From: Huff, James (NIH/NIEHS) [G]
Sent: Monday, April 03, 2017 11:31 AM
To: fiorella belpoggi; morando soffritti; peter infante; phil landrigan; jennifer sass [NRDC]; Kathryn Guyton; Dana Loomis; Kurt Straif
Subject: Who[1]s Getting Money from NIH? IARC & Ramazzini

S- thank you - not even close to the real truth - both IARC & Ramazzini are stellar pro public health agencies generating and using good science and excellent scientific methods - reported $$ figures in my view are orders of magnitude over the top — writers are clearly industry vested and anti-public health zealots - j

---

http://www.nationalreview.com/article/446335/nih-grants-ramazzini-iarc

https://goo.gl/awcwz6
Who's Getting Money from NIH?

From: Huff, James (NIH/NIEHS) [G]
Sent: Tuesday, March 28, 2017 9:37 AM
To: fiorella belpoggi; morando soffritti; phil landrigan; Kathryn Guyton; Dana Loomis; Kurt Straif
Cc: Bucher, John (NIH/NIEHS) [E]; Birnbaum, Linda (NIH/NIEHS) [E]
Subject: House Science Panel Digs Into U.S. Funding of European Institute -- Ramazzini Institute- IARC - Cong L Smith
Attachments: Ramazzini-Cong L Smith-24 Mar 2017.pdf

March 27, 2017

House Science Panel Digs Into U.S. Funding of European Institute

By Tiffany Stecker

Members of Congress are looking to investigate how the Department of Health and Human Services funds an obscure scientific institution in Italy.

House Science, Space and Technology Committee Chairman Lamar Smith (R-Texas) and Oversight Subcommittee Chairman Darin LaHood (R-Ill.) sent a letter March 24 to Health and Human Services Secretary Tom Price asking for documents they hope will clarify the financial ties between the National Institutes of Health's National Institute of Environmental Health Sciences and the Ramazzini Institute, a scientific institution in Italy focused on occupational and environmental health.

"The Committee is concerned that contracts awarded to the Ramazzini Institute and its affiliates may not meet adequate scientific integrity standards," the lawmakers said in the letter. Specifically, the panel alleges the institute accepted at least $1 million through sole-source contracts, meaning the institute did not bid against other potential recipients for the money. The letter also says that NIEHS has sent $92 million since 2009 to the institute.

The call for Ramazzini's documents dovetails with a larger campaign from the chemical industry to reform scientific agencies that conduct assessments that tend to link substances to cancer, saying these findings are misleading the public on cancer risk.

The American Chemistry Council launched a campaign in January to encourage lawmakers to "seek reform" of another European agency, the Lyon, France-based International Agency for the Research of Cancer (IARC). The agency's assessments of cancer hazards, particularly a 2015 conclusion that the herbicide glyphosate is a probable carcinogen, has triggered the ire of Monsanto Co., whose Roundup weedkiller contains glyphosate.

The Ramazzini Institute has come under fire before. The House panel questioned the Environmental Protection Agency in 2012 over Ramazzini studies used in chemical risk assessments. The Intergrated Risk Information System program used the institute's studies on the carcinogenic potential of methanol. Critics of the institute said the study's methods led to an outcome in which exposed rats were more likely to develop lymphoma and leukemia.

Representatives for the Ramazzini Institute and NIEHS could not be reached for comment.

Though the campaign doesn't specifically target the Ramazzini Institute, representatives of the initiative have linked former Ramazzini scholars with the IARC panel on glyphosate.

"CAPHR intends to promote reform of IARC. But evidence is emerging that Ramazzini and IARC are in close collaboration," said Campaign for Accuracy in Public Research spokeswoman Ana Heeren in an email.

The free-market law institute E&E Legal also sued HHS last week for withholding responses to the watchdog's public records requests on the Ramazzini Institute.

NIEHS ultimately backed the Institute on this study, finding "consistency and value" in the analyses despite some confounding aspects that made diagnoses in the rats more difficult.

Specifically, the committee is seeking communications on grants or contracts between NIEHS and Ramazzini, as well as a list of fellows employed by Ramazzini and information on specific contracts purported to be sole-source.

To contact the reporter on this story: Tiffany Stecker in Washington attstecker@bna.com

To contact the editor responsible for this story: Larry Pearl atlpearl@bna.com

For More Information

Letter from Reps. Lamar Smith and Darin LaHood on Ramazzini Institute is available at http://src.bna.com/nk4

LAMAR S. SMITH, Texas
CHAIRMAN

EDDIE BERNICE JOHNSON, Texas
RANKING MEMBER

Congress of the United States
House of Representatives

COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY

2321 RAYBURN HOUSE OFFICE BUILDING

WASHINGTON, DC 20515–6301

(202) 225–6371
www.science.house.gov

March 24, 2017

The Honorable Thomas E. Price
Secretary
U.S. Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, DC 20201

Dear Secretary Price:

The Committee on Science, Space, and Technology is conducting oversight of the National Institutes of Health's (NIH) National Institute of Environmental Health Sciences (NIEHS) contract and grant management. The Committee is investigating the scientific integrity of the work performed by NIEHS contract and grant recipients. According to public records, the Ramazzini Institute ("Ramazzini" or "the Institute"), an independent international science academy that conducts cancer related studies, benefited from at least seven sole source government contracts.[1] The Committee is concerned that contracts awarded to the Ramazzini Institute and its affiliates may not meet adequate scientific integrity standards. Additionally, these sole source contracts raise questions about the integrity of the acquisition process at NIH and NEIHS. We are writing to request documents and information to determine whether NIEHS is complying with all federal acquisition regulations and ensuring award recipients are adhering to the utmost standards of scientific integrity.

According to a March 17, 2017, media report, Italy's Ramazzini Institute has received at least thirteen different NIEHS contracts through four different third parties since 2009, totaling nearly $2 million.[2] Of the thirteen contracts, seven appear to be sole source, representing over $1 million taxpayer dollars. Further, media reports indicate that since 2009 NIEHS has directed as least $92 million in *grant* funds to the Ramazzini Institute and its U.S. affiliate.[3] If true, this raises serious questions about the integrity of the acquisition process at NIEHS.

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1 USASpending.gov, *Ramazzini Results Summary*, *available at* https://www.usaspending.gov/Pages/AdvancedSearch.aspx?sub=y&ST=C,G&FY=2017,2016,2015,2014,2013,2012,2011,2010,2009&A=0&SS=USA&k=ramazzini (last visited Mar. 23, 2017) [hereinafter USASpending.gov Results].

2 E&E Legal, Press Release, *E&E Legal Again Forced to Sue NIH for Public Records Re: U.S. Taxpayer-Funded Payments to the International Agency for Research on Cancer, Italy's Ramazzini Institute* (Mar. 17, 2017) [hereinafter *E&E Legal Again Forced to Sue NIH*]; *see also Id.*

3 *E&E Legal Again Forced to Sue NIH*, *supra* note 1.

The NIEHS conducts and provides resources for environmental health sciences with a mission "to discover how the environment effects people in order to promote healthier lives."[4] NIEHS claims an impressive record of important scientific accomplishments achieved in part by contracts awarded to institutions conducting scientific work to support the NIEHS mission.[5] According to public records and media reports, NIEHS contracted with Ramazzini and its affiliates through multiple third parties, yet it is unclear what services were rendered under these contracts.[6] Reports indicate NIEHS director Linda Birnbaum, a Ramazzini fellow, funneled millions of dollars in NIEHS grant funds to other Ramazzini fellows and their affiliates.[7] Further, since 1985, reports indicate that, in total, NIEHS has provided $315 million in grant dollars to Ramazzini fellows.[8]

More recently, the NIEHS has refused to respond to FOIA requests seeking information related to contracts between your Department, including NIH and NEIHS, and Ramazzini.[9] E&E Legal recently filed multiple lawsuits seeking materials NIEHS refused to produce through FOIA requests not only regarding contracts involving the Ramazzini Institute and grant money provided to the Institute's fellows, but also information regarding Ramazzini's U.S. affiliate's President Phil Landrigan's coordination with NIEHS.[10] According to reports, Director Birnbaum coordinated with Dr. Landrigan to publish more than two dozen Ramazzini studies in the NIEHS run journal, Environmental Health Perspectives (EHP).[11]

This is not the first instance in which this Committee raised questions regarding the scientific integrity of Ramazzini. In 2012, Committee members wrote the Environmental Protection Agency (EPA) regarding specific Ramazzini studies EPA relied on when conducting chemical risk assessments.[12] According to the EPA, agency scientists "identified discrepancies in the results of methanol studies conducted by the Ramazzini Institute."[13] As a result, EPA placed the four draft assessments that relied on the Ramazzini studies on hold, pending further review.[14] This is concerning given the continued significant funding of Ramazzini studies and publication of Ramazzini studies in the EHP.

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4 Nat'l Institute of Environmental Health Sciences, *About NIEHS*, *available at* https://www.niehs.nih.gov/about/index.cfm (last visited Mar. 23, 2017).
5 *Id.*
6 *E&E Legal Again Forced to Sue NIH*, *supra* note 1; USASpending.gov Results, *supra* note 1.
7 *E&E Legal Again Forced to Sue NIH*, *supra* note 1
8 *Id.*
9 *Id.*
10 *Id.*
11 *Id.*
12 Letter from Hon. Paul Broun & Hon. Andy Harris, H. Comm. on Science, Space, & Tech. & Hon. David Vitter & Hon. James Inhofe, U.S. Senate, to Dr. Linda Birnbaum, Director, Nat'l Toxicology Program & Dr. Paul Anastas, Asst. Admin., Office of Research and Dev. (Jan. 31. 2012).
13 Letter from Lek Kadeli, Acting Asst. Admin., U.S. Environmental Protection Agency, to Hon. Paul Broun, H. Comm. on Science, Space, & Tech. (Mar. 13, 2012).
14 *Id.*

The Committee has a responsibility to ensure that the federal government funds and engages in scientific research free from external pressures and opinions. To assist the Committee's oversight of NIEHS, please contact Committee staff by March 31, 2017, to arrange a briefing on this matter. The Committee requests communications and materials related to the scientific integrity of the work performed by NIEHS contractors and grant recipients to ensure proper stewardship of taxpayer dollars and sound science. To understand the relationship between NIEHS and Ramazzini, please provide the following documents and information as soon as possible, but no later than noon on April 7, 2017 for the time period January 1, 2009 to the present:

1. All documents and communications referring or relating to any grant issued by NIEHS to the Ramazzini Institute or any Ramazzini affiliate.

2. All documents and communications referring or relating to any contract issued by NIEHS to the Ramazzini Institute or Ramazzini affiliate.

3. All documents and communications between and among NIEHS employees and any fellow of the Ramazzini Institute or affiliated entity referring or relating to any grant or contract award.

4. All documents and communications between and among NIEHS employees referring or relating to Ramazzini or its affiliates' business practices.

5. A list of all Ramazzini fellows employed by NIH, including but not limited to, NIEHS employees.

6. Provide all contracting file documents, including but not limited to any justification and approval documents, for the following contract numbers: HHSN291200555535C, HHSN27300152, HHSN27300212, HHSN27300063, HHSN27300149, HHSN27300390, and HHSN27300230.

The Committee has jurisdiction over environmental and scientific research and development programs and "shall review and study on a continuing basis laws, programs, and Government activities" as set forth in House Rule X. This request and any documents created as a result of this request will be deemed congressional documents and property of the House Science Committee.

When producing documents to the Committee, please deliver production sets to the Majority Staff in Room 2321 of the Rayburn House Office Building and the Minority Staff in Room 394 of the Ford House Office Building. The Committee prefers, if possible, to receive all documents in electronic format. An attachment to this letter provides additional information regarding producing documents to the Committee.

If you have any questions about this request, please contact Drew Colliatie or Caroline Ingram of the Science, Space, and Technology Committee staff at 202-225-6371. Thank you for your attention to this matter.

Sincerely,

Lamar Smith
Chairman

Darin LaHood
Chairman
Subcommittee on Oversight

cc: The Honorable Eddie Bernice Johnson, Ranking Minority Member, House Committee on Science, Space and Technology

The Honorable Don Beyer, Ranking Minority Member, Subcommittee on Oversight

The Honorable Suzanne Bonamici, Ranking Minority Member, Subcommittee on Environment

Enclosure

Responding to Committee Document Requests

1. In complying with this request, you are required to produce all responsive documents, in unredacted form, that are in your possession, custody, or control, whether held by you or your past or present agents, employees, and representatives acting on your behalf. You should also produce documents that you have a legal right to obtain, that you have a right to copy or to which you have access, as well as documents that you have placed in the temporary possession, custody, or control of any third party. Requested records, documents, data or information should not be destroyed, modified, removed, transferred or otherwise made inaccessible to the Committees.

2. In the event that any entity, organization or individual denoted in this request has been, or is also known by any other name than that herein denoted, the request shall be read also to include that alternative identification.

3. The Committee's preference is to receive documents in electronic form (i.e., CD, memory stick, or thumb drive) in lieu of paper productions.

4. Documents produced in electronic format should also be organized, identified, and indexed electronically.

5. Electronic document productions should be prepared according to the following standards:

   (a) The production should consist of single page Tagged Image File ("TIF"), or PDF files.

   (b) Document numbers in the load file should match document Bates numbers and TIF or PDF file names.

   (c) If the production is completed through a series of multiple partial productions, field names and file order in all load files should match.

6. Documents produced to the Committee should include an index describing the contents of the production. To the extent more than one CD, hard drive, memory stick, thumb drive, box or folder is produced, each CD, hard drive, memory stick, thumb drive, box or folder should contain an index describing its contents.

7. Documents produced in response to this request shall be produced together with copies of file labels, dividers or identifying markers with which they were associated when the request was served.

8. When you produce documents, you should identify the paragraph in the Committee's schedule to which the documents respond.

9. It shall not be a basis for refusal to produce documents that any other person or entity also possesses non-identical or identical copies of the same documents.

10. If any of the requested information is only reasonably available in machine-readable form (such as on a computer server, hard drive, or computer backup tape), you should consult with the Committee staff to determine the appropriate format in which to produce the information.

11. If compliance with the request cannot be made in full by the specified return date, compliance shall be made to the extent possible by that date. An explanation of why full compliance is not possible shall be provided along with any partial production. Failure to provide an explanation constitutes a waiver of any objections to the subpoena.

12. In the event that a document is withheld on the basis of privilege, provide a privilege log containing the following information concerning any such document: (a) the basis for withholding the documents; (b) the type of document; (c) the general subject matter; (d) the date, author and addressee; and (e) the relationship of the author and addressee to each other; and (f) any other description necessary to identify the document and to explain the basis for not producing the document. If a claimed privilege applies to only a portion of any document, that portion only should be withheld and the remainder of the document should be produced. As used herein, "claim of privilege" includes, but is not limited to, any claim that a document either may or must be withheld from production pursuant to the constitution or any statute, rule, or regulation.

13. In complying with this request, be apprised that the U.S. House of Representatives and the Committee on Science, Space, and Technology do not recognize: any of the purported non-disclosure privileges associated with the common law including, but not limited to, the deliberative process privilege, the attorney-client privilege, and attorney work product protections; any purported privileges such as privileges over law-enforcement sensitive disclosuresor protections from disclosure under the Freedom of Information Act; or any purported contractual privileges, such as non-disclosure agreements. Any assertion by a request recipient of any such non-constitutional legal bases for withholding documents or other materials shall be of no legal force and effect and shall not provide a justification for such withholding or refusal, unless and only to the extent that the Chair of the Committee has consented to recognize the assertion as valid.

14. If any document responsive to this request was, but no longer is, in your possession, custody, or control, identify the document (stating its date, author, subject and recipients) and explain the circumstances under which the document ceased to be in your possession, custody, or control.

15. If a date or other descriptive detail set forth in this request referring to a document is inaccurate, but the actual date or other descriptive detail is known to you or is otherwise apparent from the context of the request, you are required to produce all documents which would be responsive as if the date or other descriptive detail were correct.

16. Unless otherwise specified, the time period covered by this request is from January 1, 2009 to the present.

17. This request is continuing in nature and applies to any newly-discovered information. Any record, document, compilation of data or information, not produced because it has not been

located or discovered by the return date, shall be produced immediately upon subsequent location or discovery.

18. All documents shall be Bates-stamped sequentially and produced sequentially.

19. Two sets of documents shall be delivered, one set to the Majority Staff and one set to the Minority Staff. When documents are produced to the Committee on Science, Space, and Technology, production sets shall be delivered to the Majority Staff in Room 2321 of the Rayburn House Office Building and the Minority Staff in Room 324 of the Ford House Office Building.

20. Upon completion of the document production, you should submit a written certification, signed by you or your counsel, stating that: (1) a diligent search has been completed of all documents in your possession, custody, or control which reasonably could contain responsive documents; and (2) all documents located during the search that are responsive have been produced to the Committees.

21. When representing a witness or entity before the Committee in response to a document request, request for transcribed interview, or subpoena from the Committee, or in connection with testimony before the Committee at a hearing, counsel for the witness or entity must promptly submit to the Committee a notice of appearance specifying the following: (a) counsel's name, firm or organization, and contact information; and (b) each client represented by the counsel in connection with the proceeding. Submission of a notice of appearance constitutes acknowledgement that counsel is authorized to accept service of process by the Committee on behalf of such client(s), and that counsel is bound by and agrees to comply with all applicable House and Committee rules and regulations.

Schedule Definitions

1. The term "document" means any written, recorded, or graphic matter of any nature whatsoever, regardless of how recorded, and whether original or copy, including, but not limited to, the following: memoranda, reports, expense reports, books, manuals, instructions, financial reports, working papers, records, notes, letters, notices, confirmations, telegrams, receipts, appraisals, pamphlets, magazines, newspapers, prospectuses, inter-office and intra-office communications, electronic mail (e-mail), contracts, cables, notations of any type of conversation, telephone call, meeting or other communication, bulletins, printed matter, computer printouts, teletypes, invoices, transcripts, diaries, analyses, returns, summaries, minutes, bills, accounts, estimates, projections, comparisons, messages, correspondence, press releases, circulars, financial statements, reviews, opinions, offers, studies and investigations, questionnaires and surveys, and work sheets (and all drafts, preliminary versions, alterations, modifications, revisions, changes, and amendments of any of the foregoing, as well as any attachments or appendices thereto), and graphic or oral records or representations of any kind (including without limitation, photographs, charts, graphs, microfiche, microfilm, videotape, recordings and motion pictures), and electronic, mechanical, and electric records or representations of any kind (including, without limitation, tapes, cassettes, disks, and recordings) and other written, printed, typed, or other graphic or recorded matter of any kind or nature, however produced or reproduced, and whether

preserved in writing, film, tape, disk, videotape or otherwise. A document bearing any notation not a part of the original text is to be considered a separate document. A draft or non-identical copy is a separate document within the meaning of this term.

2. The term "communication" means each manner or means of disclosure or exchange of information, regardless of means utilized, whether oral, electronic, by document or otherwise, and whether in a meeting, by telephone, facsimile, email (desktop or mobile device), text message, instant message, MMS or SMS message, regular mail, telexes, releases, or otherwise.

3. The terms "and" and "or" shall be construed broadly and either conjunctively or disjunctively to bring within the scope of this request any information which might otherwise be construed to be outside its scope. The singular includes plural number, and vice versa. The masculine includes the feminine and neuter genders.

4. The terms "person" or "persons" mean natural persons, firms, partnerships, associations, corporations, subsidiaries, divisions, departments, joint ventures, proprietorships, syndicates, or other legal, business or government entities, and all subsidiaries, affiliates, divisions, departments, branches, or other units thereof.

5. The term "identify," when used in a question about individuals, means to provide the following information: (a) the individual's complete name and title; and (b) the individual's business address and phone number.

6. The term "referring or relating," with respect to any given subject, means anything that constitutes, contains, embodies, reflects, identifies, states, refers to, deals with or is pertinent to that subject in any manner whatsoever.

7. The term "affiliate" or "affiliates" means associated business concerns, organizations, or individuals if, directly or indirectly (a) either one controls or can control the other; or (b) a third party controls or can control both, and including but not limited to "Collegium Ramazzini."

From: Arthur Lavin <alavinmd@gmail.com>
Sent: Monday, January 30, 2017 6:06 PM
To: Maureen Swanson
Cc: Robert Gould; Katie Huffling; Gina Solomon; O'Fallon, Liam (NIH/NIEHS) [E]; Jeanne Conry; Alycia Halladay; Kristie Trousdale; Gray, Kimberly (NIH/NIEHS) [E]; Beate Ritz; Nathaniel DeNicola; Elena Rios; Irva Hertz-Picciotto; Newschaffer,Craig; Pamela Miller; Melissa Rose; Jennifer McPartland; David Zucker; Laura Anderko; Rubin, I Leslie; Engel, Stephanie; Axelrad, Daniel; russ Hauser; chenai@uc.edu; Birnbaum, Linda (NIH/NIEHS) [E]; Bellinger, David. C; woodrufft@obgyn.ucsf.edu; Emily Marquez; Charlotte Brody; Asa Bradman; ted schettler; Jacqueline Barkoski; Susan Schantz; Hirtz, Deborah; Janet Maughan; Eduardo Montana; Deborah Bennett; Veena Singla; Ho Tran; Mark Miller; Lam, Juleen; Marty, Melanie@OEHHA; Annie Acosta; Eve C. Gartner; Dani M. Fallin; Frederica Perera; Tanya Khemet; Mark Mitchell; Kau, Alice (NIH/NICHD) [E]; Bruce Lanphear; rmw5@columbia.edu; Campbell, Carla; Nsedu Witherspoon; foos.brenda@epa.gov; Robert Zoeller; Webster, Thomas F; phil.landrigan@mssm.edu; Elise Miller; Sass, Jennifer; Heather; Carol Kwiatkowski; Devon Corcia Payne-Sturges; Deboarh Cory-Slechta; Jennifer Lowry; Elaine Faustman
Subject: Re: Fwd: Chemical Industry Launches New Attack on IARC

An excellent example of this era's methods, in a word Orwellian.

1984 is once again a bestseller.

Here, scientists finding which chemicals kill or maim are the villain, and those who make their money poisoning us are the heroes.

Imagine, industry launching a campaign claiming the mantle of accuracy when they are very source of disinformation.

Lies are now truth, and science is now the dissembler.

Those who would protect children ae cast as those who would harm.

And those who actually damage the developing minds of generations claim to be the protectors.

The first victim of authoritarianism is fact.

The first value of science is fact.

The nation, right now, depends on its scientists to defend the very notion of science, of reality.

I am proud to be part of this effort and eager to help in any way.

Arthur

On Jan 31, 2017 1:37 AM, "Maureen Swanson" <mswanson@ldaamerica.org> wrote:

Please see below from Tom Z. And thank you to all of you who are leading the charge against this defamation of IARC and science more broadly.

Maureen

---------- Forwarded message ----------
From: **R. Thomas Zoeller** <tzoeller@bio.umass.edu>
Date: Mon, Jan 30, 2017 at 12:28 PM
Subject: Re: Chemical Industry Launches New Attack on IARC
To: Maureen Swanson <MSwanson@ldaamerica.org>

Maureen — thanks for sending this. I can't send to the list because it is too large, but here are some important links:

FYI, the ISEE has sent a letter to Congress: http://governance.iarc.fr/ENG/Docs/ISEELettertoCongressmanChaffetz.pdf, as did the NCI: http://governance.iarc.fr/ENG/Docs/DrLowy_NCItoDrWild_IARC.pdf following Chris's letter to NCI: http://monographs.iarc.fr/ENG/News/LetterFromDrWild-to-DrCollins.pdf.

Here is a summary of Monsanto's actions since the glyphosate evaluation: http://governance.iarc.fr/ENG/Docs/Briefing_GC%20Members_Glyphosate_IARC_2016-11-25.pdf

R. Thomas Zoeller, Professor
Biology Department
University of Massachusetts Amherst
611 N Pleasant St.
Amherst, MA 01003

ph: (413) 545-2088
Fax: (413) 545-3243

http://www.bio.umass.edu/biology/about/directories/faculty/r-thomas-zoeller

> On Jan 30, 2017, at 12:23 PM, Maureen Swanson <MSwanson@ldaamerica.org> wrote:
>
> Hello,
>
> I thought we all should be aware of this new attack campaign the American Chemistry Council (ACC - the chemical industry) is launching against IARC, its scientists and science.
>
> http://www.reuters.com/article/us-health-cancer-iarc-idUSKBN1592Q6
>
> Maureen

From: Maureen Swanson <mswanson@ldaamerica.org>
Sent: Monday, January 30, 2017 12:37 PM
To: chenai@uc.edu; Newschaffer,Craig; Hirtz, Deborah; Deboarh Cory-Slechta; Dani M. Fallin; Deborah Bennett; Devon Corcia Payne-Sturges; Elise Miller; foos.brenda@epa.gov; Frederica Perera; Irva Hertz-Picciotto; Pamela Miller; phil.landrigan@mssm.edu; rmw5@columbia.edu; woodrufft@obgyn.ucsf.edu; Alycia Halladay; Annie Acosta; Arthur Lavin; Asa Bradman; Axelrad, Daniel; Beate Ritz; Bellinger, David. C; Birnbaum, Linda (NIH/NIEHS) [E]; Bruce Lanphear; Campbell, Carla; Charlotte Brody; David Zucker; Eduardo Montana; Elaine Faustman; Elena Rios; Emily Marquez; Engel, Stephanie; Eve C. Gartner; Gina Solomon; Gray, Kimberly (NIH/NIEHS) [E]; Heather; Ho Tran; Jacqueline Barkoski; Jeanne Conry; Jennifer Lowry; Jennifer McPartland; Katie Huffling; Kau, Alice (NIH/NICHD) [E]; Kristie Trousdale; Lam, Juleen; Laura Anderko; Mark Miller; Mark Mitchell; Marty, Melanie@OEHHA; Melissa Rose; Nathaniel DeNicola; Nsedu Witherspoon; O'Fallon, Liam (NIH/NIEHS) [E]; Robert Gould; Robert Zoeller; Rubin, I Leslie; russ Hauser; Sass, Jennifer; Susan Schantz; Tanya Khemet; ted schettler; Veena Singla; Webster, Thomas F; Carol Kwiatkowski; Janet Maughan
Subject: Fwd: Chemical Industry Launches New Attack on IARC
Attachments: smime.p7s

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Here is a summary of Monsanto's actions since the glyphosate evaluation: http://governance.iarc.fr/ENG/Docs/Briefing_GC%20Members_Glyphosate_IARC_2016-11-25.pdf

R. Thomas Zoeller, Professor
Biology Department
University of Massachusetts Amherst
611 N Pleasant St.
Amherst, MA 01003

ph: (413) 545-2088
Fax: (413) 545-3243

http://www.bio.umass.edu/biology/about/directories/faculty/r-thomas-zoeller

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I thought we all should be aware of this new attack campaign the American Chemistry Council (ACC - the chemical industry) is launching against IARC, its scientists and science.

http://www.reuters.com/article/us-health-cancer-iarc-idUSKBN1592Q6

Maureen

From: Sass, Jennifer <jsass@nrdc.org>
Sent: Monday, January 30, 2017 12:34 PM
To: Maureen Swanson; chenai@uc.edu; Newschaffer,Craig; Hirtz, Deborah; Deboarh Cory-Slechta; Dani M. Fallin; Deborah Bennett; Devon Corcia Payne-Sturges; Elise Miller; foos.brenda@epa.gov; Frederica Perera; Irva Hertz-Picciotto; Pamela Miller; phil.landrigan@mssm.edu; rmw5@columbia.edu; woodrufft@obgyn.ucsf.edu; Alycia Halladay; Annie Acosta; Arthur Lavin; Asa Bradman; Axelrad, Daniel; Beate Ritz; Bellinger, David. C; Birnbaum, Linda (NIH/NIEHS) [E]; Bruce Lanphear; Campbell, Carla; Charlotte Brody; David Zucker; Eduardo Montana; Elaine Faustman; Elena Rios; Emily Marquez; Engel, Stephanie; Eve C. Gartner; Gina Solomon; Gray, Kimberly (NIH/NIEHS) [E]; Heather; Ho Tran; Jacqueline Barkoski; Jeanne Conry; Jennifer Lowry; Jennifer McPartland; Katie Huffling; Kau, Alice (NIH/NICHD) [E]; Kristie Trousdale; Lam, Juleen; Laura Anderko; Mark Miller; Mark Mitchell; Marty, Melanie@OEHHA; Melissa Rose; Nathaniel DeNicola; Nsedu Witherspoon; O'Fallon, Liam (NIH/NIEHS) [E]; Robert Gould; Robert Zoeller; Rubin, I Leslie; russ Hauser; Susan Schantz; Tanya Khemet; ted schettler; Singla, Veena; Webster, Thomas F; Carol Kwiatkowski; Janet Maughan
Subject: RE: Chemical Industry Launches New Attack on IARC

Thanks Maureen. I apologize, I should have posted something about this last week. There is so much to "freak out" about, hard to pick and choose. ☹

This entire campaign should serve as a warning to all of us, that ANY government emails on this and other TENDR emails provide an opportunity for ANYONE from the public, including industry and Congress to gain access to ALL correspondence.

Here is the ACC's website for its anti-IARC campaign:
https://www.americanchemistry.com/Media/PressReleasesTranscripts/ACC-news-releases/ACC-Launches-Campaign-to-Promote-Credibility-in-Public-Health-Research.html

And, here is a report in the trade press, "Plastic News" -
http://www.plasticsnews.com/article/20170127/NEWS/170129902/acc-launches-campaign-against-iarc-decision-making-on-carcinogens

And, below, some history that I pulled together, including embedded hotlinks to letters from Congress etc:

Recently Congressional Republicans have been attacking the credibility of the IARC Monograph listings – particularly regarding Monsanto's herbicide, glyphosate. For example, in Sept 2016 Congressman Chaffetz, Chairman of the Committee on Oversight and Government Reform, sent a letter to NIH Director Dr. Francis Collins calling IARC listings "inconsistent with other scientific research" and having "generated much controversy and alarm". Chaffetz has demanded information from NIH about its funding to IARC and all its correspondence with IARC since 2012. A month later (Oct 2016) the American Chemistry Council wrote a letter thanking Rep Chaffetz for his interest in IARC, listing criticisms of IARC including lack of transparency, and questioning the use of taxpayer dollars to support IARC. In the same month, IARC wrote a response defending its chemical evaluation process. The challenge to IARC by Congress and the ACC was reported in Reuters and other media globally.

In January 2017 Chaffetz wrote two more letters from the Committee on Oversight and Government Reform, one to NIH asking for all communications between IARC staff, and on the same day another letter to the NARA Archivist letting them know that the Committee has been investigating the NIH funding and support for IARC, "a France-based organization that generated controversy for its carcinogenic classification measures". In the letter to NARA, Chaffetz notes IARC's directive to NIH staff that the work products are privileged and immune to U.S. open records laws, and asks NARA to brief the committee regarding "IARC's non-disclosure directive".

Jennifer Sass, Ph.D.
Natural Resources Defense Council, Senior Scientist
George Washington University Milken Institute School of Public Health
1152 15th St NW, Suite 300, Washington DC 20005
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Bio and Blog: https://www.nrdc.org/experts/jennifer-sass

From: Maureen Swanson [mailto:mswanson@ldaamerica.org]
Sent: Monday, January 30, 2017 12:24 PM
To: chenai@uc.edu; Newschaffer,Craig; Hirtz, Deborah; Deboarh Cory-Slechta; Dani M. Fallin; Deborah Bennett; Devon Corcia Payne-Sturges; Elise Miller; foos.brenda@epa.gov; Frederica Perera; Irva Hertz-Picciotto; Pamela Miller; phil.landrigan@mssm.edu; rmw5@columbia.edu; woodrufft@obgyn.ucsf.edu; Alycia Halladay; Annie Acosta; Arthur Lavin; Asa Bradman; Axelrad, Daniel; Beate Ritz; Bellinger, David. C; Birnbaum, Linda (NIH/NIEHS) [E]; Bruce Lanphear; Campbell, Carla; Charlotte Brody; David Zucker; Eduardo Montana; Elaine Faustman; Elena Rios; Emily Marquez; Engel, Stephanie; Eve C. Gartner; Gina Solomon; Gray, Kimberly (NIH/NIEHS) [E]; Heather; Ho Tran; Jacqueline Barkoski; Jeanne Conry; Jennifer Lowry; Jennifer McPartland; Katie Huffling; Kau, Alice (NIH/NICHD) [E]; Kristie Trousdale; Lam, Juleen; Laura Anderko; Mark Miller; Mark Mitchell; Marty, Melanie@OEHHA; Melissa Rose; Nathaniel DeNicola; Nsedu Witherspoon; O'Fallon, Liam (NIH/NIEHS) [E]; Robert Gould; Robert Zoeller; Rubin, I Leslie; russ Hauser; Sass, Jennifer; Schantz, Susan L; Tanya Khemet; ted schettler; Singla, Veena; Webster, Thomas F; Carol Kwiatkowski; Janet Maughan
Subject: Chemical Industry Launches New Attack on IARC

Hello,

I thought we all should be aware of this new attack campaign the American Chemistry Council (ACC - the chemical industry) is launching against IARC, its scientists and science.

http://www.reuters.com/article/us-health-cancer-iarc-idUSKBN1592Q6

Maureen

From: Maureen Swanson <mswanson@ldaamerica.org>
Sent: Monday, January 30, 2017 12:24 PM
To: chenai@uc.edu; Newschaffer,Craig; Hirtz, Deborah; Deboarh Cory-Slechta; Dani M. Fallin; Deborah Bennett; Devon Corcia Payne-Sturges; Elise Miller; foos.brenda@epa.gov; Frederica Perera; Irva Hertz-Picciotto; Pamela Miller; phil.landrigan@mssm.edu; rmw5@columbia.edu; woodrufft@obgyn.ucsf.edu; Alycia Halladay; Annie Acosta; Arthur Lavin; Asa Bradman; Axelrad, Daniel; Beate Ritz; Bellinger, David. C; Birnbaum, Linda (NIH/NIEHS) [E]; Bruce Lanphear; Campbell, Carla; Charlotte Brody; David Zucker; Eduardo Montana; Elaine Faustman; Elena Rios; Emily Marquez; Engel, Stephanie; Eve C. Gartner; Gina Solomon; Gray, Kimberly (NIH/NIEHS) [E]; Heather; Ho Tran; Jacqueline Barkoski; Jeanne Conry; Jennifer Lowry; Jennifer McPartland; Katie Huffling; Kau, Alice (NIH/NICHD) [E]; Kristie Trousdale; Lam, Juleen; Laura Anderko; Mark Miller; Mark Mitchell; Marty, Melanie@OEHHA; Melissa Rose; Nathaniel DeNicola; Nsedu Witherspoon; O'Fallon, Liam (NIH/NIEHS) [E]; Robert Gould; Robert Zoeller; Rubin, I Leslie; russ Hauser; Sass, Jennifer; Susan Schantz; Tanya Khemet; ted schettler; Veena Singla; Webster, Thomas F; Carol Kwiatkowski; Janet Maughan
Subject: Chemical Industry Launches New Attack on IARC

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http://www.reuters.com/article/us-health-cancer-iarc-idUSKBN1592Q6

Maureen

From: Sass, Jennifer <jsass@nrdc.org>
Sent: Monday, August 22, 2016 11:03 AM
To: Maureen Swanson; chenai@uc.edu; Newschaffer,Craig; Hirtz, Deborah; Deboarh Cory-Slechta; Dani M. Fallin; Deborah Bennett; Devon Corcia Payne-Sturges; Elise Miller; foos.brenda@epa.gov; Frederica Perera; Irva Hertz-Picciotto; Pamela Miller; phil.landrigan@mssm.edu; rmw5@columbia.edu; woodrufft@obgyn.ucsf.edu; Alycia Halladay; Annie Acosta; Arthur Lavin; Asa Bradman; Axelrad, Daniel; Beate Ritz; Bellinger, David. C; Birnbaum, Linda (NIH/NIEHS) [E]; Bruce Lanphear; Campbell, Carla; Carol Kwiatkowski; Charlotte Brody; David Zucker; Eduardo Montana; Elaine Faustman; Elena Rios; Emily Marquez; Engel, Stephanie; Eve C. Gartner; Gina Solomon; Gray, Kimberly (NIH/NIEHS) [E]; Heather; Ho Tran; Jacqueline Barkoski; Jeanne Conry; Jennifer Lowry; Jennifer McPartland; Katie Huffling; Kau, Alice (NIH/NICHD) [E]; Kristie Trousdale; Lam, Juleen; Laura Anderko; Mark Miller; Mark Mitchell; Marty, Melanie@OEHHA; Melissa Rose; Nathaniel DeNicola; Nsedu Witherspoon; O'Fallon, Liam (NIH/NIEHS) [E]; Robert Gould; Robert Zoeller; Rubin, I Leslie; russ Hauser; Schantz, Susan L; Tanya Khemet; ted schettler; Singla, Veena; Webster, Thomas F; Jennifer Hazelton; Jessica Hodge
Subject: EPA SAP on glyphosate carcinogenicity

Dear TENDR experts,

I am hoping that some of you would be willing to self-nominate for this upcoming EPA FIFRA Scientific Advisory Panel to review the potential carcinogenicity of glyphosate (the main ingredient in Monsanto's Roundup herbicide). **Nominations are due this week Thurs 25th**. Info and background below:

Nominations of candidates to serve as ad hoc members of FIFRA SAP (Oct 18-21, 2016) to review the data relevant to carcinogenicity of glyphosate, EPA Federal Register announcement 26 July 2016. Comments submitted by Thursday September 25th to Steven Knott, DFO, Office of Science Coordination and Policy (7201M); telephone number: (202) 564-0103; email address: knott.steven@epa.gov

As you know, IARC reviewed glyphosate in early 2015 and classified it as Group 2A (probable human carcinogen). Monsanto has relentlessly fought IARC's assessment since then. Another wing of WHO, the European Food Safety Agency (EFSA) reviewed glyphosate later in 2015 and found it unlikely to be carcinogenic, based on a draft assessment provided by Monsanto.

Now, it is the US EPA's turn, and a leaked draft indicates that they are leaning towards Monsanto's findings of no cancer risk.

Needless to say we are very concerned that Monsanto is putting tremendous pressure on EPA regarding what experts will be selected for the SAP in mid-October. **We think it best of people self-nominate**, rather than be nominated by an NGO. We hope that you may be willing to serve, or could recommend others that may be willing.

Warm best,
Jen

Jennifer Sass, Ph.D.
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Bio and Blog: https://www.nrdc.org/experts/jennifer-sass

From: Birnbaum, Linda (NIH/NIEHS) [E]
Sent: Sunday, November 29, 2015 2:18 PM
To: Chris Portier
Cc: Bucher, John (NIH/NIEHS) [E]
Subject: Re: EFSA Glyphosate Recommendations - EPA's hold on glyphosate -2,24,D duo

http://newsletters.environmentalhealthnews.org/t/202308/23796/153385/0/

From: Birnbaum, Linda (NIH/NIEHS) [E]
Sent: Friday, November 27, 2015 10:32 AM
To: Chris Portier
Cc: Bucher, John (NIH/NIEHS) [E]; Thomas Burke; Thomas Sinks
Subject: Re: EFSA Glyphosate Recommendations

not a problem

and Happy Thanksgiving

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S
Director, National Institute of Environmental Health Sciences
and National Toxicology Program
phone: 919-541-3201
fax: 919-541-2260
e-mail: birnbaumls@niehs.nih.gov

On Nov 27, 2015, at 8:29 AM, Chris Portier <cportier@me.com> wrote:

> Sorry Linda, John, Tom and Tom, I sent you the wrong message. That was sent to NGOs and reporters who had heard about the letter and were pestering me. This is the email I meant to send which went to the Commissioner of Health for the EC.
>
> C.

> Begin forwarded message:
>
> **From:** Chris Portier <cportier@me.com>
> **Date:** November 27, 2015 at 9:56:57 AM GMT+1
> **To:** cab-andriukaitis-webpage@ec.europa.eu, Vytenis.ANDRIUKAITIS@ec.europa.eu
> **Cc:** Bernhard.Url@efsa.europa.eu, giovanni.lavia@europarl.europa.eu, leitung@bfr.bund.de, Director@iarc.fr, Jones.jim@Epa.gov, pesticides.ppr@efsa.europa.eu, phil.hogan@ec.europa.eu, Ladislav.MIKO@ec.europa.eu, poststelle@bmel.bund.de, poststelle@bvl.bund.de, helmut.tschiersky@bvl.bund.de
> **Subject: EFSA Glyphosate Recommendations**
>
> Dear Commissioner Andriukaitis,
>
> Attached to this email is a letter from 96 prominent epidemiologists, toxicologists, statisticians and molecular biologists from 25 countries. We have banded together and write to you at this time to express our deep concern over the recent European Food Safety Agency (EFSA) decision that the widely used

herbicide, glyphosate [3]is unlikely to pose a carcinogenic hazard to humans.[2] We ask that you read our letter and share it with those who will be advising you on accepting or rejecting EFSA[1]s decision. We would greatly appreciate your sharing this with the members of the Standing Committee on Plants, Animals, Food and Feed before their next meeting on December 10, 2015. I will be in Brussels from November 30 to December 2. If you believe it would be helpful for me to discuss these concerns with you or your staff in person, please send email to this address or call +41 79 605 79 58.

Thank you for your attention to this important issue.

Sincerely,

Prof. Christopher J. Portier

cc: Mr. Phil Hogan, European Commissioner for Agriculture and Human Development

Dr. Ladislav Miko, Deputy Director-General, DG Health & Food Safety

Dr. Bernhard Url, Executive Director, EFSA

Dr. Giovanni La Via, Chair, ENVI Committee

EFSA Panel on Plant Protection Products and their Residues

Mr. Christian Schmidt, Minister of Food and Agriculture

Dr. Helmut Tschiersky, President of the Federal Office of Consumer Protection and Food Safety (BVL)

Professor Dr. Dr. Andreas Hensel, President, BFR

Dr. Christopher Wild, Director, IARC

Mr. Jim Jones, Assistant Administrator, USEPA

<EFSA-Glyphosate-Letter.pdf>

November 27, 2015

Mr. Vytenis Andriukaitis
Commissioner Health & Food Safety
European Commission
Rue de la Loi / Wetstraat 200
1049 Brussels
Belgium

Cc: (email only)
- Mr. Phil Hogan, European Commissioner for Agriculture and Human Development
- Dr. Ladislav Miko, Deputy Director-General, DG Health & Food Safety
- Dr. Bernhard Url, Executive Director, EFSA
- Dr. Giovanni La Via, Chair, ENVI Committee
- EFSA Panel on Plant Protection Products and their Residues
- Mr. Christian Schmidt, Minister of Food and Agriculture
- Dr. Helmut Tschiersky, President of the Federal Office of Consumer Protection and Food Safety (BVL)
- Professor Dr. Dr. Andreas Hensel, President, BFR
- Dr. Christopher Wild, Director, IARC
- Mr. Jim Jones, Assistant Administrator, USEPA

Open letter: Review of the Carcinogenicity of Glyphosate by EFSA and BfR

Dear Commissioner Andriukaitis,

We are a group of independent academic and governmental scientists from around the world who have dedicated our professional lives to understanding the role of environmental hazards on cancer risks and human health. We have banded together and write to you at this time to express our deep concern over the recent European Food Safety Agency (EFSA) decision[1] that the widely used herbicide, glyphosate "is unlikely to pose a carcinogenic hazard to humans." We ask that you forward the letter to the representatives of all EU member states before the next meeting of the Standing Committee on Plants, Animals, Food and Feed (December 10/11).

The EFSA decision, based upon the Renewal Assessment Report[2] provided by the German Federal Institute for Risk Assessment (BfR), runs counter to the finding earlier this year by the International Agency for Research on Cancer (IARC), the highly respected cancer arm of the World Health Organization that glyphosate is a *probable human carcinogen*. This IARC classification is based on a comprehensive assessment of the peer-reviewed toxicologic and epidemiologic literature undertaken over a 12-month period by a Working Group of 17 independent expert scientists. The IARC review linked glyphosate to dose-related increases in malignant tumors at multiple anatomical sites in experimental animals and to an increased incidence of non- Hodgkin lymphoma in exposed humans.

We reviewed these two differing decisions on the human carcinogenicity of glyphosate and conclude that the IARC WG decision is by far the more credible. The IARC WG decision was reached relying on open and transparent procedures by independent scientists who completed thorough conflict-of-interest statements and were not affiliated or financially supported in any way by the chemical manufacturing industry. It is fully referenced and depends entirely on reports published in the open, peer-reviewed biomedical literature. It is part of a long tradition of deeply researched and highly credible reports on the carcinogenicity of hundreds of chemicals issued over the past four decades by IARC and used today by international agencies and regulatory bodies around the world as a basis for risk assessment, regulation and public health policy.

In contrast, the BfR decision is not credible because it is not supported by the evidence and it was not reached in an open and transparent manner.

Accordingly, we urge you and the European Commission to disregard the flawed EFSA finding on glyphosate in your formulation of glyphosate health and environmental policy for Europe and to call for a transparent, open and credible review of the scientific literature.

The IARC Working Group Decision

The International Agency for Research on Cancer (IARC) Monographs Programme identifies environmental causes of cancer in humans and has evaluated more than 950 agents since 1971. The Monographs Programme evaluates chemicals, drugs, mixtures, occupational exposures, lifestyles and personal habits, physical agents and biological agents. Monographs are written by an ad hoc Working Group (WG) of international scientific experts over a period of about 12 months ending in an eight-day meeting. The WG evaluates all of the publically-available scientific literature on a given substance and, through a transparent and rigorous process[3], reaches a decision on the degree to which the scientific evidence supports that substance's ability to cause or not cause cancer.

For Monograph 112[4], 17 expert scientists evaluated the carcinogenic hazard for 4 insecticides and the herbicide glyphosate[5]. The WG concluded that the data for glyphosate meets the criteria to be identified as a *probable human carcinogen*. This finding stirred great debate globally on the safety of glyphosate and led to a careful evaluation by numerous agencies of the IARC monograph results when they became available on July 29, 2015.

The BfR Addendum

In October, 2015, the EFSA reported[1] on their evaluation of the Renewal Assessment Report[2] (RAR) for glyphosate. EFSA concluded that "glyphosate is unlikely to pose a carcinogenic hazard to humans and the evidence does not support classification with regard to its carcinogenic potential". Addendum 1 (the BfR Addendum) of the RAR[2] discusses the scientific rationale for differing from the IARC WG conclusion.

We have serious concerns with regard to the scientific evaluation in the BfR Addendum and feel that it is misleading regarding the potential for a dose-dependent carcinogenic hazard from exposure to glyphosate. Since the BfR Addendum is the basis for the European Food Safety Agency (EFSA) conclusion[1], it is critical that we express these concerns. We are also concerned about some of the implications of the BfR Addendum regarding the use of human data in identifying carcinogenic hazards.

Our comments to the BfR Addendum will focus on the human evidence, the animal laboratory evidence and the mechanistic evidence.

The Human Evidence

The BfR agrees with the IARC WG that there is "*limited evidence* in humans for the carcinogenicity of glyphosate". In the IARC review process, *limited evidence* is assigned if "A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence."[3] The EFSA conclusion that "glyphosate is unlikely to pose a carcinogenic hazard to humans" is inappropriate when available data support the determination of *limited evidence* of carcinogenicity in humans. The BfR Addendum (p. ii) characterizes the IARC interpretation as "precautionary" and that the BfR takes a more "cautious view" of this classification because "no consistent positive association was observed", "the most powerful study showed no effect" and that the studies "could not differentiate between the effects of glyphosate and the co-formulants". We will consider the first two arguments here and discuss the third argument at the end of this letter.

The finding of *limited evidence* by the IARC WG was for non-Hodgkin lymphoma (NHL). High-quality cohort studies are particularly valuable for determining the carcinogenicity of an agent because their design can facilitate exposure assessment and reduce the potential for certain biases. The Agricultural Health Study[6] (AHS) was the only cohort study available providing information on the carcinogenicity of glyphosate. The study had a null finding for NHL (RR 1.1, 0.7-1.9) with no apparent exposure response in the results. The BfR refers to this study as "the most powerful study" and notes that it was "negative" for NHL.

Several potential limitations of case-control studies are laid out in epidemiology textbooks[7, 8]. The BfR uses these limitations to label all of the case-control studies as unreliable. This gives the impression that all of the studies are equal in quality and unusable for an overall evaluation. This is not the case: well-designed case-control studies are recognized as an efficient alternative to cohort studies[8]. An IARC WG carefully evaluates all of the available epidemiology data, looking at the study's strengths and weaknesses. This is key to determining whether the positive associations seen in case-control studies are a reliable indication of an association or simply due to chance or methodological flaws. To provide a reasonable interpretation of the findings, an evaluation needs to properly weight studies according to their quality rather than simply count the number of positives and negatives. The meta-analyses cited in the IARC Monograph[9] and done by the WG

are excellent examples of an objective evaluation of the existence of a consistent positive association; both meta-analyses showed a statistically significant association. The BfR provided no justification for their evaluation of "no consistent positive association". Finally, despite the potential advantages of prospective cohort studies versus case-control, there are fewer cases to include in analyses, depending on the follow-up time resulting in limited statistical power. There were only 92 NHL cases included in the AHS unadjusted analysis and fewer in adjusted analyses, compared to 650 in a pooled case-control analysis from the United States[10].

The final BfR conclusion (p. 21) that "there was no unequivocal evidence for a clear and strong association of NHL with glyphosate" is misleading. IARC, like many other groups, uses three levels of evidence for human data[3]. *Sufficient evidence* means "that a causal relationship has been established" between glyphosate and NHL. IARC does not state that the evidence is *sufficient*. BfR concludes that the IARC designation of *limited evidence* was not applicable because there was not "an unequivocal and consistent excess". In fact, that is the equivalent to the criteria for *sufficient evidence*, not *limited evidence*. Thus BfR's conclusion is equivalent to concluding there is not *sufficient evidence*. Legitimate public health concerns arise when "causality is credible", i.e., when there is *limited evidence*. BfR's language is misleading and not internationally acceptable and thus fails to meet EC Guidelines.

Evidence from Animal Carcinogenicity Studies

We find the conclusions of the BfR regarding the animal carcinogenicity data to be scientifically unacceptable. The IARC WG review found a significant positive trend for renal tumors in CD-1 mice[11], a rare tumor although no comparisons of any individual exposure group to the control group were statistically significant. A significant positive trend means that the pattern seen in the data supports an increasing risk with increasing dose. The WG also identified a significant positive trend for hemangiosarcoma in male CD-1 mice[12], again with no individual exposure group significantly different from controls. Finally, the WG also saw a significant increase in the incidence of pancreatic islet cell adenomas in two studies in Sprague-Dawley rats[13-15]. In one of these rat studies, thyroid gland adenomas in females and liver adenomas in males were also increased. Thus, glyphosate was positive for malignant tumors in both of the mouse studies examined and for benign tumors in two of the five rat studies examined. By the IARC review criteria[3], the evidence in the mouse constitutes *sufficient evidence* in animals and the increased incidences of benign tumors constitutes additional support.

The BfR agreed, stating (p. 43) "it is obvious that IARC concludes on "*sufficient evidence* of carcinogenicity" because the above criteria for this conclusion are fully met." The IARC WG reached this conclusion using data that were publicly available in sufficient detail for independent scientific evaluation (a requirement of the IARC Preamble[3]). Based on the BfR Addendum, it seems there were three additional mouse studies and two additional rat studies that were unpublished but available for review. BfR reported on two additional studies with a positive trend for renal tumors, one in CD-1 mice[16], and one in Swiss-Webster mice[17]. One of these studies[16] also reported a positive trend for hemangiosarcoma. Moreover, BfR reported two studies in CD-1 mice showing significant trends for malignant

lymphoma[16, 18]. For all of the mouse tumors described above, a positive trend was seen against the concurrent control.

However, in all studies in CD-1 mice, including those reviewed by the IARC, the BfR dismisses the observed trends in tumor incidence because there are no individual treatment groups that are significantly different from controls and because the maximum observed response is reportedly within the range of the historical control data (Table 5.3-1, p. 90). Care must be taken in using historical control data to evaluate animal carcinogenicity data. In virtually all guidelines[3, 19], scientific reports[20] and publications[21-23] on this issue, the recommended first choice is the use of the concurrent controls. For instance, the Preamble to the IARC Monographs states, "it is generally not appropriate to discount a tumor response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls…". When using historical control data, they should be from studies in the same timeframe, for the same exact animal strain, preferably from the same laboratory or the same supplier and preferably reviewed by the same pathologist[19]. This was not the case for the historical control database used by BfR. One of the mouse studies[11] was clearly done before this historical control database was developed, one study[16] used Crj:CD-1 mice rather than Crl:CD-1 mice, and one study[12] did not specify the substrain and was reported in 1993 (probably started prior to 1988); hence only a single study[18] used the same mouse strain as the historical controls, but was reported more than 10 years after the historical control dataset was developed. Interestingly, the historical control data used by the BfR[24] was from studies in seven laboratories using the Charles River Laboratory CD1 mice. It is important to note that there is a second report[25] by the same authors with a larger control database using the same mouse strain from 11 laboratories over the same time period (1987-2000) showing very different results. For example, the 2000 publication[24] shows five and four studies out of 46 with renal adenomas (no more than two in any one study) and renal adenocarcinomas (one in each study) respectively whereas the 2005 report[25] shows only one study each out of 54 studies with a single renal adenoma and a single renal adenocarcinoma; all other studies had no renal tumors.

Given this evidence, it is clear that BfR differed from standard scientific practices in order to reach their conclusions. BfR reported seven positive mouse studies with three studies showing increases in renal tumors, two with positive findings for hemangiosarcomas, and two with positive findings for malignant lymphomas. BfR additionally reported two positive findings for tumors in rats. Eliminating the inappropriate use of historical data, the unequivocal conclusion is that these are not negative studies, but in fact document the carcinogenicity of glyphosate in laboratory animals.

Mechanistic Information

The BfR Addendum dismisses the WG finding that "there is strong evidence that glyphosate causes genotoxicity" by suggesting that unpublished evidence not seen by the IARC WG was overwhelmingly negative and that, since the studies that were reviewed were not done under guideline principles, they should get less weight. To maintain transparency, IARC reviews only publicly available data. Thus the use of confidential data submitted to the BfR makes it impossible for any scientist not associated with BfR to review this conclusion with scientific

confidence. Further skewing their interpretation, the BfR did not include evidence of chromosomal damage from exposed humans[24] that was highlighted in the IARC Monograph.

The BfR confirms (p. 79) that the studies evaluated by the IARC WG on oxidative stress were predominantly positive but does not agree that this is strong support for an oxidative stress mechanism. They minimize the significance of these findings predominantly because of a lack of positive controls in some studies and because many of the studies used glyphosate formulations and not pure glyphosate. The WG concluded that (p. 77) "Strong evidence exists that glyphosate, AMPA and glyphosate-based formulations can induce oxidative stress". From a scientific perspective, these types of mechanistic studies can play a key role in distinguishing between the effects of mixtures, pure substances and metabolites and we encourage the BfR to carefully review this science.

Finally, we strongly disagree that data from studies published in the peer-reviewed literature should automatically receive less weight than guideline studies. Once a chemical or its formulations are on the market, the majority of the research done on these chemicals will be done by research laboratories using various models to address specific issues related to toxicity that will often not have testing guidelines associated with them. These peer-reviewed and published findings have great value in understanding mechanisms of carcinogenicity and should be given appropriate weight in an evaluation based on study quality and not just guideline rules.

General Comments

Science moves forward based on data, careful evaluation of those data and a rigorous review of the findings and conclusions. One important aspect of this process is transparency and the ability to question or debate the findings of others. This ensures the validity of the results and provides a strong basis for decisions. Many of the aspects of transparency do not exist for the RAR[2] or the BfR Addendum. For example, citations for almost all of the references, even those from the open scientific literature, have been redacted from the document. The ability to objectively evaluate the findings of a scientific report requires a complete list of the cited supporting evidence. As another example, there are no authors or contributors listed for either document, a requirement for publication in virtually all scientific journals. This is in direct contrast to the IARC WG evaluation listing all authors, all publications and public disclosure of pertinent conflicts of interest prior to the WG meeting[26].

A second important aspect of the scientific process is a careful evaluation and analysis of the facts. Several guidelines have been devised for analyzing carcinogenicity data, most after consultation with scientists from around the world. One of the most widely used guidelines is the OECD guidance on the conduct and design of chronic toxicity and carcinogenicity studies[19] which is cited in the BfR Addendum. This OECD guidance is in contradiction to the methods used by the BfR for both historical controls and for trend analysis; the two reasons given by the BfR for dismissing these data. Thus, BfR uses the

concept of testing guidelines to exclude substantive scientific evidence from their risk assessment and ignore OECD guidelines in addressing the important issues of historical controls and trend analyses.

Due to the potential public health implications of this extensively used pesticide it is essential that all scientific evidence be freely available, reviewed openly in an objective manner, and that financial support, conflicts of interest and affiliations of authors be fully disclosed. Many aspects of the evaluation conducted by the BfR and EFSA do not meet this fundamental objective criteria and raise significant questions of validity.

Summary

The IARC WG concluded that glyphosate is a "probable human carcinogen" putting it into IARC category 2A due to *sufficient evidence* of carcinogenicity in animals, *limited evidence* of carcinogenicity in humans and *strong* mechanistic data.

- The IARC WG found an association between non-Hodgkin lymphoma and glyphosate based on the available human evidence.
- The IARC WG found significant carcinogenic effects in laboratory animals for two tumor types in two mouse studies and benign tumors in two rat studies.
- Finally, the IARC WG concluded strong evidence of genotoxicity and oxidative stress for glyphosate, entirely from publicly available research, including findings of DNA damage in the peripheral blood of exposed humans.

In their RAR, BfR concluded (Vol. 1, p. 160) "classification and labeling for carcinogenesis is not warranted" and "glyphosate is devoid of genotoxic potential".

- BfR agreed with the IARC on *limited evidence* in humans but then dismissed the association as "insufficiently consistent" with no justification.
- Using an inappropriate historical control dataset in an incorrect manner and ignoring established OECD guidelines cited in their report, BfR dismissed evidence of renal tumors in 3 mouse studies, hemangiosarcoma in 2 mouse studies and malignant lymphoma in 2 mouse studies. Thus, BfR incorrectly discarded all of the glyphosate-induced carcinogenic findings in animals as chance occurrences.
- The BfR ignored important laboratory and human evidence of genotoxicity.
- The BfR confirmed that glyphosate induces oxidative stress and dismissed this finding for lack of any other finding because they had dismissed all of the other evidence.

The most parsimonious scientific explanation of the cancers seen in humans and laboratory animals supported by the mechanistic data is that glyphosate is a *probable* human carcinogen. On the basis of this conclusion and in the absence of

contrary evidence, it is reasonable to conclude that glyphosate formulations should also be considered probable human carcinogens.

We believe that the arguments promoted by the BfR to negate the human, animal and mechanistic evidence are fundamentally and scientifically flawed and should be rejected. We strongly object to the almost non-existent weight given to studies from the literature by the BfR and the strong reliance on non-publicly available data in a limited set of assays that define the minimum data necessary for the approval of a pesticide. We believe that the IARC WG evaluation of *probably carcinogenic to humans* accurately reflects the results of the published scientific literature on glyphosate and, on the face of it, the unpublished studies to which the BfR refers. Conversely, the BfR evaluation, and consequently the EFSA evaluation, do not reflect the available science.

Thus, repeating our earlier request, we urge you and the European Commission to disregard the flawed EFSA finding on glyphosate in your formulation of glyphosate health and environmental policy for Europe and to call for a transparent, open and credible review of the scientific literature.

The views expressed in this letter are the opinion of the scientists who are listed below and DO NOT imply an endorsement or support for these opinions by any organizations to which they are affiliated.

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References

1. European Food Safety Authority, *Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate.* EFSA Journal, 2015. **13**(11): p. 4302.
2. European Food Safety Authority. *Final Addendum to the Renewal Assessment Report*. 2015; Available from: http://registerofquestions.efsa.europa.eu/roqFrontend/outputLoader?output=ON-4302.
3. IARC. *PREAMBLE TO THE IARC MONOGRAPHS* 2006; Available from: http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf.
4. Guyton, K.Z., et al., *Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate.* Lancet Oncol, 2015. **16**(5): p. 490-1.
5. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, *Glyphosate*, in *IARC Monogr Eval Carcinog Risks Hum*, I.M. Program, Editor. 2015. p. 1-92.
6. De Roos, A.J., et al., *Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study.* Environ Health Perspect, 2005. **113**(1): p. 49-54.
7. Checkoway, H., N. Pearce, and D. Kriebel, *Research methods in occupational epidemiology*. 2nd ed. Monographs in epidemiology and biostatistics. 2004, New York: Oxford University Press. xiv, 372 p.
8. Rothman, K.J., S. Greenland, and T.L. Lash, *Modern epidemiology*. 3rd ed. 2008, Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. x, 758 p.
9. Schinasi, L. and M.E. Leon, *Non-Hodgkin lymphoma and occupational exposure to agricultural pesticide chemical groups and active ingredients: a systematic review and meta-analysis.* Int J Environ Res Public Health, 2014. **11**(4): p. 4449-527.
10. De Roos, A.J., et al., *Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men.* Occup Environ Med, 2003. **60**(9): p. E11.
11. Epa, *Glyphosate; EPA Reg. # 524-308; mouse oncogenicity study*, B. William Dykstra.Toxicology, Editor. 1985.
12. JCFA, *Evaluation of certain food additives and contaminants: Forty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives*. 1999, Joint Committee on Food Additives (including C. Portier), World Health Organization/Food and Agriculture Organization: Geneva. p. 96.
13. Epa, *Second peer review of Glyphosate*. 1991. p. 1-19.
14. Epa, *Glyphosate - EPA Registration No. 524-308 - 2-Year Chronic Feeding/Oncogenicity Study in Rats with Technical Glyphosate*, I. William Dykstra.Toxicology Branch, Editor. 1991.
15. Epa, *Glyphosate; 2-Year Combined Chronic Toxicity/ Carcinogenicity Study in Sprague-Dawley Rats - List A Pesticide for Reregistration*, B. William Dykstra.Toxicology, Editor. 1991. p. 1-29.
16. Sugimoto, *18-Month Oral Oncogenicity Study in Mice.* Unpublished, designated ASB2012-11493 in BfR RAR, 1997.

17. Unknown, *A chronic feeding study of glyphosate (roundup technical) in mice.* unpublished, designated ABS2012-11491 in BfR RAR, 2001.
18. Unknown, *Glyphosate Technical: Dietary Carcinogencity Study in the Mouse.* Unpublished, designated ABS2012-11492 in BfR RAR, 2009.
19. OECD, *Guidance Document 116 on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies*, H.a.S.P. Environment, Editor. 2012, OECD: Paris.
20. NRC Committee to Review the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens, in *Review of the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens: Workshop Summary*. 2014, National Academies Press: Washington (DC).
21. Keenan, C., et al., *Best practices for use of historical control data of proliferative rodent lesions.* Toxicol Pathol, 2009. **37**(5): p. 679-93.
22. Haseman, J.K., G.A. Boorman, and J. Huff, *Value of historical control data and other issues related to the evaluation of long-term rodent carcinogenicity studies.* Toxicol Pathol, 1997. **25**(5): p. 524-7.
23. Greim, H., et al., *Evaluation of historical control data in carcinogenicity studies.* Hum Exp Toxicol, 2003. **22**(10): p. 541-9.
24. Giknis, M. and C. Clifford, *Spontaneous Neoplastic Lesions in the CrI:CD-1(ICR)BR Mouse*. 2000, Charles River Laboratories.
25. Giknis, M. and C. Clifford, *Spontaneous Neoplastic Lesions in the CrI:CD-1(ICR)BR Mouse in Control Groups from 18 Month to 2 year Studies*. 2005, Charles River Laboratories.
26. IARC Monograph 112. *List of Working Group Participants*. IARC Monogr Eval Carcinog Risks Hum 2015 26 March, 2015 [cited 2015 24 November]; Available from: http://monographs.iarc.fr/ENG/Meetings/vol112-participants.pdf.

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Sent: Friday, November 27, 2015 10:29 AM
To: Chris Portier
Cc: Bucher, John (NIH/NIEHS) [E]; Thomas Burke; Thomas Sinks
Subject: Re: EFSA Glyphosate Recommendations

did you see that EPA recently put a hold on their approval of the glyphosate/2,4-D formulation because of effects reported from Dow on non-target plants? at least it's some hold on the extensive use of this....

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On Nov 27, 2015, at 5:23 AM, Chris Portier <cportier@me.com> wrote:

> FYI. This went out this morning and is embargoed for public release until 0:00 CET on Monday.
>
> C.

> Begin forwarded message:
>
> **From:** Chris Portier <cportier@me.com>
> **Date:** November 27, 2015 at 10:25:35 AM GMT+1
> **To:** Andreas rummel <[redacted (b) (6)]>, "Sass, Jennifer" <jsass@nrdc.org>, Angeliki Lysimachou <angeliki@pan-europe.info>, Meg Sears <meg@preventcancernow.ca>, Ann Doherty <amsterdamfarmer@xs4all.nl>, Martin Pigeon <martin@corporateeurope.org>, Stéphane Foucart <foucart@lemonde.fr>, Danny Hakim <hakim@nytimes.com>
> **Subject: EFSA Glyphosate Recommendations**
>
> Dear Addressees,
>
> You have expressed an interest in opinions I or my colleagues might wish to express concerning the recent European Food Safety Agency (EFSA) decision that the widely used herbicide, glyphosate [3]is unlikely to pose a carcinogenic hazard to humans.[2] Attached to this email is an open letter from 96 prominent epidemiologists, toxicologists, statisticians and molecular biologists from 25 countries. We have banded together and written a joint criticism of aspects of the EFSA review. Public release of this letter is **EMBARGOED**! Please do not release this letter before 0:00 CET, Monday 30 November, 2015. I will be happy

to answer any questions you may have about the content of this letter; my contact information is on the letter. For those of you wishing to prepare newspaper articles or web articles on this letter and/or this issue, I have prepared three quotes from me that you are welcome to use. These are below.

Sincerely,

Prof. Christopher J. Portier

QUOTES:

[3]My reason for doing all of this work is quite simple, it does the science of risk assessment a disservice when carefully developed methods for analyzing and interpreting the evidence are put aside in favor of ad-hoc approaches that are either wrong, or not amenable to scrutiny by the broader scientific community.

For science to be effective in guiding public health decisions, there needs to be clarity, rigor, transparency, and common sense . The EFSA assessment has serious deficits in all of these areas.

Most importantly, to blindly assess the safety of pure glyphosate to which few people are exposed without considering the evidence on the glyphosate formulations that people are really exposed to is both scientifically flawed and makes little sense to the public.[2]

<EFSA-Glyphosate-Letter.pdf>

November 27, 2015

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- Dr. Bernhard Url, Executive Director, EFSA
- Dr. Giovanni La Via, Chair, ENVI Committee
- EFSA Panel on Plant Protection Products and their Residues
- Mr. Christian Schmidt, Minister of Food and Agriculture
- Dr. Helmut Tschiersky, President of the Federal Office of Consumer Protection and Food Safety (BVL)
- Professor Dr. Dr. Andreas Hensel, President, BFR
- Dr. Christopher Wild, Director, IARC
- Mr. Jim Jones, Assistant Administrator, USEPA

Open letter: Review of the Carcinogenicity of Glyphosate by EFSA and BfR

Dear Commissioner Andriukaitis,

We are a group of independent academic and governmental scientists from around the world who have dedicated our professional lives to understanding the role of environmental hazards on cancer risks and human health. We have banded together and write to you at this time to express our deep concern over the recent European Food Safety Agency (EFSA) decision[1] that the widely used herbicide, glyphosate "is unlikely to pose a carcinogenic hazard to humans." We ask that you forward the letter to the representatives of all EU member states before the next meeting of the Standing Committee on Plants, Animals, Food and Feed (December 10/11).

The EFSA decision, based upon the Renewal Assessment Report[2] provided by the German Federal Institute for Risk Assessment (BfR), runs counter to the finding earlier this year by the International Agency for Research on Cancer (IARC), the highly respected cancer arm of the World Health Organization that glyphosate is a *probable human carcinogen*. This IARC classification is based on a comprehensive assessment of the peer-reviewed toxicologic and epidemiologic literature undertaken over a 12-month period by a Working Group of 17 independent expert scientists. The IARC review linked glyphosate to dose-related increases in malignant tumors at multiple anatomical sites in experimental animals and to an increased incidence of non- Hodgkin lymphoma in exposed humans.

We reviewed these two differing decisions on the human carcinogenicity of glyphosate and conclude that the IARC WG decision is by far the more credible. The IARC WG decision was reached relying on open and transparent procedures by independent scientists who completed thorough conflict-of-interest statements and were not affiliated or financially supported in any way by the chemical manufacturing industry. It is fully referenced and depends entirely on reports published in the open, peer-reviewed biomedical literature. It is part of a long tradition of deeply researched and highly credible reports on the carcinogenicity of hundreds of chemicals issued over the past four decades by IARC and used today by international agencies and regulatory bodies around the world as a basis for risk assessment, regulation and public health policy.

In contrast, the BfR decision is not credible because it is not supported by the evidence and it was not reached in an open and transparent manner.

Accordingly, we urge you and the European Commission to disregard the flawed EFSA finding on glyphosate in your formulation of glyphosate health and environmental policy for Europe and to call for a transparent, open and credible review of the scientific literature.

The IARC Working Group Decision

The International Agency for Research on Cancer (IARC) Monographs Programme identifies environmental causes of cancer in humans and has evaluated more than 950 agents since 1971. The Monographs Programme evaluates chemicals, drugs, mixtures, occupational exposures, lifestyles and personal habits, physical agents and biological agents. Monographs are written by an ad hoc Working Group (WG) of international scientific experts over a period of about 12 months ending in an eight-day meeting. The WG evaluates all of the publically-available scientific literature on a given substance and, through a transparent and rigorous process[3], reaches a decision on the degree to which the scientific evidence supports that substance's ability to cause or not cause cancer.

For Monograph 112[4], 17 expert scientists evaluated the carcinogenic hazard for 4 insecticides and the herbicide glyphosate[5]. The WG concluded that the data for glyphosate meets the criteria to be identified as a *probable human carcinogen*. This finding stirred great debate globally on the safety of glyphosate and led to a careful evaluation by numerous agencies of the IARC monograph results when they became available on July 29, 2015.

The BfR Addendum

In October, 2015, the EFSA reported[1] on their evaluation of the Renewal Assessment Report[2] (RAR) for glyphosate. EFSA concluded that "glyphosate is unlikely to pose a carcinogenic hazard to humans and the evidence does not support classification with regard to its carcinogenic potential". Addendum 1 (the BfR Addendum) of the RAR[2] discusses the scientific rationale for differing from the IARC WG conclusion.

We have serious concerns with regard to the scientific evaluation in the BfR Addendum and feel that it is misleading regarding the potential for a dose-dependent carcinogenic hazard from exposure to glyphosate. Since the BfR Addendum is the basis for the European Food Safety Agency (EFSA) conclusion[1], it is critical that we express these concerns. We are also concerned about some of the implications of the BfR Addendum regarding the use of human data in identifying carcinogenic hazards.

Our comments to the BfR Addendum will focus on the human evidence, the animal laboratory evidence and the mechanistic evidence.

The Human Evidence

The BfR agrees with the IARC WG that there is "*limited evidence* in humans for the carcinogenicity of glyphosate". In the IARC review process, *limited evidence* is assigned if "A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence."[3] The EFSA conclusion that "glyphosate is unlikely to pose a carcinogenic hazard to humans" is inappropriate when available data support the determination of *limited evidence* of carcinogenicity in humans. The BfR Addendum (p. ii) characterizes the IARC interpretation as "precautionary" and that the BfR takes a more "cautious view" of this classification because "no consistent positive association was observed", "the most powerful study showed no effect" and that the studies "could not differentiate between the effects of glyphosate and the co-formulants". We will consider the first two arguments here and discuss the third argument at the end of this letter.

The finding of *limited evidence* by the IARC WG was for non-Hodgkin lymphoma (NHL). High-quality cohort studies are particularly valuable for determining the carcinogenicity of an agent because their design can facilitate exposure assessment and reduce the potential for certain biases. The Agricultural Health Study[6] (AHS) was the only cohort study available providing information on the carcinogenicity of glyphosate. The study had a null finding for NHL (RR 1.1, 0.7-1.9) with no apparent exposure response in the results. The BfR refers to this study as "the most powerful study" and notes that it was "negative" for NHL.

Several potential limitations of case-control studies are laid out in epidemiology textbooks[7, 8]. The BfR uses these limitations to label all of the case-control studies as unreliable. This gives the impression that all of the studies are equal in quality and unusable for an overall evaluation. This is not the case: well-designed case-control studies are recognized as an efficient alternative to cohort studies[8]. An IARC WG carefully evaluates all of the available epidemiology data, looking at the study's strengths and weaknesses. This is key to determining whether the positive associations seen in case-control studies are a reliable indication of an association or simply due to chance or methodological flaws. To provide a reasonable interpretation of the findings, an evaluation needs to properly weight studies according to their quality rather than simply count the number of positives and negatives. The meta-analyses cited in the IARC Monograph[9] and done by the WG

are excellent examples of an objective evaluation of the existence of a consistent positive association; both meta-analyses showed a statistically significant association. The BfR provided no justification for their evaluation of "no consistent positive association". Finally, despite the potential advantages of prospective cohort studies versus case-control, there are fewer cases to include in analyses, depending on the follow-up time resulting in limited statistical power. There were only 92 NHL cases included in the AHS unadjusted analysis and fewer in adjusted analyses, compared to 650 in a pooled case-control analysis from the United States[10].

The final BfR conclusion (p. 21) that "there was no unequivocal evidence for a clear and strong association of NHL with glyphosate" is misleading. IARC, like many other groups, uses three levels of evidence for human data[3]. *Sufficient evidence* means "that a causal relationship has been established" between glyphosate and NHL. IARC does not state that the evidence is *sufficient*. BfR concludes that the IARC designation of *limited evidence* was not applicable because there was not "an unequivocal and consistent excess". In fact, that is the equivalent to the criteria for *sufficient evidence*, not *limited evidence*. Thus BfR's conclusion is equivalent to concluding there is not *sufficient evidence*. Legitimate public health concerns arise when "causality is credible", i.e., when there is *limited evidence*. BfR's language is misleading and not internationally acceptable and thus fails to meet EC Guidelines.

Evidence from Animal Carcinogenicity Studies

We find the conclusions of the BfR regarding the animal carcinogenicity data to be scientifically unacceptable. The IARC WG review found a significant positive trend for renal tumors in CD-1 mice[11], a rare tumor although no comparisons of any individual exposure group to the control group were statistically significant. A significant positive trend means that the pattern seen in the data supports an increasing risk with increasing dose. The WG also identified a significant positive trend for hemangiosarcoma in male CD-1 mice[12], again with no individual exposure group significantly different from controls. Finally, the WG also saw a significant increase in the incidence of pancreatic islet cell adenomas in two studies in Sprague-Dawley rats[13-15]. In one of these rat studies, thyroid gland adenomas in females and liver adenomas in males were also increased. Thus, glyphosate was positive for malignant tumors in both of the mouse studies examined and for benign tumors in two of the five rat studies examined. By the IARC review criteria[3], the evidence in the mouse constitutes *sufficient evidence* in animals and the increased incidences of benign tumors constitutes additional support.

The BfR agreed, stating (p. 43) "it is obvious that IARC concludes on "*sufficient evidence* of carcinogenicity" because the above criteria for this conclusion are fully met." The IARC WG reached this conclusion using data that were publicly available in sufficient detail for independent scientific evaluation (a requirement of the IARC Preamble[3]). Based on the BfR Addendum, it seems there were three additional mouse studies and two additional rat studies that were unpublished but available for review. BfR reported on two additional studies with a positive trend for renal tumors, one in CD-1 mice[16], and one in Swiss-Webster mice[17]. One of these studies[16] also reported a positive trend for hemangiosarcoma. Moreover, BfR reported two studies in CD-1 mice showing significant trends for malignant

lymphoma[16, 18]. For all of the mouse tumors described above, a positive trend was seen against the concurrent control.

However, in all studies in CD-1 mice, including those reviewed by the IARC, the BfR dismisses the observed trends in tumor incidence because there are no individual treatment groups that are significantly different from controls and because the maximum observed response is reportedly within the range of the historical control data (Table 5.3-1, p. 90). Care must be taken in using historical control data to evaluate animal carcinogenicity data. In virtually all guidelines[3, 19], scientific reports[20] and publications[21-23] on this issue, the recommended first choice is the use of the concurrent controls. For instance, the Preamble to the IARC Monographs states, "it is generally not appropriate to discount a tumor response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls…". When using historical control data, they should be from studies in the same timeframe, for the same exact animal strain, preferably from the same laboratory or the same supplier and preferably reviewed by the same pathologist[19]. This was not the case for the historical control database used by BfR. One of the mouse studies[11] was clearly done before this historical control database was developed, one study[16] used Crj:CD-1 mice rather than Crl:CD-1 mice, and one study[12] did not specify the substrain and was reported in 1993 (probably started prior to 1988); hence only a single study[18] used the same mouse strain as the historical controls, but was reported more than 10 years after the historical control dataset was developed. Interestingly, the historical control data used by the BfR[24] was from studies in seven laboratories using the Charles River Laboratory CD1 mice. It is important to note that there is a second report[25] by the same authors with a larger control database using the same mouse strain from 11 laboratories over the same time period (1987-2000) showing very different results. For example, the 2000 publication[24] shows five and four studies out of 46 with renal adenomas (no more than two in any one study) and renal adenocarcinomas (one in each study) respectively whereas the 2005 report[25] shows only one study each out of 54 studies with a single renal adenoma and a single renal adenocarcinoma; all other studies had no renal tumors.

Given this evidence, it is clear that BfR differed from standard scientific practices in order to reach their conclusions. BfR reported seven positive mouse studies with three studies showing increases in renal tumors, two with positive findings for hemangiosarcomas, and two with positive findings for malignant lymphomas. BfR additionally reported two positive findings for tumors in rats. Eliminating the inappropriate use of historical data, the unequivocal conclusion is that these are not negative studies, but in fact document the carcinogenicity of glyphosate in laboratory animals.

Mechanistic Information

The BfR Addendum dismisses the WG finding that "there is strong evidence that glyphosate causes genotoxicity" by suggesting that unpublished evidence not seen by the IARC WG was overwhelmingly negative and that, since the studies that were reviewed were not done under guideline principles, they should get less weight. To maintain transparency, IARC reviews only publicly available data. Thus the use of confidential data submitted to the BfR makes it impossible for any scientist not associated with BfR to review this conclusion with scientific

confidence. Further skewing their interpretation, the BfR did not include evidence of chromosomal damage from exposed humans[24] that was highlighted in the IARC Monograph.

The BfR confirms (p. 79) that the studies evaluated by the IARC WG on oxidative stress were predominantly positive but does not agree that this is strong support for an oxidative stress mechanism. They minimize the significance of these findings predominantly because of a lack of positive controls in some studies and because many of the studies used glyphosate formulations and not pure glyphosate. The WG concluded that (p. 77) "Strong evidence exists that glyphosate, AMPA and glyphosate-based formulations can induce oxidative stress". From a scientific perspective, these types of mechanistic studies can play a key role in distinguishing between the effects of mixtures, pure substances and metabolites and we encourage the BfR to carefully review this science.

Finally, we strongly disagree that data from studies published in the peer-reviewed literature should automatically receive less weight than guideline studies. Once a chemical or its formulations are on the market, the majority of the research done on these chemicals will be done by research laboratories using various models to address specific issues related to toxicity that will often not have testing guidelines associated with them. These peer-reviewed and published findings have great value in understanding mechanisms of carcinogenicity and should be given appropriate weight in an evaluation based on study quality and not just guideline rules.

General Comments

Science moves forward based on data, careful evaluation of those data and a rigorous review of the findings and conclusions. One important aspect of this process is transparency and the ability to question or debate the findings of others. This ensures the validity of the results and provides a strong basis for decisions. Many of the aspects of transparency do not exist for the RAR[2] or the BfR Addendum. For example, citations for almost all of the references, even those from the open scientific literature, have been redacted from the document. The ability to objectively evaluate the findings of a scientific report requires a complete list of the cited supporting evidence. As another example, there are no authors or contributors listed for either document, a requirement for publication in virtually all scientific journals. This is in direct contrast to the IARC WG evaluation listing all authors, all publications and public disclosure of pertinent conflicts of interest prior to the WG meeting[26].

A second important aspect of the scientific process is a careful evaluation and analysis of the facts. Several guidelines have been devised for analyzing carcinogenicity data, most after consultation with scientists from around the world. One of the most widely used guidelines is the OECD guidance on the conduct and design of chronic toxicity and carcinogenicity studies[19] which is cited in the BfR Addendum. This OECD guidance is in contradiction to the methods used by the BfR for both historical controls and for trend analysis; the two reasons given by the BfR for dismissing these data. Thus, BfR uses the

concept of testing guidelines to exclude substantive scientific evidence from their risk assessment and ignore OECD guidelines in addressing the important issues of historical controls and trend analyses.

Due to the potential public health implications of this extensively used pesticide it is essential that all scientific evidence be freely available, reviewed openly in an objective manner, and that financial support, conflicts of interest and affiliations of authors be fully disclosed. Many aspects of the evaluation conducted by the BfR and EFSA do not meet this fundamental objective criteria and raise significant questions of validity.

Summary

The IARC WG concluded that glyphosate is a "probable human carcinogen" putting it into IARC category 2A due to *sufficient evidence* of carcinogenicity in animals, *limited evidence* of carcinogenicity in humans and *strong* mechanistic data.

- The IARC WG found an association between non-Hodgkin lymphoma and glyphosate based on the available human evidence.
- The IARC WG found significant carcinogenic effects in laboratory animals for two tumor types in two mouse studies and benign tumors in two rat studies.
- Finally, the IARC WG concluded strong evidence of genotoxicity and oxidative stress for glyphosate, entirely from publicly available research, including findings of DNA damage in the peripheral blood of exposed humans.

In their RAR, BfR concluded (Vol. 1, p. 160) "classification and labeling for carcinogenesis is not warranted" and "glyphosate is devoid of genotoxic potential".

- BfR agreed with the IARC on *limited evidence* in humans but then dismissed the association as "insufficiently consistent" with no justification.
- Using an inappropriate historical control dataset in an incorrect manner and ignoring established OECD guidelines cited in their report, BfR dismissed evidence of renal tumors in 3 mouse studies, hemangiosarcoma in 2 mouse studies and malignant lymphoma in 2 mouse studies. Thus, BfR incorrectly discarded all of the glyphosate-induced carcinogenic findings in animals as chance occurrences.
- The BfR ignored important laboratory and human evidence of genotoxicity.
- The BfR confirmed that glyphosate induces oxidative stress and dismissed this finding for lack of any other finding because they had dismissed all of the other evidence.

The most parsimonious scientific explanation of the cancers seen in humans and laboratory animals supported by the mechanistic data is that glyphosate is a *probable* human carcinogen. On the basis of this conclusion and in the absence of

contrary evidence, it is reasonable to conclude that glyphosate formulations should also be considered probable human carcinogens.

We believe that the arguments promoted by the BfR to negate the human, animal and mechanistic evidence are fundamentally and scientifically flawed and should be rejected. We strongly object to the almost non-existent weight given to studies from the literature by the BfR and the strong reliance on non-publicly available data in a limited set of assays that define the minimum data necessary for the approval of a pesticide. We believe that the IARC WG evaluation of *probably carcinogenic to humans* accurately reflects the results of the published scientific literature on glyphosate and, on the face of it, the unpublished studies to which the BfR refers. Conversely, the BfR evaluation, and consequently the EFSA evaluation, do not reflect the available science.

Thus, repeating our earlier request, we urge you and the European Commission to disregard the flawed EFSA finding on glyphosate in your formulation of glyphosate health and environmental policy for Europe and to call for a transparent, open and credible review of the scientific literature.

The views expressed in this letter are the opinion of the scientists who are listed below and DO NOT imply an endorsement or support for these opinions by any organizations to which they are affiliated.

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References

1. European Food Safety Authority, *Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate.* EFSA Journal, 2015. **13**(11): p. 4302.
2. European Food Safety Authority. *Final Addendum to the Renewal Assessment Report*. 2015; Available from: http://registerofquestions.efsa.europa.eu/roqFrontend/outputLoader?output=ON-4302.
3. IARC. *PREAMBLE TO THE IARC MONOGRAPHS* 2006; Available from: http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf.
4. Guyton, K.Z., et al., *Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate.* Lancet Oncol, 2015. **16**(5): p. 490-1.
5. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, *Glyphosate*, in *IARC Monogr Eval Carcinog Risks Hum*, I.M. Program, Editor. 2015. p. 1-92.
6. De Roos, A.J., et al., *Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study.* Environ Health Perspect, 2005. **113**(1): p. 49-54.
7. Checkoway, H., N. Pearce, and D. Kriebel, *Research methods in occupational epidemiology*. 2nd ed. Monographs in epidemiology and biostatistics. 2004, New York: Oxford University Press. xiv, 372 p.
8. Rothman, K.J., S. Greenland, and T.L. Lash, *Modern epidemiology*. 3rd ed. 2008, Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. x, 758 p.
9. Schinasi, L. and M.E. Leon, *Non-Hodgkin lymphoma and occupational exposure to agricultural pesticide chemical groups and active ingredients: a systematic review and meta-analysis.* Int J Environ Res Public Health, 2014. **11**(4): p. 4449-527.
10. De Roos, A.J., et al., *Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men.* Occup Environ Med, 2003. **60**(9): p. E11.
11. Epa, *Glyphosate; EPA Reg. # 524-308; mouse oncogenicity study*, B. William Dykstra.Toxicology, Editor. 1985.
12. JCFA, *Evaluation of certain food additives and contaminants: Forty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives*. 1999, Joint Committee on Food Additives (including C. Portier), World Health Organization/Food and Agriculture Organization: Geneva. p. 96.
13. Epa, *Second peer review of Glyphosate*. 1991. p. 1-19.
14. Epa, *Glyphosate - EPA Registration No. 524-308 - 2-Year Chronic Feeding/Oncogenicity Study in Rats with Technical Glyphosate*, I. William Dykstra.Toxicology Branch, Editor. 1991.
15. Epa, *Glyphosate; 2-Year Combined Chronic Toxicity/ Carcinogenicity Study in Sprague-Dawley Rats - List A Pesticide for Reregistration*, B. William Dykstra.Toxicology, Editor. 1991. p. 1-29.
16. Sugimoto, *18-Month Oral Oncogenicity Study in Mice.* Unpublished, designated ASB2012-11493 in BfR RAR, 1997.

17. Unknown, *A chronic feeding study of glyphosate (roundup technical) in mice.* unpublished, designated ABS2012-11491 in BfR RAR, 2001.
18. Unknown, *Glyphosate Technical: Dietary Carcinogencity Study in the Mouse.* Unpublished, designated ABS2012-11492 in BfR RAR, 2009.
19. OECD, *Guidance Document 116 on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies*, H.a.S.P. Environment, Editor. 2012, OECD: Paris.
20. NRC Committee to Review the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens, in *Review of the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens: Workshop Summary*. 2014, National Academies Press: Washington (DC).
21. Keenan, C., et al., *Best practices for use of historical control data of proliferative rodent lesions.* Toxicol Pathol, 2009. **37**(5): p. 679-93.
22. Haseman, J.K., G.A. Boorman, and J. Huff, *Value of historical control data and other issues related to the evaluation of long-term rodent carcinogenicity studies.* Toxicol Pathol, 1997. **25**(5): p. 524-7.
23. Greim, H., et al., *Evaluation of historical control data in carcinogenicity studies.* Hum Exp Toxicol, 2003. **22**(10): p. 541-9.
24. Giknis, M. and C. Clifford, *Spontaneous Neoplastic Lesions in the CrI:CD-1(ICR)BR Mouse*. 2000, Charles River Laboratories.
25. Giknis, M. and C. Clifford, *Spontaneous Neoplastic Lesions in the CrI:CD-1(ICR)BR Mouse in Control Groups from 18 Month to 2 year Studies*. 2005, Charles River Laboratories.
26. IARC Monograph 112. *List of Working Group Participants*. IARC Monogr Eval Carcinog Risks Hum 2015 26 March, 2015 [cited 2015 24 November]; Available from: http://monographs.iarc.fr/ENG/Meetings/vol112-participants.pdf.

From: Birnbaum, Linda (NIH/NIEHS) [E]
Sent: Monday, November 16, 2015 11:11 AM
To: Evans, Sharon L (NIH/NIEHS) [E]
Subject: Fwd: FYI -- huff comments on SUPPORT LETTER IARC Monograph on Glyphosate
Attachments: IARCWG112ResponseV3-huff comments.docx; ATT00001.htm

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S
Director, National Institute of Environmental Health Sciences
and National Toxicology Program
phone: 919-541-3201
fax: 919-541-2260
e-mail: birnbaumls@niehs.nih.gov

Begin forwarded message:

From: "Huff, James (NIH/NIEHS) [G]" <huff1@niehs.nih.gov>
Date: November 16, 2015 at 11:10:11 AM EST
To: "Birnbaum, Linda (NIH/NIEHS) [E]" <birnbaumls@niehs.nih.gov>
Subject: FYI -- huff comments on SUPPORT LETTER IARC Monograph on Glyphosate

Linda
You might take a look at my edit comments on the CP-glyphosate debate.
james

From: james huff <huff1@niehs.nih.gov>
Date: Monday, November 16, 2015 at 11:01
To: Chris Portier <cportier@me.com>
Subject: huff comments on SUPPORT LETTER IARC Monograph on Glyphosate

Chris
My comments are written directly on your draft letter. As mentioned most made for clarity, whilst others made for emphasis.
Added here and there, and suggested a concluding sentence.
Hope these are helpful, and useable. Let me know that you received this version.
Hello to Meike.
Best to you both, james

From: james huff <huff1@niehs.nih.gov>
Date: Friday, November 13, 2015 at 9:58
To: Chris Portier <cportier@me.com>
Subject: Re: IARC Monograph on Glyphosate

C-
Welcome. Thought you would not mind.
I am half thru your terrific letter. Making edits is about all.
Should send later today.
And of course take or leave my suggestions — mainly for clarity and some add ons.
j

From: Chris Portier <cportier@me.com>
Date: Friday, November 13, 2015 at 4:57 AM
To: James Huff <huff1@niehs.nih.gov>
Subject: Fwd: IARC Monograph on Glyphosate

James,

I actually sent this in five separate mailings because I could only send out 100 names at a time :-). Thanks for sharing this.

C.

Begin forwarded message:

From: "Budnik Lygia T., Prof. Dr. [LBudnik@uke.de]" <l.budnik@uke.de>
Date: November 12, 2015 at 11:22:01 PM GMT+1
To: cportier@me.com
Subject: WG: IARC Monograph on Glyphosate

Von: Caldwell, Jane [mailto:Caldwell.Jane@epa.gov]
Gesendet: Donnerstag, 12. November 2015 23:05
An: Budnik Lygia T., Prof. Dr. [LBudnik@uke.de]
Betreff: RE: IARC Monograph on Glyphosate

I cannot. Please send an email to Chris Portier <cportier@me.com>. It is his effort.

Jane Caldwell

From: Budnik Lygia T., Prof. Dr. [LBudnik@uke.de] [mailto:l.budnik@uke.de]
Sent: Thursday, November 12, 2015 5:03 PM
To: Caldwell, Jane <Caldwell.Jane@epa.gov>
Cc: huff1@niehs.nih.gov; cporter@me.com
Subject: WG: IARC Monograph on Glyphosate

Dear Jane, you can sign me in:

Title, Name: **Prof. Dr. Lygia Therese Budnik**
Position Title**: Head of Occupational Toxicology and Immunology**
Affiliation: **Institute for Occupational And Maritime Medicine, University Medical Center Hamburg-Eppendorf, University of Hamburg**
City, Country **Hamburg, Germany**

Best Lygia

Von: Caldwell, Jane [mailto:Caldwell.Jane@epa.gov]
Gesendet: Donnerstag, 12. November 2015 21:05
An: Budnik, Lygia T.
Betreff: FW: IARC Monograph on Glyphosate

FYI

From: Huff, James (NIH/NIEHS) [G] [mailto:huff1@niehs.nih.gov]
Sent: Thursday, November 12, 2015 2:09 PM
To: peter infante <pinfante@starpower.net>; ron.melnick@gmail.com; Lunn, Ruth (NIH/NIEHS) [E] <lunn@niehs.nih.gov>; fiorella belpoggi <belpoggif@ramazzini.it>; Caldwell, Jane <Caldwell.Jane@epa.gov>; joel_tickner@uml.edu; Dunnick, June (NIH/NIEHS) [E] <dunnickj@niehs.nih.gov>; kmb@sciencecorps.org; abraham nyska <(b) (6)>; morando soffritti <soffrittim@ramazzini.it>; phil landrigan <phil.landrigan@mssm.edu>; Lisa Lefferts <llefferts@cspinet.org>; michael jacobson <mjacobson@cspinet.org>; frank mirer <fmirer@hunter.cuny.edu>
Subject: FW: IARC Monograph on Glyphosate

Hi
You may have gotten this already; I was too lazy to read all the names but I did find-search them.
There are two emails I got.

In any event take a read and decide to sign or not. If you sign it, send to Portier. You can state I sent it to you if you want/need to.
Best, james

From: Chris Portier <cportier@me.com>
Date: Wednesday, November 11, 2015 at 7:57
To: "jmanto@creal.cat" <jmanto@creal.cat>, "kogevinas@creal.cat" <kogevinas@creal.cat>, "Margaret.Karagas@dartmouth.edu" <Margaret.Karagas@dartmouth.edu>, john dement <John.Dement@Duke.edu>, "Bengt.Jarvholm@envmed.umu.se" <Bengt.Jarvholm@envmed.umu.se>, "Alavanja, Michael (NIH/NCI) [E]" <alavanjm@exchange.nih.gov>, Maarten Bosland <boslandm@uic.edu>, "hartgep@exchange.nih.gov" <hartgep@exchange.nih.gov>, "Lubin, Jay (NIH/NCI) [V]" <lubinj@exchange.nih.gov>, "Silverman, Debra (NIH/NCI) [E]" <silvermd@exchange.nih.gov>, "Ward, Mary (NIH/NCI) [E]" <wardm@exchange.nih.gov>, Benedetto Terracini <benedetto.terracini@fastwebnet.it>, "cvictora@gmail.com" <cvictora@gmail.com>, "(b) (6)" <(b) (6)>, "(b) (6)" <(b) (6)>, "mperry@gwu.edu" <mperry@gwu.edu>, philippe grandjean <pgrandjean@health.sdu.dk>, "saracci@hotmail.com" <saracci@hotmail.com>, "(b) (6)" <(b) (6)>, "abaccare@hsph.harvard.edu" <abaccare@hsph.harvard.edu>, "dchris@hsph.harvard.edu" <dchris@hsph.harvard.edu>, "gwagner@hsph.harvard.edu" <gwagner@hsph.harvard.edu>, "Marie-Elise.Parent@iaf.inrs.ca" <Marie-Elise.Parent@iaf.inrs.ca>, "mporta@imim.es" <mporta@imim.es>, "l.rushton@imperial.ac.uk" <l.rushton@imperial.ac.uk>, "marcel.goldberg@inserm.fr" <marcel.goldberg@inserm.fr>, "john.cherrie@iom-world.org" <john.cherrie@iom-world.org>, "pietro.comba@iss.it" <pietro.comba@iss.it>, "per.gustavsson@ki.se" <per.gustavsson@ki.se>, "efonth@lsuhsc.edu" <efonth@lsuhsc.edu>, "jmclaugh@lunenfeld.ca" <jmclaugh@lunenfeld.ca>, "Berrington, Amy (NIH/NCI) [E]" <berringtona@mail.nih.gov>, "Beane-Freeman, Laura (NIH/NCI) [E]" <freemala@mail.nih.gov>, "Friesen, Melissa (NIH/NCI) [E]" <friesenmc@mail.nih.gov>, "A.Mannetje@massey.ac.nz" <A.Mannetje@massey.ac.nz>, "J.Douwes@massey.ac.nz" <J.Douwes@massey.ac.nz>, "dnc@mrc.soton.ac.uk" <dnc@mrc.soton.ac.uk>, jane hoppin <jahoppin@ncsu.edu>, "Birnbaum,

Linda (NIH/NIEHS) [E]" <birnbaumls@niehs.nih.gov>, john bucher <bucher@niehs.nih.gov>, james huff <huff1@niehs.nih.gov>, "Weinberg, Clarice (NIH/NIEHS) [E]" <weinberg@niehs.nih.gov>, "Engel, Lawrence (NIH/NIEHS) [C]" <lawrence.engel@nih.gov>, "m.hauptmann@nki.nl" <m.hauptmann@nki.nl>, "Elsebeth@pubhealth.ku.dk" <Elsebeth@pubhealth.ku.dk>, "Bernard.stewart@sesiahs.health.nsw.gov.au" <Bernard.stewart@sesiahs.health.nsw.gov.au>, "nsteenl@sph.emory.edu" <nsteenl@sph.emory.edu>, "petter.kristensen@stami.nl" <petter.kristensen@stami.nl>, "helge.kjuus@stami.no" <helge.kjuus@stami.no>, "bruce.armstrong@sydney.edu.au" <bruce.armstrong@sydney.edu.au>, "<ab.miller@sympatico.ca>" <ab.miller@sympatico.ca>, "cocco_pierluigi@tiscali.it" <cocco_pierluigi@tiscali.it>, harri vainio <Harri.Vainio@ttl.fi>, "nseixas@u.washington.edu" <nseixas@u.washington.edu>, "ricech@uc.edu" <ricech@uc.edu>, "britz@ucla.edu" <britz@ucla.edu>, "lemastgj@ucmail.uc.edu" <lemastgj@ucmail.uc.edu>, "jvena@uga.edu" <jvena@uga.edu>, "lstayner@uic.edu" <lstayner@uic.edu>, "Lynch, Charles F." <charles-lynch@uiowa.edu>, "james-merchant@uiowa.edu" <james-merchant@uiowa.edu>, "David_Kriebel@uml.edu" <David_Kriebel@uml.edu>, "michel.gerin@umontreal.ca" <michel.gerin@umontreal.ca>, "Rusyn, Ivan I" <iir@unc.edu>, "angela.pesatori@unimi.it" <angela.pesatori@unimi.it>, "pieralberto.bertazzi@unimi.it" <pieralberto.bertazzi@unimi.it>, "lorenzo.simonato@unipd.it" <lorenzo.simonato@unipd.it>, "roberta.pirastu@uniroma1.it" <roberta.pirastu@uniroma1.it>, "franco.merletti@unito.it" <franco.merletti@unito.it>, "jsamet@usc.edu" <jsamet@usc.edu>, "Elaine.Symanski@uth.tmc.edu" <Elaine.Symanski@uth.tmc.edu>, "d.heederik@uu.nl" <d.heederik@uu.nl>, "Vermeulen, R.C.H. (Roel)" <R.C.H.Vermeulen@uu.nl>, "fritschi@waimr.uwa.edu.au" <fritschi@waimr.uwa.edu.au>, "yawei.zhang@yale.edu" <yawei.zhang@yale.edu>, "mcebrian@cinvestav.mx" <mcebrian@cinvestav.mx>, "[redacted]" <[redacted]>, "wchiu@cvm.tamu.edu" <wchiu@cvm.tamu.edu>, "coccop@medicina.unica.it" <coccop@medicina.unica.it>, "aderoos@drexel.edu" <aderoos@drexel.edu>, "s-fukushima@jisha.or.jp" <s-fukushima@jisha.or.jp>, "pascal.guenel@inserm.fr" <pascal.guenel@inserm.fr>, "Herbert, Ron (NIH/NIEHS) [E]" <herbert@niehs.nih.gov>, "mlamerrill@ucdavis.edu" <mlamerrill@ucdavis.edu>, "marcelo.larramendy@gmail.com"

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Subject: IARC Monograph on Glyphosate

Dear Colleagues,

For IARC Monograph 112, 17 scientists evaluated the carcinogenic hazard for 4 insecticides and the herbicide glyphosate. The Working Group concluded that glyphosate was a probable human carcinogen. This finding stirred great debate globally on the safety of glyphosate and led to a careful evaluation of the IARC monograph results when they became available on July 29, 2015. During this period, the European Food Safety Agency (EFSA) was in the middle of a reassessment of the safety of glyphosate. The German Federal Institute for Risk Assessment (BfR) was the lead country agency in drafting the reassessment report. The draft, prior to the IARC Monograph, concluded there was no carcinogenic potential of glyphosate. In August of this year, following the release of the full Monograph on glyphosate, the BfR drafted an Addendum to their report that specifically addresses the

Monograph review. This was presented to EFSA several weeks ago and leaked by the press.

This week, EFSA will release their reassessment of glyphosate. In this review, they will again conclude that glyphosate has no carcinogenic potential. This review is based on the BfR Addendum which has some severe scientific flaws. I am concerned that this evaluation, if it stands, could weaken the effectiveness of the IARC Monograph Programme. I am also concerned that the serious flaws in the BfR Addendum, if not challenged, could continue to be used by regulatory agencies to dismiss critical science pertinent to a regulatory decision, including broad exclusion of literature data and epidemiological data.

The European Commission ENVI Committee will meet on December 1, 2015 to receive the reassessment report from EFSA. I have drafted a letter of concern that I wish to present to the ENVI Committee as they consider whether to accept or reject the EFSA evaluation. I would like to invite you to join with me in signing this open letter. I have obtained your names from many different lists, mostly from previous IARC monographs but also from other sources. It is possible I have included your name more than once on this list and I apologize for sending you multiple copies.

I am open to changes to improve the letter, but because of the short time-frame, I hope you can agree to sign on with only modest modifications (I am sending this to several hundred colleagues). I have included the letter but have not included the BfR Addendum or the Reassessment Report because of size. These are available at:

Addendum: http://www.mdr.de/fakt/fakt-glyphosat-bfr-bewertung100.html (NOTE: click on Herunterladen to download the report)
RAR: http://dar.efsa.europa.eu/dar-web/provision

The more important report is the Addendum.

If you agree to joining me in signing this letter, please respond by November 25 with the following that I can then add to my letter.

Title (Prof, Dr., …), Name
Position Title (e.g. Director, Named Chair, etc)
Affiliation
City, Country

I look forward to hearing from you.

Sincerely,

Christopher Portier

NEED A TITLE OR RE: Subject

The International Agency for Research on Cancer (IARC) Monographs Programme identifies ~~environmental~~ causes of cancer in humans and has evaluated more than 900 [985] agents SINCE 1965. [C- ACTUALLY FIRST MONO IN 1972]~~in the last few decades~~. The Monographs Programme evaluates chemicals, DRUGS, ~~complex~~ mixtures, occupational exposures, LIFE STYLES AND PERSONAL HABITS, AND physical ~~agents~~ and biological agents~~, as well as personal habits~~. Monographs are written by ~~a~~ AD HOC Working GroupS (WG) over a period of about 12 months, ENDING IN AN EIGHT DAY METING, to evaluate all of ~~the~~ RELEVANT scientific literature on a given substance and, through a transparent and rigorous process[1ADDED PREAMBLE URL], reach a decision on the degree to which the scientific ~~literature~~ EVIDENCE supports the ability of that substance to cause OR NOT cancer. For Monograph 112[2 ADDED TITLE OF MONOGRAPHS. WHY EDITOR?], 17 expert scientists evaluated the carcinogenic hazard for 4 insecticides and the herbicide glyphosate. The WG concluded that glyphosate was a 2A probable human carcinogen. This finding [2a**] stirred great debate globally on the safety of glyphosate and led to aNOTHER ~~careful~~ evaluation of the IARC monograph results when they came available on July 29, 2015. On August 31, 2015, the German Federal Institute for Risk Assessment (BfR) completed an addendum[3] (the BfR Addendum) to the Draft Renewal Assessment Report[4] (RAR) for glyphosate. This addendum was leaked by the media[5]. The Addendum draws a ~~very~~ CONSIDERABLY different conclusion on the literature than did the IARC WG. HENCE, We are ~~seriously~~ concerned about the scientific ~~quality~~ EVALUATION of the BfR Addendum and feel that it is misleading regarding the ~~potential for a~~ carcinogenic hazard from exposure to glyphosate. We are also concerned about some of the implications of the Addendum regarding the use of human data in identifying carcinogenic hazards.

**Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate.
Guyton KZ, Loomis D, Grosse Y, El Ghissassi F, Benbrahim-Tallaa L, Guha N, Scoccianti C, Mattock H, Straif K; International Agency for Research on Cancer Monograph Working Group, IARC, Lyon, France.
Lancet Oncol. 2015 May;16(5):490-1.

SUGGEST ALSO ADDING AS SUPPORT THE PEARCE ET AL RECENT PAPER IN EHP
Environ Health Perspect. 2015 Jun;123(6):507-14.
IARC monographs: 40 years of evaluating carcinogenic hazards to humans.
Pearce N, Blair A, Vineis P, [+ ~125 OTHERS]

Our comments to the BfR Addendum will focus on the human evidence, the animal laboratory evidence and the mechanistic evidence.

The Human Evidence

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The BfR agrees with the IARC WG that there is "limited evidence in humans for the carcinogenicity of glyphosate". In the IARC review process, this is defined as "A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence."[1] The BfR Addendum (p. ii) then characterizes the IARC interpretation as "precautionary" and that the BfR takes a more "cautious view" of this classification because "no consistent positive association was observed", "the most powerful study showed no effect" and that the studies "could not differentiate between the effects of glyphosate and the co-formulants". We will consider the first two arguments here and target the third argument for the end of our letter.

The finding of "limited evidence" by the IARC WG was for non-Hodgkins lymphoma (NHL). High-quality cohort studies are particularly valuable for determining the carcinogenicity of an agent because their design can facilitate exposure assessment and reduce the potential for certain biases. The Agricultural Health Study (AHS) was the only cohort study available providing information on the carcinogenicity of glyphosate. The study had a ~~very~~ RELATIVELY weak positive finding for NHL (RR 1.1, 0.7-1.9) with no apparent exposure response ~~in the results~~. The BfR refers to this study as "the most powerful study" and that it was negative for NHL.

Several theoretical limitations of case-control studies are laid out in epidemiology textbooks [6, 7]. The BfR uses these limitations to label all of the case-control studies as unreliable. This gives the impression that all of the studies are equal in quality and unusable for an overall evaluation. This is not the case: well-designed case-control studies are recognized as an efficient alternative to cohort studies [7]. An IARC WG carefully evaluates all ~~of the~~ available epidemiology data, looking at the study's strengths and weaknesses as well as the study order [STUDY ORDER???]. This is key in determining whether the positive associations seen are a reliable indication of an association or simply due to chance or methodological flaws. To provide a reasonable interpretation of the findings, an evaluation needs to properly weight studies according to their quality rather than simply count the number of positives and negatives. The meta-analysis cited in the IARC Monograph[8] and redone by the WG is an excellent example of an objective evaluation of the existence of a consistent positive trend; this meta-analysis showed a statistically significant [P<???] association. The BfR provided no justification for their evaluation of "no consistent positive association".

The final BfR conclusion (p. 22) that "there was no unequivocal evidence for a clear and strong association of NHL with glyphosate" is misleading. IARC, like many other groups, uses three levels of evidence for human data[1]. "Sufficient Evidence" means "that a causal relationship has been established" between glyphosate and NHL. The BfR conclusion can be rewritten to mean that the epidemiological data does not meet the criteria for "Sufficient Evidence" established by IARC. However, this says nothing about concern that would arise for an association that is not strong enough to be causal, but is strong enough that "that causality is credible" as does the IARC "Limited Evidence" category. THREE LEVELS -- GIVE THIRD? OR CHANGE ABOVE TO 'TWO LEVELS OF POSITIVE EVIDENCE . . .']

Evidence from ~~Chronic Exposure~~ CARCINOGENESIS Animal Studies

We are astonished [GOOD WORD BUT REALLY NEEDED? SURPRISED?] by the conclusions of the BfR regarding the animal carcinogenicity data. The IARC WG review found a significant positive trend [P<??] for renal tumors [TYPE?] in CD-1 mice[9], a rare tumour. A significant positive trend means that as the exposure increases, the pattern seen in the data supports an increasing risk with increasing dose. No comparisons of any individual exposure group to the control group were STATISTICALLY significant, ALTHOUGH THEY WERE NUMERICALLY INCREASED. The WG also identified a significant positive trend [P<??] for hemangiosarcoma in male CD-1 mice[10], again with no individual exposure group significantly different from controls. Finally, the WG also saw a significant increase in the incidence of PANCREATIC islet cell adenomas in two studies [WONDER WHY THEY DID TWO?] in Sprague-Dawley rats[11-13] [ONE REF LISTS -- I. William Dykstra AND THE OTHER -- B. William Dykstra. In one of these rat studies, thyroid GLAND adenomas in females and liver adenomas in males were also increased. [NO CARCINOMAS AT ALL??] Thus, glyphosate was positive for TOTAL malignant tumors in both ~~of the mice~~ MOUSE studies ~~examined~~ and for TOTAL benign tumors in 2 of ~~the~~ five rat studies ~~examined~~. By the IARC review criteria[1], the evidence in the mouse constitutes sufficient evidence OF CARCINOGENICITY in animals. NOT FOR RATS??

The BfR agreed, stating (p. 44) "it is obvious that IARC concludes on “sufficient evidence of carcinogenicity” because the criteria for this conclusion are fully met.” The IARC WG reached this conclusion using data that were publicly available in sufficient detail for independent scientific evaluation (a requirement of the IARC Preamble[1]). Based on the BfR Addendum, it seems there were 3 additional mouse studies and 2 additional rat studies where they had sufficient evidence [MIGHT BE CONFUSING RE IARC USE OF THESE TWO WORDS] to review the findings. BfR reported on two additional studies with a positive trend for renal tumors [TUBULAR? BENIGN? MALIG?] , one in CD-1 mice[14], and one in Swiss-Webster mice[15]. One of these studies[14] also reported a positive trend for hemangiosarcoma. Moreover, BfR reported two studies in CD-1 mice showing significant trends for malignant lymphoma[14, 16]. For all ~~of the~~ tumors ~~described~~ MENTIONED above in CD-1 mice, a positive trend was seen against the concurrent control.

However, in all cases in CD-1 mice, including those observed by the IARC, the BfR dismisses the observed trends in tumour incidence because there are no individual treatment groups which are significantly different from controls and because the maximum observed response is REPORTEDLY within the range of the historical control data (Table 5.3-1 in the Addendum). Care must be taken in using historical control data to evaluate animal carcinogenicity data. In virtually all guidelines[1, 17], scientific reports[18] and publications[19-21] on th~~e~~IS issue, the first choice should be the use of the concurrent controls. For instance, the Preamble to the IARC Monographs states, “it is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls…”. When using historical control data, it should be from the same

timeframe for the SAME exact strain, preferably from the same laboratory or the same supplier and preferably with the same pathologist[17]. This was not the case for the historical control database used by BfR. One of the mouse studies[9] was clearly done before this historical control database was developed, one study[14] used Crj:CD-1 mice rather than Crl:CD-1 mice, and 1 study[10] did not specify the substrain and was reported in 1993 (probably started prior to 1988); hence only a single study [16] used the right [RIGHT??] strain, but was reported more than 10 years after the historical control dataset was developed. Interestingly, the historical control data used by the BfR [22] was from studies in 7 laboratories using the Charles River Laboratory CD1 mice. Surprisingly, there is a second report [23] by the same authors with a larger control database using the same mouse strain from 11 laboratories over the same time period (1987-2000) showing very different results. For example, the 2000 publication[22] shows 5 and 4 studies out of 46 with adenomas (no more than 2 in any one study) and adenocarcinomas (one in each study) respectively whereas the 2005 report[23] shows only 1 study each out of 54 studies with a single adenoma and a single adenocarcinoma; all other studies had no tumors OF THE SITE ??? BECAUSE OBVIOUSLY HAD TO HAVE TUMOURS.

Given this evidence, it is ~~hard~~ DIFFICULT to perceive how ~~the~~ BfR reached theIR conclusionS ~~they provided~~. By their own evaluation, there were seven (7) positive findings in mice with three replicates for one tumor type and 2 positive findings for carcinomas in rats. After discarding the inappropriate use of historical evidence, it is no longer scientifically justifiable to refer to ~~all of~~ these NINE studies as negative.

Mechanistic Information

The BfR Addendum dismisses the IARC WG finding that "there is strong evidence that glyphosate causes genotoxicity" by suggesting that the evidence not seen by the IARC WG was overwhelmingly negative and that, since the studies that were reviewed were not done under guideline principles, they should get less weight. To maintain transparency, IARC reviews use only publicly available data [MINOR--NOT ENTIRELY TRUE; RELY ALMOST EXCLUSIVELY ON PUBLISHED DATA, AND OTHERS LIKE NTP & EPA, BUT NOT ALL PUBLICLY AVAILABLE DATA]. Thus it is impossible for any scientists not associated with BfR to review this conclusion with any degree of scientific ~~certainty~~CREDIBILITY. On the other hand, the BfR did not include GENETOX evidence from exposed humans that was highlighted in the IARC Monograph.

The BfR confirms (p. 79) that the studies evaluated by the IARC WG on oxidative stress were predominantly positive but do not agree that this is strong support for an oxidative stress mechanism. They reduce the significance of these findings predominantly because of a lack of positive controls in some studies and because many of the studies used glyphosate formulations and not pure glyphosate. The WG concluded that (p. 77) "Strong evidence exists that glyphosate, AMPA and glyphosate-based formulations can induce oxidative stress". From a scientific perspective, these types of mechanistic studies can play a key role in distinguishing between the effects of mixtures, pure substances and metabolites and we would encourage the BfR to carefully review this science.

Finally, we strongly disagree that literature data should automatically receive less weight than guideline studies; once a chemical, MIXTURES, FORMULATIONS ARE ~~is~~ on the market, the majority of ~~the~~ research done on th~~at~~ESE ~~chemical~~ will be done by ~~very competent~~ research laboratories that will use ~~unique~~ VARIOUS models to address specific issues related to toxicity that will not OFTEN have guidelines associated with them. These PEER-REVIEWED AND PUBLISHED FINDINGS have great value in understanding mechanisms of GENOTOXICITY AND carcinogenicity and should be given appropriate weight in an evaluation based on study quality and not just guideline rules.

General Comments

Science moves forward based on data, careful evaluation of that data and a rigorous review of the findings. One important aspect of this process is transparency and on the ability to question OR DEBATE the findings of others. This insures the credibility of ~~the~~ results and provides a strong basis for decisions. Many of the aspects of transparency do not exists for the BfR RAR [4] or the Addendum[3]. There are no authors or contributors listed for either document, a requirement for virtually all scientific papers. Citations for almost all of the references, even those from the open scientific literature, have been redacted from the documents. The ability to objectively evaluate the findings of a scientific report requires a complete list of the CITED supporting evidence.

A second important aspect of the scientific process is a careful evaluation and analysis of the facts. Guidelines have been devised for analyzing carcinogenicity data developed after careful consideration of scientists on a global basis. One of the most widely cited is OECD [17], which is cited in the BfR Addendum. This document gives guidance on the analysis of carcinogenicity studies in contradiction to the methods used by the BfR. Thus, BfR uses the concept of guidelines to rule out the substantive inclusion of literature data into their risk assessment, but ignores guidelines when it comes to the use of historical controls and trend analyses.

Summary

The IARC WG concluded that glyphosate is a "probable human carcinogen" putting it into IARC category 2A. In their 2013 Draft RAR, BfR concluded (Vol. 1, p. 139) "classification and labeling for carcinogenesis is not warranted" and "glyphosate is devoid of genotoxic potential". ~~How is this possible?~~ THIS BELIES THE AVAILABLE SCIENTIFIC FINDINGS. Consider the evidence and the conclusions.

The IARC WG ~~saw~~ DECIDED THERE WAS an association between NHL and glyphosate ~~in~~ BASED ON the AVAILABLE human evidence, but could not rule out chance, bias and confounding; the IARC definition of "limited evidence"[1] for epidemiological data. BfR agreed, noting that other IARC categories are "not

suitable". However the BfR concluded that an association was seen but dismissed it as insufficiently consistent.

AS FULLY SUPPORTING SCIENTIFIC EVIDENCE, The IARC WG ~~saw~~ AGREED THERE WERE significant CARCINOGENIC effects for two tumors in two mouse studies and ~~benign~~ tumors in two rat studies. The BfR confirmed the statistically significant findings by the IARC WG, and agreed that the IARC criteria of "sufficient" evidence OF CARCINOGENICITY in animals is "fully met". BfR went on to identify two more mouse studies with kidney tumors, a second mouse study with an increase in hemangiosarcomaS, and two mouse studies showing increases in malignant lymphomaS. Thus, all five mouse studies examined by the BfR were positive in at least 1 tumor site, 1 was positive in 3 tumor sites. Then using an inappropriate historical control dataset in an inappropriate way, BFR dismissES all of these GLYPHOSATE-INDUCED CARCINOGENIC findings as chance OCCURRENCES.

MECHANISTICALLY, The IARC WG concluded strong evidence of genotoxicity and oxidative stress for glyphosate, entirely from publicly available data, including ~~data~~ FINDINGS on DNA damage in PERIPHERAL blood of exposed humans. The BfR, while confirming the positive studies seen for genotoxicity dismissed them all because they were not "guideline" [MIGHT CONDSIDER ADDING " " ON THIS WORD THROUGHOUT] studies and because, in their interpretation, all of the guideline assays were negative. The BfR confirmed the positive studies seen for oxidative stress, noted some concern over these data, but concluded they could not use them because there were no other data to support a finding of carcinogenicity or genotoxicity and the mechanism cannot stand alone. THIS IGNORES BOTH THE HUMAN AND ANIMAL CARCINOGENICITY FINDINGS.

We ~~feel~~ BELIEVE that the scientific [MIGHT DELETE SCIENTIFIC HERE] arguments ~~supporting~~ PROMOTED BY the BfR ~~review~~ TO NEGATE ~~of~~ the human, animal and mechanistic evidence is fundamentally flawed and should be rejected. We are concerned that th~~is~~EIR evaluation appears to have been ~~designed~~ REACHED to achieve a pre-determined goal rather than an objective scientific EVALUATIVE review. Finally, we strongly object to the almost non-existent weight given to studies from the literature by the BfR and the strong reliance on non-publicly available data in a limited set of assays that define the minimum data necessary for the approval of a pesticide. HENCE THE IARC WG EVALUATION OF 'PROBABLY CARCINOGENIC TO HUMANS' REFLECTS BOTH A TRUE INTERPRETATION OF THE AVAILABLE EVIDENCE, AND CENTERS ON A LONG HISTORY OF IARC'S EVALUATION OF CARCINOGENIC RISKS TO HUMANS.

1. IARC, *PREAMBLE TO THE IARC MONOGRAPHS* I. Monographs, Editor. 2006: Lyon, France. p. 25. http://monographs.iarc.fr/ENG/Monographs/vol112/mono112-F06.pdf
2. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, *Glyphosate*, in Some Organophosphate Insecticides and Herbicides: Diazinon,

Glyphosate, Malathion, Parathion, and Tetrachlorvinphos *IARC Monogr Eval Carcinog Risks Hum*, I.M. Program, Editor. 2015. p. 1-92.
3. German Federal Institute for Risk Assessment, *Assessment of IARC Monographies Volume 112 (2015): Glyphosate*. 2015.
4. German Federal Institute for Risk Assessment, *Renewal Assessment Report*. 2013.
5. Das Erste. *BfRBewertung zu Glyphosat*. 2015; Available from: http://www.mdr.de/fakt/fakt-glyphosat-bfr-bewertung100.html.
6. Checkoway, H., N. Pearce, and D. Kriebel, *Research methods in occupational epidemiology*. 2nd ed. Monographs in epidemiology and biostatistics. 2004, New York: Oxford University Press. xiv, 372 p.
7. Rothman, K.J., S. Greenland, and T.L. Lash, *Modern epidemiology*. 3rd ed. 2008, Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. x, 758 p.
8. Schinasi, L. and M.E. Leon, *Non-Hodgkin lymphoma and occupational exposure to agricultural pesticide chemical groups and active ingredients: a systematic review and meta-analysis.* Int J Environ Res Public Health, 2014. **11**(4): p. 4449-527.
9. Epa, *Glyphosate; EPA Reg. # 524-308; mouse oncogenicity study*, B. William Dykstra.Toxicology, Editor. 1985.
10. JCFA, *Evaluation of certain food additives and contaminants: Forty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives*. 1999, Joint Committee on Food Additives (including C. Portier), World Health Organization/Food and Agriculture Organization: Geneva. p. 96.
11. Epa, *Second peer review of Glyphosate*. 1991. p. 1-19.
12. Epa, *Glyphosate - EPA Registration No. 524-308 - 2-Year Chronic Feeding/Oncogenicity Study in Rats with Technical Glyphosate*, I. William Dykstra.Toxicology Branch, Editor. 1991.
13. Epa, *Glyphosate; 2-Year Combined Chronic Toxicity/ Carcinogenicity Study in Sprague-Dawley Rats - List A Pesticide for Reregistration*, B. William Dykstra.Toxicology, Editor. 1991. p. 1-29.
14. Sugimoto, *18-Month Oral Oncogenicity Study in Mice.* Unpublished, designated ASB2012-11493 in BfR RAR, 1997.
15. Unknown, *A chronic feeding study of glyphosate (roundup technical) in mice.* unpublished, designated ABS2012-11491 in BfR RAR, 2001.
16. Unknown, *Glyphosate Technical: Dietary Carcinogencity Study in the Mouse.* Unpublished, designated ABS2012-11492 in BfR RAR, 2009.
17. OECD, *Guidance Document 116 on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies*, H a.S.P. Environment, Editor. 2012, OECD: Paris.
18. NRC Committee to Review the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens, in *Review of the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens: Workshop Summary*. 2014, National Academies Press: Washington (DC).
19. Keenan, C., et al., *Best practices for use of historical control data of proliferative rodent lesions.* Toxicol Pathol, 2009. **37**(5): p. 679-93.

20. Haseman, J.K., G.A. Boorman, and J. Huff, *Value of historical control data and other issues related to the evaluation of long-term rodent carcinogenicity studies.* Toxicol Pathol, 1997. **25**(5): p. 524-7.
21. Greim, H., et al., *Evaluation of historical control data in carcinogenicity studies.* Hum Exp Toxicol, 2003. **22**(10): p. 541-9.
22. Giknis, M. and C. Clifford, *Spontaneous Neoplastic Lesions in the CrI:CD-1(ICR)BR Mouse*. 2000, Charles River Laboratories.
23. Giknis, M. and C. Clifford, *Spontaneous Neoplastic Lesions in the CrI:CD-1(ICR)BR Mouse in Control Groups from 18 Month to 2 year Studies*. 2005, Charles River Laboratories.

From: Per Gustavsson <Per.Gustavsson@ki.se>
Sent: Thursday, November 12, 2015 11:45 AM
To: David Coggon; saracci; Philippe Grandjean; Maarten Bosland; 'Chris Portier'; 'Kogevinas, Manolis'
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Subject: SV: IARC Monograph on Glyphosate

Dear Chris and all,
Having read the abstract of the BfR document and the conversation below confirms to me that there are fundamental flaws in BfR's argumentation regarding the assessment of carcinogenic potential of glyphosate.
However, the role of BfR, as a risk assessment institute is different from IARCs role in risk identification, as David pointed out. This may lead to different conclusions regarding the risk to humans. However, in this case, the BfR seems not to argue in terms of magnitude of risk for exposed humans, but rather dismisses the entire qualitative evaluation by IARC.
I think this is wrong and am ready to add my signature to the letter.
All the best,
Per

Per Gustavsson, MD, professor
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Ämne: Re: IARC Monograph on Glyphosate

Dear all

I have not copied everyone in on my earlier correspondence, but I have followed the discussion on this with interest.

I think it is important to bear in mind that the IARC and EFSA operate witihin different frameworks.

IARC is about the assessment of cancer hazard - i.e. the likelihood that a chemical might, at least in some circumstances cause cancer in humans. It does not get closely involved in the assessment and management of risk.

EFSA is concerned principally with whether there is sufficient confidence that a pesticide, when used according to the conditions of its approval, will not pose an unacceptable risk to human health or the environment. The level of precaution that is applied in the face of scientific uncertainty depends on value judgements, and is not a scientific question (although scientists try to assess levels of uncertainty and communicate them to risk managers). I suspect that what EFSA will have looked at is whether, given the levels of precaution that are currently applied in the regulation of pesticides more generally, the uncertainties about possible risks of cancer from glyphosate are sufficient to warrant regulatory restrictions. That is the message that they have to get across to risk managers, and their language will be tailored to that objective.

One would be much more concerned about the science of EFSA's assessment if it led to regulatory deicisions that were out of line with those for other pesticides. Is there any evidence for that?

If people do not like the overall level of precaution for pesticides, they should lobby politicians (who ultimately are responsible for the management of risk).

David

On 12/11/2015 09:52, saracci wrote:

> Dear Chris,
> thanks for your initiative. As it occurred for the Blair/Vineis et al. (130 odd authors) paper after discussing the issue with Chris Wild I am not in a position to sign your letter as I am currently a Senior Visiting Scientist at IARC.
> I think that in particular Manolis and Philippe raise important points. The discrepancy in the evaluations of such a widely used agent should represent a better occasion than for other agents to develop (beyond your valuable letter) a comparison of both the 'theory' (objectives, criteria and methods of evaluating the evidence) and the 'practice' (how actually the work is done and by whom) of IARC and an agency like EFSA. It may be a 'diplomatically' touchy comparison but unless this is clarified people other than the very insiders will be dumbfounded by the repeated divergences between 'authoritative' scientific agencies .
> Thanks all the best Rodolfo
>
> ---
>
> From: PGrandjean@health.sdu.dk
> To: boslandm@uic.edu; cportier@me.com; kogevinas@creal.c
> Dear Chris - Thank you for this important initiative. I was on one of EFSA's panels (CONTAM) for six years and had to resign because I did not like the culture. In my experience, you have to be absolutely

certain before you can conclude. Although each opinion has a section on uncertainties, only lip service is paid to this issue and basically in the absence of solid evidence, the substance is innocuous. At the time, there were several people who had worked with ILSI for several years and then moved on to a position with EFSA. Once I asked to become a member of a WG, I was told that it was not possible, as they would then have to find a member "from the other side", although nobody could explain to me what that meant. Although I don't have any specific experience with EFSA's pesticides committee, I would not rely on EFSA being neutral, as the "balance" they try to achieve has more to do with stakeholders than with science. The opinion that we are expecting next week will be the responsibility of the PPR Panel. For your information, I have copied the names of the current members. I know at least one of them is a stakeholder representative with absolutely no experience in assessing carcinogenicity. It is not possible for me to find the names of the WG members, although there may be some overlap with the previous group. EFSA demands conflict of interest statements, and you may want to download them, but in my experience that are just regarded an administrative nuisance. So given the comments from others, I would suggest that a compromise between Manolis' suggestion and your draft should be possible, and my suggestion is to highlight IARC's multi-decade experience in such evaluations and the experience of the IARC WG members - in comparison with EFSA's lack of same. I would not venture into EFSA's problems with aspartam and BPA, but I'm sure that you are well aware that the glyphosate controversy is not the first sign that EFSA has serious bias problems. Cheers - Philippe

Colin Ockleford, Chair
Susanne Hougaard Bennekou, Vice-chair
Theo C. M. Brock, Vice-chair
Pauline Adriaanse
Philippe Berny
Sabine Duquesne
Sandro Grilli
Antonio F. Hernández-Jerez
Michael Klein
Thomas Kuhl
Ryszard Laskowski
Kyriaki Machera
Olavi Pelkonen
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Robert Smith
Michael Stemmer
Ingvar Sundh
Ivana Teodorovic
Aaldrik Tiktak
Christopher Topping
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From: Maarten Bosland [boslandm@uic.edu]
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To: 'Chris Portier'; 'Kogevinas, Manolis'
Cc: jmanto@creal.cat; Margaret.Karagas@dartmouth.edu; john.dement@duke.edu; Bengt.Jarvholm@envmed.umu.se; alavanjm@mail.nih.gov; hartgep@exchange.nih.gov; lubinj@exchange.nih.gov; silvermd@exchange.nih.gov; wardm@exchange.nih.gov; benedetto.terracini@fastwebnet.it; cvictora@gmail.com; (b) (6) (b) (6) mperry@gwu.edu; Philippe Grandjean; saracci@hotmail.com; (b) (6) ; abaccare@hsph.harvard.edu; dchris@hsph.harvard.edu; gwagner@hsph.harvard.edu; Marie-Elise.Parent@iaf.inrs.ca; mporta@imim.es; l.rushton@imperial.ac.uk; marcel.goldberg@inserm.fr; john.cherrie@iom-world.org; pietro.comba@iss.it; per.gustavsson@ki.se; efonth@lsuhsc.edu; jmclaugh@lunenfeld.ca; berringtona@mail.nih.gov; freemala@mail.nih.gov; friesenmc@mail.nih.gov; A.Mannetje@massey.ac.nz; J.Douwes@massey.ac.nz; dnc@mrc.soton.ac.uk;

Jahoppin@ncsu.edu; 'Dr. Linda Birnbaum'; 'John Bucher (NIH/NIEHS)'; 'James Huff'; Weinberg@niehs.nih.gov; lawrence.engel@nih.gov; m.hauptmann@nki.nl; Elsebeth@pubhealth.ku.dk; Bernard.stewart@sesiahs.health.nsw.gov.au; nsteenl@sph.emory.edu; petter.kristensen@stami.nl; helge.kjuus@stami.no; bruce.armstrong@sydney.edu.au; ab.miller@sympatico.ca; cocco_pierluigi@tiscali.it; Harri.Vainio@ttl.fi; nseixas@u.washington.edu; ricech@uc.edu; britz@ucla.edu; lemastgj@ucmail.uc.edu; jvena@uga.edu; lstayner@uic.edu; charles-lynch@uiowa.edu; james-merchant@uiowa.edu; David_Kriebel@uml.edu; michel.gerin@umontreal.ca; 'Rusyn, Ivan I'; angela.pesatori@unimi.it; pieralberto.bertazzi@unimi.it; lorenzo.simonato@unipd.it; roberta.pirastu@uniroma1.it; franco.merletti@unito.it; jsamet@usc.edu; Elaine.Symanski@uth.tmc.edu; d.heederik@uu.nl; 'Vermeulen, R.C.H. (Roel)'; fritschi@waimr.uwa.edu.au; yawei.zhang@yale.edu; mcebrian@cinvestav.mx; (b) (6); wchiu@cvm.tamu.edu; coccop@pacs.unica.it; aderoos@drexel.edu; s-fukushima@jisha.or.jp; pascal.guenel@inserm.fr; 'Ron Herbert'; mlamerrill@ucdavis.edu; marcelo.larramendy@gmail.com; lizbeth@correo.insp.mx; f.martin@lancaster.ac.uk; naidoos71@ukzn.ac.za; tprapamontol@gmail.com; dmreif@ncsu.edu; droy@fiu.edu; thomas.sanderson@iaf.inrs.ca; 'Martyn Smith'; thomas.kent@epa.gov; mary.wolff@mssm.edu; frederick.beland@fda.hhs.gov; m.berger@dkfz-heidelberg.de; judy.bolton@uic.edu; david.eastmond@ucr.edu; peter.karran@cancer.org.uk; david_kaufman@med.unc.edu; (b) (6); matilde.marques@ist.utl.pt; jorgen@cancer.dk; david.phillips@icr.ac.uk; h.schmeiser@dkfz-heidelberg.de; linda.t.titus-ernstoff@dartmouth.edu; dbthomas@fhcrc.org; htsuda@phar.nagoya-cu.ac.jp
Subject: RE: IARC Monograph on Glyphosate

Dear Chris:

This is a very important issue and I am very glad you are taking it up. I tend to agree with Manolis, because the large amount of data and interpretations by IARC and EFSA is impossible to review in sufficient depth to make me comfortable signing your letter. I do feel that it is very important to express strong concerns about the EFSA conclusions where the vary from the IARC evaluation and the words “serious concern” should be in a letter that we sign.

I wonder whether there is a way in which we could draft a letter that refers to not only the IARC and EFSA documents but also to your write-up because it contains some really serious problems with the EFSA document (no authors and their affiliations listed, redacted references, many inconsistencies that you have identified). So, is there a way in which you send your letter, perhaps co-signed by those who feel that they have sufficient insight in all arguments, so that a larger group could send a letter along the lines suggested by Manolis to express our strong concerns?

Maarten Bosland

From: Chris Portier [mailto:cportier@me.com]
Sent: Wednesday, November 11, 2015 10:24 AM
To: Kogevinas, Manolis
Cc: jmanto@creal.cat; Margaret.Karagas@dartmouth.edu; john.dement@duke.edu; Bengt.Jarvholm@envmed.umu.se; alavanjm@mail.nih.gov; Maarten Bosland; hartgep@exchange.nih.gov; lubinj@exchange.nih.gov; silvermd@exchange.nih.gov; wardm@exchange.nih.gov;

benedetto.terracini@fastwebnet.it; cvictora@gmail.com; [redacted]; [redacted]; mperry@gwu.edu; Pgrandjean@health.sdu.dk; saracci@hotmail.com; [redacted]; abaccare@hsph.harvard.edu; dchris@hsph.harvard.edu; gwagner@hsph.harvard.edu; Marie-Elise.Parent@iaf.inrs.ca; mporta@imim.es; l.rushton@imperial.ac.uk; marcel.goldberg@inserm.fr; john.cherrie@iom-world.org; pietro.comba@iss.it; per.gustavsson@ki.se; efonth@lsuhsc.edu; jmclaugh@lunenfeld.ca; berringtona@mail.nih.gov; freemala@mail.nih.gov; friesenmc@mail.nih.gov; A.Mannetje@massey.ac.nz; J.Douwes@massey.ac.nz; dnc@mrc.soton.ac.uk; Jahoppin@ncsu.edu; Dr. Linda Birnbaum; John Bucher (NIH/NIEHS); James Huff; Weinberg@niehs.nih.gov; lawrence.engel@nih.gov; m.hauptmann@nki.nl; Elsebeth@pubhealth.ku.dk; Bernard.stewart@sesiahs.health.nsw.gov.au; nsteenl@sph.emory.edu; petter.kristensen@stami.nl; helge.kjuus@stami.no; bruce.armstrong@sydney.edu.au; ab.miller@sympatico.ca; cocco_pierluigi@tiscali.it; Harri.Vainio@ttl.fi; nseixas@u.washington.edu; ricech@uc.edu; britz@ucla.edu; lemastgj@ucmail.uc.edu; jvena@uga.edu; lstayner@uic.edu; charles-lynch@uiowa.edu; james-merchant@uiowa.edu; David_Kriebel@uml.edu; michel.gerin@umontreal.ca; Rusyn, Ivan I; angela.pesatori@unimi.it; pieralberto.bertazzi@unimi.it; lorenzo.simonato@unipd.it; roberta.pirastu@uniroma1.it; franco.merletti@unito.it; jsamet@usc.edu; Elaine.Symanski@uth.tmc.edu; d.heederik@uu.nl; Vermeulen, R.C.H. (Roel); fritschi@waimr.uwa.edu.au; yawei.zhang@yale.edu; mcebrian@cinvestav.mx; [redacted]; wchiu@cvm.tamu.edu; coccop@medicina.unica.it; aderoos@drexel.edu; s-fukushima@jisha.or.jp; pascal.guenel@inserm.fr; Ron Herbert; mlamerrill@ucdavis.edu; marcelo.larramendy@gmail.com; lizbeth@correo.insp.mx; f.martin@lancaster.ac.uk; naidoos71@ukzn.ac.za; tprapamontol@gmail.com; dmreif@ncsu.edu; droy@fiu.edu; thomas.sanderson@iaf.inrs.ca; Martyn Smith; thomas.kent@epa.gov; mary.wolff@mssm.edu; frederick.beland@fda.hhs.gov; m.berger@dkfz-heidelberg.de; judy.bolton@uic.edu; david.eastmond@ucr.edu; peter.karran@cancer.org.uk; david_kaufman@med.unc.edu; [redacted]; matilde.marques@ist.utl.pt; jorgen@cancer.dk; david.phillips@icr.ac.uk; h.schmeiser@dkfz-heidelberg.de; linda.t.titus-ernstoff@dartmouth.edu; dbthomas@fhcrc.org; htsuda@phar.nagoya-cu.ac.jp
Subject: Re: IARC Monograph on Glyphosate

Manolis,

Thanks for your note and comments. First, to be clear, EFSA has procedures and policies for how to review this information (like the cited OECD document cited in the letter), so it is not that they do not have written procedures. Second, they have extensive experience in reviewing pesticide data; regretfully, they tend to identify faults with epidemiology data that makes it unusable and tend to be very supportive of industry interpretation of the available toxicology data. My problem is not with contradicting summaries of the data since BfR agrees with all of the IARC findings. My concern is with their dismissal of these findings as not important; that is what undermines the scientific review process used by the IARC and this is the scientific approach I am am hoping we are addressing. While this letter is somewhat detailed for something being sent to a political entity like EC ENVI, I am going to be present at the hearing and hope to provide clarity.

C.

On Nov 11, 2015, at 5:09 PM, Kogevinas, Manolis <kogevinas@creal.cat> wrote:

Hi Chris,

Thank you for this. I am not sure this is the best procedure. There is obviously a problem when in the same year we have two public organizations giving conflicting evidence for the same chemical. Even though I personally have much more faith in the IARC evaluation, EFSA is also a well known agency. EFSA, obviously, has less experience in these types of evaluations and the protocols followed are clearly less developed and standard. However, by signing the type of letter you propose I think we assume that we (those who sign) have evaluated the evidence independently and give right to IARC. I have not done this. In addition, it is not clear to me that this type of evaluation of evidence is done best through letters like the one you propose that goes into the details of the evaluations.

I would be happy to sign a letter saying (more or less):

- We have two contradicting summaries of the evidence
- IARC has a very long tradition in examining carcinogens and the procedures and protocols followed are well established and generally accepted. Based on the history of the IARC evaluations, it is most likely that the IARC working group summarized accurately the current evidence on glyphosate.
- EFSA has less established protocols for evaluating carcinogens
- We urge the ENVI committee to review critically the EFSA evaluation and particularly those aspects of the report that criticize the IARC evaluation

I would be happy to change this opinion if there are good arguments for changing,

Regards

Manolis

Manolis Kogevinas, MD, PhD
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De: Chris Portier [mailto:cportier@me.com]
Enviado el: miércoles, 11 de noviembre de 2015 13:58
Para: jmanto@creal.cat; kogevinas@creal.cat; Margaret.Karagas@dartmouth.edu; john.dement@duke.edu; Bengt.Jarvholm@envmed.umu.se; alavanjm@mail.nih.gov; Maarten Bosland; hartgep@exchange.nih.gov; lubinj@exchange.nih.gov; silvermd@exchange.nih.gov; wardm@exchange.nih.gov; benedetto.terracini@fastwebnet.it; cvictora@gmail.com; (b) (6); (b) (6); mperry@gwu.edu; Pgrandjean@health.sdu.dk; saracci@hotmail.com; (b) (6); abaccare@hsph.harvard.edu; dchris@hsph.harvard.edu; gwagner@hsph.harvard.edu; Marie-Elise.Parent@iaf.inrs.ca; mporta@imim.es; l.rushton@imperial.ac.uk; marcel.goldberg@inserm.fr; john.cherrie@iom-world.org; pietro.comba@iss.it; per.gustavsson@ki.se; efonth@lsuhsc.edu; jmclaugh@lunenfeld.ca; berringtona@mail.nih.gov; freemala@mail.nih.gov; friesenmc@mail.nih.gov; A.Mannetje@massey.ac.nz; J.Douwes@massey.ac.nz; dnc@mrc.soton.ac.uk; Jahoppin@ncsu.edu; Dr. Linda Birnbaum; John Bucher (NIH/NIEHS); James Huff; Weinberg@niehs.nih.gov; lawrence.engel@nih.gov; m.hauptmann@nki.nl; Elsebeth@pubhealth.ku.dk; Bernard.stewart@sesiahs.health.nsw.gov.au; nsteenl@sph.emory.edu; petter.kristensen@stami.nl; helge.kjuus@stami.no; bruce.armstrong@sydney.edu.au; <ab.miller@sympatico.ca>; cocco_pierluigi@tiscali.it; Harri.Vainio@ttl.fi; nseixas@u.washington.edu; ricech@uc.edu; britz@ucla.edu; lemastgj@ucmail.uc.edu; jvena@uga.edu; lstayner@uic.edu; charles-lynch@uiowa.edu; james-merchant@uiowa.edu; David_Kriebel@uml.edu; michel.gerin@umontreal.ca; Rusyn, Ivan I; angela.pesatori@unimi.it; pieralberto.bertazzi@unimi.it; lorenzo.simonato@unipd.it; roberta.pirastu@uniroma1.it; franco.merletti@unito.it; jsamet@usc.edu; Elaine.Symanski@uth.tmc.edu; d.heederik@uu.nl; Vermeulen, R.C.H. (Roel); fritschi@waimr.uwa.edu.au; yawei.zhang@yale.edu; mcebrian@cinvestav.mx; [redacted] (b) (6); wchiu@cvm.tamu.edu; coccop@medicina.unica.it; aderoos@drexel.edu; s-fukushima@jisha.or.jp; pascal.guenel@inserm.fr; Ron Herbert; mlamerrill@ucdavis.edu; marcelo.larramendy@gmail.com; lizbeth@correo.insp.mx; f.martin@lancaster.ac.uk; naidoos71@ukzn.ac.za; tprapamontol@gmail.com; dmreif@ncsu.edu; droy@fiu.edu; thomas.sanderson@iaf.inrs.ca; Martyn Smith; thomas.kent@epa.gov; mary.wolff@mssm.edu; frederick.beland@fda.hhs.gov; m.berger@dkfz-heidelberg.de; judy.bolton@uic.edu; david.eastmond@ucr.edu; peter.karran@cancer.org.uk; david_kaufman@med.unc.edu; (b) (6); matilde.marques@ist.utl.pt; jorgen@cancer.dk; david.phillips@icr.ac.uk; h.schmeiser@dkfz-heidelberg.de; linda.t.titus-ernstoff@dartmouth.edu; dbthomas@fhcrc.org; htsuda@phar.nagoya-cu.ac.jp
Asunto: IARC Monograph on Glyphosate

Dear Colleagues,

For IARC Monograph 112, 17 scientists evaluated the carcinogenic hazard for 4 insecticides and the herbicide glyphosate. The Working Group concluded that glyphosate was a probable human carcinogen. This finding stirred great debate globally on the safety of glyphosate and led to a careful evaluation of the IARC monograph results when they became available on July 29, 2015. During this period, the European Food Safety Agency (EFSA) was in the middle of a reassessment of the safety of glyphosate. The German Federal Institute for Risk Assessment (BfR) was the lead country agency in drafting the reassessment report. The draft, prior to the IARC Monograph, concluded there was no carcinogenic potential of glyphosate. In August of this year, following the release of the full Monograph on glyphosate, the BfR drafted an Addendum to their report that specifically addresses the Monograph review. This was presented to EFSA several weeks ago and leaked by the press.

This week, EFSA will release their reassessment of glyphosate. In this review, they will again conclude that glyphosate has no carcinogenic potential. This review is based on the BfR Addendum which has some severe scientific flaws. I am concerned that this evaluation, if it stands, could weaken the effectiveness of the IARC Monograph Programme. I am also concerned that the serious flaws in the BfR Addendum, if not challenged, could continue to be used by regulatory agencies to dismiss critical science pertinent to a regulatory decision, including broad exclusion of literature data and epidemiological data.

The European Commission ENVI Committee will meet on December 1, 2015 to receive the reassessment report from EFSA. I have drafted a letter of concern that I wish to present to the ENVI Committee as they consider whether to accept or reject the EFSA evaluation. I would like to invite you to join with me in signing this open letter. I have obtained your names from many different lists, mostly from previous IARC monographs but also from other sources. It is possible I have included your name more than once on this list and I apologize for sending you multiple copies.

I am open to changes to improve the letter, but because of the short time-frame, I hope you can agree to sign on with only modest modifications (I am sending this to several hundred colleagues). I have included the letter but have not included the BfR Addendum or the Reassessment Report because of size. These are available at:

Addendum: http://www.mdr.de/fakt/fakt-glyphosat-bfr-bewertung100.html (NOTE: click on Herunterladen to download the report)

RAR: http://dar.efsa.europa.eu/dar-web/provision

The more important report is the Addendum.

If you agree to joining me in signing this letter, please respond by November 25 with the following that I can then add to my letter.

Title (Prof, Dr., …), Name

Position Title (e.g. Director, Named Chair, etc)

Affiliation

City, Country

I look forward to hearing from you.

Sincerely,

Christopher Portier

From: Fontham, Elizabeth <EFonth@lsuhsc.edu>
Sent: Wednesday, November 11, 2015 12:25 PM
To: Chris Portier; Kogevinas, Manolis
Cc: jmanto@creal.cat; Margaret.Karagas@dartmouth.edu; john.dement@duke.edu; Bengt.Jarvholm@envmed.umu.se; Alavanja, Michael (NIH/NCI) [E]; Maarten Bosland; hartgep@exchange.nih.gov; Lubin, Jay (NIH/NCI) [V]; Silverman, Debra (NIH/NCI) [E]; Ward, Mary (NIH/NCI) [E]; benedetto.terracini@fastwebnet.it; cvictora@gmail.com; (b) (6); (b) (6); mperry@gwu.edu; Pgrandjean@health.sdu.dk; saracci@hotmail.com; (b) (6); abaccare@hsph.harvard.edu; dchris@hsph.harvard.edu; gwagner@hsph.harvard.edu; Marie-Elise.Parent@iaf.inrs.ca; mporta@imim.es; l.rushton@imperial.ac.uk; marcel.goldberg@inserm.fr; john.cherrie@iom-world.org; pietro.comba@iss.it; per.gustavsson@ki.se; jmclaugh@lunenfeld.ca; Berrington, Amy (NIH/NCI) [E]; Beane-Freeman, Laura (NIH/NCI) [E]; Friesen, Melissa (NIH/NCI) [E]; A.Mannetje@massey.ac.nz; J.Douwes@massey.ac.nz; dnc@mrc.soton.ac.uk; Jahoppin@ncsu.edu; Birnbaum, Linda (NIH/NIEHS) [E]; Bucher, John (NIH/NIEHS) [E]; Huff, James (NIH/NIEHS) [G]; Weinberg, Clarice (NIH/NIEHS) [E]; Engel, Lawrence (NIH/NIEHS) [C]; m.hauptmann@nki.nl; Elsebeth@pubhealth.ku.dk; Bernard.stewart@sesiahs.health.nsw.gov.au; nsteenl@sph.emory.edu; petter.kristensen@stami.nl; helge.kjuus@stami.no; bruce.armstrong@sydney.edu.au; ab.miller@sympatico.ca; cocco_pierluigi@tiscali.it; Harri.Vainio@ttl.fi; nseixas@u.washington.edu; ricech@uc.edu; britz@ucla.edu; lemastgj@ucmail.uc.edu; jvena@uga.edu; lstayner@uic.edu; Lynch, Charles F.; james-merchant@uiowa.edu; David_Kriebel@uml.edu; michel.gerin@umontreal.ca; Rusyn, Ivan I; angela.pesatori@unimi.it; pieralberto.bertazzi@unimi.it; lorenzo.simonato@unipd.it; roberta.pirastu@uniroma1.it; franco.merletti@unito.it; jsamet@usc.edu; Elaine.Symanski@uth.tmc.edu; d.heederik@uu.nl; Vermeulen, R.C.H. (Roel); fritschi@waimr.uwa.edu.au; yawei.zhang@yale.edu; mcebrian@cinvestav.mx; (b) (6); wchiu@cvm.tamu.edu; coccop@medicina.unica.it; aderoos@drexel.edu; s-fukushima@jisha.or.jp; pascal.guenel@inserm.fr; Herbert, Ron (NIH/NIEHS) [E]; mlamerrill@ucdavis.edu; marcelo.larramendy@gmail.com; lizbeth@correo.insp.mx; f.martin@lancaster.ac.uk; naidoos71@ukzn.ac.za; tprapamontol@gmail.com; dmreif@ncsu.edu; droy@fiu.edu; thomas.sanderson@iaf.inrs.ca; Martyn Smith; thomas.kent@epa.gov; mary.wolff@mssm.edu; Beland, Frederick (FDA/NCTR); m.berger@dkfz-heidelberg.de; judy.bolton@uic.edu; david.eastmond@ucr.edu; peter.karran@cancer.org.uk; david_kaufman@med.unc.edu; (b) (6); matilde.marques@ist.utl.pt; jorgen@cancer.dk; david.phillips@icr.ac.uk; h.schmeiser@dkfz-heidelberg.de; linda.t.titus-ernstoff@dartmouth.edu; dbthomas@fhcrc.org; htsuda@phar.nagoya-cu.ac.jp
Subject: RE: IARC Monograph on Glyphosate

I too have looked at both and I think the proposed letter approach is best.

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Sent: Wednesday, November 11, 2015 10:24 AM
To: Kogevinas, Manolis
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Subject: Re: IARC Monograph on Glyphosate

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Thanks for your note and comments. First, to be clear, EFSA has procedures and policies for how to review this information (like the cited OECD document cited in the letter), so it is not that they do not have written procedures. Second, they have extensive experience in reviewing pesticide data; regretfully, they tend to identify faults with epidemiology data that makes it unusable and tend to be very supportive of industry interpretation of the available toxicology data. My problem is not with contradicting summaries of the data since BfR agrees with all of the IARC findings. My concern is with their dismissal of these findings as not important; that is what undermines the scientific review process used by the IARC and this is the scientific approach I am am hoping we are addressing. While this letter is somewhat detailed for something being sent to a political entity like EC ENVI, I am going to be present at the hearing and hope to provide clarity.

C.

> On Nov 11, 2015, at 5:09 PM, Kogevinas, Manolis <kogevinas@creal.cat> wrote:
>
> Hi Chris,
> Thank you for this. I am not sure this is the best procedure. There is obviously a problem when in the same year we have two public organizations giving conflicting evidence for the same chemical. Even though I personally have much more faith in the IARC evaluation, EFSA is also a well known agency. EFSA, obviously, has less experience in these types of evaluations and the protocols followed are clearly less developed and standard. However, by signing the type of letter you propose I think we assume that we (those who sign) have evaluated the evidence independently and give right to IARC. I have not done this. In addition, it is not clear to me that this type of evaluation of evidence is done best through letters like the one you propose that goes into the details of the evaluations.
>
> I would be happy to sign a letter saying (more or less):
> - We have two contradicting summaries of the evidence

- IARC has a very long tradition in examining carcinogens and the procedures and protocols followed are well established and generally accepted. Based on the history of the IARC evaluations, it is most likely that the IARC working group summarized accurately the current evidence on glyphosate.
- EFSA has less established protocols for evaluating carcinogens
- We urge the ENVI committee to review critically the EFSA evaluation and particularly those aspects of the report that criticize the IARC evaluation

I would be happy to change this opinion if there are good arguments for changing,
Regards

Manolis

Manolis Kogevinas, MD, PhD
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E-Mail: kogevinas@creal.cat
www.creal.cat

De: Chris Portier [mailto:cportier@me.com]
Enviado el: miércoles, 11 de noviembre de 2015 13:58
Para: jmanto@creal.cat; kogevinas@creal.cat; Margaret.Karagas@dartmouth.edu; john.dement@duke.edu; Bengt.Jarvholm@envmed.umu.se; alavanjm@mail.nih.gov; Maarten Bosland; hartgep@exchange.nih.gov; lubinj@exchange.nih.gov; silvermd@exchange.nih.gov; wardm@exchange.nih.gov; benedetto.terracini@fastwebnet.it; cvictora@gmail.com; (b) (6); (b) (6); mperry@gwu.edu; Pgrandjean@health.sdu.dk; saracci@hotmail.com; (b) (6); abaccare@hsph.harvard.edu; dchris@hsph.harvard.edu; qwagner@hsph.harvard.edu; Marie-Elise.Parent@iaf.inrs.ca; mporta@imim.es; l.rushton@imperial.ac.uk; marcel.goldberg@inserm.fr; john.cherrie@iom-world.org; pietro.comba@iss.it; per.gustavsson@ki.se; efonth@lsuhsc.edu; jmclaugh@lunenfeld.ca; berringtona@mail.nih.gov; freemala@mail.nih.gov; friesenmc@mail.nih.gov; A.Mannetje@massey.ac.nz; J.Douwes@massey.ac.nz; dnc@mrc.soton.ac.uk; Jahoppin@ncsu.edu; Dr. Linda Birnbaum; John Bucher (NIH/NIEHS); James Huff; Weinberg@niehs.nih.gov; lawrence.engel@nih.gov; m.hauptmann@nki.nl; Elsebeth@pubhealth.ku.dk; Bernard.stewart@sesiahs.health.nsw.gov.au; nsteenl@sph.emory.edu; petter.kristensen@stami.nl; helge.kjuus@stami.no; bruce.armstrong@sydney.edu.au; <ab.miller@sympatico.ca>; cocco_pierluigi@tiscali.it; Harri.Vainio@ttl.fi; nseixas@u.washington.edu; ricech@uc.edu; britz@ucla.edu; lemastgj@ucmail.uc.edu; jvena@uga.edu; lstayner@uic.edu; charles-lynch@uiowa.edu; james-merchant@uiowa.edu; David_Kriebel@uml.edu; michel.gerin@umontreal.ca; Rusyn, Ivan I; angela.pesatori@unimi.it; pieralberto.bertazzi@unimi.it; lorenzo.simonato@unipd.it; roberta.pirastu@uniroma1.it; franco.merletti@unito.it; jsamet@usc.edu; Elaine.Symanski@uth.tmc.edu; d.heederik@uu.nl; Vermeulen, R.C.H. (Roel); fritschi@waimr.uwa.edu.au; yawei.zhang@yale.edu; mcebrian@cinvestav.mx; (b) (6); wchiu@cvm.tamu.edu; coccop@medicina.unica.it; aderoos@drexel.edu; s-fukushima@jisha.or.jp; pascal.guenel@inserm.fr; Ron Herbert; mlamerrill@ucdavis.edu; marcelo.larramendy@gmail.com; lizbeth@correo.insp.mx; f.martin@lancaster.ac.uk; naidoos71@ukzn.ac.za; tprapamontol@gmail.com; dmreif@ncsu.edu; droy@fiu.edu; thomas.sanderson@iaf.inrs.ca; Martyn Smith; thomas.kent@epa.gov; mary.wolff@mssm.edu; frederick.beland@fda.hhs.gov; m.berger@dkfz-heidelberg.de; judy.bolton@uic.edu; david.eastmond@ucr.edu; peter.karran@cancer.org.uk; david_kauf

man@med.unc.edu; [redacted]; matilde.marques@ist.utl.pt; jorgen@cancer.dk; david.phillips@icr.ac.uk; h.schmeiser@dkfz-heidelberg.de; linda.t.titus-ernstoff@dartmouth.edu; dbthomas@fhcrc.org; htsuda@phar.nagoya-cu.ac.jp
Asunto: IARC Monograph on Glyphosate

Dear Colleagues,

For IARC Monograph 112, 17 scientists evaluated the carcinogenic hazard for 4 insecticides and the herbicide glyphosate. The Working Group concluded that glyphosate was a probable human carcinogen. This finding stirred great debate globally on the safety of glyphosate and led to a careful evaluation of the IARC monograph results when they became available on July 29, 2015. During this period, the European Food Safety Agency (EFSA) was in the middle of a reassessment of the safety of glyphosate. The German Federal Institute for Risk Assessment (BfR) was the lead country agency in drafting the reassessment report. The draft, prior to the IARC Monograph, concluded there was no carcinogenic potential of glyphosate. In August of this year, following the release of the full Monograph on glyphosate, the BfR drafted an Addendum to their report that specifically addresses the Monograph review. This was presented to EFSA several weeks ago and leaked by the press.

This week, EFSA will release their reassessment of glyphosate. In this review, they will again conclude that glyphosate has no carcinogenic potential. This review is based on the BfR Addendum which has some severe scientific flaws. I am concerned that this evaluation, if it stands, could weaken the effectiveness of the IARC Monograph Programme. I am also concerned that the serious flaws in the BfR Addendum, if not challenged, could continue to be used by regulatory agencies to dismiss critical science pertinent to a regulatory decision, including broad exclusion of literature data and epidemiological data.

The European Commission ENVI Committee will meet on December 1, 2015 to receive the reassessment report from EFSA. I have drafted a letter of concern that I wish to present to the ENVI Committee as they consider whether to accept or reject the EFSA evaluation. I would like to invite you to join with me in signing this open letter. I have obtained your names from many different lists, mostly from previous IARC monographs but also from other sources. It is possible I have included your name more than once on this list and I apologize for sending you multiple copies.

I am open to changes to improve the letter, but because of the short time-frame, I hope you can agree to sign on with only modest modifications (I am sending this to several hundred colleagues). I have included the letter but have not included the BfR Addendum or the Reassessment Report because of size. These are available at:

Addendum: http://www.mdr.de/fakt/fakt-glyphosat-bfr-bewertung100.html (NOTE: click on Herunterladen to download the report)
RAR: http://dar.efsa.europa.eu/dar-web/provision

The more important report is the Addendum.

If you agree to joining me in signing this letter, please respond by November 25 with the following that I can then add to my letter.

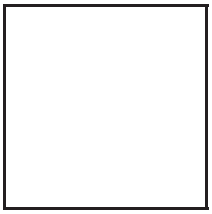
Title (Prof, Dr., …), Name
Position Title (e.g. Director, Named Chair, etc)
Affiliation

City, Country

I look forward to hearing from you.

Sincerely,

Christopher Portier



From: anthony miller <ab.miller@sympatico.ca>
Sent: Wednesday, November 11, 2015 12:24 PM
To: Marcelo Larramendy; Chris Portier
Cc: jmanto@creal.cat; kogevinas@creal.cat; Margaret.Karagas@dartmouth.edu; john.dement@duke.edu; Bengt.Jarvholm@envmed.umu.se; Alavanja, Michael (NIH/NCI) [E]; Maarten Bosland; hartgep@exchange.nih.gov; Lubin, Jay (NIH/NCI) [V]; Silverman, Debra (NIH/NCI) [E]; Ward, Mary (NIH/NCI) [E]; benedetto.terracini@fastwebnet.it; cvictora@gmail.com; (b) (6); (b) (6); mperry@gwu.edu; Pgrandjean@health.sdu.dk; saracci@hotmail.com; (b) (6); abaccare@hsph.harvard.edu; dchris@hsph.harvard.edu; gwagner@hsph.harvard.edu; Marie-Elise.Parent@iaf.inrs.ca; mporta@imim.es; l.rushton@imperial.ac.uk; marcel.goldberg@inserm.fr; john.cherrie@iom-world.org; pietro.comba@iss.it; per.gustavsson@ki.se; efonth@lsuhsc.edu; John McLaughlin; Berrington, Amy (NIH/NCI) [E]; Beane-Freeman, Laura (NIH/NCI) [E]; Friesen, Melissa (NIH/NCI) [E]; A.Mannetje@massey.ac.nz; J.Douwes@massey.ac.nz; dnc@mrc.soton.ac.uk; Jahoppin@ncsu.edu; Birnbaum, Linda (NIH/NIEHS) [E]; Bucher, John (NIH/NIEHS) [E]; Huff, James (NIH/NIEHS) [G]; Weinberg, Clarice (NIH/NIEHS) [E]; Engel, Lawrence (NIH/NIEHS) [C]; m.hauptmann@nki.nl; Elsebeth@pubhealth.ku.dk; Bernard.stewart@sesiahs.health.nsw.gov.au; nsteenl@sph.emory.edu; petter.kristensen@stami.nl; helge.kjuus@stami.no; Bruce Armstrong; cocco_pierluigi@tiscali.it; Harri Vainio; nseixas@u.washington.edu; ricech@uc.edu; britz@ucla.edu; lemastgj@ucmail.uc.edu; jvena@uga.edu; lstayner@uic.edu; Lynch, Charles F.; james-merchant@uiowa.edu; David_Kriebel@uml.edu; michel.gerin@umontreal.ca; Rusyn, Ivan I; angela.pesatori@unimi.it; pieralberto.bertazzi@unimi.it; lorenzo.simonato@unipd.it; roberta.pirastu@uniroma1.it; franco.merletti@unito.it; jsamet@usc.edu; Elaine.Symanski@uth.tmc.edu; d.heederik@uu.nl; Vermeulen, R.C.H. Roel; fritschi@waimr.uwa.edu.au; yawei.zhang@yale.edu; mcebrian@cinvestav.mx; (b) (6); Weihsueh Chiu; coccop@medicina.unica.it; aderoos@drexel.edu; s-fukushima@jisha.or.jp; pascal.guenel@inserm.fr; Herbert, Ron (NIH/NIEHS) [E]; Michele Andrea La Merrill; lizbeth@correo.insp.mx; Francis L Martin; naidoos71@ukzn.ac.za; tprapamontol@gmail.com; David Reif; droy@fiu.edu; Thomas Sanderson; Martyn Smith; thomas.kent@epa.gov; mary.wolff@mssm.edu; Beland, Frederick (FDA/NCTR); m.berger@dkfz-heidelberg.de; judy.bolton@uic.edu; david.eastmond@ucr.edu; peter.karran@cancer.org.uk; david_kaufman@med.unc.edu; (b) (6); matilde.marques@ist.utl.pt; jorgen@cancer.dk; david.phillips@icr.ac.uk; h.schmeiser@dkfz-heidelberg.de; linda.t.titus-ernstoff@dartmouth.edu; David Thomas; htsuda@phar.nagoya-cu.ac.jp
Subject: RE: IARC Monograph on Glyphosate

Dear all

I had hesitated to distribute my comments to everyone, so earlier I sent my congratulations to Chris, agreeing with his approach, though suggesting a few minor editorial changes.

However, given the subsequent correspondence, I feel I must react to the statement by Manolis, in particular his statement "However, by signing the type of letter you propose I think we assume that we (those who sign) have evaluated the evidence independently and give right to IARC. I have not done this. In addition, it is not clear to me that this type of evaluation of evidence is done best through letters like the one you propose that goes into the details of the evaluations."

That is not my position. What I feel is that it is desirable that we support the approach by the IARC WG in this instance. Chris has done a very good job in identifying the deficiencies in the EFSA rebuttal of the IARC's WG's

conclusions. Because of this, I am prepared to add my name to the letter. That may seem strange to at least two of you who know that I dissented, both within the WG and subsequently publicly to the conclusions on the IARC WG responsible for Handbook 15 (Evaluation of Breast Screening). That was a situation where I had fully evaluated the epidemiological evidence (and produced some of it) so I agree with the principle that dissension is at times reasonable, but in the present instance I see no reason to dissent.

Tony

From: marcelo.larramendy@gmail.com
Date: Wed, 11 Nov 2015 14:01:36 -0300
Subject: Re: IARC Monograph on Glyphosate
To: cportier@me.com
CC: jmanto@creal.cat; kogevinas@creal.cat; Margaret.Karagas@dartmouth.edu; john.dement@duke.edu; Bengt.Jarvholm@envmed.umu.se; alavanjm@mail.nih.gov; boslandm@uic.edu; hartgep@exchange.nih.gov; lubinj@exchange.nih.gov; silvermd@exchange.nih.gov; wardm@exchange.nih.gov; benedetto.terracini@fastwebnet.it; cvictora@gmail.com; (b) (6); (b) (6); mperry@gwu.edu; Pgrandjean@health.sdu.dk; saracci@hotmail.com; (b) (6); abaccare@hsph.harvard.edu; dchris@hsph.harvard.edu; gwagner@hsph.harvard.edu; Marie-Elise.Parent@iaf.inrs.ca; mporta@imim.es; l.rushton@imperial.ac.uk; marcel.goldberg@inserm.fr; john.cherrie@iom-world.org; pietro.comba@iss.it; per.gustavsson@ki.se; efonth@lsuhsc.edu; jmclaugh@lunenfeld.ca; berringtona@mail.nih.gov; freemala@mail.nih.gov; friesenmc@mail.nih.gov; A.Mannetje@massey.ac.nz; J.Douwes@massey.ac.nz; dnc@mrc.soton.ac.uk; Jahoppin@ncsu.edu; birnbaumls@niehs.nih.gov; bucher@niehs.nih.gov; huff1@niehs.nih.gov; Weinberg@niehs.nih.gov; lawrence.engel@nih.gov; m.hauptmann@nki.nl; Elsebeth@pubhealth.ku.dk; Bernard.stewart@sesiahs.health.nsw.gov.au; nsteenl@sph.emory.edu; petter.kristensen@stami.nl; helge.kjuus@stami.no; bruce.armstrong@sydney.edu.au; ab.miller@sympatico.ca; cocco_pierluigi@tiscali.it; Harri.Vainio@ttl.fi; nseixas@u.washington.edu; ricech@uc.edu; britz@ucla.edu; lemastgj@ucmail.uc.edu; jvena@uga.edu; lstayner@uic.edu; charles-lynch@uiowa.edu; james-merchant@uiowa.edu; David_Kriebel@uml.edu; michel.gerin@umontreal.ca; iir@unc.edu; angela.pesatori@unimi.it; pieralberto.bertazzi@unimi.it; lorenzo.simonato@unipd.it; roberta.pirastu@uniroma1.it; franco.merletti@unito.it; jsamet@usc.edu; Elaine.Symanski@uth.tmc.edu; d.heederik@uu.nl; R.C.H.Vermeulen@uu.nl; fritschi@waimr.uwa.edu.au; yawei.zhang@yale.edu; mcebrian@cinvestav.mx; (b) (6); wchiu@cvm.tamu.edu; coccop@medicina.unica.it; aderoos@drexel.edu; s-fukushima@jisha.or.jp; pascal.guenel@inserm.fr; herbert@niehs.nih.gov; mlamerrill@ucdavis.edu; lizbeth@correo.insp.mx; f.martin@lancaster.ac.uk; naidoos71@ukzn.ac.za; tprapamontol@gmail.com; dmreif@ncsu.edu; droy@fiu.edu; thomas.sanderson@iaf.inrs.ca; martynts@berkeley.edu; thomas.kent@epa.gov; mary.wolff@mssm.edu; frederick.beland@fda.hhs.gov; m.berger@dkfz-heidelberg.de; judy.bolton@uic.edu; david.eastmond@ucr.edu; peter.karran@cancer.org.uk; david_kaufman@med.unc.edu; (b) (6); matilde.marques@ist.utl.pt; jorgen@cancer.dk; david.phillips@icr.ac.uk; h.schmeiser@dkfz-heidelberg.de; linda.t.titus-ernstoff@dartmouth.edu; dbthomas@fhcrc.org; htsuda@phar.nagoya-cu.ac.jp

Dear Christopher,

I have been through your message as well as Monolis' suggestion.
However, I totally agree with the point of view clearly stated by Manolis.

Regards,

Marcelo Larramendy

Prof. Marcelo L. Larramendy, Ph.D.
Principal Researcher CONICET
School of Natural Sciences and Museum
National University of La Plata
La Plata, Argentina

On Wed, Nov 11, 2015 at 9:57 AM, Chris Portier <cportier@me.com> wrote:

> Dear Colleagues,
>
> For IARC Monograph 112, 17 scientists evaluated the carcinogenic hazard for 4 insecticides and the herbicide glyphosate. The Working Group concluded that glyphosate was a probable human carcinogen. This finding stirred great debate globally on the safety of glyphosate and led to a careful evaluation of the IARC monograph results when they became available on July 29, 2015. During this period, the European Food Safety Agency (EFSA) was in the middle of a reassessment of the safety of glyphosate. The German Federal Institute for Risk Assessment (BfR) was the lead country agency in drafting the reassessment report. The draft, prior to the IARC Monograph, concluded there was no carcinogenic potential of glyphosate. In August of this year, following the release of the full Monograph on glyphosate, the BfR drafted an Addendum to their report that specifically addresses the Monograph review. This was presented to EFSA several weeks ago and leaked by the press.
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RAR: http://dar.efsa.europa.eu/dar-web/provision

The more important report is the Addendum.

If you agree to joining me in signing this letter, please respond by November 25 with the following that I can then add to my letter.

Title (Prof, Dr., …), Name
Position Title (e.g. Director, Named Chair, etc)
Affiliation
City, Country

I look forward to hearing from you.

Sincerely,

Christopher Portier

From: Marcelo Larramendy <marcelo.larramendy@gmail.com>
Sent: Wednesday, November 11, 2015 12:02 PM
To: Chris Portier
Cc: jmanto@creal.cat; kogevinas@creal.cat; Margaret.Karagas@dartmouth.edu; john.dement@duke.edu; Bengt.Jarvholm@envmed.umu.se; Alavanja, Michael (NIH/NCI) [E]; Maarten Bosland; hartgep@exchange.nih.gov; Lubin, Jay (NIH/NCI) [V]; Silverman, Debra (NIH/NCI) [E]; Ward, Mary (NIH/NCI) [E]; benedetto.terracini@fastwebnet.it; cvictora@gmail.com; (b) (6); (b) (6); mperry@gwu.edu; Pgrandjean@health.sdu.dk; saracci@hotmail.com; (b) (6); abaccare@hsph.harvard.edu; dchris@hsph.harvard.edu; gwagner@hsph.harvard.edu; Marie-Elise.Parent@iaf.inrs.ca; mporta@imim.es; l.rushton@imperial.ac.uk; marcel.goldberg@inserm.fr; john.cherrie@iom-world.org; pietro.comba@iss.it; per.gustavsson@ki.se; efonth@lsuhsc.edu; jmclaugh@lunenfeld.ca; Berrington, Amy (NIH/NCI) [E]; Beane-Freeman, Laura (NIH/NCI) [E]; Friesen, Melissa (NIH/NCI) [E]; A.Mannetje@massey.ac.nz; J.Douwes@massey.ac.nz; dnc@mrc.soton.ac.uk; Jahoppin@ncsu.edu; Birnbaum, Linda (NIH/NIEHS) [E]; Bucher, John (NIH/NIEHS) [E]; Huff, James (NIH/NIEHS) [G]; Weinberg, Clarice (NIH/NIEHS) [E]; Engel, Lawrence (NIH/NIEHS) [C]; m.hauptmann@nki.nl; Elsebeth@pubhealth.ku.dk; Bernard.stewart@sesiahs.health.nsw.gov.au; nsteenl@sph.emory.edu; petter.kristensen@stami.nl; helge.kjuus@stami.no; bruce.armstrong@sydney.edu.au; <ab.miller@sympatico.ca>; cocco_pierluigi@tiscali.it; Harri.Vainio@ttl.fi; nseixas@u.washington.edu; ricech@uc.edu; britz@ucla.edu; lemastgj@ucmail.uc.edu; jvena@uga.edu; lstayner@uic.edu; Lynch, Charles F.; james-merchant@uiowa.edu; David_Kriebel@uml.edu; michel.gerin@umontreal.ca; Rusyn, Ivan I; angela.pesatori@unimi.it; pieralberto.bertazzi@unimi.it; lorenzo.simonato@unipd.it; roberta.pirastu@uniroma1.it; franco.merletti@unito.it; jsamet@usc.edu; Elaine.Symanski@uth.tmc.edu; d.heederik@uu.nl; Vermeulen, R.C.H. (Roel); fritschi@waimr.uwa.edu.au; yawei.zhang@yale.edu; mcebrian@cinvestav.mx; (b) (6); Weihsueh Chiu; coccop@medicina.unica.it; aderoos@drexel.edu; s-fukushima@jisha.or.jp; pascal.guenel@inserm.fr; Herbert, Ron (NIH/NIEHS) [E]; Michele Andrea La Merrill; lizbeth@correo.insp.mx; Francis L Martin; naidoos71@ukzn.ac.za; tprapamontol@gmail.com; David Reif; droy@fiu.edu; Thomas Sanderson; Martyn Smith; thomas.kent@epa.gov; mary.wolff@mssm.edu; Beland, Frederick (FDA/NCTR); m.berger@dkfz-heidelberg.de; judy.bolton@uic.edu; david.eastmond@ucr.edu; peter.karran@cancer.org.uk; david_kaufman@med.unc.edu; (b) (6); matilde.marques@ist.utl.pt; jorgen@cancer.dk; david.phillips@icr.ac.uk; h.schmeiser@dkfz-heidelberg.de; linda.t.titus-ernstoff@dartmouth.edu; dbthomas@fhcrc.org; htsuda@phar.nagoya-cu.ac.jp
Subject: Re: IARC Monograph on Glyphosate

Dear Christopher,

I have been through your message as well as Monolis' suggestion.
However, I totally agree with the point of view clearly stated by Manolis.

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Marcelo Larramendy

Prof. Marcelo L. Larramendy, Ph.D.
Principal Researcher CONICET
School of Natural Sciences and Museum

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This week, EFSA will release their reassessment of glyphosate. In this review, they will again conclude that glyphosate has no carcinogenic potential. This review is based on the BfR Addendum which has some severe scientific flaws. I am concerned that this evaluation, if it stands, could weaken the effectiveness of the IARC Monograph Programme. I am also concerned that the serious flaws in the BfR Addendum, if not challenged, could continue to be used by regulatory agencies to dismiss critical science pertinent to a regulatory decision, including broad exclusion of literature data and epidemiological data.

The European Commission ENVI Committee will meet on December 1, 2015 to receive the reassessment report from EFSA. I have drafted a letter of concern that I wish to present to the ENVI Committee as they consider whether to accept or reject the EFSA evaluation. I would like to invite you to join with me in signing this open letter. I have obtained your names from many different lists, mostly from previous IARC monographs but also from other sources. It is possible I have included your name more than once on this list and I apologize for sending you multiple copies.

I am open to changes to improve the letter, but because of the short time-frame, I hope you can agree to sign on with only modest modifications (I am sending this to several hundred colleagues). I have included the letter but have not included the BfR Addendum or the Reassessment Report because of size. These are available at:

Addendum: http://www.mdr.de/fakt/fakt-glyphosat-bfr-bewertung100.html (NOTE: click on Herunterladen to download the report)
RAR: http://dar.efsa.europa.eu/dar-web/provision

The more important report is the Addendum.

If you agree to joining me in signing this letter, please respond by November 25 with the following that I can then add to my letter.

Title (Prof, Dr., …), Name
Position Title (e.g. Director, Named Chair, etc)
Affiliation
City, Country

I look forward to hearing from you.

Sincerely,

Christopher Portier

From: Elsebeth Lynge <elsebeth@sund.ku.dk>
Sent: Wednesday, November 11, 2015 11:26 AM
To: Kogevinas, Manolis; Chris Portier; jmanto@creal.cat; Margaret.Karagas@dartmouth.edu; john.dement@duke.edu; Bengt.Jarvholm@envmed.umu.se; Alavanja, Michael (NIH/NCI) [E]; Maarten Bosland; hartgep@exchange.nih.gov; Lubin, Jay (NIH/NCI) [V]; Silverman, Debra (NIH/NCI) [E]; Ward, Mary (NIH/NCI) [E]; benedetto.terracini@fastwebnet.it; cvictora@gmail.com; [redacted (b) (6)]; [redacted (b) (6)]; mperry@gwu.edu; Pgrandjean@health.sdu.dk; saracci@hotmail.com; [redacted (b) (6)]; abaccare@hsph.harvard.edu; dchris@hsph.harvard.edu; gwagner@hsph.harvard.edu; Marie-Elise.Parent@iaf.inrs.ca; mporta@imim.es; l.rushton@imperial.ac.uk; marcel.goldberg@inserm.fr; john.cherrie@iom-world.org; pietro.comba@iss.it; per.gustavsson@ki.se; efonth@lsuhsc.edu; jmclaugh@lunenfeld.ca; Berrington, Amy (NIH/NCI) [E]; Beane-Freeman, Laura (NIH/NCI) [E]; Friesen, Melissa (NIH/NCI) [E]; A.Mannetje@massey.ac.nz; J.Douwes@massey.ac.nz; dnc@mrc.soton.ac.uk; Jahoppin@ncsu.edu; Birnbaum, Linda (NIH/NIEHS) [E]; Bucher, John (NIH/NIEHS) [E]; Huff, James (NIH/NIEHS) [G]; Weinberg, Clarice (NIH/NIEHS) [E]; Engel, Lawrence (NIH/NIEHS) [C]; m.hauptmann@nki.nl; Elsebeth Lynge; Bernard.stewart@sesiahs.health.nsw.gov.au; nsteenl@sph.emory.edu; petter.kristensen@stami.nl; helge.kjuus@stami.no; bruce.armstrong@sydney.edu.au; ab.miller@sympatico.ca; cocco_pierluigi@tiscali.it; Harri.Vainio@ttl.fi; nseixas@u.washington.edu; ricech@uc.edu; britz@ucla.edu; lemastgj@ucmail.uc.edu; jvena@uga.edu; lstayner@uic.edu; Lynch, Charles F.; james-merchant@uiowa.edu; David_Kriebel@uml.edu; michel.gerin@umontreal.ca; Rusyn, Ivan I; angela.pesatori@unimi.it; pieralberto.bertazzi@unimi.it; lorenzo.simonato@unipd.it; roberta.pirastu@uniroma1.it; franco.merletti@unito.it; jsamet@usc.edu; Elaine.Symanski@uth.tmc.edu; d.heederik@uu.nl; Vermeulen, R.C.H. (Roel); fritschi@waimr.uwa.edu.au; yawei.zhang@yale.edu; mcebrian@cinvestav.mx; [redacted (b) (6)]; wchiu@cvm.tamu.edu; coccop@medicina.unica.it; aderoos@drexel.edu; s-fukushima@jisha.or.jp; pascal.guenel@inserm.fr; Herbert, Ron (NIH/NIEHS) [E]; mlamerrill@ucdavis.edu; marcelo.larramendy@gmail.com; lizbeth@correo.insp.mx; f.martin@lancaster.ac.uk; naidoos71@ukzn.ac.za; tprapamontol@gmail.com; dmreif@ncsu.edu; droy@fiu.edu; thomas.sanderson@iaf.inrs.ca; Martyn Smith; thomas.kent@epa.gov; mary.wolff@mssm.edu; Beland, Frederick (FDA/NCTR); m.berger@dkfz-heidelberg.de; judy.bolton@uic.edu; david.eastmond@ucr.edu; peter.karran@cancer.org.uk; david_kaufman@med.unc.edu; [redacted (b) (6)]; matilde.marques@ist.utl.pt; jorgen@cancer.dk; david.phillips@icr.ac.uk; h.schmeiser@dkfz-heidelberg.de; linda.t.titus-ernstoff@dartmouth.edu; dbthomas@fhcrc.org; htsuda@phar.nagoya-cu.ac.jp
Subject: Re: IARC Monograph on Glyphosate

Dear Chris and Manolis,

I support the suggestion from Manolis.

Best wishes
Elsebeth

On 11/11/15 17.09, "Kogevinas, Manolis" <kogevinas@creal.cat> wrote:

>Hi Chris,
>Thank you for this. I am not sure this is the best procedure. There is
>obviously a problem when in the same year we have two public
>organizations giving conflicting evidence for the same chemical.

> Even though I personally have much more faith in the IARC evaluation,
>EFSA is also a well known agency. EFSA, obviously, has less experience
>in these types of evaluations and the protocols followed are clearly
>less developed and standard. However, by signing the type of letter
>you propose I think we assume that we (those who
>sign) have evaluated the evidence independently and give right to IARC.
>I have not done this. In addition, it is not clear to me that this type
>of evaluation of evidence is done best through letters like the one
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>evidence on glyphosate.
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>EFSA has less established protocols for evaluating carcinogens
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>We urge the ENVI committee to review critically the EFSA evaluation and
>particularly those aspects of the report that criticize the IARC
>evaluation
>
>I would be happy to change this opinion if there are good arguments for
>changing, Regards
>
>Manolis
>----------
>Manolis Kogevinas, MD, PhD
>
>Professor and co-Director
>Centre for Research in Environmental Epidemiology (CREAL) IMIM
>(Hospital del Mar Research Institute)
>
>88 Dr Aiguader Rd,
>Barcelona 08003, Spain
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>Telf +34-93 214 7332 (direct)
>Telf +34-93 214 7330 (Mrs M Ferrer, secretary) Fax +34-93 214 7302
>E-Mail:
>kogevinas@creal.cat <mailto:kogevinas@imim.es> www.creal.cat
><http://www.creal.cat/>
>
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>
>
>De: Chris Portier [mailto:cportier@me.com]
>
>Enviado el: miércoles, 11 de noviembre de 2015 13:58
>Para: jmanto@creal.cat; kogevinas@creal.cat;

>Margaret.Karagas@dartmouth.edu; john.dement@duke.edu;
>Bengt.Jarvholm@envmed.umu.se; alavanjm@mail.nih.gov; Maarten Bosland;
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>lemastgj@ucmail.uc.edu; jvena@uga.edu; lstayner@uic.edu;
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>lorenzo.simonato@unipd.it; roberta.pirastu@uniroma1.it;
>franco.merletti@unito.it; jsamet@usc.edu; Elaine.Symanski@uth.tmc.edu;
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>tprapamontol@gmail.com; dmreif@ncsu.edu; droy@fiu.edu;
>thomas.sanderson@iaf.inrs.ca; Martyn Smith; thomas.kent@epa.gov;
>mary.wolff@mssm.edu; frederick.beland@fda.hhs.gov;
>m.berger@dkfz-heidelberg.de; judy.bolton@uic.edu;
>david.eastmond@ucr.edu; peter.karran@cancer.org.uk;
>david_kaufman@med.unc.edu; [redacted];
>matilde.marques@ist.utl.pt; jorgen@cancer.dk; david.phillips@icr.ac.uk;
>h.schmeiser@dkfz-heidelberg.de; linda.t.titus-ernstoff@dartmouth.edu;
>dbthomas@fhcrc.org; htsuda@phar.nagoya-cu.ac.jp
>Asunto: IARC Monograph on Glyphosate
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>RAR: http://dar.efsa.europa.eu/dar-web/provision

>
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>
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>
>
>
>Title (Prof, Dr., Š), Name
>
>Position Title (e.g. Director, Named Chair, etc)
>
>Affiliation
>
>City, Country
>
>
>
>I look forward to hearing from you.
>
>
>
>Sincerely,
>
>Christopher Portier
>
>
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>
>Antes de imprimir este mensaje o cualquiera de los documentos adjuntos,
>por favor compruebe que es verdaderamente necesario.
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>penalty of incurring legal responsibilities.
>
>Before printing this message or any attachments, please check that it
>is really necessary.
>
>
>
>

From: Chris Portier <cportier@me.com>
Sent: Wednesday, November 11, 2015 11:24 AM
To: Kogevinas, Manolis
Cc: jmanto@creal.cat; Margaret.Karagas@dartmouth.edu; john.dement@duke.edu; Bengt.Jarvholm@envmed.umu.se; Alavanja, Michael (NIH/NCI) [E]; Maarten Bosland; hartgep@exchange.nih.gov; Lubin, Jay (NIH/NCI) [V]; Silverman, Debra (NIH/NCI) [E]; Ward, Mary (NIH/NCI) [E]; benedetto.terracini@fastwebnet.it; cvictora@gmail.com; (b) (6); (b) (6); mperry@gwu.edu; Pgrandjean@health.sdu.dk; saracci@hotmail.com; (b) (6); abaccare@hsph.harvard.edu; dchris@hsph.harvard.edu; gwagner@hsph.harvard.edu; Marie-Elise.Parent@iaf.inrs.ca; mporta@imim.es; l.rushton@imperial.ac.uk; marcel.goldberg@inserm.fr; john.cherrie@iom-world.org; pietro.comba@iss.it; per.gustavsson@ki.se; efonth@lsuhsc.edu; jmclaugh@lunenfeld.ca; Berrington, Amy (NIH/NCI) [E]; Beane-Freeman, Laura (NIH/NCI) [E]; Friesen, Melissa (NIH/NCI) [E]; A.Mannetje@massey.ac.nz; J.Douwes@massey.ac.nz; dnc@mrc.soton.ac.uk; Jahoppin@ncsu.edu; Birnbaum, Linda (NIH/NIEHS) [E]; Bucher, John (NIH/NIEHS) [E]; Huff, James (NIH/NIEHS) [G]; Weinberg, Clarice (NIH/NIEHS) [E]; Engel, Lawrence (NIH/NIEHS) [C]; m.hauptmann@nki.nl; Elsebeth@pubhealth.ku.dk; Bernard.stewart@sesiahs.health.nsw.gov.au; nsteenl@sph.emory.edu; petter.kristensen@stami.nl; helge.kjuus@stami.no; bruce.armstrong@sydney.edu.au; ab.miller@sympatico.ca; cocco_pierluigi@tiscali.it; Harri.Vainio@ttl.fi; nseixas@u.washington.edu; ricech@uc.edu; britz@ucla.edu; lemastgj@ucmail.uc.edu; jvena@uga.edu; lstayner@uic.edu; Lynch, Charles F.; james-merchant@uiowa.edu; David_Kriebel@uml.edu; michel.gerin@umontreal.ca; Rusyn, Ivan I; angela.pesatori@unimi.it; pieralberto.bertazzi@unimi.it; lorenzo.simonato@unipd.it; roberta.pirastu@uniroma1.it; franco.merletti@unito.it; jsamet@usc.edu; Elaine.Symanski@uth.tmc.edu; d.heederik@uu.nl; Vermeulen, R.C.H. (Roel); fritschi@waimr.uwa.edu.au; yawei.zhang@yale.edu; mcebrian@cinvestav.mx; (b) (6); wchiu@cvm.tamu.edu; coccop@medicina.unica.it; aderoos@drexel.edu; s-fukushima@jisha.or.jp; pascal.guenel@inserm.fr; Herbert, Ron (NIH/NIEHS) [E]; mlamerrill@ucdavis.edu; marcelo.larramendy@gmail.com; lizbeth@correo.insp.mx; f.martin@lancaster.ac.uk; naidoos71@ukzn.ac.za; tprapamontol@gmail.com; dmreif@ncsu.edu; droy@fiu.edu; thomas.sanderson@iaf.inrs.ca; Martyn Smith; thomas.kent@epa.gov; mary.wolff@mssm.edu; Beland, Frederick (FDA/NCTR); m.berger@dkfz-heidelberg.de; judy.bolton@uic.edu; david.eastmond@ucr.edu; peter.karran@cancer.org.uk; david_kaufman@med.unc.edu; (b) (6); matilde.marques@ist.utl.pt; jorgen@cancer.dk; david.phillips@icr.ac.uk; h.schmeiser@dkfz-heidelberg.de; linda.t.titus-ernstoff@dartmouth.edu; dbthomas@fhcrc.org; htsuda@phar.nagoya-cu.ac.jp
Subject: Re: IARC Monograph on Glyphosate

Manolis,

Thanks for your note and comments. First, to be clear, EFSA has procedures and policies for how to review this information (like the cited OECD document cited in the letter), so it is not that they do not have written procedures. Second, they have extensive experience in reviewing pesticide data; regretfully, they tend to identify faults with epidemiology data that makes it unusable and tend to be very supportive of industry interpretation of the available toxicology data. My problem is not with contradicting summaries of the data since BfR agrees with all of the IARC findings. My concern is with their dismissal of these findings as not important; that is what undermines the scientific review process used by the IARC and this is the scientific approach I am am hoping we are addressing. While this letter is somewhat detailed for something being sent to a political entity like EC ENVI, I am going to be present at the hearing and hope to provide clarity.

C.

On Nov 11, 2015, at 5:09 PM, Kogevinas, Manolis <kogevinas@creal.cat> wrote:

Hi Chris,
Thank you for this. I am not sure this is the best procedure. There is obviously a problem when in the same year we have two public organizations giving conflicting evidence for the same chemical. Even though I personally have much more faith in the IARC evaluation, EFSA is also a well known agency. EFSA, obviously, has less experience in these types of evaluations and the protocols followed are clearly less developed and standard. However, by signing the type of letter you propose I think we assume that we (those who sign) have evaluated the evidence independently and give right to IARC. I have not done this. In addition, it is not clear to me that this type of evaluation of evidence is done best through letters like the one you propose that goes into the details of the evaluations.

I would be happy to sign a letter saying (more or less):

- We have two contradicting summaries of the evidence
- IARC has a very long tradition in examining carcinogens and the procedures and protocols followed are well established and generally accepted. Based on the history of the IARC evaluations, it is most likely that the IARC working group summarized accurately the current evidence on glyphosate.
- EFSA has less established protocols for evaluating carcinogens
- We urge the ENVI committee to review critically the EFSA evaluation and particularly those aspects of the report that criticize the IARC evaluation

I would be happy to change this opinion if there are good arguments for changing,
Regards

Manolis

Manolis Kogevinas, MD, PhD
Professor and co-Director
Centre for Research in Environmental Epidemiology (CREAL)
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www.creal.cat

De: Chris Portier [mailto:cportier@me.com]
Enviado el: miércoles, 11 de noviembre de 2015 13:58
Para: jmanto@creal.cat; kogevinas@creal.cat; Margaret.Karagas@dartmouth.edu; john.dement@duke.edu; Bengt.Jarvholm@envmed.umu.se; alavanjm@mail.nih.gov; Maarten Bosland; hartgep@exchange.nih.gov; lubinj@exchange.nih.gov; silvermd@exchange.nih.gov; wardm@exchange.nih.gov; benedetto.terracini@fastwebnet.it; cvictora@gmail.com; (b) (6) ; (b) (6) ; mperry@gwu.edu; Pgrandjean@health.sdu.dk; saracci@hotmail.com; (b) (6) ; abaccare@hsph.harvard.edu; dchris@hsph.harvard.edu; gwagner@hsph.harvard.edu; Marie-Elise.Parent@iaf.inrs.ca; mporta@imim.es; l.rushton@imperial.ac.uk; marcel.goldberg@inserm.fr; john.cherrie@iom-world.org; pietro.comba@iss.it; per.gustavsson@ki.se; efonth@lsuhsc.edu; jmclaugh@lunenfeld.ca; berri

ngtona@mail.nih.gov; freemala@mail.nih.gov; friesenmc@mail.nih.gov; A.Mannetje@massey.ac.nz; J.Douwes@massey.ac.nz; dnc@mrc.soton.ac.uk; Jahoppin@ncsu.edu; Dr. Linda Birnbaum; John Bucher (NIH/NIEHS); James Huff; Weinberg@niehs.nih.gov; lawrence.engel@nih.gov; m.hauptmann@nki.nl; Elsebeth@pubhealth.ku.dk; Bernard.stewart@sesiahs.health.nsw.gov.au; nsteenl@sph.emory.edu; petter.kristensen@stami.nl; helge.kjuus@stami.no; bruce.armstrong@sydney.edu.au; <ab.miller@sympatico.ca>; cocco_pierluigi@tiscali.it; Harri.Vainio@ttl.fi; nseixas@u.washington.edu; ricech@uc.edu; britz@ucla.edu; lemastgj@ucmail.uc.edu; jvena@uga.edu; lstayner@uic.edu; charles-lynch@uiowa.edu; james-merchant@uiowa.edu; David_Kriebel@uml.edu; michel.gerin@umontreal.ca; Rusyn, Ivan I; angela.pesatori@unimi.it; pieralberto.bertazzi@unimi.it; lorenzo.simonato@unipd.it; roberta.pirastu@uniroma1.it; franco.merletti@unito.it; jsamet@usc.edu; Elaine.Symanski@uth.tmc.edu; d.heederik@uu.nl; Vermeulen, R.C.H. (Roel); fritschi@waimr.uwa.edu.au; yawei.zhang@yale.edu; mcebrian@cinvestav.mx; (b) (6) ; wchiu@cvm.tamu.edu; coccop@medicina.unica.it; aderoos@drexel.edu; s-fukushima@jisha.or.jp; pascal.guenel@inserm.fr; Ron Herbert; mlamerrill@ucdavis.edu; marcelo.larramendy@gmail.com; lizbeth@correo.insp.mx; f.martin@lancaster.ac.uk; naidoos71@ukzn.ac.za; tprapamontol@gmail.com; dmreif@ncsu.edu; droy@fiu.edu; thomas.sanderson@iaf.inrs.ca; Martyn Smith; thomas.kent@epa.gov; mary.wolff@mssm.edu; frederick.beland@fda.hhs.gov; m.berger@dkfz-heidelberg.de; judy.bolton@uic.edu; david.eastmond@ucr.edu; peter.karran@cancer.org.uk; david_kaufman@med.unc.edu; (b) (6) ; matilde.marques@ist.utl.pt; jorgen@cancer.dk; david.phillips@icr.ac.uk; h.schmeiser@dkfz-heidelberg.de; linda.t.titus-ernstoff@dartmouth.edu; dbthomas@fhcrc.org; htsuda@phar.nagoya-cu.ac.jp
Asunto: IARC Monograph on Glyphosate

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Title (Prof, Dr., …), Name
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I look forward to hearing from you.

Sincerely,

Christopher Portier

From: Kogevinas, Manolis <kogevinas@creal.cat>
Sent: Wednesday, November 11, 2015 11:09 AM
To: Chris Portier; jmanto@creal.cat; Margaret.Karagas@dartmouth.edu; john.dement@duke.edu; Bengt.Jarvholm@envmed.umu.se; Alavanja, Michael (NIH/NCI) [E]; Maarten Bosland; hartgep@exchange.nih.gov; Lubin, Jay (NIH/NCI) [V]; Silverman, Debra (NIH/NCI) [E]; Ward, Mary (NIH/NCI) [E]; benedetto.terracini@fastwebnet.it; cvictora@gmail.com; (b) (6) (b) (6); mperry@gwu.edu; Pgrandjean@health.sdu.dk; saracci@hotmail.com; (b) (6); abaccare@hsph.harvard.edu; dchris@hsph.harvard.edu; gwagner@hsph.harvard.edu; Marie-Elise.Parent@iaf.inrs.ca; mporta@imim.es; l.rushton@imperial.ac.uk; marcel.goldberg@inserm.fr; john.cherrie@iom-world.org; pietro.comba@iss.it; per.gustavsson@ki.se; efonth@lsuhsc.edu; jmclaugh@lunenfeld.ca; Berrington, Amy (NIH/NCI) [E]; Beane-Freeman, Laura (NIH/NCI) [E]; Friesen, Melissa (NIH/NCI) [E]; A.Mannetje@massey.ac.nz; J.Douwes@massey.ac.nz; dnc@mrc.soton.ac.uk; Jahoppin@ncsu.edu; Birnbaum, Linda (NIH/NIEHS) [E]; Bucher, John (NIH/NIEHS) [E]; Huff, James (NIH/NIEHS) [G]; Weinberg, Clarice (NIH/NIEHS) [E]; Engel, Lawrence (NIH/NIEHS) [C]; m.hauptmann@nki.nl; Elsebeth@pubhealth.ku.dk; Bernard.stewart@sesiahs.health.nsw.gov.au; nsteenl@sph.emory.edu; petter.kristensen@stami.nl; helge.kjuus@stami.no; bruce.armstrong@sydney.edu.au; ab.miller@sympatico.ca; cocco_pierluigi@tiscali.it; Harri.Vainio@ttl.fi; nseixas@u.washington.edu; ricech@uc.edu; britz@ucla.edu; lemastgj@ucmail.uc.edu; jvena@uga.edu; lstayner@uic.edu; Lynch, Charles F.; james-merchant@uiowa.edu; David_Kriebel@uml.edu; michel.gerin@umontreal.ca; Rusyn, Ivan I; angela.pesatori@unimi.it; pieralberto.bertazzi@unimi.it; lorenzo.simonato@unipd.it; roberta.pirastu@uniroma1.it; franco.merletti@unito.it; jsamet@usc.edu; Elaine.Symanski@uth.tmc.edu; d.heederik@uu.nl; Vermeulen, R.C.H. (Roel); fritschi@waimr.uwa.edu.au; yawei.zhang@yale.edu; mcebrian@cinvestav.mx; (b) (6); wchiu@cvm.tamu.edu; coccop@medicina.unica.it; aderoos@drexel.edu; s-fukushima@jisha.or.jp; pascal.guenel@inserm.fr; Herbert, Ron (NIH/NIEHS) [E]; mlamerrill@ucdavis.edu; marcelo.larramendy@gmail.com; lizbeth@correo.insp.mx; f.martin@lancaster.ac.uk; naidoos71@ukzn.ac.za; tprapamontol@gmail.com; dmreif@ncsu.edu; droy@fiu.edu; thomas.sanderson@iaf.inrs.ca; Martyn Smith; thomas.kent@epa.gov; mary.wolff@mssm.edu; Beland, Frederick (FDA/NCTR); m.berger@dkfz-heidelberg.de; judy.bolton@uic.edu; david.eastmond@ucr.edu; peter.karran@cancer.org.uk; david_kaufman@med.unc.edu; (b) (6); matilde.marques@ist.utl.pt; jorgen@cancer.dk; david.phillips@icr.ac.uk; h.schmeiser@dkfz-heidelberg.de; linda.t.titus-ernstoff@dartmouth.edu; dbthomas@fhcrc.org; htsuda@phar.nagoya-cu.ac.jp
Subject: RE: IARC Monograph on Glyphosate

Hi Chris,
Thank you for this. I am not sure this is the best procedure. There is obviously a problem when in the same year we have two public organizations giving conflicting evidence for the same chemical. Even though I personally have much more faith in the IARC evaluation, EFSA is also a well known agency. EFSA, obviously, has less experience in these types of evaluations and the protocols followed are clearly less developed and standard. However, by signing the type of letter you propose I think we assume that we (those who sign) have evaluated the evidence independently and give right to IARC. I have not done this. In addition, it is not clear to me that this type of evaluation of evidence is done best through letters like the one you propose that goes into the details of the evaluations.

I would be happy to sign a letter saying (more or less):

- We have two contradicting summaries of the evidence

- IARC has a very long tradition in examining carcinogens and the procedures and protocols followed are well established and generally accepted. Based on the history of the IARC evaluations, it is most likely that the IARC working group summarized accurately the current evidence on glyphosate.
- EFSA has less established protocols for evaluating carcinogens
- We urge the ENVI committee to review critically the EFSA evaluation and particularly those aspects of the report that criticize the IARC evaluation

I would be happy to change this opinion if there are good arguments for changing,
Regards

Manolis

Manolis Kogevinas, MD, PhD
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E-Mail: kogevinas@creal.cat
www.creal.cat

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Subject: IARC Monograph on Glyphosate
Attachments: IARCWG112ResponseV3.docx

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The International Agency for Research on Cancer (IARC) Monographs Programme identifies environmental causes of cancer in humans and has evaluated more than 900 agents in the last few decades. The Monographs Programme evaluates chemicals, complex mixtures, occupational exposures, physical agents and biological agents, as well as personal habits. Monographs are written by a Working Group (WG) over a period of about 12 months to evaluate all of the scientific literature on a given substance and, through a transparent and rigorous process[1], reach a decision on the degree to which the scientific literature supports the ability of that substance to cause cancer. For Monograph 112[2], 17 expert scientists evaluated the carcinogenic hazard for 4 insecticides and the herbicide glyphosate. The WG concluded that glyphosate was a probable human carcinogen. This finding stirred great debate globally on the safety of glyphosate and led to a careful evaluation of the IARC monograph results when they came available on July 29, 2015. On August 31, 2015, the German Federal Institute for Risk Assessment (BfR) completed an addendum[3] (the BfR Addendum) to the Draft Renewal Assessment Report[4] (RAR) for glyphosate. This addendum was leaked by the media[5]. The Addendum draws a very different conclusion on the literature than did the IARC WG. We are seriously concerned about the scientific quality of the BfR Addendum and feel that it is misleading regarding the potential for a carcinogenic hazard from exposure to glyphosate. We are also concerned about some of the implications of the Addendum regarding the use of human data in identifying carcinogenic hazards.

Our comments to the BfR Addendum will focus on the human evidence, the animal laboratory evidence and the mechanistic evidence.

The Human Evidence

The BfR agrees with the IARC WG that there is "limited evidence in humans for the carcinogenicity of glyphosate". In the IARC review process, this is defined as "A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence."[1] The BfR Addendum (p. ii) then characterizes the IARC interpretation as "precautionary" and that the BfR takes a more "cautious view" of this classification because "no consistent positive association was observed", "the most powerful study showed no effect" and that the studies "could not differentiate between the effects of glyphosate and the co-formulants". We will consider the first two arguments here and target the third argument for the end of our letter.

The finding of "limited evidence" by the IARC WG was for non-Hodgkins lymphoma (NHL). High-quality cohort studies are particularly valuable for determining the carcinogenicity of an agent because their design can facilitate exposure assessment and reduce the potential for certain biases. The Agricultural Health Study (AHS) was the only cohort study available providing information on the carcinogenicity of glyphosate. The study had a very weak positive finding for NHL (RR 1.1, 0.7-1.9) with no apparent

exposure response in the results. The BfR refers to this study as “the most powerful study” and that it was negative for NHL.

Several theoretical limitations of case-control studies are laid out in epidemiology textbooks [6, 7]. The BfR uses these limitations to label all of the case-control studies as unreliable. This gives the impression that all of the studies are equal in quality and unusable for an overall evaluation. This is not the case: well-designed case-control studies are recognized as an efficient alternative to cohort studies [7]. An IARC WG carefully evaluates all of the available epidemiology data, looking at the study’s strengths and weaknesses as well as the study order. This is key in determining whether the positive associations seen are a reliable indication of an association or simply due to chance or methodological flaws. To provide a reasonable interpretation of the findings, an evaluation needs to properly weight studies according to their quality rather than simply count the number of positives and negatives. The meta-analysis cited in the IARC Monograph[8] and redone by the WG is an excellent example of an objective evaluation of the existence of a consistent positive trend; this meta-analysis showed a statistically significant association. The BfR provided no justification for their evaluation of “no consistent positive association”.

The final BfR conclusion (p. 22) that “there was no unequivocal evidence for a clear and strong association of NHL with glyphosate” is misleading. IARC, like many other groups, uses three levels of evidence for human data[1]. “Sufficient Evidence” means “that a causal relationship has been established” between glyphosate and NHL. The BfR conclusion can be rewritten to mean that the epidemiological data does not meet the criteria for “Sufficient Evidence” established by IARC. However, this says nothing about concern that would arise for an association that is not strong enough to be causal, but is strong enough that “that causality is credible” as does the IARC “Limited Evidence” category.

Evidence from Chronic Exposure Animal Studies

We are astonished by the conclusions of the BfR regarding the animal carcinogenicity data. The IARC WG review found a significant positive trend for renal tumors in CD-1 mice[9], a rare tumour. A significant positive trend means that as the exposure increases, the pattern seen in the data supports an increasing risk with increasing dose. No comparisons of any individual exposure group to the control group were significant. The WG also identified a significant positive trend for hemangiosarcoma in male CD-1 mice[10], again with no individual exposure group significantly different from controls. Finally, the WG also saw a significant increase in the incidence of islet cell adenomas in two studies in Sprague-Dawley rats[11-13]. In one of these rat studies, thyroid adenomas in females and liver adenomas in males were also increased. Thus, glyphosate was positive for malignant tumors in both of the mice studies examined and for benign tumors in 2 of the five rat studies examined. By the IARC review criteria[1], the evidence in the mouse constitutes sufficient evidence in animals.

The BfR agreed, stating (p. 44) "it is obvious that IARC concludes on “sufficient evidence of carcinogenicity” because the criteria for this conclusion are fully met.” The IARC WG

reached this conclusion using data that were publicly available in sufficient detail for independent scientific evaluation (a requirement of the IARC Preamble[1]). Based on the BfR Addendum, it seems there were 3 additional mouse studies and 2 additional rat studies where they had sufficient evidence to review the findings. BfR reported on two additional studies with a positive trend for renal tumors, one in CD-1 mice[14], and one in Swiss-Webster mice[15]. One of these studies[14] also reported a positive trend for hemangiosarcoma. Moreover, BfR reported two studies in CD-1 mice showing significant trends for malignant lymphoma[14, 16]. For all of the tumors described above in CD-1 mice, a positive trend was seen against the concurrent control.

However, in all cases in CD-1 mice, including those observed by the IARC, the BfR dismisses the observed trends in tumour incidence because there are no individual treatment groups which are significantly different from controls and because the maximum observed response is within the range of the historical control data (Table 5.3-1 in the Addendum). Care must be taken in using historical control data to evaluate animal carcinogenicity data. In virtually all guidelines[1, 17], scientific reports[18] and publications[19-21] on the issue, the first choice should be the use of the concurrent controls. For instance, the Preamble to the IARC Monographs states, "it is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls…". When using historical control data, it should be from the same timeframe for the exact strain, preferably from the same laboratory or the same supplier and preferably with the same pathologist[17]. This was not the case for the historical control database used by BfR. One of the mouse studies[9] was clearly done before this historical control database was developed, one study[14] used Crj:CD-1 mice rather than Crl:CD-1 mice, and 1 study[10] did not specify the substrain and was reported in 1993 (probably started prior to 1988); hence only a single study [16] used the right strain, but was reported more than 10 years after the historical control dataset was developed. Interestingly, the historical control data used by the BfR [22] was from studies in 7 laboratories using the Charles River Laboratory CD1 mice. Surprisingly, there is a second report [23] by the same authors with a larger control database using the same mouse strain from 11 laboratories over the same time period (1987-2000) showing very different results. For example, the 2000 publication[22] shows 5 and 4 studies out of 46 with adenomas (no more than 2 in any one study) and adenocarcinomas (one in each study) respectively whereas the 2005 report[23] shows only 1 study each out of 54 studies with a single adenoma and a single adenocarcinoma; all other studies had no tumors.

Given this evidence, it is hard to perceive how the BfR reached the conclusion they provided. By their own evaluation, there were seven (7) positive findings in mice with three replicates for one tumor type and 2 positive findings for carcinomas in rats. After discarding the inappropriate use of historical evidence, it is no longer scientifically justifiable to refer to all of these studies as negative.

Mechanistic Information

The BfR Addendum dismisses the WG finding that "there is strong evidence that glyphosate causes genotoxicity" by suggesting that the evidence not seen by the IARC WG was overwhelmingly negative and that, since the studies that were reviewed were not done under guideline principles, they should get less weight. To maintain transparency, IARC reviews use only publicly available data. Thus it is impossible for any scientists not associated with BfR to review this conclusion with any degree of scientific certainty. On the other hand, the BfR did not include evidence from exposed humans that was highlighted in the IARC Monograph.

The BfR confirms (p. 79) that the studies evaluated by the IARC WG on oxidative stress were predominantly positive but do not agree that this is strong support for an oxidative stress mechanism. They reduce the significance of these findings predominantly because of a lack of positive controls in some studies and because many of the studies used glyphosate formulations and not pure glyphosate. The WG concluded that (p. 77) "Strong evidence exists that glyphosate, AMPA and glyphosate-based formulations can induce oxidative stress". From a scientific perspective, these types of mechanistic studies can play a key role in distinguishing between the effects of mixtures, pure substances and metabolites and we would encourage the BfR to carefully review this science.

Finally, we strongly disagree that literature data should automatically receive less weight than guideline studies; once a chemical is on the market, the majority of the research done on that chemical will be done by very competent research laboratories that will use unique models to address specific issues related to toxicity that will not have guidelines associated with them. These have great value in understanding mechanisms of carcinogenicity and should be given appropriate weight in an evaluation based on study quality and not just guideline rules.

General Comments

Science moves forward based on data, careful evaluation of that data and a rigorous review of the findings. One important aspect of this process is transparency and on the ability to question the findings of others. This insures the credibility of the results and provides a strong basis for decisions. Many of the aspects of transparency do not exists for the BfR RAR [4] or the Addendum[3]. There are no authors or contributors listed for either document, a requirement for virtually all scientific papers. Citations for almost all of the references, even those from the open scientific literature, have been redacted from the documents. The ability to objectively evaluate the findings of a scientific report requires a complete list of the supporting evidence.

A second important aspect of the scientific process is a careful evaluation and analysis of the facts. Guidelines have been devised for analyzing carcinogenicity data developed after careful consideration of scientists on a global basis. One of the most widely cited is [17] which is cited in the BfR Addendum. This document gives guidance on the analysis of carcinogenicity studies in contradiction to the methods

used by the BfR. Thus, BfR uses the concept of guidelines to rule out the substantive inclusion of literature data into their risk assessment, but ignores guidelines when it comes to the use of historical controls and trend analyses.

Summary

The IARC WG concluded that glyphosate is a "probable human carcinogen" putting it into IARC category 2A. In their 2013 Draft RAR, BfR concluded (Vol. 1, p. 139) "classification and labeling for carcinogenesis is not warranted" and "glyphosate is devoid of genotoxic potential". How is this possible? Consider the evidence and the conclusions.

The IARC WG saw an association between NHL and glyphosate in the human evidence, but could not rule out chance, bias and confounding; the IARC definition of "limited evidence"[1] for epidemiological data. BfR agreed, noting that other IARC categories are "not suitable". However the BfR concluded that an association was seen but dismissed it as insufficiently consistent.

The IARC WG saw significant effects for two tumors in two mouse studies and benign tumors in two rat studies. The BfR confirmed the statistically significant findings by the IARC WG, and agreed that the IARC criteria of "sufficient" evidence in animals is "fully met". BfR went on to identify two more mouse studies with kidney tumors, a second mouse study with an increase in hemangiosarcoma, and two mouse studies showing increases in malignant lymphoma. Thus, all five mouse studies examined by the BfR were positive in at least 1 tumor site, 1 was positive in 3 tumor sites. Then using an inappropriate historical control dataset in an inappropriate way, dismiss all of these findings as chance.

The IARC WG concluded strong evidence of genotoxicity and oxidative stress for glyphosate, entirely from publicly available data, including data on DNA damage in blood of exposed humans. The BfR, while confirming the positive studies seen for genotoxicity dismissed them all because they were not guideline studies and because, in their interpretation, all of the guideline assays were negative. The BfR confirmed the positive studies seen for oxidative stress, noted some concern over these data, but concluded they could not use them because there were no other data to support a finding of carcinogenicity or genotoxicity and the mechanism cannot stand alone.

We feel that the scientific arguments supporting the BfR review of the human, animal and mechanistic evidence is fundamentally flawed and should be rejected. We are concerned that this evaluation appears to have been designed to achieve a pre-determined goal rather than an objective scientific review. Finally, we strongly object to the almost non-existent weight given to studies from the literature by the BfR and the strong reliance on non-publicly available data in a limited set of assays that define the minimum data necessary for the approval of a pesticide.

1. IARC, *PREAMBLE TO THE IARC MONOGRAPHS* I. Monographs, Editor. 2006: Lyon, France. p. 25.
2. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, *Glyphosate*, in *IARC Monogr Eval Carcinog Risks Hum*, I.M. Program, Editor. 2015. p. 1-92.
3. German Federal Institute for Risk Assessment, *Assessment of IARC Monographies Volume 112 (2015): Glyphosate*. 2015.
4. German Federal Institute for Risk Assessment, *Renewal Assessment Report*. 2013.
5. Das Erste. *BfRBewertung zu Glyphosat*. 2015; Available from: http://www.mdr.de/fakt/fakt-glyphosat-bfr-bewertung100.html.
6. Checkoway, H., N. Pearce, and D. Kriebel, *Research methods in occupational epidemiology*. 2nd ed. Monographs in epidemiology and biostatistics. 2004, New York: Oxford University Press. xiv, 372 p.
7. Rothman, K.J., S. Greenland, and T.L. Lash, *Modern epidemiology*. 3rd ed. 2008, Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. x, 758 p.
8. Schinasi, L. and M.E. Leon, *Non-Hodgkin lymphoma and occupational exposure to agricultural pesticide chemical groups and active ingredients: a systematic review and meta-analysis.* Int J Environ Res Public Health, 2014. **11**(4): p. 4449-527.
9. Epa, *Glyphosate; EPA Reg. # 524-308; mouse oncogenicity study*, B. William Dykstra.Toxicology, Editor. 1985.
10. JCFA, *Evaluation of certain food additives and contaminants: Forty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives*. 1999, Joint Committee on Food Additives (including C. Portier), World Health Organization/Food and Agriculture Organization: Geneva. p. 96.
11. Epa, *Second peer review of Glyphosate*. 1991. p. 1-19.
12. Epa, *Glyphosate - EPA Registration No. 524-308 - 2-Year Chronic Feeding/Oncogenicity Study in Rats with Technical Glyphosate*, I. William Dykstra.Toxicology Branch, Editor. 1991.
13. Epa, *Glyphosate; 2-Year Combined Chronic Toxicity/ Carcinogenicity Study in Sprague-Dawley Rats - List A Pesticide for Reregistration*, B. William Dykstra.Toxicology, Editor. 1991. p. 1-29.
14. Sugimoto, *18-Month Oral Oncogenicity Study in Mice.* Unpublished, designated ASB2012-11493 in BfR RAR, 1997.
15. Unknown, *A chronic feeding study of glyphosate (roundup technical) in mice.* unpublished, designated ABS2012-11491 in BfR RAR, 2001.
16. Unknown, *Glyphosate Technical: Dietary Carcinogencity Study in the Mouse.* Unpublished, designated ABS2012-11492 in BfR RAR, 2009.
17. OECD, *Guidance Document 116 on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies*, H.a.S.P. Environment, Editor. 2012, OECD: Paris.
18. NRC Committee to Review the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens, in *Review of the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens: Workshop Summary*. 2014, National Academies Press: Washington (DC).

19. Keenan, C., et al., *Best practices for use of historical control data of proliferative rodent lesions.* Toxicol Pathol, 2009. **37**(5): p. 679-93.
20. Haseman, J.K., G.A. Boorman, and J. Huff, *Value of historical control data and other issues related to the evaluation of long-term rodent carcinogenicity studies.* Toxicol Pathol, 1997. **25**(5): p. 524-7.
21. Greim, H., et al., *Evaluation of historical control data in carcinogenicity studies.* Hum Exp Toxicol, 2003. **22**(10): p. 541-9.
22. Giknis, M. and C. Clifford, *Spontaneous Neoplastic Lesions in the CrI:CD-1(ICR)BR Mouse*. 2000, Charles River Laboratories.
23. Giknis, M. and C. Clifford, *Spontaneous Neoplastic Lesions in the CrI:CD-1(ICR)BR Mouse in Control Groups from 18 Month to 2 year Studies*. 2005, Charles River Laboratories.

From: Franklin e Mirer <fmirer@hunter.cuny.edu>
Sent: Wednesday, September 16, 2015 10:09 PM
To: Landrigan, Philip; Huff, James (NIH/NIEHS) [G]; morando soffritti; fiorella belpoggi; peter infante; Dunnick, June (NIH/NIEHS) [E]; Lunn, Ruth (NIH/NIEHS) [E]; Jerrold M Ward; Frank Johnson; Jirles, Bill (NIH/NIEHS) [E]; Bucher, John (NIH/NIEHS) [E]
Subject: RE: Glyphosate poses health risks
Attachments: image001.png; image002.png; image003.gif; image006.png; image007.png

Ps: there's going to be pushback. You guys have to read the full monograph to be able to defend against Monsanto and maybe EPA.

From: Landrigan, Philip [mailto:phil.landrigan@mssm.edu]
Sent: Wednesday, September 16, 2015 3:58 PM
To: 'Huff, James (NIH/NIEHS) [G]'; morando soffritti; fiorella belpoggi; peter infante; Dunnick, June (NIH/NIEHS) [E]; Lunn, Ruth (NIH/NIEHS) [E]; Franklin e Mirer; Jerrold M Ward; Frank Johnson; Jirles, Bill (NIH/NIEHS) [E]; Bucher, John (NIH/NIEHS) [E]
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Subject: Glyphosate poses health risks

Glyphosate poses health risks

http://www.dailytidings.com/article/20150909/OPINION/150909862/-1/LIFE0102

From: Franklin e Mirer <fmirer@hunter.cuny.edu>
Sent: Wednesday, September 16, 2015 9:29 PM
To: Landrigan, Philip; Huff, James (NIH/NIEHS) [G]; morando soffritti; fiorella belpoggi; peter infante; Dunnick, June (NIH/NIEHS) [E]; Lunn, Ruth (NIH/NIEHS) [E]; Jerrold M Ward; Frank Johnson; Jirles, Bill (NIH/NIEHS) [E]; Bucher, John (NIH/NIEHS) [E]
Subject: RE: Glyphosate poses health risks
Attachments: image001.png; image002.png; image003.gif; image006.png; image007.png; AIHA mirer-risk assessment-1504-edited.docx

Attached is a commentary which is in press at the AIHA publication Synergist, which goes to 12,000 AIHA members. The tag line is ³50 Shades of Gray²

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Subject: Glyphosate poses health risks

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ABC's and Asbestos Risk Assessment

Subtitle Tk

By Frank Mirer

"ABC" stands for "Anything but Chrysotile," the central theme of the asbestos industry's response to asbestos hazards. I've mostly stayed away from commentary on asbestos because so many excellent scientists got there first, and because I don't work in the area. Nevertheless, having recently read the article "Miracle Mineral: New Information and New Models Are Transforming Asbestos Risk Assessment" from the February 2014 *Synergist*, I'd like to address the risk assessment issues.

My main points are that there's really nothing "new" in the science since the middle 1990's; a comprehensive review ending in 2008 produced no shift; ~~that~~ even if there were something new, it has no impact on the need for worker and environmental protection; and that science does support a ban on asbestos because effective protections can't be implemented.

This is an issue where quantitative treatment of potency can illuminate our understanding of protective measures.

The toxic potential, toxic potency, and controls for all forms of asbestos ~~should be~~are largely settled questions by now, at least in the developed world (excepting Quebec). In the developed world, the major problems are legacy of past use, leaving burdens of asbestos removal and illness from past exposures. But continuing use ~~in the developing world~~ (India, China) and Eastern Europe and in the developing world is adding to the world's legacy. The potential of chrysotile asbestos to cause mesothelioma should also be a settled question. Reversing the verdict linking chrysotile to mesothelioma would open an attack on the fraction of asbestos victims in the U.S. who are able to get compensation through the courts.

The "new" interest arises from an EPA effort in the early 2000s to update its Integrated Risk Information System (IRIS) assessment for community exposure to asbestos, probably to address cleanup issues in Libby, Montana Libbly is~~, a community~~ contaminated with amphibole asbestos from vermiculite mining. The two major forms of asbestos are chrysotile, mined in Quebec and elsewhere; and amphiboles (amosite, crocidolite), mined mostly outside Canada and now rarely used. The EPA effort rekindled longstanding claims that chrysotile asbestos does not cause mesothelioma, and is substantially less potent in causing lung cancer than the amphiboles. These claims were not accepted by any authoritative group~~s~~.

OSHA RISK ASSESSMENT

Following issuance of OSHA's 1986 standard, which brought the PEL for asbestos from 2 f/ml to 0.2, a lawsuit by the AFL-CIO Building and Construction Trades Department compelled OSHA to reopen the record on a number of issues, including whether the PEL allowed too much disease. On remand, a standard with a PEL of 0.1 f/ml for all forms of asbestos was issued in 1994 based on a quantitative analysis of results of about a dozen mortality studies. The quantitative assessments projected that the risk to workers exposed to the 0.2 f/ml PEL was 6.7 cancers per 1,000 workers, with an additional 5 per 1,000 risk of asbestosis. At 0.1 f/ml the risk was estimated at about 3.4 per thousand for cancer, and presumably 2.5 per 1,000 for asbestosis.

Risks above 1 per 1,000 are considered significant in the occupational environment, but lower risks might also be considered significant. (Most OSHA 6(b) PELs, including asbestos, allow much more risk than 1 per 1,000 because of claimed feasibility limitations.)

OSHA's 1994 explanation for the standard also addressed monitoring. OSHA stated that "the rulemaking reinforces OSHA's tentative conclusion that workplace asbestos levels of 0.05 f/cc cannot be measured reliably"; OSHA opined that 0.1 f/ml might be the limit of reliable measurement under working conditions. Even though the stated limit of detection for asbestos can be quite a bit lower with high volume or long duration samples in clean environments, the routine detection of significant exposures by current personal sampling techniques is questionable.

Thus, the authoritative statement by OSHA declares a significant risk of cancer and asbestosis at the current PEL, and opines that asbestos exposure can't reliably be measured by PCM at levels approximate to the PEL. Exposures that can't be measured reliably can't be controlled reliably.

EPA ASSESSMENT

EPA's IRIS cancer risk estimate for asbestos was established in 1993, using ~~OSHA's~~ data and methods similar to OSHA's, and projected risks~~was~~ essentially the same as that of OSHA. EPA focused on much lower risk levels and longer duration of exposure. However, EPA continued pursuing the asbestos risk assessment, commissioning a meta-analysis of epidemiological data initially reported to EPA in 1999 and modified in 2001, 2003, and eventually 2008 in response to comments by the EPA Scientific Advisory Board (SAB). Following a public meeting in 2008, the SAB remained critical of the risk assessment results, and the effort to promulgate a new IRIS assessment for all forms of asbestos was dropped. (I was supported by the American Trial Lawyers Association to prepare comments for the 2008 EPA proceedings on asbestos.)

Although EPA never adopted the analysis reviewed in 2008, it was published by the contractors, Crump and Berman, in *Critical Review in Toxicology*. Calculation of potency factors from epidemiology studies is a bit of a black box, but what went into the box were several dozen study results for lung cancer and mesothelioma. Lung cancer and mesothelioma potency factors for chrysotile and amphibole asbestos were compared. The controversy was generated by the possibility that EPA might adopt the contractors' conclusion:

[block quote: left indent]

The best estimates of the potency of chrysotile [for mesothelioma] ranged from zero only up to 1/200th of the potency of amphibole asbestos.… Furthermore, the hypothesis that chrysotile does not cause mesothelioma could not be rejected in any analysis that allowed at least some amphibole contamination in locations where exposures were principally to chrysotile.… [F]or lung cancer… the best estimates of the potency of chrysotile were at least sixfold smaller than corresponding estimates for amphibole asbestos.

[end block quote]

Crump and Berman also noted that potency factors were much more consistent within process type (mining, textile, asbestos cement) than by fiber type.

When these findings were presented for public comment at a meeting of the SAB, most commenters and SAB members rejected the conclusions. The arguments were summarized in the *American Journal of Industrial Medicine*. Criticisms included the way in which exclusion of particular studies affected the results, and the uncertainty of exposure assessment. These

commenters noted that the lung cancer potency factors varied by fifty-fold across individual studies, and mesothelioma potency factors varied by thirty-fold.

The focus on the association or lack of association of chrysotile exposure with mesothelioma is lawsuit driven, not public health driven. A study in the *British Journal of Cancer* established that lung cancer kills at least twice and maybe as many as 10 times as many workers as mesothelioma, and there is no debate that chrysotile exposure is associated with lung cancer. Protection against lung cancer by itself would drive the protective measures now in place. However, it's also generally believed that mesothelioma victims receive compensation in liability suits, while lung cancer victims are mostly out of luck. So breaking the link between chrysotile and mesothelioma would have been a windfall for defendants.

The association of exposure to all forms of asbestos (including chrysotile) with mesothelioma (and lung cancer) has been stated by at least 12 authoritative or governmental sources.

The most recent and prominent assessment is an IARC update published in 2010. In addition to mesothelioma and lung cancer, the working group found sufficient evidence that all forms of asbestos caused cancer of the larynx and ovaries, split on colorectal cancer, and found limited evidence for cancer of the stomach and pharynx. The monograph also summarized laboratory studies. The laboratory studies by inhalation collected by IARC show increased potency (more tumors at comparable exposure levels) of chrysotile compared to amphiboles for lung cancer and mesothelioma. These studies provide no evidence that amphiboles are more potent than chrysotile.

Since the IARC monograph, several dozen additional publications support the IARC conclusions and support the link of chrysotile and mesothelioma.

SIGNIFICANT RISK

Even if chrysotile is somewhat less potent than amphibole exposure, a significant risk of cancer remains at the current OSHA PEL and the limits of routine measurement. The inability to measure and control dangerous exposures supports a ban on asbestos. The link between chrysotile and mesothelioma has not been broken.

[box]

RESOURCES

American Journal of Industrial Medicine: "Developments in asbestos cancer risk assessment" (November 2009).

British Journal of Cancer: "Estimating the asbestos-related lung cancer burden from mesothelioma mortality" (March 2012).

Code of Federal Regulations: 29 CFR Parts 1910, 1915, and 1926, **http:bit.ly/oshaasbestosstandard** (August 1994).

Critical Reviews in Toxicology: "A Meta-Analysis of Asbestos-Related Cancer Risk That Addresses Fiber Size and Mineral Type" (2008).

International Agency for Research on Cancer: "Asbestos (Chrysotile, Amosite, Crocidolite, Tremolite, Actinolite, and Anthophyllite)," **http://bit.ly/iarcasbestos** (2010).

International Journal of Occupational and Environmental Health: "Asbestos Brief" (March 2007).

[end box]

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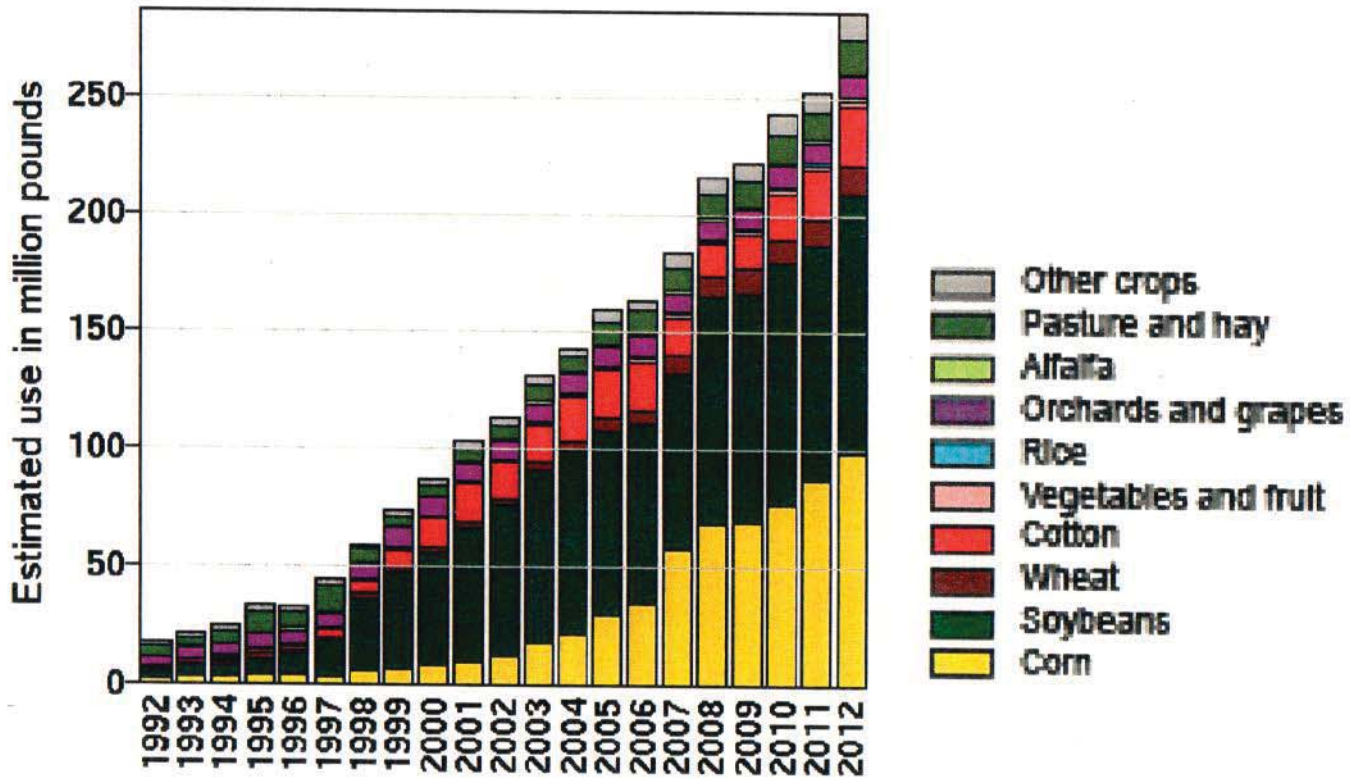
http://www.dailytidings.com/article/20150909/OPINION/150909862/-1/LIFE0102

Glyphosate Use by Year and Crop



have not been verified as such. One bioinformaticist's "driver mutation" is another's "passenger mutation." Basket studies are a good way of deriving preliminary information on mutations that are potentially responsive in humans to a specific drug — but to design such studies for every potential target mutation, for all possible drugs, in all possible anatomical sites, will be beyond the capacity of our current investigator- and company-initiated system of trials. Plans are under way for larger phase 2 studies such as the National Cancer Institute's Molecular Analysis for Therapy (NCI MATCH) II study, which will enroll about 1000 patients in about 20 mutation-specific groups, but even a larger effort like that one will capture only a small fraction of the targeted therapies being used off-label on the basis of tumor-sequencing data.

Thus, the basket trials are a useful first step in what should be a multistep process. The next step, where feasible, could be larger anatomical-site–specific phase 3 trials comparing the drug–mutation combination with the standard of care. In addition, given the sample-size, logistic, and financial constraints that make phase 3 studies difficult for less-common cancers and less-common mutations, establishment of registries of off-label use would be extremely helpful. Aggregated observational data will always be superior to "n of 1" anecdotes or small series. Precedents exist, including the "phase 4" postmarketing surveillance studies that the FDA has mandated in order to gather evidence regarding both possible differences in efficacy for various subgroups and long-term toxicity. Some cancer centers and professional societies are collaborating to develop regional databases. It is critical that results from these databases become as transparent as those from clinical trials — proprietary databases will lead to competing but unverifiable claims. Developing such observational databases is far from trivial, but the costs per patient would be small in relation to the monthly costs of many of the targeted therapies. Perhaps the plural of anecdote could be data after all.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Harvard T.H. Chan School of Public Health (D.J.H.) and Boston University (R.B.D.) — both in Boston.

1. Collins FS, Hamburg MA. First FDA authorization for next-generation sequencer. N Engl J Med 2013;369:2369-71.
2. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003;348:994-1004.
3. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507-16.
4. Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med 2012;366:883-92.
5. Menis J, Hasan B, Besse B. New clinical research strategies in thoracic oncology: clinical trial design, adaptive, basket and umbrella trials, new end-points and new evaluations of response. Eur Respir Rev 2014;23:367-78.

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GMOs, Herbicides, and Public Health

Philip J. Landrigan, M.D., and Charles Benbrook, Ph.D.

Genetically modified organisms (GMOs) are not high on most physicians' worry lists. If we think at all about biotechnology, most of us probably focus on direct threats to human health, such as prospects for converting pathogens to biologic weapons or the implications of new technologies for editing the human germline. But while those debates simmer, the application of biotechnology to agriculture has been rapid and aggressive. The vast majority of the corn and soybeans grown in the United States are now genetically engineered. Foods produced from GM crops have become ubiquitous. And unlike regulatory bodies in 64 other countries, the Food and Drug Administration (FDA) does not require labeling of GM foods.

Two recent developments are dramatically changing the GMO landscape. First, there have been sharp increases in the amounts and numbers of chemical herbicides applied to GM crops, and still further increases — the largest in a generation — are scheduled to occur in the next few years. Second, the International Agency for Research on Cancer (IARC) has classified glyphosate, the herbicide most widely used on GM crops, as a "probable human carcinogen"[1] and classified a second herbicide, 2,4-dichlorophenoxyacetic acid (2,4-D), as a "possible human carcinogen."[2]

The application of genetic engineering to agriculture builds

on the ancient practice of selective breeding. But unlike traditional selective breeding, genetic engineering vastly expands the range of traits that can be moved into plants and enables breeders to import DNA from virtually anywhere in the biosphere. Depending on the traits selected, genetically engineered crops can increase yields, thrive when irrigated with salty water, or produce fruits and vegetables resistant to mold and rot.

The National Academy of Sciences has twice reviewed the safety of GM crops — in 2000 and 2004.[3] Those reviews, which focused almost entirely on the genetic aspects of biotechnology, concluded that GM crops pose no unique hazards to human health. They noted that genetic transformation has the potential to produce unanticipated allergens or toxins and might alter the nutritional quality of food. Both reports recommended development of new risk-assessment tools and postmarketing surveillance. Those recommendations have largely gone unheeded.

Herbicide resistance is the main characteristic that the biotechnology industry has chosen to introduce into plants. Corn and soybeans with genetically engineered tolerance to glyphosate (Roundup) were first introduced in the mid-1990s. These "Roundup-Ready" crops now account for more than 90% of the corn and soybeans planted in the United States.[4] Their advantage, especially in the first years after introduction, is that they greatly simplify weed management. Farmers can spray herbicide both before and during the growing season, leaving their crops unharmed.

But widespread adoption of herbicide-resistant crops has led to overreliance on herbicides and, in particular, on glyphosate.[5] In the United States, glyphosate use has increased by a factor of more than 250 — from 0.4 million kg in 1974 to 113 million kg in 2014. Global use has increased by a factor of more than 10. Not surprisingly, glyphosate-resistant weeds have emerged and are found today on nearly 100 million acres in 36 states. Fields must be now be treated with multiple herbicides, including 2,4-D, a component of the Agent Orange defoliant used in the Vietnam War.

The first of the two developments that raise fresh concerns about the safety of GM crops is a 2014 decision by the Environmental Protection Agency (EPA) to approve Enlist Duo, a new combination herbicide comprising glyphosate plus 2,4-D. Enlist Duo was formulated to combat herbicide resistance. It will be marketed in tandem with newly approved seeds genetically engineered to resist glyphosate, 2,4-D, and multiple other herbicides. The EPA anticipates that a 3-to-7-fold increase in 2,4-D use will result.

In our view, the science and the risk assessment supporting the Enlist Duo decision are flawed. The science consisted solely of toxicologic studies commissioned by the herbicide manufacturers in the 1980s and 1990s and never published, not an uncommon practice in U.S. pesticide regulation. These studies predated current knowledge of low-dose, endocrine-mediated, and epigenetic effects and were not designed to detect them. The risk assessment gave little consideration to potential health effects in infants and children, thus contravening federal pesticide law. It failed to consider ecologic impact, such as effects on the monarch butterfly and other pollinators. It considered only pure glyphosate, despite studies showing that formulated glyphosate that contains surfactants and adjuvants is more toxic than the pure compound.

The second new development is the determination by the IARC in 2015 that glyphosate is a "probable human carcinogen"[1] and 2,4-D a "possible human carcinogen."[2] These classifications were based on comprehensive assessments of the toxicologic and epidemiologic literature that linked both herbicides to dose-related increases in malignant tumors at multiple anatomical sites in animals and linked glyphosate to an increased incidence of non-Hodgkin's lymphoma in humans.

These developments suggest that GM foods and the herbicides applied to them may pose hazards to human health that were not examined in previous assessments. We believe that the time has therefore come to thoroughly reconsider all aspects of the safety of plant biotechnology. The National Academy of Sciences has convened a new committee to reassess the social, economic, environmental, and human health effects of GM crops. This development is welcome, but the committee's report is not expected until at least 2016.

In the meantime, we offer two recommendations. First, we believe the EPA should delay implementation of its decision to permit use of Enlist Duo. This decision was made in haste. It was based on poorly designed and outdated studies and on an incomplete assessment of human exposure and environmental effects. It would have benefited from deeper consideration of independently funded studies published in the peer-reviewed literature.

And it preceded the recent IARC determinations on glyphosate and 2,4-D. Second, the National Toxicology Program should urgently assess the toxicology of pure glyphosate, formulated glyphosate, and mixtures of glyphosate and other herbicides.

Finally, we believe the time has come to revisit the United States' reluctance to label GM foods. Labeling will deliver multiple benefits. It is essential for tracking emergence of novel food allergies and assessing effects of chemical herbicides applied to GM crops. It would respect the wishes of a growing number of consumers who insist they have a right to know what foods they are buying and how they were produced. And the argument that there is nothing new about genetic rearrangement misses the point that GM crops are now the agricultural products most heavily treated with herbicides and that two of these herbicides may pose risks of cancer. We hope, in light of this new information, that the FDA will reconsider labeling of GM foods and couple it with adequately funded, long-term postmarketing surveillance.

An audio interview with Dr. Landrigan is available at NEJM.org

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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1. Guyton KZ, Loomis D, Grosse Y, et al. Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. Lancet Oncol 2015;16:490-1.
2. Loomis D, Guyton K, Grosse Y, et al. Carcinogenicity of lindane, DDT, and 2,4-dichlorophenoxyacetic acid. Lancet Oncol 2015 June 22 (Epub ahead of print).
3. National Research Council, Committee on Identifying and Assessing Unintended Effects of Genetically Engineered Foods on Human Health. Safety of genetically engineered foods: approaches to assessing unintended health effects. Washington, DC: National Academies Press, 2004.
4. Adoption of genetically engineered crops in the U.S. Washington, DC: Department of Agriculture, Economic Research Service (http://www.ers.usda.gov/data-products/adoption-of-genetically-engineered-crops-in-the-us.aspx).
5. Duke SO. Perspectives on transgenic, herbicide-resistant crops in the United States almost 20 years after introduction. Pest Manag Sci 2015;71:652-7.

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From: Krimsky, Sheldon <Sheldon.Krimsky@tufts.edu>
Sent: Thursday, August 20, 2015 1:12 PM
To: Pete Myers; Karp, Harvey; Prins, Gail; Lanphear, Bruce; Cranmer, Joan; Cory-Slechta, Deborah; Peter Orris; Prof. Fred vom Saal; Terry Collins; Howard Snyder; Peter DeFur; Ho, Shuk-mei; Zoeller, Tom; Ted Schettler; Ozonoff, David; Hayes, Tyrone; Woodruff, Tracey; Dr. Steve Heilig; Stahlhut, Richard; Philip Landrigan; Hunt, Pat; Birnbaum, Linda (NIH/NIEHS) [E]; Shanna Swan; Hauser, Russ; Bruce Blumberg; Amy Kostant; Bernard Weiss; Kalee Kreider; Laura Vandenberg; Emily Copeland; Carl-Gustaf Bornehag; Michael Antoniou; Steve Gilbert; Leonardo Trasande; Amy Itescu; John A McLachlan; mcone@ngs.org; Janet Raloff >; Heindel, Jerry (NIH/NIEHS) [E]; Heather Patisaul
Subject: RE: Landrigan & Benbrook's NEJM article
Attachments: STHV GMO ILLUSORY CONSENSUS.pdf

Having just read Landrigan and Benbrook's article in NEJM on GMOs, I thought I should send around this recently published piece on GMO health effects.

Best,

Shelly

Article

Science, Technology, & Human Values
1 32

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An Illusory Consensus behind GMO Health Assessment

Sheldon Krimsky[1]

Abstract

Prominent scientists and policymakers assert with confidence that there is no scientific controversy over the health effects of genetically modified organisms (GMOs)—that genetically modified crops currently in commercial use and those yet to be commercialized are inherently safe for human consumption and do not have to be tested. Those who disagree are cast as "GMO deniers." This article examines scientific reviews and papers on GMOs, compares the findings of professional societies, and discusses the treatment of scientists who have reported adverse effects in animal feeding experiments. This article concludes by exploring the role that politics and corporate interests have had in distorting an honest inquiry into the health effects of GMO crops.

Keywords

expertise, methodologies, methods, politics, power, governance, academic disciplines and traditions, GMOs, genetically modified crops, health assessment, conflict of interest, scientific controversy

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Introduction

This article is written in three parts. First, I examine the scientific literature through the systematic reviews of animal feeding experiments and the findings of professional societies on the health assessment of genetically modified (genetically modified organism [GMO]) crops. Second, I discuss the reception among segments of the scientific community of two high-visibility published research papers that found adverse effects in animal feeding studies. Third, I discuss the implications of my analysis for how people should understand the current state of science regarding the health assessment of GMOs as well as how it informs science, technology, and society (STS) studies.

The scientific literature on the health effects of GMO crops falls into three clusters. One group of authors (cluster 1) states that there is no need for testing GMO products, as long as you know the proteins coded by the transferred genes and the host organisms. The transgenic products are considered as safe or safer than traditional hybrid crops or other non-transgenic methods.

Another group of authors (cluster 2) makes as strong a claim that each GMO product must be tested for a variety of possible effects. They assert that science cannot, a priori, claim that a product of genetic modification is safe without undertaking a testing program that includes multiyear and multigenerational tests in animals fed on the transgenic crop. Finally, a third group of scientific authors (cluster 3) asserts in their published articles that some GMO crops, when fed to animals, have exhibited harmful effects compared to non-GMO controls, and these results should draw attention to human health concerns.

As an example of cluster 1 scientists, Richard Roberts (2004), Nobel Laureate in Physiology or Medicine, wrote, ‘‘hundreds of studies and tests have been done on GMO safety and we have seen no scientific evidence that GMOs are inherently more dangerous than crops produced by traditional plant breeding.’’ Nicolia et al. (2014) wrote in their review of genetic engineering crop safety research, ‘‘We have reviewed the scientific literature on GE crop safety for the last 10 years that catches the scientific consensus matured since GE plants became widely cultivated worldwide, and we can conclude that the scientific research conducted so far has not detected any significant hazard directly connected with the use of GM crops.’’ Peter Lachman (1999) of the British Academy of Medical Sciences stated, ‘‘There is no experimental evidence nor any plausible mechanism by which the process of genetic modification can make plants hazardous to human

beings." He dismisses the allergenicity mechanism or the use of antibiotic resistance markers in the GMO as beside the point. Regarding allergenicity, Lachman argued, since we know the allergen before we transplant the gene, it is to be expected that it would be allergenic in the new plant. It is not a new risk. Concerning antibiotic resistant genes, Lachman (1999, 69) noted, "The practice of leaving antibiotic resistant markers in the GM plant ... is a hypothetical risk that antibiotic resistance could spread to gut flora." Lachman called an end to the scientific controversy in 1999 before it barely began.

Gro Harlem Brundtland (Wilson and Highfield 2002), World Health Organization (WHO) Director General, stated that the available evidence shows that GM foods are "not likely to present human health risks" and therefore "these foods may be eaten." Jacques Diouf (2002), Food and Agriculture Organization (FAO) Director General, announced that current scientific research confirms the safety of GM food. And Norman Borlaug (2014), Nobel Laureate, said to a packed hall consisting of researchers and food scientists in Nairobi, "There is no evidence to indicate that biotechnology is dangerous. After all, mother nature has been doing this kind of thing for God knows how long."

Both skeptics and non-skeptics of GMOs purport to debunk the myths of their opponents. *Popular Science* magazine cited as an illustration GM apples in its article "Core Truths: 10 common GMO claims debunked." After interviewing nearly a dozen scientists, *Popular Science* reported (Borel 2014) that consumers should not have much to fear about GMOs. In contrast, a 123-page monograph published in Earth Open Source (Antoniou, Robinson, and Fagan 2012) debunked the myths of GMO advocates. Each side of the debate uses the term "myth" pejoratively against an opponent to describe allegedly false claims, false logic, or a biased interpretation of science. A *National Geographic* story (Achenbach 2015) connected GMO skeptics to climate change deniers. What does the actual science tell us about the health assessment of GMOs?

Systematic Reviews

To gain some understanding of how the safety issues were addressed in the scientific literature, I did a search in *PubMed* and *Web of Science* for systematic reviews of GMO health effects from 2008 to 2014, which examined animal feeding studies. Eight reviews published in refereed publications were found. The conclusions of the reviewers were distributed across my three clusters. The first review (Maghari and Ardekani 2011) noted, "Many scientific data indicate that animals fed by GM crops have been harmed or

even died. Rats exposed to transgenic potatoes or soya had abnormal young sperm; cows, goats, buffalo, pigs and other livestock grazing on Bt-maize, GM cottonseed and certain biotech corn showed complications including early deliveries, abortions, infertility and also many died."

A second review (Domingo and Bordonaba 2011) found, " . . . the number of studies specifically focused on safety assessment of GM plants is still limited. However, it is important to remark that for the first time, a certain equilibrium in the number of research groups suggesting, on the basis of their studies, that a number of varieties of GM products (mainly maize and soybeans) are as safe and nutritious as the respective conventional non-GM plant, and those raising still serious concerns, was observed. Moreover, it is worth mentioning that most of the studies demonstrating that GM foods are as nutritional and safe as those obtained by conventional breeding, have been performed by biotechnology companies or associates, which are also responsible of [sic] commercializing these GM plants." According to the reviewers, there is still a lively controversy over the health effects of GMOs.

After commenting on the small number of available studies, a third review (Dona and Arvanitouannis 2009) reported, "The results of most of the rather few studies conducted with GM foods indicate that they may cause hepatic, pancreatic, renal, and reproductive effects and may alter hematological, biochemical, and immunologic parameters the significance of which remains unknown. The above results indicate that many GM foods have some common toxic effects. Therefore, further studies should be conducted in order to elucidate the mechanism dominating this action."

A fourth review (Snell et al. 2012) concluded, "Results from all the 24 studies do not suggest any health hazards and, in general, there were no statistically significant differences within parameters observed. However, some small differences were observed, though these fell within the normal variation range of the considered parameters and thus had no biological or toxicological significance . . . . The studies reviewed present evidence to show that GM plants are nutritionally equivalent to their non-GM counterparts and can be safely used in food and feed." The authors acknowledged there were statistically significant differences between GMO and non-GMO crops in some parameters that were not health related. This raises the question of whether the crops are "substantially equivalent."

The fifth scientific review was published by the European Food Safety Association (EFSA 2014). Like many agency reviews, it typically is prepared by a scientific panel and has many scientific reviewers commenting on drafts before it is released. "The EFSA GMO panel concludes that the proposed uses of MON 87769 soybean oil in foods will not result in intakes

of stearidonic acid (SDA) with diverse effects and that the other changes in the dietary fatty acid pattern are unlikely to have negative nutritional consequences for humans. The EFSA GMO panel notes that the quantitative dietary estimates described here would have to be revisited if the oil produced by the soybean MON 87769 were to be extensively used in food products not considered in this assessment, for example as dietary supplements or to modify animal feed products.''

A sixth review (Bawa and Anilakumar 2013), covering a range of health, environmental, and social issues, found, ''As the health effects are unknown, many people prefer to stay away from these foods'' and ''not much is known about their long-term effects on human beings.'' The authors conclude by saying, ''One has to agree that there are many opinions about scarce data on the potential health risks of GM food crops, even though these should have been tested for and eliminated before their introduction.''

The seventh review (Magana-Gomez and Calderon de la Barca 2008) reported, ''The most common result [of animal feeding experiments] has been that there were no effects at the macroscopic level; however, organelles and other subcellular structures are clearly affected, as shown at ultramicroscopic levels.'' They also noted that there are no standardized methods for evaluating GM foods and the ''necessity of testing GM crops case by case has been established.''

The eighth and final review (Zhang and Shi 2011) focused on the question: do GM crops affect animal reproduction? The authors concluded, ''It appears that there are no adverse effects of GM crops on many species of animals in acute and short-term feeding studies, but serious debates of effects of long-term and multigenerational feeding studies remain.'' Other scientists (de Vendômois et al. 2010) concur on the need for long-term studies. ''Lifetime studies for laboratory animals consuming GMOs must be performed, by contrast to what is done today, like the two-year long tests on rats for some pesticides or some drugs. Such tests could be associated to transgenerational, reproductive or endocrine research studies.''

One cannot read these systematic reviews and conclude that the science on health effects of GMOs has been resolved within the scientific community (see Table 1; Newman 2013). The eight reviewers made different choices about the endpoints they evaluated, the journal articles selected in their review (although there was considerable overlap), how they weighted the importance of individual studies, and how they interpreted the weight of evidence on the findings of health effects. These differences in methodology help to account for the variation in their findings.

Table 1. Eight Reviews on the Health Effects of GMOs.

Journal Review	Main Point
Maghari, B. M., and A. M. Ardekani. 2011. "Genetically Modified Foods and Social Concerns." *Avicenna Journal of Medical Biotechnology* 3 (3): 109-17 (July September).	Many scientific data indicate that animals fed by GM crops have been harmed or even died. Rats exposed to transgenic potatoes or soya had abnormal young sperm. Cows, goats, buffalo, pigs, and other livestock grazing on Bt-maize, GM cottonseed, and certain biotech corn showed complications including early deliveries, abortions, infertility, and also many died.
Domingo, J. L., and J. G. Bordonaba. 2011. "A Literature Review on the Safety Assessment of Genetically Modified Plants." *Environment International* 37 (4): 734-42.	Most products have been found nutritionally safe, although the majority of the studies were associated with the industry producers.
Dona, A., and I. S. Arvanitouannis. 2009. "Health Risks of Genetically Modified Foods." *Critical Reviews in Food Science and Nutrition* 49 (2): 164-75.	The results of most studies with GM foods indicate that they may cause some common toxic effects such as hepatic, pancreatic, renal, or reproductive effects and may alter the hematological, biochemical, and immunological parameters.
Snell, C., A. Bernheim, J.-B. Berge, Marcel Kuntzd, Gérard Pascale, Alain Parisf, and Agnès E. Ricrochb. 2012. "Assessment of the Health Impact of GM Plant Diets in Long-term and Multigenerational Animal Feeding Trials: A Literature Review." *Food & Chemical Toxicology* 50 (3-4): 1134-48.	The studies reviewed present evidence to show that GM plants are nutritionally equivalent to their non-GM counterparts and can be safely used in food and feed.
EFSA (European Food Safety Authority). 2014. "Scientific Opinion on Application (EFSA-GMO-UK-2009-76) for the Placing on the Market of Soybean MON 87769." *EFSA Journal* 12 (5): 3644-85.	The majority of animal feeding experiments did not indicate clinical effects or histopathological abnormalities in organs or tissues of exposed animals. In some cases, adverse effects were noted but were difficult to interpret due to shortcomings in the studies.

(continued)

Table 1. (continued)

Journal Review	Main Point
Bawa, A. S., and K. R. Anilakumar. 2013. "Genetically Modified Foods: Safety, Risks and Public Concerns A Review." *Journal of Food Science & Technology* 50 (6): 1035-46.	As health effects of GMOs are unknown, many people prefer to stay away from these foods. In addition, not much is known about their long-term effects on human beings.
Magana-Gomez, J. A., and A. M. Calderon de la Barca. 2008. "Risk Assessment of Genetically Modified Crops for Nutrition and Health." *Nutrition Reviews* 67 (1): 1-16.	The most common result [of animal feeding experiments] has been that there were no effects at the macroscopic level; however, organelles and other subcellular structures are clearly affected, as shown at ultramicroscopic levels. There are no standardized methods for evaluating GM foods and the necessity of testing GM crops case by case has been established.
Zhang, W., and F. Shi. 2011. "Do Genetically Modified Crops Affect Animal Reproduction? A Review of the Ongoing Debates." *Animal* 5 (7): 1048-59.	There were no adverse effects of GM crops for many species of animals in acute or short-term feeding studies, but serious debate still surrounds long-term and multigenerational feeding studies. Long-term multigenerational feeding studies are clearly necessary to further investigate this issue.

Allergenicity

It has been confirmed without great surprise to plant geneticists that allergenic proteins can be transferred via their DNA from one plant to another. A laboratory experiment transferred a gene from a peanut to a soybean and demonstrated that people with peanut allergies showed allergenic responses to the transgenic soybean (Nordlee et al. 1996). Such products, where known allergens are transferred from one food to another that is allergen free, would not be permitted, certainly not without labeling.

What is less well understood is whether a non-allergenic protein in one food type can be transferred via its genes to another food type and become allergenic. Some scientists took it for granted that the transferred protein would behave as it did in its parental crop.

Testing for allergenicity without testing food on people can present some problems. Animal feeding studies do not provide the best assessment of human allergens. Animal immune systems are not always a good model for humans. Nevertheless, animal studies can reveal changes in proteins in transgenic crops. A food fed to mice in the original crop without immune responses can show allergenic responses when fed to mice in the transgenic crop. This is an important indicator that the protein was modified. When a gene is moved from one crop to another, this effect has been known to occur. Genes may be fungible (genes from one organism can be transferred and expressed in the cells of another, even across dissimilar species), but their products are not always identical.

This was learned in Australia from an experiment performed at the national research organization Commonwealth Scientific and Industrial Research Organisation. A decadelong research project focuses on developing genetically modified peas with pesticide resistance. Scientists (Campbell et al. 2011) took a gene from the common bean (*Phaseolis vulgaris*) that synthesized a protein capable of killing sea weevil pests and transferred it to the pea (*Pisum salivum*). The protein tested in the bean does not cause an allergic reaction in mice or humans. But after the protein was expressed in the pea, it was learned that its structure was modified slightly. When the gene for the protein was transferred to peas, the structural change in the protein could be responsible for its unanticipated immune effects in mice.

Scientists are not entirely sure why a transplanted gene undergoes a protein modification. The term ''post translational modification'' is used to describe the protein change. It cannot be assumed that a naturally occurring protein will be identical to a protein produced in a GM plant, suggesting that each protein transfer must be tested for allergenicity.

It is now well understood that genes do not always encode a fixed three-dimensional protein structure. The term ''intrinsically disordered protein'' has been introduced to describe proteins that lack a fixed three-dimensional structure. It has been reported that 33 percent of eukaryotic proteins contain disordered segments (Ward et al. 2004). Also, intrinsically unstructured proteins have been connected to a number of diseases. What has not been studied is whether GMOs, through posttranslational modification, have a higher frequency of proteins containing disordered segments.

Developmental biologist Stuart Newman (2009, 27) discusses the uncertainties of transplanting new genes into a plant's genome. ''Throwing an entirely new component into a plant's biological mix can potentially change the hundreds to thousands of potentially toxic molecules every plant is

capable of manufacturing .... GM transgenesis can inadvertently induce extensive scrambling of the genome.''

Lee et al. (2013) repeated the bean pea experiment and reached very different results. They found that transgenic alpha-amylase inhibitor peas, chickpeas, and cowpeas as well as non-transgenic beans were all allergenic in a species of mice. If that is corroborated, then the issue of posttranslational modification of transgenes for allergenicity has to be reevaluated. Until that is investigated, it remains uncertain whether allergenicity is an emergent property of transgenic plants.

Professional Societies

Another approach for gauging whether there is scientific consensus over the health effects of GMOs is to consult the opinion of professional associations. For many in the United States, the soundest advice about scientific or medical matters is provided by the National Academies of Science (NAS) because their studies are performed by carefully chosen scientific panels that offer their interpretation of the best published science. In 2004, the NAS published the *Safety of Genetically Engineered Foods: Approaches to Assessing Unintended Health Effects.* Among the findings of the report was, ''All evidence evaluated to date indicates that unexpected and unintended compositional changes arise with all forms of genetic modification, including genetic engineering. Whether such compositional changes result in unintended health effects is dependent upon the nature of the substances altered and the biological consequences of the compounds. To date, no adverse health effects attributed to genetic engineering have been documented in the human population'' (NAS 2004, 8).

The Academy report supports safety assessment of foods that have undergone compositional changes. ''The committee recommends that compositional changes that result from all genetic modification in food, including genetic engineering, undergo an appropriate safety assessment. The extent of an appropriate safety assessment should be determined prior to commercialization'' (NAS 2004, 8).

Because the addition of a foreign gene into a food substance is not considered a food additive, according to the 1992 Food and Drug Administration (FDA) policy, the product does not have to meet the standard of safety for chemical food additives, namely, reasonable certainty that no harm will result from intended uses of consumption. ''There is no burden on the food manufacturer to demonstrate the safety of food products that are not food additives'' (NAS 2004, 131). The NAS report provides a pre- and

post-market framework for assessing the safety of GMOs on a case-by-case basis.

The FDA has classified GM foods as "generally regarded as safe" known as "GRAS" and has a reporting mechanism but not a mandatory testing policy (Druker 2015). According to the NAS (2004, 8), "All evidence evaluated to date indicates that unexpected and unintended compositional changes arise with all forms of genetic modification, including genetic engineering .... To date, no adverse health effects attributed to genetic engineering have been documented in the human population."

Even as the NAS asserts its confidence in the safety of transgenic foods, it recommends pre-market assessment of all new food prior to commercialization, but emphasizes that the policy to assess products should not be based exclusively on their methods of breeding (NAS 2004, 9). The Academy also acknowledges "there remain sizable gaps in our ability to identify compositional changes that result from genetic modification of organisms intended for food" (NAS 2004, 15).

The British Medical Association (BMA) issued its first statement on GMOs in 1999 when it advised that there should be a moratorium on the commercial planting of GM crops. The BMA report titled *The Impact of Genetic Modification on Agriculture, Food and Health* warned that "any adverse effects from GMOs are likely to be irreversible. As we cannot yet know whether there are any serious risks to the environment or human health, the precautionary principle [when a product or policy is suspected of causing harm, even in the absence of scientific consensus and definitive evidence of risk, the burden of proof is to demonstrate that it is not harmful before taking action.] should apply." An updated report by the BMA in 2004 expressed less concern about the health risks of current GMOs. "The potential for GM foods to cause harmful health effects is very small .... However, safety concerns cannot, as yet, be dismissed completely on the basis of information currently available" (BMA 2004, 3). The report also noted that "the few robust studies that have looked for health effects have been short term and specific. There is a lack of evidence-based research with regard to medium and long-term effects on health and the environment."

In 2003, BMA (Scotland) welcomed a report of the Scottish Parliament that the risk assessment of GMOs was flawed. BMA (Scotland) testified that "There is insufficient evidence to show whether or not there are potential health risks from exposure to Genetically Modified Organisms (GMOs). The only way to try and answer this question is to actually look in a systematic way for adverse effects on human health" (BMA 2003).

The Indiana State Medical Association and the Illinois State Medical Society introduced resolutions to the American Medical Association (AMA) supporting Federal legislation and/or regulations to require labeling of food with genetically engineered (GE) ingredients. As of 2012, the AMA Council of Delegates did not support mandatory labeling of GMOs without evidence of material differences between bioengineered foods and their traditional counterparts. The AMA Council affirmed that no long-term health effects have been detected from the use of transgenic crops and GM foods. The Council and the AMA do support mandatory pre-market systematic safety assessments of bioengineered foods in lieu of a voluntary notification policy and the development and validation of additional techniques for the detection and assessment of unintended effects (AMA 2012).

The American Public Health Association, the American Nurses Association, the Illinois Public Health Association, and the California State Medical Association have passed resolutions calling for labeling of GE food.

The professional toxicologists also issued a policy statement in 2003 through the Society of Toxicology with a perspective akin to cluster 1 scientists, ''The available scientific evidence indicates that the potential adverse health effects arising from biotechnology-derived foods are not different in nature from those created by conventional breeding practices for plant, animal, or microbial enhancement, and are already familiar to toxicologists.'' However, it also added, ''Methods have not yet been developed by which whole foods (as compared with single chemical components) can be fully evaluated for safety. Progress also needs to be made in developing definitive methods for the identification and characterization of protein allergens, and this is currently a major focus of research.'' And while rather optimistic about the safety of existing GMOs, the report of the Society makes it clear that the methods to test the food and the passive reporting system are deficient. ''The level of safety of current (''biotechnology-derived'') BD foods to consumers appears to be equivalent to that of traditional foods. Verified records of adverse health effects are absent, although the current passive reporting system would probably not detect minor or rare adverse effects, nor can it detect a moderate increase in common effects such as diarrhea. However, this is no guarantee that all future genetic modifications will have such apparently benign and predictable results. A continuing evolution of toxicological methodologies and regulatory strategies will be necessary to ensure that this level of safety is maintained'' (Society of Toxicology 2003).

The American Academy of Environmental Medicine (AAEM), an organization formed in 1965 largely made up of MDs who identify themselves as clinical ecologists, a medical specialty not recognized by more traditional

medical associations, issued a policy statement on GMOs acknowledging adverse impacts of animal studies (AAEM 2009). "[S]everal animal studies indicate serious health risks associated with GM food consumption including infertility, immune dysregulation, accelerated aging, dysregulation of genes associated with cholesterol synthesis, insulin regulation, cell signaling, and protein formation, and changes in the liver, kidney, spleen and gastrointestinal system. There is more than a casual association between GM foods and adverse health effects." In contrast, the Royal Society of Canada (RSC) concluded that GMOs pose no inherent risk. While not unduly concerned about GMO health effects based on 2001 evidence, the RSC (2001, 48) questioned the nature of the evidence in its statement "that regulatory requirements related to toxicological assessment of GM food appeared to be ad hoc and provided little guidance either as to when specific studies would be required or what types of studies would be most informative. The [RSC] Panel was unaware of any validated study protocols currently available to assess the safety of GM food in their entirety (as opposed to food constituents) in a biological and statistically meaningful manner." Among its recommendations, the RSC (2001, 50) Panel called upon federal officials in Canada to establish "clear criteria regarding when and what types of toxicological studies are required to support the safety of novel constituents derived from transgenic plants."

The conclusions of the chosen group of professional associations mirror the disparity found in the systematic reviews. Medical and scientific societies have reached their consensus positions by selecting the studies each deems credible and important and by preferentially weighing the evidence those studies provide, even as some societies question the reliability or sufficiency of those studies. It is not unusual for expert panels to differ in their conclusions and advice. Building on the work of Erving Goffman, science studies scholars have applied the metaphor of dramaturgy, where science advisory panels engage in a type of performance, to understand the factors that determine how information gets presented to the public (front stage) and which conclusions get negotiated in the back rooms (back stage). The study of GMO science panels provides fertile ground for such an analysis (Hilgartner 2000).

Individual Studies

Thus far, I have identified twenty-six studies in the scientific literature that have reported adverse effects or uncertainties of GMOs fed to animals (Table 2). In this section, I shall focus on two of those published studies

Table 2. Articles Citing Adverse Effects or Uncertainties on the Health Effects of GMOs.

Fares, N. H., and A. K. El-Sayed. 1998. "Fine Structure Changes in the Ileum of Mice Fed on Endotoxin-treated Potatoes and Transgenic Potatoes." *Natural Toxins* 6 (6): 219-33.

Ewen, S. W. B., and A. Pusztai. 1999. "Effects of Diets Containing Genetically Modified Potatoes Expressing *Galanthus nivalis* Lectin on Rat Small Intestine." *Lancet* 354 (9187): 1353-54.

Birch, A. N. E., I. E. Geoghegan, M. E. N. Majerus, J. W. McNicol, C. A. Hackett, A. M. R. Gatehouse, and J. A. Gatehouse. 1999. "Tri-trophic Interactions Involving Pest Aphids, Predatory 2-spot Ladybirds and Transgenic Potatoes Expressing Snowdrop Lectin for Aphid Resistance." *Molecular Breeding* 5 (1): 75-83.

Malatesta, M., C. Caporaloni, S. Gavaudan, M. B. L. Rocchi, S. Serafini, C. Tiberi, and G. Gazzanelli. 2002. "Ultrastructural Morphometrical and Immunocytochemical Analysis of Hepatocyte Nuclei from Mice Fed on Genetically Modified Soybean." *Cell Structure Function* 27 (5): 173-80.

Malatesta, M., C. Caporaloni, L. Rossi, S. Battistelli, M. B. L. Rocchi, F. Tonucci, and G. Gazzanelli. 2002. "Ultrastructural Analysis of Pancreatic Acinar Cells from Mice Fed on Genetically Modified Soybean." *Journal of Anatomy* 201 (5): 409-15.

Malatesta, M., M. Biggiogera, E. Manuali, M. B. L. Rochhi, B. Baldelli, and G. Gazzanelli. 2003. "Fine Structural Analyses of Pancreatic Acinar Cell Nuclei from Mice Fed on Genetically Modified Soybean." *European J. Histochemistry* 47 (4): 385-99.

Pryme, I. F., and Rolf Lembcke. 2003. "In Vivo Studies on Possible Health Consequences of Genetically Modified Food and Feed with Particular Regard to Ingredients Consisting of Genetically Modified Plant Materials." *Nutrition and Health* 17 (1): 1-8.

Vecchio, L., B. Cisterna, M. Malatesta, T. Martin, and B. Biggiogera. 2004. "Ultrastructural Analysis of Testes from Mice Fed on Genetically Modified Soybean." *European Journal of Histochemistry* 48 (4): 449-54.

Prescott, V. E., P. M. Campbell, A. Moore, J. Mattes, M. E. Rothenberg, P. S. Foster, T. J. Higgins, and S. P. Hogan. 2005. "Transgenic Expression of Bean Alpha-amylase Inhibitor in Peas Results in Altered Structure and Immunogenicity." *Journal of Agriculture Food & Chemistry* 53 (23): 9023-30.

Tudisco, R., F. Lombardi, F. Bovera, D. ďAngelo, M. I. Cutrignelli, V. Mastellone, V. Terzi, L. Avallone, and F. Infascelli. 2006. "Genetically Modified Soy Bean in Rabbit Feeding: Detection of DNA Fragments and Evaluation of Metabolic Effects by Enzymatic Analysis." *Animal Science* 82 (2): 193-99.

Ermakova, I. V. 2006. "Genetically Modified Soy Leads to the Decrease of Weight and High Mortality of Rat Pups of the First Generation. Preliminary Studies." *EcosInform* 1:4-9. (in Russian)

Sagstad, A., M. Sanden, Ø. Haugland, A. C. Hansen, P. A. Olsvik, and G. I. Hemre. 2007. "Evaluation of Stress- and Immune-response Biomarkers in Atlantic Salmon for Different Levels of Bt Maize." *Journal of Fish Diseases* 30 (4): 201-12.

(continued)

Table 2. (continued)

Seralini, G.-E., D. Cellier, and J. S. de Vendomois. 2007. "New Analysis of Rat Feeding Study with GM Maize Reveals Signs of Hepatorenal Toxicity." *Archives of Environmental Contaminant Toxicology* 52 (4): 596-602.

Malatesta, M., F. Boraldi, G. Annovi, Beatrice Baldelli, Serafina Battistelli, Marco Biggiogera, and Daniela Quaglino. 2008. "A Long-term Study on Female Mice Fed on a Genetically Modified Soybean: Effects on Liver Ageing." *Histochemistry Cell Biology* 130 (5): 967-77.

Finamore, A., M. Roselli, S. Britti, G. Monastra, R. Ambra, A. Turrini, and E. Mengheri. 2008. "Intestinal and Peripheral Immune Response to MON810 Maize Ingestion to Weaning and Old Mice." *Journal of Agriculture Food & Chemistry* 56 (23): 11533-39.

Velimirov, A., C. Binter, and J. Zentek. 2008. "Biological Effects of Transgenic Maize NK 603xMON810 Fed in Long Term Reproduction Studies in Mice." Forschungsberichte de Sektion IV Band 3/2008, 105. Vienna, Austria. Accessed July 22, 2015. http://www.biosicherheit.de/pdf/aktuell/zentek studie 2008.pdf.

Kilic, A., and M. T. Akay. 2008. "A Three Generation Study with Genetically Modified Bt Corn in Rats: Biochemical and Histopathological Investigation." *Food & Chemical Toxicology* 46 (3): 1164-70.

Cisterna, B., F. Flach, L. Vecchio, S. M. L. Barabino, S. Battistelli, T. E. Martin, M. Malatesta, and M. Biggiogera. 2008. "Can a Genetically-modified Organism-containing Diet Influence Embryo Development? A Preliminary Study on Pre-implantation Mouse Embryos." *European Journal of Histochemistry* 52 (4): 263-67.

Bøhn, T., R. Primicerio, D. O. Hessen, and T. Traavik. 2008. "Reduced Fitness of Daphnia Magna Fed a Bt Transgenic Maize Variety." *Archives of Environmental Contamination and Toxicology* 55 (4): 584-92.

Trabalza-Marinucci, M., E. Chiaradia, G. Brandi, C. Rondini, L. Avellini, C. Giammarini, S. Costarelli, G. Acuti, C. Orlandi, and G. Filippini. 2008. "A Three Year Longitudinal Study on the Effects of a Diet Containing Genetically Modified Bt176 Maize on the Health Status and Performance on Sheep." *Livestock Science* 113 (2-3): 178-90.

Sissener, N. H., M. Sanden, A. M. Bakke, A. Krogdahl, and G. I. Hemre. 2009. "A Long Term Trial with Atlantic Salmon (*Salmo salar* L.) Fed Genetically Modified Soy; Focusing General Health and Performance before, during and after the Parr smolt Transformation." *Aquaculture* 294 (1-2): 108-17.

Atremis, D., and I. S. Arvantioyannis. 2009. "Health Risks of Genetically Modified Foods." *Critical Reviews in Food Science and Nutrition* 49 (2): 164-75.

de Vendômois, J. Spiroux, F. Roullier, D. Cellier, and Gilles-Eric Séralini. 2009. "A Comparison of the Effects of Three GM Corn Varieties on Mammalian Health." *Int. J. Biological Sciences* 5 (7): 706-26.

Aris, A., and S. Leblanc. 2011. "Maternal and Fetal Exposure to Pesticides Associated to Genetically Modified Foods in Eastern Township of Quebec, CA." *Reproductive Toxicology* 31 (4): 528-33.

(continued)

Table 2. (continued)

Séralini, G.-E., E. Clair, R. Mesnage, Steeve Gress, Nicolas Defarge, Manuela Malatesta, Didier Hennequin, and Joël Spiroux de Vendômois. 2012. "Long Term Toxicity of a Roundup Herbicide and a Roundup-tolerant Genetically Modified Maize." *Food and Chemical Toxicology* 50:4221-31 (retracted 2014) republished in *Environmental Sciences Europe* 26:1-17 (2014).
Carrnan, J. A., H. R.Vlieger, L. J. Ver Steeg, V. Sneller, G. Robinson, C. Clinch-Jones, J. Haynes, and J. Edwards. 2013. "A Long-term Toxicology Study on Pigs Fed a Combined Genetically Modified Soy and Maize Diet." *Journal of Organic Systems* 8 (1): 38-54.

in order to provide an in-depth analysis of the receptivity of their work by the scientific community.

The animal feeding study that created the largest media response was published in the *Lancet* in 1999. No one in the field of medicine needs an introduction to this journal, which began publication in 1823 and has a Journal Impact Factor of 39. The article in question was authored by Stanley Ewen, Department of Pathology at the University of Aberdeen and Arpad Pusztai, Rowett Research Institute in Aberdeen. Rowett is largely a government-funded research institute focusing on animal and human nutrition. They fed GM potatoes to rats and observed damage to their intestines and immune systems.

Pusztai is an internationally recognized expert on lectins, plant-protective proteins with insecticidal properties. He had published about 300 scientific papers, including two in *Nature*, and published two books: he was coeditor of *Lectins: Biomedical Perspectives* (Taylor and Francis; Pusztai and Bardocz 1995) and coauthor of *Handbook of Plant Lectins* (John Wiley; van Damme et al. 1998).

Pusztai reported that the Rowett Institute had a major research collaboration with a pharmaceutical company. According to the contract with Rowett, the company had intellectual property rights on all research at the institute pertaining to lectins in the human gut, even research the company did not fund. The company was interested in the role lectins might play in the prevention of gut damage in chemoradiation therapy. Pusztai noted, "So, everything which we did in this field belonged to them," including his GM potato research (2002a, 80).

The story began in 1995 when the Scottish Office of Agriculture, Environment and Fisheries Department (SOAEFD) reported funding for a new research program on evaluating the safety of GM crops. According to

Pusztai, there were no peer-reviewed studies on the safety of GM crops at the time. He submitted a fifty-page proposal. It was among twenty-eight proposals, which were eventually whittled down to eight that were sent out for peer review. Pusztai's proposal was accepted and he was awarded 1.6 million pounds for doing the study. There were three research units involved: the Scottish Crop Research Institute (SCRI), the University of Durham's Department of Biology, and the Rowett Institute.

Pusztai reported that Rowett had a profit-sharing agreement with Axis-Genetics, which financed the development of the GM potato. If the potato were eventually commercialized, Rowett would share the profits. Pusztai (2002a, 85) wrote, "We thought that GM potatoes would be ok because it's a great idea."

In a talk he delivered on May 7, 1999, to the British Hungarian Fellowship in South Kensington, UK, Pusztai said that he believed that GM potatoes were destined for a commercial market, and he thought that they should be tested to know whether they were safe to eat. They had two transgenic genetic lines of potatoes with insecticidal lectin genes from the snowdrop (*Galanthus nivalis*). At the time Pusztai (2002b, 74) wrote "there are many opinions on the safety of GM food but very few data published in peer reviewed journals."

The Nature of the Experiment

Pusztai and his team decided to study a transgenic potato with a gene from a white-flowering, spring blooming Eurasian plant called a snowdrop. They chose a gene that coded for a lectin protein. The snowdrop species selected was *G. nivalis*. The lectin gene is called *G. nivalis* agglutinin or GNA. The idea of genetically modifying plants for insect resistance was in the air at the time. There were experiments underway in the late 1990s for encoding GNA in wheat so the crop would be resistant to grain aphids (Stogar et al. 1999).

Pusztai stated his hypothesis for the experiment, "It was thought that comparison of the histological parameters of the gut of rats fed potato diets containing either GM potatoes, or non-GM potatoes with or without being supplemented with GNA should give a clear indication whether GNA gene insertion had affected the nutritional and physiological impact of potatoes on the mammalian gut" (Ewen and Pusztai 1999a).

Pusztai and his group chose to incorporate the snowdrop lectin into the potato because they believed it would not cause a health problem for the animals. They had done experiments where freestanding GNA proteins

were introduced into the rats' diet without adverse effects. Pusztai (2002a, 70) wrote that he had experimental assurances that GNA was a safe lectin and the gene coding it a safe gene. He also published a study of transgenic peas fed to rats and reported "that the nutritional value of diets containing transgenic or parent peas was remarkably similar" and were "without major harmful effects on their growth, metabolism and health" (Pusztai et al. 1999, 1603, 1597).

Pusztai's study used two transgenic potato lines that were developed at the Scottish Research Institute, each with a lectin gene from snowdrop. They had four experimental groups of male nineteen-day-old rats, believing that any adverse effects would likely show up in younger animals (Pryme and Lembcke 2003).

GM and non-GM potatoes came from the same field site. Each of the two GM potato lines was fed to separate groups of rats, and another group was fed the parental non-GMO potato spiked with the GNA protein. There were also controls fed the standard rat feed. Ewen and Pusztai (1999a) wrote, "We compared the histological indices of the gut of rats fed potato diets containing GM potatoes, non-GM potatoes, or non-GM potatoes supplemented with GNA, to find out whether GNA gene insertion had affected the nutritional and physiological impact of potatoes on the mammalian gut."

Two commentators noted in their 2003 publication *Nutrition and Health* "Pusztai's studies . . . are remarkable in that the experimental conditions were varied and several ways were found by which to demonstrate possible health effects of GM-foods" (Pryme and Lembcke 2003).

In 1998, Dr. Pusztai accepted an interview on a program titled *World in Action*. He said that his group had observed adverse changes to the intestines and immune systems of rats fed GM potatoes. He also said that "If I had the choice I would certainly not eat it [GM potatoes]" and that "I find it's very unfair to use our fellow citizens as guinea pigs" (Randerson 2008). For a short time, the Rowett Institute was proud of Pusztai's media attention. But soon thereafter, the institute suspended Pusztai and used misconduct procedures to seize his data. His contract was not renewed, and while suspended he was banned from speaking publicly and thereafter forced to retire.

Pusztai wrote that the Rowett Institute had a major research program with a pharmaceutical company, which funded many of the projects on lectins in the human gut. "So everything we did in this field belonged to the company, so the GM potato project also belonged to the company . . . . The company was interested in a way to use lectins for the prevention of gut

damage in chemo-radiation therapy .... In a sense we were sold to them [the company] lock, stock and barrel .... The company, in fact, disowned us, in order to avoid bad publicity" (2002a, 80).

Because the data were likely held by his colleague Stanley Ewen, Rowett could not restrict its publication. The results of the study were varied and complex. The principal conclusions were published in *The Lancet* on October 16, 1999. In brief, the authors reported that the rats fed on the GM diet, compared to controls, grew less well, exhibited unusual changes in their tissue, and were found to have immune problems, which did not occur when the rats were fed free GNA lectin proteins.

The authors suggested that some of the adverse effects they observed were possibly a result of the transformation of the potato with the transgene and was not a consequence of the lectins per se. The two lines of the GM potatoes derived from the same transformation event exhibited some different effects. The authors surmised that genes are inserted into different positions in the potato chromosome and in some placements may interfere with the plant's own gene expression.

A scientific committee of the Royal Society of London told Pusztai that his results were obtained by poor experimentation, bad design, and wrong conclusions. According to *The Guardian* and the journal *Science as Culture*, Pusztai responded, "Supposedly in my previous 270 papers, some 40 of them with the same design and methodology, I was scientifically alright, but then suddenly I had a mental breakdown" (Randerson 2008, 18; Pusztai 2002a). There were 919 media stories published from 1998 through early 2015 on the Pusztai affair without conclusive evidence of why his experiment was allegedly deficient.

Criticisms

There were two stages of criticisms of Pusztai's work: the prepublication review and the post-publication review. In the former, there was a review of the methodology of the proposal and there were six members of the Scottish Royal Society who looked at a range of documents prior to publication at the request of the head of Rowett. There were also six reviewers for *The Lancet.* The post-publication criticisms came immediately after *The Lancet* article was published. Prior to publication, *The Guardian* wrote that Professor Peter Lachmann, British immunologist, Emeritus professor at the University of Cambridge, and Fellow of the Royal Society, phoned the editor of *The Lancet* and threatened him if he published the Pusztai paper (Flynn and Gillard 1999). Lachmann confirmed that he made the call but

denied that he threatened the editor. Lachmann was an author of the Royal Society's 1998 highly favorable report on GMOs.

A widely reported story line goes as follows: in 1999, Lachmann tried to persuade the editor of *The Lancet* not to publish Árpád Pusztai's research on the adverse effects of GM potatoes on rats on the grounds that it was not sound science. *The Lancet*'s editor, Richard Horton, received what he described as an aggressive phone call from Lachmann. Dr. Horton said he was called at his office in central London on the morning of Wednesday October 13, two days before the Lancet published the paper by Pusztai.

Dr. Horton, editor of *The Lancet* since 1995, said the phone call began in a "very aggressive manner." He said he was called "immoral" and accused of publishing Dr. Pusztai's paper, which he "knew to be untrue." Toward the end of the call, Dr. Horton said the caller told him that if he published the Pusztai paper, it would "have implications for his personal position" as editor. *The Lancet* is owned by Reed Elsevier, one of Europe's largest scientific publishing houses (Flynn and Gillard 1999). Lachmann's own account of the Pusztai affair can be found in *Panic Nation* (2005). He categorically denies making the threat to Richard Horton.

When *The Lancet* received the manuscript from Ewen and Pusztai, it was sent to six referees, whereas the usual peer review has two to three referees. Five of the six referees recommended the paper for publication, while one referee was strongly against publication. In addition, that referee transgressed a long-standing norm of the journal to keep reviews to the editor confidential by disclosing his negative review to the press. *The Lancet* published the article despite the pressures to do otherwise. The attacks against Pusztai were unrelenting. He and Ewen responded to a number of his critics in *The Lancet* (Ewen and Pusztai 1999b). Pusztai left Rowett and periodically has commented on the incident. To this date, no one has made an effort to replicate his study. The episode left Pusztai's otherwise distinguished career in shambles.

The Séralini Case

The second most highly publicized study was led by Gilles-Eric Séralini, a professor of molecular biology at the University of Caen in Normandy, France. He is the founder and president of the scientific advisory board of the nonprofit Committee of Research and Independent Information on Genetic Engineering (CRIIGEN), an association that was in the public record. Funding from CRIIGEN was acknowledged in Séralini's papers.

In 2009, Séralini and eight other authors published a paper in the *International Journal of Biological Sciences* that discussed the relevant criteria

that should be used to evaluate GMOs. Their paper raised questions about what regulatory agencies use to undertake risk assessments involving mammalian feeding experiments of GMOs (Séralini et al. 2009). By that time Monsanto had been undertaking short-term tests (ninety days) on certain GMO food products. The authors considered the current criteria to be fostering false negative results because of sample size and statistical design. Referring to some experiments that found adverse effects from GMOs the authors stated, ''These GM-linked effects are then considered as signs of toxicity in the ninety-days, not proofs of toxicity'' (Séralini et al. 2009, 442).

The authors proposed new tests of increased duration and larger number of rats in order to increase the sensitivity or resolution power of the tests. ''We call for more serious standardized tests such as those used for pesticides or drugs, on at least three mammalian species tested for at least three months, employing larger sample sizes and up to one and two years before commercialization'' (Séralini et al. 2009, 442). Long-term tests were not popular with industry because of the time and expense. Ironically, when Séralini undertook such tests, his published results drew considerable criticism.

In 2012, Séralini headed a study on the long-term toxicity of the herbicide *Roundup* (Monsanto's trade name for a glyphosate-based herbicide) and *Roundup* tolerant GM maize. The scientific group was interested in evaluating the health effects of *Roundup*, which consisted of the herbicide glyphosate and other additives called adjuvants, as well as the GM crop that was made herbicide tolerant from the transgenes (GM maize NK603). In prior feeding experiments, some showed effects and some showed no effects for both *Roundup* and the GM plant. The group used the Organisation for Economic Co-operation and Development (OECD) Guideline 408 but went beyond it. They were very clear in their paper that they were not using a carcinogenesis protocol, which requires fifty rats per group. They used ten rats per group that were fed three doses of the GMO. They found that *Roundup* delivered to rats at concentrations below officially set safety limits ''induce severe hormone-dependent mammary, hepatic and kidney disturbances'' (Séralini et al. 2012, 4230). Female rats developed large mammary tumors more often than and before controls. Liver congestion and necrosis were between 2.5 and 5.5 times higher in treated males than controls. Males showed four times more palpable tumors than controls. Most of the adverse effects were kidney related. Séralini et al. reported adverse effects for the GM maize alone, for *Roundup* alone, and for GM maize with *Roundup* residues.

The paper was published on line September 19, 2012, and within a very short time letters of criticism began flooding the journal. They charged Séralini with conflict of interest because of his association with the nonprofit CRIIGEN. He was criticized for using too few animals, the wrong strain of rats, for violating protocols of a carcinogen study, and for using poor statistics. Séralini had to deal with about fifty points of criticism.

A few months later, Editor-in-chief A. Wallace Hayes wrote an editorial on the review process for manuscripts submitted to *Food and Chemical Toxicology*. It covered some broad themes such as conflict of interest, selection of peer reviewers, post-publication review including letters to the editor, and responses to comments by the authors. It is everything you would expect from a transparent editor-in-chief discussing the manuscript review process. Hayes only gets specific in the first sentence. ''Manuscripts submitted to *Food and Chemical Toxicology* (FCT), such as the Seralini et al September 2012 publication, are subjected to a rigorous peer review process.'' (The accent aigu was omitted from Séralini's name.) In selecting out the Séralini et al. paper in the editorial, it appears to the reader that the editor-in-chief stands behind the judgment of the peer review process, particularly with this article. That's what makes the next stage of this case much more difficult to understand.

Séralini and his colleagues (2013) wrote an eight-page response to the critical letters attacking their 2012 publication. They began with two points of clarification about their study. First, they said that their study is the first long-term detailed research on mammals exposed to a highly diluted pesticide in its total formulation with adjuvants. In other words, they were not testing simply the active ingredient glyphosate. The adjuvants are added in the formulation because they make the herbicide more effective. Secondly, they noted that their work is not the final word on toxicological effects of GM maize (NK603 and *Roundup*). They noted that their research is the first step in studying long-term health effects of GMOs that should be replicated independently. Séralini was criticized for not following OECD guidelines in doing such experiments, but as he pointed out, there are no such guidelines for *in vivo* studies of GMO toxicity. He was criticized for using too few animals. His response was that ten animals in each sex group was recommended by OECD in 1981. People criticized him because he did not use the protocols for a carcinogen study. He responded that his study was not a carcinogen study but rather a long-term, full toxicological study. Nevertheless, he was required to report any lesions or tumors, which he did. He was criticized for the type of rats he used and the low number and for how he presented the data, which, critics said, placed too much emphasis

on tumors. He was brought to task for claiming *Roundup* was an endocrine disruptor, while studies reported glyphosate had not shown hormonal effects. The criticisms included a finding of breach of ethics for letting the rat tumors grow too large when the rats should have been euthanized. They even charged him with conflicts of interest. Séralini et al. responded to about forty-five individual criticisms, taking them point-by-point. He responded to the criticism that no adverse effects have been observed in farm animals or humans.

> Some critics have emphasized that no adverse effects have been reported on either farm animals or in the human population of the USA who have consumed an unknown mixture GMO crop derived food. Such claims are scientifically unsound for the following reasons. First, it is important to note that there have been neither epidemiological studies of the human population nor monitoring of farm animals in an attempt to correlate any ill-health observed with the consumption of a given GM crop. Second, it should be recalled that farm animals are not reared to live for the entire duration of their natural lifespan, and thus usually do not live long enough to develop long-term chronic diseases, which contrasts with the rats in our life-long experiment. If any studies in lactating cows are conducted, biological analyses performed are far less complete than those done in regulatory tests using rodents including in our study. Third, as there is no labeling of GMO food and feed in the USA, the amount consumed is unknown, and no ''control group'' exists. Thus, without a clear traceability or labeling, no epidemiological survey can be performed. (Séralini et al. 2013, 481)

It is rare in scientific publishing to find such a preponderance of criticism directed at a peer-reviewed publication and equally as rare to find such an extensive and detailed response to the criticism seven published pages.

With pressure building on the journal editorial staff from strident letters, some declaring fraud in the Séralini et al. paper, in late fall 2013 the editor-in-chief requested that Séralini retract the paper. As told by Séralini et al.,

> On 19 November, 2013, the editor-in-chief requested the retraction of our study while recognizing that the data were not incorrect and that there was no misconduct and no fraud or intentional misinterpretation in our complete raw data an unusual or even unprecedented action in scientific publishing. The editor argued that no conclusions could be drawn because we studied 10 rats per group over 2 years, because they were Sprague Dawley rats, and because the data were inconclusive on cancer. Yet this was known at the time of submission of our study. Our study was however never intended

> to be a carcinogenicity study. We never used the word 'cancer' in our paper. (2014, 13)

Several months after Séralini refused to retract his paper, an unsigned editorial was published in the journal early in 2014 issuing a retraction notice for the paper. While unsigned, the editorial was presumably authored or approved by the editor-in-chief. The retraction editorial stated that the editor-in-chief requested from the corresponding author the permission to review the raw data. The editor-in-chief commended Séralini for "his commitment to the scientific process." What followed was probably unprecedented in the history of science publishing. First, the editor-in-chief supplied his justification for the retraction.

> Unequivocally, the Editor-in-Chief found no evidence of fraud or intentional misrepresentation of the data. However, there is a legitimate cause for concern regarding both the number of animals in each study group and the particular strain selected. The low number of animals had been identified as a cause for concern during the initial review process, but the peer-review decisions ultimately weighed that the work still had merit despite its limitations. A more in-depth look at the raw data revealed that no definitive conclusions can be reached with this small sample size regarding the role of either NK603 or glyphosate in regards to overall mortality or tumor incidence. Given the known high incidence of tumors in the Sprague-Dawley rats, normal variability cannot be excluded as the cause of the higher mortality and incidence observed in the treated groups. Ultimately, the results presented while not incorrect are inconclusive, and therefore do not reach the threshold of publication for *Food and Chemical Toxicology*. The retraction is only on the inconclusiveness of this one paper. (FCT 2014, 244)

One might ask whether a paper's "lack of definitive results" is a justification for retraction. Some of Séralini's supporters cited the retraction guidelines of the Committee on Publication Ethics (COPE 2009) to answer this question. COPE has four conditions for justifying a retraction. "Journal editors should consider retracting a publication if: (1) they have clear evidence that the findings are unreliable, either as a result of misconduct (e.g. data fabrication) or honest error (e.g. miscalculation or experimental error); (2) the findings have previously been published elsewhere without proper cross referencing, permission or justification (i.e. cases of redundant publication); (3) it constitutes plagiarism; (4) it reports unethical research." There is nothing close to the justification "lack of definitive

results." The International Committee of Medical Journal Editors (ICMJE) is another well-respected journal publication organization that provides guidelines for all journals and requirements for its members on publication ethics. ICMJE links retraction of articles to scientific misconduct, which they consider (but is not necessarily limited to) data fabrication and data falsification including deceptive manipulation of images and plagiarism. They refer to COPE's recommendations on retraction or expressions of concern (ICMJE 2013, 7).

In their response to the retraction, Séralini and his colleagues (2014b) argued that post hoc standards for papers that have found adverse findings of GMOs are far higher than the standards for papers that have found no differences between GMOs and parental plants. Monsanto-funded studies using similar strains and numbers of mice were not retracted because of deficient methods. When a Monsanto study found differences in multiple organ functions between the GM and non-GM feeding groups, they dismissed the differences as not biologically meaningful (Hammond et al. 2004).

A former member of the editorial board of FCT wrote a letter to the editor that was published in the journal. "I feel ashamed about your resent decision to retract Séralini's paper previously accepted for publication after a full review process, which I tend to believe, had been performed seriously as usual for a journal of high quality like FCT. I also feel ashamed because your decision gives support for those who argue and even claim that scientific research (especially in biosciences) is less and less independent and more and more subject to industry pressure. Your decision can be interpreted as a will to eliminate scientific information that does not help support industrial interests is, in my view, unacceptable" (Roberfroid 2014, 390). This raises the question of whether conflict of interest could be a factor in how the GMO health studies are executed and interpreted. In another unusual event, after Séralini's paper was retracted by *Food & Chemical Toxicology*, it was republished by 2014 in *Environmental Sciences Europe* (Séralini et al. 2012).

GMO Conflict of Interest

It has been well established in social science research that in some fields there is a funding effect in science from corporate sponsorship of research. That means that corporate-funded science tends to produce results that are consistent with corporate financial interests. The effect has been found in tobacco research, drug studies, and to a lesser extent in chemical health and

safety studies (Bekelman, Li, and Gross 2003; Bourgeois 2010; Krimsky 2005). I found three papers on conflicts of interest (COIs) and GMOs. The first paper, authored by a group of researchers in Portugal and published in the journal *Food Policy* (Diels et al. 2011), undertook a systematic review of the scientific literature drawing from the *Medline* and *Web of Science* databases starting with 3,626 references on GMOs and winnowing those down to ninety-four articles that meet their criteria. Their main finding was that papers where COIs were identified showed a tendency to produce outcomes favorable to the commercial interests of the stakeholders. They found one of the forty-four papers with a COI was unfavorable toward GMOs while eight of the thirty-five with no COI were unfavorable toward GMOs. This means that without a COI, there was a 23 percent chance of reaching an unfavorable conclusion and with a COI only a 2 percent chance.

The second paper was a published commentary that focused on conflicts of interest of those criticizing Séralini's papers (Séralini et al. 2014). The authors note that a new assistant editor of biotechnology joined the journal *Food and Chemical Toxicology* after Séralini's article was published and that this assistant editor previously worked for Monsanto for seven years. The authors interpret the decision to retract their paper a little over a year after it was appropriately refereed grew out of the role of the new assistant editor who had a conflict of interest as a former employee of Monsanto.

A third paper discussed the conflicts of interest at the European Food Safety Authority (EFSA), a weak counterpart to the US FDA since it issues advisories to members of the European Union. According to its website, "The European Food Safety Authority (EFSA) [an independent European agency funded by the EU budget that operates separately from the European Commission, European Parliament and EU Member States] is the keystone of European Union (EU) risk assessment regarding food and feed safety .... EFSA provides independent scientific advice and clear communication on existing and emerging risks" (EFSA). The agency reviewed the Séralini et al. publication and published the results in the *EFSA Journal* in 2012. EFSA found the study to be "inadequately designed, analysed" and discounted Séralini's response to critics concluding that the study is of "insufficient scientific quality for safety assessments."

Robinson et al. (2013) argued that the EFSA has been rife with conflicts of interest. For example, the chair of EFSA's management board had a longstanding relationship with the industry funded International Life Sciences Institute (ILSI). They claim that in 2010 more than half of the EFSA experts on the GMO panel had financial conflicts of interest. The agency had been cited by the Ombudsman for failing to manage conflicts of interest and

despite changes still has not distanced itself from ILSI and thus does not represent an independent review of Séralini's work. Among the points raised by Robinson et al. is that when differences are found between GMOs and non-GMO counterparts, several authors, including those funded by industry, dismiss the findings as being within the normal range of variation and are not biologically relevant. "An EFSA opinion allows industry to define biological relevance on a case-by-case basis" (Robinson et al. 2013, 2).

Conclusion

I began this article with the testimonials from respected scientists that there is literally no scientific controversy over the health effects of GMOs. My investigation into the scientific literature tells another story. I found twenty-six animal feeding studies that have shown adverse effects or animal health uncertainties (Table 2). The eight review articles were mixed in their assessment of the health effects of GMOs (Table 1). The analysis of how two respected scientists were treated so poorly by the scientific community over their peer-reviewed work raises questions about likely political and ideological influences in the science. I could find no comparable case in the history of science where someone's published and peer-reviewed work was retracted because it was not definitive. Comparable works that found GMOs equivalent to their non-GMO parental strain were not retracted for the same reason since they too were not definitive. It has been argued that the weight of evidence is favorable to the hypothesis that the current family of commercialized GMOs is safe to humans and animals because there is a preponderance of articles establishing that point. In risk assessment, the number of studies that reveal a risk can be more significant than a larger number of studies that do not. Imagine a hundred flights to test a new aircraft. Ninety-five prove safe. Five flights produce electrical problems, failed landing gear, and a wing collapse. Does one just negate the five flights and go with the weight of evidence? Those five flights are very significant, perhaps because the aircraft was pushed beyond standard flight operations but within its design limits.

When there is a controversy about the risk of a consumer product, instead of denying the existence of certain studies, the negative results should be replicated to see if they hold up to rigorous testing. This point was made by the 300 scientists who signed a joint statement that was published in *Environmental Sciences Europe*. The statement "does not assert that GMOs are unsafe or safe. Rather the statement concludes that the scarcity and

contradictory nature of the scientific evidence published to date prevents conclusive claims of safety, or lack of safety, of GMOs'' (Hilbeck et al. 2015, 1). David Schubert, professor at the Salk Institute, summarized the state of affairs of the GMO controversy as follows: ''To me, the only reasonable solution is to require that all GM plant products be tested for long-term toxicity and carcinogenicity before being brought to market'' (2002, 969). Until the twenty-six studies, or at least the best of them, are replicated and shown to be false positives, we have an obligation to treat these studies with respect and concern. My results have broad implications for the study of scientific and medical controversies, whether climate change, endocrine disruptors, statins, or mercury preservatives in vaccines. STS scholarship is best accomplished when it approaches a controversial issue systemically and includes a deep analysis of the primary science, a review of the function of professional societies, an analysis of the peer review process of journals, a study of the political climate and its impact on science and on federal regulatory agencies which set policy, the media's role in shaping public understanding or misunderstanding, and the role that financial interests play in scientific risk analysis. All of these factors are brought into play in the GMO debate, about which I have argued that the putative consensus about the inherent safety of transgenic crops is premature.

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References

AAEM (American Academy of Environmental Medicine). 2009. ''Position Statement on GMOs.'' May 8. Accessed July 19, 2014. http://www.aaemonline.org/gmopost.html.

Achenbach, J. 2015. ''Why Do Many Reasonable People Doubt Science?'' *National Geographic* 14 (5). Accessed March 2, 2015. http://ngm.nationalgeographic.com/2015/03/science-doubters/achenbach-text.

American Medical Association, Action of the House of Delegates. 2012. ''Annual Meeting: Council on Science and Public Health Report 2.'' CSAPH Report 2-A-12. Accessed July 21, 2015. http://www.ama-assn.org/ama/pub/about-

ama/our-people/ama-councils/council-science-public-health/reports/2012-reports.page. https://download.ama-assn.org/resources/doc/csaph/x-pub/a12-csaph2-bioengineeredfoods.pdf.

Antoniou, M., C. Robinson, and J. Fagan. 2012. *GMO Myths and Truths: An Evidence-based Examination of the Claims Made for the Safety and Efficacy of Genetically Modified Crops*. London, UK: Earth Open Source. Accessed February 20, 2015. http://earthopensource.org/wordpress/downloads/GMO-Myths-and-Truths-edition2.pdf.

Bawa, A. S., and K. R. Anilakumar. 2013. "Genetically Modified Foods: Safety, Risks and Public Concerns A Review." *Journal of Food Science & Technology* 50 (6): 1035-46.

Bekelman, J. E., Y. Li, and C. P. Gross. 2003. "Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A Systematic Review." *Journal of the American Medical Association* 289 (4): 454-65. (January 22-29, 2003).

BMA (British Medical Association). 1999. "Press Releases Archive." May 18, 1999. Accessed July 17, 2014. http://web2.bma.org.uk/pressrel.nsf/wall/1E731484333E2965802568F5005430C6?OpenDocument.

BMA (British Medical Association). 2003. "Press Release Archive." January 14, 2003. Accessed July 17, 2014. http://web2.bma.org.uk/pressrel.nsf/wall/F1DCEF13942969B980256CAE00599823?OpenDocument.

BMA (British Medical Association, Board of Science and Education). 2004. *Genetically Modified Foods and Health: A Second Interim Statement*. London, UK: British Medical Association. Accessed July 5, 2015. http://www.argenbio.org/adc/uploads/pdf/bma.pdf.

Borel, B. 2014. "Core Truths: 10 Common GMO Claims Debunked." *Popular Science* 285 (1): 57. Accessed July 15, 2014. http://www.popsci.com/article/science/core-truths-10-common-gmo-claims-debunked.

Borlaug, N. 2014. Accessed February 17, 2015. http://articles.economictimes.indiatimes.com/2014-08-06/news/52514586 1 gm-crops-gm-foods-bt-cotton.

Bourgeois, F. 2010. "Drug Trials Funded by Industry Are More Likely to Publish Favorable Results." *Annals of Internal Medicine* 153 (3): 158-66.

Brundtland, G. H. 2002. Accessed February 17, 2015. http://www.afro.who.int/en/media-centre/pressreleases/item/457-who-director-general-speaks-on-gm-foods.html.

Campbell, P. M., D. Reiner, A. E. Moore, R.-Y. Lee, M. M. Epstein, and T. J. V. Higgins. 2011. "Comparison of the Alpha-amylase Inhibitor-1 from Common Bean (*Phaseolus vulgaris*) Varieties and Transgenic Expression in Other Legumes-post-translational Modifications and Immunogenicity." *Journal of Agriculture Food Chemistry* 59 (11): 6047-54.

COPE (Committee on Publication Ethics). Accessed January 16, 2015. http://publicationethics.org/files/retraction%20guidelines.pdf.

CRIIGEN (Committee of Research and Independent Information on Genetic Engineering). Legal status. Revised July 7, 2008. Accessed July 30, 2015. http://www.criigen.org/user/pdf/CRIIGEN statuts.pdf.

de Vendômois, J. Spiroux, D. Cellier, C. Vélot, Emilie Clair, Robin Mesnage, and Gilles-Eric Séralini. 2010. "Debate on GMOs Health Risks after Statistical Findings in Regulatory Tests." *International Journal of Biological Sciences* 6 (6): 590-98.

Diels, J., M. Cunha, C. Manaia, B. Sabugosa-Madeira, and M. Silva. 2011. "Association of Financial or Professional Conflict of Interest to Research Outcomes on Health Risks or Nutritional Assessment Studies of Genetically Modified Crops." *Food Policy* 36 (2): 197-203.

Diouf, J. 2002. Accessed February 17, 2015. http://www.eufic.org/article/en/food-technology/gmos/artid/gmos-debate/.

Domingo, J. L., and J. G. Bordonaba. 2011. "A Literature Review on the Safety Assessment of Genetically Modified Plants." *Environment International* 37 (4): 734-42.

Dona, A., and I. S. Arvanitouannis. 2009. "Health Risks of Genetically Modified Foods." *Critical Reviews in Food Science and Nutrition* 49 (2): 164-75.

Druker, Steven. 2015. *Altered Genes, Twisted Truth*. Fairfield, IA: Clear River Press.

EFSA (European Food and Safety Authority). 2012. "Final Review of the Séralini et al. (2012) Publication on a 2-year Rodent Feeding Study with Glyphosate Formulations and GM Maize NK603 First Published Online on September 19, 2012 in Food and Chemical Toxicology." *EFSA Journal* 10 (11): 2986-96.

EFSA (European Food Safety Authority). 2014. "Scientific Opinion on Application (EFSA-GMO-UK-2009-76) for the Placing on the Market of Soybean MON 87769." *EFSA Journal* 12 (5): 3644-85.

Ewen, S. W. B., and A. Pusztai. 1999a. "Effects of Diets Containing Genetically Modified Potatoes Expressing *Galanthus nivalis* Lectin on Rat Small Intestine." *The Lancet* 354 (9187): 1353-54.

Ewen, S. W. B., and A. Pusztai. 1999b. "GM Food Debate: Reply." *The Lancet* 354 (9191): 1726-27.

FCT (Food & Chemical Toxicology, Editor-in-chief). 2014. "Retraction Notice to: Long Term Toxicity of a Roundup Herbicide and a Roundup-tolerant Genetically Modified Maize." *Food & Chemical Toxicology* 63:244.

Flynn, L., and M. S. Gillard. 1999. "Pro-GM Scientist 'Threatened Editor.'" *The Guardian*, October 31. Accessed July 22, 2015. http://www.theguardian.com/science/1999/nov/01/gm.food.

Hammond, B., R. Dudek, J. Lemen, and M. Nemeth. 2004. "Results of a 13 Week Safety Assurance Study with Rats Fed Grain from Glyphosate Tolerant Corn." *Food & Chemical Toxicology* 42 (6): 1003-14.

Hilbeck, A., R. Binmelis, N. Defarge, Ricarda Steinbrecher, András Székács, Fern Wickson, Michael Antoniou, Philip L. Bereano, Ethel Ann Clark, Michael Hansen, Eva Novotny, Jack Heinemann, Hartmut Meyer, Vandana Shiva, and Brian Wynne. 2015. "No Scientific Consensus on GMO Safety." *Environmental Sciences Europe* 27 (4): 1-6.

Hilgartner, Stephen. 2000. *Science on Stage: Expert Advice as Public Drama*. Stanford, CA: Stanford University Press.

ICMJE (International Committee of Medical Journal Editors). 2013. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. 1-17, 7. Accessed January 17, 2015. http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/scientific-misconduct-expressions-of-concern-and-retraction.html.

Krimsky, S. 2005. "The Funding Effect in Science and Its Implications for the Judiciary." *Journal of Law & Public Policy* 13 (3): 43-68.

Lachman, P. 1999. "Letter. Health Risks of Genetically Modified Foods." *The Lancet* 354 (9172): 69.

Lee, R., D. Reiner, G. Dekan, A. E. Moore, T. J. Higgins, and M. M. Epstein. 2013. "Genetically Modified α-amylase Inhibitor Peas Are Not Specifically Allergenic in Mice." *Plos One* 8 (1): 1-9.

Magana-Gomez, J. A., and A. M. Calderon de la Barca. 2008. "Risk Assessment of Genetically Modified Crops for Nutrition and Health." *Nutrition Reviews* 67 (1): 1-16.

Maghari, B. M., and A. M. Ardekani. 2011. "Genetically Modified Foods and Social Concerns." *Avicenna Journal of Medical Biotechnology* 3 (3): 109-17.

National Academy of Sciences. 2004. *The Safety of Genetically Engineered Foods: Approaches to Assessing Unintended Health Effects*. Washington, DC: National Academies Press.

Newman, Stuart. 2009. "Genetically Modified Foods and the Attack on Nature." *Capitalism Nature Socialism* 20 (2): 22-31.

Newman, Stuart. 2013. "The State of the Science." *GeneWatch* 26 (1): 24-25.

Nicolia, A., A. Manzo, F. Veronesi, and D. Roselini. 2014. "An Overview of the Last 10 Years of Genetically Engineered Crop Safety Research." *Critical Reviews in Biotechnology* 34 (1): 77-88.

Nordlee, J. A., S. L. Taylor, J. A. Townsend, L. A. Thomas, and R. K. Bush. 1996. "Identification of a Brazil-nut Allergen in Transgenic Soybeans." *The New England Journal of Medicine* 334 (11): 688-92.

Pryme, I. F., and R. Lembcke. 2003. "In Vivo Studies on Possible Health Consequences of Genetically Modified Food and Feed with Particular Regard to Ingredients Consisting of Genetically Modified Plant Materials." *Nutritional and Health* 17 (1): 1-8.

Pusztai, A. 1999. "A Talk to the British Hungarian Fellowship, South Kensington, UK." May 7. Accessed February 20, 2015. www.i-sis.org.uk/arpad.php.

Pusztai, A., G. G. Bardocz, R. Alonso, M. J. Chrispeels, H. E. Schroeder, L. M. Tabe, and T. J. Higgins. 1999. "Expression of the Insecticidal Bean a-amylase Inhibitor Transgene Has Minimal Detrimental Effect on the Nutritional Value of Peas Fed to Rats at 30% of the Diet." *Journal of Nutrition* 129 (8): 1597-603.

Pusztai, A. 2002a. "GM Food Safety: Scientific and Institutional Issues." *Science as Culture* 11 (1): 69-92.

Pusztai, A. 2002b. "Can Science Give Us the Tools for Recognizing Possible Health Risks of GM Food?" *Nutrition and Health* 16 (2): 73-84.

Pusztai, A., and S. Bardocz, eds. 1995. *Lectins: Biomedical Perspectives*. London, UK: Taylor & Francis.

Randerson, J. 2008. "Arpad Pusztai: Biological Divide." *The Guardian*. January 15. Accessed March 2, 2015. http://www.theguardian.com/education/2008/jan/15/academicexperts.highereducationprofile.

Roberfroid, M. 2014. "Letter to the Editor." *Food & Chemical Toxicology* 65 (3): 390.

Roberts, R. 2004. "GMOs Are a Key to Addressing Global Hunger." *Boston Globe*, May 23, 2004. Accessed July 22, 2015. https://www.bostonglobe.com/opinion/2014/05/23/gmos-are-key-tool-addressing-global-hunger/SPlNunvL15WjovCpXvsihJ/story.html.

Robinson, C., N. Holland, D. Leioup, and H. Muilerman. 2013. "Conflicts of Interest at the European Food Safety Authority Erode Public Confidence." *Journal of Epidemiology & Community Health* 67 (9): 717-20.

RSC (Royal Society of Canada). 2001. *Elements of Precaution: Recommendations for the Regulation of Food Biotechnology in Canada*. January 2001. Accessed June 6, 2015. https://rsc-src.ca/sites/default/files/pdf/GMreportEN.pdf.

Schubert, D. 2002. "A Different Perspective on GM Food." *Nature Biotechnology* 20 (10): 969.

Séralini, G.-E., E. Clair, R. Mesnage, Steeve Gress, Nicolas Defarge, Manuela Malatesta, Didier Hennequin, and Joël Spiroux de Vendômois. 2012. "Long Term Toxicity of a Roundup Herbicide and a Roundup-tolerant Genetically Modified Maize." *Food and Chemical Toxicology* 50 (11): 4221-31 (retracted 2014). Republished in *Environmental Sciences Europe* 26 (14): 1-17 (2014).

Séralini, G.-E., R. Mesnage, N. Defarge, Steeve Gress, Didier Hennequin, Emilie Clair, Manuela Malatesta, and Joël Spiroux de Vendômois. 2013. "Answers to Critics: Why There Is a Long Term Toxicity Due to a Roundup-tolerant Genetically Modified Maize and to a Roundup Herbicide." *Food & Chemical Toxicology* 53 (3): 476-83.

Séralini, G.-E., R. Mesnage, N. Defarge, and J. Spiroux de Vendômois. 2014. ''Conflicts of Interests, Confidentiality and Censorship in Health Risk Assessment: The Example of an Herbicide and GMO.'' *Environmental Sciences Europe* 26 (13): 1-6.

Séralini, G.-E., R. Mesnage, and N. Defarge. 2014. ''Conclusiveness of Toxicity Data and Double Standards.'' *Food & Chemical Toxicology* 69 (7):357-59.

Séralini, G.-E., J. Spiroux de Vendômois, D. Cellier, Charles Sultan, Marcello Buiatti, Lou Gallagher, Michael Antoniou, and Krishna R. Dronamraju. 2009. ''How Subchronic and Chronic Health Effects Can Be Neglected for GMOs, Pesticides or Chemicals.'' *International Journal of Biological Sciences* 5 (5): 438-43.

Snell, C., A. Bernheim, J. B. Berge, M. Kuntz, G. Pascal, A. Paris, and A. E. Ricroch. 2012. ''Assessment of the Health Impact of GM Plant Diets in Long-term and Multigenerational Animal Feeding Trials: A Literature Review.'' *Food & Chemical Toxicology* 50 (3-4): 1134-48.

Society of Toxicology, Ad Hoc Working Group. 2003. ''Society of Toxicology Position Paper: The Safety of Genetically Modified Foods Produced through Biotechnology.'' *Toxicological Sciences* 71 (1): 2-8.

Stogar, E., S. Williams, P. Christou, R. E. Down, and J. A. Gatehouse. 1999. ''Expression of the Insecticidal Lectin from Snowdrop (*Galanthus nivalis* Agglutinin; (GNA) in Transgenic Wheat Plants: Effects on Predation by the Grain Aphid *Sitobion avenae*.'' *Molecular Breeding* 5 (1): 65-73.

van Damme, E. J. M., W. J. Permans, A. Pusztai, and S. Bardocz. 1998. *Handbook of Plant Lectins: Properties and Biomedical Applications*. New York: John Wiley.

Ward, J. J., J. S. Sodhi, L. J. McGriffin, B. F. Buxton, and D. T. Jones. 2004. ''Prediction and Functional Analysis of Native Disorder in Proteins from Three Kingdoms of Life.'' *Journal of Molecular Biology* 337 (3): 635-45.

Wilson, Margaret, and Roger Highfield. 2002. ''Starving Zambia rejects America's GM maize.'' The Daily Telegraph (London), October 30. Accessed July 30, 2015. http://www.panapress.com/WHO-Director-General-clears-air-on-genetically-modified-food 13-461942-18-lang2-index.html.

Zhang, W., and F. Shi. 2011. ''Do Genetically Modified Crops Affect Animal Reproduction? A Review of the Ongoing Debates.'' *Animal* 5 (7): 1048-59.

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From: Kathy Burns <kmb@sciencecorps.org>
Sent: Wednesday, August 19, 2015 10:08 PM
To: Huff, James (NIH/NIEHS) [G]; 'Po Chan'; 'joe ladou'; 'jennifer sass [NRDC]'; 'peter infante'; 'barry castleman'; Ron Melnick; olden.kenneth@epa.gov
Cc: Phil Landrigan; 'John Vandenberg'; McCarthy. gina@Epa. gov; 'Dorothy Wigmore'
Subject: GMOs, Herbicides, and Public Health - Landrigan & Benbrook - YES!

Regarding Huff's message below -
Charles Benbrook (Landrigan' s co-author on the recent pesticide article) worked on pesticides in Congress in the 1980s and was the author of the "Benbrook Report", a three volume series on the Congressional exposing the concealment of toxicity data and other violations of public trust by EPA and pesticide manufacturers.

The toxicology data that the industry was required to submit, including information on the ability of many pesticides to cause birth defects and many other serious health effects, was kept secret by EPA. Litigation caused it to be released (thanks to NRDC and others) in the early 1980s. Benbrook and a terrific California Senator helped me obtain the data. We summarized it in a book called Pesticides and Human Health (Springer-Verlag Press) and hoped it would result in health protective policies.

Benbrook was treated badly in Washington and ultimately went elsewhere, still fighting the good fight. Our book largely fell on deaf ears in the US, though it was used extensively in Europe. The pesticide office at EPA continued on its merry way, covering up the majority of damning evidence on hazardous pesticides and ignoring most birth defects using various excuses. Good people within EPA tried to leverage change, using evaluations carried out by other offices (e.g., the policy office) to force changes, but they were largely unsuccessful.

I'm incredibly grateful that Benbrook is still fighting on this front. It is very discouraging work. But since most of us are exposed to pesticides in our food and many people deal with them every day in their water and air, it's worth whatever we can put into this work.

GMO is just the latest twist on a long legacy hazards. Meanwhile, OPP tries to assure us that the re-introduction of arsenic as a pesticide and the use of chlorpyrifos and other health hazards are safe "when use as directed". Their actions have had tragic consequences. We should support any and all efforts to have full and honest science made available to the public and those tasked with protecting them.

Obviously a sea change at OPP is an essential first step. I hope that ORD, the only part of EPA with the scientific credentials to tackle this, will take on this very long-standing problem. The truth is that we have sufficient evidence on arsenic and many other pesticides to prevent them from harming more people. What we lack is an agency with the will to act on what is and has been known for many years. We need to support them in efforts to tackle this problem.

The ball is in their court. After so many decades of agricultural workers becoming sick and dying far too early and children unnecessarily doomed to lives less than fully realized, I hope that EPA will choose the difficult but honorable path.

Regards,
Kathleen Burns, Ph.D.

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Subject: GMOs, Herbicides, and Public Health -- P.J. Landrigan and C. Benbrook | N Engl J Med --

FYI - sent this note to John Bucher and Linda Birnbaum.
Po — wonder if back then you recommended a long term carcinogenesis study? I remember in late 1980s you and I worked hard to propose a long-term study on Arsenic Trioxide but was out voted by NTP.
Best, james

From: James Huff <huff1@niehs.nih.gov>
Date: Wednesday, August 19, 2015 at 8:48 PM
To: john bucher <bucher@niehs.nih.gov>, "Birnbaum, Linda (NIH/NIEHS) [E]" <birnbaumls@niehs.nih.gov>
Subject: GMOs, Herbicides, and Public Health -- P.J. Landrigan and C. Benbrook | N Engl J Med --

Hi
Just came out today. U must have seen it earlier. Re comments below re what NTP 'should' do, might be good idea to write letter to NEJM stating what NTP has, is, and will/not do re Glyphosate. I recall Po Chan/Joel Mahler did a toxicology study back in 1992** [attached]. Over the years I urged [unsuccessfully] that NTP Tox Study Reports mention/explain what NTP is doing or plans to do on the same chemical in these Tox Reports. I don't recall/know whether NTP has or is doing anything further. Nothing additional appears to be done or planned, according to http://ntp.niehs.nih.gov/testing/status/agents/ts-m88067.html. Just think if NTP had done an in utero/+30 month carcinogenesis exposure study after the 90-day that would have been done and reported in later 1990s.
j

GMOs, Herbicides, and Public Health
P.J. Landrigan and C. Benbrook | N Engl J Med 2015;373:693-695

"First, we believe the EPA should delay implementation of its decision to permit use of Enlist Duo. This decision was made in haste. Second, the National Toxicology Program should urgently assess the toxicology of pure glyphosate, formulated glyphosate, and mixtures of glyphosate and other herbicides."
https://www.nejm.org/action/doSecureKeyLogin?uuid=6418306&dateTime=201508290000&key=mg2gckWqf7ESM2n%2Bxz2z23SpPO7pbPCyQvoFGYtQAuM%3D&uri=/doi/full/10.1056/NEJMp1505660?query=TOC

**Toxic Rep Ser. 1992 Jul;16:1-D3. NTP technical report on the toxicity studies of Glyphosate (CAS No. 1071-83-6) Administered In Dosed Feed To F344/N Rats And B6C3F1 Mice. Chan P, Mahler J.
http://www.ncbi.nlm.nih.gov/pubmed/12209170

have not been verified as such. One bioinformaticist's "driver mutation" is another's "passenger mutation." Basket studies are a good way of deriving preliminary information on mutations that are potentially responsive in humans to a specific drug — but to design such studies for every potential target mutation, for all possible drugs, in all possible anatomical sites, will be beyond the capacity of our current investigator- and company-initiated system of trials. Plans are under way for larger phase 2 studies such as the National Cancer Institute's Molecular Analysis for Therapy (NCI MATCH) II study, which will enroll about 1000 patients in about 20 mutation-specific groups, but even a larger effort like that one will capture only a small fraction of the targeted therapies being used off-label on the basis of tumor-sequencing data.

Thus, the basket trials are a useful first step in what should be a multistep process. The next step, where feasible, could be larger anatomical-site–specific phase 3 trials comparing the drug–mutation combination with the standard of care. In addition, given the sample-size, logistic, and financial constraints that make phase 3 studies difficult for less-common cancers and less-common mutations, establishment of registries of off-label use would be extremely helpful. Aggregated observational data will always be superior to "n of 1" anecdotes or small series. Precedents exist, including the "phase 4" postmarketing surveillance studies that the FDA has mandated in order to gather evidence regarding both possible differences in efficacy for various subgroups and long-term toxicity. Some cancer centers and professional societies are collaborating to develop regional databases. It is critical that results from these databases become as transparent as those from clinical trials — proprietary databases will lead to competing but unverifiable claims. Developing such observational databases is far from trivial, but the costs per patient would be small in relation to the monthly costs of many of the targeted therapies. Perhaps the plural of anecdote could be data after all.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Harvard T.H. Chan School of Public Health (D.J.H.) and Boston University (R.B.D.) — both in Boston.

1. Collins FS, Hamburg MA. First FDA authorization for next-generation sequencer. N Engl J Med 2013;369:2369-71.
2. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003;348:994-1004.
3. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507-16.
4. Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med 2012;366:883-92.
5. Menis J, Hasan B, Besse B. New clinical research strategies in thoracic oncology: clinical trial design, adaptive, basket and umbrella trials, new end-points and new evaluations of response. Eur Respir Rev 2014;23:367-78.

DOI: 10.1056/NEJMp1508144

GMOs, Herbicides, and Public Health

Philip J. Landrigan, M.D., and Charles Benbrook, Ph.D.

Genetically modified organisms (GMOs) are not high on most physicians' worry lists. If we think at all about biotechnology, most of us probably focus on direct threats to human health, such as prospects for converting pathogens to biologic weapons or the implications of new technologies for editing the human germline. But while those debates simmer, the application of biotechnology to agriculture has been rapid and aggressive. The vast majority of the corn and soybeans grown in the United States are now genetically engineered. Foods produced from GM crops have become ubiquitous. And unlike regulatory bodies in 64 other countries, the Food and Drug Administration (FDA) does not require labeling of GM foods.

Two recent developments are dramatically changing the GMO landscape. First, there have been sharp increases in the amounts and numbers of chemical herbicides applied to GM crops, and still further increases — the largest in a generation — are scheduled to occur in the next few years. Second, the International Agency for Research on Cancer (IARC) has classified glyphosate, the herbicide most widely used on GM crops, as a "probable human carcinogen"[1] and classified a second herbicide, 2,4-dichlorophenoxyacetic acid (2,4-D), as a "possible human carcinogen."[2]

The application of genetic engineering to agriculture builds

on the ancient practice of selective breeding. But unlike traditional selective breeding, genetic engineering vastly expands the range of traits that can be moved into plants and enables breeders to import DNA from virtually anywhere in the biosphere. Depending on the traits selected, genetically engineered crops can increase yields, thrive when irrigated with salty water, or produce fruits and vegetables resistant to mold and rot.

The National Academy of Sciences has twice reviewed the safety of GM crops — in 2000 and 2004.[3] Those reviews, which focused almost entirely on the genetic aspects of biotechnology, concluded that GM crops pose no unique hazards to human health. They noted that genetic transformation has the potential to produce unanticipated allergens or toxins and might alter the nutritional quality of food. Both reports recommended development of new risk-assessment tools and postmarketing surveillance. Those recommendations have largely gone unheeded.

Herbicide resistance is the main characteristic that the biotechnology industry has chosen to introduce into plants. Corn and soybeans with genetically engineered tolerance to glyphosate (Roundup) were first introduced in the mid-1990s. These "Roundup-Ready" crops now account for more than 90% of the corn and soybeans planted in the United States.[4] Their advantage, especially in the first years after introduction, is that they greatly simplify weed management. Farmers can spray herbicide both before and during the growing season, leaving their crops unharmed.

But widespread adoption of herbicide-resistant crops has led to overreliance on herbicides and, in particular, on glyphosate.[5] In the United States, glyphosate use has increased by a factor of more than 250 — from 0.4 million kg in 1974 to 113 million kg in 2014. Global use has increased by a factor of more than 10. Not surprisingly, glyphosate-resistant weeds have emerged and are found today on nearly 100 million acres in 36 states. Fields must be now be treated with multiple herbicides, including 2,4-D, a component of the Agent Orange defoliant used in the Vietnam War.

The first of the two developments that raise fresh concerns about the safety of GM crops is a 2014 decision by the Environmental Protection Agency (EPA) to approve Enlist Duo, a new combination herbicide comprising glyphosate plus 2,4-D. Enlist Duo was formulated to combat herbicide resistance. It will be marketed in tandem with newly approved seeds genetically engineered to resist glyphosate, 2,4-D, and multiple other herbicides. The EPA anticipates that a 3-to-7-fold increase in 2,4-D use will result.

In our view, the science and the risk assessment supporting the Enlist Duo decision are flawed. The science consisted solely of toxicologic studies commissioned by the herbicide manufacturers in the 1980s and 1990s and never published, not an uncommon practice in U.S. pesticide regulation. These studies predated current knowledge of low-dose, endocrine-mediated, and epigenetic effects and were not designed to detect them. The risk assessment gave little consideration to potential health effects in infants and children, thus contravening federal pesticide law. It failed to consider ecologic impact, such as effects on the monarch butterfly and other pollinators. It considered only pure glyphosate, despite studies showing that formulated glyphosate that contains surfactants and adjuvants is more toxic than the pure compound.

The second new development is the determination by the IARC in 2015 that glyphosate is a "probable human carcinogen"[1] and 2,4-D a "possible human carcinogen."[2] These classifications were based on comprehensive assessments of the toxicologic and epidemiologic literature that linked both herbicides to dose-related increases in malignant tumors at multiple anatomical sites in animals and linked glyphosate to an increased incidence of non-Hodgkin's lymphoma in humans.

These developments suggest that GM foods and the herbicides applied to them may pose hazards to human health that were not examined in previous assessments. We believe that the time has therefore come to thoroughly reconsider all aspects of the safety of plant biotechnology. The National Academy of Sciences has convened a new committee to reassess the social, economic, environmental, and human health effects of GM crops. This development is welcome, but the committee's report is not expected until at least 2016.

In the meantime, we offer two recommendations. First, we believe the EPA should delay implementation of its decision to permit use of Enlist Duo. This decision was made in haste. It was based on poorly designed and outdated studies and on an incomplete assessment of human exposure and environmental effects. It would have benefited from deeper consideration of independently funded studies published in the peer-reviewed literature.

And it preceded the recent IARC determinations on glyphosate and 2,4-D. Second, the National Toxicology Program should urgently assess the toxicology of pure glyphosate, formulated glyphosate, and mixtures of glyphosate and other herbicides.

Finally, we believe the time has come to revisit the United States' reluctance to label GM foods. Labeling will deliver multiple benefits. It is essential for tracking emergence of novel food allergies and assessing effects of chemical herbicides applied to GM crops. It would respect the wishes of a growing number of consumers who insist they have a right to know what foods they are buying and how they were produced. And the argument that there is nothing new about genetic rearrangement misses the point that GM crops are now the agricultural products most heavily treated with herbicides and that two of these herbicides may pose risks of cancer. We hope, in light of this new information, that the FDA will reconsider labeling of GM foods and couple it with adequately funded, long-term postmarketing surveillance.

An audio interview with Dr. Landrigan is available at NEJM.org

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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1. Guyton KZ, Loomis D, Grosse Y, et al. Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. Lancet Oncol 2015;16:490-1.
2. Loomis D, Guyton K, Grosse Y, et al. Carcinogenicity of lindane, DDT, and 2,4-dichlorophenoxyacetic acid. Lancet Oncol 2015 June 22 (Epub ahead of print).
3. National Research Council, Committee on Identifying and Assessing Unintended Effects of Genetically Engineered Foods on Human Health. Safety of genetically engineered foods: approaches to assessing unintended health effects. Washington, DC: National Academies Press, 2004.
4. Adoption of genetically engineered crops in the U.S. Washington, DC: Department of Agriculture, Economic Research Service (http://www.ers.usda.gov/data-products/adoption-of-genetically-engineered-crops-in-the-us.aspx).
5. Duke SO. Perspectives on transgenic, herbicide-resistant crops in the United States almost 20 years after introduction. Pest Manag Sci 2015;71:652-7.

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National Toxicology Program
Toxicity Reports Series
Number 16

NTP Technical Report on Toxicity Studies of

Glyphosate

(CAS No. 1071-83-6)

Administered in Dosed Feed to F344/N Rats and B6C3F$_1$ Mice

Po C. Chan, PhD, and Joel F. Mahler, DVM,
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NIH Publication 92-3135
July 1992

United States Department of Health and Human Services
Public Health Service
National Institutes of Health

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The NTP report on the toxicity studies of glyphosate is based on disposition studies conducted at the College of Pharmacy, University of Arizona, Tucson, AZ, in November, 1987; 13-week studies performed between May and September, 1988, at Southern Research Institute, Birmingham, AL; and 14-day studies performed in 1990 at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

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Evaluated experiment, interpreted results, and reported findings

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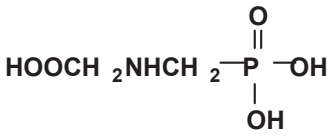
Glyphosate



Molecular Formula: $C_3H_8NO_5P$

CAS Number: 1071-83-6

Molecular Weight: 169.1

Synonyms: Glyphosate, technical grade; Glycine, N-(phosphonomethyl); N-phosphonomethyl glycine; N-(phosphonomethyl)glycine; MON 0573; MON 2139.

ABSTRACT

Glyphosate is a systemic, broad-spectrum, post-emergence herbicide used for non-selective weed control. It was selected for study because of its widespread use, potential for human exposure, and the lack of published reports concerning comprehensive toxicity or carcinogenicity evaluations.

Chemical disposition, 13-week toxicity, and mutagenicity studies of glyphosate were conducted. In disposition studies, male F344/N rats were administered an oral dose (5.6 or 56 mg/kg) of ^{14}C-glyphosate. Blood, urine, fecal, and tissue samples were collected and analyzed for radioactivity. Within 72 hours after glyphosate dosing, 20-30% of the administered radioactivity was eliminated via urine, 70-80% via feces, and about 1% of the radioactivity remained in the tissues. Studies following oral, intravenous, and intraperitoneal administration of glyphosate indicated that the urinary radioactivity represented the amount of glyphosate absorbed and that the fecal radioactivity represented the amount unabsorbed from the gastrointestinal tract.

In the 13-week toxicity studies, groups of 10 male and female F344/N rats and B6C3F$_1$ mice were administered glyphosate in feed at 0, 3125, 6250, 12500, 25000, or 50000 ppm. Glyphosate administration induced increases in serum bile acids, alkaline phosphatase, and alanine aminotransferase activities in rats, suggesting mild toxicity to the hepatobiliary system. Clinical pathology measurements were not performed with mice. No histopathologic lesions were observed in the livers of rats or mice. There was no evidence of adverse effects on the reproductive system of rats or mice. Cytoplasmic alteration was observed in the parotid and submandibular salivary glands of rats and parotid salivary glands in mice. The salivary gland effects of glyphosate were demonstrated to be mediated through an adrenergic mechanism which could be blocked by the adrenergic antagonist, propanolol.

Glyphosate was not mutagenic in *Salmonella*, and did not induce micronuclei in mice. The no-observed-adverse-effect level (NOAEL) for the salivary gland lesions was 3125 ppm in the diet for mice. A NOAEL could not be determined from the rat study.

PEER REVIEW

Peer Review Panel

The members of the Peer Review Panel who evaluated the draft report on the toxicity studies on glyphosate on July 10, 1991, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, panel members act to determine that the design and conditions of the NTP studies were appropriate and to ensure that the toxicity study report presents the experimental results and conclusions fully and clearly.

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Summary of Peer Review Comments

On July 9 and 10, 1991, the Technical Reports Review Subcommittee of the Board of Scientific Counselors for the National Toxicology Program met in Research Triangle Park, NC, to review the draft technical report on toxicity studies of glyphosate.

Dr. Po Chan, NIEHS, introduced the short-term toxicity studies of glyphosate by reviewing the uses and rationale for the study, findings from chemical disposition studies, experimental design, and results.

Dr. Garman, a principal reviewer, said that the report was thoroughly prepared and detailed, and that it did an excellent job reviewing the background for the study and the available literature on glyphosate. He added that the isoproterenol/propranolol study included in the report is quite interesting and helps establish the mechanism for salivary gland alteration.

Dr. Garman said that certain details of the salivary gland alteration study should be clarified, namely, which type of glandular acinus within the submandibular salivary gland was most affected by glyphosate, and whether, in Table 11, only the parotid salivary gland was assayed in measuring the severity of changes brought on by glyphosate treatment. Dr. J. Mahler, NIEHS, said the severity grades were based on the parotid glands only.

Dr. Goodman, another principal reviewer, said the report was well-written. He suggested that the the lack of of any reproductive toxicity attributable to glyphosate treatment was an important finding and should be included in the abstract of the report.

After further discussion of editorial matters, Dr. Longnecker accepted the report on behalf of the panel.

INTRODUCTION

Glyphosate is a nonvolatile white solid with a melting point of 200°C and a negligible vapor pressure. It is soluble to 1.2% in water at 25°C but is not soluble in organic solvents (Beste, 1983). Glyphosate has been available commercially since 1974. It is marketed as Roundup® (comprised of the isopropylamine salt of glyphosate (41.0%) and inert ingredients, including surfactants), and as Rodeo® (which contains the isopropylamine salt of glyphosate (53.5%) and inert ingredients). The surfactant in Roundup® facilitates foliage absorption. Roundup® is used as a nonselective, systemic, broad-spectrum, post-emergence herbicide for managing vegetation in agriculture and forestry; Rodeo® is used for aquatic weed control. Information on production volume, sales, and the identity of the "inert ingredients" is proprietary.

The mechanism of phytotoxic action of glyphosate is inhibition of the 5-enolpyruvylshikimate-3-phosphate synthase (EC 2.5.1.19) activity, thus blocking aromatic amino acid synthesis (Amrhein *et al.*, 1980, 1981). The resulting reduction in protein synthesis causes cessation of growth and, eventually, cellular disruption and death. Glyphosate has nonspecific, metal-chelating properties (Glass, 1984); it inhibits enzymes which require transitional metal cations for activity such as the 3-deoxy-2-oxo-D-arabino-heptulosonate-7-phosphate synthase and 5-dehydroquinate synthase (Ghassemi *et al.*, 1982; Hoagland and Duke, 1982). Glyphosate's effectiveness as a phytotoxin is due in part to its low molecular weight and high water solubility, which aid its rapid absorption and translocation by plant tissues; it is not metabolized to any significant degree in plant tissues (Ghassemi *et al.*, 1982).

Glyphosate is strongly adsorbed to soils and is not readily leached. The mobility of glyphosate in the soil is affected by soil type, phosphate level, and pH. Adsorption of glyphosate is higher in soils containing clay and organic matter than in sandy loam soils, but lower in high-phosphate or high-pH soils. It is susceptible to degradation, possibly by microbial co-metabolism (Sprankle *et al.*, 1975), and thus relatively nonpersistent in soils. Information provided by Monsanto to the U.S. Environmental Protection Agency reportedly showed the half-life of glyphosate in soil normally was less than 60 days (U.S. EPA, 1979). The half-life was 17 to 19 weeks in sandy soil and 3 weeks in silt loam (Ghassemi *et al.*, 1982). Newton *et al.* (1984) reported the half-lives of glyphosate in a forest-brush field ecosystem in Oregon after aerial spray were 10.4 to 26.6 days in the foliage and litter, 40.2 days for exposed soil, and 29.2 days for litter-covered soil. However, Stark (1983) reported that residues still may be found in the soil for 2 years or longer. The major degradation product of glyphosate in soil is (aminomethyl)phosphonic acid. Minor metabolites include N-methylaminomethylphosphonic acid, glycine, N-dimethylaminomethylphosphonic acid, and hydroxy-methylphosphonic acid (Ghassemi *et al.*, 1982; Rueppel *et al.*, 1977; Sprankle *et al.*, 1975).

No information is available on the absorption of glyphosate after oral administration to mammals. Wester *et al.* (1991) reported poor absorption of glyphosate, as Roundup®, after dermal application to rhesus monkeys. It has been reported that glyphosate does not bioaccumulate in living cells (Ghassemi *et al.*, 1982) because of its high water solubility and the absence of any active processes which concentrate or conserve glyphosate.

Fifty-six cases of unspecified toxicities associated with exposure to Roundup® were reported in Japan between June, 1984, and March, 1986 (Sawada *et al.*, 1988). Analyses showed that the surfactants used in the formulation, rather than glyphosate *per se*, were the main cause of toxicity. A similar conclusion was reached by Folmar *et al.* (1979) in evaluating the toxicity of a technical-grade glyphosate (MON 0573), the isopropylamine salt of glyphosate (MON 0139), Roundup® (MON 2139), and the Roundup® surfactant (MON 0818) in aquatic species. Wan *et al.* (1989) confirmed that the surfactant MON 0818 is a more potent toxicant to salmonids than glyphosate, MON 8709, or Roundup®. The authors further demonstrated that the toxicity of glyphosate to salmonids is affected by the hardness and pH of the water; glyphosate is more toxic to juvenile salmonids in soft water than in hard water (Wan *et al.*, 1989).

The acute lethal oral dose (LD_{50}) of glyphosate without surfactants is 4873 mg/kg for rats and 1568 mg/kg for mice (Bababunmi *et al.*, 1978); the acute lethal dose by intraperitoneal injection is 235 mg/kg for rats and 130 mg/kg for mice (Olorunsogo and Bababunmi, 1980). Glyphosate administered intragastrically to rats at 1 mMol/kg daily for 2 weeks had no effect on kidney and intestinal drug-metabolizing enzymes, including aryl hydrocarbon hydroxylase, ethoxycoumarin-O-deethylase, epoxide hydrolase, or UDP-glucuronosyltransferase (with 4-nitrophenol or 4-methylumbelliferone as the aglycone) (Ahotupa *et al.*, 1983). In rats administered glyphosate intragastrically at 500 mg/kg (3 mMol/kg) for 4 days followed by 300 mg/kg (1.8 mMol/kg) for 10 days, there were significant decreases in the activities of hepatic cytochrome c reductase, cytochrome P-450 mediated diphenyloxazole hydroxylase, ethoxycoumarin O-deethylase and mono-oxygenase, and the intestinal aryl hydrocarbon hydroxylase (Hietanen *et al.*, 1983). Uncoupling of oxidative phosphorylation was observed in isolated rat liver mitochondria incubated with glyphosate *in vitro* (Bababunmi *et al.*, 1979). It has been postulated that uncoupling of mitochondrial oxidative phosphorylation may play a major role in glyphosate intoxication (Olorunsogo *et al.*, 1979). Support of the hypothesis was provided by studies demonstrating inhibition of the energy-linked nicotinamide nucleotide transhydrogenase reaction in intact mitochondria isolated from the livers of rats 5 hours following intraperitoneal dosing with 15 mg/kg or more glyphosate. In these studies, glyphosate probably exerts its toxic effect first by uncoupling oxidative phosphorylation, which in turn interferes with the energy-requiring transhydrogenase reaction in the cell (Olorunsogo 1982a, 1982b).

Glyphosate was nominated for study by the California Regional Water Quality Control Board-North Coast Region, State of California, because it was found in water runoff in areas of glyphosate use. The NTP selected glyphosate for toxicity evaluation because of widespread use, its potential for human exposure, and the lack of published reports concerning comprehensive toxicity or carcinogenicity evaluations. The NTP studies included genetic toxicity studies, disposition studies in F344/N rats, and 13-week dosed feed toxicity studies in F344/N rats and $B6C3F_1$ mice. A 14-day study with male F344/N rats also was conducted to investigate a possible adrenergic mechanism in the pathogenesis of a salivary gland change, as noted in the 13-week studies. Copies of proprietary reports of toxicity studies performed by Monsanto Corporation were made available to the NTP for use in designing its glyphosate studies.

MATERIALS AND METHODS

Procurement and Characterization of Glyphosate

The glyphosate used in all studies was obtained from Monsanto Agricultural Products (St. Louis, MO). Samples of glyphosate were analyzed at Midwest Research Institute and found to be approximately 99% pure. The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with the structure of glyphosate and available literature references. Elemental analysis results for carbon, hydrogen, nitrogen, and phosphorous agreed with theoretical values. Karl Fischer titrimetry indicated 0.18 ± 0.04% water. Titration of the acidic functional groups with tetrabutylammonium hydroxide indicated a purity of 98.6 ± 0.4%. Analysis by thin-layer chromatography indicated a major spot and 2 trace impurities. Analyses indicated glyphosate, when mixed with feed and stored in at room temperature in the dark, was stable for at least 3 weeks.

The ^{14}C-glyphosate [N-(phosphono-^{14}C-methyl)-glycine, 1.97 mCi/mM, radiochemical purity 99%] and Roundup® used in the disposition studies also were obtained from Monsanto.

Disposition Studies

Male F344/N rats (170-280 g, purchased from Harlan-Sprague-Dawley (Indianapolis, IN), were fasted overnight before dosing. Between 8 a.m. and 10 a.m., each rat received a single gavage dose of ^{14}C-glyphosate in deionized, distilled water, at levels of either 5.6 or 56 mg/kg body weight. The rats were housed individually in metabolic cages and fed Wayne Lab Blox rat chow and deionized water *ad libitum*.

Urine and feces were collected for 72 hours, at 24-hour intervals. One hundred □l of urine was mixed with 20 ml of Betaphase scintillation cocktail and analyzed for ^{14}C using a Beckman LS 2800 liquid scintillation counter (Beckman Instruments, Inc., Fullerton CA). Feces were weighed and mixed in 15 ml of 0.5 M NaOH for 24 hours before homogenization. Aliquots of fecal homogenate were oxidized in a United Technologies Packard Model 306 oxidizer (Packard Instrument Co., Downers Grove, IL), then analyzed for ^{14}C with the Beckman LS 2800.

At termination, aliquots of brain, heart, lung, liver, kidney, spleen, testes, muscle, skin, fat, small and large intestine, stomach, and blood were collected. The samples were weighed, oxidized, and analyzed for ^{14}C as described above; the contents of the small and large intestines and the stomach were analyzed separately for radioactivity. The resulting values were combined and added to the last fecal time point.

Groups of rats were given a single dose of 5.6 mg glyphosate/kg intravenously via the tail vein (dose volume 1.0 ml/kg), intraperitoneally, or orally to study the elimination of glyphosate following various routes of administration. Urine and feces were collected and analyzed for radioactivity over a 24-hour period.

Additional groups of rats were pretreated with Roundup® at 0.5 or 10 ppm in drinking water. for 16 days to determine the effect of the surfactants and inert ingredients on glyphosate absorption. The rats received a single oral dose of [^{14}C]-glyphosate (5.6 mg/kg), either on day one, prior to treatment with Roundup®, or on day 16 of treatment.

Blood samples were obtained by cardiac puncture from rats given the oral doses of glyphosate at 5.6 or 56 mg/kg, to determine the effect of dose on the absorption of glyphosate from the gastrointestinal tract. The samples were analyzed for radioactivity according to previously described procedures.

13-Week Study Design

Groups of 10 male and 10 female F344/N rats and B6C3F$_1$ mice were given glyphosate in feed at dietary concentrations of 0 ppm (0%), 3125 ppm (0.3125%), 6250 ppm (0.625%), 12500 ppm (1.25%), 25000 ppm (2.5%), or 50000 ppm (5.0%). Ten additional rats/sex were included at each dietary level for evaluation of hematologic and clinical pathology parameters. Male and female F344/N rats and B6C3F$_1$ mice used in this study were produced under strict barrier conditions at Simonsen Laboratories (Gilroy, CA). The animals were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats and mice were shipped to the study laboratory at 31 and 38 days of age, quarantined at the study laboratory for 12 and 11 days, and placed on study at 43 days and 49 days of age, respectively. Blood samples were collected and the sera analyzed for viral titers from 5 animals per sex and species at study start and at termination in the 13-week studies. Data from 5 viral screens performed in rats and 12 viral screens performed in mice showed that there were no positive antibody titers (Boorman *et al.*, 1986; Rao *et al*, 1989, 1989a). Additional details concerning study design and performance are listed in Table 1.

Animals surviving to the end of the studies were killed with carbon dioxide. The heart, right kidney, liver, lung, right testis, and thymus were weighed. Sperm morphology and vaginal cytology evaluations were performed at the end of the study and during the preceding 2 weeks on rats and mice from the untreated controls and 3 highest dose groups (0, 12500, 25000, and 50000 ppm). Blood smears were prepared from mice for determination of micronuclei in erythrocytes.

A necropsy was performed on all animals. Organs and tissues were examined for gross lesions (Table 1). Tissues were preserved in 10% neutral buffered formalin. Following dehydration and embedding, tissues were sectioned at approximately 5 □M, stained with hematoxylin and eosin, then examined microscopically. A complete histopathologic evaluation was conducted on all animals in the untreated control group and the highest dose group (50000 ppm). The single identified target organ, the salivary gland, was examined in all dosed groups. Tissues examined for rats and mice of both sexes are listed in Table 1.

Upon completion of the histologic evaluation of the 13-week study by the laboratory pathologist, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent pathology laboratory where quality assessment was performed; the results were reviewed and evaluated through an NTP Pathology Review. The final diagnoses represent a consensus of contractor and review pathologists.

For clinical pathology studies, male and female rats were anesthetized with a mixture of carbon dioxide and oxygen (70%:30%), and blood samples were collected from the retroorbital sinus using heparinized microcapillary tubes. Samples for determination of hematologic and biochemical variables were collected from additional study animals on study days 5 and 21, and from the regular study animals at 13 weeks. Blood samples for hematologic analyses (approximately 0.5 ml) were collected in plastic tubes coated with potassium EDTA (Microvette CB 1000, Sarstedt, Numbrecht, Germany) and held at room temperature. Samples for biochemical analyses (approximately 0.75 ml) were collected in plastic tubes containing serum separator gel (Microtainer serum separator tube, Becton Dickinson, Rutherford, NJ). These samples were allowed to clot for 30 minutes at room temperature. At the end of this period, samples were centrifuged at 5000 g for 10 minutes and serum was removed for biochemical analyses.

Automated hematologic analyses were performed with an Ortho ELT-8 hematology system (Ortho Diagnostics Systems, Inc., Westwood, NJ). The following variables were measured: erythrocyte, leukocyte, and platelet counts; mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and mean corpuscular hemoglobin (MCH); hematocrit (HCT); and hemoglobin concentration (HGB). Leukocyte differentials were determined by microscopic evaluation of Wright-stained blood smears. Reticulocytes were stained by mixing equal volumes of blood with new methylene blue stain. Relative numbers of reticulocytes, determined by microscopic examination of approximately 1000 erythrocytes, were converted to absolute counts based on the total erythrocyte count.

Analyses of biochemical variables in serum were performed using a Roche Cobas Fara chemistry system (Roche Diagnostics Systems, Nutley, NJ). For the following variables, reagent kits and applications developed by the manufacturer were used: alanine aminotransferase (ALT), total protein, albumin, urea nitrogen (UN), creatinine, creatine kinase (CK), and alkaline phosphatase (AP). For determinations of sorbitol dehydrogenase (SDH) and total bile acids, reagent kits were obtained from Sigma Chemical Company (St. Louis, MO) and applications were developed in-house for the chemistry analyzer.

Reproductive Toxicity

In screening for potential reproductive toxicity, the caudal, epididymal, and testicular weights, sperm motility, sperm count per gram caudal tissue, and testicular spermatid head count were evaluated at necropsy. Vaginal cytology was evaluated on animals during the 2 weeks just preceding necropsy, using procedures outlined by Morrissey *et al.* (1988). For the 12 days prior to sacrifice, females were subject to vaginal lavage with saline. The aspirated cells were air-dried onto slides, stained with Toluidine Blue O, and cover slipped. The relative preponderance of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were used to identify the stages of the estrual cycle.

Sperm motility was evaluated at necropsy as follows: The left epididymis was removed and quickly weighed; the cauda epididymis was removed at the junction of the vas deferens and the corpus

TABLE 1 Experimental Design and Materials and Methods in the 13-Week Studies of Glyphosate

Study Dates May -- September, 1988	**Type and Frequency of Observation** Observed 2 x d for mortality/moribundity; 1 x wk for clinical signs of toxicity; weighed initially, 1 x wk, and at necropsy; food consumption was measured.
Strain and Species F344/N rats; B6C3F$_1$ mice	**Diet** NIH-07 feed and water *ad libitum*
Animal Source Simonsen Laboratories, Gilroy, CA	**Animal Room Environment** Temp.: 67 - 74^{o}F; relative humidity 40 - 89%; 10 air exchanges/hour; 12 h fluorescent light/day
Study Laboratory Southern Research Institute, Birmingham, AL	**Time Held Before Study** Rats -- 12 days; Mice -- 11 days
Size of Study Groups 10 males and 10 females of each species per dose group. Rats were housed 5 per cage; mice were individually caged.	**Age When Placed on Study** Rats - 43 days; Mice - 49 days
Doses Rats and mice -- 0, 3125, 6250, 12500, 25000, or 50000 ppm in feed	**Duration of Dosing** Rats - daily for 13 weeks; Mice - daily for 13 weeks
Method of Animal Distribution Animals were assigned to groups using a stratified weight method and then assigned to study groups in random order.	**Age When Killed** Rats -- 135-137 days; Mice -- 142-144 days
Necropsy and Histologic Examinations: Complete necropsies were performed on all animals. Complete histopathologic examination was conducted on the control and the highest treatment group (50000 ppm); the target organ, salivary gland, was examined in all lower dose groups; the following tissues were examined microscopically for all controls and 50000 ppm group animals: adrenal glands, bone (femur, including marrow and epiphysis), brain (three sections: frontal cortex and basal ganglia, parietal cortex and thalamus, cerebellum and pons), esophagus, eyes (if grossly abnormal), gall bladder (mice), gross lesions and tissue masses with regional lymph nodes, heart, intestine (duodenum, jejunum, ileum, cecum, colon, rectum), kidneys, liver, lungs and mainstem bronchi, lymph nodes (mandibular, mesenteric), mammary gland and adjacent skin, nasal cavity and turbinates (three sections), ovaries, pancreas, parathyroid glands, pituitary gland, preputial or clitoral glands, prostate gland, salivary glands, spinal cord and sciatic nerve (if neurologic signs were present), spleen, stomach (including forestomach and glandular stomach), testes/epididymis, seminal vesicle, thigh muscle, thymus, thyroid gland, trachea, urinary bladder, uterus, vagina (from animals used in SMVCE). Organ weights (to the nearest mg) obtained from all core study animals include: liver, thymus, right kidney, right testis, heart and lungs. Hematologic and serum chemical analyses were performed; sperm motility and vaginal cytology was evaluated in rats and mice exposed to 0, 12500, 25000, and 50000 ppm.	

epididymis, then weighed. Warm (37°C) Tyrodes buffer (mice) or test yolk buffer (rats) was applied to two pre-warmed slides, and a small cut was made in the distal cauda epididymis.

The sperm that extruded from the epididymis were dispersed throughout the solution, cover-slipped, and counted immediately on a warmed microscope stage. Two independent observers counted the number of moving and non-moving sperm in 5 fields of 30 sperm or less per field. After sperm sampling for motility evaluation, the cauda was placed in phosphate buffered saline (PBS), gently chopped with a razor blade, and allowed to sit for 15 minutes. The remaining clumps of tissue were removed, the solution was mixed gently, then heat-fixed at 65°C. Sperm density was subsequently determined using a hemocytometer.

To quantify spermatogenesis, the left testis was weighed, frozen and stored. After thawing, testicular spermatid head count was determined by removing the tunica albuginea and homogenizing the testis in PBS containing 10% DMSO. Homogenization-resistant spermatid

nuclei were enumerated using a hemocytometer; the data were expressed as spermatid heads per total testis, and per gram of testis.

Study of the Mechanism of Induction of Salivary Gland Lesions by Glyphosate

Because of the morphologic similarity between a salivary gland change noted in the 13-week studies of glyphosate and a salivary gland lesion previously reported to result from treatment with the adrenergic agonist, isoproterenol, a study was designed to test the hypothesis that the salivary gland effect of glyphosate was mediated through an adrenergic mechanism. For this study, male F344/N rats (200-250 g) were obtained from Charles River Laboratories (Raleigh, NC) and were randomized to 5 groups with 4 animals per group. Glyphosate was administered to the appropriate groups by dosed feed, while control groups were fed control NIH-07 diet. The adrenergic agents, isoproterenol and propranolol, were administered by continuous subcutaneous infusion by osmotic minipumps. Treatment groups are shown in Table 2.

TABLE 2 Treatment Groups in the Study to Determine the Mechanism of Induction of Salivary Gland Lesions by Glyphosate

Group	Feed	Pump
1	control	vehicle (water + 0.1% ascorbate)
2	glyphosate (50000 ppm)	vehicle
3	glyphosate (50000 ppm)	propranolol (~1.2 mg/kg/day)
4	control	isoproterenol (~1.0 mg/kg/day)
5	control	isoproterenol + propranolol

One day prior to initiating glyphosate-dosed feed, all rats were anesthetized with methoxyflurane and osmotic minipumps (Alzet model 2002, pumping rate 0.55 $\pm$ 0.03 ml/h, Alza Corporation, Palo Alto, CA) were implanted subcutaneously. Group 1 (negative control) was fed standard NIH-07 diet and implanted with pumps containing vehicle (sterile water + 0.1% ascorbic acid). Group 2 was fed NIH-07 diet containing glyphosate (50000 ppm) and implanted with vehicle pumps. Group 3 was fed 50000 ppm glyphosate-dosed feed and implanted with pumps containing the adrenergic antagonist propranolol (Sigma Chemical Co., St. Louis, MO, 25 mg/ml vehicle). As a positive control, Group 4 was administered the adrenergic agonist, isoproterenol (Sigma Chemical Co., St. Louis, MO, 20 mg/ml vehicle), by pump and fed normal diet. Group 5 animals (blocking controls) were implanted with both isoproterenol and propranolol pumps and fed normal diet. The rats were identified by tail tattoo and weighed one day prior to initiation of dosed feed and at study termination. Food consumption was measured every other day. After 14 days of treatment, the left parotid and submandibular/sublingual glands were removed and weighed separately, after which the glands were cut into small pieces, placed into a 2.5% glutaraldehyde/2.0% paraformaldehyde solution, and processed for electron microscopy. The right parotid and submandibular/sublingual glands were removed and placed in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin (H&E) and Alcian Blue (pH 2.5)-periodic acid Schiff (AB-PAS).

Genetic Toxicity Studies

Mutagenicity Studies

Mutagenicity studies of glyphosate in *Salmonella typhimurium* were conducted as described in Zeiger *et al.* (1988). Glyphosate was tested for genotoxicity in *S. typhimurium* strains TA100, TA1535, TA97, and TA98 using the plate-incorporation assay in both the absence or presence of Aroclor 1254-induced S9 from male Syrian hamster liver or male Spraque-Dawley rat liver. Glyphosate was dissolved in distilled water and tested at doses up to 10,000 □g/plate. A positive response is defined in this assay as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants which was not dose-related, not reproducible, or of insufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment.

Mouse Peripheral Blood Micronucleus Test

At the termination of the 13-week study, blood smears were prepared from peripheral blood samples obtained by cardiac puncture of dosed and control mice. The slides were stained with Hoechst 33258/pyronin Y (MacGregor *et al.*, 1983). Ten thousand normochromatic erythrocytes from each animal were scored for micronuclei.

Statistical Methods

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between dosed and control groups in the analysis of continuous variables. Organ and body weight data, which are approximately normally distributed, were analyzed using the parametric multiple comparisons procedures of Williams (1971, 1972, 1986) and Dunnett (1955). Clinical pathology and hematology data, which typically have skewed distributions, were analyzed using the nonparametric multiple comparisons methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of dose-response trends and to determine whether a trend-sensitive test (Williams, Shirley) was more appropriate for pairwise comparisons than a test capable of detecting departures from monotonic dose-response (Dunnett, Dunn). If the P-value from Jonckheere's test was greater than or equal to 0.10, Dunn's or Dunnett's test was used rather than Shirley's or Williams' test.

The outlier test of Dixon and Massey (1951) was employed to detect extreme values. No value selected by the outlier test was eliminated unless it was at least twice the next largest value or at most half of the next smallest value.

Analysis of Vaginal Cytology Data

Since the data are proportions (the proportion of the observation period that an animal was in a given estrous state), an arcsine transformation was used to bring the data into closer conformance with normality assumptions. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for the simultaneous equality of measurements across dose levels.

Analysis of Micronuclei Data

Statistical analyses for micronuclei were completed using linear trend tests on polychromatic erythrocytes data and log-transformed data for normochromatic erythrocytes, and analysis of variance on ranks (ANOVA) for percentage polychromatic cells among total erythrocytes. The frequency of micronuclei in the dosed groups was compared with the frequency determined for the concurrent untreated control animals using the Student t-test.

Quality Assurance

The 13-week toxicity studies of glyphosate were performed in compliance with FDA Good Laboratory Practices regulations (21 CFR 58). The Quality Assurance Unit of Southern Research Institute performed audits and inspections of protocols, procedures, data, and reports throughout the course of the studies. The operations of the Quality Assurance Unit were monitored by the NTP.

RESULTS

Disposition Studies

More than 90% of the radioactivity from either a 5.6 or 56 mg/kg oral dose of [^{14}C]-glyphosate was eliminated within 72 hours. Approximately 50% was eliminated in the feces in the first 24 hours; urinary elimination of radioactivity was essentially complete by 12 hours. The apparent decrease in cumulative percentage eliminated in urine after the 5.6 mg/kg oral dose probably is due to interindividual variation, and variances (from 10 to 3) in the number of animals per time point. In contrast, following an intravenous dose of [^{14}C]-glyphosate at 5.6 mg/kg, 90% of radioactivity was eliminated in urine in the first 6 hours (Table 3).

TABLE 3 Cumulative Percentage of Oral or I.V. Dose of Glyphosate Eliminated in Urine and Feces[a]

	Oral 5.6 mg/kg		Oral 56 mg/kg		I.V. 5.6 mg/kg	
Time (Hours)	Urine	Feces	Urine	Feces	Urine	Feces
6	10 ± 5	7 ± 11			90 ± 7	0.3 ± 0.2
12	31 ± 10	28 ± 10			95 ± 9	0.5 ± 0.5
24	26 ± 14	55 ± 13	28 ± 10	47 ± 12	98 ± 11	3 ± 2
48	18 ± 2	71 ± 8	33 ± 12	57 ± 15		
72	19 ± 2	74 ± 5	34 ± 12	58 ± 15		

[a] N = 3-10

TABLE 4 Percentage of Dose in Tissues Following Oral Administration of Glyphosate at 5.6 mg/kg[a]

	Time (h)				
Tissue	3[b]	6[b]	12[b]	24[c]	96[c]
Small Intestine	7.72 ± 1.74	10.20 ± 5.49	4.12 ± 2.25	0.48 ± 0.51	0.03 ± 0.01
Large Intestine	1.21 ± 1.07	0.51 ± 0.01	0.46 ± 0.28	0.17 ± 017	0.01 ± 0.00
Liver	0.10 ± 0.00	0.07 ± 0.04	0.11 ± 0.01	0.14 ± 0.08	0.05 ± 0.05
Kidney	0.36 ± 0.19	0.48 ± 0.42	0.31 ± 0.06	0.10 ± 0.07	ND
Skin	0.70 ± 0.45	0.18 ± 0.25	0.21 ± 0.12	ND[d]	ND
Blood	0.28 ± 0.01	0.18 ± 0.06	0.31 ± 0.10	0.03 ± 0.06	ND
Tissue Total	12.00 ± 0.33	11.67 ± 6.29	5.54 ± 2.35	0.89 ± 0.84	0.10 ± 0.06

[a] Data represented as percent of dose administered ± standard deviation.

[b] N = 2 rats.

[c] N = 3 rats.

[d] ND notes that the values were not determined as the amount of radioactivity in the samples was below the level of accurate analytical measurement (<100 dpm).

The tissue distribution of radioactivity from a single oral 5.6 mg/kg dose of [^{14}C]-glyphosate is presented in Table 4. At time points up to 24 hours, most of the radioactivity was found in the gastrointestinal tract; only 1% remained in the tissues at 24 hours.

In animals given a 56 mg/kg oral dose, the peak blood level of radioactivity occurred later than in those given a 5.6 mg/kg oral dose (1 hour vs. 2 hours); the peak blood concentration was more than 30 times higher following the 56 mg/kg oral dose (Figure 1). Radioactivity rapidly declined in

blood following a 5.6 mg/kg i.v. dose (Figure 2). The blood radioactivity vs. time plot fits a 2-compartment model with an alpha (distribution) phase of about 0.5 hour and a beta (elimination) phase of 13 hours.

Rats were exposed to Roundup® (the isopropylamine salt of glyphosate and added surfactants) in drinking water at concentrations of 0.5 to 100,000 ppm for 9 to 16 days. No differences were observed in the elimination of an oral dose of 5.6 mg/kg [^{14}C]-glyphosate following any of these exposures, as compared with the elimination of a similar dose 1 day prior to beginning administration of Roundup® (data not shown).

13-Week Studies in F344/N Rats

All animals survived until the end of the study. Diarrhea was observed in the 50000 ppm groups of both sexes for the first 50 days, though not thereafter. In males, reduced weight gains were observed in the 25000 and 50000 ppm groups. The final mean body weight of the 50000 ppm group was approximately 18% less than that of controls (Table 5 and Figure 3). In females, there was only a marginal effect on body weight gain, with the high dose group 5% lighter than controls at the end of the study (Figure 3). In male rats, small increases in relative organ weights were observed for liver, kidney, and testicle; a decrease in relative weight was observed in the thymus (Appendix A, Table A1). In females, changes in organ weights were minor and could not be related definitely to treatment. There were no treatment-related effects on food consumption throughout the study. The mean, time-weighted chemical consumption for each group, based on food intake, is given in Table 5.

TABLE 5 Survival, Weight Gain, and Feed Consumption of F344/N Rats in the 13-Week Dosed Feed Study of Glyphosate

Dose (ppm) In Feed	Survival[a]	Mean Body Weight (grams) Initial	Final	Change[b]	Final Weight Relative to Controls (%)[c]	Average Feed Consumption[d]	Glyphosate Consumed[e]
MALE							
0	10/10	115	353	238		17	0
3125	10/10	111	352	241	100	17	205
6250	10/10	111	338	227	96	17	410
12500	10/10	113	345	232	98	17	811
25000	10/10	108	332	224	94	17	1678
50000	10/10	112	290	178	82	15	3393
FEMALE							
0	10/10	95	191	96		11	0
3125	10/10	92	190	98	100	11	213
6250	10/10	94	194	100	102	11	421
12500	10/10	96	193	97	101	11	844
25000	10/10	92	186	94	97	11	1690
50000	10/10	95	181	86	95	10	3393

a Number of animals surviving at 13 weeks/number/dose group.
b Mean weight change of the animals in each dose group.
c (Dosed group mean/Control group mean) x 100.
d Average food consumption in gm/animal/day.
e Estimated, mean, time-weighted chemical consumption in mg/kg/day.

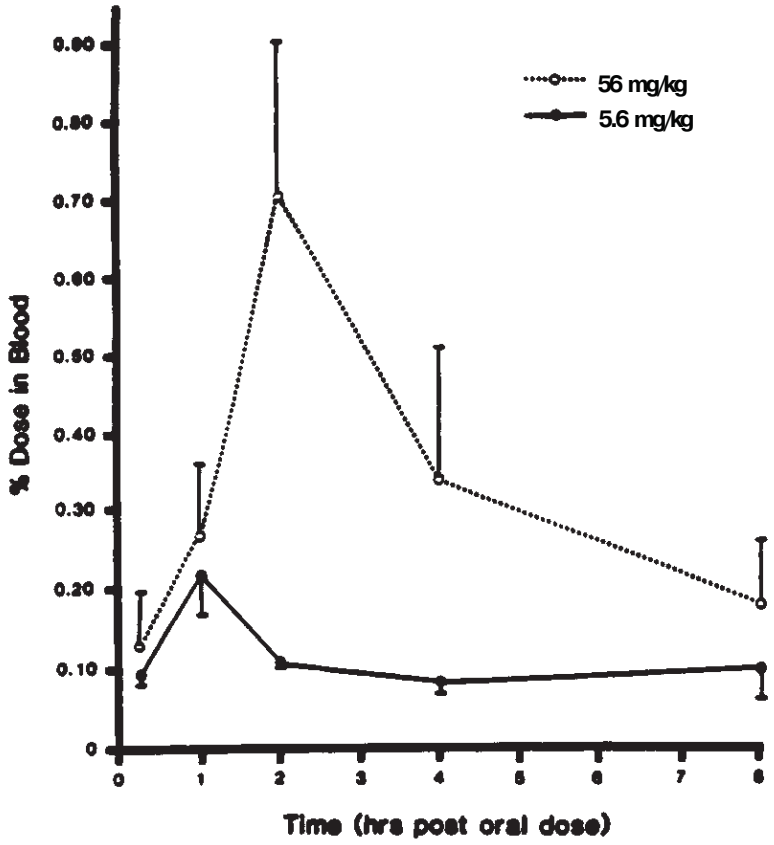


Figure 1 Blood Levels of ^{14}C-Glyphosate Following Oral Administration of ^{14}C-Glyphosate at 5.6 or 56 mg/kg (% dose ± standard deviation)

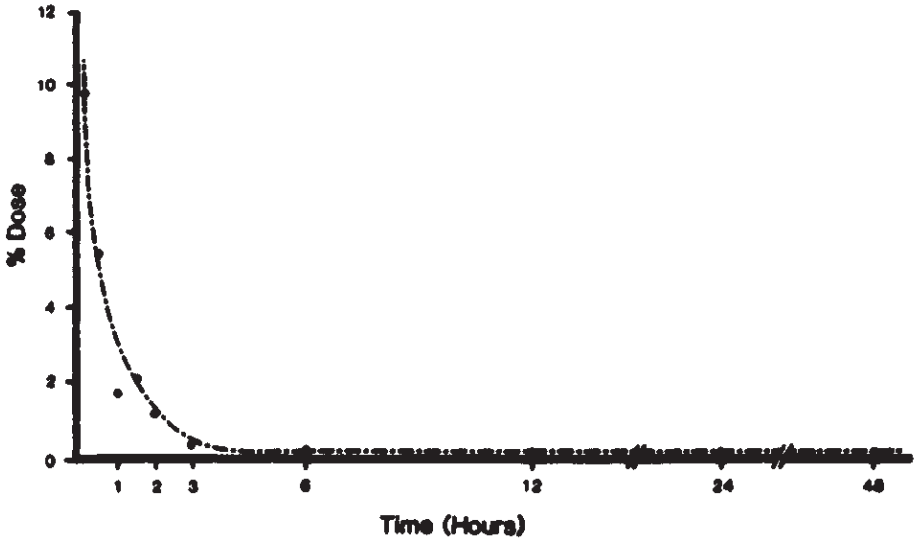
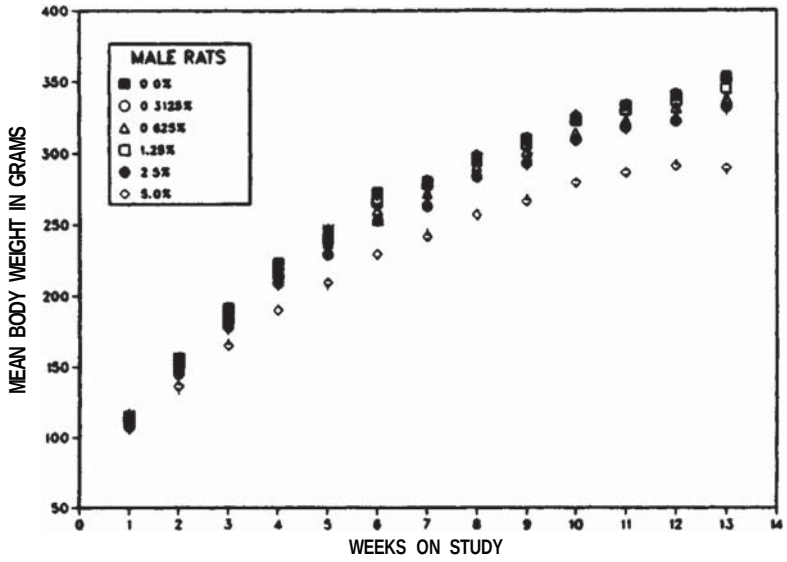


Figure 2 Levels of Radioactivity in Blood after a Single i.v. Dose of 5.6 mg/kg Glyphosate (2 rats per time point, results averaged).



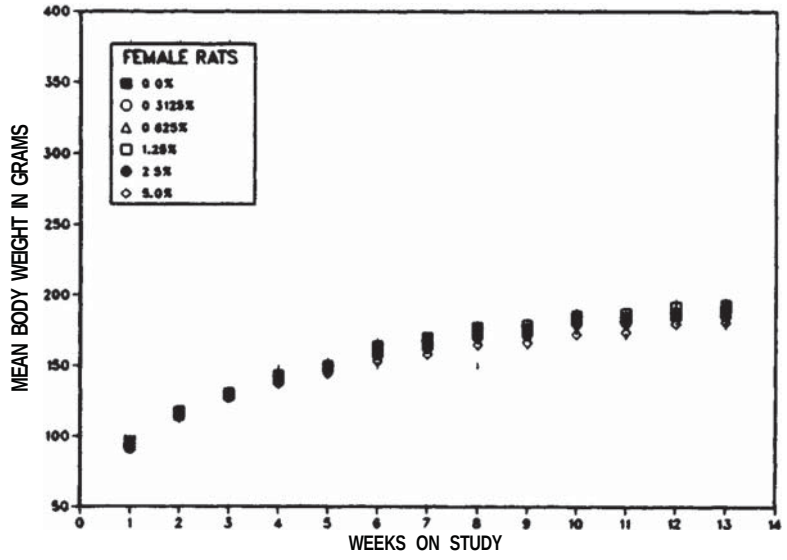


Figure 3 **Body Weights of F344/N Rats Exposed to Glyphosate by Dosed Feeding for 13 Weeks**

Chemically-related changes in hematological parameters observed in male rats at 13 weeks included mild increases in hematocrit and RBC at 12500, 25000, and 50000 ppm, hemoglobin at 25000 and 50000 ppm, and platelets at 50000 ppm. In female rats, minimal but significant increases occurred in lymphocyte and platelet counts, WBC, MCH, and MCV. Treatment-related alterations in clinical chemistry parameters included increases in alkaline phosphatase in males and in females at all time points, alanine aminotransferase activity in males and females at all time points except 90 days, total bile acids at days 23 and 90 in males and at day 23 in females, total protein in females at all time points, and sporadic increases in urea nitrogen and albumin (Appendix B).

In reproductive studies, male rats experienced a significant decrease (20%) in sperm counts in the 25000 and 50000 ppm groups. Left caudal, epididymal and testicular weights, epididymal sperm motility, total spermatid heads/testes, and total spermatid heads/g caudal tissue were not different from those of controls (Appendix C, Table C1). Female rats had a longer estrous cycle length (5.4 days vs. 4.9 days) in the 50000 ppm group compared to controls (Appendix C, Table C1).

At necropsy, no gross lesions were observed that were considered possibly related to glyphosate administration. Morphologic changes attributed to glyphosate were observed microscopically in the parotid and submandibular salivary glands of male and female rats. Salivary gland lesions were diagnosed as "cytoplasmic alteration" and consisted of basophilic change and hypertrophy of acinar cells. These changes were more evident in the parotid gland in which the normal granular, eosinophilic staining cytoplasm of the acinar epithelial cells was replaced by basophilic and finely vacuolated cytoplasm (Plate 1). This effect varied in distribution from multifocal in less severe cases, imparting a mottled tinctorial staining appearance to the gland, to diffuse involvement in higher dose animals. In addition, acinar cells appeared swollen, resulting in enlargement of secretory acini and a relative reduction in the number of secretory ducts seen. Nuclei of affected acinar cells were hyperchromatic. In the submandibular salivary gland, similar cytoplasmic tinctorial changes and hypertrophic effects were observed (Plate 2). The sublingual gland was not detectably altered.

A no-effect level for cytoplasmic alteration of the parotid and submandibular salivary glands in this study was not reached. One control female rat had a small basophilic focus in the parotid gland which was typical of the spontaneous lesion occasionally seen in rats. Table 6 presents incidence and severity data of glyphosate-induced cytoplasmic alteration of the salivary glands from the 13-week dosed feed study in rats. No other lesions in rats appeared related to glyphosate administration.

TABLE 6 Incidence and Severity of Cytoplasmic Alteration of the Parotid and Submandibular Salivary Glands (combined) in F344/N Rats in the 13-Week Dosed Feed Study of Glyphosate

Dose (ppm)	0	3125	6250	12500	25000	50000
MALES	0/10	6/10 (1.0)*	10/10 (1.0)	10/10 (1.8)	10/10 (2.7)	10/10 (2.9)
FEMALES	0/10	8/10 (1.0)	10/10 (1.0)	10/10 (2.1)	10/10 (2.4)	10/10 (3.0)

* Average severity score based on a scale of 1=minimal, 2=mild, 3=moderate, 4=marked.

13-Week Studies in B6C3F$_1$ Mice

Body weight gains were depressed in the 2 highest dose groups of both sexes (Table 7 and Figure 4). There were 2 early deaths in the study: An untreated female was accidentally killed, and a high dose female died from undetermined causes (Table 7). Increases in relative organ weights were observed in the heart, kidney, liver, lung, thymus, and testis of male mice (Appendix A, Table A2). There were no differences in food consumption between the dosed and control groups.

TABLE 7 Survival, Weight Gain, and Feed Consumption of B6C3F$_1$ Mice in the 13-Week Dosed Feed Study of Glyphosate

Dose (ppm) in Feed	Survival[a]	Mean Body Weight (grams) Initial	Final	Change[b]	Final Weight Relative to Controls(%)[c]	Average Feed Consumption[d]	Glyphosate Consumed[e]
MALE							
0	10/10	23.5	32.1	8.6		4.6	0
3125	10/10	23.2	31.1	7.9	97	4.5	507
6250	10/10	23.4	31.5	8.1	98	4.7	1065
12500	10/10	23.2	30.3	7.1	94	4.9	2273
25000	10/10	23.0	28.6	5.6	89	5.1	4776
50000	10/10	23.5	26.7	3.2	83	5.3	10780
FEMALE							
0	9/10	18.9	27.9	9.0		5.4	0
3125	10/10	18.4	28.6	10.2	103	5.8	753
6250	10/10	18.2	26.2	8.0	94	5.3	1411
12500	10/10	18.8	26.9	8.1	96	5.2	2707
25000	10/10	18.5	26.2	7.7	94	5.3	5846
50000	9/10	18.5	25.1	6.6	90	5.2	11977

a Number of animals surviving at 13 weeks/number in dose group.
b Mean weight change of the animals in each dose group.
c (Dosed group mean/Control group mean) x 100.
d Average food consumption in gm/animal/day.
e Estimated, mean, time-weighted chemical consumption in mg/kg/day.

A "dark" salivary gland in a high-dose male was the only significant gross finding at necropsy. No effects were observed on sperm motility or estrual cycle length. Treatment-related microscopic changes were limited to the parotid salivary gland; the changes consisted of a diffuse increase in basophilia of the acinar cells, diagnosed as "cytoplasmic alteration." In more severely affected glands, the cells and acini also appeared enlarged with an associated relative reduction in the number of ducts. Submandibular and sublingual glands were not detectably altered. The incidence and severity of cytoplasmic alteration of the parotid salivary gland was dose-related (Table 8).

TABLE 8 Incidence and Severity of Cytoplasmic Alteration of the Parotid Salivary Gland in B6C3F$_1$ Mice in the 13-Week Glyphosate-Dosed Feed Study

Dose (ppm)	0	3125	6250	12,500	25,000	50,000
MALES	0/10	0/10	5/10 (1.0)*	9/10 (1.6)	10/10 (2.8)	10/10 (4.0)
FEMALES	0/10	0/10	2/10 (1.0)	9/10 (1.3)	10/10 (2.1)	10/10 (3.1)

* Average severity score based on a scale of 1=minimal, 2=mild, 3=moderate, 4=marked.

Plate 1 Parotid salivary gland of control rat (1a) and 50000 ppm dose group rat (1b) from the 13-week dosed feed study of glyphosate. Note swelling and basophilia of acini (A) and decreased relative number of ducts (D) in the glyphosate-treated animal compared to control. 150X

Plate 2 Submandibular salivary gland of control rat (2a) and 50000 ppm dose group rat (2b) from the 13-week dosed feed study of glyphosate. Note slight enlargement and mottled staining of acini (A) and decreased relative number of ducts (D) in the glyphosate-treated animal compared to control. 150X

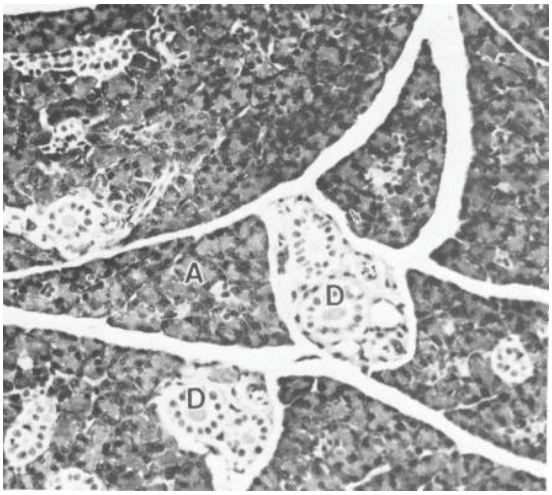


Plate 1 (a)

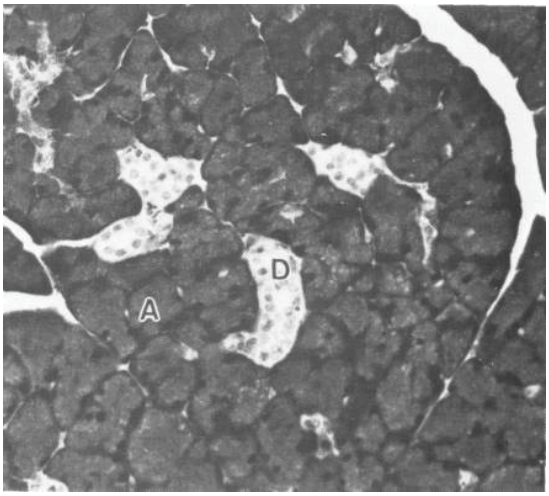


Plate 1 (b)

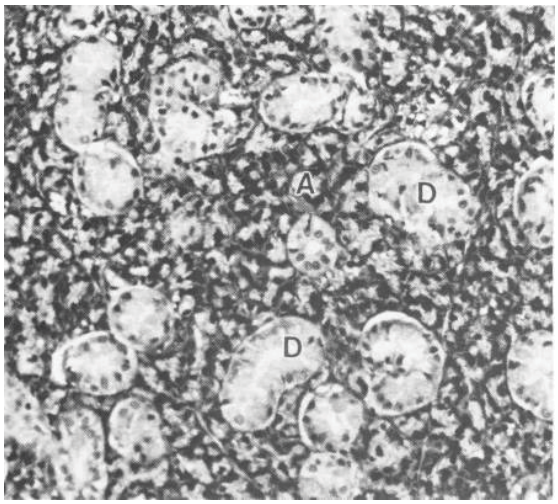


Plate 2 (a)

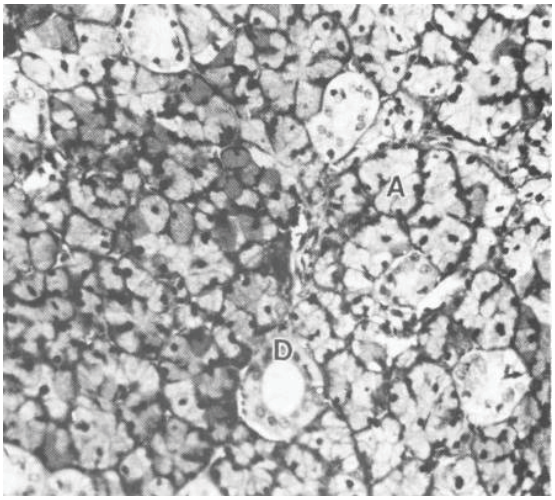


Plate 2 (b)

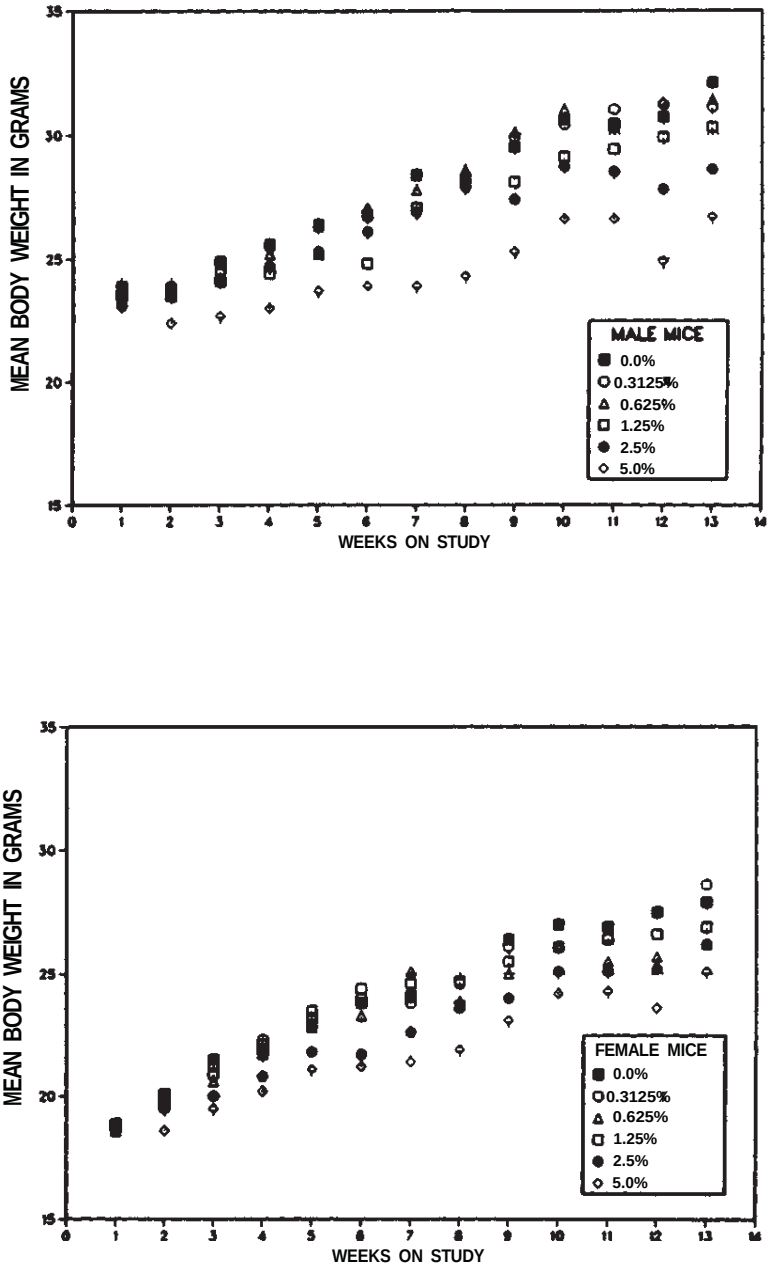


Figure 4 Body Weights of B6C3F$_1$ Mice Exposed to Glyphosate by Dosed Feeding for 13 Weeks

Mechanism of Induction of Salivary Gland Lesion

Cytoplasmic alteration of salivary gland acinar cells induced by glyphosate in the 13-week studies was similar morphologically to the reported effect of chronic treatment with the adrenergic mediator isoproterenol. To test the hypothesis that the salivary gland effect of glyphosate is mediated through an adrenergic mechanism, a special study was designed in which rats were concurrently administered glyphosate by dosed feed and/or adrenergic agents by subcutaneous minipump infusion.

All rats survived to the end of the 14-day study; the implanted minipumps were well-tolerated. Rats receiving isoproterenol were hypoactive and had increased respiratory rates on day 1 following pump implantation, but were normal by the following day. Feces of rats receiving glyphosate-dosed feed were observed to be slightly softer in consistency and wetter than normal in appearance by study day 7; perianal fecal staining was also evident in several of these animals. Average food consumption and body weight gains are presented by group in Table 9. It is apparent that there was no food avoidance in those groups receiving the glyphosate-dosed feed; there was a significant decrease in body weight gains in those groups, however.

TABLE 9 Feed Consumption and Weight Gain of F344/N Rats in the 14-Day Mechanism Study of Glyphosate

Treatment Group (diet/pump)	Food Consumption (gm/rat/day)	Weight Gain (gm)
1 (control diet/vehicle)	14.4	16.0 ± 2.9
2 (glyphosate/vehicle)*	17.6	6.3 ± 2.0
3 (glyphosate/propranolol)*	20.4	6.0 ± 2.4
4 (control diet / isoproterenol)	14.9	16.7 ± 1.6
5 (control diet/isoproterenol + propranolol)	15.0	17.5 ± 8.0

* Glyphosate was given in the diet at a concentration of 50000 ppm.

Parotid and submandibular/sublingual salivary gland weight data are shown in Table 10. Both isoproterenol, the adrenergic agonist given by subcutaneous infusion, and glyphosate, in dosed feed, induced significant enlargement of these glands, glyphosate having much greater effect than isoproterenol. The parotid was the much more affected of the two glands. The adrenergic antagonist, propranolol, inhibited the effect of both isoproterenol and glyphosate on salivary gland weights. In the parotid, there was approximately a 50% increase in gland weight following isoproterenol administration, an effect blocked completely blocked by concurrent administration of propranolol. Glyphosate induced an almost 3-fold increase in parotid weight, an effect significantly inhibited, though not completely, by propranolol. These trends were paralleled by smaller changes in submandibular/sublingual gland weights.

Microscopically, both isoproterenol and glyphosate given in the 14-day study induced lesions in the parotid gland similar to those seen in the 13-week study. These lesions consisted of cytoplasmic basophilic change, fine vacuolation, and swelling of acinar cells, diagnosed collectively as cytoplasmic alteration. A distinct gradation in the severity of these lesions was possible based on the extent of involvement and degree of tinctorial alteration and cell enlargement present.

TABLE 10 Salivary Gland Weights of F344/N Rats in the 14-day Mechanism Study of Glyphosate

Group (diet/pump)	Parotid		Submandibular/Sublingual	
	Absolute (mg)	Relative*	Absolute (mg)	Relative*
1 (control diet/vehicle)	126.2 ± 16.4	0.50 ± 0.08	209.7 ± 14.8	0.83 ± 0.04
2 (glyphosate/vehicle)	354.0 ± 37.5	1.47 ± 0.12	375.0 ± 26.3	1.56 ± 0.07
3 (glyphosate/propranolol)	245.0 ± 10.4	1.06 ± 0.06	261.0 ± 6.4	1.13 ± 0.04
4 (control diet / isoproterenol)	194.2 ± 15.6	0.76 ± 0.06	259.7 ± 10.6	1.03 ± 0.03
5 (control diet/isoproterenol + propranolol)	137.2 ± 19.1	0.55 ± 0.07	225.5 ± 7.8	0.91 ± 0.05

* mg/g body weight

Glyphosate-treated animals were most severely affected; glands from all these animals were characterized by diffuse, intense basophilic change of acinar cells with clearly evident acinar enlargement, resulting in a relative reduction in the number of ducts present. Concurrently, the cytoplasm of affected cells was finely vacuolated, and nuclei were hyperchromatic and displaced more basally by increased cytoplasmic volume. In serial sections stained with Alcian Blue/periodic acid Schiff (AB/PAS), areas of cytoplasmic alteration were seen to be associated with loss of PAS positive staining of secretory granules. Animals receiving the adrenergic antagonist, propranolol, subcutaneously and concurrently with glyphosate-dosed feed were clearly protected from the more severe lesions. All animals dosed with isoproterenol were likewise affected with cytoplasmic alteration of salivary acinar cells; basophilic tinctorial change in these animals was multifocal to diffuse, and hypertrophy was less prominent than in the glyphosate group. Propranolol resulted in only modest protection from isoproterenol effects based on histomorphology. The incidence and average severity of cytoplasmic alteration of the parotid gland is shown in Table 11.

Cytoplasmic alteration of the submandibular gland was detectable by light microscopy only in the glyphosate-dosed animals (Table 11). The lesion consisted primarily of cellular and acinar swelling with a relative reduction in the number of duct profiles per field. Tinctorial change was less of a component of the submandibular lesion than in the parotid, with most acinar cells being slightly more pale staining than controls, with scattered individual cells or acini being more basophilic, imparting a mottled staining pattern to the tissue. AB-PAS reactivity was essentially unchanged in affected glands.

TABLE 11 Incidence and Severity of Cytoplasmic Alteration of the Salivary Glands of F344/N Rats in the 14-Day Mechanism Study of Glyphosate

Group (Feed/Pump)	Parotid	Submandibular	Sublingual
1 (control diet/vehicle)	1/4 (1.0) *	0/4	0/3
2 (glyphosate/vehicle)	4/4 (4.0)	4/4	0/4
3 (glyphosate/propranolol)	3/4 (1.5)	4/4	0/2
4 (control diet / isoproterenol)	4/4 (2.7)	0/4	0/1
5 (control diet/isoproterenol + propranolol)	4/4 (2.0)	0/4	0/4

* Average severity grades for parotid gland lesions in affected animals, based on the following scale: 1=Focal change; 2=Multifocal, confluent change; 3=Diffuse change; 4=Diffuse change with intense basophilia and marked acinar swelling.

Plate 3 Electron micrograph of parotid acinar cells from a control male rat. Note electron dense secretory granules (S) and parallel arrays of rough endoplasmic reticulum (R). 5520X

Plate 4 Electron micrograph of parotid acinar cell from a male rat treated with isoproterenol, 1 mg/kg/day subcutaneously for 14 days. There is an increase in cell size and in electron lucency of secretory granules (S). Rough endoplasmic reticulum (R) is abundant. 5520X

Plate 5 Electron micrograph of parotid acinar cell from male rat treated with glyphosate, 50000 ppm dosed feed for 14 days. Cellular changes are similar to those of the isoproterenol-treated animal but with an even greater increase in cell size and electron lucency of secretory granules (S). Granules are also increased in size. 5520X

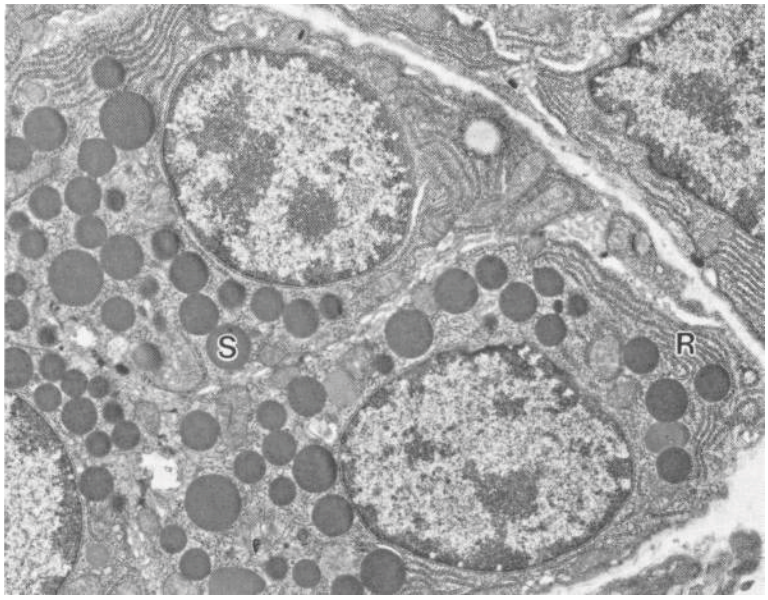


Plate 3

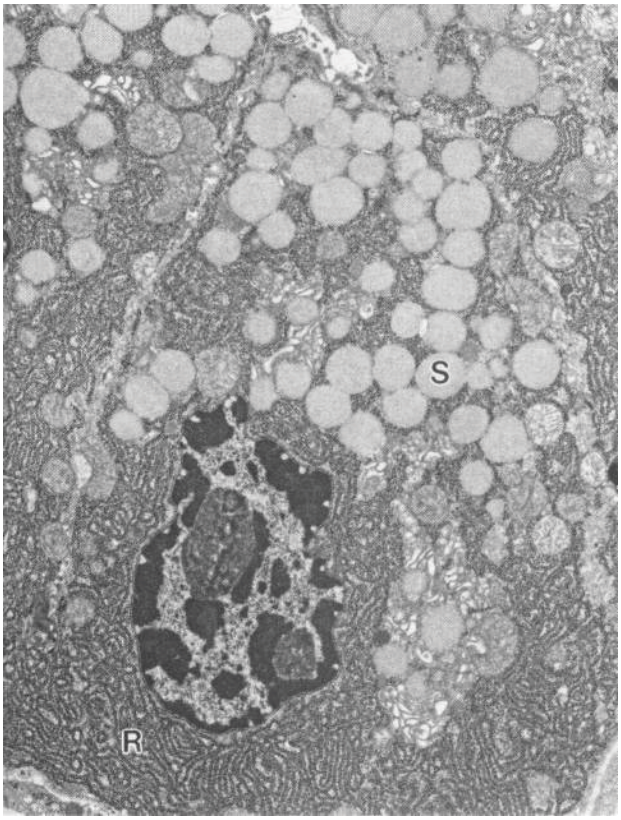


Plate 4

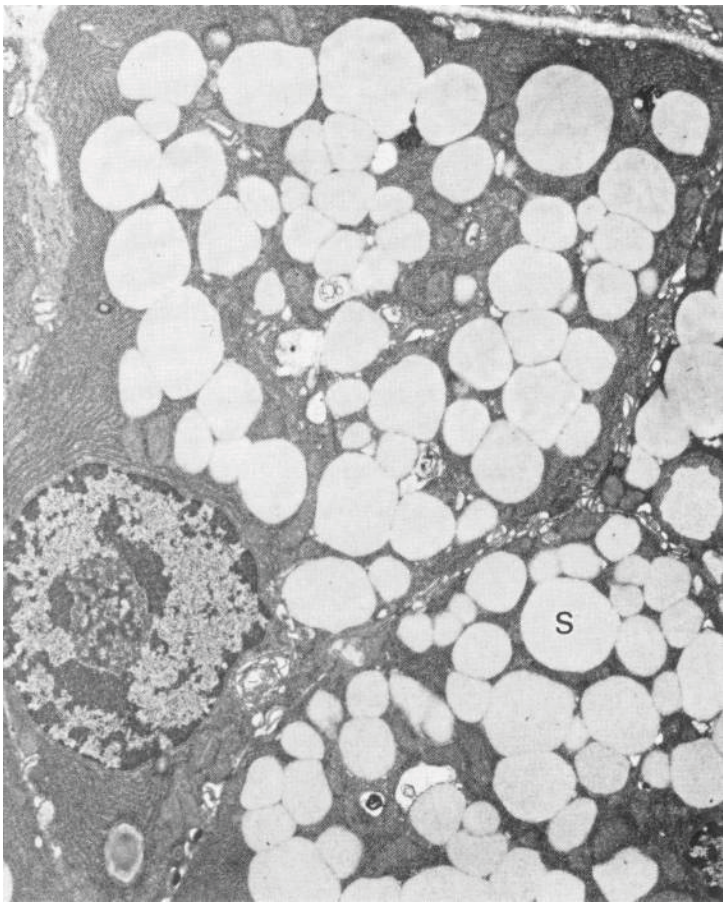


Plate 5

The lesions of the submandibular gland were more subtle than those in the parotid; differences in the severity of the cytoplasmic alteration in this gland were not appreciable by light microscopy. There was no definite, inhibitory effect of propanolol on the incidence of the glyphosate-induced change detected histologically in the submandibular gland. No microscopic change was observed in this gland in rats treated with isoproterenol. No changes in morphology or Alcian blue-periodic acid Schiff reactivity were seen in the sublingual glands examined from any groups.

Parotid and submandibular acinar cells from control, isoproterenol-treated, and glyphosate-treated animals were examined ultrastructurally. Parotid acinar cells of the control animals were of typical appearance, with basally oriented nuclei surrounded by rough endoplasmic reticulum (Plate 3). Electron dense secretory granules were concentrated in the apical cytoplasm. In contrast, secretory granules from the isoproterenol-treated animals were electron lucent in affected cells (Plate 4). Also, these cells obviously were enlarged, as evident from the increased cell area when compared to control cells at equivalent magnification; the number of secretory granules and volume of rough endoplasmic reticulum seemed to be increased concurrently. Similar changes, though of greater magnitude, were seen in parotid acinar cells from the glyphosate-dosed rats (Plate 5). There was a further progression in the lucency of the secretory granules, and the granules were noticeably enlarged and coalescent. Abundant rough endoplasmic reticulum surrounded the granules and nuclei, and the overall cell area was increased.

Ultrastructurally, control submandibular acini contained both mucous- and serous-type cells. Mucous cells were more prominent due to their larger size, central location within the acinus, and the large number of confluent, electron-lucent mucous granules. Serous cells were small and peripherally located in the acinus, and the electron-dense granules were few in number and relatively inconspicuous. Both cell types were dark-staining and contained abundant rough endoplasmic reticulum. In submandibular acini from the isoproterenol-treated animals, cells appeared swollen due to an increase in the number of granules; granules were heterogeneously stained, most with finely granular contents and others with granular stippling surrounding a more electron-dense core. Submandibular cells and acini from the glyphosate-exposed animals were markedly enlarged due to cytoplasmic engorgement with secretory granules, mostly of the lucent type, with some more heterogenous as seen in the isoproterenol animals. In these cells, granules were not limited to apical areas as in the controls but diffusely present throughout the cytoplasm. It could not be determined if the serous or mucous glandular acini were selectively affected by glyphosate.

Genetic Toxicology

Glyphosate (0-10000 □g/plate) did not induce gene mutations in *Salmonella typhimurium* strains TA100, TA1535, TA97, or TA98 when tested in a preincubation protocol in the presence and the absence of Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Appendix D, Table D1). Peripheral blood normochromatic erythrocytes from male and female mice were analyzed at the termination of the 13-week feed study for frequency of micronuclei; no increase in micronuclei was observed in either males or females at any dietary concentration of glyphosate (Appendix D, Table D2).

DISCUSSION

Disposition studies showed that after a dose of glyphosate at either 5.6 or 56 mg/kg, over 70% of the administered dose was eliminated within 24 hours. Tissue distribution data indicate most of the radioactivity was in the gastrointestinal tract following oral administration, indicating the compound may not be completely absorbed. Comparison of the pattern of elimination following i.v. and oral administration of [^{14}C]-glyphosate also supports the conclusion that the compound is incompletely absorbed. Radioactivity is eliminated primarily in feces after oral administration and primarily in urine following i.v. administration. If the usual assumption is made that i.v. administration represents the fate of a completely absorbed dose, then about 30% of the 5.6 mg/kg oral dose of glyphosate was absorbed; there is some evidence that a relatively higher percentage of the 56 mg/kg dose was absorbed. The 10-fold increase in dose resulted in a 30-fold increase in peak blood concentration. There also was a trend toward a higher percentage of the 56 mg/kg dose being eliminated in urine, but the differences were not statistically significant. Perhaps there is some interaction between glyphosate and the stomach/intestinal contents that binds a relatively larger percentage of the low dose, making it less available for absorption.

In the 13-week studies, glyphosate did not affect survival of F344/N rats or B6C3F$_1$ mice. Body weight gains were depressed in rats and mice at the 2 highest dose levels; weight gain depression was more severe in males than in females. Kubena *et al.* (1981) reported that body weight gains were reduced (about 50%) in male and female chicks fed a diet containing 6080 ppm of the isopropylamine salt of glyphosate for 21 days, beginning at 1 day of age; the calcium and magnesium content of the tibiotarsus bone was increased compared to controls. There were no differences in body weights in chicks fed a dose of 608 ppm or lower. In the Kubena study (which did not mention feed palatability) and in our 13-week study, the possibility of reduced food intake in the high dose groups cannot be ruled out; more food tends to be spilled when it is not palatable, and our food consumption measurements did not account for scattered feed. Poor palatability of feed containing high concentrations of glyphosate is suggested by the finding that rats drank less water containing Roundup® at 10000 ppm or higher. Another possibility is that the higher concentrations of glyphosate in feed result in poor absorption of dietary components from the GI tract. However, if uncoupling of oxidative phosphorylation, as proposed by Olorunsogo *et al.* (1979) and Bababunmi *et al.* (1979), is occurring as a result of glyphosate ingestion, then a reduction in weight gain for a given amount of food consumed would be expected.

Hematologic effects in rats dosed with glyphosate were unremarkable and generally consistent with mild dehydration (increases in RBC counts, hematocrit, and hemoglobin concentrations). This conclusion also is supported by the mild increases that occurred at various time points in serum concentrations of urea nitrogen, total protein and albumin. Mild but significant increases in concentrations of TBA and in activities of serum alanine aminotransferase and alkaline phosphatase at multiple time points in male and female rats are consistent with an hepatobiliary effect. These findings likely reflect hepatocellular leakage or perhaps single cell necrosis (ALT) and cholestasis (TBA and ALP). Increases in absolute and relative liver weights in female rats also were suggestive of an effect of glyphosate on the liver, and support the clinical pathology findings. However, the lack of histopathologic evidence for a treatment-related effect on the liver indicates the mild nature of the hepatotoxicity. Vainio *et al.* (1983) reported an absence of peroxisome

proliferation or hypolipidemia in male Wistar rats given Roundup® daily by gavage at 300 mg/kg, 5 times a week for 2 weeks; these daily doses were more than 10-fold lower than those achieved in the highest dose groups in the current study.

Measures of sperm density, or the number of sperm/g caudal epididymal tissue, were reduced somewhat in male rats in the 2 highest dose groups; other spermatozoal measurements were not different from controls in rats or mice. There was a slight lengthening of the estrous cycle in high dose female rats, but the biologic significance of these findings, if any, is not known.

It is noteworthy that the U.S. Environmental Protection Agency, after reviewing an unpublished 2-year carcinogenicity study of glyphosate in CD-1 mice, announced that there was "an equivocal carcinogenic response, possibly causing a slight increase in the incidence of renal tubular adenomas in male mice at the highest dose tested (30000 ppm)." A carcinogenicity study in rats has yet to be reviewed (Anonymous, 1991). In the present study, however, the salivary gland was identified as the sole target organ for glyphosate toxicity in both rats and mice. The lesion was diagnosed as cytoplasmic alteration of the acinar epithelial cells, consisting of increased basophilic staining and vacuolation of cytoplasm, and enlargement of cells and acini. This lesion was limited to the parotid gland in mice but affected both parotid and submandibular glands in rats; the sublingual gland was not affected. Salivary gland lesions are relatively uncommon in toxicity studies; however, both spontaneous and chemically-induced changes of a similar nature to those seen in the glyphosate study have been described. So-called "basophilic hypertrophic foci" occasionally may be seen as a spontaneous lesion in the parotid gland of rats and mice (Chiu and Chen, 1986); however, these are infrequent and focal in nature. More extensive and diffuse basophilic and hypertrophic change has been described in subchronic studies with some chemicals, such as doxylamine (Jackson and Blackwell, 1988) and methapyrilene (Jackson and Sheldon, 1984). By far, the most extensive and detailed studies of these changes in salivary glands have been done with sympathomimetic agents -- for example, the adrenergic agonist, isoproterenol, which induces striking morphologic changes in salivary glands (Schneyer, 1962; Fukuda, 1968). As with glyphosate's effects on the salivary glands, isoproterenol affects the parotid and submandibular glands but not the sublingual. This is due to the fact that, in the rat, the acini of the parotid and submandibular are richly supplied with adrenergic fibers, while the sublingual gland is devoid of adrenergic innervation (Nordenfelt, 1967). Because glyphosate and isoproterenol are similar in both the morphologic effects induced in the salivary glands and the gland specificity of those effects, it was hypothesized that glyphosate-related lesions were mediated through an adrenergic mechanism. A study was designed to test this hypothesis.

Two weeks' exposure to glyphosate by dosed feed resulted in marked increases in parotid and submandibular salivary gland weights. This effect on salivary gland weights is similar to that of isoproterenol, both as described in the literature (Schneyer, 1962) and as seen in the positive control group of this study. Increased salivary gland weights were associated histologically with cytoplasmic alteration of acinar cells. This effect was more marked in the parotid than in the submandibular gland. In the parotid, the cytoplasmic change induced by both glyphosate and isoproterenol was associated with a loss of the normal PAS-positive reactivity of the secretory granules, indicating either a loss of the granules or a change in their chemical composition. The sublingual gland was not affected histologically by either glyphosate or isoproterenol, demonstrating target specificity of glyphosate- and isoproterenol-associated lesions to those salivary glands which are innervated by adrenergic fibers (Nordenfelt, 1967).

The effect of adrenoreceptor stimulation on parotid acinar cells has been described by ultrastructural and morphometric criteria to be increases in cell size, primarily due to increases in the number and size of secretory granules, as well as changes in the staining of these granules from electron dense to lucent, interpreted to represent a mucoid transformation of the cell (Schneyer, 1962; Henriksson, 1982; Carlsoo *et al.*, 1984). These findings are identical to those found upon electron microscopic examination of parotid cells from animals treated with both glyphosate and isoproterenol in this study, the effects varying only in degree between the chemicals. Ultrastructural effects in the submandibular gland were similar between these compounds, though of a less well-defined nature, These effects consisted of cell enlargement due to accumulation of lucent or heterogenous staining mucoid type granules, although it was not clear whether the serous or mucous cells of the acinus were being affected. This study led to the conclusion that the salivary gland effect is mediated through an adrenergic mechanism, as evidenced by (1) inhibition of the glyphosate-induced effect by the adrenergic antagonist, propranolol; (2) the similarity between the effects of glyphosate and the adrenergic agonist, isoproterenol; and (3) the specificity of those effects for salivary glands with adrenergic innervation. The biologic significance of this finding is unknown. In addition to basophilic and hypertrophic morphologic changes of acinar cells, treatment with isoproterenol has been associated with increased cell proliferation in the parotid gland (Schneyer *et al.*, 1967). This suggests that if glyphosate is acting through an adrenergic pathway, it may likewise induce hyperplasia in this gland, possibly predisposing it to neoplastic change; however, this is not considered likely, since spontaneous basophilic, hypertrophic foci of the parotid, as well as of the pancreas (an anatomically similar tissue) are not considered to be preneoplastic lesions. Moreover, there was no increased incidence in rats of salivary gland tumors in a 2-year study of methapyrilene (personal communication, Dr. I. Hirono, Fujita Gakuen Health University, Japan, May 17, 1991), a chemical which induced similar salivary gland lesions as glyphosate in subchronic studies.

The results of the *Salmonella typhimurium* assays and micronuclei tests showed no evidence that glyphosate is genotoxic. A similar conclusion was drawn by Li and Long (1988) after evaluating glyphosate in a battery of genotoxicity assays including *Salmonella typhimurium* reversion, *E. coli* WP-2 reversion, CHO/HGPRT gene mutation, hepatocyte/DNA repair, and *in vivo* rat bone marrow cytogenetics. Moriya *et al.* (1983) also reported negative findings in *Salmonella* (TA100, TA98, TA1535, TA1537, and TA1538) and *E. coli* (WP2 hcr) assays.

In summary, these studies demonstrated that glyphosate was incompletely absorbed from the gastrointestinal tract and excreted in the urine after oral administration. The unabsorbed portion of the dose was excreted in feces. There was no evidence of genetic or reproductive toxicity of glyphosate. At doses of 25000 and 50000 ppm in the feed, glyphosate reduced body weight gain, caused cytoplasmic alteration and hypertrophy of salivary gland acinar cells, and elevated serum bile acids, alkaline phosphatase, and alanine aminotransferase activities, although there was no histopathologic evidence of liver injury. The effects on salivary glands appeared to be adrenergically mediated and could be counteracted by the adrenergic antagonist propranolol. The no-observed-adverse effect level (NOAEL) for the salivary gland lesion was 3125 ppm in the feed for mice, but the lesion was observed at all dose levels studied in rats.

REFERENCES

Ahotupa, M., Hietanen, E., Mantyla, E., and Vainio, H. (1983) Enhancement of extrahepatic drug metabolism by phenoxyacid herbicides and clofibrate, in Rydstrjom, J., Montehus, J., and Bengtsson, M. (eds.), *Extrahepatic Drug Metabolism and Chemical Carcinogenesis*. Amsterdam: Elsevier Science Publishers, pp. 245-6.

Amrhein, N., Deus, B., Gehrke, P., Hollander, H., Schab, J., Schulz, A., Steinrucken, H.C. (1981) Interference of glyphosate with the shikimate pathway. *Proc. Plant Growth Regul. Soc. Am.,* **8,** 99-106.

Amrhein, N., Schab, J., Steinrucken, H.C. (1980) The mode of action of the herbicide glyphosate. *Naturwissensch* **67,** 356-357.

Anonymous (1991) Glyphosate tolerances proposed. *Pesticide & Toxic Chemical News,* February 13.

Bababunmi, E.A., Olorunsogo, O. O., and Bassir, O. (1978) Toxicology of glyphosate in rats and mice. *Toxicol. Appl. Pharmacol.*, **45,** 319-320.

Bababunmi, E.A., Olorunsogo, O.O., and Bassir, O. (1979) The uncoupling effect of N-(phosphonomethyl) glycine on isolated rat liver mitochondria. *Biochem. Pharmacol.* **28,** 925-927.

Beste, C.E. (1983) *Herbicide Handbook of the Weed Science Society of America*, 5th Edition. Weed Science Society of America, pp. 258-263.

Boorman, G.A., Hickman, R.L., Davis, G.W., Rhode, L.S., White, N.W., Griffin, T.A., Mayo, J., and Hamm, T.E., Jr. (1986) Serological titers to murine viruses in 90-day and 2-year studies, in Hamm, T. E., Jr., (ed.), *Complications of Viral and Mycoplasmal Infections in Rodents to Toxicology Research and Testing*, New York: Hemisphere, pp 11-23.

Carlsoo, B., Danielsson, A., Henriksson, R., Jonsson, G., and Sunstrom, S. (1984) Inhomo-geneities in glycoprotein cytochemistry of secretory granules in rat parotid acinar cells after selective beta-1 adrenoceptor stimulation. *Archs. Oral. Biol.* **29**(12), 953-958.

Chiu, T. and Chen, H.C. (1986) Spontaneous basophilic hypertrophic foci of the parotid glands of rats and mice. *Vet. Path.* **23,** 606-609.

Dixon, W., and Massey, F. (1951) *Introduction to Statistical Analysis*. New York: McGraw Hill, pp. 145-147.

Dunn, O.J. (1964) Multiple comparisons using rank sums. *Technometrics* **6,** 241-252.

Dunnett, W. (1955) A multiple comparison procedure for comparing several treatments with a control. *J. Am. Stat. Assoc.* **50,** 1095-1121.

Folmar, L.C., Sanders, H.O., and Julin, A.M. (1979) Toxicity of the herbicide glyphosate and several of its formulations to fish and aquatic invertebrates. *Arch. Environm. Contam. Toxicol.* **8,** 269-278.

Fukuda, M. (1968) The influence of isoprenaline and propranolol on the submaxillary gland of the rat. *Jap. J. Pharmac.* **18,** 185-199.

Ghassemi, M., Quinlivan, S., and Dellarco, M. (1982) Environmental effects of new herbicides for vegetation control in forestry. *Environ. Int.* **7,** 389-402.

Glass, R.L. (1984) Metal complex formation by glyphosate. *J. Agric. Food Chem.* **32,** 1249-1253.

Henriksson, R. (1982) Beta-1 and beta-2 adrenoceptor agonists have different effects on rat parotid acinar cells. *Am. J. Physiol.* **242**(5), G481.

Hietanen, E., Linnainmaa, K., Vainio, H. (1983) Effects of phenoxyherbicides and glyphosate on the hepatic and intestinal biotransformation activities in the rat. *Acta. Pharmacol. Toxicol.* **53,** 103-112.

Hoagland, R.E. and Duke, S.O. (1982) Biochemical effects of glyphosate [N-(phosphono-methyl)glycine]. *ACS Symp. Ser.* **181,** 175-205.

Jackson, C.D., and Blackwell, B. (1988) Subchronic studies of doxylamine in Fischer 344 rats. *Fundam. Appl. Toxicol.* **10,** 243-253.

Jackson, C.D. and Sheldon, W. (1984) 90-day subchronic report on methapyrilene (neutral drinking water) in Fischer 344 rats, NCTR Technical Report for Experiment No. 382. Jefferson, AR: National Center for Toxicological Research.

Jonckheere, A.R. (1954) A distribution-free k-sample test against ordered alternatives. *Biometrika* **41,** 133-145.

Kubena, L.F., Smalley, H.E., and Farr, F.M. (1981) Influence of Glyphosate [N-(phosphonomethyl) glycine] on performance and selected parameters in broilers. *Poultry Sci.* **60,** 132-136.

Li, A.P., and Long, T.J. (1988) An evaluation of the genotoxic potential of glyphosate. *Fundam. Appl. Toxicol.* **10,** 537-546.

MacGregor, J.T., Wehr, C.M., and Langlois, R.G. (1983) A simple fluorescent staining procedure for micronuclei and RNA in erythrocytes using Hoechst 33258 and pyronin Y. *Mutat. Res.* **120,** 269-275.

Moriya, M., Ohta, T., Watanabe, K., Miyazawa, T., Kato, K., and Shirasu, Y. (1983) Further mutagenicity studies on pesticides in bacterial reversion systems. *Mutat. Res.* **116,** 185-216.

Morrison, D. F. (1976) *Multivariate Statistical Methods*. New York: McGraw Hill, pp. 170-179.

Morrissey, R.E., Schwetz, B.A., Lamb, J.G., IV, Ross, M.C., Teague, J.L., and Morris, R.W. (1988) Evaluation of rodent sperm, vaginal cytology, and reproductive organ weight data from National Toxicology Program thirteen-week studies. *Fundam. Appl. Toxicol.* **11,** 343-358.

Newton, M., Howard, K.M., Kelpsas, B.R., Danhaus, R., Lottman, M., and Dubelman, S. (1984) Fate of glyphosate in an Oregon forest ecosystem. *J. Agric. Food Chem.* **32,** 1144-1151.

Nordenfelt, I. (1967) Metabolism of transmitter substances in salivary glands, in Schneyer, L.H., and Schneyer, C.A., (eds.), *Secretory Mechanisms of Salivary Glands*. New York: Academic Press, pp. 142-154.

Olorunsogo, O.O. (1982a) Defective nicotinamide nucleotide transhydrogenase reaction in hepatic mitochondria of N-(phosphonmeklthyl)-glycine treated rats. *Biochem. Pharmacol.* **31,** 2191-2192.

Olorunsogo, O.O. (1982b) Inhibition of energy-dependent transhydrogenase reaction by N-(phosphonomethyl) glycine in isolated rat liver mitochondria. *Toxicol. Lett.* **10,** 91-95.

Olorunsogo, O.O. and Bababunmi, E.A. (1980) Interference of herbicides with mitochondrial oxidative phosphorylation: the N-(phosphonomethyl)glycine model. *Toxicol. Lett.* **(Spec. Issue 1),** 148.

Olorunsogo, O.O., Bababunmi, E.A., and Bassir, O. (1979) Effects of glyphosate on rat liver mitochondria *in vivo*. *Bull. Environm. Contam. Toxicol.* **22,** 357-364.

Rao, G.N., Haseman, J.K., and Edmonson, J. (1989) Influence of viral infections on body weight, survival, and tumor prevalence in Fischer 344/NCr rats on two-year studies. *Lab. Animal Sci.* **39**, 389-393.

Rao, G.N., Piegorsch, W.W., Crawford, D.D., Edmondson, J., and Haseman, J.K. (1989a) Influence of viral infections on body weight, survival, and tumor prevalence of B6C3F$_1$ (C57BL/6N X C3H/Hen) mice in carcinogenicity studies. *Fund. Appl. Toxicol.* **13,** 156-164.

Rueppel, M., Brightwell, B.B., Schaefer, J., and Marvel, J.T. (1977) Metabolism and degradation of glyphosate in soil and water. *J. Agric. Food Chem.* **25,** 517-528.

Sawada, Y., Nagai, Y., Ueyama, M., and Yamamoto, I. (1988) Probable toxicity of surface-active agent in commercial herbicide containing glyphosate. *The Lancet* **1,** 299.

Schneyer, C.A. (1962) Salivary gland changes after isoproterenol-induced enlargement. *Am J. Physiol.* **203,** 232-236.

Schneyer, C.A., Finley, W.H., and Finley, S.C. (1967) Increased chromosome number of rat parotid cells after isoproterenol. *Proc. Soc. Exp. Biol. Med.* **125,** 722.

Shirley, E. (1977) A non-parametric equivalent of William's test for contrasting increasing dose levels of a treatment. *Biometrics* **33,** 386-389.

Sprankle, P., Meggitt, W.F., and Penner, D. (1975) Absorption, mobility, and microbial degradation of glyphosate in the soil. *Weed Science* **23,** 229-234.

Stark, J. (1983) Persistence of herbicides in forest soils. *Weeds and Weed Control*, **24,** 275-286.

U.S. Environmental Protection Agency (U.S. EPA) (1979) Information provided based on review of glyphosate registration files (majority of the data originally supplied by Monsanto Company). Washington, D.C.

Vainio, H., Linnainmaa, K., Kahonen, M., Nickels, J., Hietanen, E., Marniemi, J., and Peltonen, P. (1983) Hypolipidemia and peroxisome proliferation induced by phenoxyacetic acid herbicides in rats. *Biochem. Pharmacol.* **32,** 2775-2779.

Wan, M.T., Watts, R.G., and Moul, D.J. (1989) Effects of different dilution water types on the acute toxicity to juvenile Pacific salmonids and rainbow trout of glyphosate and its formulated products. *Bull. Environ. Contam. Toxicol.* **43,** 378-385.

Wester, R.C., Melendres, J., Sarason, R., McMaster, J., and Maibach, H.I. (1991) Glyphosate skin binding, absorption, residual tissue distribution, and skin decontamination. *Fundam. Appl. Toxicol.* **16,** 725-732.

Williams, D.A. (1971) A test for differences between treatment means when several dose levels are compared with a zero dose control. *Biometrics* **27,** 103-117.

Williams, D.A. (1972) The comparison of several dose levels with a zero dose control. *Biometrics* **28,** 519-531.

Williams, D.A. (1986) A note on Shirley's nonparametric test for comparing several dose levels with a zero control. *Biometrics* **42,** 183-186.

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., and Mortelmans, K. (1988) Salmonella mutagenicity tests. IV. Results from the testing of 300 chemicals. *Environ. Molec. Mutagen.* **11** (Suppl 12), 1-158.

APPENDIX A

Organ Weights and Organ-Weight-to-Body-Weight Ratios

TABLE A1 Organ Weights and Organ-Weight-to-Body-Weight Ratios for F344/N Rats in the 13-Week Feed Study of Glyphosate[1]

	0 ppm	3125 ppm	6250 ppm	12,500 ppm	25,000 ppm	50,000 ppm
MALE						
n	10	10	10	10	10	10
Necropsy body wt	358 ± 5	358 ± 7	351 ± 5	350 ± 5	340 ± 5*	305 ± 7**
Heart						
Absolute	1 02 ± 0 02	1 01 ± 0 03	0 96 ± 0 02	1 02 ± 0 02	0 96 ± 0 02	0 89 ± 0 03**
Relative	2 83 ± 0 03	2 82 ± 0 04	2 74 ± 0 03	2 91 ± 0 04	2 83 ± 0 04	2 92 ± 0 05
Right Kidney						
Absolute	1 21 ± 0 02	1 29 ± 0 04	1 20 ± 0 02	1 21 ± 0 03	1 24 ± 0 02	1 16 ± 0 03
Relative	3 38 ± 0 06	3 61 ± 0 06	3 42 ± 0 05	3 46 ± 0 07	3 65 ± 0 06**	3 82 ± 0 06**
Liver						
Absolute	13 28 ± 0 32	14 45 ± 0 49	13 74 ± 0 31	13 81 ± 0 34	14 58 ± 0 41	12 52 ± 0 41
Relative	37 1 ± 1 0	40 3 ± 0 9*	39 2 ± 0 8*	39 5 ± 0 6*	42 8 ± 1 0**	41 0 ± 0 6**
Lungs						
Absolute	1 41 ± 0 02	1 32 ± 0 03	1 30 ± 0 05	1 33 ± 0 03	1 27 ± 0 04**	1 21 ± 0 04**
Relative	3 95 ± 0 08	3 69 ± 0 08	3 70 ± 0 12	3 80 ± 0 07	3 73 ± 0 08	3 99 ± 0 11
Right Testis						
Absolute	1 42 ± 0 03	1 48 ± 0 02	1 40 ± 0 02	1 40 ± 0 08	1 44 ± 0 02[2]	1 45 ± 0 04
Relative	3 95 ± 0 05	4 15 ± 0 06	4 00 ± 0 04	4 00 ± 0 20	4 24 ± 0 06*[2]	4 76 ± 0 05**
Thymus						
Absolute	0 33 ± 0 01	0 31 ± 0 01	0 30 ± 0 01	0 31 ± 0 02	0 30 ± 0 01	0 24 ± 0 01**
Relative	0 92 ± 0 04	0 86 ± 0 03	0 86 ± 0 05	0 88 ± 0 05	0 87 ± 0 04	0 80 ± 0 03*
FEMALE						
n	10	10	10	10	10	10
Necropsy body wt	189 ± 3	189 ± 3	194 ± 3	191 ± 2	185 ± 3	184 ± 5
Heart						
Absolute	0 64 ± 0 01	0 63 ± 0 01	0 63 ± 0 01	0 63 ± 0 02	0 61 ± 0 01	0 60 ± 0 02
Relative	3 36 ± 0 05	3 31 ± 0 07	3 23 ± 0 06	3 31 ± 0 08	3 30 ± 0 05	3 27 ± 0 09
Right Kidney						
Absolute	0 71 ± 0 02	0 71 ± 0 02	0 71 ± 0 02	0 72 ± 0 01	0 71 ± 0 02	0 73 ± 0 01
Relative	3 73 ± 0 09	3 73 ± 0 09	3 66 ± 0 09	3 77 ± 0 05	3 81 ± 0 06	3 99 ± 0 09*
Liver						
Absolute	5 93 ± 0 13	6 07 ± 0 10	6 40 ± 0 17	6 35 ± 0 14	6 42 ± 0 18	6 10 ± 0 20
Relative	31 4 ± 0 7	32 1 ± 0 7	33 0 ± 0 9	33 3 ± 0 6	34 6 ± 0 6*	33 2 ± 0 7*
Lungs						
Absolute	0 94 ± 0 02	0 91 ± 0 04	0 90 ± 0 02	0 89 ± 0 01	0 93 ± 0 03	0 88 ± 0 03
Relative	4 95 ± 0 08	4 81 ± 0 16	4 67 ± 0 08	4 64 ± 0 06	4 99 ± 0 10	4 80 ± 0 08
Thymus						
Absolute	0 26 ± 0 01	0 24 ± 0 01	0 24 ± 0 01	0 23 ± 0 01*	0 23 ± 0 01*	0 23 ± 0 01*
Relative	1 35 ± 0 04	1 27 ± 0 04	1 23 ± 0 03	1 18 ± 0 04**	1 25 ± 0 05	1 25 ± 0 03

[1] Organ weights and body weights are given in grams, organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)

[2] n=9

* Statistically significantly different (P≤0 05) from the control group by Williams' test or Dunnett's test

** Statistically significantly different (P≤0 01) from the control group by Williams' test or Dunnett's test

TABLE A2 Organ Weights and Organ-Weight-to-Body-Weight Ratios for B6C3F$_1$ Mice in the 13-Week Feed Study of Glyphosate[1]

	0 ppm	3125 ppm	6250 ppm	12,500 ppm	25,000 ppm	50,000 ppm
MALE						
n	10	10	10	10	10	10
Necropsy body wt	32 0 ± 1 0	31 8 ± 1 1	32 4 ± 0 6	31 9 ± 0 9	29 4 ± 0 7*	27 2 ± 0 4**
Heart						
Absolute	0 145 ± 0 003	0 149 ± 0 004	0 161 ± 0 006	0 168 ± 0 006*	0 153 ± 0 007	0 153 ± 0 007
Relative	4 56 ± 0 14	4 71 ± 0 11	4 98 ± 0 17	5 31 ± 0 22**	5 21 ± 0 20**	5 60 ± 0 20**
Right Kidney						
Absolute	0 279 ± 0 006	0 295 ± 0 006	0 313 ± 0 011	0 320 ± 0 009*	0 316 ± 0 014	0 278 ± 0 012
Relative	8 74 ± 0 15	9 35 ± 0 24	9 68 ± 0 31*	10 07 ± 0 27**	10 75 ± 0 40**	10 18 ± 0 31**
Liver						
Absolute	1 39 ± 0 05	1 46 ± 0 07	1 54 ± 0 06	1 43 ± 0 05	1 38 ± 0 04	1 28 ± 0 04
Relative	43 4 ± 0 9	45 8 ± 0 8	47 5 ± 1 3*	45 0 ± 0 9*	47 0 ± 0 8*	47 1 ± 1 0*
Lungs						
Absolute	0 159 ± 0 003	0 173 ± 0 007	0 188 ± 0 012	0 183 ± 0 005	0 179 ± 0 010	0 174 ± 0 007
Relative	5 00 ± 0 16	5 45 ± 0 16	5 81 ± 0 37*	5 78 ± 0 20*	6 11 ± 0 35**	6 38 ± 0 20**
Right Testis						
Absolute	0 118 ± 0 002	0 117 ± 0 003	0 122 ± 0 003	0 116 ± 0 003	0 120 ± 0 003	0 119 ± 0 004
Relative	3 71 ± 0 12	3 69 ± 0 10	3 77 ± 0 07	3 66 ± 0 06	4 08 ± 0 10**	4 37 ± 0 11**
Thymus						
Absolute	0 036 ± 0 002	0 037 ± 0 002	0 042 ± 0 002	0 040 ± 0 002	0 36 ± 0 002	0 038 ± 0 002
Relative	1 14 ± 0 08	1 15 ± 0 05	1 31 ± 0 07	1 26 ± 0 05	1 21 ± 0 05	1 39 ± 0 05**
FEMALE						
n	9	10	10	10	10	9
Necropsy body wt	28 8 ± 0 7	28 7 ± 0 6	27 1 ± 0 6	28 7 ± 0 4	27 0 ± 0 6*	25 6 ± 0 3**
Heart						
Absolute	0 143 ± 0 008	0 138 ± 0 004	0 140 ± 0 007	0 135 ± 0 004	0 132 ± 0 005	0 124 ± 0 004*
Relative	4 98 ± 0 21	4 83 ± 0 16	5 17 ± 0 26	4 72 ± 0 17	4 90 ± 0 20	4 86 ± 0 18
Right Kidney						
Absolute	0 214 ± 0 009	0 235 ± 0 007	0 217 ± 0 009	0 222 ± 0 005	0 212 ± 0 005	0 212 ± 0 006
Relative	7 45 ± 0 21	8 22 ± 0 28	8 02 ± 0 31	7 75 ± 0 18	7 87 ± 0 23	8 28 ± 0 22
Liver						
Absolute	1 37 ± 0 06	1 37 ± 0 03	1 33 ± 0 04	1 32 ± 0 03	1 27 ± 0 03	1 18 ± 0 03**
Relative	47 5 ± 1 3	47 8 ± 1 1	49 1 ± 0 9	45 9 ± 1 0	46 9 ± 0 7	46 1 ± 0 9
Lungs						
Absolute	0 182 ± 0 007	0 175 ± 0 005	0 181 ± 0 011	0 180 ± 0 005	0 167 ± 0 007	0 171 ± 0 006
Relative	6 33 ± 0 19	6 12 ± 0 22	6 69 ± 0 39	6 29 ± 0 21	6 21 ± 0 31	6 67 ± 0 22
Thymus						
Absolute	0 056 ± 0 003	0 049 ± 0 002	0 055 ± 0 004	0 048 ± 0 003	0 044 ± 0 003**	0 045 ± 0 002**
Relative	1 94 ± 0 08	1 71 ± 0 06	2 01 ± 0 15	1 68 ± 0 11	1 61 ± 0 09	1 75 ± 0 07

[1] Organ weights and body weights are given in grams, organ-weight-to body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)

* Statistically significantly different (P≤0 05) from the control group by Williams' test or Dunnett s test

** Statistically significantly different (P≤0 01) from the control group by Williams' test or Dunnett s test

APPENDIX B

Hematology and Clinical Chemistry

TABLE B1 Hematology Data for F344/N Rats in the 13-Week Feed Study of Glyphosate[1]

Analysis	0 ppm	3125 ppm	6250 ppm	12,500 ppm	25,000 ppm	50,000 ppm
MALE						
n	10	10	10	10	10	10
Hematocrit (%)						
Day 5	38.4 ± 1.1	39.4 ± 0.7[2]	40.2 ± 0.3	40.8 ± 0.4	38.9 ± 0.4[3]	40.4 ± 0.6[3]
Day 21	43.7 ± 0.6	44.9 ± 0.4	44.2 ± 0.5	44.8 ± 0.4	43.7 ± 0.4[2]	42.9 ± 0.8
Day 90	45.2 ± 0.3	44.9 ± 0.2	45.9 ± 0.4	46.0 ± 0.5*	47.8 ± 1.1**	48.4 ± 0.5**
Hemoglobin (g/dL)						
Day 5	12.9 ± 0.4	13.3 ± 0.3[2]	13.6 ± 0.2	13.7 ± 0.1	13.0 ± 0.2[3]	13.7 ± 0.2[3]
Day 21	15.0 ± 0.2	15.4 ± 0.2	15.2 ± 0.2	15.3 ± 0.1	15.1 ± 0.2[2]	14.8 ± 0.3
Day 90	14.9 ± 0.1	14.8 ± 0.1	15.1 ± 0.1	15.1 ± 0.1	15.6 ± 0.3*	15.9 ± 0.2**
Erythrocytes (10^6/μL)						
Day 5	6.40 ± 0.21	6.76 ± 0.24[2]	6.72 ± 0.10	6.87 ± 0.12	6.49 ± 0.17[3]	6.72 ± 0.16[3]
Day 21	7.63 ± 0.11	7.99 ± 0.10	7.79 ± 0.10	7.89 ± 0.09	7.68 ± 0.08[2]	7.62 ± 0.15
Day 90	9.36 ± 0.06	9.32 ± 0.05	9.47 ± 0.09	9.58 ± 0.09*	9.91 ± 0.21**	9.97 ± 0.08**
Reticulocytes (10^6/μL)						
Day 5	0.62 ± 0.12	0.46 ± 0.16[2]	0.52 ± 0.13	0.40 ± 0.13	0.49 ± 0.14[3]	0.64 ± 0.17[3]
Day 21	0.10 ± 0.02	0.09 ± 0.02	0.11 ± 0.01	0.16 ± 0.03	0.10 ± 0.02[2]	0.09 ± 0.02
Day 90	0.04 ± 0.01	0.05 ± 0.01	0.05 ± 0.01	0.05 ± 0.01	0.04 ± 0.01	0.03 ± 0.01
Mean cell volume (fL)						
Day 5	60.0 ± 0.9	58.6 ± 1.3[2]	59.9 ± 0.7	59.6 ± 1.0	60.1 ± 1.2[3]	60.1 ± 0.7[3]
Day 21	57.3 ± 0.4	56.3 ± 0.5	56.8 ± 0.2	56.8 ± 0.4	57.0 ± 0.4[2]	56.3 ± 0.3
Day 90	48.2 ± 0.2	48.2 ± 0.1	48.5 ± 0.2	47.9 ± 0.2	48.3 ± 0.2	48.5 ± 0.3
Mean cell hemoglobin (pg)						
Day 5	20.2 ± 0.4	19.7 ± 0.4[2]	20.2 ± 0.2	20.0 ± 0.3	20.1 ± 0.4[3]	20.4 ± 0.3[3]
Day 21	19.7 ± 0.2	19.2 ± 0.2*	19.6 ± 0.1	19.4 ± 0.1	19.7 ± 0.1[2]	19.4 ± 0.1
Day 90	15.9 ± 0.1	15.9 ± 0.1	16.0 ± 0.1	15.8 ± 0.1	15.8 ± 0.1	15.9 ± 0.1
Mean cell hemoglobin concentration (g/dL)						
Day 5	33.5 ± 0.2	33.7 ± 0.1[2]	33.7 ± 0.2	33.5 ± 0.1	33.5 ± 0.2[3]	33.9 ± 0.2[3]
Day 21	34.4 ± 0.1	34.1 ± 0.2	34.5 ± 0.2	34.3 ± 0.1	34.6 ± 0.2[2]	34.5 ± 0.2
Day 90	33.0 ± 0.2	33.0 ± 0.2	33.0 ± 0.1	32.8 ± 0.1	32.7 ± 0.2	32.9 ± 0.1
Platelets (10^3/μL)						
Day 5	1004.7 ± 17.8	1003.9 ± 38.9[2]	1029.2 ± 38.8	990.7 ± 28.4	1051.0 ± 17.1[3]	1093.3 ± 19.8*[3]
Day 21	753.8 ± 19.9	761.1 ± 14.0	758.9 ± 14.1	801.7 ± 16.4*	794.2 ± 15.9*[2]	756.0 ± 19.4
Day 90	603.3 ± 13.3	617.8 ± 6.2	611.7 ± 9.2	592.3 ± 8.8	624.5 ± 9.9	672.5 ± 15.9**
Leukocytes (10^3/μL)						
Day 5	4.75 ± 0.71	4.66 ± 0.72[2]	6.10 ± 0.58	5.87 ± 0.52	3.85 ± 0.55[3]	6.91 ± 0.74[3]
Day 21	6.80 ± 0.68	7.54 ± 0.47	7.13 ± 0.70	7.84 ± 0.74	5.98 ± 0.94[2]	6.69 ± 0.64
Day 90	9.59 ± 0.29	9.42 ± 0.50	8.10 ± 0.36*	8.78 ± 0.37	8.91 ± 0.59	10.30 ± 0.47
Segmented neutrophils (10^3/μL)						
Day 5	0.59 ± 0.09	0.69 ± 0.09[2]	0.70 ± 0.09	0.87 ± 0.06	0.61 ± 0.07[3]	0.70 ± 0.12[3]
Day 21	0.95 ± 0.10	0.94 ± 0.06	0.91 ± 0.13	0.75 ± 0.10	0.59 ± 0.08*[2]	0.81 ± 0.14
Day 90	1.45 ± 0.18	1.26 ± 0.13	1.07 ± 0.17	1.24 ± 0.11	1.15 ± 0.15	1.19 ± 0.09
Lymphocytes (10^3/μL)						
Day 5	4.02 ± 0.68	3.78 ± 0.61[2]	5.20 ± 0.50	4.81 ± 0.48	3.08 ± 0.47[3]	6.00 ± 0.68[3]
Day 21	5.59 ± 0.57	6.32 ± 0.43	5.96 ± 0.56	6.74 ± 0.65	5.26 ± 0.85[2]	5.70 ± 0.54
Day 90	7.70 ± 0.24	7.55 ± 0.38	6.70 ± 0.32	7.10 ± 0.35	7.21 ± 0.54	8.38 ± 0.41
Monocytes (10^3/μL)						
Day 5	0.12 ± 0.03	0.18 ± 0.04[2]	0.16 ± 0.04	0.16 ± 0.03	0.16 ± 0.06[3]	0.23 ± 0.05[3]
Day 21	0.22 ± 0.07	0.26 ± 0.06	0.22 ± 0.04	0.32 ± 0.07	0.11 ± 0.03[2]	0.14 ± 0.03
Day 90	0.34 ± 0.10	0.52 ± 0.14	0.22 ± 0.07	0.37 ± 0.07	0.42 ± 0.10	0.61 ± 0.17
Eosinophils (10^3/μL)						
Day 5	0.01 ± 0.01	0.01 ± 0.01[2]	0.04 ± 0.02	0.01 ± 0.01	0.00 ± 0.00[3]	0.04 ± 0.02[3]
Day 21	0.04 ± 0.02	0.05 ± 0.02	0.07 ± 0.03	0.05 ± 0.02	0.04 ± 0.02[2]	0.02 ± 0.01
Day 90	0.13 ± 0.04	0.08 ± 0.02	0.11 ± 0.03	0.08 ± 0.03	0.13 ± 0.04	0.11 ± 0.03

TABLE B1 Hematology Data for F344/N Rats in the 13-Week Feed Study of Glyphosate (continued)

Analysis	0 ppm	3125 ppm	6250 ppm	12,500 ppm	25,000 ppm	50,000 ppm
FEMALE						
n	10	10	10	10	10	10
Hematocrit (%)						
Day 5	40 8 ± 0 6	40 9 ± 0 8[2]	39 9 ± 0 7	41 0 ± 0 4	41 2 ± 0 7	42 4 ± 0 6
Day 21	47 8 ± 0 8	45 8 ± 0 6	46 1 ± 0 5	46 5 ± 0 5	47 1 ± 0 6	46 6 ± 0 4
Day 90	45 1 ± 0 3	45 8 ± 0 5	45 3 ± 0 3	46 0 ± 0 3	45 6 ± 0 5	45 4 ± 0 6
Hemoglobin (g/dL)						
Day 5	13 6 ± 0 2	13 5 ± 0 2[2]	13 2 ± 0 3	13 5 ± 0 1	13 7 ± 0 2	14 3 ± 0 2*
Day 21	16 1 ± 0 3	15 6 ± 0 2	15 5 ± 0 2	15 7 ± 0 2	15 9 ± 0 2	15 9 ± 0 1
Day 90	14 9 ± 0 1	15 1 ± 0 1	15 0 ± 0 1	15 0 ± 0 1	15 0 ± 0 1	15 1 ± 0 2
Erythrocytes (10^6/μL)						
Day 5	6 90 ± 0 10	7 03 ± 0 20[2]	6 79 ± 0 15	7 04 ± 0 12	7 07 ± 0 14	7 50 ± 0 15**
Day 21	8 33 ± 0 15	7 98 ± 0 10	8 03 ± 0 09	8 10 ± 0 08	8 21 ± 0 08	8 24 ± 0 07
Day 90	8 85 ± 0 04	8 96 ± 0 08	8 80 ± 0 05	8 98 ± 0 06	8 86 ± 0 09	8 79 ± 0 12
Reticulocytes (10^6/μL)						
Day 5	0 13 ± 0 08	0 22 ± 0 11[2]	0 26 ± 0 11	0 27 ± 0 16	0 20 ± 0 09	0 64 ± 0 15**
Day 21	0 03 ± 0 01	0 03 ± 0 01	0 03 ± 0 01	0 03 ± 0 01	0 02 ± 0 01	0 02 ± 0 00
Day 90	0 08 ± 0 02	0 07 ± 0 02	0 10 ± 0 01	0 07 ± 0 02	0 06 ± 0 01	0 09 ± 0 02
Mean cell volume (fL)						
Day 5	59 0 ± 0 5	58 6 ± 0 9[2]	58 9 ± 0 8	58 3 ± 0 7	58 1 ± 0 7	56 7 ± 0 7*
Day 21	57 3 ± 0 3	57 4 ± 0 3	57 4 ± 0 2	57 6 ± 0 2	57 4 ± 0 3	56 3 ± 0 4
Day 90	51 1 ± 0 1	51 3 ± 0 2	51 6 ± 0 4	51 4 ± 0 2	51 4 ± 0 2	51 7 ± 0 2**
Mean cell hemoglobin (pg)						
Day 5	19 7 ± 0 2	19 2 ± 0 3[2]	19 4 ± 0 3	19 3 ± 0 3	19 4 ± 0 3	19 0 ± 0 2
Day 21	19 4 ± 0 1	19 5 ± 0 1	19 3 ± 0 1	19 4 ± 0 1	19 4 ± 0 1	19 3 ± 0 1
Day 90	16 8 ± 0 1	16 8 ± 0 1	17 0 ± 0 1	16 8 ± 0 1	17 0 ± 0 1	17 2 ± 0 1*
Mean cell hemoglobin concentration (g/dL)						
Day 5	33 3 ± 0 2	32 9 ± 0 1[2]	33 0 ± 0 2	33 0 ± 0 2	33 3 ± 0 2	33 6 ± 0 1
Day 21	33 7 ± 0 1	34 0 ± 0 3	33 7 ± 0 1	33 8 ± 0 2	33 8 ± 0 2	34 2 ± 0 2
Day 90	33 0 ± 0 2	32 9 ± 0 1	33 1 ± 0 1	32 7 ± 0 1	33 0 ± 0 2	33 3 ± 0 2
Platelets (10^3/μL)						
Day 5	1041 6 ± 16 5	1012 2 ± 23 4[2]	1051 9 ± 25 3	986 4 ± 18 4	1051 7 ± 31 9	1009 4 ± 31 8
Day 21	715 9 ± 15 4	714 6 ± 27 5	712 3 ± 15 9	713 2 ± 11 9	695 3 ± 13 8	697 0 ± 15 6
Day 90	616 9 ± 10 3	651 5 ± 12 6*	664 9 ± 18 1*	671 1 ± 7 4**	653 0 ± 8 2*[2]	663 8 ± 12 1**
Leukocytes (10^3/μL)						
Day 5	4 12 ± 0 59	4 29 ± 0 48[2]	4 68 ± 0 85	4 37 ± 0 62	6 16 ± 0 82	5 16 ± 0 57
Day 21	5 91 ± 0 63	6 23 ± 0 92	6 66 ± 0 71	6 07 ± 0 76	6 14 ± 1 02	5 84 ± 1 04
Day 90	6 16 ± 0 37	6 95 ± 0 27	7 13 ± 0 29	7 27 ± 0 39*	7 32 ± 0 26*	7 42 ± 0 37*
Segmented neutrophils (10^3/μL)						
Day 5	0 57 ± 0 09	0 38 ± 0 06[2]	0 56 ± 0 10	0 47 ± 0 07	0 66 ± 0 14	0 57 ± 0 06
Day 21	0 81 ± 0 10	0 62 ± 0 11	0 76 ± 0 12	0 67 ± 0 11	0 64 ± 0 10	0 59 ± 0 13
Day 90	1 32 ± 0 13	1 39 ± 0 16	1 22 ± 0 09	1 43 ± 0 16	1 22 ± 0 08	1 08 ± 0 13
Lymphocytes (10^3/μL)						
Day 5	3 36 ± 0 50	3 79 ± 0 43[2]	3 94 ± 0 73	3 62 ± 0 49	5 05 ± 0 62	4 29 ± 0 51
Day 21	4 85 ± 0 53	5 35 ± 0 78	5 60 ± 0 60	5 13 ± 0 65	5 30 ± 0 91	5 07 ± 0 91
Day 90	4 42 ± 0 23	5 15 ± 0 22*	5 49 ± 0 31**	5 38 ± 0 30*	5 65 ± 0 27**	6 01 ± 0 41**
Monocytes (10^3/μL)						
Day 5	0 18 ± 0 04	0 11 ± 0 04[2]	0 15 ± 0 06	0 23 ± 0 07	0 42 ± 0 11	0 24 ± 0 08
Day 21	0 22 ± 0 05	0 23 ± 0 05	0 24 ± 0 05	0 21 ± 0 03	0 18 ± 0 04	0 15 ± 0 03
Day 90	0 27 ± 0 08	0 33 ± 0 07	0 38 ± 0 06	0 44 ± 0 05	0 34 ± 0 06	0 29 ± 0 07

TABLE B1 Hematology Data for F344/N Rats in the 13-Week Feed Study of Glyphosate (continued)

Analysis	0 ppm	3125 ppm	6250 ppm	12,500 ppm	25,000 ppm	50,000 ppm
FEMALE (continued)						
n	10	10	10	10	10	10
Eosinophils ($10^3/\mu L$)						
Day 5	0 01 ± 0 01	0 01 ± 0 01[2]	0 01 ± 0 01	0 03 ± 0 02	0 05 ± 0 02	0 04 ± 0 02
Day 21	0 04 ± 0 02	0 07 ± 0 03	0 10 ± 0 02	0 06 ± 0 02	0 03 ± 0 02	0 03 ± 0 02
Day 90	0 14 ± 0 03	0 09 ± 0 02	0 06 ± 0 02	0 07 ± 0 02	0 11 ± 0 02	0 06 ± 0 02

[1] Mean ± standard error for groups of 10 animals, unless otherwise specified
[2] n=9
[3] n=8
* Statistically significantly different (P≤0 05) from the control group by Dunn's test or Shirley's test
** Statistically significantly different (P≤0 01) from the control group by Dunn's test or Shirley's test

TABLE B2 Clinical Chemistry Data for F344/N Rats in the 13-Week Feed Study of Glyphosate[1]

Analysis	0 ppm	3125 ppm	6250 ppm	12,500 ppm	25,000 ppm	50,000 ppm
MALE						
n	10	10	10	10	10	10
Urea nitrogen (mg/dL)						
Day 5	20.0 ± 0.7	19.9 ± 0.9	21.1 ± 0.7	19.9 ± 0.4	20.0 ± 0.8[2]	19.7 ± 0.6
Day 21	20.3 ± 0.6	20.2 ± 0.7	19.4 ± 0.8	20.9 ± 0.6	20.2 ± 0.7[2]	20.3 ± 0.6
Day 90	22.1 ± 0.5	22.8 ± 0.6	24.3 ± 0.7*	22.2 ± 0.5	23.5 ± 0.6	25.2 ± 0.8**
Creatinine (mg/dL)						
Day 5	0.55 ± 0.03	0.54 ± 0.02	0.55 ± 0.03	0.52 ± 0.02	0.49 ± 0.03[2]	0.52 ± 0.02
Day 21	0.58 ± 0.01	0.58 ± 0.02	0.54 ± 0.04	0.58 ± 0.02	0.55 ± 0.03[2]	0.54 ± 0.01
Day 90	0.56 ± 0.02	0.59 ± 0.02	0.57 ± 0.01	0.53 ± 0.02	0.55 ± 0.02	0.53 ± 0.02
Total protein (g/dL)						
Day 5	6.1 ± 0.1	6.0 ± 0.1	6.0 ± 0.1	6.0 ± 0.1	6.0 ± 0.1[2]	6.1 ± 0.1
Day 21	6.3 ± 0.1	6.3 ± 0.1	6.2 ± 0.1	6.2 ± 0.1	6.3 ± 0.1[2]	6.2 ± 0.1
Day 90	6.9 ± 0.0	6.9 ± 0.1	7.0 ± 0.1	6.8 ± 0.1	6.9 ± 0.1	7.1 ± 0.1
Albumin (g/dL)						
Day 5	3.6 ± 0.1	3.6 ± 0.1	3.5 ± 0.1	3.6 ± 0.1	3.6 ± 0.0[2]	3.7 ± 0.1
Day 21	3.8 ± 0.1	3.8 ± 0.1	3.8 ± 0.0	3.7 ± 0.0	3.7 ± 0.1[2]	3.8 ± 0.1
Day 90	3.7 ± 0.1	3.8 ± 0.1	3.9 ± 0.1*	3.8 ± 0.1	3.8 ± 0.1	4.0 ± 0.1**
Alkaline phosphatase (IU/L)						
Day 5	764 ± 20	798 ± 25	816 ± 19	876 ± 28**	888 ± 21**[2]	928 ± 30**
Day 21	528 ± 11	543 ± 13	557 ± 15	601 ± 16**	639 ± 12**[2]	627 ± 11**
Day 90	289 ± 7	283 ± 9	293 ± 8	299 ± 4	306 ± 6	253 ± 16
Alanine aminotransferase (IU/L)						
Day 5	50 ± 2	53 ± 2	57 ± 1**	67 ± 3**	62 ± 4**[2]	65 ± 3**
Day 21	44 ± 2	46 ± 1	49 ± 1*	50 ± 1*	51 ± 1**[2]	47 ± 2*
Day 90	46 ± 2	53 ± 2**	52 ± 2*	57 ± 2**	65 ± 6**	53 ± 2**
Creatine phosphokinase (IU/L)						
Day 5	544 ± 87	714 ± 173	587 ± 92	615 ± 120	587 ± 125[2]	911 ± 139*
Day 21	488 ± 56	477 ± 47	637 ± 168	577 ± 75	523 ± 59[2]	531 ± 29
Day 90	247 ± 49	219 ± 78	226 ± 40	169 ± 13	242 ± 35	242 ± 25
Sorbitol dehydrogenase (IU/L)						
Day 5	6 ± 0	7 ± 1	7 ± 0	7 ± 1	6 ± 0[2]	6 ± 0
Day 21	5 ± 0[2]	6 ± 0	6 ± 1	6 ± 1	5 ± 0[2]	5 ± 0
Day 90	10 ± 1	8 ± 1	8 ± 0	9 ± 0	9 ± 1	8 ± 1
Bile acids (μmol/L)						
Day 5	30.60 ± 3.56	23.80 ± 2.63	30.20 ± 4.56	30.90 ± 3.52	35.56 ± 4.97[2]	38.00 ± 3.63
Day 21	19.33 ± 2.01[2]	19.70 ± 2.10	22.60 ± 2.77	26.80 ± 2.26*	31.00 ± 3.58**[2]	32.80 ± 4.35**
Day 90	12.40 ± 1.10	15.30 ± 2.66	11.30 ± 0.63	13.00 ± 1.15	15.40 ± 1.19	20.90 ± 1.62**
FEMALE						
n	10	10	10	10	10	10
Urea nitrogen (mg/dL)						
Day 5	22.1 ± 0.6	20.5 ± 0.7	20.7 ± 0.6	20.9 ± 0.7	20.9 ± 1.0	19.0 ± 0.5**
Day 21	19.6 ± 1.0	18.3 ± 1.0	20.1 ± 1.1	19.1 ± 0.7	19.4 ± 1.0	17.6 ± 0.5
Day 90	22.4 ± 0.7	23.2 ± 0.7	22.8 ± 0.5	24.5 ± 1.0*	24.2 ± 0.7*	24.2 ± 1.2
Creatinine (mg/dL)						
Day 5	0.55 ± 0.03	0.54 ± 0.01	0.47 ± 0.05	0.52 ± 0.03	0.54 ± 0.02	0.50 ± 0.02
Day 21	0.58 ± 0.02	0.58 ± 0.02	0.58 ± 0.02	0.55 ± 0.02	0.55 ± 0.02	0.57 ± 0.03[2]
Day 90	0.60 ± 0.02	0.63 ± 0.02	0.63 ± 0.02	0.62 ± 0.02	0.61 ± 0.03	0.64 ± 0.02
Total protein (g/dL)						
Day 5	6.15 ± 0.11	6.01 ± 0.10	5.97 ± 0.05	5.97 ± 0.08	5.92 ± 0.07	5.85 ± 0.06*
Day 21	6.46 ± 0.09	6.17 ± 0.10	6.20 ± 0.06*	6.20 ± 0.09	6.17 ± 0.07*	6.06 ± 0.13**
Day 90	6.93 ± 0.12	7.01 ± 0.06	6.76 ± 0.08	6.86 ± 0.07	6.71 ± 0.11	6.49 ± 0.12*

TABLE B2 Clinical Chemistry Data for F344/N Rats in the 13-Week Feed Study of Glyphosate (continued)

Analysis	0 ppm	3125 ppm	6250 ppm	12,500 ppm	25,000 ppm	50,000 ppm
FEMALE (continued)						
n	10	10	10	10	10	10
Albumin (g/dL)						
Day 5	3 57 ± 0 07	3 62 ± 0 07	3 49 ± 0 04	3 49 ± 0 08	3 47 ± 0 05	3 44 ± 0 05
Day 21	4 00 ± 0 09	3 87 ± 0 07	3 98 ± 0 06	3 79 ± 0 08	3 92 ± 0 07	3 79 ± 0 08
Day 90	4 31 ± 0 08	4 33 ± 0 08	4 09 ± 0 10	4 26 ± 0 07	4 13 ± 0 07*	3 99 ± 0 09*
Alkaline phosphatase (IU/L)						
Day 5	615 ± 17	653 ± 18	669 ± 21	679 ± 20*	731 ± 21**	771 ± 13**
Day 21	374 ± 17	406 ± 10	432 ± 13*	432 ± 11*	464 ± 14**	501 ± 15**
Day 90	231 ± 10	224 ± 2	240 ± 8	248 ± 10	291 ± 6**	319 ± 11**
Alanine aminotransferase (IU/L)						
Day 5	45 ± 3	51 ± 2*	49 ± 2*	53 ± 2**	55 ± 2**	62 ± 4**
Day 21	33 ± 1	38 ± 1**	42 ± 2**	41 ± 1**	44 ± 1**	47 ± 1**
Day 90	44 ± 3	42 ± 2	44 ± 1	46 ± 2	54 ± 2**	54 ± 2**
Creatine phosphokinase (IU/L)						
Day 5	559 ± 79	599 ± 55	586 ± 74	744 ± 114	663 ± 109	724 ± 53
Day 21	434 ± 50	414 ± 72	656 ± 225	345 ± 57	421 ± 72	294 ± 45*
Day 90	304 ± 29	247 ± 37	237 ± 35	277 ± 45	289 ± 24	277 ± 32
Sorbitol dehydrogenase (IU/L)						
Day 5	5 ± 0	5 ± 0	5 ± 0	5 ± 0	5 ± 0	5 ± 0
Day 21	5 ± 0	5 ± 0	5 ± 0	5 ± 0	5 ± 0	6 ± 1
Day 90	4 ± 0	4 ± 0	5 ± 0	5 ± 0	4 ± 0	4 ± 0
Bile acids (μmol/L)						
Day 5	24 00 ± 3 67	28 30 ± 1 64	27 10 ± 2 29	25 70 ± 4 70	29 30 ± 4 04	33 89 ± 3 96[2]
Day 21	12 90 ± 2 12	15 90 ± 2 79	19 20 ± 4 02	19 50 ± 2 71	22 40 ± 3 43*	26 00 ± 3 97**
Day 90	25 20 ± 3 09	24 20 ± 3 00	30 50 ± 5 66	16 60 ± 1 73	27 60 ± 6 09	40 00 ± 4 67

[1] Mean ± standard error for groups of 10 animals, unless otherwise specified
[2] n=9
* Statistically significantly different (P≤0 05) from the control group by Dunn's test or Shirley's test
** Statistically significantly different (P≤0 01) from the control group by Dunn's test or Shirley's test

APPENDIX C

Reproductive Tissue Evaluations and Estrous Cycle Characterization

TABLE C1 Summary of Reproductive Tissue Evaluations and Estrous Cycle Length in F344/N Rats in the 13-Week Feed Study of Glyphosate

Study Parameters[1]	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
MALE				
Weights (g)				
Necropsy body weight	385 ± 5	350 ± 5	340 ± 5*	305 ± 7**
Left epididymal tail	0.170 ± 0.004	0.168 ± 0.006	0.167 ± 0.004	0.179 ± 0.006
Left testis	1.54 ± 0.03	1.52 ± 0.05	1.56 ± 0.03	1.56 ± 0.02
Left epididymis	0.448 ± 0.007	0.437 ± 0.016	0.440 ± 0.004	0.452 ± 0.007
Spermatozoal measurements				
Concentration (10^6)	610 ± 36	561 ± 23	485 ± 23**	486 ± 23**
Motility (%)	91 ± 1	92 ± 1	92 ± 2	91 ± 1
Spermatid count (mean/10^{-4} mL suspension)	70.15 ± 3.00	65.33 ± 5.49	67.23 ± 2.05	69.00 ± 1.71
Spermatid heads (10^7/testis)	14.03 ± 0.60	13.07 ± 1.10	13.45 ± 0.41	14.06 ± 0.36
Spermatid heads (10^7/g testis)	9.10 ± 0.35	8.48 ± 0.64	8.63 ± 0.30	9.04 ± 0.20
FEMALE				
Estrous cycle length (days)	4.90 ± 0.10	5.00 ± 0.07	4.90 ± 0.10	5.40 ± 0.21*

[1] Data presented as mean ± standard error; n=10. Differences from the control group for testicular, epididymal, and epididymal tail weights are not significant by Dunnett's test; spermatozoal measurements were not significant by Dunn's test or Shirley's test.

* Statistically significantly different (P≤0.05) from the control group by Williams' test or Shirley's test.

** Statistically significantly different (P≤0.01) from the control group by Williams' test or Shirley's test.

TABLE C2 Summary of Reproductive Tissue Evaluations and Estrous Cycle Length in B6C3F$_1$ Mice in the 13-Week Feed Study of Glyphosate

Study Parameters[1]	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
MALE				
Weights (g)				
Necropsy body weight	32 0 ± 1 0	31 9 ± 0 9	29 4 ± 0 7*	27 2 ± 0 4**
Left epididymal tail	0 015 ± 0 001	0 014 ± 0 001	0 014 ± 0 001	0 014 ± 0 001
Left testis	0 110 ± 0 002	0 111 ± 0 003	0 111 ± 0 002	0 110 ± 0 003
Left epididymis	0 044 ± 0 001	0 043 ± 0 002	0 044 ± 0 001	0 042 ± 0 001
Spermatozoal measurements				
Concentration (10^6)	1162 ± 44	1370 ± 130	1189 ± 60	1308 ± 97
Motility (%)	91 ± 1	91 ± 1	92 ± 1	89 ± 1
Spermatid count (mean/10^4 mL suspension)	67 20 ± 2 30	63 18 ± 3 06	61 93 ± 1 92	65 40 ± 2 89
Spermatid heads (10^7/testis)	2 15 ± 0 07	2 02 ± 0 10	1 98 ± 0 06	2 09 ± 0 09
Spermatid heads (10^7/g testis)	19 61 ± 0 92	18 17 ± 0 71	17 87 ± 0 60	18 99 ± 0 73
FEMALE				
Estrous cycle length (days)	4 06 ± 0 06[2]	4 00 ± 0 00	4 00 ± 0 00	4 00 ± 0 00[2]

[1] Data presented as mean ± standard error, n=10 except where noted Differences from the control group for testicular, epididymal, and epididymal tail weights are not significant by Dunnett's test, spermatozoal measurements were not significant by Dunn's test Estrous cycle length was not significant by Dunn's test

[2] n=9

* Statistically significantly different (P≤0 05) from the control group by Williams' test

** Statistically significantly different (P≤0 01) from the control group by Williams' test

APPENDIX D

Genetic Toxicology

TABLE D1 Mutagenicity of Glyphosate in *Salmonella typhimurium*[1]

Strain	Dose (μg/plate)	Revertants/plate[2] -S9 Trial 1	-S9 Trial 2	+ hamster S9 10%	+ hamster S9 30%	+ rat S9 10%	+ rat S9 30%
TA100	0	127 ± 7 3	111 ± 1 5	162 ± 7 9	148 ± 8 7	147 ± 16 1	169 ± 4 1
	33	120 ± 14 8	97 ± 5 5	176 ± 6 6		158 ± 2 3	
	100	124 ± 9 9	134 ± 6 0	151 ± 8 1	156 ± 7 5	148 ± 10 2	154 ± 9 0
	333	107 ± 10 5	122 ± 11 3	133 ± 3 7	142 ± 3 3	142 ± 3 5	136 ± 4 3
	1000	133 ± 3 8	109 ± 9 3	106 ± 2 3	117 ± 15 6	137 ± 3 0	133 ± 8 5
	3333	99 ± 3 8	103 ± 11 4	101 ± 6 8	131 ± 1 9	150 ± 14 0	131 ± 11 1
	10,000				18 ± 6 6[3]		52 ± 38 5[3]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[4]		422 ± 14 1	433 ± 6 7	514 ± 22 9	590 ± 15 9	419 ± 13 7	490 ± 16 5
TA1535	0	20 ± 2 2	21 ± 3 1	14 ± 0 7	17 ± 3 8	18 ± 4 6	13 ± 1 7
	33	18 ± 1 2	13 ± 2 2	15 ± 3 4	15 ± 1 2	11 ± 2 2	12 ± 0 9
	100	15 ± 1 7	17 ± 2 0	12 ± 1 0	13 ± 2 0	14 ± 0 9	13 ± 3 0
	333	11 ± 0 9	17 ± 4 0	10 ± 3 6	12 ± 0 3	11 ± 1 2	10 ± 1 5
	1000	11 ± 0 3	15 ± 0 7	12 ± 1 2	11 ± 1 3	12 ± 2 5	11 ± 0 3
	3333	4 ± 0 9	9 ± 0 7	10 ± 1 2	11 ± 1 0	10 ± 0 6	9 ± 1 8
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		269 ± 8 7	479 ± 32 9	196 ± 12 5	411 ± 12 3	146 ± 12 2	89 ± 14 2
TA97	0	172 ± 7 2	171 ± 2 3	180 ± 16 8	159 ± 8 3	190 ± 7 8	205 ± 2 5
	10		151 ± 14 4	177 ± 9 2		179 ± 10 1	
	33	173 ± 6 0	178 ± 6 9	168 ± 18 3	212 ± 3 8	203 ± 12 5	212 ± 2 8
	100	174 ± 3 5	190 ± 5 2	159 ± 9 2	159 ± 10 3	154 ± 4 2	160 ± 20 0
	333	142 ± 16 9	136 ± 3 2	135 ± 9 8	162 ± 6 3	119 ± 8 7	186 ± 14 7
	1000	100 ± 6 8	93 ± 3 1	116 ± 8 7	139 ± 16 4	86 ± 1 5	174 ± 5 4
	3333	0 ± 0 0[3]			74 ± 15 9		63 ± 19 5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		331 ± 13 6	501 ± 48 5	412 ± 27 3	451 ± 5 0	385 ± 18 6	283 ± 13 4
TA98	0	23 ± 2 5	25 ± 0 9	40 ± 1 5	32 ± 3 5	27 ± 1 8	24 ± 3 7
	33	16 ± 0 9	17 ± 2 1	27 ± 2 1		24 ± 2 1	
	100	15 ± 2 1	23 ± 3 2	34 ± 3 5	25 ± 2 3	25 ± 2 7	26 ± 1 5
	333	15 ± 2 0	14 ± 2 9	22 ± 1 5	27 ± 1 7	23 ± 2 7	27 ± 2 9
	1000	15 ± 1 2	15 ± 0 6	31 ± 2 9	25 ± 3 1	23 ± 2 7	20 ± 1 5
	3333	8 ± 2 3	15 ± 0 9	25 ± 0 3	19 ± 2 2	Toxic	13 ± 2 3
	10,000				2 ± 0 3		0 ± 0 0[3]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		667 ± 85 0	785 ± 24 7	346 ± 3 5	274 ± 32 1	275 ± 24 2	87 ± 12 4

[1] Study performed at SRI, International The detailed protocol and these data are presented in Zeiger *et al* (1988)

[2] Revertants are presented as mean ± standard error from three plates

[3] Slight toxicity

[4] The positive controls in the absence of metabolic activations were 4-nitro-*o*-phenylenediamine (TA98), sodium azide (TA100 and TA1535), and 9-aminoacridine (TA97) The positive control for metabolic activation with all strains was 2-aminoanthracene

TABLE D2 Frequency of Micronuclei in B6C3F$_1$ Mouse Peripheral Blood Erythrocytes in the 13-Week Feed Study of Glyphosate[1]

Concentration (mg/kg)	Number of Mice	% Micronucleated Cells (mean ± standard error)
MALE		
0 0	10	0 07 ± 0 01
0 3	10	0 08 ± 0 01
0 6	10	0 09 ± 0 01
1 3	10	0 10 ± 0 01
2 5	10	0 10 ± 0 01
5 0	10	0 09 ± 0 02
Positive control[2]	3	1 04 ± 0 16
FEMALE		
0 0	9	0 04 ± 0 01
0 3	10	0 06 ± 0 01
0 6	10	0 05 ± 0 01
1 3	10	0 06 ± 0 01
2 5	10	0 05 ± 0 01
5 0	8	0 05 ± 0 01

[1] Smears were prepared from peripheral blood samples obtained by cardiac puncture of dosed and control animals at the termination of the 13 week study Slides were stained with Hoechst 33258/pyronin Y (MacGregor *et al*, 1983) Ten thousand normochromatic erythrocytes from each animal were scored for micronuclei No significant elevation in the frequency of micronucleated erythrocytes was observed in either male or female mice administered glyphosate in dosed feed

[2] Male mice were treated for 4 weeks with 0 2% urethane in drinking water These animals were not part of the subchronic study, but were added as a measure of quality control for the assay

From: Landrigan, Philip <phil.landrigan@mssm.edu>
Sent: Wednesday, July 22, 2015 8:41 AM
To: Birnbaum, Linda (NIH/NIEHS) [E]
Cc: Bucher, John (NIH/NIEHS) [E]
Subject: RE: Glyphosate and GMOs
Attachments: image006.png; image007.png; image008.gif; image009.png; image010.png; image011.png; image012.png; image013.png

Linda

Thanks. I shall make the nomination and encourage others to do so as well

Phil

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From: Birnbaum, Linda (NIH/NIEHS) [E] [mailto:birnbaumls@niehs.nih.gov]
Sent: Wednesday, July 22, 2015 8:40 AM
To: Landrigan, Philip
Cc: Bucher, John (NIH/NIEHS) [E]
Subject: RE: Glyphosate and GMOs

Hi Phil

Thanks for sharing this. We are talking with the Ramazzini Institute re their proposed study of glyphosate.

We would welcome a nomination of glyphosphate and its mixtures toe the NTP testing program. The forms are available on the web.

Linda

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S.
Director, National Institute of Environmental Health Sciences
and National Toxicology Program
phone: 919-541-3201
fax: 919-541-2260
e-mail: birnbaumls@niehs.nih.gov

From: Landrigan, Philip [mailto:phil.landrigan@mssm.edu]
Sent: Tuesday, July 21, 2015 1:25 PM
To: Birnbaum, Linda (NIH/NIEHS) [E]
Subject: Glyphosate and GMOs

Linda,

I am writing to give you a heads-up that *The New England Journal of Medicine* has accepted the attached Perspective article titled ²GMOs, Herbicides and Public Health². It will appear sometime in the next month or so.

I am sending it to you for your general interst and also because we include a specific recommendation that NTP should test glyphosate, and I did not want you to be caught off guard. You probably also know that the Ramazzini Institute is moving forward with a plan to do a carcinogenesis bioassay of glyphosate

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Attachments: image001.png; image002.png; image003.gif; image004.png; image005.png

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From: Bucher, John (NIH/NIEHS) [E]
Sent: Tuesday, July 21, 2015 4:41 PM
To: Masten, Scott (NIH/NIEHS) [E]
Subject: Re: Glyphosate and GMOs

I know how they got to 2A. And if you have a few minutes tomorrow and want to catch Jameson over lunch at the RoC review, he can tell you because he did the historical database search.
I read Phil[1]s paper.

From: "Masten, Scott (NIH/NIEHS) [E]" <masten@niehs.nih.gov>
Date: Tuesday, July 21, 2015 at 4:33 PM
To: "John R. Bucher" <bucher@niehs.nih.gov>
Subject: Re: Glyphosate and GMOs

Id like to get your thoughts when you have a few minutes in the next couple of days. The IARC monograph is due out this month. I really don[1]t understand how they got to 2A.

If you didn[1]t open Landrigan's file, there is this one-liner:

...theNationalToxicologyProgram should urgentlyassessthetoxicologyofpure glyphosate, formulated glyphosate and mixtures of glyphosate and other herbicides.

From: "Bucher, John (NIH/NIEHS) [E]" <bucher@niehs.nih.gov>
Date: Tuesday, July 21, 2015 at 2:02 PM
To: Scott Masten <masten@niehs.nih.gov>
Cc: "Thayer, Kristina (NIH/NIEHS) [E]" <thayer@niehs.nih.gov>, "Walker, Nigel (NIH/NIEHS) [E]" <walker3@niehs.nih.gov>, "Wolfe, Mary (NIH/NIEHS) [E]" <wolfe@niehs.nih.gov>
Subject: FW: Glyphosate and GMOs

From: "Birnbaum, Linda (NIH/NIEHS) [E]" <birnbaumls@niehs.nih.gov>
Date: Tuesday, July 21, 2015 at 1:51 PM
To: "John R. Bucher" <bucher@niehs.nih.gov>
Cc: "Evans, Sharon L (NIH/NIEHS) [E]" <EvansS@niehs.nih.gov>
Subject: Fwd: Glyphosate and GMOs

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S
Director, National Institute of Environmental Health Sciences
and National Toxicology Program
phone: 919-541-3201
fax: 919-541-2260
e-mail: birnbaumls@niehs.nih.gov

Begin forwarded message:

From: "Landrigan, Philip" <phil.landrigan@mssm.edu>
Date: July 21, 2015 at 1:25:22 PM EDT
To: 'Linda Birnbaum' <birnbaumls@niehs.nih.gov>
Subject: Glyphosate and GMOs

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I am sending it to you for your general interst and also because we include a specific recommendation that NTP should test glyphosate, and I did not want you to be caught off guard. You probably also know that the Ramazzini Institute is moving forward with a plan to do a carcinogenesis bioassay of glyphosate

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GMOs, Herbicides, and Public Health

Philip J. Landrigan, M.D., and Charles Benbrook, Ph.D.

Genetically modified organisms (GMOs) are not high on most physicians' worry lists. If we think at all about biotechnology, most of us probably focus on direct threats to human health such as prospects for converting pathogens to biologic weapons or the implications of new technologies for editing the human germline. But while those debates simmer, the application of biotechnology to agriculture has been rapid and aggressive. The vast majority of the corn and soybeans grown in the United States are now genetically engineered. Foods produced from GM crops have become ubiquitous. And unlike regulatory bodies in 64 other countries, the US Food and Drug Administration (FDA) does not require labeling of GM foods.

Two recent developments are dramatically changing the GMO landscape. First, there have been sharp increases in the amounts and numbers of chemical herbicides applied to GM crops, and still further increases — the largest in a generation — are scheduled to occur in the next few years. Second, the International Agency for Research on Cancer (IARC) has classified glyphosate, the herbicide most widely used on GM crops, as "probably carcinogenic to humans" [1] and classified a second herbicide, 2, 4-dichlorophenoxyacetic acid (2,4-D), as a "possible human carcinogen".[2]

The application of genetic engineering to agriculture builds on the ancient practice of selective breeding. But unlike traditional selective breeding, genetic engineering vastly expands the range of traits that can be moved into plants and enables breeders to import DNA from virtually anywhere in the biosphere. Depending on the traits selected, genetically engineered crops can increase yields, thrive when irrigated with salty water, or produce fruits and vegetables resistant to mold and rot.

The National Academy of Sciences has twice reviewed the safety of GM crops — in 2000 and

2004.[3] Those reviews, which focused almost entirely on the genetic aspects of biotechnology, concluded that GM crops pose no unique hazards to human health. They noted that genetic transformation has potential to produce unanticipated allergens or toxins and might alter the nutritional quality of food. Both reports recommended development of new risk-assessment tools and postmarketing surveillance. Those recommendations have largely gone unheeded.

Herbicide resistance is the main characteristic that the biotechnology industry has chosen to introduce into plants. Corn and soybeans with genetically engineered tolerance to glyphosate (Roundup [TM]) were first introduced in the mid-1990s. These "Roundup-Ready" crops now account for more than 90% of the corn and soybeans planted in the United States.[4] Their advantage, especially in the first years after introduction, is that they greatly simplify weed management. Farmers can spray herbicide both before and during the growing season, leaving their crops unharmed.

But widespread adoption of herbicide-resistant crops has led to overreliance on herbicides and, in particular, on glyphosate.[5] In the United States, glyphosate use has increased more than 250-fold — from 0.4 million kg in 1974 to 113 million kg in 2014. Global use has increased more than 10-fold. Not surprisingly, glyphosate-resistant weeds have emerged and are found today on nearly 100 million acres in 36 states. Fields must be now be treated with multiple herbicides, including 2, 4-D, a component of the Agent Orange defoliant used in the Vietnam War.

The first of the two developments that raise fresh concerns about the safety of GM crops is a 2014 decision by the Environmental Protection Agency (EPA) to approve EnlistDuo, a new combination herbicide comprised of glyphosate plus 2, 4-D. EnlistDuo was formulated to combat herbicide resistance. It will be marketed in tandem with newly approved seeds genetically engineered to resist glyphosate, 2, 4-D, and multiple other herbicides. EPA anticipates that a 3-to-7-fold increase in 2, 4-D use will result.

In our view, the science and the risk assessment supporting the EnlistDuo decision are flawed. The science consisted solely of toxicological studies commissioned by the herbicide manufacturers in the

1980s and 1990s and never published, a not uncommon practice in US pesticide regulation. These studies predated current knowledge of low-dose, endocrine-mediated and epigenetic effects and were not designed to detect them. The risk assessment gave little consideration to potential health effects in infants and children thus contravening federal pesticide law. It failed to consider ecologic impacts such as effects on the Monarch butterfly and other pollinators. It considered only pure glyphosate, despite studies showing that formulated glyphosate containing surfactants and adjuvants is more toxic than the pure compound.

The second new development is the determination by IARC in 2015 that glyphosate is a "probable human carcinogen" [1] and 2, 4-D a "possible human carcinogen".[2] These classifications were based on comprehensive assessments of the toxicological and epidemiologic literature that linked both herbicides to dose-related increases in malignant tumors at multiple anatomic sites in experimental animals and linked glyphosate to an increased incidence of non-Hodgkin's lymphoma in humans.

These developments suggest that GM foods and the herbicides applied to them may pose hazards to human health that were not examined in previous assessments. We believe that the time has therefore come to thoroughly reconsider all aspects of the safety of plant biotechnology. The National Academy of Sciences has convened a new committee to reassess the social, economic, environmental, and human health impacts of GM crops. This is welcome, but the committee's report is not expected until at least 2016.

In the meantime, we offer two recommendations. First, EPA should delay implementation of its decision to permit use of EnlistDuo. This decision was made in haste. It was based on poorly designed and outdated studies and on an incomplete assessment of human exposure and environmental impacts. It would have benefited from deeper consideration of independently funded studies published in the peer-reviewed literature. It preceded the recent IARC determinations on glyphosate and 2, 4-D. Second, the National Toxicology Program should urgently assess the toxicology of pure glyphosate, formulated

glyphosate and mixtures of glyphosate and other herbicides.

Finally, we believe the time has come to revisit the United States' reluctance to label GM foods. Labeling will deliver multiple benefits. It is essential for tracking emergence of novel food allergies and assessing effects of chemical herbicides applied to GM crops. It would respect the wishes of a growing number of consumers who insist they have a right to know what foods they are buying and how those foods were produced. And the argument that there is nothing new about genetic rearrangement misses the point that GM crops are now the agricultural products most heavily treated with herbicides and that two of these herbicides may pose risks of cancer. We hope, in light of this new information, that FDA will reconsider labeling of GM foods and couple it with adequately funded long-term postmarketing surveillance.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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References

1. Guyton KZ, Loomis D, Grosse Y, et al. Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon and glyphosate. *Lancet Oncology* 2015. S1470-2045 (15)70134-8.
3. Loomis D, Guyton K, Grosse Y et al. Carcinogenicity of lindane, DDT, and 2, 4-dichlorophenoxyacetic acid. *Lancet Oncology* 2015. S1470-2045 (15) 00081-9.
3. National Research Council, Committee on Identifying and Assessing Unintended Effects of

Genetically Engineered Foods on Human Health. Safety of Genetically Engineered Foods: Approaches to Assessing Unintended Health Effects. Washington DC: National Academies Press, 2004.

4. US Department of Agriculture, Economic Research Service. Adoption of Genetically Engineered Crops in the U.S. Available at: http://www.ers.usda.gov/data-products/adoption-of-genetically- engineered-crops-in-the-us.aspx. [Accessed 7 April 2015].
5. Duke SO: Perspectives on transgenic, herbicide-resistant crops in the USA almost 20 years after introduction. *Pest Manag Sci* 2015 May;71(5):652-7