of 58 cases and 23 controls, Hardell et al[39] found positive associations between prostate cancer and HCB (odds ratio [OR], 3.15; 95% confidence interval [95% CI], 1.04-9.54), *p,p'*-DDE (OR, 2.39; 95% CI, 0.81-7.09), trans-chlordane (OR, 3.49; 95% CI, 1.08-11.2), and MC6 (OR, 2.71; 95% CI, 0.87-8.42). With the exception of HCB, none of the ORs achieved statistical significance and all point estimates were imprecise due to the small number of study participants.

In summary, a number of specific pesticides have been linked to prostate cancer risk in occupational settings in an increasing number of studies. In many cases, this risk seems to be enhanced by a family history of prostate cancer. Although the enhanced prostate cancer risk may be a result of common occupational exposures among family members, there is increasing evidence that specific genetic polymorphisms in key genetic pathways may play an important etiologic role. Since the "at-risk genetic polymorphisms" are relatively common in the population, controlling the pesticide exposure rather than genetic testing may be the more desirable public health cancer control measure. Occupational exposures to some, but not all, OP and chlorinated pesticides have been associated with prostate cancer, but other pesticide categories have also been implicated in prostate cancer etiology. Studies of other pesticides with interesting preliminary gene environment analyses are now being completed.

Non-Hodgkin Lymphoma

NHLs are a heterogeneous group of over 20 different B- and T-cell neoplasms affecting the immune system/lymphatic system and arising primarily in the lymph nodes.[114,115] Interest in the etiology of NHL has increased

because incidence rates have nearly doubled in Western countries during the interval from the 1960s through the mid-1990s. The established risk factors for NHL include genetic susceptibility and a previous history of malignant disease[116] and different immunosuppressive states including human immunodeficiency virus; autoimmune diseases such as Sjogren syndrome, systemic lupus erythematosus, rheumatoid arthritis, and psoriasis; and celiac disease.[117] Organ transplant recipients receiving immunosuppressive therapy are at a more than 100-fold excess risk of NHL.[118] However, these conditions cannot account for the increases observed.[118] Exposure to pesticides, particularly phenoxy acid herbicides, has been suggested as a cause of NHL,[119] but the evidence has been inconsistent. In Sweden, Hardell et al observed a 6-fold increased risk of NHL among those who used phenoxy acid herbicides.[120] In Kansas, Hoar et al observed a significant 2-fold increased risk among those who used phenoxy acid herbicides and the risk was highest for those who used 2,4-dichlorophenoxyacetic acid (2,4-D) for 21 days or more during the course of 1 year.[121] In Nebraska, a nonsignificant 50% excess risk of NHL was observed among users of 2,4-D, but the risk did increase to over 3-fold for those who used the herbicide 20 or more days per year.[122] Little evidence of an association between phenoxy acid herbicides and NHL was observed in New Zealand,[123] Washington state,[62] or Minnesota and Iowa.[124] A meta-analysis of 13 case-control studies published between 1993 and 2005 observed an overall significant meta-OR between occupational exposure to pesticides and NHL (OR, 1.35; 95% CI, 1.2-1.5). When observations were limited to those individuals with more than 10 years of exposure, the risk increased (OR, 1.65; 95% CI, 1.08-1.95).[125] While the meta-analysis supports the hypothesis that pesticides are associated with NHL, they lack sufficient detail about pesticide exposure and other information on risk factors for hematopoietic cancers to identify specific causes.[125]

Since the publication of the meta-analysis by Merhi et al,[125] several new population-based studies have been published suggesting that specific pesticides play an important role in NHL etiology. In a case-cohort study using a population-based prospective Danish cohort of 57,053 persons, 256 cohort members were diagnosed with NHL.[126] Eight pesticides and 10 polychlorinated biphenyls congeners were measured in adipose tissue collected at enrollment, prior to cancer onset among the 256 NHL cases and in 256 cancer-free individuals randomly selected from the cohort. A higher risk of NHL was observed among those with higher prediagnostic adipose tissue levels of DDT, cis-nonachlor, and oxychlordane than among those with lower adipose tissue levels.[126] No clear association was found between NHL and polychlorinated biphenyls. A Swedish study by Eriksson et al of 910 cases and 1016 controls observed a significant excess risk of NHL associated with the phenoxy herbicide 2-methyl-4-chlorophenoxyacetic acid. (MCPA) (OR, 2.81; 95% CI, 1.27-6.22) and glyphosate (OR, 2.02; 95% CI, 1.16-3.71). Insecticides overall demonstrated an OR of 1.28 (95% CI, 0.96-1.72) and impregnating agents (ie material used as a water-repellent and antifungal treatment of wood, brick, plaster, and roof tiles) showed an OR of 1.57 (95% CI, 1.07-2.30). 2,4-D and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) have been banned from Sweden and therefore could not be evaluated.[47] Several important observations have been made in a population-based case-control study conducted in 6 Canadian provinces including Quebec, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia with cases diagnosed between September 1, 1991 and December 31, 1994. An increased risk of 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).[51] In this same case-control study, 6 pesticides/pesticide analytes also showed a significant association with NHL (beta-hexachlorocyclohexane, *p, p'*-dichloro-DDE, HCB, mirex, oxychlordane, and transnonachlor).[127] 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). However, 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 plasma levels of HCB, beta-HCB, or DDE.[46] In yet another case-control study from the 6 Canadian provinces, the risk of NHL increased with the number of different pesticides used.[53] ORs increased even further when the analyses were restricted to "potentially carcinogenic" pesticides; one pesticide had an OR of 1.30 (95% CI, 0.90-1.88), 2 to 4 pesticides had an OR of 1.54 (95% CI, 1.11-2.12), and more than 4 pesticides had an OR of 1.94 (95% CI, 1.17-3.23). These results are somewhat similar to those reported by De Roos et al, who pooled data from 3 NHL case-control studies conducted in the 1980s in 4 American Midwestern states. A superadditive effect was observed in which atrazine amplified the risk of NHL when used in combination with several other pesticides including alachlor, diazinon, and carbofuran.[128] In yet another article from the 6 Canadian provinces study, the joint effect of pesticide exposure and immune suppression was preliminarily evaluated.[61] Study participants with asthma or hay fever had nonsignificantly elevated risks of NHL associated with the use of MCPA (OR, 2.67; 95% CI, 0.90-7.93) compared with participants without any of these conditions (OR, 0.81; 95% CI, 0.39-1.70).

Two epidemiological studies reported that the association of NHL with pesticides was largely limited to NHL cases with the t(14;18) chromosomal translocation.[43,52] In the study by Schroeder et al conducted in Iowa and Minnesota, patients with NHL with the t(14:18) translocation were found to have significantly elevated levels of dieldrin (OR, 3.7; 95% CI, 1.9-7.0), lindane (OR, 2.3; 95% CI, 1.3-3.9), toxaphene (OR, 3.0; 95% CI, 1.5-6.1), and atrazine (OR, 1.7; 95% CI, 1.0-2.8).[52] In the study by Chiu et al conducted in Nebraska, farmers diagnosed with NHL with a t(14:18) translocation were found to have significantly elevated levels of dieldrin (OR, 2.4; 95% CI, 0.8-7.0), toxaphene (OR, 3.2; 95% CI, 0.8-12.5), and lindane (OR, 3.5; 95% CI, 1.4-8.4) compared with nonfarmers. In the prospective AHS, lindane use was associated with a significantly elevated risk of NHL.[44] In a Dutch cohort of workers involved in the manufacturing of chlorophenoxy herbicides, predicted TCDD levels were associated with a significant increase in mortality from NHL (OR, 1.36; 95% CI, 1.06-1.74).[45]

Cytogenetic and molecular studies of individuals exposed to a number of pesticides, such as lindane and 2,4-D, are beginning to reveal a role of pesticides in the induction of chromosomal rearrangements, particularly the t(14;18) translocation that occurs with high frequency in patients with NHL.[57] This translocation appears to be one step in the progression of a normal cell to a cancer cell; however, it is unclear whether pesticides (or other toxicants) cause the t(14;18) translocation or whether they are generated during the course of malignant transformation as a result of the developing genomic instability that arises during disease progression. Polymerase chain reaction-based quantitation of the t(14;18) translocation frequency in peripheral blood lymphocytes, as described by Fuscoe,[129] might be a promising biomarker to use in studies of pesticide-exposed populations. A direct connection between agricultural pesticide use, frequency of the t(14;18) translocation in the blood, and malignant progression to follicular lymphoma has been observed in a prospective cohort study of farmers.[130] This study indicated that the t(14;18) translocation appeared to be an early event in NHL and suggested a molecular connection between agricultural pesticides, the t(14;18) translocation frequency in the blood, and clonal progression, but links to specific pesticides were not possible. However, the mechanistic molecular connection between pesticides and the t(14;18) translocation is still unclear and establishing this link will require much more work. Nevertheless, the higher prevalence of the t(14;18) translocation in pesticide-exposed workers compared with controls is a provocative finding and the replication of this finding in another pesticide-exposed population will be an important follow-up study. Moreover, for the t(14;18) translocation to be used as a biomarker, these findings would ideally be validated in an animal model treated with pesticides. This would provide an even stronger case for studying this biomarker in human populations.

We identified 15 studies that reported on nonoccupational exposure to pesticides and NHL. The vast majority of these studies focused on OC insecticides (11 of 15 studies) and used serum,[48,58,131] plasma,[46,54-56,59] or adipose tissue[53,60,126] concentrations of the OC compounds as the estimate of exposure. Of these 11 studies, 7 measured chlordane/heptachlor or their metabolite (eg, oxychlordane, heptachlor epoxide) concentrations. Four studies[55,60,126,127] observed positive associations between chlordanes and NHL, whereas the 3 other studies did not observe an association.[48,54,58]

In addition to oxychlordane and related compounds (eg, heptachlor), 10 of these studies examined the association between concentrations of DDT or its metabolite, DDE, and NHL. Five studies[48,55,60,126,127] demonstrated either positive or suggestive associations, whereas the other 5 studies[46,54,56,59,131] did not observe an association between DDT or DDE and NHL.

While a number of other OC insecticides were measured in these studies, coverage of specific insecticides was less frequent. For instance, only one study[127] assayed for mirex, finding a positive association (OR, 1.44; 95% CI, 1.08-1.92). Conversely, HCB was assessed in 8 of these studies,[46,48,54,55,58,60,126,127] of which only one observed an association. β-Hexachlorocyclohexane concentrations were positively associated with NHL in only 2[52,123] of the 6 studies that measured it in either plasma, serum, or adipose tissue. Dieldrin levels were assayed in 4 studies,[54,58,60,126] with only one[54] finding evidence of a positive association with NHL.

In summary, NHL is not one disease but many related diseases with seemingly different etiologies. Few studies of pesticides have been large enough to evaluate the potential link between NHL subtypes and specific pesticide exposures. Nonetheless, new evidence linking NHL with specific chlorinated pesticide use and 2 studies linking the number of different pesticides used with NHL give further support to earlier findings suggesting that specific pesticides are etiologically linked to NHL. Preliminary evidence suggests asthma, allergies, or asthma and allergies and hay fever combined with the use of specific pesticides (eg, MCPA) may enhance the risk of NHL. Although it is possible that t(14;18) translocations are an initiating event in a causative cascade leading to an NHL subtype, follicular lymphoma, much more work needs to be done to establish this. Nevertheless, it has been shown that NHL subtypes with t(14;18) translocations are associated with the chlorinated insecticides dieldrin, lindane, and toxaphene and the triazine herbicide atrazine. Lindane also has been

observed to be directly associated with NHL in a large prospective study performed in the United States. In yet another large case-control study in Sweden, the authors linked the use of glyphosate and MCPA to NHL. Although the epidemiological evidence for certain pesticides and NHL is growing, little is known about the biological/toxicological mechanisms by which these compounds may be contributing to this disease (Table 5).

Leukemia

Childhood Leukemia

Acute lymphocytic leukemia comprises about 80% of all childhood leukemia cases, while acute myeloid leukemia comprises most of the remaining 20%.[49] Male children have a higher incidence of leukemia overall compared with female children. It is estimated that less than 10% of childhood leukemia cases have an identified etiology. Established associations include ionizing radiation, Down syndrome, and other genetic syndromes.[132] In the United States and Europe, there is concern that overall rates of childhood cancer have been increasing since 1970.[133] Early life exposures to pesticides are suspected to be responsible for some of these childhood leukemias. A number of recent systematic reviews of the etiological literature[134-137] reached a somewhat similar conclusion (ie, the current literature is limited). Chief among these limitations are that exposure measures relying on substitutes for information about parental pesticide use itself such as in farm-related activities or crops produced has proven to be inadequate; case-control studies tended to suffer from at least some case-recall bias; cohort studies have been too small to generate a sufficient number of exposed cases, thereby mitigating firm etiological conclusions; many available studies (both case-control and cohort) were too small to reliably evaluate leukemia subtypes and all were too small to identify specific pesticides that might be linked to childhood leukemia; and controlling for potentially confounding factors is difficult when so little is known about the etiology of childhood leukemia generally. Nonetheless, a number of important observations have been made in meta-analyses associated with these reviews (ie, an excess risk of overall leukemia is observed with maternal pesticide exposure from home and garden use[135] or maternal occupational exposure but not with paternal occupational pesticide exposure).[136,137] Meta-analyses of childhood leukemia were elevated for prenatal maternal occupational exposure to both insecticides and herbicides.[136] While elevated risks of childhood leukemia were also observed in meta-analyses of children living in homes where professional pesticide applications were done before pregnancy, during pregnancy, and during the first 3 years of the child's life,[134] Vinson et al observed the maternal-associated leukemia risks to be particularly high for exposures that took place prior to birth.[135] While data are limited, it seems both acute lymphocytic leukemia and acute myeloid leukemia in children may be linked to pesticide exposure.[136] Excess childhood leukemia risks did not appear to be related to the proximity of a home to a farm,[137] nor to carpet-tested levels of chlordane, DDT, DDE, methoxychlor, or pentachlorophenol.[138]

Experimental studies in animal models support the biological plausibility of a link between maternal pesticide exposure and leukemia because the exposure of pregnant females to carcinogens can produce cancer in offspring.[139] Transplacental exposure to select fungicides produced lymphomas in mice.[140] Furthermore, the role of epigenetics in germ cell genomic reprogramming has gained increased attention since it was shown that exposure of gestating female rats during the period of gonadal development to either vinclozolin (a fungicide) or methoxychlor (an insecticide) induced elevated incidences of male infertility and altered sperm quality in offspring up to 4 generations.[141,142] Moreover, prostate lesions, altered gene expression patterns, and cancer were detected in some adult progeny.[142] These provocative findings have caused renewed interest in developmental and reproductive toxicities, such as childhood leukemias, caused by environmental chemicals. At this point, work in this area is in a nascent stage of development and much more needs to be done.

Linking specific pesticides to childhood leukemia would most likely lead to the cancelation of registration of that pesticide in the United States and many other nations. Since such a specific link has not yet been made, prudent public health policy would dictate limiting maternal exposure to pesticides prenatally and during early child- hood and limiting direct childhood exposure whenever possible.

Adult Leukemia

Adult-onset leukemias are a heterogeneous category of hematopoietic malignancies, including chronic and acute subtypes that have different etiologies. Causal associations with leukemia have been demonstrated for 3 agents: benzene,[63] formaldehyde,[64] and ionizing radiation.[143] Other suspected occupational causes include pesticides, infectious agents, electromagnetic fields, and solvents and aromatic hydrocarbons.[144]

A meta-analysis of 14 cohort studies of workers in plants manufacturing pesticides showed a meta-rate ratio of 1.43 (95% CI, 1.05-1.94) for leukemia.[145] A recent meta-analysis of 13 cases and controls examining the association between occupational exposures and hematopoietic cancers observed an OR of 1.35 (95% CI, 0.9-2.0).[125] Epidemiological evidence was insufficient to permit the identification of a specific pesticide in either of these meta-analyses.

OPs have been associated with leukemia and other immunologically related cancers in the epidemiological literature.[65,146-151] The leukemogenic effects of OPs may be related to immune function perturbation. In the AHS, leukemia risk was elevated for the high category of intensity-weight exposure-days for the OP insecticide fonofos (relative risk [RR], 2.67; 95% CI, 1.06-6.70 [*P* value for trend = .04])[148] and diazinon was associated with leukemia (RR, 3.36; 95% CI, 1.08-10.49 [*P* value for trend = 0.026]).[149] A positive association with leukemia was also observed for several herbicides including metribuzin, a selective triazinone herbicide (RR, 2.42; 95% CI, 0.82-7.19 [*P* value for trend = .08]),[150] and the use of the herbicides alachlor[151] and S-ethyl-N,N-dipropylthiocarbamate (EPTC),[65] although the risk associated with both of these herbicides was limited to the highest exposure group and thus further follow-up will be necessary.

The IARC has judged that the weight of evidence suggests that the OC insecticides chlordane, heptachlor, DDT, and toxaphene are possible human carcinogens, whereas other OCs are not classifiable as to their carcinogenicity.[66] In the AHS, chemical-specific associations with leukemia were observed for chlordane/heptachlor (RR, 2.1 [95% CI, 1.1-3.9]), which are structurally related compounds that occur together in technical-grade products of each chemical.[44]

In a prospective study of peripheral blood obtained up to 77 months before a diagnosis of chronic lymphocytic leukemia (CLL) was made, prediagnostic B-cell clones were present in 44 of 45 patients with CLL.[67] Use of B-cell clones as prediagnostic markers of CLL may be a valuable tool in evaluating the link between specific pesticides and CLL.

While the evidence linking pesticide exposure to leukemia is abundant, the evidence linking a specific pesticide to a specific leukemia subtype, which could be used to more stringently regulate use of the pesticide or cancel its registration, is largely nonexistent. Recent epidemiological evidence linking specific pesticides to leukemia has established hypotheses that need to be evaluated in other studies (eg, the associations between leukemia overall and diazinon [an OP insecticide currently in widespread use] and several OC insecticides no longer in use in the United States or other developed countries are of particular interest).[65,66,146-151] Linking leukemia to specific pesticides that are used at high levels occupationally should help to identify the chemical agents responsible for childhood cancers as well. The use of preclinical biomarkers (eg, monoclonal B-cell lymphocytosis) to study the etiology of CLL may be a powerful approach for this leukemia subtype.[67] In addition, it has been shown that arylhydrocarbon receptor activation and cyclooxygenase-2 overexpression in lymphoma cell lines lead to resistance to apoptosis,[152] which might be relevant for the development of lymphomas in vivo caused by pesticide exposures.

Multiple Myeloma

Multiple myeloma is a malignancy of the blood, characterized by a clonal expansion of plasma cells and the production of a monoclonal immunoprotein that can be found in the blood or urine. Clonal expansion of plasma cells is accompanied by osteolytic bone destruction, renal failure, anemia, and hypercalcemia.[153] Following a diagnosis of multiple myeloma, the median length of survival is approximately 3 years. Approximately 21,700 new cases are diagnosed annually.[99] Incidence among blacks is twice that among whites but the survival among blacks is significantly better compared with whites.[154] The underlying cause of multiple myeloma is unknown.[153]

A systematic review of case-control studies of the role of occupational exposure to pesticides in the development of multiple myeloma showed a pooled OR for working farmers of 1.39 (95% CI, 1.18-1.65) and an OR for pesticide exposure of 1.47 (95% CI, 1.11-1.94). For working on a farm for more than 10 years, the OR was 1.87 (95% CI, 1.15-3.16).[125] None of these studies, however, was able to identify a specific exposure that was associated with multiple myeloma. In the AHS, an excess risk of multiple myeloma was observed in the cohort.[155] In a follow-up study, a 1.42-fold (95% CI, 1.00-fold to 1.81-fold) risk of multiple myeloma was observed among cohort members in North Carolina compared with the rest of the state, but a similar excess risk was not observed in Iowa.[21] The cause of this excess could not yet be explained, but a separate analysis of the AHS cohort observed a statistically significant risk of multiple myeloma among pesticide applicators in the highest exposure group for the insecticide permethrin (RR, 5.72; 95% CI, 2.76-11.87 [*P* value for trend = .01]) compared with never-users.[156] A cautious interpretation of these results is warranted because the analysis was driven by only 10 exposed cases in the highest exposure group. Positive associations between the fungicide captan (OR, 2.35; 95% CI, 1.11-3.27) and the insecticide carbaryl (OR, 1.89; 95% CI, 0.98-3.67) and multiple myeloma were observed in a recent Canadian population-based case-control study conducted among men in 6 Canadian provinces (ie, Quebec, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia).[186] The study consisted of 342 multiple myeloma cases and 1506 controls.

Recent data have shown that multiple myeloma is consistently preceded by monoclonal gammopathy of undetermined significance (MGUS).[157] MGUS is a premalignant plasma cell proliferative disorder without

symptoms or evidence of end-organ damage, but cases do have a lifelong 1% annual risk of progression to multiple myeloma.

In the AHS cohort, the age-adjusted prevalence of MGUS was 1.9-fold (95% CI, 1.3-fold to 2.7-fold) higher among male pesticide applicators compared with men from Olmsted County, Minnesota.[158] In the AHS cohort, a 5.6-fold (95% CI, 1.9-fold to 16.6-fold), 3.9-fold (95% CI, 1.5-fold to 10.0- fold), and 2.4-fold (95% CI, 1.1-fold to 5.3-fold) increased risk of MGUS was observed among users of the chlorinated insecticide dieldrin, the fumigant mixture carbon tetrachloride/carbon disulfide, and the fungicide chlorothalonil, respectively. A previous AHS examination determined that a relationship between exposure and disease is not likely confounded by farming or nonfarming activities.[68]

In summary, although the evidence linking pesticide exposure to multiple myeloma has increased in recent years, few studies have been able to assess the link between specific pesticides and multiple myeloma or its precursor MGUS. It is therefore not surprising that we do not yet observe consistent associations. Clearly, additional epidemiological evidence is needed to test the hypothesis that specific pesticides are positively associated with multiple myeloma before firm conclusions can be reached. The use of preclinical biomarkers of multiple myeloma (ie, MGUS) may be a powerful approach to evaluate these etiological hypotheses.

Nonoccupational OC Insecticide Exposure and Breast Cancer

Breast cancer is the most common cancer among women in the United States, accounting for an estimated 226,870 cases in 2012 and 39,510 deaths.[99] Male breast cancer is relatively rare, with an estimated 2190 cases in 2012 and 410 deaths.[99] Epidemiologic studies of occupational pesticide exposure and breast cancer risk are quite limited. Conversely, the open literature is replete with epidemiologic studies that have investigated nonoccupational exposure to OC compounds, including OC insecticides. Given this paucity in occupational studies, we will focus only on the nonoccupational studies of OC insecticides and breast cancer.

In 1993, Wolff et al[159] published a report observing that the risk of breast cancer was higher among women with high serum concentrations of DDE, the major metabolite of DDT, compared with women with low levels. Since then, a substantial number of epidemiologic studies have been conducted and published investigating this hypothesis.

In 2002, Calle et al[160] published a review article evaluating the then-current literature and concluded that: "At present, there is substantial epidemiologic evidence regarding the possible association between organochlorines (as measured in blood and adipose tissue) and the risk of breast cancer. The evidence does not support an association."[160]

Lopez-Cervantes et al[161] arrived at a similar conclusion using meta-analysis to review the epidemiologic evidence for tissue DDE concentrations and breast cancer. In our current review, we update the literature since 2002. We identified 11 published studies[32,162-171] that reported on associations between measured serum, plasma, or adipose tissue concentrations of OC insecticides and breast cancer, which were not included in either the review by Calle et al or Lopez-Cervantes et al.[160,161] Two studies[162,167] were excluded from our review because risk estimates (eg, ORs) were not reported. A third study[32] was excluded because the case definition included prevalent breast cancer. Of the remaining 8 studies, the results were mixed. While 4 studies[163,165,169,170] did not observe an association between OC concentrations, the other 4 studies[164,166,168,171] did observe positive associations.

However, an important caveat to this conclusion remains largely unexplored: the importance that age at exposure may have in breast cancer development. Lopez-Cervantes et al point out that there is a paucity of evidence regarding exposure at critical time periods.[161] Exposures that occur during early life and adolescence are hypothesized to have etiologic importance for breast cancer.[172,173] During mammary gland development, breast epithelium may be particularly susceptible to environmental carcinogens.[174,175] For instance, exposure to ionizing radiation at an early age confers an increased risk of developing breast cancer as compared with exposure that occurs at later ages.[176,177] Regarding early-life exposure to OC insecticides and breast cancer risk, Cohn et al[168] conducted a nested case-control study among a cohort of female members of the Kaiser Permanente Health Plan in Oakland, California and used stored blood samples that were collected between 1959 and 1967 to assay for serum *p,p'*-DDT. They found that that increasing serum *p,p'*-DDT concentrations were positively associated with breast cancer risk, but only among those women exposed prior to 14 years of age.[168] Caution is warranted in interpreting the results for this one study. While the unique circumstances surrounding the study permitted the investigation of early-life exposure to DDT and future breast cancer risk during a time when DDT was actively being used in the United States, replication will be difficult, as the authors note. Overall, these additional studies do not provide compelling evidence to revise the overall conclusion of the previous reviews that the evidence does not support an association between OC insecticides and breast cancer risk.

While the number of epidemiologic studies that have investigated OC compounds is substantial, few epidemiologic studies have been conducted to investigate

non-OC pesticides and breast cancer risk. We identified just 8 published studies that reported on nonoccupational and non-OC insecticide exposure and breast cancer.[178-185] Of these 8 reports, 4 were case-control studies[181-184] that lacked pesticide-specific exposure information and the fourth was an ecologic study in design.[185] The 3 remaining studies[178-180] assessed exposure to a number of specific pesticides, but overall, these studies are too few to provide a meaningfully review.

Conclusions

Assessing the magnitude of the cancer risk from pesticide exposures in the workplace can be difficult because exposures are usually intermittent, pesticide metabolites have a short half-life, and biomarkers of exposure are often nonspecific to the exposure. Assessing cancer risk from pesticide exposures in the general environment is even more challenging. Nonetheless, the available scientific evidence does strongly suggest that pesticides do cause cancer in both those who use the pesticides directly and those who are exposed because of applications others make. The problem may well be more extreme in developing counties where regulatory controls are weaker or nonexistent.

The mechanisms by which pesticides cause cancer are probably numerous, but are incompletely understood. Cancer risk does not seem to be limited to one functional class of pesticides (eg, herbicide, insecticide, or fungicide) or to one chemical class (eg, OCs, OPs, or triazines). Direct genotoxicity is an important mechanism but many nongenotoxic mechanisms seem to be operating as well. Genetic susceptibility to the carcinogenic effects of some pesticides also appears to be an important aspect of the disease mechanism. The genetic susceptibilities that have been identified to date are common to large segments of the population and therefore do not lend themselves to controlling risk through the identification of susceptible individuals. Controlling exposures is the key to limiting cancer risk. Well-designed epidemiological studies with molecular components will help to identify human carcinogens currently on the market, while an increased understanding of the underlying mechanisms of carcinogenesis will help prevent the introduction of new carcinogens to the marketplace.

Until a more complete understanding of pesticide carcinogenesis is achieved, balancing the potential, albeit uncertain, carcinogenic risk with the health benefits derived from the use of pesticides that can mitigate disease-carrying pests or increase fruit and vegetable production will remain a public health and clinical quandary. In the meantime, health care providers should emphasize the importance of minimizing personal exposures to all pesticides to control cancer risk. ■

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An Evaluation Of Glyphosate Use And The Risks Of Non-Hodgkin Lymphoma Major Histological Sub-Types In The North American Pooled Project (Napp)

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Objectives: Glyphosate is a commonly used herbicide worldwide. Some epidemiological studies have linked exposure with the development of non-Hodgkin lymphoma (NHL), a group of cancers with distinct risk factors and etiologies. This study aimed to evaluate possible associations between glyphosate exposure and NHL risk. Methods: The NAPP, composed of pooled case-control studies from the US 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 lymphatohematopoietic cancer, and personal protective equipment. Results: Cases who ever used glyphosate had elevated NHL risk overall (OR=1.51, 95% CI: 1.18, 1.95). The highest risks were found for "other" sub-types (OR=1.91, 95% CI: 1.20, 3.04). Subjects who used glyphosate for >5 years had increased SLL risk (OR=2.58, 95% CI: 1.03, 6.48). Compared to non-handlers, those who handled glyphosate for >2 days/year had significantly elevated odds of NHL overall (OR=2.66, 95% CI: 1.61, 4.40) and FL (OR=2.36, 95% CI: 1.06, 5.29), DLBCL (OR=3.11, 95% CI: 1.61, 6.00), and other (OR=2.99, 95% CI: 1.10, 8.09) sub-types. There were suggestive increases in NHL risk overall with more lifetime days of use but this trend was not statistically significant (p=0.065). Conclusion: This study provides some evidence that glyphosate use may be associated with increased NHL risk. Effects may differ by histological sub-type. The large sample size of the NAPP enabled a detailed investigation despite some inconsistent results across different exposure metrics.

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