IN DEFENSE OF SCIENTIFIC INTEGRITY: EXAMINING THE IARC MONOGRAPH PROGRAMME AND GLYPHOSATE REVIEW

HEARING

BEFORE THE

COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY
HOUSE OF REPRESENTATIVES

ONE HUNDRED FIFTEENTH CONGRESS

SECOND SESSION

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IN DEFENSE OF SCIENTIFIC INTEGRITY: EXAMINING THE IARC MONOGRAPH PROGRAMME AND GLYPHOSATE REVIEW

TUESDAY, FEBRUARY 6, 2018

HOUSE OF REPRESENTATIVES,
COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY,
Washington, D.C.

The Committee met, pursuant to call, at 10:06 a.m., in Room 2318 of the Rayburn House Office Building, Hon. Lamar Smith [Chairman of the Committee] presiding.

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
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Full Committee

In Defense of Scientific Integrity: Examining the IARC Monograph Programme and Glyphosate Review

Tuesday, February 6, 2018
10:00 a.m.
2318 Rayburn House Office Building

Witnesses

Dr. Anna Lowit, Senior Science Advisor, Office of Pesticide Programs, Environmental Protection Agency

Dr. Timothy Pastoor, CEO, Pastoor Science Communications

Dr. Jennifer Sass, Senior Scientist, Natural Resources Defense Council

Dr. Robert Tarone, (retired) Mathematical Statistician, U.S. National Cancer Institute and Biostatistics Director, International Epidemiology Institute

U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY

HEARING CHARTER

Tuesday, February 6, 2018

TO: Members, Committee on Science, Space and Technology

FROM: Majority Staff, Committee on Science, Space, and Technology

SUBJECT: Full Committee Hearing: "*In Defense of Scientific Integrity: Examining the IARC Monograph Programme and Glyphosate Review*"

The Committee on Science, Space and Technology will hold a hearing titled *In Defense of Scientific Integrity: Examining the IARC Monograph Programme and Glyphosate Review* on Tuesday, February 6, 2018, at 10:00 a.m. in Room 2318 of the Rayburn House Office Building.

Hearing Purpose:

The purpose of the hearing is to examine the scientific underpinnings, principles, and procedures at the International Agency for Research on Cancer's (IARC) Monograph Programme. This hearing will use the review of glyphosate by both IARC and the Environmental Protection Agency (EPA) as a case study.

Witness List

- **Dr. Anna Lowit**, Senior Science Advisor, Office of Pesticide Programs, Environmental Protection Agency
- **Dr. Timothy Pastoor**, CEO, Pastoor Science Communications
- **Dr. Jennifer Sass**, Senior Scientist, Natural Resources Defense Council
- **Dr. Robert Tarone**, (retired) Mathematical Statistician, U.S. National Cancer Institute and Biostatistics Director, International Epidemiology Institute

Staff Contact

For questions related to the hearing, please contact Majority Staff at 202-225-6371.

Chairman SMITH. The Committee on Science, Space, and Technology will come to order. Without objection, the Chair is authorized to declare recesses of the Committee at any time.

Welcome to today's hearing entitled "In Defense of Scientific Integrity: Examining the IARC Monograph Programme and Glyphosate Review."

I recognize myself for five minutes for an opening statement, and then I'll recognize the opening—I mean the Ranking Member as well.

Today, we will examine the U.S. taxpayer-funded IARC Monograph Programme and its assessment of the herbicide glyphosate, more commonly known as Roundup. We must ensure that the underlying science behind assessments that influence policy and the public is based on sound science. The American people deserve to know the truth about which substances are safe and which ones pose a risk. Glyphosate is the most widely used herbicide in the world. Americans and people across the globe rely on these crops for high quality, affordable food.

There are real repercussions to IARC's unsubstantiated claims, which are not backed by reliable data. Labeling requirements will drive costs up for farmers and consumers and create unjustified public fear. IARC's irresponsible handling of data does real harm to job creators and the public's view of the scientific process.

Agencies such as IARC have a responsibility to adhere to the scientific method and evaluate all relevant scientific studies, weigh the evidence, and come to a conclusion that can be reproduced. Following the scientific method also means forming a conclusion only after all data has been considered.

According to information gathered by the Committee, there appear to be serious problems with the science underlying IARC's assessment of glyphosate. The news media recently revealed evidence of data deletion and manipulation of draft assessments before final publication. IARC's conclusion about glyphosate relied only on data that was favorable to its conclusion and ignored contradictory data.

In its assessment, IARC did no direct evaluation of glyphosate's effect on humans, no evaluation whatsoever. Specifically, IARC appears to have intentionally omitted data that showed glyphosate does not cause cancer. It's no surprise that the Monograph Programme has refused to publish any of its draft assessments. If there is nothing to hide, why the secrecy?

The manipulation of scientific data and lack of transparency is not the only defect in IARC's glyphosate assessment. Besides altering the data used in the assessment, the Monograph Working Group failed to consider the most significant study on human exposure to glyphosate. The Agricultural Health Study, which was a result of a collaboration of several federal agencies such as the National Cancer Institute, National Institute of Environmental Health Sciences, and the Environmental Protection Agency presented information they had collected on over 50,000 humans. Aaron Blair, the Chair of the Monograph Programme at the time, admitted in a deposition that the study would, quote, "altered IARC's analysis," end quote. However, this study was not considered by IARC.

In 2015, IARC published its findings on glyphosate, categorizing the herbicide as "probably" causing cancer. It has become apparent

that the Monograph on glyphosate uses nothing more than cherry-picked science created by those who have a financial stake in the resulting conclusions.

The Monograph Programme is alone in its determination that glyphosate poses a cancer threat. Both the EPA and EFSA, a European regulatory agency, have reviewed glyphosate and determined that the chemical is unlikely to cause cancer. Last December, the EPA released a draft Human Health Risk Assessment evaluating the potential of glyphosate to cause cancer. The EPA body of research was then evaluated by a Scientific Advisory Panel composed of experts appointed during the Obama Administration. The EPA's draft assessment reviewed IARC's glyphosate Monograph and came to the conclusion that glyphosate is unlikely to cause cancer.

The Committee has written several letters expressing concerns about the lack of sound science and biases found in IARC's program. When asked to provide a witness for this hearing, IARC Director Wild refused to attend. No doubt he could not defend IARC's glyphosate findings. The selective use of data and the lack of public disclosure raise questions about why IARC should receive any government funding in the future.

[The prepared statement of Chairman Smith follows:]

COMMITTEE ON
SCIENCE, SPACE, & TECHNOLOGY
Lamar Smith, Chairman

For Immediate Release
February 6, 2018

Media Contacts: Thea McDonald, Brandon VerVelde
(202) 225-6371

Statement by Chairman Lamar Smith (R-Texas)

In Defense of Scientific Integrity: Examining the IARC Monograph Programme and Glyphosate Review

Chairman Smith: Today we will examine the U.S. taxpayer-funded IARC Monograph Programme and its assessment of the herbicide glyphosate, more commonly known as Roundup. We must ensure that the underlying science behind assessments that influence policy and the public is based on sound science.

The American people deserve to know the truth about which substances are safe and which ones pose a risk. Glyphosate is the most widely used herbicide in the world. Americans and people across the globe rely on these crops for high quality, affordable food.

There are real repercussions to IARC's unsubstantiated claims, which are not backed by reliable data. Labeling requirements will drive costs up for farmers and consumers and create unjustified public fear. IARC's irresponsible handling of data does real harm to job creators and the public's view of the scientific process.

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The selective use of data and the lack of public disclosure raise questions about why IARC should receive any government funding in the future.

###

Chairman SMITH. That concludes my opening statement, and the Ranking Member, the gentlewoman from Texas, is recognized for hers.

Ms. JOHNSON. Thank you very much, Mr. Chairman.

Chemicals have the potential to greatly improve our quality of life when developed and produced in a responsible manner. However, when produced or proliferated irresponsibly or without sufficient understanding of their potential impacts, chemicals can pose a grave and significant risk to every one of us.

Unfortunately, by the time we realize the harm being caused by unsafe exposure to such toxic chemicals, the damage has often already been done, and we're left regretting the fact that there might have been preventative actions we could have taken to protect ourselves if we had a better understanding of the hazards. If we knew then what we know now, would we have filled our homes, schools, businesses, hospitals with asbestos? Would we have supported the widespread installation of lead pipes to provide us with our daily drinking water? Most Americans who have had to suffer or who have seen their children and other loved ones suffer through the adverse health effects of exposures to dangerous chemicals would likely say no, of course not.

The chemicals we are discussing today—glyphosate—is already one of the most widely used chemicals in agriculture. For example, it is the key ingredient in Monsanto's herbicide Roundup that has helped farmers get greater yield of corn and other agriculture products. However, the widespread prevalence of glyphosate has raised serious concerns about its toxicity and potential cancer-causing properties.

That is why the work done by independent chemical assessment organizations like the World Health Organization and its International Agency for Research on Cancer is so critical to protecting the public health of—those organizations evaluate without prejudice or concern about profits, the health habits—hazards and risks posed by exposure to toxic chemicals. By contrast, there's been extensive documentation of efforts by the chemical industry to bias the science and public perception of their chemicals to protect their financial interests rather than the public health. If we are truly interested in defending scientific integrity, we should be doing more than simply hearing from the industry-friendly scientists.

As my colleagues may be aware, the EPA's Office of Inspector General has been investigating allegations that Monsanto attempted to influence officials at the Environmental Protection Agency who were central to EPA's own review of glyphosate, as well as potential collusion by those officials with Monsanto. If this Committee really wishes to do oversight in defense of scientific integrity, those allegations would certainly seem to be worthy of our attention. However, I am not holding my breath that the majority will undertake such an investigation.

Mr. Chairman, chemical companies will continue to innovate and manufacture chemicals that seek to improve human life, and I support their initiatives in doing so. But such innovations should not come at the cost of human health. That is why the work of independent organizations like IARC is so important and why we in

Congress should be supporting that work rather than attempting to undercut it.

The minority staff has produced a staff report that documents some of the tactics Monsanto has used to undermine this IARC Monograph and scientific findings and glyphosate in general, and I'm attaching this report to my statement.

I thank you, Mr. Chairman, and I yield back.

[The prepared statement of Ms. Johnson follows:]

OPENING STATEMENT
Ranking Member Eddie Bernice Johnson (D-TX)

House Committee on Science, Space, and Technology
"In Defense of Scientific Integrity:
Examining the IARC Monograph Programme and Glyphosate Review"
February 6, 2018

Mr. Chairman, chemicals have the potential to greatly improve our quality of life, when developed and produced in a responsible manner. However, when produced or proliferated irresponsibly or without sufficient understanding of their potential impacts, chemicals can pose a grave and significant risk to every one of us. Unfortunately, by the time we realize the harm being caused by unsafe exposure to such toxic chemicals, the damage has often already been done, and we are left regretting the fact that there might have been preventative actions we could have taken to protect ourselves if we had a better understanding of the hazards.

If we knew then, what we know now, would we have filled our homes, schools, businesses, and hospitals with asbestos? Would we have supported the widespread installation of lead pipes to provide us with daily drinking water? Most Americans who have had to suffer, or who have seen their children and other loved ones suffer, through the adverse health effects of exposures to dangerous chemicals would likely say **no**, of course not.

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That is why the work done by independent chemical assessment organizations, like the World Health Organization and its International Agency for Research on Cancer (IARC), is so critical to protecting the public health as those organizations evaluate, without prejudice or concern about profits, the health hazards and risks posed by exposure to toxic chemicals. By contrast, there has been extensive documentation of efforts by the chemical industry to bias the science and public perception of their chemicals to protect a financial interest rather than the public health.

If we are truly interested in defending scientific integrity, we should be doing more than simply hearing from industry-friendly scientists. As my colleagues may be aware, the EPA's Office of Inspector General has been investigating allegations that Monsanto attempted to influence officials at the Environmental Protection Agency (EPA) who were central to EPA's own review of glyphosate as well as potential collusion by those officials with Monsanto. If this Committee really wishes to do oversight in defense of scientific integrity, those allegations would certainly seem to be worthy of our attention. However, I'm not holding my breath that the Majority will undertake such an investigation.

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The Minority Staff has produced a staff report that documents some of the tactics Monsanto has used to undermine the IARC monograph and scientific findings on glyphosate in general. I am attaching this report to my statement.

Thank you. I yield back.

[The Minority Staff Report follows:]

Spinning Science & Silencing Scientists:

A Case Study in How the Chemical Industry Attempts to Influence Science

Minority Staff Report
Prepared for Members of the
Committee on Science, Space & Technology
U.S. House of Representatives
February 2018

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Introduction. On February 6, 2018, the Committee on Science, Space, and Technology is scheduled to hold a hearing entitled, *"In Defense of Scientific Integrity: Examining the IARC Monograph Programme and Glyphosate Review."* The chemical glyphosate is a herbicide most commonly found in Monsanto's commercial weed-killer Roundup. Committee Chairman Lamar Smith scheduled this hearing after months of letter writing criticizing the IARC review of glyphosate and examining the EPA's actions on glyphosate. Many of the criticisms contained in the Committee's letters regarding IARC mimic criticisms that the chemical industry has leveled on the IARC process. Since these industry talking points are apparently the basis for both a Congressional investigation as well as a Committee hearing, Minority Committee Staff have written this staff report to better inform the Committee Members about the chemical industry tactics which have ultimately produced these industry talking points. The report necessarily focuses on the Monsanto Company due to their primary role in inventing, selling, and marketing glyphosate and glyphosate resistant seeds. This report is based in no small part on documents that have been made publically available due to ongoing third-party litigation with Monsanto.[1] These newly released public documents have revealed in an unprecedented manner the tactics of the chemical industry in attacking public health science related to their products.

Background. In March 2015, the World Health Organization's (WHO's) International Agency for Research on Cancer (IARC), based in Lyon, France, released a hazard assessment that found glyphosate to be "probably carcinogenic to humans." In December 2017, the EPA released a draft human health risk assessment that concluded, "glyphosate is not likely to be carcinogenic to humans." There are significant differences between these two types of assessments because they attempt to evaluate different questions. According to IARC, "A cancer 'hazard' is an agent that is capable of causing cancer under some circumstances, while a cancer 'risk' is an estimate of the carcinogenic effects expected from exposure to a cancer hazard." As more scientific data is gathered and analyzed to more fully understand the impacts of glyphosate on human health, it is important for the science to lead the way, and for industry and politicians to remain on the sidelines. But that has not happened.

There is significant evidence that Monsanto launched a disinformation campaign to undermine IARC's classification of glyphosate as a probable carcinogen. A multi-district litigation court case against Monsanto regarding potential adverse health consequences of exposures to glyphosate has revealed hundreds of pages of internal Monsanto e-mails, memorandums, and other records that clearly show Monsanto engaged in a decades-long concerted effort to fend off any evidence suggesting potential adverse human health effects from glyphosate and more recently to undermine IARC's findings. They ghost wrote scientific articles on glyphosate, established front groups to help amplify their anti-IARC message and scientific evidence they did not like, and they attempted to silence scientists who reached conclusions questioning glyphosate's safety.

[1] The Monsanto Papers, Baum, Hedlund, Aristei & Goldman, accessed here: https://www.baumhedlundlaw.com/toxic-tort-law/monsanto-roundup-lawsuit/monsanto-secret-documents/

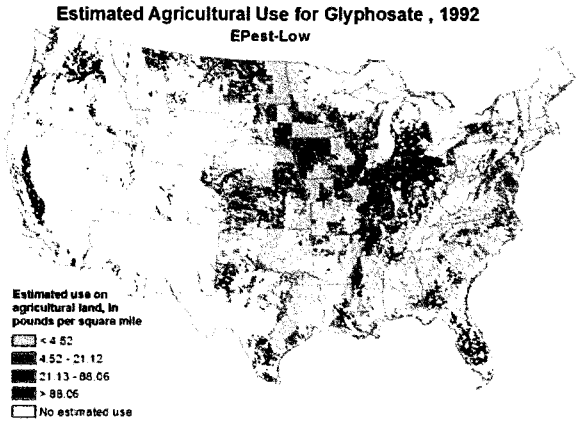
While there are divergent conclusions between IARC and other science agencies, including the EPA, regarding the potential human health hazard of glyphosate, even Monsanto's own scientists acknowledged in internal e-mails that Roundup, the glyphosate containing weed-killer that Monsanto sells, does cause damage. "Glyphosate is OK, but the formulated product causes the damage," one Monsanto researcher wrote in an email.[2] "You cannot say that Roundup is not a carcinogen," wrote another Monsanto toxicologist. "We have not done the necessary testing on the formulation to make that statement."[3] What we do know is that the use of glyphosate has exploded across the United States and around the world since it first came on the market in 1974. In the U.S. alone its use has grown from 11 million pounds in 1987 to nearly 300 million pounds in 2016. Recent studies have also shown that it is prevalent in the U.S. food supply from crackers and cookies to honey and wine. Several studies have also shown that glyphosate is detectible in around 90% of the U.S. population.

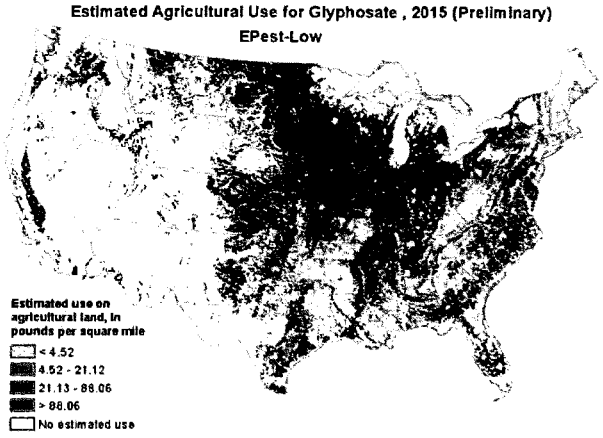
This report describes some of the tactics Monsanto has used to control the public debate about glyphosate as well as the scientific studies that have been conducted to assess its potential harm. These efforts appear aimed at corrupting and disrupting any honest, thorough and complete scientific evaluation of glyphosate and its potential adverse impact on the public's health.

[2] Email from William Heydens to Donna Farmer and Richard Dirks, Subject: "RE: European Commission Endocrine Disrupters developments (1)," April 25, 2002, accessed here: http://baumhedlundlaw.com/pdf/monsanto-documents/37-Monsanto-Executive-Admits-Studies-Demonstrate-Formulated-Roundup-Does-the-Damage.pdf.
[3] Email from Donna Farmer to Monsanto employees, Subject: "RE: Agitation against Roundup," Nov. 22, 2003, accessed here: http://baumhedlundlaw.com/pdf/monsanto-documents/27-Internal-Monsanto-Email-You-Cannot-Say-That-Roundup-is-not-a-Carcinogen.pdf.

Glyphosate use in the United States from 1992 to 2015

(Source: U.S. Geological Survey[4])





[4] Glyphosate use in the U.S. 1992: https://water.usgs.gov/nawqa/pnsp/usage/maps/show_map.php?year=1992&map=GLYPHOSATE&hilo=H; Glyphosate use in the U.S. 2015: https://water.usgs.gov/nawqa/pnsp/usage/maps/show_map.php?year=2015&map=GLYPHOSATE&hilo=H

MONSANTO

Key Players. The individuals listed below are some of the key players mentioned in the internal Monsanto e-mails and records cited in this report. Brief descriptions of their affiliation with Monsanto and their activities surrounding glyphosate are summarized below.

- **John Acquavella:** Former Monsanto Company Scientist, Paid Monsanto Consultant. Currently works as a Consultant/Professor Clinical Epidemiology, Aarhus University.
- **Bruce Chassy:** Professor Emeritus at the University of Illinois Department of Food Science and Human Nutrition and Monsanto grant recipient. Chassy helped organize writing campaigns to scientific journals criticizing studies on glyphosate at Monsanto's request and runs a non-profit called Academics Review that Monsanto reportedly helped to establish to provide an "independent" voice supporting glyphosate and other issues of interest to Monsanto.
- **Donna R. Farmer**: Monsanto's lead toxicologist and a Monsanto employee since 1991.
- **A. Wallace ("Wally") Hayes:** Former Editor-in-Chief for Vision and Strategy at *Food and Chemical Toxicology* journal, which, during his tenure, published and retracted the Seralini rat study. Reportedly was paid $16,000 by Monsanto in a consulting contract.
- **William F. Heydens**: Currently Monsanto's Product Safety Assessment Strategy Lead.
- **Larry Kier**: Former Monsanto toxicologist. Authored, "Review of genotoxicity studies of glyphosate and glyphosate-based formulations," which found glyphosate posed no risk to humans.
- **David J. Kirkland:** Monsanto contractor who was a co-author with Larry Kier on the study "Review of genotoxicity studies of glyphosate and glyphosate-based formulations."
- **Henry Miller:** Stanford Hoover Institution fellow and former contributor to *Forbes*. In 2015, Miller published a *Forbes* article critical of IARC that was solicited–and largely ghostwritten –by Monsanto. *Forbes* cut ties with Miller and retracted his articles when they discovered his failure to disclose ties with Monsanto.
- **Dr. James Parry** was a Geneticist at Swansea University in the United Kingdom who was hired by Monsanto in 1999 to evaluate the genotoxicity of glyphosate. Monsanto refused to conduct additional tests at his request and attempted to "move him from his position."
- **Eric Sachs:** Monsanto Science and Policy lead since 2005; botanist and plant geneticist.
- **David A. Saltmiras:** Former Monsanto Company Toxicology Manager and author on the so-called Greim Study that refuted animal data indicating glyphosate's carcinogenicity.
- **Gilles-Éric Séralini**. French molecular biologist who conducted a study that found rats fed glyphosate-tolerant corn treated with Roundup had an increased risk of developing tumors. The study, published in the journal *Food and Chemical Toxicology*, was retracted by journal editor and Monsanto contractor A. Wallace Hayes.

Monsanto's IARC Battle Plan. Prior to IARC's March 2015 classification of glyphosate as a Group 2A agent that was "probably carcinogenic to humans," Monsanto knew that the existing scientific evidence regarding potential ill-health effects from exposure to glyphosate was not on their side, according to their own internal e-mails. In October 2014, Monsanto scientist William Heydens wrote in an e-mail with the Subject hearing "IARC Evaluation of Glyphosate," "[W]hile we have vulnerability in the area of epidemiology, we also have potential vulnerabilities in the other areas that IARC will consider, namely, exposure, genetox, and mode of action..."[5]

International Agency Research on Cancer

World Health Organization

By February 2015, a battle plan to confront what they suspected would be bad news for glyphosate was already underway.[6] "We should assume and prepare for the outcome of a 2B rating (*possible* human carcinogen); a 2A rating (*probable* human carcinogen) is possible but less likely." Glyphosate received the 2A rating by IARC. According to several key records unsealed in the multi-district litigation against Monsanto, including the company's "Preparedness and Engagement Plan for IARC Carcinogen Rating of Glyphosate," dated February 17, 2015, Monsanto was ready for a full-borne defense of glyphosate when IARC released its Monograph on glyphosate in March 2015.[7]

The Monsanto attack plan included efforts to "amplify" their message that glyphosate was safe pointing to industry-sponsored studies and industry-placed news stories. They sought to generate industry "outrage" over what they thought would be a 2B rating. They had plans to address these "new allegations" regarding the potential hazard of glyphosate and to "neutralize" the impact. They also sought to "amplify" the "positive" message about glyphosate's safety via social media platforms including Twitter and Facebook. They turned to industry trade groups, such as CropLife and industry front groups, such as Genetic Literacy Project and Academics Review as platforms of support for industry spokespersons. They also sought third-party experts to "blog, op/ed, tweet and/or link, repost, retweet, etc." They were planning an onslaught of actions to help undermine IARC and to embolden their justifications to dismiss IARC's scientific findings. They have carried out that battle plan in a consistent and very aggressive manner ever since.

Separately from Monsanto's attacks on IARC they have also tried to wield their influence at the Environmental Protection Agency (EPA) as well. In some instances, they have objected to key scientists sitting on EPA science panels reviewing glyphosate's safety. There have also been questions about other tactics. In May 2017 the EPA's Office of Inspector General opened "an investigation into reports that an EPA employee may have colluded with Monsanto to conduct a biased review of glyphosate," according to the IG's letter announcing the investigation.[8]

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[5] Email from William Heydens to Monsanto employees, Subject: "IARC Evaluation of Glyphosate," October 15, 2014, accessed here: http://baumhedlundlaw.com/pdf/monsanto-documents/35-Monsanto-Admits-Company-Faces-Issues-in-Epidemiology-Exposure-Genotoxicity-and-Mode-of-Action.pdf

[6] Monsanto internal document, "Glyphosate: IARC," (also referred to as the Monsanto IARC Battle Plan by the media) February 23, 2015, accessed here: http://baumhedlundlaw.com/pdf/monsanto-documents/72-Document-Details-Monsantos-Goals-After-IARC-Report.pdf

[7] Ibid.

[8] See: Tiffany Stecker, "Watchdog May Find EPA-Monsanto Links on Pesticides Routine," Bloomberg Energy & Environment Report, June 8, 2017, accessed here: https://www.bna.com/watchdog-may-find-n73014453069/

Ghostwriting. Internal Monsanto e-mails show that Monsanto scientists "ghost wrote" scientific journal articles on glyphosate. It is clear from these e-mails, revealed in court documents, that ghostwriting articles on glyphosate was a concerted effort by the company. Monsanto scientists wanted to both steer the scientific studies away from identifying potential adverse human health effects from exposure to glyphosate and they wanted other "independent" scientists listed on these studies to provide the aura of objectivity and independence.

Monsanto did this on several occasions. The internal e-mails show a clear and consistent attempt by some Monsanto scientists to obfuscate their roles in writing, directing and funding glyphosate-related studies. Equally disturbing are examples where they attempted to bury scientific study results that *did* show potential adverse effects from glyphosate exposures. Many of these e-mails portray Monsanto scientists as less interested in discovering if glyphosate and Monsanto's herbicide Roundup could have toxic effects and more interested in developing studies that showed no potential ill health effects and had the veneer of independence and objectivity. The e-mails and other records unsealed in the Monsanto court case regarding Roundup have begun to pull back the curtain on those claims and the company's extraordinary efforts to discredit the scientific conclusions made by IARC on glyphosate and to undermine the reputation of the science agency.

Ghostwriting Greim. In 2015, Monsanto anticipated, based on the scientific evidence that was publicly available, that IARC would classify glyphosate as either a Group 2B agent (*possibly* carcinogenic to humans) or Group 2A agent (*probably* carcinogenic to humans). In preparation, they sought to publish new papers countering the animal data used by IARC, which ultimately concluded in March 2015 that glyphosate was a Group 2A agent, "*probably* carcinogenic to humans." In an email between Monsanto scientists Bill Heydens and Donna Farmer, they discuss what became known as the "Greim paper" – a 2015 study published in *Critical Reviews in Toxicology* whose listed authors include Helmut Greim and David Saltmiras.[9] In the emails, they contemplate paying for a study to combat problematic findings, but determine a cheaper option would be to "ghost-write the Exposure Tox & Genetox sections… [and] add Greim and Kier or Kirkland to have their names on the publication, but we would be keeping the cost down by us doing the writing and they would just edit & sign their names so to speak."[10] The paper, published in March 2015 with Greim as the lead author, concluded: "After almost forty years of commercial use, and multiple regulatory approvals including toxicology evaluations, literature

[9] Greim H, Saltmiras D, Mostert V, Strupp C, "Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies," *Critical Reviews in Toxicology*, March 2015, accessed here: https://www.ncbi.nlm.nih.gov/pubmed/25716480.

[10] Email from William Heydens to Donna Farmer, cc David Saltmiras and other Monsanto employees, Subject: "RE: IARC Planning," February 19, 2015, accessed here: https://www.baumhedlundlaw.com/pdf/monsanto-documents/Email-Correspondence-Wherein-William-Heydens-Suggests-Experts-Could-Edit-and-Sign-Their-Names-to-Scientific-Paper.pdf.

reviews, and numerous human health risk assessments, the clear and consistent conclusions are that glyphosate is of low toxicological concern, and no concerns exist with respect to glyphosate use and cancer in humans." That conclusion dismissed or ignored multiple other studies that have questioned glyphosate's safety.

Multiple internal Monsanto records show that whatever role Greim had in the study, Monsanto scientists were clear that they were in charge and conducted the bulk of the work on the paper. One internal Monsanto power-point slide says Monsanto could use Greim and one or two other external authors on the paper they envisioned but that the "Majority of writing can be done by Monsanto, keeping OS$ down."[11] David Saltmiras, a Monsanto scientist who was a co-author with Greim on the paper, wrote a description of his work for Monsanto in August 2015 labelled "Glyphosate Activities." He wrote that he "ghost wrote cancer review paper Greim et al. (2015)."[12]

E-mail from Monsanto's William Heydens to Donna Farmer and cc'd to David Saltmiras, et. al., February 19, 2015.

Subject: RE: IARC Planning

"A LESS EXPENSIVE/MORE PALATABLE APPROACH MIGHT BE TO INVOLVE EXPERTS ONLY FOR THE AREAS OF CONTENTION, EPIDEMIOLOGY AND POSSIBLY MOA [MODE OF ACTION] (DEPENDING ON WHAT COMES OUT OF THE IARC MEETING), AND WE GHOST-WRITE THE EXPOSURE TOX & GENETOX SECTIONS. AN OPTION WOULD BE TO ADD GREIM AND KIER OR KIRKLAND TO HAVE THEIR NAMES ON THE PUBLICATION, BUT WE WOULD BE KEEPING THE COST DOWN BY US DOING THE WRITING AND THEY WOULD JUST EDIT & SIGN THEIR NAMES SO TO SPEAK. RECALL THAT IS HOW WE HANDLED WILLIAMS KROES & MUNRO, 2000."[6]

The Greim paper became a focal point of Monsanto's objections to IARC, with the company claiming that if it had been considered, the classification of glyphosate would have been different. While the definition of ghostwriting often differs from this situation – typically meaning that the true author is unnamed – Monsanto itself referred to this process as "ghostwriting" multiple times. In addition, e-mails from Monsanto scientists show that this was not the first time they had "ghostwritten" a journal article on glyphosate. One e-mail says that Monsanto scientists had also

[11] Monsanto internal presentation, "Proposal for Post-IARC Meeting Scientific Projects DRAFT," May 11, 2015, accessed here: https://www.baumhedlundlaw.com/pdf/monsanto-documents/Monsanto-Proposal-for%20Post-IARC-Meeting-Scientific-Projects.pdf.

[12] David Saltmiras custodial document, "Glyphosate Activities," August 4, 2015, accessed here: http://baumhedlundlaw.com/pdf/monsanto-documents/18-Monsanto-Scientist-Admits-to-Ghostwriting-Cancer-Review-Paper.pdf.

ghostwritten an article and had the independent scientists simply edit and sign their names to the paper back in 2000.[13]

Too close for comfort. On the other extreme, Monsanto, at times, has sought to have former Monsanto scientists distance themselves from Monsanto's scientific studies to maintain the charade of independence they have attempted to convey on Monsanto-directed research. In 2015, after the release of the IARC monograph on glyphosate, Monsanto put together a supposedly independent "expert panel review" to dispute the IARC classification. Their effort to bury Monsanto ties to the panel was complicated by a retired Monsanto scientist who was now consulting for the company, John Acquavella. He objected to his name being omitted from a poster listing the names of authors and experts on that panel. Heydens responded to his objection by explaining that management "would not be able to use your or Larry [Kier] as Panelists / authors because of your prior employment at Monsanto." Acquavella was blunt in his response, writing back, "I don't think that will be okay with my panelists. We call that ghost writing and it is unethical." [14]

E-mail from John Acquavella (retired Monsanto scientist) to William Heydens (Monsanto scientist), November 3, 2015, 2:55 p.m.

Subject: Re: Glyphosate Expert Panel Poster at 2015 SRA Annual Meeting

"I DON'T THINK THAT WILL BE OKAY WITH MY PANELISTS. WE CALL THAT GHOST WRITING AND IT IS UNETHICAL."[10]

E-mail from William Heydens (Monsanto scientist) to John Acquavella (retired Monsanto scientist), November 3, 2015, 1:49 p.m.

Subject: Re: Glyphosate Expert Panel Poster at 2015 SRA Annual Meeting

"I THOUGHT WE DISCUSSED PREVIOUSLY THAT IT WAS DECIDED BY OUR MANAGEMENT THAT WE WOULD NOT BE ABLE TO USE YOU OR LARRY AS PANELISTS/AUTHORS BECAUSE OF YOUR PRIOR EMPLOYMENT AT MONSANTO..."

[13] Email from William Heydens to Donna Farmer, cc David Saltmiras and other Monsanto employees, Subject: "RE: IARC Planning," Feb. 19, 2015, accessed here: https://www.baumhedlundlaw.com/pdf/monsanto-documents/Email-Correspondence-Wherein-William-Heydens-Suggests-Experts-Could-Edit-and-Sign-Their-Names-to-Scientific-Paper.pdf;
See: Gary M.Williams, Robert Kroes and Ian C.Munro, "Safety Evaluation and Risk Assessment of the Herbicide Roundup and Its Active Ingredient, Glyphosate, for Humans," *Regulatory Toxicology and Pharmacology,* Volume 31, Issue 2, April 2000, Accessed here:
https://www.sciencedirect.com/science/article/pii/S0273230099913715?via%3Dihub;
Despite the evidence in the Monsanto e-mails some of the independent scientists mentioned by Monsanto regarding the "ghost writing" of articles have said they would never do such a thing. See: Warren Cornwall, "Update: After quick review, medical school says no evidence Monsanto ghostwrote professor's paper," *Science Magazine*, March 23, 2017, accessed here: http://www.sciencemag.org/news/2017/03/update-after-quick-review-medical-school-says-no-evidence-monsanto-ghostwrote.

[14] Emails between John Acquavella, William Heydens, and Donna Farmer, Subject: "John, Glyphosate Expert Panel Poster at 2015 SRA Annual Meeting,"Nov. 3 – 6, 2015, accessed here: http://baumhedlundlaw.com/pdf/monsanto-documents/6-Monsanto-Consultant-Protests-Ghostwriting.pdf.

The next day Acquavella writes that he "can't be part of deceptive authorship on a presentation or publication" and he schools his former Monsanto co-workers in the ethics of authorship by including excerpts of the International Committee of Medical Journal Editors (ICJME) recommendations regarding authorship.[15]

E-mail from John Acquavella (retired Monsanto scientist) to William Heydens (Monsanto scientist), and cc'd to Donna Farmer
November 4, 2015,

Subject: Re: Glyphosate Expert Panel Poster at 2015 SRA Annual Meeting

"YOU GUYS KNOW ME. I CAN'T BE A PART OF DECEPTIVE AUTHORSHIP ON A PRESENTATION OR PUBLICATION. PLEASE NOTE THE ICJME GUIDELINES BELOW THAT EVERYONE GOES BY TO DETERMINING WHAT IS HONEST/ETHICAL REGARDING AUTHORSHIP." [10]

Two days later Monsanto's Heydens attempts to backtrack and set the record straight after a phone call with Acquavella and Donna Farmer. He describes this whole episode as a "huge misunderstanding around authorship."[16]

Ultimately, a later email indicates that Monsanto listed Acquavella as an author. In fact, the abstract, *"Expert Panel Review of the Carcinogenic Potential of the Herbicide Glyphosate,"* as published in the Society for Risk Analysis' 2015 Annual Meeting also included Williams, Greim, Kier and Kirkland, who Monsanto scientists had named in internal e-mails as individuals they had or believed they could ghost write scientific studies on glyphosate for, although Monsanto scientists would do the bulk of the writing.[17]

E-mail from Erich Sachs to various other Monsanto employees, including Donna Farmer and David Saltmiras,
February 24, 2015

Subject: Re: Opportunity: Glyphosate and IARC

JOHN V AND I TALKED TO HENRY MILLER TODAY. HENRY AGREED TO AUTHOR AN ARTICLE ON FORBES.COM JOHN WILL WORK WITH A TEAM INTERNALLY TO PROVIDE A DRAFT AND HENRY WILL EDIT/ADD TO MAKE IT HIS OWN. THE ARTICLE CAN BE LIVE SAME DAY IT IS COMPLETED.

Hiring journalists to discredit IARC.
In Monsanto's effort to discredit IARC, they sought to recruit writers to publish pieces echoing their criticisms of IARC's process. In February 2015, one month before IARC published their glyphosate monograph that found glyphosate to be a "probable human carcinogen," Monsanto scientist Eric Sachs reached out to Henry Miller, a

[15] Ibid.
[16] Ibid.
[17] Society for Risk Analysis 2015 Annual Meeting Abstracts, Dec. 6-10, 2015, Arlington, Virginia, see page 136, Williams, GM, et. al., "Expert Panel Review of the Carcinogenic Potential of the Herbicide Glyphosate," accessed here: http://www.sra.org/sites/default/files/pdf/events/Abstracts%202015.pdf

Forbes contributor and a Medical Doctor and Fellow in Scientific Philosophy and Public Policy at Stanford University's Hoover Institute, a conservative think tank. Sachs prompted Miller on the desired content of the article, writing, "Ideally, your article would precede the IARC decision. Why not set the table with the weight of scientific evidence before IARC convenes? Then, regardless of what they do, your article will set the state for a science-based response."[18] Miller agreed – and, after a follow-up email, requested a "high quality draft" from Monsanto.[19] Officials at the company quickly got to work and provided Miller with a draft that was posted on the *Forbes* website largely unchanged. The article was published on March 17, 2015, with the title: "March Madness from the United Nations."[20]

When this ghostwriting was discovered, Miller was fired by *Forbes.* In a statement to Retraction Watch, a *Forbes* representative said: "All contributors to *Forbes.com* sign a contract requiring them to disclose any potential conflicts of interest and only publish content that is their own original writing. When it came to our attention that Mr. Miller violated these terms, we removed all of his posts from *Forbes.com* and ended our relationship with him."[21]

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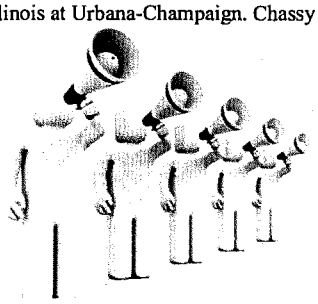
[18] Email from Eric Sachs to Henry Miller, Subject "Opportunity: Glyphosate and IARC," Feb. 23, 2015, accessed here: http://baumhedlundlaw.com/pdf/monsanto-documents/21-Internal-Monsanto-Email-Detailing-Company-Effort-to-Preemptively-Criticize-IARC-Ahead-of-Glyphosate-Report.pdf.
Pull quote citation: Email from Eric Sachs to Donna Farmer, David Saltmiras, and other Monsanto employees, Feb. 24, 2015, link above.

[19] Email from Henry Miller to Eric Sachs, Subject: "Re: IARC Outcomes, Process, and Response," March 12, 2015, accessed here: http://baumhedlundlaw.com/pdf/monsanto-documents/22-Internal-Email-Demonstrating-Monsanto-Ghostwriting-Article-Criticizing-IARC-for-Press.pdf.

[20] Henry Miller, "March Madness from the United Nations," Forbes, March 17, 2015, accessed here: https://web.archive.org/web/20170220012554/https:/www.forbes.com/sites/henrymiller/2015/03/20/march-madness-from-the-united-nations/#21e081ee2e9.

[21] Andrew P. Han, "Unearthed emails: Monsanto connected to campaign to retract GMO paper," Aug. 10, 2017, Retraction Watch, accessed here: http://retractionwatch.com/2017/08/10/unearthed-docs-monsanto-connected-campaign-retract-gmo-paper/

Orchestrate Outcry. Henry Miller, whose clandestine ties to Monsanto got him removed as a contributor at *Forbes*, co-authored a piece on *Forbes.com* in September 2012 with Bruce Chassy, the former head of the Department of Food Science and Nutrition at the University of Illinois at Urbana-Champaign. Chassy too has opaque ties to Monsanto.[22] He received funds from Monsanto for research through the University of Illinois and he would later be recruited to defend Monsanto on the chemical industry website GMO Answers[23] and established a non-profit website called Academics Review with Monsanto's assistance.[24] The article Miller and Chassy wrote for *Forbes* critiqued a study of glyphosate by French microbiologist Gilles-Eric Seralini in the journal *Food and Chemical Toxicology (FCT)* that found that the glyphosate containing herbicide Roundup and genetically modified glyphosate-resistant corn caused tumors in rats.[25]



This spelled trouble for Monsanto's Roundup Ready crops. Monsanto was tipped off about the publication of the Seralini paper by *FCT*'s Editor in Chief for Vision and Strategy, Wally Hayes. On September 26, 2012 Monsanto scientist David Saltmiras sent an e-mail to colleagues and wrote: "Wally Hayes (*FCT* Editor in Chief) called me this morning in response to my voice mail yesterday. He expressed concern that to date he has only received links to blogs, web postings, media releases, etc. and no formal letters to the Editor" regarding the Seralini article.[26] He needed more.

E-mail from Monsanto's Eric Sachs to David Saltmiras, William Heydens, et. al., September 26, 2012.

Subject: RE: Letters to the Editor?

"I TALKED TO BRUCE CHASSY AND HE WILL SEND HIS LETTER TO WALLY HAYES DIRECTLY AND NOTIFY OTHER SCIENTISTS THAT HAVE SENT LETTERS TO DO THE SAME. HE UNDERSTANDS THE URGENCY."[22]

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[22] Tom Philpott, "These Emails Show Monsanto Leaning on Professors to Fight the GMO PR War," Mother Jones, Oct. 2, 2015, accessed here: https://www.motherjones.com/food/2015/10/monsanto-professors-gmo-pr/.

[23] "A University of Illinois Professor Joins the Fight," Sept. 5, 2015, New York Times, accessed here: https://www.nytimes.com/interactive/2015/09/05/us/document-chassy.html

[24] Stacy Malkan, "Monsanto Fingerprints Found All Over Attack On Organic Food," Dec. 6, 2017, HuffPost, accessed here: https://www.huffingtonpost.com/stacy-malkan/monsanto-fingerprints-fou_b_10757524.html ; "Academics Review – About," accessed here: http://academicsreview.org/about-academic-review/

[25] Gilles-Eric Seralini et al., "Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize," Food and Chemical Toxicology, Sept. 19, 2012, accessed here: https://ac.els-cdn.com/S0278691512005637/1-s2.0-S0278691512005637-main.pdf?_tid=58d0db10-0a9c-11e8-b8f6-00000aacb35f&acdnat=1517852905_42d9615555402636b3cd425628eb849f.

[26] Email from David Saltmiras to Eric Sachs, William Heydens, and other Monsanto employees, Subject: "Letters to the Editor?", Sept. 26, 2015, accessed here: http://baumhedlundlaw.com/pdf/monsanto-documents/7-Monsanto-Personnel-Discusses-Plan-Seeking-Retraction-of-Serlani-Glyphosate-Study.pdf.

Pull quote citation: Email from Eric Sachs to Monsanto employees, Sept. 26, 2012, link above.

Internal Monsanto records show that Monsanto started aggressively attempting to attack the Seralini paper through third-parties. Monsanto began working their network of scientists.

Monsanto's Daniel Goldstein to Monsanto scientist Eric Sachs, September 28, 2012

Subject: RE: Slides – Seralini Publication

"I WAS UNCOMFORTABLE EVEN LETTING SHAREHOLDERS KNOW WE ARE AWARE OF THIS LTE.... IT IMPLIES WE HAD SOMETHING TO DO WITH IT-OTHERWISE HOW DO WE HAVE KNOWLEDGE OF IT? ....

WE ARE BEING ASKED TO KEEP INTERNAL CORRESPONDENCE DOWN ON THIS SUBJECT."[24]

Monsanto scientists were encouraging and soliciting third parties to criticize the Seralini paper and call out flaws in hopes of putting enough pressure on the *FCT* journal to retract the study. One of the people they turned to was Bruce Chassy who wrote to Hayes complaining about the Seralini paper. But some Monsanto scientists worried because they did not want their fingerprints on any public campaign to retract the paper. "We should not provide ammunition for Seralini, GM critics and the media to charge that Monsanto used its might to get this paper retracted," wrote Monsanto scientist Eric Sachs.[27] Others agreed, including Monsanto's Daniel Goldstein, who wrote: "We are being asked to keep internal correspondence down on this subject."[28]

While Monsanto's quiet third-party efforts seemed to help, there was something else working in Monsanto's favor. Wally Hayes, the *FCT* editor who was also a professor at the Harvard School of Public Health had apparently signed a consulting agreement on August 21, 2012, with Monsanto just before the Seralini paper dispute heated up. A letter dated September 7, 2012 from Monsanto to Hayes, just three weeks before Hayes and Saltmiras began talking about the Seralini paper, was identified as an "Authorization Letter" to the August 21, 2012 Consulting Agreement. The letter said that Hayes' services in setting up a Latin America South Toxicology Expert Panel, slated to begin on September 7, 2012, would pay him $400 an hour, not to exceed $3,200 per day, for a total of $16,000. David Saltmiras was listed as Monsanto's representative for the project.[29]

The Seralini paper was officially retracted by Hayes and *FCT* in 2013.[30] Hayes told the *New York Times* that he had not been under contract with Monsanto at the time of the retraction and was paid by the company only after he left the journal. "Monsanto played no role whatsoever in

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[27] Ibid.

[28] Email from Daniel Goldstein to Eric Sachs and Yong Gao, Subject: "RE: Slides- Seralini Publication," Sept. 28, 2012, accessed here: http://baumhedlundlaw.com/pdf/monsanto-documents/14-Monsanto-Emails-Confirming-Undisclosed-Involvement-in-Successful-Retraction-of-Serlani-Study.pdf

[29] "Authorization Letter to Consulting Agreement dated August 21, 2012, between Prof. A. Wallace Hayes and Monsanto Company," Aug. 21, 2012, accessed here: http://baumhedlundlaw.com/pdf/monsanto-documents/10-Monsanto-Consulting-Agreement-with-Food-and-Chemical-Toxicology-Editor.pdf.

[30] Andrew Pollack, "Paper Tying Rat Cancer to Herbicide Is Retracted," New York Times, Nov. 28, 2013, accessed here: http://www.nytimes.com/2013/11/29/health/paper-tying-rat-cancer-to-herbicide-is-retracted.html.

the decision that was made to retract," he told the newspaper. "It was based on input that I got from some very well-respected people, and also my own evaluation," he said.[31]

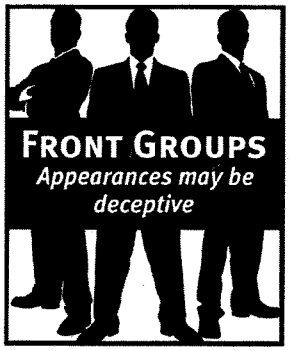
Meanwhile, Monsanto's Saltimiras's own "business performance" plan for FY2013 touts his own success in these efforts. "Successfully facilitate numerous third party expert letters to the editor which were subsequently published, reflecting the numerous significant deficiencies, poor study design, biased reporting and selective statistics employed by Seralini," Saltmiras wrote in his review.[32] The website Retraction Watch noted however, "An FCT investigation found no evidence of fraud, misconduct, or gross error, [in the Seralini paper], which are required by Committee on Publication Ethics (COPE) guidelines for retraction; however, FCT cited COPE guidelines in their retraction notice anyway."[33]

[31]Danny Hakim, "Monsanto Emails Raise Issue of Influencing Research on Roundup Weed Killer," New York Times, Aug 1, 2017, accessed here: https://www.nytimes.com/2017/08/01/business/monsantos-sway-over-research-is-seen-in-disclosed-emails.html.

[32] Internal Monsanto document by David Saltmiras, "FY2013," Aug. 20, 2013, accessed here: http://baumhedlundlaw.com/pdf/monsanto-documents/8-Monsanto-Scientist-Admits-to-Leveraging-Relationship-with-Food-and-Chemical-Toxicology-Journal.pdf.

[33]Andrew P. Han, "Unearthed emails: Monsanto connected to campaign to retract GMO paper," Retraction Watch, Aug 10, 2017, accessed here" http://retractionwatch.com/2017/08/10/unearthed-docs-monsanto-connected-campaign-retract-gmo-paper/.

Establish Front Groups. Media reports have pointed to several seemingly independent non-profit groups as having close ties to Monsanto. Some were reportedly established with assistance from Monsanto in order to serve as a platform to confront scientific findings revealing potential health hazards from glyphosate while concealing Monsanto's direct involvement. This confront-and-conceal approach is nothing new. These tactics have been used by the tobacco industry, energy sector and chemical companies. They often have innocuous-sounding names – for instance, the Campaign for Accuracy in Public Health Research (CAPHR), which is run by the American Chemistry Council (ACC). In this case, the ACC has not attempted to hide their ties with CAPHR and even announced its launch in January 2017. The organization's primary target is IARC.[34] The group's initial press release said: "In particular, CAPHR will seek reform of the International Agency for Research on Cancer's (IARC) Monographs Program, which evaluates the carcinogenic hazard of substances and behaviors."[35]



Other front groups are more secretive. Academics Review was co-founded by Bruce Chassy. The site was founded in January 2010 to "ensure that sound science is widely and easily available." It describes itself as "an association of academic professors, researchers, teachers and credentialed authors from around the world" who "stand against falsehoods, half-baked assertions and theories or claims not subjected to this kind of rigorous review."[36] What it does not reveal are the close ties between Chassy and Monsanto. But one e-mail exchange between Monsanto's Eric Sachs and Chassy shows Monsanto was interested in using the site to its advantage as long as it was able to hide its involvement. "The key will be

E-mail from Monsanto's Eric Sachs to Bruce Chassy, co-founder of Academics Review.

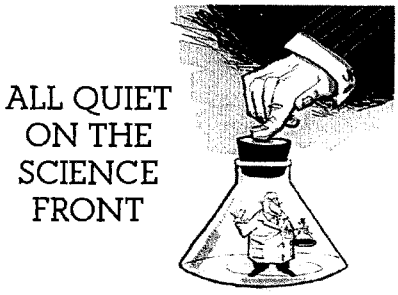
November 30, 2010

"YOU AND I NEED TO TALK MORE ABOUT THE "ACADEMICS REVIEW" SITE AND CONCEPT. I BELIEVE THAT THERE IS A PATH TO A PROCESS THAT WOULD BETTER RESPOND TO SCIENTIFIC CONCERNS AND ALLEGATIONS. ... FROM MY PERSPECTIVE THE PROBLEM IS ONE OF EXPERT ENGAGEMENT AND THAT COULD BE SOLVED BY PAYING EXPERTS TO PROVIDE RESPONSES. ... THE KEY WILL BE KEEPING MONSANTO IN THE BACKGROUND SO AS NOT TO HARM THE CREDIBILITY OF THE INFORMATION." [33]

[34] Campaign for Accuracy in Public Health Research, "IARC," accessed here: http://campaignforaccuracyinpublichealthresearch.com/iarc/.
[35] American Chemistry Council, "ACC Launches Campaign to Promote Credibility in Public Health Research," Jan. 25, 2017, accessed here: https://www.americanchemistry.com/Media/PressReleasesTranscripts/ACC-news-releases/ACC-Launches-Campaign-to-Promote-Credibility-in-Public-Health-Research.html.
[36] Academics Review, "Purpose," accessed here: http://academicsreview.org/about-academic-review/purpose/.

keeping Monsanto in the background so as not to harm the credibility of the information," wrote Sachs.[37]

Silence Scientists. Monsanto and other large corporate interests use multiple tactics in their attempts to delay regulations, deter the publication of scientific findings that endanger their corporate profits, and degrade scientific institutions, such as IARC, that are independent and a threat to an industry's influence and a challenge to their disinformation campaigns. Sometimes they also attack specific scientists who are independent and pose a potential threat to their objectives and activities as a result of their scientific studies, interests or integrity.



Dr. Peter Infante, a renowned and highly respected epidemiologist, has been the victim of industry attacks for four decades due to his solid scientific findings on the cancer-causing properties of chemicals such as formaldehyde and benzene and arsenic. In the early 1980s, when he was a senior official at the Occupational Safety and Health Administration (OSHA) the House Science Committee held a hearing on the "Proposed firing of Dr. Peter Infante by OSHA" due to pressure on OSHA from the Formaldehyde Institute.[38] The oversight hearing was led by then Representative Al Gore, and OSHA eventually backed down from its attempt to fire Dr. Infante. More recently it has been the glyphosate industry led by CropLife America, the national trade association that represents the manufacturers, formulators and distributors of pesticides, that has gone after Dr. Infante.

In 2016, Dr. Infante was selected as a Member of the Environmental Protection Agency's Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) on the Evaluation of the Human Carcinogenic Potential of Glyphosate. In October 2016, CropLife sent a letter to the EPA citing concerns about the SAP,[39] specifically citing Dr. Infante's participation. The CropLife letter stated that Dr. Infante had biases against industry and should therefore be removed from the Panel. Dr. Infante sent a rebuttal letter[40] to the EPA as did the Center for Food Safety defending Dr. Infante.[41] However, prior to the December 2016 meeting of the SAP, EPA officials removed Dr. Infante from the SAP on glyphosate without

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[37] Email from Eric Sachs to Bruce Chassy, Subject: "Questions," Nov. 30, 2010, accessed here: https://www.usrtk.org/wp-content/uploads/2016/01/Sachs-AR.pdf.

[38] "Proposed Firing of Dr. Peter Infante by OSHA: A Case Study in Science and Regulation," Subcommittee on Investigations and Oversight of the Committee on Science and Technology, U.S. House of Representatives, July 16, 1981, accessed here: https://babel.hathitrust.org/cgi/pt?id=mdp.39015082337588;view=1up;seq=8.

[39] Letter from CropLife to EPA, Oct. 12, 2016, accessed here: http://191hmt1pr08amfq62276etw2.wpengine.netdna-cdn.com/wp-content/uploads/2016/01/CLA-Comments-on-SAP-Disqualification-10-12-16.pdf.

[40] "Comment submitted by Peter F. Infante, Consultant, Peter F. Infante Consulting, LLC," Regulations.gov, Oct. 21, 2016, accessed here: https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0385-0439.

[41] Comment submitted by Center for Food Safety to EPA, "RE: Scientific Advisory Panel meeting on glyphosate's carcinogenic potential," Dec. 12, 2016, accessed here: http://www.centerforfoodsafety.org/files/glyphosate-sap-infante-letter--cfs-12-12-16_02026.pdf.

explanation.[42] At Scott Pruitt's EPA, where he has intentionally removed independent scientists from the Agency's science advisory boards so that he can stack them with more industry-funded scientists, this was not a tremendous surprise, but one that is disappointing nonetheless.

E-mail from Monsanto's Donna Farmer, April 17, 1999 (recipients unknown)

Subject: Meeting Minutes

"DR. PARRY CONCLUDED ON HIS EVALUATION OF THE FOUR ARTICLES THAT GLYPHOSATE IS CAPABLE OF PRODUCING GENOTOXICITY BOTH IN VIVO AND IN VITRO... IN ORDER TO MOVE DR. PARRY FROM HIS POSITION WE WILL NEED TO PROVIDE HIM WITH THE ADDITIONAL INFORMATION AS WELL AS ASKING HIM TO CRITICALLY EVALUATE THE QUALITY OF ALL THE DATA INCLUDING THE OPEN LITERATURE STUDIES. ... MARK WILL ALSO EXPLORE HIS INTEREST (IF WE CAN TURN HIS OPINION AROUND) IN BEING A SPOKESPERSON FOR US FOR THESE TYPE OF ISSUES." [39]

Dr. James Parry. It is important to understand that Monsanto's aggressive tactics regarding its efforts to defend glyphosate and its highly successful product Roundup have been going on for decades. Like so many chemical-based products, however, as scientific evidence of potential worry accumulate, the potential threat to the commercial viability and sustainability of the product can grow. It is clear from the substantive documents that have come to light recently that Monsanto has been fending off those sorts of threats for many years.

In the past, Monsanto has even sought to silence their own scientists, when they discovered evidence of potential adverse human health effects from exposures to glyphosate. Back in 1999, Monsanto's contracted scientist, Dr. James Parry, a geneticist at Swansea University in the United Kingdom, was one of them. Monsanto hired Parry to evaluate the genotoxicity of glyphosate, and, to their disappointment, Parry concluded that "glyphosate is capable of producing genotoxicity both in vivo and in vitro by a mechanism based upon the production of oxidative damage."[43] Disturbingly, internal Monsanto e-mails show that Monsanto scientists contemplated ways to "move Dr. Parry from his position"[44] regarding the toxicity of glyphosate. Parry also signed a secrecy agreement with Monsanto in April 1999. The contents of the agreement are not known, but it does not appear that Dr. Parry ever published his findings regarding glyphosate's genotoxicity.

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[42] "Panel Member Roster, Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel, Open Meeting, December 13-16, 2016," Regulations.gov, Nov. 28, 2016, accessed here: https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0385-0454.

[43] Email from Donna Farmer to unknown recipients, Subject: "Meeting Minutes 2/25," April 17, 1999, accessed here: http://baumhedlundlaw.com/pdf/monsanto-documents/38-Email-Shows-Former-Monsanto-Expert-Confirmed-Biological-Plausibility-of-Glyphosate-as-Carcinogen.pdf.

[44] Ibid.

As part of Parry's review, he suggested additional studies into the genotoxicity of glyphosate. Monsanto was opposed to funding these additional studies, however, and Bill Heydens expressed his disappointment in the Parry review in an email to colleagues and expressed the importance of finding a pro-glyphosate advocate. This was important, he wrote, because Monsanto was "currently very vulnerable in this area" regarding the genotoxicity of glyphosate. "We want to find/develop someone who is comfortable with the genetox profile of glyphosate/Roundup and who can be influential with regulators and scientific outreach operations when genetox issues arise," added Heydens.[45]

E-mail from Monsanto's William Heydens to Erik Jacobs, et. al., April 10, 2001

Subject: RE: Propachlor sample request

"DATA GENERATED BY ACADEMICS HAS ALWAYS BEEN A MAJOR CONCERN FOR US IN THE DEFENSE OF OUR PRODUCTS. ... CONSIDER THE RAMIFICATIONS OF A POSITIVE RESPONSE ON EUROPEAN AND US REGISTRATIONS." [42]

In 2001, Parry reached out to Monsanto again to obtain a sample of another herbicide, Propachlor, so he could conduct studies on it. Monsanto employees disagreed on how to handle this request. Mark Martens supported providing the samples, so as to "keep prof Parry happy which will make him a good proponent of glyphosate." Bill Heydens, however, had concerns. "Data generated by academics has always been a major concern for us in the defense of our products," he wrote.[46]

Conclusion. The incidents and tactics outlined in this report are, unfortunately, not surprising when it comes to the chemical industry. These same tactics were employed by the chemical industry with regards to lead and a host of other chemicals. They also mimic the tobacco industry's efforts to muddy the science surrounding the health effects of smoking. These efforts have been thoroughly documented, perhaps most notably in David Michaels book, "Doubt is Their Product: How Industry's Assault on Science Threatens Your Health," and in "Merchants of Doubt," by Naomi Oreskes and Erik M. Conway. These industry efforts oftentimes only come to light through disclosure of internal industry documents through the discovery process during litigation. The disclosures made during tobacco litigation revealed the inner workings of the "science for hire" industry and industry's tactics to undercut legitimate science. Likewise, this report relies heavily on documents which have been publically released in the ongoing litigation with Monsanto. That litigation is ongoing, and many documents and deposition transcripts remain under court seal. As these documents continue to be released to the public, more revelations about industry tactics and influence will undoubtedly come to light.

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[45] Email from William Heydens to Mark Martens, Larry Kier, and Donna Farmer, Subject: "RE: Parry report," Sept. 16, 1999, accessed here: https://www.baumhedlundlaw.com/pdf/monsanto-documents/Email-from-William-Heydens-Monsanto-Vulnerable-on-Gene-Tox-After-Parry.pdf.

[46] Email from William Heydens to Mark Martens and other Monsanto employees, Subject: "RE: Propachlor sample request," April 10, 2001, accessed here: https://www.baumhedlundlaw.com/pdf/monsanto-documents/Email-Exchange-Responding-to-Dr-James-Parry-Request-to-Test-Propachlor-Monsanto-Herbicide.pdf.

Given the public policy implications of the IARC and EPA reviews of glyphosate (and other chemicals), staff wanted to ensure that Members had the most up to date information concerning the troubling industry led efforts to discredit the IARC process and exert undue influence at the EPA.

Chairman SMITH. Okay. Thank you, Ms. Johnson.

Mr. WEBER. Mr. Chairman?

Chairman SMITH. Yes, the gentleman from Texas, Mr. Weber.

Mr. WEBER. If I may, I have reservations about entering this report into the record. This Committee received the minority's report—staff report late last night and has not had sufficient time to completely review this report for factual accuracy. I am aware at this time——

Ms. JOHNSON. I didn't—oh, sorry.

Mr. WEBER. —of at least one statement of questionable accuracy. It's on page 15 and 16. The minority's report appears to suggest that the current EPA Administrator Mr. Scott Pruitt was somehow involved in the December 2016 decision to remove Dr. Peter Infante from EPA's Science Advisory Panel to review glyphosate. Mr. Chairman, Dr. Infante was removed during the SAP during President—from the SAP during President Obama's term while Gina McCarthy was the Administrator. And since Greg Pruitt was sworn in February 17, 2017, there really is no rational basis to justify this claim. So I hope the minority will be able to explain that statement.

I yield, Mr. Chairman.

Chairman SMITH. Thank you, Mr. Weber.

Ms. JOHNSON. Mr. Chairman?

Chairman SMITH. And the gentlewoman from Texas is recognized.

Ms. JOHNSON. I did not request unanimous consent. I simply said I will be attaching the report to my statement.

Chairman SMITH. I think Mr. Weber's point was that it contained something that was not accurate and not factual and we hope you'll take a look at that.

Ms. JOHNSON. I hope everyone will take a look at it.

Chairman SMITH. Okay. Well, Mr. Weber went into some detail as to what was inaccurate, and we'll look forward to your response later on. Thank you, Ms. Johnson. Thank you, Mr. Weber.

The gentleman from Oklahoma, the Vice Chairman of the Committee, Mr. Lucas, is recognized for an opening statement.

Mr. LUCAS. Thank you, Chairman Smith, for holding this hearing on the important topic of scientific integrity of the International Agency for Research on Cancer's Monograph Programme. I look forward to hearing from our panel of expert witnesses this morning and want to thank them for their voluntary appearance before this Committee.

First recognized by the World Health Organization in 1965, IARC began as a French initiative to find and root out cancer both in France and around the world. In pursuit of this goal, one of IARC's many endeavors was the identification and classification of known carcinogens. This has come to be known as the Monograph Programme. While the effort at the time represented the best modern understanding of cancer and the environmental causes, the methods of IARC's Monograph Programme have remained largely unchanged over the years, even as our understanding of cancer has evolved.

This has caused IARC to reach conclusions that not only create unnecessary fear in people, but in some cases causes IARC to reach

conclusions that are contradictions to the best available science. This is unfortunate in any scientific program but is completely unacceptable in one in which the United States, through the NIH and through NIEHS, provides the majority of the funding. This is even more true when IARC's conclusions are then utilized as the basis of regulations, for instance, in places such as California of products like Roundup that contain glyphosate.

In 2015, the IARC Monograph Programme categorized glyphosate as "probably carcinogenic to humans." As Chairman Smith explained, IARC's glyphosate Monograph contained substantial portions of alterations and deletions, it appears, to aid the Monograph in drawing a particular conclusion.

While the appearance of agenda-driven manipulation is troubling on its own, it's even more so when considering that IARC's final conclusion is not only on the fringe of the scientific world but is completely and totally by itself. The respected scientific bodies such as the Environmental Protection Agency, the European Food Safety Agency, or IARC's own parent body, the WHO, has repeatedly found there to be no risk posed to humans when glyphosate is used as directed. Yet, the IARC Monograph Program persists, reviewing and labeling over 900 substances as "possible" or "probable" carcinogens over the past 40-plus years, while the only labeling—only labeling one as noncarcinogenic.

IARC's explanation for all this is that they simply assess hazard and not risk; therefore, the actual probability that these substances cause cancer cannot be gleaned from their Monographs. If left unchallenged, this would excuse IARC's bad behavior and give a de facto blessing to their refusal to bring their scientific methods into the modern age. This kind of shoddy work is unacceptable from any scientific body, let alone one funded by the American taxpayer.

The modern agricultural revolution, of which glyphosate and other IARC-labeled "carcinogenic" herbicides have played an enormous role, has helped feed the world and enabled struggling nations to grow and gain a footing on the world stage. All of this, however, is threatened by IARC's flawed scientific analysis. Far too often, farmers, ranchers, and small businesses find themselves on the receiving end of burdensome regulations like those that stem from IARC's misleading assessments. We should be working to reduce the burdens of these hardworking Americans, not funding the growth of them.

And when a federal or international agency makes decisions that have the potential to directly and negatively impact American citizens, we in Congress have a duty to ask questions to address the concerns of our constituents. Similarly, when a federal or international agency utilizes American tax dollars to reach conclusions that directly contradict the overwhelming majority of scientific knowledge, we have a duty to ask how they came to that conclusion.

This Committee has, on several occasions, attempted to gain a greater understanding of IARC's decision-making process. Unfortunately, the Committee's simple request for IARC to provide a witness to testify on the Monograph Programme has been met with resistance. The pursuit of an awesome goal like the eradication of cancer should not, cannot, prevent us from asking questions re-

garding the processes and methods utilized to reach a certain conclusion. Simply because an organization has a commendable goal should never mean the conclusions it draws are beyond reproach.

I look forward to hearing from our witnesses today not only about the problems in the methods and procedures of the IARC Monograph Programme, of which there are many, but also about the fixes they believe that can be made to bring the Monograph Programme back into line with modern science.

And with that, Mr. Chairman, I yield back the balance of my time.

[The prepared statement of Mr. Lucas follows:]

COMMITTEE ON
SCIENCE, SPACE, & TECHNOLOGY
Lamar Smith, Chairman

For Immediate Release
February 6, 2018

Media Contacts: Thea McDonald, Brandon VerVelde
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Statement by Vice Chairman Frank Lucas (R-Okla.)

In Defense of Scientific Integrity: Examining the IARC Monograph Programme and Glyphosate Review

Vice Chairman Lucas: Thank you, Chairman Smith, for holding this hearing today on the important topic of the scientific integrity of the International Agency for Research on Cancer's (IARC) Monograph Programme. I look forward to hearing from our panel of expert witnesses this morning and want to thank them for their voluntary appearance before this committee.

First recognized by the World Health Organization (WHO) in 1965, IARC began as a French initiative to find and root out cancer both in France and around the world. In pursuit of this goal, one of IARC's many endeavors was the identification and classification of known carcinogens. This has come to be known as the Monograph Programme.

While the effort at the time represented the most modern understanding of cancer and its environmental causes, the methods of IARC's Monograph Programme have remained largely unchanged over the years, even as our understanding of cancer has evolved.

This has caused IARC to reach conclusions that not only create unnecessary fear in people, but, in some cases, even causes IARC to reach conclusions that contradict the best available science.

This is unfortunate in any scientific program, but is completely unacceptable in one where the United States, through the NIH and NIEHS, provides the majority of funding. This is even more true when IARC's conclusions are then utilized as the basis for regulation in California of products, like Roundup, that contain glyphosate.

In 2015, the IARC Monograph Programme categorized glyphosate as "probably carcinogenic to humans." As Chairman Smith explained, IARC's glyphosate monograph contained substantial portions of alterations and deletions, it appears, to aid the monograph in drawing a particular conclusion.

While the appearance of agenda-driven manipulation is troubling on its own, it is even more so when considering that IARC's final conclusion is not only on the fringe of the scientific world, but is completely and totally by itself.

Respected scientific bodies such as the Environmental Protection Agency, the European Food Safety Agency or the IARC's parent body, the WHO, have repeatedly found there to be no risk posed to humans when glyphosate is used as directed. Yet, the IARC Monograph

Program persists, reviewing and labeling over 900 substances as "possible" or "probable" carcinogens over the last 40-plus years all the while only labeling one as non-carcinogenic.

IARC's explanation for all this is that they simply assess hazard and not risk, therefore the actual probability that these substances cause cancer cannot be gleaned from their monographs. If left unchallenged, this would excuse IARC's bad behavior and give a de facto blessing to their refusal to bring their scientific methods into the modern age. This kind of shoddy work is unacceptable from any scientific body, let alone one funded by the American taxpayer.

The modern agricultural revolution, of which glyphosate and other IARC-labeled "carcinogenic" herbicides have played an enormous role, has helped to feed the world and enabled struggling nations to grow and gain a footing on the world stage. All of this, however, is threatened by IARC's flawed scientific analysis.

Far too often, farmers, ranchers and small businesses find themselves on the receiving end of burdensome regulations, like those that stem from IARC's misleading assessments. We should be working to reduce the burdens of these hardworking Americans, not funding the growth of them; and when a federal or international agency makes decisions that have the potential to directly and negatively impact American citizens, we in Congress have a duty to ask questions and address the concerns of our constituents.

Similarly, when a federal or international agency utilizes American tax dollars to reach conclusions that directly contradict the overwhelming majority of scientific knowledge, we have a duty to ask how they came to that conclusion. This committee has, on several occasions, attempted to gain a greater understanding of IARC's decision-making processes. Unfortunately, the committee's simple request for IARC to provide a witness to testify on the Monograph Programme has been met with resistance.

The pursuit of an awesome goal like the eradication of cancer should not, and cannot, prevent us from asking questions regarding the processes and methods utilized to reach a certain conclusion. Simply because an organization has a commendable goal should never mean the conclusions it draws are beyond reproach.

I look forward to hearing from our witnesses today not only about the problems in the methods and procedures of the IARC Monograph Programme, of which there are many, but also about the fixes they believe can be made to bring the Monograph Programme back in line with modern science.

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Chairman SMITH. Thank you, Mr. Lucas.

And the gentlewoman from Oregon, the Ranking Member of the Environmental Subcommittee, is recognized for her statement.

Ms. BONAMICI. Thank you, Mr. Chairman. I'm glad we're having this hearing today about the chemical review process.

Ranking Member Johnson is correct. For too long industries' influence on this process has endangered the public's health and safety. Today, there is an assault on independent scientists and independent scientific organizations by the Trump Administration particularly by the Environmental Protection Agency. It is important that we review the methods and tactics that industry has used to influence this Administration and attack independent scientific organizations like the World Health Organization's International Agency for Research on Cancer or IARC.

This hearing today will focus on IARC's hazard assessment of glyphosate, a key ingredient in Monsanto's Roundup broad-spectrum herbicide used to kill weeds and grasses. In 2015, IARC determined that glyphosate was probably carcinogenic to humans. Other reviews, including a draft Human Health Risk Assessment released by the EPA in December, concluded that glyphosate is not likely to be carcinogenic to humans. Part of that discrepancy may be because these reviews have investigated different issues.

IARC conducts hazard assessments while EPA conducts risk assessments. According to IARC, a cancer hazard is an agent that is capable of causing cancer under some circumstances while a cancer risk is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. Although there seems to be some confusion about these distinct scientific procedures of analysis and the science on this issue still appears unsettled, the attacks by the chemical industry to discredit individual scientists and scientific organizations such as IARC is not.

Internal Monsanto records show that company employees have ghostwritten scientific journal articles on glyphosate, attempted to orchestrate a public outcry over IARC's glyphosate findings, and have targeted specific independent scientists for attack. At a time when most of us are sensitive to the cries of fake news the Monsanto records show in their own words that they have sought to amplify positive messages about glyphosate on social media, neutralize the impact of the IARC decision on glyphosate, and to use industry front groups as a platform for IARC observers and industry spokespersons.

Attempts by industry to mischaracterize the scientific debate appear intended to undercut the scientific evidence regarding the possible dangers of glyphosate and its potential impact on human health. We must make sure any chemical review is not undone by undue corporate influence or misleading scientific studies.

This is all the more important when the chemicals under review are so widely used. Glyphosate has been used as an herbicide in the United States since 1974, and its use in the United States has grown from 11 million pounds in 1987 to nearly 300 million pounds in 2016. Since its introduction in the United States 1.8 million tons of glyphosate have been applied across the country, and 9.4 million tons of glyphosate has been used on crops around the world. Recent studies have shown that this widescale use of glyphosate has had

an impact on our food supplies and communities. Glyphosate has been detected in crackers, cookies, cereals, as well as in organic honey and oatmeal.

Chemical exposures, just like exposures to asbestos or lead or other potentially toxic substances, occur regardless of whether we sit on the left or the right of a particular political issue. The public health implications of these exposures are felt by all Americans and all people. That is exactly why an independent scientific review that is not unfairly or surreptitiously influenced by industry is necessary. We need to come to conclusions regarding the scientific evidence concerning glyphosate's potential impact on human health in a transparent and complete manner.

I look forward to hearing the testimony of our witnesses today, and I'm glad Dr. Jennifer Sass from the Natural Resources Defense Council is here. More than six years ago, Dr. Sass wrote a report titled "The Delay Game: How the Chemical Industry Ducks Regulation of the Most Toxic Substances." It's important that the Committee hear her perspective on these issues.

[The prepared statement of Ms. Bonamici follows:]

OPENING STATEMENT
Ranking Member Suzanne Bonamici (D-OR)
of the Subcommittee on Environment

Committee on Science, Space & Technology
"In Defense of Scientific Integrity: Examining the IARC Monograph Programme and Glyphosate Review"
February 6, 2018

Thank you. Mr. Chairman.

I am glad we are having this hearing today on the chemical review process. Ms. Johnson is correct; for too long industry's influence on this process has endangered the public's health and safety. Today, there is an assault on independent scientists and independent scientific organizations by the Trump Administration, particularly the Environmental Protection Agency. It is important we review the methods and tactics that industry has used to influence this Administration and attack independent scientific organizations like the World Health Organization's International Agency for Research on Cancer (IARC).

This hearing will focus on IARC's hazard assessment of glyphosate, a key ingredient in Monsanto's Roundup broad-spectrum herbicide used to kill weeds and grasses. In 2015, IARC determined that glyphosate was "probably carcinogenic to humans." Other reviews, including a draft human health risk assessment released by the EPA in December concluded that "glyphosate is not likely to be carcinogenic to humans." Part of that discrepancy may be because these reviews have investigated different issues. IARC conducts ***hazard assessments*** while EPA conducts ***risk assessments***. According to IARC, "A cancer 'hazard' is an agent that is capable of causing cancer under some circumstances, while a cancer 'risk' is an estimate of the carcinogenic effects expected from exposure to a cancer hazard."

While there seems to be confusion about these distinct scientific procedures of analysis, and the science on this issue still appears unsettled, the attacks by the chemical industry to discredit individual scientists and scientific organizations such as IARC is not.

Internal Monsanto records show they have ghost written scientific journal articles on glyphosate, attempted to orchestrate a public outcry over IARC's glyphosate findings, and have targeted specific independent scientists for attack. At a time when most of us are sensitive to the cries of "fake news," the Monsanto records show in their own words they have sought to "amplify" "positive" messages about glyphosate on social media, "neutralize" the impact of the IARC decision on glyphosate, and to use industry front groups as a "platform for IARC observers and industry spokesperson[s]."

Attempts by industry to mischaracterize the scientific debate appear intended to undercut the scientific evidence regarding the possible dangers of glyphosate and its potential impact on human health. We must make sure any chemical review is not undone by undue corporate influence or misleading scientific studies.

This is all the more important when the chemicals under review are so widely used. Glyphosate has been used as an herbicide in the United States since 1974 and that its use in the U.S. has grown from 11 million pounds in 1987 to nearly 300 million pounds in 2016. Since its introduction in the U.S. 1.8 million tons of glyphosate have been applied across the country and 9.4 million tons of glyphosate has been used on crops around the world.

Recent studies have shown that this wide scale use of glyphosate has had an impact on our food supplies and communities. Glyphosate has been detected in crackers, cookies and cereals, as well as in organic honey and oatmeal.

Chemical exposures, just like exposures to asbestos or lead, or other potentially toxic substances occur regardless of whether you sit to the left or the right of a particular political issue. The public health implications of these exposures are felt by all Americans, and all people. That is exactly why an independent scientific review that is not unfairly or surreptitiously influenced by industry is necessary. We need to come to conclusions regarding the scientific evidence concerning glyphosate's potential impact on human health in a transparent and complete manner.

I look forward to hearing the testimony of our witnesses today, particularly Dr. Jennifer Sass from the Natural Resources Defense Council (NRDC). More than six years ago, Dr. Sass wrote a report titled: *"The Delay Game: How the Chemical Industry Ducks Regulation of the Most Toxic Substances."* I think it is important that the Committee hear her perspective on these issues.

Thank you Mr. Chairman. I yield back.

Ms. BONAMICI. And before I yield back, Mr. Chairman, I have three responses from Dr. Christopher Wild, the Director of IARC, responding to inquiries you made late last year. In summary, Dr. Wild provides factually supported rebuttals to criticisms you and others have made about the IARC glyphosate Monograph, and I ask that these documents be made part of the record.

Chairman SMITH. Without objection.

[The information appears in Appendix II]

Ms. BONAMICI. And I yield back the balance of my time. Thank you, Mr. Chairman.

Chairman SMITH. Thank you, Ms. Bonamici. And I'll introduce our witnesses now. Our first witness today is Dr. Anna Lowit, Senior Science Advisor in the Office of Pesticide Programs at the Environmental Protection Agency. Dr. Lowit has been a toxicologist in OPP's Health Effects Division since 1998. During this time, she has provided expert technical advice and guidance on issues related to toxicity, testing human risk assessment, and science policy issues. She was elected co-Chair of the Interagency Coordinating Committee on the Validation of Alternative Methods, a committee of representatives from 16 federal agencies that require, generate, or disseminate toxicological and safety testing information. In January, she was named the recipient of the Society of Toxicology's 2018 Enhancement of Animal Welfare Award. Dr. Lowit received her master's of science and Ph.D. in environmental toxicology from the University of Tennessee.

Our next witness is Dr. Timothy Pastoor, CEO of Pastoor Science Communications. In addition, he is President of the Health and Environmental Science Institute, a D.C.-based nonprofit organization. With over 30 years of international experience, Dr. Pastoor has been involved with fundamental toxicity testing, mode-of-action research, and Human Health Risk Assessment. For the majority of his career, he led toxicology and risk assessment experts in the conduct of safety, health, and environmental studies to assess risk to humans and the environment. He retired in 2015 and founded the company Pastoor Science Communications, LLC, centered around his passion for advancing sound science. Dr. Pastoor received a Ph.D. in toxicology from the University of Michigan.

Our third witness is Dr. Jennifer Sass, Senior Scientist at the Natural Resources Defense Council. She is also a professorial lecturer in the Environmental and Occupational Health Department at George Washington University. In her work with the NRDC, Dr. Sass brings a highly specialized expertise in U.S. chemicals policy. She has published peer-reviewed journals on the regulation of toxic chemicals and emerging contaminants such as nanomaterials. Dr. Sass earned a master's degree and a Ph.D. in anatomy and cell biology from the University of Saskatchewan Canada and has done postdoctoral work in toxicology at the University of Maryland.

Our final witness today is Dr. Robert Tarone, a Biostatistics Director at the International Epidemiology Institute for 14 years before retiring in 2016. Previously, he was a mathematical statistician at the U.S. National Cancer Institute and a professor in the Department of Medicine at Vanderbilt University. During his career, Dr. Tarone has provided statistical assistance to a wide variety of laboratory and clinical researchers, including investigators in

the field of immunology, DNA repair, and cancer-prone inherited diseases. He received his bachelor of science, master's of arts, and Ph.D. all in mathematics from the University of California Davis.

We recognize and appreciate and welcome you all. And, Dr. Lowit, if you will begin.

TESTIMONY OF DR. ANNA LOWIT,
SENIOR SCIENCE ADVISOR,
OFFICE OF PESTICIDE PROGRAMS,
ENVIRONMENTAL PROTECTION AGENCY

Dr. LOWIT. Good morning, Chairman Smith, Ranking Member Johnson, and the rest of the Members of the Committee. My name is Anna Lowit. I serve as a Science Advisor for EPA's Office of Pesticide Programs. I have a Ph.D. in environmental toxicology and have worked in the area of pesticide risk assessment and toxicology for nearly 20 years.

EPA regulates the manufacture and use of all pesticides in the United States and establishes maximum levels for pesticide residues in food, safeguarding the Nation's food supply, workers, and the general public.

In addition to evaluating new pesticides before they can enter the market, EPA reevaluates existing pesticides at least every 15 years under a program known as registration review. EPA must complete registration review for more than 700 pesticides by October 1 of 2022. In 2017, EPA evaluated more than 120 pesticides using the risk assessment process.

Glyphosate, commonly known as Roundup, was initially registered by EPA in 1974. Glyphosate is one of the most widely used herbicides in the United States with about 270 million pounds of active ingredient applied annually. Glyphosate is used on a large number of crops, primarily corn and soybean, and is commonly used by homeowners.

Registration review for glyphosate was initiated in 2009 using the statutory registration review process applied to all registered pesticides. As part of this process, several types of assessments have been initiated, including evaluations of human health, ecological risk, carcinogenicity, endocrine disruption, and risk to pollinators. The assessments are subject to extensive technical review and public comment throughout the review process.

EPA released the draft Human Health and Ecological Risk Assessments in December of 2017. Glyphosate is considered to have little to no hazard when exposure is to the skin or when inhaled. Effects in laboratory animals were only seen through ingestion at very high doses. In the case of glyphosate, the Human Health Risk Assessment was developed with conservative exposure assumptions. Even with these conservative assumptions, no risk to humans, including infants and children, were identified. This conclusion showing no risk to humans is consistent with risk assessment findings in other countries and by international organizations such as Canada and the European Food Safety Authority.

Glyphosate was also subject to endocrine screening. Based on weight-of-evidence considerations, there's no convincing evidence of

potential interaction with estrogen, androgen, or thyroid pathways, and no additional endocrine related studies are considered necessary.

In 2016, EPA conducted a comprehensive analysis of all the available laboratory animal carcinogenicity, mutagenicity, and epidemiology data to inform the human risk—the human cancer-causing potential of glyphosate. EPA presented its evaluation to the FIFRA Scientific Advisory Panel and received the panel's recommendation in March of 2017. The Agency's cancer issue paper was updated to incorporate revisions, and based on the comprehensive analysis of all available data and reviews, EPA concluded that glyphosate is not likely to be carcinogenic to humans.

While the draft Human Health and Ecological Risk Assessments are already publicly available on EPA's website, the official public comment period for the draft risk assessments and supporting science evaluations will soon be announced in the Federal Register. EPA will evaluate the public comments and, if needed, will revise the risk assessments and then issue a proposed interim decision for public comment. If necessary, the proposed interim decision may include labeling changes and other risk mitigation measures. After public comments on the proposed interim decision are received and evaluated, EPA will issue an interim decision. EPA plans to complete a final decision after an endangered species assessment is complete.

Thank you for the opportunity to testify today, and I'm looking forward to questions from you and the Members.

[The prepared statement of Dr. Lowit follows:]

TESTIMONY OF

ANNA B. LOWIT

SCIENCE ADVISOR, OFFICE OF PESTICIDE PROGRAMS

U.S. ENVIRONMENTAL PROTECTION AGENCY

BEFORE THE

HOUSE COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY

February 6, 2018

Good morning Chairman Smith, ranking Member Johnson and members of the committee. My name is Anna Lowit. I serve as the Science Advisor in the Office of Pesticide Programs of the U.S. Environmental Protection Agency. I have a Ph.D. in Environmental Toxicology from the University of Tennessee and have worked at the EPA since 1998. In my role as Science Advisor, I provide advice and guidance to senior management and staff concerning toxicity testing, risk assessment, and science policy issues of national and international importance related to pesticides.

The EPA regulates the manufacture and use of all pesticides in the United States and establishes maximum levels for pesticide residues in food, thereby safeguarding the nation's food supply, workers, and the general public. The EPA implements the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA); the Pesticide Registration Improvement Act (PRIA); and key parts of the Food Quality Protection Act (FQPA) and Federal Food, Drug, and Cosmetic Act (FFDCA), along with the Endangered Species Act. Under these statutes, new pesticides and new

uses of existing pesticides are evaluated before they can enter the market. In addition, existing pesticides are re-evaluated at least every 15 years to determine whether they continue to meet the standard for registration. This program is known as registration review.[1] The EPA must complete registration review by October 1, 2022, for all pesticides registered as of October 1, 2007.

The process the EPA uses for evaluating the potential for human health and ecological effects of a pesticide is called risk assessment. The EPA uses the risk assessment process established by the 1983 National Research Council in the report on "Risk Assessment in the Federal Government: Managing the Process."[2] This process is widely used across the federal government and considers how toxic a chemical may be, what exposures may occur to a chemical, and the issues and uncertainties associated with a calculated risk. In fiscal year 2017, the EPA evaluated more than 120 pesticides using the risk assessment process.

The EPA's Office of Pesticides Programs is a science driven organization, employing more than 300 scientists. To evaluate the hazard of pesticides effects, we employ toxicologists, epidemiologists, botanists, and biologists. To evaluate the exposure of pesticides, the office employs industrial hygienists, chemists, physical scientists, agronomists, geologists, hydrologists, and environmental engineers. The office has entomologists and microbiologists who ensure the products we register are efficacious. The EPA also has statisticians, mathematicians, computer scientists, and experts in the Geographic Information System to support predictive modeling approaches. Our scientists work together in interdisciplinary teams

[1] See https://www.epa.gov/pesticide-reevaluation/registration-review-process
[2] National Research Council. 1983. *Risk Assessment in the Federal Government: Managing the Process*. Washington, DC: The National Academies Press. Available at https://doi.org/10.17226/366.

to evaluate the complex science associated with pesticide risk assessment. Our scientists also routinely work with risk managers and attorneys to support science based decision making in accordance with the relevant statutes. Within the limits defined by federal statutes, we also consider the benefits of pesticides to users, growers, and to society.

Scientists in the EPA's Office of Pesticides Programs work collaboratively with other program offices and regions within the EPA such as the Office of Water, the Office of Air, and the Office of Children's Health Protection. We engage with and depend upon input from the agency's Office of Research and Development to help solve some our most challenging science issues. In addition, the EPA's scientists are involved in projects with states and other federal agencies such as the U.S. Department of Agriculture, the Food and Drug Administration, the National Institute for Environmental Health Sciences, the U.S. Geological Survey, and the Centers for Disease Control and Prevention on numerous topics. The agency is involved internationally with at the Organisation for Economic Co-operation and Development (OECD) and the World Health Organization (WHO) to support harmonization and advancing risk assessment science. The EPA's methods are broadly accepted on an international basis. Many countries have adopted the methods developed and used by the EPA.

Under FIFRA, the EPA requires substantial amounts of toxicology and exposure data to be collected and submitted for pesticide registration. For example, numerous studies involving laboratory animals are conducted on a variety of pesticidal effects such as cancer and systemic toxicity.. The FQPA requires specific consideration of the potential for infants and children to be sensitive to pesticides. Accordingly, the EPA requires testing on developmental toxicity and

reproductive toxicity and often specific evaluations on neurotoxicity and brain development. Multiple species are tested, namely rats, mice, dogs, rabbits, birds, fish, plants, bees and other insects. These tests range in their duration of exposure from a single day up to the entire lifetime of the laboratory animal and are conducted in different routes of exposure such as oral, dermal, inhalation.

Risk is not only a function of the toxicity of a chemical, it is also related to exposure that can occur due to its use. The EPA quantifies exposure to all facets of the U.S. population by considering diet and drinking water, as well as from other possible contact with pesticides both in the general population and as part of their job. The EPA also considers exposure in the environment to various plant and animal species. Many types of diverse data are required to evaluate such exposure patterns. These include monitoring of pesticide users (e.g., occupational exposure), behavioral information (e.g., dietary intake patterns), data intended to quantify how pesticides behave in the environment (e.g., chemical fate, transport, and persistence), as well as data to quantify what pesticides could end up in food (e.g., residue from crops where a pesticide is applied). These data requirements are found in 40 CFR Part 158.

To ensure data quality and consistency, the EPA has standard guidelines for how testing is to be conducted. The EPA's test guidelines are largely harmonized with those established internationally by the OECD. Harmonized test guidelines reduce the burden on chemical producers and conserve scientific resources, including reducing use of laboratory test animals while maintaining a thorough evaluation of the toxicity profile of pesticides.

The EPA strives for transparency in our scientific analysis. Our science policies, guidance documents, and guidelines have been through peer review and public comments, and are publicly available. The agency's scientists develop independent, objective evaluations of studies sponsored by pesticide registrants and those available in the open scientific literature. The EPA's science reviews are publicly available in the federal docket and the agency's scientists routinely give presentations to the public and to other scientific experts. The EPA frequently meets with stakeholders, including industry, growers, non-governmental organizations, and states, on numerous issues pertaining to pesticides.

The EPA uses a tiered approach to conduct risk assessment in order to focus its efforts on areas where additional refinement is needed. This is practical from both a regulatory and resource perspective, as it allows the EPA and the regulated community to focus on critical issues and refine as needed, and conserves resources. In this approach, the EPA starts with highly conservative risk assessment then adds refinement as appropriate. For example, when dietary intake is evaluated, the EPA might assume the entirety of a particular crop is treated using the maximum allowable amount of pesticide when crops are not actually produced this way. As a refinement, information related to how much of a particular crop is treated could be considered. Amounts in food close to the point of consumption, such as sampled from a grocery store, is another refinement.

Glyphosate (commonly known as Roundup®) was initially registered by the EPA in 1974. Glyphosate acid and several related glyphosate salt compounds are also registered pesticides. Glyphosate is one of the most widely used agricultural pesticides in the United States,

with approximately 270 million pounds of active ingredient applied annually (2011-2015). Glyphosate is used on a large number of agricultural crops, primarily glyphosate-resistant corn and glyphosate-resistant soybeans. Glyphosate also makes up 40 percent of the total pounds of herbicides sold in the U.S. residential consumer market for use on lawns and turf. Other important uses are direct uses in aquatic systems and rights-of-way for total vegetation control.

Registration review for glyphosate was initiated in 2009. As mentioned above, the EPA has a statutory registration review process that is being applied to all registered pesticides, including glyphosate, involving evaluation of significant amounts of scientific information. As part of this process, several types of assessments have been initiated including evaluations of human health, ecological risk, carcinogenicity, endocrine disruption, and risk to pollinators and endangered species. The assessments are subject to extensive technical review and public comment at several time points throughout the review process.

The EPA released the draft human health and ecological risk assessments on December 18, 2017.[3] The EPA's human health review evaluated dietary, residential/non-occupational, aggregate, and occupational exposures. Glyphosate is considered to have little to no hazard when exposure is to the skin and when it is inhaled. Effects in laboratory animals were only seen through ingestion at high doses. In the case of glyphosate, the human health risk assessment was developed with high end assumptions known to be overestimates of exposure. However, even with these assumptions, no risk to humans, including infants and children, were identified. This conclusion about showing no risk to humans is consistent with risk assessment findings in other

[3] See https://www.epa.gov/ingredients-used-pesticide-products/draft-human-health-and-ecological-risk-assessments-glyphosate.

countries and international organizations such as Canada, Australia, and the European Food Safety Authority.

As required under the FFDCA, glyphosate was subject to endocrine screening as part of the EPA's Endocrine Disruptor Screening Program (EDSP). The EPA received and reviewed all the required Tier 1 assay data. Based on weight of evidence considerations, there is no convincing evidence of potential interaction with the estrogen, androgen or thyroid pathways, and no additional EDSP related studies are considered necessary.

In 2015, the International Agency on the Research for Cancer (IARC) released its final conclusions that glyphosate is "probably carcinogenic to humans (Group 2A)."[4] In 2016, the EPA conducted a comprehensive analysis of all the available laboratory animal carcinogenicity, mutagenicity, and epidemiology data to inform the human carcinogenic potential of glyphosate. In December 2016, the EPA presented its evaluation to the FIFRA Scientific Advisory Panel (SAP). The EPA received the SAP's recommendations in March 2017. The agency's cancer issue paper was updated to incorporate revisions based on the SAP's report. Based on the comprehensive analysis of all available data and reviews, the EPA concludes that glyphosate is "not likely to be carcinogenic to humans." The EPA's cancer classification for glyphosate is based on a weight of evidence evaluation in accordance with the agency's 2005 Guideline for Carcinogen Risk Assessment.[5] The dataset considered by the EPA included studies submitted for registration of glyphosate, as well as studies identified in the open literature as part of a systematic review.

[4] See http://monographs.iarc.fr/ENG/Monographs/vol112/mono112-10.pdf.
[5] See https://www.epa.gov/risk/guidelines-carcinogen-risk-assessment.

There are some fundamental differences between the IARC review and the EPA's review of glyphosate. For instance:

- IARC only considers data that has been published or accepted for publication in the openly available scientific literature. As a result, IARC only considered 10 laboratory animal cancer studies whereas the EPA includes 14 laboratory animal cancer studies in its evaluation;
- IARC does not consider exposure and only bases its decision on the hazard of a chemical where the EPA considers exposure as a critical component of the cancer evaluation;
- IARC's conclusion is inconsistent with the international community, where the EPA's conclusion that glyphosate is "not likely to be carcinogenic to humans," is consistent with other countries and international organizations including: Australia (2013), Canada (2015), Japan (2016), New Zealand (2016), the European Food Safety Authority (EFSA) (2015), Germany (2014), the European Chemicals Agency (ECHA) (2017) and the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Meeting on Pesticide Residues (JMPR) (2016).

On November 9, 2017, the National Cancer Institute, which is part of the National Institutes of Health (NIH), published a new epidemiology study entitled "Glyphosate Use and Cancer Incidence in the Agricultural Health Study".[6] The Agricultural Health Study (AHS) is a prospective cohort of more than 57,000 licensed pesticide applicators in Iowa and North Carolina. The results of this new study, which has a longer follow up period than previously

[6] J Natl Cancer Inst. 2017 Nov 15. doi: 10.1093/jnci/djx247, available at https://www.ncbi.nlm.nih.gov/pubmed/29155945.

available evaluations of the AHS cohort, provide additional strong support for the agency's conclusion that glyphosate is "not likely to be carcinogenic to humans."

In an ecological risk assessment, the EPA evaluates the potential that exposure to pesticides may cause harmful effects to non-target organisms. The effects can be direct, such as fish deaths from a pesticide entering waterways, or birds do not reproduce normally after ingesting contaminated fish, or indirect, such as a bird that can't reproduce because the plant it requires for nesting has been stunted by pesticide exposure. Specific to glyphosate, the ecological risk assessment indicates that there is potential for effects on birds (surrogates for reptiles and terrestrial-phase amphibians), mammals, and terrestrial and aquatic plants but not fish (surrogates for aquatic-phase amphibians) or aquatic invertebrates. Available data show low toxicity for honeybees and other terrestrial invertebrates.

While the draft human health and ecological risk assessments are already publicly available on the EPA website[7], the official public comment period for the registration review of the draft glyphosate risk assessments and supporting science evaluations will soon be announced in the Federal Register. Once announced, this will begin the official public comment period which is anticipated to last for 60 days. After public comments are received on the risk assessment, if needed, the EPA will revise its risk assessments and issue a Proposed Interim Decision for public comment. If necessary, the Proposed Interim Decision will include proposed labeling changes and other risk mitigation measures. After public comments on the Proposed Interim Decision are received and evaluated, the EPA will issue an Interim Decision. The EPA

[7] See https://www.epa.gov/pesticides/epa-releases-draft-risk-assessments-glyphosate.

plans to complete a Final Decision after an evaluation of risks to pollinators and an endangered species assessment is complete. In addition, the EPA plans to initiate endangered species consultation with the U.S. Fish and Wildlife Service and the National Marine Fisheries Service by 2020. As mentioned earlier, registration review must be completed by 2022.

In sum, the EPA has a statutory registration review process that is being systematically and transparently applied to glyphosate and all other pesticides reviewed by EPA. The EPA's pesticide risk assessments are based upon science and are subject to extensive science technical review and public comment. Draft risk assessments on glyphosate for human health and ecological effects are publically available at this time.

Thank you for the opportunity to testify today. I will be happy to answer any questions you and the other members may have.

Anna B. Lowit, Ph.D., received her Ph.D. in Environmental Toxicology from the University of Tennessee in 1998. Dr. Lowit has worked on pesticide risk assessment for nearly 20 years. Dr. Lowit currently serves as the Science Advisor in the U.S. Environmental Protection Agency's Office of Pesticide Programs. Dr. Lowit is currently one of the co-chairs of Interagency Coordinating Committee on the Validation of Alternative Methods and leads multidisciplinary teams on a variety of cross cutting topics. She also has experience in cumulative risk assessments, science integration along multiple lines of evidence, and improving the use of quantitative approaches in human health risk assessment.

Chairman SMITH. Thank you, Dr. Lowit.
And Dr. Pastoor?

**TESTIMONY OF DR. TIMOTHY PASTOOR,
CEO, PASTOOR SCIENCE COMMUNICATIONS**

Dr. PASTOOR. Chairman Smith—good morning, Mr. Chairman, Ranking Member Johnson, and the distinguished Members of this Committee. Thank you for inviting me to this important hearing on a very important subject.

I am representing myself and nine other co-authors of a paper that we wrote. These are individuals that are—that come from the private sector and the public sector, professors that come from both the United States and the European area, as well as retired senior scientists from the United States EPA.

My testimony today is going to focus on the scientific process that IARC uses, which the nine authors that I co-authored the paper with have concluded is badly outmoded and in need—in bad need of significant revision or termination. The reason is because the program uses an antiquated and irrelevant hazard classification scheme to simply declare a substance to be carcinogenic or not and provides no context about when, why, or how that substance might actually cause that effect.

Let me illustrate it this way. I would imagine that most of the people in this room have consumed water or food or both that contained a substance that IARC Monographs Programme has declared to be carcinogenic. How does that make you feel? Well, the problem with that is that it's a simple declaration about something that is in your food that could cause cancer. What I'm talking about is caffeic acid. Caffeic acid is found in a number of foods that we eat every day that are part of a healthy diet, including things like grapes, apples, blueberries, lemons, oranges, and it goes on. And oh, by the way, caffeic acid is also part of the cup of coffee that I have in front of me today. Declaring that caffeic acid is a carcinogenic substance is really of no help when you just state it that way. It needs to have context.

As a toxicologist, I'm frequently asked by family and friends what it means when they hear something is declared to be possibly or potentially carcinogenic. What they want to know is how likely is that to happen to me, my family, my friends. It's an important subject. My answer is always the same. It depends on how potent the chemical is, the substance is, and how much exposure is required to cause that effect.

Let's take potency first. Unfortunately, the IARC Monograph Programme fails to provide the crucial context of potency and instead lumps highly potent substances like plutonium, sulfur mustard, and neutron radiation in the same cancer classification as processed meat and salted fish. Clearly, there's a difference, but the IARC Monographs Programme fails to account for potency.

My wife is a registered nurse and an integrative healer who likes to use plant-based remedies. When I tell her that aloe vera and ginkgo biloba are classified by IARC as possibly carcinogenic, she rolled her eyes and said—oh, and by the way, they're classified in the same category with fuel, oil, and gasoline, she simply kind of rolled her eyes back and say, "No, that can't be."

Such a classification scheme defies common sense, and yet IARC has maintained this hazard classification scheme for well over—in nearly half-a-century. Along with neglecting the important feature of potency, IARC Monographs Programme also fails to account for potential exposure. Why is that important? Because the central tenet of toxicology is the dose makes the poison. And the best way of giving you a good analogy of that is aspirin. A little bit of aspirin is not going to do anything. A couple tablets of aspirin will relieve your headache, and a bottle of aspirin can kill you. But where IARC stops is labeling something as being able to kill you. What good is that information without the context of benefits and dose?

Nearly all 21st-century regulatory processes such as Dr. Lowit described just previously account for potency and exposure in their evaluation and therefore the likelihood that an adverse effect like cancer could occur. It's known as risk assessment. However, the IARC Monograph Programme is not risk-based and instead is stuck in a hazard classification scheme created a half-a-century ago with no consideration of potency or exposure.

In addition to being out of step with 21st-century science, the IARC Monograph Programme has also lost credibility because of serious flaws in process. I'm here to talk about the science, not the process, but that is a concerning issue.

Outdated science and flawed process are not without consequence. Telling you that IARC has pegged caffeic acid as a carcinogenic substance in your food and coffee does nothing other than sow fear and uncertainty, which is unhelpful and irrelevant at best and irresponsible at worst. The IARC Monograph Programme needs to be either significantly reformed or abolished.

Thank you very much, Mr. Chairman.

[The prepared statement of Dr. Pastoor follows:]

Testimony of

Timothy Pastoor, PhD, DABT, ATS
(Biography at end of testimony)

Pastoor Science Communications, LLC

To

The U.S. House of Representatives

Committee on Science, Space, and Technology

Hearing Title:

In Defense of Scientific Integrity: Examining the IARC Monograph Programme and Glyphosate Review

February 6, 2018

Change or Abolish the IARC Monograph Program

The International Agency for Research on Cancer Monographs[1] program is an antiquated review process that is based on the state of scientific knowledge a half a century ago. It has done little to keep up with advances in science and the protection of human health in the intervening years. While cancer classification systems such as IARC's may have served a useful purpose when they were created, they are as irrelevant today as the telegraph or 8-track tape player. They provide little to no useful information and do more to confuse the public – and policy makers -- than to protect public health.

In addition to being out of step with 21st century science, the IARC Monograph program has lost credibility because of serious flaws in its process. Lack of transparency and accountability in this once venerable program have led to numerous allegations of questionable ethical practices, undisclosed conflicts of interest, and opinions that run counter to worldwide scientifically-based consensus conclusions.

Outdated science and flawed process are not without consequence. Declarations by the Monograph program have sown unnecessary fears about useful and safe products and deflected enormous resources away from useful investments in public health. The science and process of the IARC Monograph program needs to be either significantly reformed or abolished.

Why is the IARC Monograph program so out of step with advanced health protection agencies such as the US EPA, Health Canada, the European Food Safety Authority (EFSA), and the United Kingdom Committee on Carcinogenicity, just to name a few? There are several reasons articulated in a publication[2] co-authored by myself and nine other senior scientists from academia, government, and private enterprises, but the primary issue is that the program fails to consider key factors such as potency and potential human exposure in its declarations of carcinogenicity.

Back in the 16th century, Paracelsus noted that "the dose makes the poison." He understood that anything – anything at all – at a high enough dose is poisonous, but at a low enough dose that same substance will be completely harmless. The same holds true for substances that could possibly cause cancer. Many things that could cause cancer at extremely high doses are harmless at levels likely encountered by human beings.

IARC simply ignores this essential fact. As a result, it lumps bacon, sausage, sulfur mustard gas, and plutonium together in the same category, Group 1, as definitely carcinogenic. IARC makes this declaration based on its *confidence* in the information it reviews and NOT on the likelihood that a particular substance has the potency or levels of human exposure that would cause cancer. Many of its conclusions are based on long-term, multi-year dosing of animals with unreasonably high amounts of a substance – well beyond what a human will ever be exposed to. Despite the absurdity of this kind of test, IARC nonetheless declares a substance to be carcinogenic. This approach is now being realized as

[1] This testimony focuses on the IARC Monographs program and not on the broader IARC institution, which is highly respected as a key center for cancer research and awareness. References in this text to "IARC" should be inferred as the IARC Monographs program.

[2] Boobis, A.R., et al., Classification schemes for carcinogenicity based on hazard-identification have become outmoded and serve neither science nor society, Regulatory Toxicology and Pharmacology (2016), http://dx.doi.org/10.1016/j.yrtph.2016.10.014

untenable and disconnected with 21st century science, modern public health protection, and communication of appropriate health practices.

In fact, if one were to take IARC seriously, there would be little if anything we could eat because many of the foods that contribute to what is universally considered a healthy diet would be suspected as causing cancer. To give just a few of many possible examples, take caffeic acid, which IARC classified as a Group 2B carcinogen, and which is found in a wide variety of fruits, vegetables and other foods, including grapes, apples, wine, blueberries, lemons, oranges, beets, broccoli, cabbage, carrots, cauliflower, lettuce, kale, onions, peas...not to mention coffee. And that's the short list. What do we do with a declaration that caffeic acid is a "possible human carcinogen"?

Or take acetaldehyde in bread and the popular plant-based remedies, ginkgo biloba and aloe vera, all of which are also classified by IARC to be group 2B, "possibly carcinogenic to humans."[3]

This kind of classification has almost zero informational value if, as IARC does, it ignores the all-important considerations of potency and exposure. Potency is important because it is the "punch" or power a substance has to induce a carcinogenic effect. Exposure is important because it considers how much of a substance we are likely to be exposed to under any reasonable scenario in the real world. This is an absolutely key element in limiting adverse effects. There are a wide variety of substances that may be labeled as carcinogenic based on high-dose, long-term studies, but in real life we could never consume enough or be exposed to enough to suffer adverse consequences.

How much is too much? This is the central question. In our personal lives, we spend considerable parts of our day considering that very question on so many critical issues. How much sugar should I put in my coffee? How much coffee should I drink today? Should I have **one** beer or two or more? What might be too much? Yet this important consideration is absent in IARC cancer classifications.

Let's take sunlight, for instance, which IARC classifies in Group 1 ("carcinogenic to humans"). We should indeed consider the adverse consequence, or hazard, we might encounter from too much sunlight, i.e. sunburn or skin cancer. The solution is not to simply stay inside all day. Sunlight is also important in enabling the body's production of Vitamin D.[4] So do we make the decision about going outside ONLY considering the adverse consequences, or hazard, in mind? Or do we make a rational decision and control our overall exposure – maybe wear a hat -- and enjoy ourselves in the meantime.

What we are doing when we quantify how much is too much is the same as what risk regulators must do in setting permissible levels of exposure. Risk assessors use this same procedure with chemicals: what is the hazard and how much exposure is too much? Declaring that a chemical causes cancer or is an endocrine disruptor is only half the story. The other half is declaring the amount that could cause that adverse effect and setting limits that protect the public from being exposed to too much. This is what is known as a "risk assessment."

Regulatory agencies around the world follow this straightforward "risk assessment" technique to protect public health. The United States Environmental Protection Agency has very clear guidance on how it identifies a chemical hazard, quantifies potential exposure, and manages risk. The policies and

[3] https://monographs.iarc.fr/ENG/Classification/ClassificationsAlphaOrder.pdf

[4] at least 50% of the world's population suffers from Vitamin D insufficiency, which can lead to increased mortality (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3356951/)

procedures to do so have been developed over the years, and have evolved as scientific knowledge has evolved and deepened since the inception of the USEPA in the early 1970's. The USEPA and other national and international risk-based health protection agencies have kept up with the science and are continuing to develop better ways to identify hazards of chemicals and couple that knowledge with exposure science. Science marches on.

Unfortunately, the IARC Monographs program has not kept up. Originally established a half century ago to identify agents that CAN cause cancer, the IARC Monograph program stops at what is called "hazard identification." It provides a simple yes/no and then, if yes, a classification category (1, 2A, 2B, 3, or 4), depending on the degree of confidence for a causal link to cancer (not, as many assume, the degree to which an agent is likely to cause cancer). IARC still uses this outmoded scheme despite advances in the sciences that have illuminated better ways to understand and regulate potential cancer-causing agents. The program must shift from a "hazard-only" scheme to a process that incorporates potency and exposure, and expresses its conclusions in risk assessment terms.

Furthermore, the IARC Monographs program, with its antiquated classification system, has taken on the evaluation of extremely well studied and carefully regulated chemicals such as glyphosate. At best this is a duplication of effort and at worst is an opportunity to sow confusion in the public's mind.

Along with being a scientifically antiquated program, serious questions have been raised about the integrity of IARC's process. Any agency whose evaluations are used to influence public health decisions must be transparent and fully accountable to the public. If this committee and the member countries of IARC do not address the numerous allegations of questionable ethical practices, undisclosed conflicts of interest, and lack of transparency, then the scientific reforms suggested here will be irrelevant.

There are certain basic standards of accountability, transparency, and simply good science on which IARC presently falls short that should be the guideposts for any effective reform of the monograph process. These include:

- Selecting working group and other advisory members with necessary expertise, regardless of affiliation;
- Declaring the affiliation and potential conflicts of interest of all participants;
- Considering ALL available data;
- Providing a clear explanation why certain data are or are not included in the review;
- Adhering to the principles of systematic review, such as those described by The National Toxicology Program's Office of Health Assessment and Translation (OHAT) and Cochrane Consumer Network;
- Fully communicating the results of the agency's review in a timely manner;
- Including the opinions of all reviewers and the degrees of consensus and dissent.

In conclusion, the IARC monograph program served its purpose 50 years ago to flag substances, including chemicals, that may be of concern. But it is now outmoded. Every effort must be made to bring their review process up-to-date with advances in scientific knowledge, focus on those substances not otherwise well regulated, and communicate that process openly and accurately to the public. The alternative is to abolish the program.

Biography

Timothy Pastoor, PhD, DABT, ATS

Dr. Pastoor obtained his PhD in toxicology from the University of Michigan, is certified by the American Board of Toxicology (DABT) and is a Fellow of the Academy of Toxicological Sciences (ATS). Dr. Pastoor is president of the Health and Environmental Sciences Institute (HESI) and is a Board member of the International Life Sciences Institute (ILSI) and the American Council on Science and Health (ACSH). Dr. Pastoor retired in 2015 from Syngenta as Principal Scientist and founded the company Pastoor Science Communications, LLC that is centered around his passion for sound science, communicated well.

Dr. Pastoor has over 35 years of international experience in fundamental toxicity testing, mode of action research, and human health risk assessment. For most his career, including positions with DuPont, ICI, Zeneca, Novartis, and Syngenta, Dr. Pastoor led toxicology and risk assessment experts in the conduct of safety, health, and environmental studies to assess risk to humans and the environment. In those roles, he was involved in toxicological research projects and product development and was frequently asked to interact with media, community groups, legislators, and regulatory agencies. He is a frequent lecturer on toxicology and risk assessment subjects.

In his "retirement" Dr. Pastoor has remained actively engaged in science, toxicology, risk assessment, and science communication. He is also finding time to help the University of North Carolina develop the Professional Science Masters program in toxicology. As founder and CEO of Pastoor Science Communications and through his role as HESI president, he is leading global groups from academia, government, and corporations in developing consensus on difficult scientific issues.

Tim is an avid fly fisherman and photographer, and hopes his knees allow him to continue playing tennis for many years to come.

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Abstracted biography for introductions:

Dr. Pastoor obtained his PhD in toxicology from the University of Michigan, is certified by the American Board of Toxicology (DABT), is a Fellow of the Academy of Toxicological Sciences (ATS), and is president of the Health and Environmental Sciences Institute (HESI). Dr. Pastoor retired in 2015 from Syngenta as Principal Scientist and founded the company Pastoor Science Communications, LLC that is centered around his passion for sound science, communicated well.

Chairman SMITH. Thank you, Dr. Pastoor.
And Dr. Sass?

TESTIMONY OF DR. JENNIFER SASS,
SENIOR SCIENTIST, NATURAL RESOURCES DEFENSE COUNCIL

Dr. SASS. Thank you very much for the opportunity to speak to—before this Committee today about this very important topic of scientific integrity, the IARC Monographs, and the important evaluation of glyphosate. I very much appreciate coming before you today.

I've been employed for 17 years at NRDC, the Natural Resources Defense Council, and I have advanced degrees in anatomy and cell biology with specific expertise in environmental health, developmental biology, neurobiology, and molecular biology and am also familiar with the Pesticide Office operations that Dr. Anna Lowit is Science Advisor before because on many, many occasions I've testified either with written or oral comments are both to the Pesticide Office following their review of pesticides and registration, including glyphosate. In addition, I've represented NRDC for over a decade on stakeholder advisory panels to the Pesticide Office so have participated as a public and stakeholder member in those processes.

I also have knowledge of the IARC practices, having been invited to a meeting, a week-long meeting to look at arsenic and water disinfection byproducts by the Chair at the time the Chief of the Monograph Programme Dr. Jerry Rice, who is a colleague of Dr. Tarone's. There have been two Chairs since then, and the current Chair, Dr. Kurt Straif, was also working at the Monograph Programme during that time, so he brings with his leadership continuity to that program and to IARC's commitment to environmental public health and scientific excellence.

IARC has undertaken over 1,000 substances for evaluation, including important ones like asbestos, tobacco smoke, secondhand smoke, diesel exhaust, formaldehyde, vinyl chloride and arsenic, methylene chloride benzene, and many others. There—many of these—not all of them, but many of them also come with people—stakeholders that have deep economic interests in these substances, and although there have been many, the Director Dr. Christopher Wild of IARC right now stated that the pressure that IARC has received in response to listing glyphosate as a probable human carcinogen group 2A has resulted in unprecedented coordinated efforts to undermine the evaluation, the program, and the organization.

These efforts are largely sponsored and coordinated by the agrochemical industry that sought to support its own regulation—its registration and approval of glyphosate in the United States and around the world, to defend itself in litigation against farmers that were once Monsanto customers and are now cancer patients, and to prevent the labeling of glyphosate-containing products as a carcinogen in the State of California, which would inform the public.

Dr. Jonathan Samet called these strategies that could be traced to the playbook of the tobacco industry to discredit findings related to active and passive smoking. And I would characterize them the same way.

This hearing is part of a kickoff that happened a few months after the IARC Monographs were made public where an article in The Hill was published asking for exactly this, for the stripping of funding for the IARC Programme by Dr. Bruce Chassy, who failed to acknowledge that he was funded by Monsanto.

As far as the science goes, IARC did not ignore relevant studies. They included all the relevant studies, including the Agriculture Health Study and other review articles that they looked at that were sponsored by many—many were sponsored by Monsanto or the agrochemical industry, as well as published articles. But the key with IARC is that they need to be publicly available. It doesn't necessarily have to be published but publicly available. How else can they verify the findings?

In contrast, EPA's 2017 assessment did rely on some of these review articles that—where the underlying studies were not made public. And I know the Dr. Tarone is going to talk about some of those. I would ask Dr. Tarone how long it took him to evaluate the underlying data and studies in those because the Greim, et al., for example, was only provided 30 days before the IARC meeting, so there's no way it could have been properly evaluated based on a review article.

The IARC has been following systematic methods that are improved worldwide, and in conclusion, I would like to say that, fundamentally, this hearing is about the ability of a public health agency to call a carcinogen a carcinogen even if that carcinogen makes a huge amount of money for powerful corporations.

Thank you.

[The prepared statement of Dr. Sass follows:]

NATURAL RESOURCES DEFENSE COUNCIL

Testimony of Jennifer Sass, Ph.D., Senior Scientist
Natural Resources Defense Council
Healthy People & Thriving Communities Program

US House Committee on Science, Space, and Technology
Full Committee Hearing - In Defense of Scientific Integrity:
Examining the IARC Monograph Programme and Glyphosate Review.
Washington, D.C., February 6, 2018[1]

Tuesday, February 6, 2018 - 10:00am
2318 Rayburn House Office Building

[1] https://science.house.gov/legislation/hearings/full-committee-hearing-defense-scientific-integrity-examining-iarc-monograph

Introduction

Thank you for the opportunity to speak before this Committee on this very important topic of Scientific Integrity, the IARC Monographs, and Glyphosate.

I have been employed full-time as a Senior Scientist with the Natural Resources Defense Council (NRDC) since 2001. I have advanced degrees in Anatomy and Cell Biology, with specific expertise in developmental biology, neurobiology, molecular biology, and environmental health. In my position with NRDC, I am responsible for reviewing the science underlying many of the federal regulations of industrial chemicals and pesticides. I have published over forty-five articles in peer-reviewed scientific journals, including many pertaining to pesticide hazards and regulations.

I developed an understanding of U.S. pesticide regulations and of the operations of the EPA Office of Pesticide Programs through various activities. On numerous occasions, I have provided written and oral testimony to the Pesticide Office on the registration of dozens of pesticides, including glyphosate. Additionally, I represented NRDC for over a decade as an active member of the EPA/U.S. Department of Agriculture (USDA) Pesticide Program Dialogue Committee (PPDC), a stakeholder committee that provides feedback to the Pesticide Office on various issues related to pesticide regulatory, policy, and program implementation issues. Through my years of work on the PPDC, from 2001 to 2013, I also served on issue-specific PPDC workgroups to provide more in-depth perspectives and advice on pesticide issues, including input on strategic approaches for implementation of the Food Quality Protection Act (FQPA).

I also have knowledge of the policies and practices of the International Agency for Research on Cancer (IARC), having read and referenced many IARC chemical assessments over almost two decades. In 2002, when IARC was reviewing styrene (Volume 82) I was publicly critical of IARC's practice at the time of allowing financially-conflicted scientists to participate as voting members of the Committee. In response, the Chief of the Programme at that time, Dr. Jerry Rice, invited me to attend a week-long meeting at which IARC would review arsenic and some drinking water disinfection byproducts (Volume 84). I attended as an observer (non-voting), and was given full access to observe the Working Group and its sub-discipline groups, as well as join participants for meals, etc. Dr. Rice was correct, I was extremely impressed with the scientific rigor of the process and the output. While I continued to advocate for financially-conflicted individuals to be prevented from voting, I acknowledged even then that Dr. Rice was right to be proud of the Monograph Programme's scientific work, then and even more so now. I have not participated in any IARC Monograph meetings since that one single time. There have been two Chiefs of the Monograph Programme since Dr. Rice, with the current one, Dr. Kurt Straif, having worked for the Monograph Programme under both his predecessors. Dr. Straif's leadership brings continuity to IARC's commitment to environmental public health and scientific excellence.

IARC has undertaken the evaluation of over 900 substances including asbestos, tobacco smoke and later second-hand smoke, diesel exhaust, formaldehyde, vinyl chloride, viruses, carbon nanotubes, arsenic, methylene chloride, benzene, and about nine hundred others. IARC assessments inform global cancer prevention strategies.

Because of its scientific excellence and its scientific and regulatory relevance, IARC enjoys overwhelming support from the global scientific and medical community. A few years ago, 124 scientists and health professionals from diverse scientific disciplines, from around the world co-authored a published account of the last forty years of IARC Monographs, noting the Programme's role in identifying carcinogenic substances to inform policies and practices that prevent harm and save lives (Pearce et al, 2015).

In a published review on the industry-led criticisms of the IARC Monographs, Dr. Jonathan Samet, a prestigious medical professor and frequent Chair of National Academies committees, writes, "the types *of concerns raised about the IARC monograph program are also archetypical of strategies for creating 'doubt' about scientific evidence that has policy implications. Such strategies can be traced to the 'playbook' of the tobacco industry for discrediting findings related to active and passive smoking (14,15). One tactic has been to question the processes used to draw causal inferences and the integrity and potential conflicts of interest of those doing so. The IARC processes are robust and transparent and as concluded by Pearce and his 123 colleagues, not flawed and biased.*" (Samet 2015)[2]

In my testimony I address a few examples of those tobacco-industry tactics applied to glyphosate, and the agrochemical industry attack on the IARC Monographs.

Agrochemical Industry Opposition

IARC Director Christopher Wild stated that his Agency has experienced "unprecedented, coordinated efforts to undermine the evaluation, the program and the organization" in response to listing glyphosate in 2015 as a probable human carcinogen (Group 2A). [3] These efforts are largely sponsored and coordinated by the agrochemical industry that has sought to: support glyphosate registration and approval; defend itself against litigation claims by thousands of farmers that were once Monsanto Co. customers and are now cancer patients; and, prevent labeling of glyphosate-containing products as a carcinogen in the State of California.

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[2] Samet JM. The IARC monographs: critics and controversy. Carcinogenesis. 2015 Jul;36(7):707-9. https://academic.oup.com/carcin/article/36/7/707/1800366

[3] IARC briefing paper Jan 2018 http://governance.iarc.fr/ENG/Docs/BriefingGCSC_FINAL_29012018.pdf and IARC webpage on glyphosate: https://www.iarc.fr/en/media-centre/iarcnews/2016/glyphosate_IARC2016.php

Today's hearing supports the agrochemical industry agenda to discredit and ultimately defund IARC. In September 2015 the New York Times reported that emeritus food professor Bruce Chassy received funding from Monsanto Co. to lobby the EPA to block regulation of GMO products.[4] Almost a year later Chassy wrote an opinion-editorial in The Hill, "NIH needs public examination after giving millions to rogue UN agency".[5] However, Chassy's editorial failed to disclose his work with Monsanto Co., instead identifying himself only as, "a researcher at the NIH for 21 years before moving to the University of Illinois at Urbana-Champaign as a department head and assistant dean, and is now professor emeritus of Food Science and Human Nutrition." What Chassy failed to disclose is that the nonprofit he runs called Academics Review received $300,000 from the Monsanto Co.-funded trade group BIO in both 2014 and 2015. This industry money is the majority of Academics Review's funding and Chassy runs it with his wife.[6]

What I've touched upon here is only a small part of the well documented public relations campaign to soften up public opinion about the agrichemical industry and create a venue to pressure agencies to block regulations, and try to discredit and silence public health and scientific institutes that may show some harm from their profitable products.

IARC Response

IARC has ably defended itself from all substantive criticisms in public documents, letters to this Committee which are publicly accessible on the IARC website, or in other public reports.[7] Additionally, over 100 non-industry scientists across many scientific and medical disciplines and from dozens of public Universities and Institutes in the US and worldwide – including myself - have expressed confidence generally for the IARC process and specifically in the IARC Monograph for glyphosate (Portier et al 2016).[8]

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[4] Food Industry Enlisted Academics in G.M.O. Lobbying War, Emails Show. Eric Lipton. Sept 5, 2015. NY Times. https://www.nytimes.com/2015/09/06/us/food-industry-enlisted-academics-in-gmo-lobbying-war-emails-show.html

[5] Bruce Chassy. The Hill. 10/24/16. http://thehill.com/blogs/pundits-blog/healthcare/302484-nih-needs-public-examination-after-giving-millions-to-rouge-un

[6] Paul Thacker, 07/21/2017. The Progressive. http://progressive.org/magazine/how-the-biotech-industry-cultivates-positive-media/

[7] IARC briefing paper Jan 2018 http://governance.iarc.fr/ENG/Docs/BriefingGCSC_FINAL_29012018.pdf

[8] Portier CJ, Armstrong BK, Baguley BC, Baur X, Belyaev I, Bellé R, Belpoggi F, Biggeri A, Bosland MC, Bruzzi P, Budnik LT, Bugge MD, Burns K, Calaf GM, Carpenter DO, Carpenter HM, López-Carrillo L, Clapp R, Cocco P, Consonni D, Comba P, Craft E, Dalvie MA, Davis D, Demers PA, De Roos AJ, DeWitt J, Forastiere F, Freedman JH, Fritschi L, Gaus C, Gohlke JM, Goldberg M, Greiser E, Hansen J, Hardell L, Hauptmann M, Huang W, Huff J, James MO, Jameson CW, Kortenkamp A, Kopp-Schneider A, Kromhout H, Larramendy ML, Landrigan PJ, Lash LH, Leszczynski D, Lynch CF, Magnani C, Mandrioli D, Martin FL, Merler E, Michelozzi P, Miligi L, Miller AB, Mirabelli D, Mirer FE, Naidoo S, Perry MJ, Petronio MG, Pirastu R, Portier RJ, Ramos KS, Robertson LW, Rodriguez T, Röösli M, Ross MK, Roy D, Rusyn I, Saldiva P, Sass J, Savolainen K, Scheepers PT, Sergi C, Silbergeld EK, Smith MT, Stewart BW, Sutton P, Tateo F,

I will add my own perspective here.

The IARC Monographs have clearly described published guidelines called the "Preamble to the Monographs".[9] The guidelines describe the separate criteria for reviewing evidence from animal studies, epidemiologic information, and mechanistic data, and then integrating the data into an overall evaluation. All evaluations are made by Working Groups of experts, and have included over 1,200 scientists from over 50 countries. Scientific data is evaluated in subgroups, and then by all members of the Working Group in a plenary session, where revisions and extensive discussions often occur. There are also procedural guidelines for ensuring transparency, and for identifying and managing conflicts of interest and stakeholder involvement. Government, industry, NGO observers, and others can attend the Working Group meetings; the glyphosate meeting was attended by Monsanto Co. and other agrochemical industry representatives as observers.[10]

For its glyphosate assessment, IARC identified 17 scientific experts from 11 countries (Volume 112, 2017).[11] A list of Working Group candidates is posted in advance of the meeting, along with their disclosure of relevant financial conflicts, and public comments are invited. In advance of the meeting, Working Group members are asked to review an often very large stack of scientific papers relevant to each person's area of expertise, and provide a draft summary for discussion at the in-person meeting.

All information used for the evaluation must be published or otherwise publicly available with enough detail to enable independent scientific examination. For this reason, some Monsanto-sponsored review articles were left out, where the underlying studies cited in the review article were not available to the Working Group or to the public. For example, Greim et al (2015), a review article of animal toxicology that was sponsored and co-authored by Monsanto Co., is discussed in the IARC monograph, but was not relied upon because the studies in the paper were not publicly available.[12]

Terracini B, Thielmann HW, Thomas DB, Vainio H, Vena JE, Vineis P, Weiderpass E, Weisenburger DD, Woodruff TJ, Yorifuji T, Yu IJ, Zambon P, Zeeb H, Zhou SF. Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA). J Epidemiol Community Health. 2016 Aug;70(8):741-5. doi: 10.1136/jech-2015-207005. Epub 2016 Mar 3.

[9] http://monographs.iarc.fr/ENG/Preamble/index.php

[10] Participants for the IARC Monograph Volume 112. https://monographs.iarc.fr/ENG/Meetings/vol112-participants.pdf

[11] http://monographs.iarc.fr/ENG/Monographs/vol112/index.php

[12] Greim H, Saltmiras D, Mostert V, Strupp C. Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies. Crit Rev Toxicol. 2015 Mar;45(3):185-208.

Helmut Greim also chaired a 'scientific panel' funded by auto companies to respond to the 2005 IARC evaluation of diesel exhaust. Greim's panel conducted studies on monkeys at a lab in Albuquerque New Mexico, exposed them in a chamber to diesel exhaust. However, the studies were rigged because the

IARC has been criticized by Dr. Tarone, also a paid Monsanto Co. consultant, arguing that IARC could have used, "A supplement to the review paper [that] contains summary pathology tables for each of the rodent studies reviewed".[13] But, summary tables are not original studies, and do not provide the detail necessary for an independent examination, and thus the Working Group could not independently verify the conclusions. Similarly, the IARC Monograph determined that a Monsanto-sponsored review of genotoxicity studies by Kier and Kirkland (2013) also "did not meet the criteria for data inclusion as laid out in the Preamble to the IARC Monographs" because the original studies were not available publicly available. IARC requires information to be publicly available as a requirement for full transparency of how the Working Group came to its conclusions. In addition, peer reviewed publications and reports contain enough detail on the study materials, methods, and results so that peer reviewers and readers can independently evaluate the study quality, including any possible confounders and biases.

In stark contrast to IARC, the 2017 EPA glyphosate assessment acknowledges that, "data and summaries provided in Greim et al (2015) and Kier and Kirkland (2013)[14] were relied upon for the current evaluation" (EPA 2016, 2017). Thus, EPA relied upon a Monsanto-sponsored summary of a Monsanto-sponsored study that EPA could not independently scrutinize – the full studies are not available to the public and do not even seem to have been made available to EPA. In a small footnote, EPA identified that all review articles except one "were funded and/or linked to Monsanto Co. or other registrants."[15]

On occasion, the Monographs have been wrongly accused of a bias towards too readily classifying a substance as carcinogenic. However, to date the IARC Monographs have evaluated over 1,000 agents, all with at least enough cancer data to support a nomination for consideration. Yet, only 120 are classified as known human carcinogens (Group 1) and only about 80, including glyphosate, as probable human carcinogens (Group 2A).[16] That makes a total of 200 agents, only about 20 percent, that are classified in the strongest two categories. The overwhelming majority of agents that have been reviewed by IARC – about 80 percent - are classified as either possibly carcinogenic to humans (Group 2B, 300 agents) or not classifiable (Group 3, 500 agents). The third category – not classifiable – has far more entries than any other single class, and even more than the first two combined (Group 1 and 2A). Thus,

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cars in the chambers were using the "cheating" device that reduced emissions. In addition to bad science, it was also unethical, given that it is completely unnecessary to test monkeys in a chamber, when people are walking around exposed to these diesel fumes every day. The study was never published, but was widely criticized and the story reported in the NY Times. https://www.nytimes.com/2018/01/25/world/europe/volkswagen-diesel-emissions-monkeys.html

[13] Tarone RE. On the International Agency for Research on Cancer classification of glyphosate as a probable human carcinogen. Eur J Cancer Prev. 2018 Jan;27(1):82-87. https://www.ncbi.nlm.nih.gov/pubmed/27552246

[14] Kier LD, Kirkland DJ. Review of genotoxicity studies of glyphosate and glyphosate-based formulations. Crit Rev Toxicol. 2013 Apr;43(4):283-315. Review. https://www.ncbi.nlm.nih.gov/pubmed/23480780

[15] EPA 2017 glyphosate cancer assessment. See Page 22 and Footnote 11.

[16] http://monographs.iarc.fr/ENG/Classification/index.php

the data do not support a bias towards classifying chemicals in the higher groups; in fact, most are determined to have too little data to classify.

There has been public criticism by Monsanto Co. and some Majority Members of this Congressional Committee that a member of the glyphosate Working Group, Dr. Aaron Blair, withheld a pre-publication update of the National Cancer Institute Agricultural Health Study (AHS), and, further, that if the Working Group had been provided with this update, then it would have altered the final classification of glyphosate as a Group 2A probable human carcinogen.[17] That story was reported in Reuters, and subsequently shown by former Reuters reporter and veteran journalist Carey Gillam to contain critical factual errors, and to have been orchestrated by Monsanto Co..[18] The misleading Reuters story relies on court documents obtained from Monsanto Co., and quotes Monsanto Co. consultant Bob Tarone as an "independent" expert not associated with Monsanto Co. Dr. Blair himself states that his opinions held at the IARC meeting has not changed, which IARC pointed out in a response letter to this Committee.[19]

The IARC Director, Dr. Christopher Wild, responded in a letter to this Committee that in fact the AHS is a decades-long prospective epidemiologic study, with "incremental updates published periodically," all of which were included by the IARC Working Group in the Monograph.[20] Since the previous AHS reports did not identify an association between non-Hodgkin lymphoma (NHL) and glyphosate, and the most recent incremental update, in 2017, also did not identify such an association, then it's hard to see how the recent update alters the previous reports. In addition, the recent update was not published until 2017, a full 2.5 years after the meeting of the IARC Working Group, indicating that it was unpublished at the time of the meeting.

It is also inappropriate to argue that null studies can even nullify completely unrelated studies that are positive, that do report a link to NHL or other cancers. As if, just because you don't have cancer, my cancer goes away. That isn't the way science works, and it isn't the way cancer works either. The updated AHS report does not call into question the IARC conclusions, which are based on many studies across multiple disciplines, including studies sponsored by Monsanto Co.

Lost or buried in much of the reporting of the recent update of the AHS study is that the study did find some evidence of a possible association between glyphosate and another type of blood cancer called acute myeloid leukemia (AML). The AHS study authors warn that, "Given the

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[17] See Letter from Reps. Lamar Smith, Andy Biggs, and Frank Lucas to IARC Director Dr. Christopher Wild. December 8, 2017. http://governance.iarc.fr/ENG/Docs/SST_IARC12082017.pdf

[18] https://www.huffingtonpost.com/entry/monsanto-spin-doctors-target-cancer-scientist-in-flawed_us_594449eae4b0940f84fe2e57

[19] IARC letter January 11, 2018, referencing a videotaped deposition of Dr. Blair, March 20, 2017. http://governance.iarc.fr/ENG/Docs/CPWild_Smith_Biggs_Lucas_20180111.pdf

[20] See response from Dr. Wild to the Committee on Science, Space and Technology, January 11, 2018. http://governance.iarc.fr/ENG/Docs/CPWild_Smith_Biggs_Lucas_20180111.pdf

prevalence of use of this herbicide worldwide, expeditious efforts to replicate these findings are warranted".[21] The increase risk of AML was over 2-fold higher in highest exposed applicators compared with the never exposed applicators. The possible link with leukemia should be very concerning to the public and particularly to pesticide applicators, because AML is a very serious fast-growing cancer, with only about one-quarter of the people that have it surviving longer than 5 years. The EPA 2017 Cancer Assessment acknowledges these new data, but considers them too limited and simply says it will continue to follow the literature.[22]

In summary, the Monograph process: relies only on publicly available studies of sufficient detail for a peer assessment, including both industry and non-industry studies; follows a systematic review approach using internationally agreed upon best practices; is the consensus product of a Working Group of non-IARC experts; invites observers including industry stakeholders to attend all aspects of the Working Group meetings including sub-groups and plenary voting sessions; will report in the Monographs if there is a significant dissenting perspective among Working Group members (there was no such dissent on the glyphosate finding); does not alter any findings or conclusions that are not agreed to during the meeting of the Working Group.

EPA Glyphosate Cancer Assessment – Process Problems

The EPA Pesticide Office seems to have a questionable and non-transparent process for conducting its pesticide cancer assessments. Perhaps most alarming are revelations of a disturbing level of communication and collaboration between Monsanto Co. and senior EPA official Jess Rowland, who headed up the EPA Cancer Assessment Review Committee for glyphosate and many other pesticides. Monsanto Co. internal emails made available by U.S. RTK reveal that Rowland told a Monsanto Co. employee in 2015 that he would try to prevent the Department of Health and Human Services from conducting its own glyphosate hazard assessment, which then came to pass. Monsanto Co.'s regulatory liaison commented in a 2015 email that Rowland "could be useful as we move forward with ongoing glyphosate defense," and Rowland has since left EPA. The concerns of collusion sparked an investigation by the EPA Inspector General that is still ongoing.[23]

EPA's Pesticide Office seems to be failing the test of public scrutiny for its policy decisions as well. The Scientific Advisory Panel (SAP) that reviewed the 2016 assessment disagreed with EPA's classification of "not likely to be carcinogenic to humans' at doses relevant to human health risk assessment. First, the SAP agreed that the Pesticide Office had inappropriately

[21] Andreotti G, Koutros S, Hofmann JN, Sandler DP, Lubin JH, Lynch CF, Lerro CC, De Roos AJ, Parks CG, Alavanja MC, Silverman DT, Beane Freeman LE. Glyphosate Use and Cancer Incidence in the Agricultural Health Study. J Natl Cancer Inst. 2017 Nov 9. https://www.ncbi.nlm.nih.gov/pubmed/29136183

[22] Revised glyphosate issue paper: evaluation of carcinogenic potential. EPA Office of Pesticide Programs. December 12, 2017. Section 3.5.2 (1), p. 53

[23] Paul Thacker. Huffington Post. 06/06/2017. https://www.huffingtonpost.com/entry/epa-inspector-general-probing-collusion-with-monsanto_us_59372108e4b0aba888b99dca

conflated a hazard statement (not likely to be carcinogenic) with a risk characterization (at doses relevant to risk assessment) without having conducted an exposure and risk assessment. [24] Second, most of the SAP members supported the stronger classification of "suggestive evidence of cancer". Third, the SAP had concerns that the Pesticide Office had failed to follow its Agency-wide Cancer Guidelines in ways that biased the conclusions towards the least protective "not likely" classification. The SAP's report is in agreement with EPA's Office of Research and Development (ORD), including that the Pesticide Office had inappropriately dismissed cancer evidence by failing to conduct a systematic review and that a "not likely" cancer descriptor was inappropriate and inconsistent with the tumor evidence. [25]

Both the 2016 and 2017 glyphosate cancer assessments follow a systematic review process being developed by EPA's Office of Chemical Safety and Pollution Prevention (OCSPP). This office, known as the Toxics Office, is now under the management of Nancy Beck, a chemical industry lobbyist prior to her recent political appointment at EPA. Dr. Beck's previous foray into developing risk assessment guidelines was a failure, as evidenced by the National Academies conclusion that the draft government-wide risk assessment bulletin which she authored while at the Office of Management and Budget (OMB) was "fundamentally flawed" and the unprecedented recommendation for its withdrawal (NAS 2007).[26]

The systematic review approach used by EPA in the glyphosate cancer assessment is inconsistent in critical ways with best practices, and recommendations of the National Academies (NRC 2014; NRC 2017). [27] The approaches used in OCSPP do not meet the standard of transparency and public review of the IRIS program, which recently received praise from EPA's Science Advisory Board (SAB): "The program has fully adopted the principles of systematic review ...it is now standard practice for the [IRIS] program to engage stakeholders in an early scoping and problem formulation phase, thereby allowing stakeholders to provide important input at the very beginning of the process." [28] It is unclear why the Pesticide Office is not coordinating with the IRIS program to share resources, save time, and implement the IRIS systematic review process that has been developed with public and stakeholder input, and favorable review by the National Academies and SAB.

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[24] SAP meeting, December 2016. P. 80, 86-87. https://www.epa.gov/sites/production/files/2017-03/documents/december_13-16_2016_final_report_03162017.pdf

[25] Summary of ORD comments on OPP's glyphosate cancer assessment, December 14, 2015. https://usrtk.org/wp-content/uploads/2017/03/ORDcommentsonOPPglyphosate.pdf

[26] Available at http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=11811

[27] National Research Council. 2014. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: The National Academies Press. https://doi.org/10.17226/18764
National Academies of Sciences, Engineering, and Medicine. 2017. Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals. Washington, DC: The National Academies Press. https://doi.org/10.17226/24758.

[28] Science Advisory Board comments on EPA's response to recommendations on the Integrated Risk Information System. September 1, 2017. EPA-SAB-17-008. Available at: https://yosemite.epa.gov/sab/SABPRODUCT.NSF/RSSRecentAdditionsBOARD/A9A9ACCE42B6AA0E8525818E004CC597/$File/EPA-SAB-17-008.pdf

Instead, the EPA's glyphosate cancer assessment is being conducted according to a purported systematic review process that has not been subjected to public and stakeholder engagement, or peer review. Further, it veers from the National Academies and IRIS best practices in several important ways, all of which are promoted by the chemical industry,[29] and favor industry outcomes:

- preferentially relying on Guideline studies, which are conducted by the regulated industry to support the approval of its products;
- preferentially relying on studies following so-called Good Laboratory Practices (GLP), which are required by industry product-testing labs to prevent malfeasance and misconduct;
- over-emphasizing the requirement to understand the mechanism of toxicity, so that many studies of adverse effects in people are dismissed because the mechanism of disease is not fully understood;
- using methods to score studies that score guideline and GLP studies higher;
- misusing a 'weight of evidence' (WOE) approach to pit studies that find adverse effects against studies that don't, to dismiss the effects studies.

The EPA Pesticides Office leans on all of the above chemical industry tactics to dismiss the following evidence that EPA acknowledges would support a "suggestive" classification for glyphosate (EPA Cancer Assessment, Section 6.6.2, p. 141-142):

- Non-statistically significant non-Hodgkin's lymphoma (NHL) across studies, and in a meta-analysis sponsored by Monsanto Co. (Chang and Delzell 2016)[30] that, according to EPA, found results similar to IARC (EPA Cancer Assessment, p. 64);
- Limited evidence of a possible exposure-response relationship between glyphosate exposure and NHL in case-control studies;
- A statistically significant trend in tumors in several animal cancer studies, and two studies with statistically significant tumor incidence at the highest doses tests, compared with concurrent controls;
- Evidence of genotoxic effects in a limited number of tests including damage to DNA and chromosomes.

In each of the cancer evidence streams summarized by EPA above – human, animal, and cellular studies – there were also studies that didn't find a link between glyphosate and cancer, or

[29] Rick Becker comments on behalf of the American Chemistry Council on Data Quality in Toxicology Studies: A key element in systematic review for evaluating chemical risks. March 20, 2013. Submitted to the National Toxicology Program.
https://ntp.niehs.nih.gov/ntp/ohat/evaluationprocess/presentations/march2013/becker20130320_508.pdf

[30] Chang ET, Delzell E. Systematic review and meta-analysis of glyphosate exposure and risk of lymphohematopoietic cancers. J Environ Sci Health B. 2016;51(6):402-34.

glyphosate and cellular damage that could lead to cancer.[31] Most prominent among these no-effect studies are the industry-sponsored review articles of Greim et al (2015) and Kier and Kirkland (2013) that are heavily cited in EPA's cancer assessment, but dismissed by IARC because the underlying studies were not published or otherwise publicly available.

The Pesticide Office concludes that, "In summary, considering the entire range of information for the weight-of-evidence, the evidence outlined above to potentially support the 'suggestive evidence of carcinogenic potential' descriptor are [sic] contradicted by other studies of equal or higher quality and, therefore, the data do not support this cancer classification descriptor." (page 142) The Pesticide Office therefore concludes that, "The strongest support is for 'not likely to be carcinogenic to humans'. "(page 143). The OCSPP systematic review as applied to the glyphosate cancer assessment leads to the inclusion of systemic flaws that make the glyphosate assessment biased toward industry, inconsistent with best practices identified by the National Academy, unreliable and unprotective of human health.

Only one agent has ever been classified by IARC in the lowest category, Group 4, probably not carcinogenic. The chemical is caprolactam, used in nylon and plastics (Volume 39, 1999). This is because, in accordance with the IARC guidelines, to classify a chemical into Group 4 requires affirmative evidence of lack of carcinogenicity, as opposed to simply a lack of evidence. The U.S. EPA Cancer Guidelines apply similarly stringent criteria to classify a substance as "not likely to be carcinogenic to humans", that is, "when the available data are considered robust for deciding that there is no basis for human hazard concern" (Guidelines, p. 2-57). such as, "animal evidence that demonstrates lack of carcinogenic effect in both sexes in well-designed and well-conducted studies in at least two appropriate animal species (*in the absence of other animal or human data suggesting a potential for cancer effects*)." Against the requirements of its own guidelines, this is the category into which EPA has now placed glyphosate. We would welcome a committee hearing to more closely examine the scientific and procedural integrity of the Pesticide Office's assessment of glyphosate health risks.

Conclusion

Fundamentally, this hearing is about the ability of a public health agency to call a carcinogen a carcinogen, even if it makes a huge amount of money for a powerful corporation. Of course, even without IARC, or IRIS, (or the National Toxicology Program's Report on Carcinogens), the cancers will still occur – with their obvious terrible toll on individuals, families, health care costs, and the economy – but the suffering will be in vain because the tumors won't be counted, and the causes won't be tracked. IARC Monographs are considered essential for

[31] In some cases, the Pesticide Office tried to cast doubt on the glyphosate cancer evidence by: using a different statistical method (pair-wise instead of trend tests); comparing tumor evidence with historical laboratory records of control animals instead of control animals within the same experiment (some with lab records over 10 years old); or discounting the tumors in the high dose groups (EPA 2017 pages 141-142).

informing cancer prevention strategies and effective public health decision-making around the world.[32] As several cancer assessment experts recently wrote, "the interference by economic interests in cancer evaluations conducted by public heath institutions do not bode well for the free flow of scientific information that informs and protects the public and workers from clear risks of cancer".[33] Are we willing to sell out the public's right to know about harmful chemicals in the places we work, live, and play, just so that Monsanto Co. can sell more glyphosate?

Thank you for the opportunity to address this Committee.

Respectfully,

[32] Lorenzo Richiardi, Benedetto Terracini; International Agency for Research on Cancer. The first 50 years, International Journal of Epidemiology, Volume 45, Issue 3, 1 June 2016, Pages 967–968, https://doi.org/10.1093/ije/dyv331

[33] Infante PF, Melnick R, Vainio H, Huff J. Commentary: IARC Monographs Program and public health under siege by corporate interests. Am J Ind Med, online 3 February 2018. DOI: 10.1002/ajim.22811. http://onlinelibrary.wiley.com/doi/10.1002/ajim.22811/full

J. Sass Short Professional Biography:

Jennifer Sass is a Senior Scientist at the Natural Resources Defense Council (since 2001), an environmental non-profit organization. She also holds a position as part-time faculty at George Washington University Milken School of Public Health (since 2008). Sass is a Board Member of the NIEHS National Toxicology Program Board of Scientific Counselors (since 2016). Sass is an Authorized GreenScreen Practitioner (2016). Sass is well versed in environmental health science and policy particularly pertaining to the US review and regulation of chemicals including pesticides, nanomaterials and emerging contaminants. She has published over four dozen articles in peer-reviewed journals. She regularly provides testimony and scientific briefings for the U.S. Congress and participates in stakeholder and expert scientific federal advisory committees. She holds BSc, MSc, and PhD (1998) degrees from the University of Saskatchewan, College of Medicine, Department of Anatomy and Cell Biology, and a Post-Doctoral Certificate (2000) from the University of Maryland, College of Medicine, Program in Human Health and the Environment.

Chairman SMITH. Thank you, Dr. Sass.
And Dr. Tarone.

**TESTIMONY OF DR. ROBERT TARONE,
(RETIRED) MATHEMATICAL STATISTICIAN,
U.S. NATIONAL CANCER INSTITUTE
AND BIOSTATISTICS DIRECTOR,
INTERNATIONAL EPIDEMIOLOGY INSTITUTE**

Dr. TARONE. Good morning. My European Journal of Cancer Prevention paper differs from most of the published criticisms that you may have seen in the press and elsewhere of the IARC glyphosate classification. My paper critiques the deliberations of the working group completely on IARC's terms.

I accept that IARC is evaluating hazard rather than risk, that the IARC criteria for determining hazard are reasonable and that the body of studies relied upon by IARC is sufficiently complete to provide a valid assessment of glyphosate. My critique concludes that the IARC classification of glyphosate as a probable carcinogen resulted from a flawed and incomplete evaluation of the very rodent cancer studies that they relied upon.

Although the working group concluded that there was sufficient evidence that glyphosate was an animal carcinogen, I conclude that a proper summary of the rodent studies would have difficulty supporting even the conclusion that there is limited evidence that glyphosate is an animal carcinogen. And I just want to discuss briefly one of several examples in which exculpatory rodent data were excluded by IARC.

IARC concluded that glyphosate caused cancer in animals primarily on the basis of two studies in CD- mice. In the first study, groups of 50 male and female mice were fed diets with—containing increasing dose levels of glyphosate for two years. The original study report noted a positive trend in renal adenomas in male mice. The tumor counts were 0,0,1,3 at increasing dose levels, and this corresponds to a P value of .019 based on an exact test for dose-response.

Additional pathological examination of renal tumors in this study revealed one new adenoma in an unexposed mouse, and three of the original renal tumors were upgraded from adenomas to carcinomas. So for the final tumor counts after pathology review, they were 0,0,1,2 for carcinomas, P value of .063, and 1,0,1,3 for carcinomas and adenomas combined, P equals .065.

Now, these marginally significant findings were considered to be particularly consequential by the IARC working group because of the alleged extreme rarity of such tumors in CD–1 mice, and it was concluded from this study and the study alone that glyphosate caused renal tumors in male mice.

Now, there was no a priori expectation that glyphosate should cause kidney tumors, and ordinarily such a small increase in tumors would not be considered especially noteworthy since around 20 organs and tissues are typically evaluated in each rodent study. Nonetheless, even that small observed increase would be of concern if there was also evidence of an increase in renal tumors for female mice in that same study. Thus, I was surprised to see that the fe-

male data were not reported with a remarkable sentence stating, quote, "No data on tumors of the kidney were provided for female mice."

IARC has been evaluating rodent studies for over 40 years and is aware that the renal tumor rates for female mice would've been provided in the same report that provided the male tumor rates. IARC's staff should've been highly motivated to acquire these tumor rates. I obtained the female tumor rates for my review of glyphosate rodent studies in the journal Critical Reviews in Toxicology. This is the Greim, et al., paper that Dr. Sass referred to.

For females, no renal tumors were observed, so there was no evidence of an increase in kidney tumors for female mice exposed to the same high levels of glyphosate as males. But even though there was no evidence that glyphosate caused renal tumors in female mice in this study, the working group still might have argued for a sex-specific effect if there was evidence of such an effect in the second CD–1 mouse study they relied upon. But inexplicably, in spite of devoting three—and I apologize for the—there's an error in the printed comments; it's three not two paragraphs to the discussion of renal tumors observed in the first mouse study, there is no mention at all of kidney pathology in the one paragraph devoted to the second mouse study, which is simply astounding. IARC staff should've been highly motivated to acquire the renal tumor rates from the second study because of the male results in the first study.

The renal tumor rates for the second study were also provided in a review paper. For males, the renal tumor counts at increasing glyphosate exposure level were two, two, zero, and zero, and this is P equals .042, but for an inverse association, decreasing tumor rates with increasing exposure level. And it's also noteworthy that two of these supposedly extremely rare renal tumors were observed in the unexposed mice in this study. Taken together, these two studies provide no evidence whatsoever to support the conclusion that glyphosate causes renal tumors in male mice, contrary to the working group conclusion. And for completeness no tumors were observed for female mice in the second study.

In conclusion, my published paper notes other instances in which rodent tumor rates that supported the conclusion that glyphosate caused tumors were included in IARC deliberations while tumor rates from those same studies that did not support that conclusion were excluded. The systematic exclusion of exculpatory evidence is inexcusable, particularly when it's practiced by an influential source such as the IARC Monograph Programme. My paper was published online in August of 2016, and not one of the specific claims of data exclusion in that paper has been refuted. And reports since my paper was published and depositions of key working group members related to lawsuits filed against Monsanto have fully substantiated the facts presented and questions raised my paper.

[The prepared statement of Dr. Tarone follows:]

Comments on the IARC classification of glyphosate as a probable human carcinogen

Committee on Science, Space and Technology

February 6, 2018

Robert E. Tarone, PhD

The IARC Monograph Working Groups evaluate three types of evidence in assessing the potential carcinogenicity of an agent; animal carcinogenicity studies, epidemiologic studies of cancer risk in humans, and "mechanistic and other relevant data". For each of the first two categories (animal and human studies) the evaluation leads to a conclusion that there is sufficient evidence of carcinogenicity, limited evidence of carcinogenicity, inadequate evidence of carcinogenicity, or evidence suggesting lack of carcinogenicity. The evaluation of mechanistic and other relevant data is not as formalized, and there is some subjectivity in how this evaluation contributes to the final carcinogen classification. The overall classification of an agent depends largely on the summary conclusions regarding the strength of evidence from the animal studies and the human studies. Of particular importance with regard to my European Journal of Cancer Prevention paper on the glyphosate classification, if the Working Group concludes that there is sufficient evidence that the agent is an animal carcinogen then the agent will be assigned to Group 2B (possibly carcinogenic to humans), Group 2A (probably carcinogenic to humans), or Group 1 (carcinogenic to humans).

In explaining occasional differences between IARC classifications and those of other regulatory bodies worldwide, IARC often notes that its Monograph Program evaluates cancer hazard rather than cancer risk. The following paragraph is from page 2 of the current Preamble to every published Monograph.

> A cancer 'hazard' is an agent that is capable of causing cancer under some circumstances while a cancer 'risk' is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. The *Monographs* are an exercise in evaluating cancer hazards, despite the historical presence of the word 'risks' in the title. The distinction between hazard and risk is important, and the *Monographs* identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could endanger risks that are significantly higher.

This distinction could provide a plausible explanation for why the conclusion in IARC Monograph 112 on the carcinogenic potential of glyphosate differed from

that of other bodies (e.g., the EFSA and JMPR, both of which concluded that glyphosate exposure from food consumption was not likely to be carcinogenic), but my paper points out a more basic problem with the IARC glyphosate classification.

Additional questions have been raised about the IARC glyphosate deliberations, including the selection of studies IARC chose to rely upon in evaluating glyphosate (IARC has stricter criteria for selecting studies than many regulatory bodies) and the makeup of the Working Group (e.g., the inclusion of an invited specialist affiliated with the Environmental Defense Fund). These issues are not considered in my paper. My paper critiques the deliberations of the Working Group that evaluated glyphosate on IARC's terms. I accept that IARC is evaluating hazard rather than risk, that the IARC criteria for determining carcinogenic hazard are reasonable, and that the body of studies relied upon by IARC is sufficiently complete to provide a valid assessment of the carcinogenic potential of glyphosate. My critique concludes that the IARC classification of glyphosate as a probable carcinogen was the result of a flawed and incomplete evaluation of the very rodent cancer studies that IARC relied upon. Although the Working Group concluded that there was sufficient evidence that glyphosate was an animal carcinogen, I conclude that a proper summary of the rodent studies relied upon by IARC would not even support the conclusion that there is limited evidence that glyphosate is an animal carcinogen. Without the conclusion that there is sufficient evidence that glyphosate is animal carcinogen, the IARC criteria would not have supported the overall classification of glyphosate as a probable human carcinogen.

IARC concluded that there was sufficient evidence that glyphosate caused cancer in animals, primarily on the basis of two studies in CD-1 mice. In the first study, groups of 50 male and female CD-1 mice were fed diets containing 0, 1000, 5000, and 30000 parts per million glyphosate over a two year period. The original study report noted a positive trend in renal tubule adenomas in male CD-1 mice. The tumor rates were 0/49, 0/49, 1/50, and 3/50 at increasing dose levels ($p=0.019$). The US EPA requested additional pathological examination of renal tumors in this study, including the convening of a Pathology Working Group. One

additional renal tubule adenoma was discovered in the unexposed control group, and three of the original renal tubule tumors were upgraded from adenomas to carcinomas. Thus the final tumor rates after the pathological review for carcinomas were 0/49, 0/49, 1/50, and 2/50 (p=0.063), and for carcinomas and adenomas combined were 1/49, 0/49, 1/50, and 3/50 (p=0.065). These marginally significant findings were considered particularly consequential by the IARC Working Group because of the alleged rarity of such renal tumors in CD-1 mice, and it was concluded that this study showed that glyphosate caused renal tubule tumors in male CD-1 mice.

There was no *a priori* expectation that glyphosate should cause kidney tumors, and ordinarily such a small increase in tumors with increasing dose level would not be considered especially noteworthy, particularly since around 20 organs and tissues are typically evaluated pathologically in rodent carcinogenicity studies. Nonetheless, even the small observed increase would be of concern if there was also evidence of an increase in renal tubule tumors for female mice in the same study or for male or female mice in the second CD-1 mouse study relied upon by IARC. Thus, the following sentence from the glyphosate chapter of Monograph 112 in the discussion of the first CD-1 mouse study is remarkable: "No data on tumours of the kidney were provided for female mice." IARC has been evaluating rodent carcinogenicity studies for over 40 years, and is aware that the renal tumor rates for female mice would have been provided in the original study report that provided the male tumor rates. IARC staff should have been able to acquire the female tumor rates. In fact, they should have been motivated to acquire the female renal tumor rates because of the male results. I obtained the female renal tubule tumor rates for the first CD-1 mouse study from a review of glyphosate rodent studies published in Critical Reviews in Toxicology (Greim et al., 2015). For females the tumor rates were 0/50, 0/50, 0/50, and 0/50. That is, there was no evidence from female mice exposed to the same high levels of glyphosate for an increase in kidney tumors. The review paper by Greim et al. was discussed briefly in the summary of the Working Group deliberations in Monograph 112, but the review and its accompanying supplemental material were, for the most part, discounted.

Even though there was no evidence that glyphosate caused tumors in female CD-1 mice in this study, the Working Group still might have argued for a sex-specific carcinogenic effect, particularly if there was evidence of such an effect in the second CD-1 mouse study relied upon by IARC. Inexplicably, however, in spite of devoting two paragraphs to the discussion of renal tubule tumors observed in first CD-1 mouse study, there is no mention whatsoever of kidney pathology in the one paragraph of the Monograph 112 glyphosate chapter devoted to the second CD-1 mouse study. Again, IARC staff should have been motivated to acquire the renal tumor rates from the second study because of the male results from the first study. No explanation has been offered by IARC for this disturbing omission of relevant kidney tumor data. The renal tubule tumor rates from the second study were also provided in the supplemental material of the Greim et al. review paper. Male and female mice were exposed to dose levels slightly lower than those in the first CD-1 mouse study, and for males the renal tubule tumor rates at increasing glyphosate exposure level were 2/50, 2/50, 0/50, and 0/50 ($p=0.042$ for an ***inverse*** association with glyphosate dose level). That is, while a marginally significant increase in renal tubule tumors was observed for males in the first mouse study based on small numbers of tumors, a marginally significant decrease in renal tubule tumors was observed in the second mouse study based on small numbers. It should also be noted that two of the supposedly extremely rare renal tumors were observed in the unexposed mice in this study. Taken together these two studies provide no evidence whatsoever to support the conclusion that glyphosate causes renal tumors in male mice. For female mice in the second study the tumor rates were 0/50, 0/49, 0/50, and 0/50. Thus, there is no evidence from the two mouse studies relied upon by the Working Group that glyphosate causes renal tumors in male or female mice.

My published paper notes other instances in which rodent tumor rates which might support a conclusion that glyphosate is associated with tumor risk were included in the Monograph 112 glyphosate deliberations, while tumor rates from the same studies that do not support an association between glyphosate exposure and tumor risk were excluded. Such systematic exclusion of exculpatory evidence is outrageous, particularly when it is practiced by an influential source

such as the IARC Monograph Program. My paper was published online in August of 2016, and not one of the claims in the paper has been refuted. In addition to critiquing the Monograph 112 Working Group summary of rodent studies I also raised questions about the summary of epidemiologic studies by the Working Group. Publications since August 2016 and depositions of key Working Group members relating to lawsuits filed against Monsanto after the IARC glyphosate classification was announced in March of 2015 have substantiated the facts presented, and questions raised, in my paper.

I have no conflict of interest whatsoever with regard to glyphosate or Monsanto. Since my retirement in June of 2016 I have received no payment for any of my continued scientific efforts. No payment was received for writing the European Journal of Cancer Prevention paper, nor was I requested by anyone to write the paper. The decision to write the paper was mine alone, after I discovered the serious scientific errors made by IARC in the glyphosate deliberations. Nobody else contributed in any way to the writing of the paper.

References

Greim H, Saltmiras D, Mostert V, Strupp C (2015). Evaluation of carcinogenic potential of the herbicide glyphosate, drawing from tumor incidence data from fourteen chronic/carcinogenicity rodent studies. *Crit Rev Toxicol* **45**:185-208.

Tarone RE (2018). On the International Agency for Research on Cancer classification of glyphosate as a probable human carcinogen. *Eur J Cancer Prev* **27**:82-87

OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Tarone, Robert Ernest

eRA COMMONS USER NAME (credential, e.g., agency login): TARONER

POSITION TITLE: Biostatistics Director

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of California, Davis	B.S.	06/68	Mathematics
University of California, Davis	M.S.	06/69	Mathematics
University of California, Davis	Ph.D.	06/74	Mathematics

A. Personal Statement

I have extensive experience in providing statistical direction and analysis in a variety of areas of medical research that are relevant to the goals of the numerous and varied proposed investigations of determinants of disease in the Southern Community Cohort Study. As a Mathematical Statistician at the National Cancer Institute I was heavily involved in providing statistical assistance to a wide variety of laboratory and clinical researchers, including investigators in the fields of immunology, DNA repair, and cancer-prone inherited diseases. In addition, I was involved in the design, conduct and statistical analysis of several large scale observational studies, including the ALTS trial of HPV testing to detect cervical cancer, the nationwide NCI case-control study of electromagnetic fields and childhood leukemia risk, the prospective Agricultural Health Study, and the NCI case-control study of cell phones and brain tumor risk. I have also had extensive experience, while at the International Epidemiology Institute and Vanderbilt University Department of Medicine, in the conduct of retrospective and prospective cohort studies to evaluate potential health risks in numerous areas of environmental and occupational epidemiology. In summary, my record of statistical collaboration in productive laboratory and epidemiologic research demonstrates that I am well qualified for my role in the proposed project.

1. Signorello L.B., Cai Q., Tarone R.E., McLaughlin J.K. & Blot W.J. (2009). Racial differences in serum cotinine levels of smokers. Dis Markers 27(5):187-92. PMID: 20037205
2. Lipworth L., Mumma M.T., Cavanaugh K., Edwards T.L., Ikizler T.A., Tarone R.E., McLaughlin JK, Blot WJ. (2012). Incidence and predictors of end stage renal disease among low income blacks and whites. PLoS One 7(10): e48407. PMID: 23110237
3. Lipworth, L., Fazio S., Kabagambe E.K., Munro H., Nwazue B.C., Tarone R.E., McLaughlin J.K., Blot W.J. & Sampson U.K. (2014). A prospective study of statin use and mortality among 67,385 blacks and whites in the Southeastern United States. Clin Epidemiol 19(6):15-25. PMID: 24379700
4. Sonderman, J.S., Munro H.M., Blot W.J., Tarone, R.E. & McLaughlin, J.K. (2014). Suicides, accidents, and other external causes of death among blacks and whites in the Southern Community Cohort Study. PLoS One 9(12):e114852. PMID: 25486418

B. Positions and Honors

Positions and Employment

1971 - 74	Associate in Biostatistics, Department of Epidemiology and Preventive Medicine, UCD, Davis, CA
1974 - 76	Staff Fellow, Division of Cancer Cause and Prevention, National Institutes of Health, Bethesda, MD
1976 - 93	Mathematical Statistician, Division of Cancer Etiology, National Institutes of Health, Bethesda, MD
1993 - 02	Chief, Statistical Research and Applications Section, Division of Cancer Epidemiology and Genetics, National Institutes of Health, Bethesda, MD
2003 - 12	Professor, Department of Medicine, Vanderbilt University, Nashville, TN
2002 -	Biostatistics Director, International Epidemiology Institute, Rockville, MD

Other Experience and Professional Memberships

1969 - 71	Medical Corpsman, United States Army
1974 -	American Statistical Association
1983 -	International Statistical Institute (elected member)

Honors

1979	Public Health Service Special Achievement Award
1983	Fellow, American Statistical Association
1992	National Institutes of Health Director's Award
1999	Division of Cancer Epidemiology and Genetics Exemplary Service Award
2001	National Institutes of Health Merit Award

C. Contribution to Science

1. I have derived and published a number of statistical methods for a variety of problems arising in biomedical research. These include nonparametric tests for censored survival data, methods for testing for heterogeneity of odds ratios across several strata, a method for combining relative risk estimates from multiple strata or studies, tests incorporating information on historical control tumor rates in animal carcinogenesis bioassays, estimation methods for identifiable contrasts in age-period-cohort analyses of disease rates, and statistical methods for the analysis of in vitro cell survival data from colony forming assays.

    a. Tarone, R.E. & Ware, J. (1977). On distribution-free tests for equality of survival distributions. Biometrika, 64:156-60.
    b. Tarone, R.E. (1982). The use of historical control information in testing for a trend in proportions. Biometrics, 38:215-20.
    c. Tarone, R.E., Scudiero, D.A. & Robbins, J.H. (1983). Statistical methods for in vitro cell survival assays. Mutat Res, 111(1):79-96. PMID: 6621576
    d. Tarone, R.E. & Chu, K.C. (1996). Evaluation of birth cohort patterns in population disease rates. Am J Epidemiol, 143(1):85-91. PMID: 8533751

2. Although ecologic analyses disease rates, either over time or across geographic areas, must be interpreted cautiously, a number of my publications have developed methods for strengthening inferences from such analyses. Application of these methods has provided evidence that breast cancer rates in U.S. women decreased for women born after 1945, that changes in cigarette smoking can be detected in lung cancer rates in early adulthood (20-34 years of age), and that decreases in prostate cancer and breast cancer death rates were partly a result of early detection via PSA testing and mammography screening, respectively.

    a. Tarone, R.E. & Chu, K.C. (1992). Implications of birth cohort patterns in interpreting trends in breast cancer rates. J Natl Cancer Inst, 84(18):1402-10. PMID: 1512791
    b. Grauman, D.J., Tarone, R.E., Devesa, S.S. & Fraumeni, J.F. Jr. (2000). Alternate ranging methods for cancer mortality maps. J Natl Cancer Inst, 92(7):534-43. PMID: 10749908
    c. Jemal, A., Chu, K.C. & Tarone, R.E. (2001). Recent trends in lung cancer mortality in the United States. J Natl Cancer Inst, 93(4):277-83. PMID: 11181774

d. Chu, K.C., Tarone, R.E. & Freeman, H.P. (2003). Trends in prostate cancer mortality among black men and white men in the United States. Cancer, 97(6):1507-16. PMID: 12627516

3. A long-standing interest in the control of the false-positive error rate in medical research has led to several publications, on both the methodologic and the philosophic issues involved in reducing the publication of false-positive results. The publications document the magnitude of the problem and provide guidance on reducing the probability of reporting false-positive findings.

   a. Tarone, R.E. (1990). A modified Bonferroni method for discrete data. Biometrics, 46(2):515-22. PMID: 2364136
   b. Boffetta, P., McLaughlin, J.K., La Vecchia, C., Tarone, R.E., Lipworth, L. & Blot, W.J. (2008). False-positive results in cancer epidemiology: a plea for epistemological modesty. J Natl Cancer Inst, 100(14):988-95. PMC2467434
   c. Ioannidis, J.P.A., Tarone, R. & McLaughlin, J.K. (2011). The false positive to false negative ratio in epidemiologic studies. Epidemiology, 22(4):450-6. PMID: 21490505
   d. McLaughlin JK, Tarone RE. False positives in cancer epidemiology. Cancer Epidemiol Biomarkers Prev 2013;22(1):11-15. PMID: 23118145

4. I have been involved in the design and analysis of numerous cohort studies to evaluate the impact of lifestyle, environmental or occupational risk factors on disease risk. These studies have resulted in numerous publications on a wide variety of both disease endpoints and risk factors.

   a. Alavanja, M.C., Samanic, C., Dosemeci, M., Lubin, J., Tarone, R., Lynch, C.F., Knott, C., Thomas, K., Hoppin, J.A., Barker, J., Coble, J., Sandler, D.P. & Blair, A. (2003). Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. Am J Epidemiol, 157(9):800-14. PMID: 12727674
   b. Sigurdson, A.J., Doody, M.M., Rao, R.S., Freedman, D.M., Alexander, B.H., Hauptmann, M., Mohan, A.K., Yoshinaga, S., Hill, D.R., Tarone, R., Mabuchi, K., Ron, E. & Linet, M.S. (2003). Cancer incidence in the US radiologic technologists health study, 1983-1998. Cancer, 97(12):3080-9. PMID: 12784345
   c. Lipworth, L., Sonderman, J.S., Mumma, M.T., Tarone, R.E., Marano, D.E., Boice, J.D. Jr. & McLaughlin, J.K. (2011). Cancer mortality among aircraft manufacturing workers: an extended follow-up. J Occup Environ Med, 53(9):992-1007. PMID: 21866047
   d. Sonderman, J.S., Munro, H.M., Blot, W.J., Tarone, R.E. & McLaughlin, J.K. (2014). Suicides, accidents, and other external causes of death among blacks and whites in the Southern Community Cohort Study. PLoS One, 9(12):e114852. PMC4259484

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1vOivVFkLq95f/bibliograpahy/48692470/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

2R01 CA092447-10 (Blot, Signorello) 09/30/01 – 08/31/16
NIH/NCI
Southern Community Cohort Study
The major goal of this project is to investigate the causes of racial disparities in the occurrence of cancer in the southern United States.
Role: Co-Investigator

5P50CA098131-12 (Arteaga) 09/17/13 – 08/31/18
NIH/NCI
Spore In Breast Cancer – Project 3 (Identification of Prognostic Factors for Triple Negative Breast Cancer)

Project 3: The proposed two-year study will be supported by the current cycle of the breast cancer SPORE grant, with subsequent replication of findings to be sought within the NBHS and SCCS populations as part of research for the planned renewal of the SPORE grant.
Role: IEI PD/PI

Completed Research Support

5 U01 CA137026-02 (Boice) 08/01/10 - 07/31/15
NIH/NCI
Cancer Mortality among Military Participants at U.S. Nuclear Weapons Tests
To evaluate the risk of radiation-induced cancers and quantify the risk in terms of low-dose radiation received gradually from external exposures and from inhaled or ingested radionuclides in fallout among military participants at aboveground nuclear weapons tests in Nevada and the Pacific testing areas.
Role: Statistician

Chairman SMITH. Thank you, Dr. Tarone.

Dr. Lowit, in your testimony you mentioned that when mice were injected with large doses of glyphosate that some did manifest symptoms of cancer-like conditions but that when the mice were just exposed to glyphosate, there was no effect. There were no symptoms. It seems to me that that's a huge difference. No one is suggesting that humans be injected with large doses of glyphosate. Why is it that IARC doesn't acknowledge the distinction between high doses that are being injected and simple exposure or inhalation, which has not resulted in any cancer-like symptoms? And it seems to me that they are intentionally misleading the American people, and maybe they have some kind of a vendetta against chemical companies, but why or how do you explain the lack of honesty and openness and transparency by IARC?

Dr. LOWIT. So thank you, Chairman Smith, for that question. So I'm sorry if my South Carolina accent comes out. So it's ingest, so I—through the oral route, not inject through the——

Chairman SMITH. Okay. Ingest——

Dr. LOWIT. Ingest through the oral route.

Chairman SMITH. Okay.

Dr. LOWIT. So I apologize for that lack of clarity.

Chairman SMITH. But my——

Dr. LOWIT. So the question is—so I think it's important that—I'm not going to comment on the value of the IARC process. I can tell you that EPA has been fully transparent in our evaluation. Our draft issue paper was reviewed by the Scientific Advisory Panel. In fact, the transcript from that meeting is publicly accessible. We're now looking forward to public comment on our white paper for the cancer.

Chairman SMITH. Any—was that—I didn't understand that. It's just a statement as to why you think they have been less than transparent?

Dr. LOWIT. I think that's—I'm not going to debate the transparency of IARC.

Chairman SMITH. Okay.

Dr. LOWIT. What we have done at EPA whereas in cases where IARC has looked at review articles, we've acquired the raw study reports, so we've been able to look at information. The full study reports for IARC cannot do that.

Chairman SMITH. I'm just curious. When you talked about large doses of ingestion by the mice, how much are you talking about? A large percentage of their body weight or how much were they—did they ingest?

Dr. LOWIT. So in terms of toxicology studies, often studies—and with glyphosate are in the ingestion of hundreds of milligrams per kilogram per day and what we define as the limit dose. Internationally, most regulatory organizations recognize 1,000 milligrams per kilogram per day as international standard for the limit dose. And in most—in many cases, glyphosate studies are actually done at that limit dose——

Chairman SMITH. Okay.

Dr. LOWIT. —which is why we conclude there's very little hazard.

Chairman SMITH. And it's very unlikely that any human would ingest anything near to that equivalent amount?

Dr. LOWIT. Oh, no.

Chairman SMITH. Okay. Dr. Pastoor, you pointed out—and I was going to highlight as well—that I think IARC has found that something like 999 out of 1,000 substances created cancer. Only one was deemed to be probably not cancer-causing. Do you think that their process is flawed, their investigations are flawed, and do you think they have predetermined conclusions they're trying to reach?

Dr. PASTOOR. They may or may not. I can't really comment in particular on glyphosate. I'm not here representing a critique or a defense of glyphosate. But what I would say is that there is a flaw in their scientific process. When you don't take into consideration potency—which, Chairman Smith, you just brought up—is that if a significant portion of a body weight of an animal is being overwhelmed with a particular chemical, whether it's glyphosate or anything else, and you're declaring something to be carcinogenic, that's erroneous science. That's offsetting. That's misinforming the public, and it doesn't serve any process and it's actually more harmful than helpful.

Chairman SMITH. Okay. I agree. And I like that phrase "erroneous science." I'm going to adopt it in this case and maybe in other instances as well.

Dr. Tarone, you wrote a paper in 2016 and you came to the conclusion that IARC's designation of glyphosate was a result of a, quote, "flawed and incomplete evaluation of experimental evidence." What is the general scientific community's response been to that paper? And what was IARC's response?

Dr. TARONE. There's been surprisingly little response actually. I've been amazed.

Chairman SMITH. Okay.

Dr. TARONE. But with regard to IARC, I mean, this paper has gone through an incredible—I mean, it's the weirdest experience I've ever had in 44 years of publishing in peer-reviewed journals. And it's—I mean, I just—really, it's stunning. But IARC did eventually submit a letter to the journal responding to my paper, and I received this in January of 2016. And—no, 2017, I'm sorry, and I responded to their letter. And I assumed that both letters would be published in the journal along with the paper. IARC's letter was not responsive to any of the specific criticisms I raised.

Chairman SMITH. Okay.

Dr. TARONE. They complained about, you know, "Who wrote—who paid you to do this and what role did they play in writing and editing the paper?" They raised technical issues about what constitutes a research study and that this wasn't a research study, but they didn't deal with any of the specifics.

Chairman SMITH. Okay.

Dr. TARONE. And for some reason neither letter was published, and I've never been fully clear about why.

Chairman SMITH. Okay.

Dr. TARONE. I don't know. I can't figure out why that happened.

Chairman SMITH. The point being IARC was not responsive to the substance of your——

Dr. TARONE. Not to the substance, and as I said, nobody has specifically refuted any of the claims that I've made about the exclusion——

Chairman SMITH. Okay.

Dr. TARONE. —of rodent studies that should have been included.

Chairman SMITH. Okay. Thank you, Dr. Tarone. That concludes my time.

And the gentlewoman from Texas, the Ranking Member, Ms. Eddie Bernice Johnson, is recognized for her questions.

Ms. JOHNSON. Thank you very much, Mr. Chairman.

Let me precede my question with this statement. I don't believe any company puts anything on the market that they knowingly know that it harms people. I think it's like the little book Who Moved My Cheese? Sometimes, it's hard to change when you find out what the facts are. And so—and every company that has any respect for itself is going to defend itself when it can.

But I want to ask Dr. Sass. Can you discuss the importance of keeping the development of scientific assessments on chemicals such as glyphosate and other toxic chemicals free from undue influence by industries or others? An example is what are the consequences if chemical risk assessments are driven by industry, and more importantly, if industry-sponsored chemical assessments are given the same weight and authority as truly independent scientific studies?

Dr. SASS. Thank you. I would like to comment on that, and I think that glyphosate is a perfect example of where that's happening because we can really see the difference in when you have an IARC assessment, which is a public health agency of the World Health Organization that links it to some level of carcinogenicity probably carcinogenic in humans. And then you have—based—including on Monsanto's studies and other studies supported by the registrant, and then you have agencies that are calling it not likely carcinogenic, EPA, which is a regulatory agency.

And I want to talk about some of those differences because the impact on public health is severe potentially. First of all, Mr. Smith's comment about the doses that there—that they were—that—well, what Anna suggested what—that they were at high doses, I want to talk about the limit dose for a quick second because it has a toxicological definition, and these studies did not exceed it. So an arbitrary 1,000 mgs per kg per day was not what IARC used. They used a toxicological definition. And these studies didn't exceed it at the high dose, so they should have been included.

Dr. Pastoor's statement referencing 16th century Paracelsus medicine, to then criticize IARC being half-a-century behind is just ridiculous. Paracelsus did say the dose makes the poison, and there's a lot of truth in that, but that's not the whole truth. The truth is that what's being missed here is considering vulnerable populations potentially. We need to protect the EPA, and regulatory agencies need to be able to protect the whole population, so—including pregnant women and children, elders, people with preexisting diseases and chronic diseases, people that are high-end users or highly exposed in—as well as the Keith Richards of the world. We need to bracket all of those people and protect them.

And, Dr. Tarone, I do have some answers for the exclusion of those rodent data, but primarily, they weren't available to IARC and IARC relies on public data. The data sets were huge. They

were hidden in appendices. The IARC only had it 30 days in advance. But in addition, had IARC had those data, it would have likely come up with an even stronger link to cancer because there was even more tumors than Dr. Greim, the author of that review article, had revealed. Those have all come to light now through EFSA, so the European Food Safety Authority. They've been reanalyzed separately by non-industry scientists. And we now know that there's data that also show tumors in the animals linking to malignant lymphomas and hemangiosarcomas, which, Dr. Tarone, I think you didn't analyze. I think you may have focused on the kidney tumors only.

So, in addition, Dr. Greim, the author of that paper, is not only of questionable scientific integrity for failing to report all those tumors but also ethical potential as well. He's the main author in some diesel emissions studies that put monkeys into chambers being reported in the New York Times right now. So——

Dr. TARONE. Can I respond?

Mr. LUCAS. [Presiding] Dr. Tarone, would that be appropriate for the Ranking Member?

Ms. JOHNSON. Yes.

Mr. LUCAS. It's her time. Please respond.

Dr. TARONE. Well, it's totally incorrect to say that IARC should not have acquired those data because if—and I want to say something about the Greim paper. I relied on the Greim paper only for the data. They included supplemental tables with that review paper that included the underlying basic tables of tumor rates from every study that they reviewed. So I was not relying on Greim, et al., for their conclusion in any sense. I was only relying on it for the data.

Dr. SASS. Well, the summary tables can be used, and EPA had those data for years, probably decades and didn't ask for the underlying data, so to blame IARC for not having gotten it in 30 days——

Mr. LUCAS. The gentlelady's time is expired.

The Chair would note to my colleagues we now have a series of three votes underway that, once the votes are over, we will return and continue this hearing. And with that, the hearing will stand in recess subject to the call of the Chair.

[Recess.]

Mr. LUCAS. This full Committee hearing of the Science Committee is reconvened. I will return to regular order, and I believe I was the next one in line to ask questions, so I'll recognize myself for five minutes.

And with that, I turn to Mr. Tarone. Would you care to expand and explain a little bit more about your analysis of the Monograph 112 program and all those issues?

Dr. TARONE. Yes. I specifically want to answer a couple of issues that Dr. Sass raised. First with regard to hemangiosarcomas, I did consider hemangiosarcomas, and it in fact is one of the examples in which IARC excluded exculpatory data. In the second mouse study where they did not discuss renal tumors, they emphasized the finding in hemangiosarcomas that Dr. Sass referred to. And there were four hemangiosarcomas in the highest dose group, and that was all—none in the other three groups.

But in the first mouse study, the one where they spent three paragraphs on renal tumors, they didn't mention hemangiosarcomas, so it's the same thing that happened with renal tumors. So—and it turns out that in that study there was one hemangioma in the low-dose group and one hemangiosarcoma in the mid-dose group and none in the highest-dose group. And by the way, that highest-dose group, glyphosate was three percent of the diet that they ate for every day for two years. It's an incredibly high dose. So you would have—if what they saw in the second study was a true high dose effect, you would have expected to see it in the first study. And—but again that was not even mentioned in the IARC Monograph.

And Dr. Sass also raised the issue of the accuracy of the tumor rates that I got from the supplemental tables in the Critical Reviews in Toxicology paper. And in fact, as I pointed out at the end of my comments, everything in my paper has in fact been substantiated by things published since, including comments submitted to the EPA glyphosate SAP by Chris Portier, who was the scientific expert for the IARC working group. And his comments were presenting his statistical analysis of all of the rodent studies that EPA was considering. And they considered many more than IARC, but they also considered all the studies that IARC relied upon.

If you look at his tables upon which his analysis was based, in every case in which I indicated in my paper that IARC had excluded tumor rates, those tumor rates are in those tables in the comments he submitted to EPA. They were included in his EPA analysis, which is an admission that they should have been included in the IARC analysis. Moreover, they were exactly the rates that I reported that I got from the supplementary tables in the Greim, et al., review. So certainly, Christopher Portier now thinks that those rates are okay.

Mr. LUCAS. Thank you, Doctor.

Dr. Pastoor, could you visit with us for a moment about the ways in which the current Monograph Programme classification system on carcinogenicity might be outdated? Expand on that, please.

Dr. PASTOOR. Well, the primary reason that it's outdated and outmoded and needs to either be scrapped or considerably revised is because they stick with a hazard classification system. All they do is declare something as being carcinogenic or not. Modern 21st-century risk-assessment-oriented regulatory programs such as what Dr. Lowit has described with the United States EPA uses that risk-based system to put hazard in context of risk: how much would cause that effect; what is the potency of that particular chemical? IARC was created over—nearly 50 years ago, and they really haven't progressed beyond the point of only classifying things by its carcinogenicity but not putting it in the context of risk.

Mr. LUCAS. Thank you. I think with that now I will yield back and turn to—I think in the next order would be the gentleman Mr. Tonko for five minutes for questions.

Mr. TONKO. Thank you, Mr. Chair. And welcome, everyone.

This hearing has been framed around the need to uphold scientific integrity standards in publicly funded research. If that is a serious concern for this Committee, then I implore us to take up

H.R. 1358, which I've authored, the Scientific Integrity Act. This Congress has a duty assigned directly to this Committee to ensure that public or publicly funded science is conducted, reviewed, communicated to the public and incorporated into policymaking transparently and free from distorting political, ideological, financial, or other undue influence.

Public science informs national policy on everything from pesticides to power grids. Our nation's cities and States need credible information to prepare for climate change. Our families deserve to know if unsafe chemicals are being sprayed on their food, dumped in their water, or added into the products they buy. As representatives, we need to reach conclusions on these high-stakes questions based on rigorous independent scientific facts, not predetermined opinions. We have a duty to ensure that political interference of the scientific process and attacks on the work of federal scientists do not get in the way of our responsibility to safeguard our public health and our national security.

The rules and norms of our public science are standards that have made America a leading light in the global scientific community for decades. We have seen those standards being actively and deliberately eroded over the past year. Scientists should always be held to the highest ethical and professional standards. In return, it is our job to uphold standards that ensure scientists are not impugned for reporting their impartial findings.

The Scientific Integrity Act restores our baseline for scientific independence by requiring every federal agency that funds or conducts scientific research to establish clear scientific integrity standards and set basic requirements for how the agency will adhere to those principles.

Science is not about getting the results you want. Scientific integrity is about ensuring a process and atmosphere in which the science leads us to real, unvarnished results. The issue we should be focused on is whether glyphosate is safe, and finding the answer to this question is too important for us to let this be a partisan issue. These are chemicals that people have in their homes. This is on the food our children eat. We should be able to trust that the science we rely upon to make public health decisions is not being distorted or manipulated.

While the tactics used by industry to influence science may have dramatic negative consequences on the independence and credibility of scientific review boards or advisory panels, the real victims of this kind of designed ignorance are everyday people. Without credible science to determine safe levels of exposure, millions of people around our country will be at risk.

Dr. Sass, how do science agencies like IARC function in order to protect the public health?

Dr. SASS. Thank you. IARC and other public health institutes put out very credible information about the potential hazards of chemicals and other substances. After reviewing all the data, IARC, for the glyphosate assessment, brought experts from all over the world from multiple different countries. They have different areas of expertise. They all come together as a working group. They—all of the discussion of all of the data—publicly available data is done in front of everybody. There's a plenary session where

people get to also discuss what the different subject matter experts have come up with in their area.

And the result of these very credible, transparent, publicly generated hazard assessments is to then support potentially risk assessments but also to support nonregulatory or even non-risk-related decisions that can be made, for example, not only by government regulatory agencies but also by forward-thinking companies and businesses looking to work with safer or less toxic or less hazardous chemicals are starting to replace it in their products. There's retailers that care about this. There's a whole area of green chemistry that's very interested in this, and of course medical professionals, occupational health experts, all of these people care about understanding the hazard of materials even if they don't—haven't—there hasn't been a full risk assessment to understand potency and dose-response and the other things that come afterwards.

Mr. TONKO. And why is it important that independent bodies review chemicals for potential exposure risks?

Dr. SASS. Well, all the available data should be looked at. I believe that, but that's also what the agencies believe and it's what IARC did. Many of the studies that relied on were supported or sponsored by the regulated industry, and that's fine. That's normal. That happens. But there are systematic review procedures for reviewing and evaluating confidence in those studies on a lot of different parameters. And if all of those different parameters aren't available to do a proper robust review and assessment of the confidence, then it's more difficult.

And so we should—instead of a priori making decisions about what data is in or out of the pot, it should all be looked at and reviewed, which is what IARC did.

Mr. TONKO. Thank you. Mr. Chair, I have several documents which I would like included in the record, including the Monsanto battle plan, laying out their preliminary attack on IARC, the IARC preamble defining the roles of working group members and participants, a list of participants from the IARC glyphosate Monograph, commentaries by several scientists on the strength of the IARC glyphosate evaluation, the FIFRA Science Advisory Panel report from December 2016 concluding that EPA did not follow its own guidelines for carcinogen risk assessment in evaluating glyphosate, and a letter from the United Nations special rapporteur stressing how essential the work of the National Institute of Environmental Health Science is to protecting human rights.

Mr. LUCAS. Without objection.

[The information appears in Appendix II]

Mr. LUCAS. And the gentleman's time is expired.

Mr. TONKO. Thank you, Mr. Chair.

Mr. LUCAS. The Chair now turns to the gentleman from Texas, Mr. Babin, for five minutes.

Mr. BABIN. Thank you, Mr. Chairman. I appreciate it. And thank you to the witnesses for being here.

Dr. Anna Lowit, if you don't mind, the EPA's risk assessment process explicitly includes opportunities for experts who did not contribute to the assessment to review and comment on a draft of the scientific analysis, is that correct?

Dr. LOWIT. That's correct.

Mr. BABIN. Okay. The EPA's risk assessments like the one on glyphosate developed by the Office of Pesticide Programs are also subjected to rigorous independent peer review. Is that correct?

Dr. LOWIT. So EPA's cancer evaluation has been subject to the FIFRA Scientific Advisory Panel. That's true.

Mr. BABIN. Okay. As I understand it, the National Academies, which is similar to IARC, develops reports by expert panels and has outside peer reviews and evaluate each and every report to ensure scientific accuracy. However, unlike EPA and NAS, IARC Monographs do not employ any independent outside peer reviews. Instead an IARC Monograph working group collaborates behind closed doors to select studies, analyze data, and reach conclusions. So without any public engagement or independent scientific peer review, the working group acts hand-in-hand with IARC staff as judges, juries, and executioners. Clearly, these IARC procedures fall well short of meeting 21st-century standards for transparency and scientific credibility. And I would like to know if you agree with that.

Dr. LOWIT. So what I can answer is EPA's transparent approach, that our cancer evaluation was reviewed by the FIFRA—excuse me—Scientific Advisory Panel. The transcript from that meeting is actually publicly available. Our document is now available for public—will be open for public comment. It's been released on our docket, and so our process is quite transparent.

Mr. BABIN. Do any of the other witnesses agree with that statement? Now, let me repeat it. Without any public engagement or independent scientific peer review, the working group acts hand-in-hand with IARC staff as judge, jury, and executioner. IARC procedures fall well short of meeting 21st-century standards of transparency and scientific credibility. Would you other three agree with that? Dr. Pastoor?

Dr. PASTOOR. Yes, I would generally agree with that. I think IARC needs to be brought up to the standards of transparency that is exhibited by the United States EPA.

Mr. BABIN. Okay. Thank you. Dr. Sass?

Dr. SASS. I disagree because the meetings are open at IARC. Observers are invited. Monsanto was present. Other regulatory interests can also be present, so they're public in that sense that anybody who wants to be present can.

And I also want to point out that EPA's Scientific Advisory Panel review of the "not likely" classification didn't agree with that classification.

Mr. BABIN. Dr. Tarone?

Dr. TARONE. Yes, I wouldn't agree completely with the statement, but what I believe is that right now the Monograph Programme appears to think they have—they're accountable to no one, so I do need—I do think that they need to be brought in and show some accountability to somebody. The fact that they did what they did with the glyphosate working group, I mean, that should not happen. The exclusion of exculpatory rodent studies many times, there's just absolutely no way that should happen, so I would just like to see more accountability.

Mr. BABIN. Absolutely. Okay. Is it scientifically proper to redo a peer-reviewed study's data analysis with a different statistical analysis than was originally used for the study and then use this reanalysis without first ensuring that it undergoes robust independent peer review? Dr. Lowit?

Dr. LOWIT. So the first half of your question is about reevaluating scientific data, and I would agree with that statement, that that is actually part of an independent evaluation of those data is often to reevaluate the statistics. And EPA has actually in fact redone some of the statistics for the glyphosate cancer evaluation.

Mr. BABIN. Okay.

Dr. LOWIT. The second part of your question is about peer review. Peer review is important, and in the case of the cancer evaluation, we did have our statistics evaluated as part of the Scientific Advisory Panel.

Mr. BABIN. Thank you very much.

And Dr. Tarone, could I ask you that question?

Dr. TARONE. I have no problem with people doing independent different types of statistical analysis, although, you know, it does have to be peer-reviewed because sometimes you can pull tricks, you know, get the result you want. I mean, there's a lot of data dredging, p-hacking it's sometimes called that goes on. So peer review is essential, though, when you're evaluating multiple different types of statistical analyses.

Mr. BABIN. Absolutely. And my time is expired, Mr. Chairman. Thank you.

Mr. LUCAS. The gentleman's time is indeed expired.

The Chair now recognizes the gentleman from California, Mr. McNerney, for five minutes.

Mr. MCNERNEY. Well, thank you, Mr. Chairman, and I thank the witnesses.

Dr. Sass, have you ever heard the term chemical trespass?

Dr. SASS. Yes, I have. It's when you find a chemical in—usually an industrial chemical not naturally occurring in your body that you didn't give permission for it to be there.

Mr. MCNERNEY. So do you think that term applies to our hearing this morning?

Dr. SASS. I do and not just to glyphosate but certainly glyphosate. I mean, my guess is that there's not many people in the United States that are unexposed to glyphosate because of how widespread its use is. It's almost 300 million pounds annually, and every—in agriculture, and every one of those pounds are put out onto our fields, our food supplies, get into our rivers and streams and drinking water, sources of drinking water.

Mr. MCNERNEY. Well, some studies claim that human exposure to glyphosate has increased by 500 percent in 25 years. What kind of risks are associated with this kind of proliferation of exposure?

Dr. SASS. So we don't understand the risks, and that's one of the things that I think that EPA, you know, should be doing is taking on a proper risk assessment after a proper hazard assessment where they acknowledge that there's a carcinogenic risk and then do a proper slope factor. There's proper mechanisms to do that. But the increase is being shown in people's urine, and we're—so we know that for sure. And that's why I think that there's probably

no unexposed population, that we're exposed on a daily or routine basis.

Mr. MCNERNEY. Is it also present in mother's milk?

Dr. SASS. It is. It's widespread and it's—because it's water-soluble, it is present in all those fluids.

Mr. MCNERNEY. So even the youngest members of our society are being highly exposed to this chemical?

Dr. SASS. It is, and that's what brings up this dose poison fallacy, this 16th-century, you know, dose poison thing is that although it is true that, you know, we can't be poisoned if we don't dose ourselves, that's true if we're not exposed, it's also true that there's vulnerable populations. And how each of us react to those are differently—are very different so that a pregnant woman or a reproductive-age man or woman might be much more vulnerable to certain effects, reproductive effects, for example. Or if we're exposed to a carcinogen when we're young while our tissues are developing and growing and taking in—as they take in nutrients taking in those toxic chemicals, that could be a much more damaging time. And then the health impacts can be hardwired into the system, whereas, for example, if I'm exposed to a dose of lead, I have probably no reaction to the same dose of lead that could cause irreparable permanent harm in a developing child.

Mr. MCNERNEY. Thank you. Some folks are critical of the World Health Organization, and other folks are critical of the EPA's risk assessment. Can you explain how those assessments differ?

Dr. SASS. Sure. I mean, primarily, for some reason the—a lot of the criticism which I think isn't fair is on whether IARC considered some studies that actually weren't available to it at the time. And my only answer is they've got to look at publicly available data. That's a rule they made in advance. Industry knows that in advance. If it wants to get those studies to them in advance, they could have done so. The chemicals are nominated. They have plenty of time to do that if they want to. The—fundamentally, though, some of the ways they're looking at it are, for example, EPA is not looking at the high-dose tumors. The animals have tumors at high doses, but there's no other indication of toxicity to the animals at those doses, so there's no real reason not to consider those tumor effects to be real or valid. Like I say, instead of using an arbitrary number, to actually use toxicological ways of assessing whether those doses should be considered. So that's one important thing is to consider those doses.

The other thing is to—when you look at it, does there have to be a clear dose-response? EPA is throwing out data if there wasn't an—increasing tumors with increasing doses in every study, for example, and that's not appropriate because many reasons. One is that we don't—we—animals react differently, so you have to use your statistics to do that. EPA has used a certain statistical test. I argue some different statistical tests. The EPA cancer guideline says EPA should use whichever one provides the most health-protective outcome.

Mr. MCNERNEY. Thank you. Mr. Chairman, I have an article published this morning by the POLITICO describing the European Parliament's decision to create a special committee to investigate potential failings in the EU system for reviewing pesticides such as

glyphosate. The committee will look at whether the European Commission followed appropriate regulations and avoided conflict of interest when it decided to renew the license for another five years. I would like to introduce this story for the record.

Mr. LUCAS. Without objection.

[The information appears in Appendix II]

Mr. MCNERNEY. Thank you. And I yield back.

Mr. LUCAS. The gentleman yields back.

The Chair now turns to the gentleman from Arizona, Mr. Biggs, for five minutes.

Mr. BIGGS. Thank you, Mr. Chairman. I appreciate all the witnesses being here today.

And I'll start with Dr. Pastoor. You touched on your testimony, but I'd like you to expand if you would on additional examples besides glyphosate that were perhaps classified in a misleading way by IARC.

Dr. PASTOOR. Well, you know, the—what I was trying to get at in my testimony is that things like caffeic acid, arachidonic, these are chemicals that we find in our diet naturally. And by just simply declaring them to be carcinogenic is not helpful to the American public. They need some context with that. And my criticism of IARC is they don't provide that kind of context.

Mr. BIGGS. And so—still with you, Dr. Pastoor. The—you've described that as a misleading way to classify these potential hazards, and you've advocated for a risk assessment as opposed to hazard assessment. And I thought—and I don't want to misinterpret, but I thought I heard Dr. Sass refer to this kind of dose-level-type thing as being 16th-century—a 16th-century approach. Do you want to rebut that?

Dr. PASTOOR. I definitely do. I think it's absolutely as true as it was in the 16th century. And the best example I can give is the one I gave earlier on aspirin is that the dose makes the poison. It's just as good at a low—in fact, the actual statement by Paracelsus in the 16th century was that the difference between a medicine and a poison is the dose. Aspirin is a good example of that. Two tablets will relieve your headache. A bottle full of it will kill you. That's the dose makes the poison. It's as true today as it was back in the 16th century and long before that.

It's important to realize that because in some of these studies that are being cited here, whether it's glyphosate or otherwise, these are animals that have been packed full of some of these chemicals for a lifetime. And I'm probably one of the few people in this room that's actually conducted those very studies. And they go on for two years. They're given to animals at the maximum dose that they can get, and even though Dr. Sass refers to the animals not having any adverse effects, they're getting as much as three percent of their diet of that particular chemical. That's outrageous. It's something that no human would ever see, and the results are meaningless and not useful in the context of risk assessment and communication of that information to the American public.

Mr. BIGGS. And, Dr. Lowit, I want to just ask you quickly—I don't want my time to totally expire here, but the EPA sets tolerance levels for residue of glyphosate, and you've talked about the actual exposure to chemicals, not simply ask if a chemical could

ever be a carcinogen. And EPA takes a different approach than IARC. Why does EPA take the approach it takes?

Dr. LOWIT. So EPA is a risk-based organization, which is consistent with federal statute and largely for the reasons that Dr. Pastoor just explained, that it is important to assess not only the hazard but the exposure of a particular chemical. And it is at that intersection of hazard and exposure where we understand risk. And our job is to understand risk to the American people.

Mr. BIGGS. And I'm going to close out here by just covering a couple of statements. We've heard one of—previous questioners—when he was giving his statement prior to asking question says we don't want the, quote, "science we rely on is not distorted or manipulated," close quote. He didn't want that—our science to be distorted or manipulated. And additionally, the idea of independent bodies look at this—we want independent bodies to be looking at these types of chemicals and potential hazards to us.

But what if there is a conflict of interest? And I'm going to introduce—Mr. Chairman, without objection, I'd like to introduce a letter written in 2002, 15 years ago or so, by one of our panelists Dr. Sass where she noted that IARC's working groups are made behind closed doors, no transcripts of the deliberations are publicly available. Most significant, the voting of the working group members is never made public. This lack of transparency and lack of public oversight makes peer review impossible.

In the letter that we received back from Dr. Wild, at this point there's no indication that any of the processes have changed in the last 16 years, and thus, I'm very concerned about IARC and their processes in this issuing these monologues and—or, excuse me, Monographs. And with that, Mr. Chairman, I introduce that letter.

Mr. LUCAS. Without objection.

[The information appears in Appendix II]

Mr. LUCAS. The gentleman yields back the balance of his time?

Mr. BIGGS. I do, thank you.

Mr. LUCAS. And the gentleman—or the Chair now turns to the gentleman from Colorado, Mr. Perlmutter, for five minutes.

Mr. PERLMUTTER. Thanks, Mr. Chair.

And, Dr. Sass, I'm just going to ask you a pretty open-ended question. I've been able to sit through some of this testimony. Obviously, there's some very different approaches and opinions just listening to the last 15 minutes. So are there some issues that you think really need to be brought out in more detail? And if so, what are they?

Dr. SASS. Thank you. With regards to the IARC 2002 letter, which I point out is quite a long time ago, at that time that was three Chiefs of the Monograph Programme ago, and at that point we were concerned that they were allowing people with financial conflicted—conflicts of interest to be part of the voting working group. And since then, they have established conflict guidelines that are world-renowned. They're very well-respected, they're very well-implemented, and those kinds of things are well-tracked and well-reported, and so there's a comfort level. And so those issues are not—have not been relevant for a long time.

As far as the differences between the two assessments, it really is a difference between whether you're doing the hazard only and

then going to risk assessment or whether you're conflating them together. And IARC is a hazard only. They just say whether there's an association with cancer or not, and then if you want to do a risk assessment or deregulatory actions, those things will come differently.

I do not understand why the EPA is not going through its process to develop a slope factor and a dose response and a potency estimate and instead just doing—calling it not likely, dismissing quite a lot of evidence of tumors.

And you're wrong about Dr. Portier. He's actually updated his tables, and there's quite a few tumors there, which I would be happy to submit or have someone else—have him submit to the record that have been disregarded.

What I don't understand is why the Pesticide Office is working with the EPA's Office of Chemical Safety and Pollution Prevention, which is the science policy office, which is headed by Dr. Nancy Beck, a former chemical industry lobbyist, to implement a systematic review procedure for its data that was reviewed by the National Academies in 2007 and was called fundamentally flawed, something the National Academies have never called anything before, instead of, for example, working with the EPA IRIS program, the Integrated Risk Information System program, which is in the Office of Research and Development, the science office of EPA, and which could work with them to develop potency estimates and slope factors and then a risk assessment at that point.

Mr. PERLMUTTER. So—let me see. So the real difference here is one is just sort of purely data-driven in determining, you know, whether or not there's potential carcinogens, and then there's kind of a political and, you know, policy decision being made as to, okay, it's risky, it's not, the dose is okay, the dose is not okay, but it's problematic to begin with, but we've looked at it on behalf of the EPA and the country and say, you know, this is okay, but there's a problem. Is that—am I off?

Dr. SASS. No, you are spot on.

Mr. PERLMUTTER. Okay. Well, then with that, I'm going to yield back.

Mr. LUCAS. Before the gentleman yields back, would he yield to the doctor from the EPA for a comment?

Mr. PERLMUTTER. Sure. Which—yes.

Mr. LUCAS. Dr. Lowit.

Dr. LOWIT. Thank you for that. So I just think it's important that we make sure the record is accurate. The Office of Pesticide Program is actually part of the Office of Chemical Safety and Pollution Prevention. And in fact Dr. Sass' comments about systematic review and the IRIS program are inaccurate. The IRIS program, as publicly discussed in many venues in the last year, is actually moving to a systematic review which is the recommendations of the National Academies of Sciences. So EPA's evaluation is consistent with the National Academies.

Mr. PERLMUTTER. Dr. Sass, do you have a comment on that?

Dr. SASS. Yes, there's two different systematic reviews happening within EPA and parallel. One is being developed by Dr. Nancy Beck, a former ACC American Chemistry Council lobbyist until very recently, and one is being developed by the scientist within

the IRIS program. The IRIS program, it doesn't prioritize or preferentially treat industry-supplied data, whereas the other systematic review does. For example, guideline studies—GLP it's called, good laboratory practices, which were developed for industry studies specifically to stop them from lying and cheating about their data. If you apply systematic review properly, you would look at all the data with the same rules.

Mr. LUCAS. The gentleman's time is expired.

Mr. PERLMUTTER. My time is expired. I yield back to the Chair.

Mr. LUCAS. And on that note, the Chair is going to turn to the gentleman from Louisiana, Mr. Higgins, for five minutes.

Mr. HIGGINS. Thank you, Mr. Chairman. I thank the panelists for appearing before us today.

We have certainly challenging issues in front of us regarding what's real and what's not. We all want to protect the American people from unnecessary harm, but we also want to move forward with sound science as we do so. So this is a bipartisan effort, and I'm quite sure that the scientists before us and the experts that have testified before us and have met with us in our offices agree that we have a common goal here. The American farmer feeds the world.

And the studies that I've read, including EPA reports and various other research documents, use verbiage like "most likely" and "probable" and "potentially increased risk" regarding the primary chemical within Roundup. It's a herbicide used to increase crop yield.

So I clearly recall a few years ago the rumor that plastic bottles cause cancer. It was widespread. Now, we all drink from plastic bottles. I've never seen a colleague eat the bottle.

So the usage of Roundup in reality on farms across America and in households is used very carefully because it's very expensive. They use computerized dispersion on large farm machinery to carefully disperse the stuff. Protective clothing is worn.

So I would say that a hungry child that the American farmer feeds across the world by the compassion and generosity of our nation, Mr. Chairman, a hungry child is concerned about the—overcoming that hunger at that moment with food provided by the American farmer, as opposed to most likely, probable, or potentially increased risk of cancer sometime down the line.

So I have a question. You said something, Dr. Lowit, very interesting earlier. You stated that EPA conducted its assessment of glyphosate with conservative risk assumption. Can you please clarify for us what that means? What is a conservative risk assumption?

Dr. LOWIT. So as a measure to be resource efficient in our risk assessment process, we use a tiering process when we evaluate exposure. Our tier 1 assessments use high-end estimates that are health protective and often even compound those assumptions together. And in the case of glyphosate we've done a health protective tier 1 level for—in most cases—assessment that uses health protective conservative assumptions and came to the conclusion, despite those conservative assumptions, that there's no risk to humans, including infants and children.

Mr. HIGGINS. Would you recommend changes to the IARC to make this program—in this program to ensure transparency and reliable reporting to the public that you're attempting to inform? Is there some improvement or streamlining of the scientific process where data can be shared amongst perhaps conflicting conclusions by various scientists, including scientists from other—from organizations from other nations? Can there be more transparency and inclusion of scientific data so that we can come to a conclusion? Because, you know, the loss of Roundup would definitely hurt the production of crop yield across the world, and there'd be an immediate impact felt worldwide. So do you have suggestions on how to improve the process so we can arrive at the truth ultimately?

Dr. LOWIT. So EPA is not bound by our IARC conclusions, as noted in my testimony. We've come to the conclusion that glyphosate is not likely carcinogenic to humans, and that's similar to many other nations in the world, including our Canadian colleagues and the European Food Safety——

Mr. HIGGINS. European colleagues. I concur.

Dr. Sass, could you add to that?

Dr. SASS. Well, the European assessment is being investigated because it's been shown that they took the first draft from Monsanto and they barely redlined it. So I don't think that should be held up as the high bar.

And as far as transparency and the use of glyphosate, I just think a proper risk assessment should be done. And what's happening here is that the EPA is doing the hazard assessment calling it not likely without doing the slope factor and the risk assessment I'm guessing because it favor Monsanto's interest for selling it abroad.

Mr. HIGGINS. Do you recommend that Roundup be pulled from the market?

Dr. SASS. No, that has not been our recommendation.

Mr. HIGGINS. Thank you. Mr. Chairman, I yield back.

Mr. LUCAS. The gentleman yields back.

The Chair now recognizes my neighbor from the great State of Kansas, Dr. Marshall, for five minutes.

Mr. MARSHALL. Well, thank you, Chairman. And I guess I would start by—you had a standing joke with my pastor, and every week he would ask me, "Does coffee cause cancer this week, Doc?" And I would say, "Well, I hope not" because I usually had a cup of coffee in my hands. So I just continue to be amazed. I'm reading this and I see that IARC, once upon a time, actually said it was a carcinogen, so that shocks me.

I'm also a little bit surprised to see that the United States has given $48 million to IARC, which is located in Lyon, France, a beautiful place by accounts of all the paintings I've seen of that area, but I'm not sure why we're spending American dollars over there.

You know, to go to my question, I'll start with Dr. Pastoor, the first one. Obviously, there's a big difference between hazard and risk, and on its webpage, IARC contends that it does not make a judgment about risk. So IARC says it does not make a judgment about risk. However, on the front page of its Monograph, it states that it evaluates carcinogenic risk to humans. This seems really

misleading. I'm a biochemist. I'm a physician. You can go down the dirt here a little bit if you want to, but if it's not saying—talking about making judgment regarding to risk, saying something is carcinogenic is exactly declaring it's a risk. Can you help me understand this better?

Dr. PASTOOR. Representative Marshall, thank you for that question because that's core to the testimony that I'm giving today, and that's that the difference between the word hazard and risk is absolutely crucially important because if a patient comes to you and says, "Well, what should I do about caffeic acid?" or caffeine or whatever they're asking you about, you have to put that in context, minimize your exposure or avoid it altogether, whatever it is.

What IARC does is stops with half a loaf, half of the description. They're just saying it's carcinogenic and leaves it at that point. It is not a risk assessment. It's simply a hazard assessment. That's not useful. It's actually injurious. It's also I think irresponsible, and I think it's harmful to the American public.

Mr. MARSHALL. And one of our jobs here in Congress is to prioritize the dollars we do have on research. And in Kansas we have big issues with the sugarcane aphid, with the wheat mosaic virus. I mean, to me, prioritizing monies for those would seem to be—take precedent over this.

I'll go to Dr. Lowit with my next question. I think just to hammer this point home, explain to me the EPA—so I'm new to Congress. How does the EPA make its assessment? Is it hazards only? When you determine what chemicals are safe or not, do you use just the hazard assessment or how do you do it?

Dr. LOWIT. So, consistent with federal statute, EPA does risk assessments, so we evaluate both the hazard and the exposure and then evaluate them together.

Mr. MARSHALL. Does that often lead to a—are there examples of some chemicals that are a hazard only and—as opposed to a risk as well?

Dr. LOWIT. As a general rule, no. EPA does risk assessment, not hazard assessment.

Mr. MARSHALL. Okay. Thank you. I yield back.

Mr. LUCAS. The gentleman yields back. I believe everyone's had an opportunity for questions.

Does the Ranking Member have any concluding comments?

Ms. JOHNSON. I don't. Thank you.

Mr. LUCAS. The Ranking Member does not.

The Chair simply wishes to thank our panel for being here and to express our appreciation for the insights gained today. Obviously, this is a subject matter that we will continue to delve into with great depth.

And in particular to our fellow public official from the EPA, I appreciate the challenges you're caught between.

With that, the record will remain open for two weeks for additional written comments and written questions from the Members.

This hearing is adjourned.

[Whereupon, at 12:32 p.m., the Committee was adjourned.]

Appendix I

Answers to Post-Hearing Questions

ANSWERS TO POST-HEARING QUESTIONS

Responses by Dr. Anna Lowit

HOUSE COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY

"In Defense of Scientific Integrity: Examining the IARC Monograph Programme and Glyphosate Review"

Dr. Anna Lowit, Senior Science Advisor, Office of Pesticide Programs, U.S. Environmental Protection Agency

Questions submitted by Rep. Lamar Smith, Chairman, Committee on Science, Space, and Technology

Dr. Sass noted the importance of EPA protecting all populations from health risks posed by chemicals, implying that EPA does not do this.

1. ***Does EPA consider risks to sensitive subpopulations, including children, when it conducts pesticide risk assessments and determines allowable exposures?***

EPA conducts risk assessments prior to establishing tolerances (maximum residue limits) for pesticide residues on food. In conducting these assessments, as required by the Food Quality Protection Act (FQPA), EPA considers the special susceptibility of children to pesticides by using an additional tenfold (10X) safety factor when setting and reassessing tolerances unless adequate data are available to support a different factor. Based on the data requirements in 40 CFR Part 158, food use pesticides typically have toxicology studies to evaluate effects in pregnant animals and their fetuses and young rats up through adulthood. In the specific case of glyphosate, EPA has seven such toxicology studies. In addition, as standard practice in deriving regulatory values, EPA applies a tenfold factor to account for human variability, including potentially sensitive populations.

Responses by Dr. Timothy Pastoor

HOUSE COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY

"In Defense of Scientific Integrity: Examining the IARC Monograph Programme and Glyphosate Review"

Dr. Timothy Pastoor, CEO, Pastoor Science Communications

Questions submitted by Rep. Lamar Smith, Chairman, Committee on Science, Space, and Technology

In 2003, Dr. Sass stated that "all deliberations of the IARC working group are made 'behind closed doors,' and that no transcripts of the deliberations are publicly available. Most significant, the voting of the working group members is never made public. This lack of transparency, and lack of public oversight makes peer-review impossible." Dr. Sass explained that the statement was made many years ago, and she no longer held those criticisms after being invited to a Monograph Programme meeting.

1. ***Has the IARC Monograph Programme changed its practices since 2003 in a way that makes the quoted statement no longer applicable?***

The IARC Monograph Programme[1] has not changed in any substantive way that would make their process any more transparent. In fact, modest changes since 2003 have done more to ensconce their practices and have made the deliberation table smaller and, in effect, moved the table to a darker room. Along with the scientific shortcomings pointed out in a paper[2] that I co-authored with nine other scientists, Dr. Sass's criticisms of the Monograph Programme's closed-door policies, including lack of transcripts and voting records as well as public oversight was true in 2003 and is still true today.

Observing IARC's working practices up close should have verified that the Programme is actually designed to be closed. Whether or not this is deemed to be an acceptable practice, the Programme has been diligent in clearly describing procedures that carefully selects what the Programme considers acceptable meeting participants, shields them from data and communication not provided by the Programme, and keeps deliberations closely guarded. This process is part of the Programme's Preamble and has been reconsidered and reaffirmed since 2003.

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[1] My comments are related to IARC's Monograph Programme and do not necessarily refer to IARC on the whole. I will refer to the IARC Monograph Programme as either "the Monograph Programme" or "the Programme".

[2] Boobis, A.R., Cohen, S., Dellarco, V., Doe, J.E., Fenner-Crisp, P.A., Moretto, A., Pastoor, T.P., Schoeny, R., Seed, J., Wolf, D.C., Classification schemes for carcinogenicity based on hazard-identification have become outmoded and serve neither science nor society, Regulatory Toxicology and Pharmacology (2016), http://dx.doi.org/10.1016/j.yrtph.2016.10.014

Central to Dr. Sass's 2003 criticism is peer review, which means that the output of the Working Group should be reviewed by scientists outside of the Programme. Peer review is fundamental in scientific deliberations; however, the Programme does not solicit or consider review of its conclusions by the public even though Advisory Groups have requested some form of public input[3]. Any scientific deliberation with the scope and impact of the IARC Monograph Programme should be reviewed, just like any manuscript that may be published in a journal, and the additional viewpoints of the reviewers carefully considered. For example, the US EPA put in place processes for expert input, discussion, and transparency that should be guideposts for revising the Monograph Programme. Dr. Sass's 2003 criticism was valid then as it is now.

The Programme has been challenged to consider a broader slate of experts on the Working Group[4], including those from the private sector with valuable in-depth knowledge on a particular substance. This request has been consistently rebuffed for fear of bias. Whereas bias is a legitimate concern, clear acknowledgements of orientation and potential conflicts would offset this concern and augment the Working Group with important and constructive input. Furthermore, such invited experts should be given an opportunity to draft sections of the monograph that pertain to their expertise. Currently, that is not the case. Invited experts and observers are kept at arm's length. Dr. Sass's invitation as an observer was strictly that: to observe, but not participate. If she or others have specific and valuable capabilities and knowledge regarding a particular substance, they should be allowed full participation or, at the very least, opportunities for input on data and draft monographs.

Given that there is no record of voting, as pointed out by Dr. Sass, and because only "consensus" conclusions are published, there is no way to discover whether consensus is a majority vote (with minority opinions) or truly an agreement among the experts. The Programme would benefit greatly by having votes made public and the voices of dissenting experts made known. One way of doing so would be to have a minority report. However, neither the votes nor minority opinions are made public.

Whereas the Monograph Programme convenes experts of international standing and has articulated its procedures, there is much that could be done to improve the legitimate concerns

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[3] From: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans INTERNAL REPORT 05/001 Report of the Advisory Group to Recommend Updates to the Preamble to the IARC Monographs 4–6 MAY 2005: "**6c. Public comments on first drafts.** There was a request that first drafts should be completed well before the meeting and placed on the IARC website for public comment [ECETOC/IISRP]. Another commenter noted that since first drafts are sent to Observers, they should also be made available to others who request them [Huff]."

[4] Manolis Kogevinas: "...IARC is obsolete regarding the openness of the evaluation procedures. It would be impossible to establish procedures similar to those used by the USEPA, but measures should be taken to identify interested parties and to allow the expression of their views. This later could be done through the presence of a few partners at the meeting in Lyon (say corresponding to a max of 10-20% of the number of voting members in the working group), and also procedures that allow the submission of written comments to the working group even if not present." From: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Advisory Group to Recommend Updates to the Preamble, Lyon, France: 4-6 May 2005, Comments from recent meeting chairs and subgroup chairs on the 1991version of the Preamble.

expressed by Dr. Sass 15 years ago. To that end, I include relevant text from my February 6, 2018 testimony, which articulates the essential elements of transparency and integrity:

Along with being a scientifically antiquated program, serious questions have been raised about the integrity of IARC's process. Any agency whose evaluations are used to influence public health decisions must be transparent and fully accountable to the public. If this committee and the member countries of IARC do not address the numerous allegations of questionable ethical practices, undisclosed conflicts of interest, and lack of transparency, then the scientific reforms suggested here will be irrelevant.

There are certain basic standards of accountability, transparency, and simply good science on which IARC presently falls short that should be the guideposts for any effective reform of the monograph process. These include:

- Selecting working group and other advisory members with necessary expertise, regardless of affiliation;
- Declaring the affiliation and potential conflicts of interest of all participants;
- Considering ALL available data;
- Providing a clear explanation why certain data are or are not included in the review;
- Adhering to the principles of systematic review, such as those described by The National Toxicology Program's Office of Health Assessment and Translation (OHAT) and Cochrane Consumer Network;
- Fully communicating the results of the agency's review in a timely manner;
- Including the opinions of all reviewers and the degrees of consensus and dissent.

Dr. Sass referred to "systematic review" and stated that there are two versions being developed.

2. ***What is "systematic review," why is it important, and how should the IARC Monographs Programme use it?***

Systematic review is a well-defined, stepwise process to acquire, select, and evaluate a broad array of data for decision making. Perhaps the best-defined process was developed by the Office of Health Assessment and Translation (OHAT) of the United States National Toxicology Program[5]. The "Handbook" is based on other, similar processes such as Cochrane Collaboration, Navigation Guide, GRADE Working Group, CAMARADES, SYRCLE[6]. All of these processes seek to collect ALL information, transparently evaluate the scientific and contributory value of each study and draw conclusions that are scientifically and procedurally credible.

Although the Monograph Programme has considered systematic review, the Programme has shown little evidence of employing it. In a 2014 Advisory Group review[7], the Programme considered incorporating systematic review in its procedures. However, the Programme's Preamble has not been revised to reflect this sentiment and the practices of the Programme give no evidence that such a structured and transparent process has been put in place. I am not aware of one, much less two, versions of systematic review being developed by the Programme.

OHAT's process is illustrated in "Figure 1" and "Figure 3", which are reproduced from the OHAT handbook. Three notable points can be seen in these figures: one is that public comment is a feature of each stage of the systematic review. As stated in my answer to Rep. Smith's first question, peer review and public input is fundamental to robust scientific review.

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[5] Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration

[6] Footnote taken from the OHAT Handbook:
GRADE Working Group - Grading of Recommendations Assessment, Development and Evaluation (short GRADE) Working Group began in the year 2000 as an informal collaboration of people with an interest in addressing the shortcomings of present grading systems in health care.
CAMARADES (Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies) provides a supporting framework for groups involved in the systematic review and meta-analysis of data from experimental animal studies. As of December 2014, CAMARADES has five global national co-ordinating centres: University of Edinburgh, Florey Institute of Neuroscience & Mental Health, Radboud University Nijmegen Medical Centre, University of California San Francisco and Ottawa Hospital Research Institute.
SYRCLE (SYstematic Review Centre for Laboratory animal Experimentation) was officially founded in 2012. SYRCLE
focuses on the execution of SRs of animal studies towards more evidence-based translational medicine.

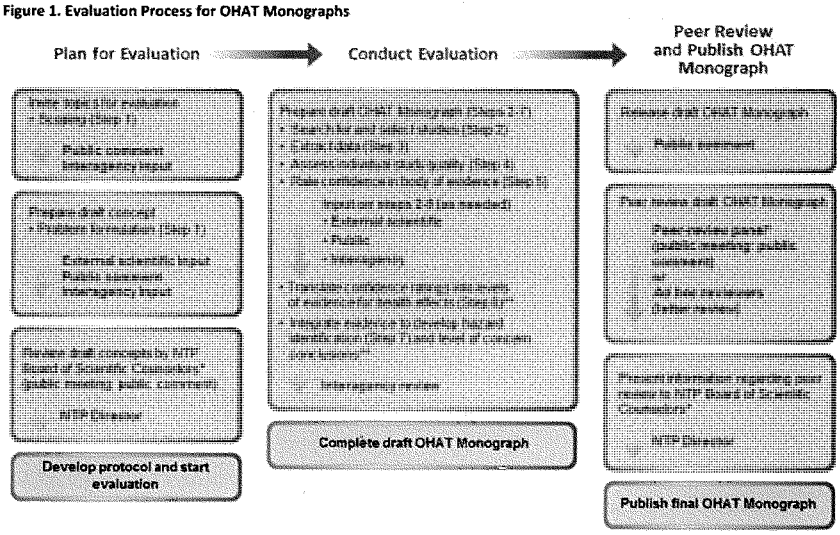
[7] IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Internal Report 14/002, Report of the Advisory Group to Recommend priorities for IARC Monographs during 2015-2019, 7-9 April 2014; Section 2.2.

Second, studies and data from a broad range of sources, not just published studies, are considered and are evaluated for quality before being used. By evaluating for quality, the studies are given proper weight in deriving conclusions.

Third, as shown in "Figure 3", the OHAT process integrates *exposure* into the evaluation to give proper context to the toxicological conclusions so that a "level of concern" can be communicated. Combining toxicological conclusions with exposure is risk assessment, which is the way hazard data (toxicity) is given proper context in communicating to the public the likelihood an effect may occur in human populations. Unlike all major human health regulatory agencies, the IARC Monograph Programme is hazard-based and not risk based. The Monograph Programme titles itself as evaluating carcinogenic *risks* to human when in fact it does not. It is a *hazard* identification process, stopping at the toxicological conclusions, providing no context of exposure or risk. As I stated in my testimony, this is confusing and unhelpful to the public and decision makers who need scientists to describe the potential impact on their lives from substances as diverse as plutonium, red meat, or aloe vera.

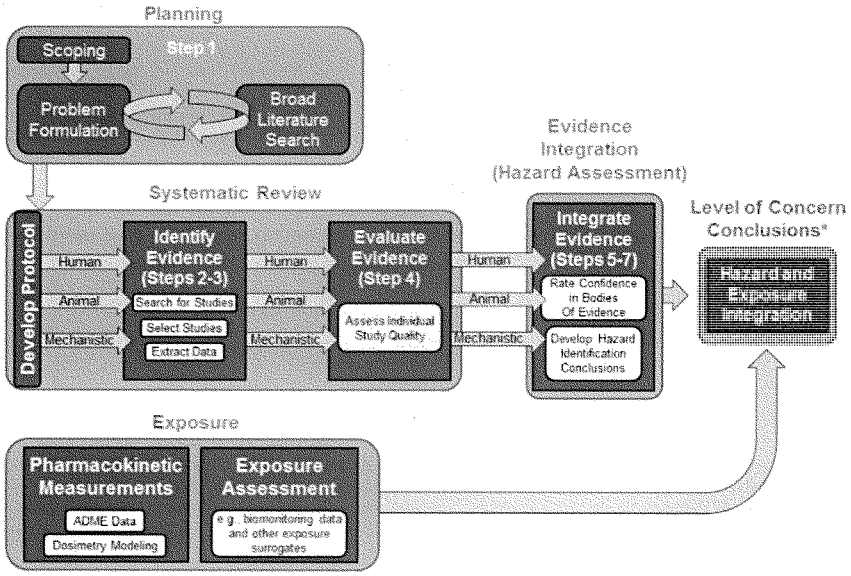
The Monograph Programme should adopt systematic review procedures, such as the OHAT process, and should revise the Preamble and working practices to reflect such adoption.

Figure 1. Evaluation Process for OHAT Monographs



The use of systematic methods is in the evaluation planning and conduct phases and consists of Steps 1–7 (Rooney *et al.* 2014)
* federally chartered advisory group
** not included in state-of-science evaluation or expert panel workshop report

Figure 3. Systematic Review in the Context of an OHAT Hazard Identification or Level of Concern Conclusion



ADME = absorption, distribution, metabolism, excretion

*NTP is currently updating the NTP approach for reaching level of concern conclusions (expected 2016/2017)

Responses by Dr. Jennifer Sass

HOUSE COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY

"In Defense of Scientific Integrity: Examining the IARC Monograph Programme and Glyphosate Review"

Dr. Jennifer Sass, Senior Scientist, Natural Resources Defense Council

Questions submitted by Rep. Suzanne Bonamici, Ranking Member, Subcommittee on Environment

Dr. Sass, the chemical industry has a long history of attempting to influence the scientific conversation around its products and their potential health dangers, and it appears that Monsanto has engaged in a campaign to influence the dialogue surrounding glyphosate. Unfortunately, we seem to hear daily reminders of just how dangerous misinformation and misdirection can be.

1. ***How has Monsanto attempted to influence the classification of glyphosate, while attempting to conceal their own involvement in those actions?***

Monsanto appears to have undertaken a public relations and lobbying campaign to undermine the IARC's scientific work. The industry-led criticisms of the IARC Monographs are part of a public relations campaign documented in internal Monsanto documents made public as a result of court proceedings. These documents are available at the USRTK.org public website[1] and summarized in part in the report by the Minority Staff of the House Science Committee, "Spinning Science and Silencing Scientists: A Case Study in How the Chemical Industry Attempts to Influence Science".[2] These efforts include:

- Monsanto supported websites such as Genetic Literacy Project and Academics Review to give the false impression that non-industry third parties are defending the safety of its cancer-causing products and attacking IARC's credibility and conclusions.[3] The websites failed to disclose ties to Monsanto;[4]
- Monsanto sponsored academics to publish papers in scientific journals defending glyphosate's safety, and attacking IARC's credibility and conclusions;[5]

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[1] USRTK.org documents at https://usrtk.org/wp-content/uploads/2017/03/ORDcommentsonOPPglyphosate.pdf

[2]https://usrtk.org/wp-content/uploads/2018/02/REVISED-FINAL-Minority-Staff-Report-on-Glyphosate-2.6.2018.pdf

[3] For example, Genetic Literacy Project. See https://gmo.geneticliteracyproject.org/FAQ/is-glyphosate-roundup-dangerous/. Also see Academics Review website: http://academicsreview.org/2015/03/iarc-glyphosate-cancer-review-fails-on-multiple-fronts/

[4] https://usrtk.org/hall-of-shame/jon-entine-the-chemical-industrys-master-messenger/

[5] https://www.npr.org/sections/thesalt/2017/03/15/520250505/emails-reveal-monsantos-tactics-to-defend-glyphosate-against-cancer-fears

• Monsanto worked with European and US officials at EFSA and USEPA to develop glyphosate assessments that deny a link between glyphosate and cancer, following the same talking points as Monsanto and citing Monsanto-sponsored reports.[6]

These attack strategies are aggressively promoted by corporate chemical trade organizations that include Monsanto among its members: the International Life Sciences Institute[7] (representing food manufacturers); CropLife America International[8] (representing Agrochemical manufacturers); and the American Chemistry Council[9] (representing chemical manufacturers) that was dubbed "The Cancer Lobby" by NY Times columnist Nicholas Kristof.[10]
The chemical industry attack on IARC has also been described in a scientific journal publication authored by Dr. Jonathan Samet, a prestigious medical professor and frequent Chair of National Academies committees as, "...archetypical of strategies for creating 'doubt' about scientific evidence that has policy implications. Such strategies can be traced to the 'playbook' of the tobacco industry for discrediting findings related to active and passive smoking."[11]

2. ***If Monsanto, and other chemical companies, can routinely succeed in manipulating the scientific record, what does that mean for scientific bodies like IARC or EPA's IRIS program, and most importantly for the public's health and safety?***

Americans rely on objective public policy to protect them from hazards in their environment. Unbiased chemical assessment provided by bodies like WHO-IARC and EPA-IRIS have been instrumental in providing credible scientific information about chemical hazards. This information is used to support regulatory measures to limit or prevent harmful chemical exposures, as well as non-regulatory interests such as innovative green chemistry strategies, medical and health providers, reduced risk product formulators and manufacturers, retailers, and consumers. Manipulation of the scientific record by private or political interests will block the potentially lifesaving information from reaching the public for policy or even individual consideration.

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[6] https://www.nrdc.org/experts/jennifer-sass/monsanto-mouthpieces-house-science-committee-epa-eu-efsa
[7] http://ilsina.org/about-us/membership/
[8] https://monsanto.com/company/partnerships/q/is-monsanto-in-any-way-affiliated-with-croplife-international/
[9] https://www.americanchemistry.com/Membership/MemberCompanies/
[10] NYTimes Oct 6, 2012. http://www.nytimes.com/2012/10/07/opinion/sunday/kristof-the-cancer-lobby.html
[11] Jonathan M. Samet; The IARC monographs: critics and controversy, Carcinogenesis, Volume 36, Issue 7, 1 July 2015, Pages 707–709, https://doi.org/10.1093/carcin/bgv062

Dr. Sass, after the IARC decision, California's Office of Environmental Health Hazard Assessment (OEHHA), decided to include glyphosate on the state's list of products known to cause cancer. That listing would require Monsanto to include a warning label on its product. Monsanto is suing to stop the labeling requirement.

3. ***With everything you know about glyphosate, wouldn't it be better for consumers to have that information before they decide to purchase and use the product? Don't our communities and families deserve to know exactly what chemicals they are spraying in their parks and backyards?***

In additional to sound federal policy, Americans must make individual decisions to protect themselves from environmental hazards. These decisions are only effective when informed by objective science that is free of financial influence and clearly conveyed to the consumer. Indeed, there is nothing new about using labels to help the public make informed decisions. Labels based on independent science are already used to reduce poor health outcomes related to nicotine consumption, household chemical interactions, or fetal impacts related to alcohol consumption.

When science clearly indicates risks to human and environmental health- such as the case with glyphosate, the public must be informed of those risks as a way to make prudent decisions and to lower future societal costs. The health risks posed by glyphosate include potentially elevated risks of blood cancers such as non-Hodgkin lymphoma (NHL) and possibly also acute myeloid leukemia (AML). AML is a very serious fast-growing cancer, with a five-year survival rate of only 27%. The Agricultural Health Study found a possible association at the 90% confidence level. The IARC Working Group identified epidemiologic studies from the US, Canada and Sweden that reported an elevated risk of non-Hodgkin lymphoma (NLH), a type of blood cancer, associated with exposure to glyphosate, even after adjusting for exposure to other pesticides. Most Americans would likely want to know if a chemical that they are using in their communities, homes and around their families are associated with any form of cancer or other adverse health outcomes.

We cannot let Monsanto's attack on IARC over glyphosate set a precedent. Allowing vested interests to successfully control and censor the science that raises concern about the safety of their products will encourage other manufacturers of harmful chemicals to attack science rather than improving their products and providing meaningful information to protect their customers.

Responses by Dr. Robert Tarone

HOUSE COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY

"In Defense of Scientific Integrity: Examining the IARC Monograph Programme and Glyphosate Review"

Dr. Robert Tarone, (retired) Mathematical Statistician, U.S. National Cancer Institute and Biostatistics Director, International Epidemiology Institute

Questions submitted by Rep. Lamar Smith, Chairman, Committee on Science, Space, and Technology

Aaron Blair, the chair of the IARC working group on glyphosate knew of exculpatory epidemiological data from the Agricultural Health Study, but did not share that knowledge with other working group members. An advanced draft of the updated AHS was circulating between its authors in early 2013 and they published a subset of the data in 2014 without the inclusion of herbicide data – a decision you described in your 2016 paper as "difficult to comprehend or justify." The study was finally published in December 2017.

1. ***Given your extensive history of over 300 scientific publications, your direct experience with publishing data from the AHS, and the state of the draft manuscript in 2013, why do you believe it took AHS this long to publish this most recent data?***

I remain puzzled by the failure of the AHS investigators to include the herbicide results in their 2014 PLoS One paper. The main reason I have seen given in the press for the exclusion of herbicides is that the paper was getting too long, but I don't buy that explanation. PLoS One is an online publication and the instructions for the authors clearly state that there is no restriction on paper length or the amount of data presented (e.g., the number of tables or figures in a paper). As noted in my European Journal of Cancer Prevention paper, the previous similar AHS publications (i.e., looking at one disease and exposure to various pesticides) had all included pesticides from all four classes (i.e., herbicides, insecticides, fungicides, and fumigants), even though most, if not all, of the previous papers were published in print journals for which there are page restrictions. The fact that herbicides constituted the class of pesticides excluded from the 2014 PLoS One paper is particularly difficult to understand. The March 2013 draft manuscript was clearly intended for a print journal (there were supplementary tables that were to be published online – a common practice now for most print journals), and the primary tables to be included in the text of the print paper were restricted to only 16 pesticides – those for which the authors judged there to be strong a priori evidence for an association with NHL. Ten of these sixteen prioritized pesticides were herbicides, so the authors went from focusing primarily on herbicides (because of prior evidence) in the Spring of 2013 to excluding all herbicides in the Fall of 2014. The 2017 paper was restricted to glyphosate, so the AHS investigators have still not published the results for NHL risk and the other 17 herbicides. David Spiegelhalter was quoted in the June 14, 2017 Reuters article on the AHS draft papers as concluding that none of the herbicides showed evidence of an association with NHL, an assessment that I agree with. Investigators sometimes fall in love with their favorite hypotheses, and the focus on herbicides in the March 2013 draft paper is consistent with my perception that many AHS investigators

believed it likely that herbicides were responsible for increased NHL risk in Midwest farmers. Perhaps they were so disappointed in the negative herbicide results that they excluded them from the 2014 PLoS One paper, hoping that with the accrual of additional NHL cases from longer follow-up some of the herbicide results might turn positive.

This is not explicitly an IARC problem, because the IARC criteria require that deliberations of Working Groups be restricted to data from published papers. The AHS is so well known and respected, however, that one would think that an exception might have been made in the glyphosate deliberations, particularly since Aaron Blair was the Working Group chairman and could have presented the updated AHS results for glyphosate and NHL during deliberations. This would have required a departure from strict IARC criteria, however, so I view this as primarily an AHS problem

In your testimony you alleged that a scientific publication summarizing rodent study data (Greim et al.) was provided to IARC staff 30 days prior to the working group meeting and that this was too late for data to be reviewed adequately. Records made available as part of ongoing litigation demonstrate that IARC staff were alerted to the availability of Greim et al. on the day it became available online, which was also the data submission deadline for the monograph working group. Additionally, the chair of the animal data subgroup for the monograph stated that he did not receive a copy of Greim et al. prior to the Monograph 112 meeting and therefore did not have time to incorporate the data into the monograph.

2. ***Based on these facts, does the inability to consider Greim et al. appear to be a problem with the timing of when IARC staff received the publication or with the delay by IARC staff in providing the publication to the animal data subgroup?***

I have never alleged anything (in testimony or in my paper) about whether the Greim et al. paper was received by IARC in a timely fashion. What I know about the Monograph 112 Working Group deliberations on glyphosate comes from my reading of the glyphosate chapter in Monograph 112. It was Dr. Sass who alleged in her testimony that the Greim et al. paper was only provided 30 days prior to the Working Group meeting and that this was too short a time for it to be reviewed adequately. I have assumed that since the IARC Monograph 112 Working Group cited in the reference list, deliberated upon, and discussed the Greim et al. paper in the Glyphosate chapter that it had met all IARC criteria for inclusion in Monograph 112 Working Group deliberations. The Working Group discounted the paper, but if anyone on the Working Group or on IARC staff had taken the time to read it they would have seen that the summary tumor data from all rodent studies (including all those relied upon by IARC) were made available in supplementary online tables. The fact that the Greim et al. paper might have been provided too late for careful review does not absolve IARC staff or the Working Group members from the responsibility of doing a thorough and careful evaluation of those rodent studies that IARC relied upon in the glyphosate deliberations. How is it possible that they could devote three paragraphs to discuss male renal tumors in the first CD-1 mouse study, but then not even discuss renal tumor pathology in the one paragraph devoted to the second CD-1 mouse study? Similarly, how could they emphasize a high dose male finding for hemangiosarcomas in the second CD-1 mouse study, but not even mention hemangiosarcomas in the discussion of the first CD-1 mouse study, in which the mice were exposed to even higher glyphosate levels than in the second mouse study? IARC has been evaluating rodent tumor studies for over 40 years and IARC staff knew that there were renal tumor data from the second mouse study and hemangiosarcoma data from the first mouse study. It is inconceivable that IARC staff could find only the renal tumor data for male mice from the first CD-1 mouse study and only the hemangiosarcoma data for male and female mice from the second CD-1 mouse study. All relevant tumor data should have been provided to the Working Group members for consideration in their deliberations. Including only tumor data that supported the conclusion that glyphosate causes tumors in mice while excluding tumor data from the very same studies that refuted that

conclusion was inexcusable, scientifically unjustifiable, and renders the IARC classification of glyphosate as a possible human carcinogen invalid.

Appendix II

Additional Material for the Record

DOCUMENTS SUBMITTED BY REPRESENTATIVE SUZANNE BONAMICI

DR. WILD LETTER (JANUARY 11, 2018)

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&
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&
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Ref.: RC/69/2-USA; IMO/75/2-112
CPW/mg

11 January 2018

Dear Congressmen Smith, Biggs and Lucas,

I refer to your letter dated 8 December 2017. I welcome the further opportunity to address the Committee's questions and to provide additional clarifications regarding the issues you raise about the Monographs Programme of the International Agency for Research on Cancer (IARC).

Regarding your allegations concerning Dr Christopher Portier, IARC is not aware of any contractual relationship existing between Dr Portier and litigation lawyers relating to glyphosate at the time of the Monograph meeting in March 2015, when glyphosate was evaluated. However, IARC did take account of other real or apparent conflict of interests declared by Dr Portier, specifically his part-time role with the Environmental Defense Fund. On this basis, IARC invited his participation in the meeting as an *Invited Specialist*[1] and his declared conflict of interest was made public on the IARC Monograph website.

Like all other meeting participants, including *Observers*[2] and *Representatives*[3], Dr Portier had full access to draft documents and discussions during the meeting, and was recognized to speak at the meeting. However, as an Invited Specialist, Dr Portier was not a member of the *Working Group*[4] that was responsible for the critical reviews and evaluations developed during the meeting, including the work performed in sub-groups assessing the epidemiology, animal bioassays or other relevant mechanistic data. Moreover, none of the 16 Working Group members - or any other meeting participant (including the *Observer* from Monsanto, other *Observers*, and the US EPA *Representative*) - signaled any attempt at undue influence by Dr Portier. Accordingly, any

[1] As specified in IARC (2006). Preamble to the IARC Monographs. http://monographs.iarc.fr/ENG/Preamble/.
[2] *Id.*
[3] *Id.*
[4] *Id.*

allegation that Dr Portier unduly influenced the Working Group and the consensus evaluation reached does not, to my knowledge, have any factual basis.

Regarding Dr Portier's activities subsequent to this meeting, IARC does not have any official relationship through which to influence such activities and can bear no responsibility for them. You additionally refer to Dr Portier having chaired a "*glyphosate Advisory Group*"[5], but there was no such group. What Dr Portier chaired, in April 2014, was the "Advisory Group to Recommend Priorities for IARC Monographs during 2015-2019". This Advisory Group comprised 21 members from 13 countries and recommended over 80 different agents for IARC to consider for evaluation over the five-year period mentioned, one of which was glyphosate. The IARC Secretariat took the decision on the five agents to be reviewed at the Monograph meeting in March 2015.

With respect to the Agricultural Health Study (AHS), it is important to recognize that this is a prospective study that has been ongoing since the 1990s in two US States (Iowa and North Carolina). Publications about the AHS date back more than 20 years[6], and incremental updates are published periodically. It is therefore incorrect that "*the study was just recently published for the first time*"[7]. Even the most recent publication, appearing in 2017 - some 30 months after the Monograph evaluation of glyphosate - is not a "final" publication, as the study is ongoing.

At the time of the Working Group's 2015 classification of glyphosate, several peer-reviewed publications from the AHS were available[8]. As the AHS is a large and well-conducted study, it was one of the key ones evaluated by the Working Group. The AHS is mentioned in the IARC Monograph on glyphosate[9], counter to any suggestion that it "*should have been mentioned*"[10] but was not. In fact, in the Monograph[11], the published AHS results are tabulated, described in text, and analysed as part of the Working Group's meta-analysis of non-Hodgkin lymphoma risk.

At the time of the IARC evaluation, the AHS did not report an association between non-Hodgkin lymphoma and glyphosate. However, this null finding in the AHS did not outweigh the positive associations found in other epidemiological studies. The Working Group took this into account in concluding that there is "*limited*"[12] evidence of carcinogenicity in studies of cancer in humans. While it is accurate that "*much of the research relied upon by the Monograph was on animals*"[13], it should be noted that the classification of glyphosate in Group 2A is also based on this "*limited*" evidence of cancer in humans, inclusive of the AHS, as well as on the "strong evidence that glyphosate causes genotoxicity"[14].

The latest publication from the AHS, in 2017, is an incremental update with a longer time of follow-up that includes more cancer cases. Consistent with the prior results included in the IARC Monograph, the newly published AHS update did not find an association between non-Hodgkin lymphoma and glyphosate. New data on increased leukemia risk with glyphosate exposure in the

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[5] Letter from Hon. Lamar Smith, Hon. Andy Biggs and Hon. Frank Lucas to Dr Christopher Wild (Dec 8, 2017).
[6] See Alavanja et al. (1996). Agricultural Health Study. Environ Health Perspect,104(4):362–9, as cited in the IARC Monograph on glyphosate.
[7] Letter from Hon. Lamar Smith, Hon. Andy Biggs and Hon. Frank Lucas to Dr Christopher Wild (Dec 8, 2017).
[8] See IARC Monograph on glyphosate: IARC Working Group on the Evaluation of Carcinogenic Risk to Humans (2017). Some Organophosphate Insecticides and Herbicides. International Agency for Research on Cancer, Lyon, France. http://monographs.iarc.fr/ENG/Monographs/vol112/index.php
[9] *Id.*
[10] Letter from Hon. Lamar Smith, Hon. Andy Biggs and Hon. Frank Lucas to Dr Christopher Wild (Dec 8, 2017).
[11] See IARC Monograph on glyphosate: IARC Working Group on the Evaluation of Carcinogenic Risk to Humans (2017). Some Organophosphate Insecticides and Herbicides. International Agency for Research on Cancer, Lyon, France. http://monographs.iarc.fr/ENG/Monographs/vol112/index.php
[12] As specified in IARC (2006). Preamble to the IARC Monographs. http://monographs.iarc.fr/ENG/Preamble/
[13] Letter from Hon. Lamar Smith, Hon. Andy Biggs and Hon. Frank Lucas to Dr Christopher Wild (Dec 8, 2017).
[14] See IARC Monograph on glyphosate: IARC Working Group on the Evaluation of Carcinogenic Risk to Humans (2017). Some Organophosphate Insecticides and Herbicides. International Agency for Research on Cancer, Lyon, France. http://monographs.iarc.fr/ENG/Monographs/vol112/index.php

AHS were not, however, available to the Working Group in 2015. Because the IARC Monograph classification reflects the consensus view of an independent expert Working Group, based on a systematic review of all publicly available studies, it is inappropriate to speculate about how new data from one study (including on increased leukemia risk) might change that expert opinion.

With regard to the quotation of Dr Aaron Blair, this appears selective and therefore is prone to misinterpretation. As a whole, the testimony given by Dr Blair does not support any change in the classification of glyphosate. To the contrary, when asked, "*Has anything you've been shown by Monsanto's lawyers in the 3 hours and 40 minutes that he questioned you changed the opinions that you had at the IARC meeting about glyphosate and non-Hodgkin lymphoma?*", Dr Blair answered, "*No*"[15].

With respect to the confidentiality of deliberative documents, we note that reports from the US National Research Council routinely indicate that, "*the review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.*"[16] The European Food Safety Authority (EFSA) differs from the US National Research Council on several key procedural aspects, including not publically disclosing the identity of the peer reviewers and the meeting attendees. EFSA also differs from other international agencies (including IARC) with respect to some transparency issues, including "*public access to data used in determining scientifically significant conclusions that affect policy*"[17], and the reliance on draft materials developed by those with vested interests. Options to improve transparency and conflict of interest disclosure in EFSA decisions are currently being explored[18].

The Monographs, in full agreement with the principles of transparency and importance of "*public access to data used in determining scientifically significant conclusions that affect policy*"[12], rely on published research, and do not cite unpublished or "secret data". IARC invites scientific stakeholders, in limited numbers, seeking to balance participation "*from constituencies with differing perspectives*" to participate in its meetings. All participants at Monograph meetings have full access to the draft documents and discussions, and may be recognized to speak. As publicly announced two months in advance of the meeting on glyphosate, IARC included various *Observers*, including from Monsanto, noting their disclosed conflicts of interests. However, only the Working Group of independent experts drafts the critical reviews and evaluations. Individuals with real or perceived conflicts of interest of any kind may not draft text that pertains to the description or interpretation of cancer data.

Finally, like the US National Research Council, the IARC Monographs assure the integrity of the process by maintaining confidentiality of draft documents and of the scientific peer review comments. IARC's practices are also consistent with the Joint Meeting on Pesticide Residues (JMPR) (jointly administered by the FAO and WHO), which evaluated glyphosate in 2016, particularly with regard to the confidentiality of draft and deliberative documents, the determination of conclusions and decisions by consensus from all participants, and the adoption of the final report by the "entire Meeting"[19].

In all, the rigorous published procedures followed in every Monograph meeting reflect IARC's close adherence to the highest principles of transparency, independence and scientific integrity.

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[15] Videotaped deposition of Aaron Earl Blair, PhD. March 20, 2017. MDL No. 2741, Case No. 16-md-0271-VC. United States District Court, Northern District of California.
[16] Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde (2011). https://www.ncbi.nlm.nih.gov/books/NBK208227/; Review of EPA's Integrated Risk Information System (IRIS) Process (2014). https://www.ncbi.nlm.nih.gov/books/NBK230074/;
[17] Letter from Hon. Lamar Smith, Hon. Andy Biggs and Hon. Frank Lucas to Dr Christopher Wild (Dec 8, 2017).
[18] See https://www.efsa.europa.eu/en/corporate/pub/independencepolicy171026
[19] See http://www.who.int/foodsafety/publications/jmpr_guidance_document_1.pdf?ua=1

This approach has permitted the Monographs to thoroughly evaluate many important agents, including tobacco, hepatitis and human papilloma viruses, alcohol, air pollution and radiation, providing a foundation for many effective cancer control measures.

In this regard, I wish to acknowledge the valuable support of the US National Institutes of Health and our other sponsors. We recognize the importance of awards such as the one to the Monographs Programme in enabling scientific excellence at IARC, and also that such awards are only merited based on successful scientific peer review of the sponsor. In respect of oversight and accountability, the Programme is also responsive to IARC's governing bodies (Scientific and Governing Councils) and to the international scientific community. Accordingly, each IARC scientific Section is subject to in-depth external peer-review on a five-year cycle with a panel comprised of IARC Scientific Council Members and additional subject-specific external scientists further information about the governance of IARC is available at http://www.iarc.fr/en/about/governance.php. These scientific peer reviews have had an essential role in maintaining the scientific excellence of IARC, as reflected in an independent assessment, based on scientific bibliographic analysis, placing IARC in the top 2% of medical research organizations worldwide[20].

While assuring you of my commitment to the oversight and accountability of the Agency to its funding sponsors, its governing bodies and the international scientific community, I remain available to respond to further questions you may have about the IARC Monograph Working Group evaluation of glyphosate. Without prejudice to IARC's willingness to facilitate your review by voluntarily responding to reasonable and substantiated requests for information received from appropriate authorities, IARC would be grateful if the House Science Committee would take all necessary measures to ensure that the immunity of the Organization, its officials and experts, as well as the inviolability of its archives and documents, are fully respected.

Yours sincerely,

Christopher P. Wild, PhD
Director

[20] See http://www.excellencemapping.net/

DR. WILD LETTER (NOVEMBER 20, 2017)

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Ref.: RC/69/2-USA; IMO/75/2-112
CPW/mg

20 November 2017

Dear Congressmen Smith and Biggs,

I refer to your letter dated 1 November 2017. I am pleased to provide a written response to the issues you raise about the Monographs programme of the International Agency for Research on Cancer (IARC). In replying, I note that this information is given without prejudice and does not constitute a waiver of the immunities and inviolability of archives enjoyed by the World Health Organization (WHO) and IARC.

The IARC Monographs are consensus evaluations developed by Working Groups of independent experts, free from vested interests. As IARC explained to the reporter cited in your letter, changes made to draft documents are the result of deliberation between Working Group members and for this reason are not attributable to any particular scientist. For all Monograph evaluations, drafts prepared over the months prior to a meeting form the basis of open and detailed scientific debate during the eight-day meeting in Lyon and are modified by the Working Group as a result. The final Monograph evaluation represents the scientific consensus of the whole Working Group and does not have individually authored sections. IARC staff (secretariat to the meeting) do not draft or revise the Monograph text, which is the preserve of Working Group members.

During the Monograph meeting in March 2015 at which glyphosate was evaluated, Dr Christopher Portier was an Invited Specialist. Invited Specialists do not serve as meeting chair or subgroup chair, nor do they draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations. In April 2014, when Dr Portier chaired the Advisory Group to Recommend Priorities for IARC Monographs 2015-2019, he did not have any contractual relationships with litigation lawyers relating to glyphosate nor any other declared activities that could be considered as creating a real or perceived conflict of interest. The Advisory Group

comprised 21 members from 13 countries and their recommendations were published in *The Lancet Oncology*[1] and on the IARC website[2].

In the interests of transparency, the IARC Monographs are based on independent scientific review of published research and not on the basis of unpublished or "secret data" unavailable publicly. According to this principle and as required by its Preamble[3], the IARC Monograph on glyphosate[4] did not include any unpublished information on the Agricultural Health Study (AHS). Therefore, it is false to assert that Dr Blair was in a position to withhold critical information from IARC, about the AHS or any other unpublished study, for that matter. The Working Group did consider the published report from the AHS.

This same principle of independent scientific review and verification explains differences between a draft document and the published Monograph text referred to by Ms Kelland. Most of these differences specifically relate to a review article[5] co-authored by a Monsanto scientist and which has been the subject of investigative reporting concerning "ghost-writing"[6]. The draft Monograph document seen by Ms Kelland reported the conclusions of the authors of this review article. During the Monographs consensus meeting, the Working Group considered that information in the review article and its supplement was insufficient for independent evaluation of the individual studies and the conclusions reached by the Monsanto scientist and other authors. As a result, the draft was revised, and the text in the published Monograph is the consensus opinion of the Working Group. Nevertheless, the Monograph factually describes the review article and the reported findings (see pages 34–35 and 40–41).

Draft and deliberative materials are not made public, in order to protect the Working Group scientists from interference by vested interests. The position of IARC and the WHO concerning the public release of deliberative documents, or records of deliberative scientific discussions, is consistent with standard practice in scientific committees. Individual Working Group members contacted IARC to express concerns when being pressed to respond to allegations about the scientific debate that took place during the Monograph meeting. In this light, IARC issued a reminder to all parties not to pressure or intimidate scientists in relation to their role as Working Group members[7].

Draft documents are available, however, to all scientists attending the Monograph meetings, including Observers from industry. IARC was pleased to welcome various scientific Observers to the glyphosate Monograph meeting, including from Monsanto. The Monsanto Observer was quoted in the media as saying: "The meeting was held in accordance with IARC procedures. Dr Kurt Straif, the director of the Monographs, has an intimate knowledge of the rules in force and insisted that they be respected."[8]

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[1] Straif K *et al.* (2014). Future priorities for the IARC Monographs. *Lancet Oncol*, 15, 683-684. http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045%2814%2970168-8/fulltext

[2] IARC (2014). Report of the Advisory Group to Recommend Priorities for IARC Monographs during 2015–2019. http://monographs.iarc.fr/ENG/Publications/internrep/14-002.pdf

[3] IARC (2006). Preamble to the IARC Monographs. http://monographs.iarc.fr/ENG/Preamble/index.php.

[4] IARC Working Group on the Evaluation of Carcinogenic Risk to Humans (2017). Some Organophosphate Insecticides and Herbicides. http://monographs.iarc.fr/ENG/Monographs/vol112/index.php

[5] Greim H *et al.* (2015). Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies. *Crit Rev Toxicol*, 45, 185–208. PMID:25716480

[6] http://abonnes.lemonde.fr/planete/article/2017/10/04/monsanto-papers-desinformation-organisee-autour-du-glyphosate_5195771_3244.html; http://www.europarl.europa.eu/cmsdata/129120/PH%20Glyphosate_Gillam.pdf; https://www.bloomberg.com/news/articles/2017-08-09/monsanto-was-its-own-ghostwriter-for-some-safety-reviews

[7] http://www.iarc.fr/en/media-centre/iarcnews/2016/glyphosate_IARC2016.php

[8] http://abonnes.lemonde.fr/planete/article/2017/10/18/glyphosate-monsanto-tente-une-derniere-man-uvre-pour-sauver-le-roundup_5202606_3244.html

In summary, the cancer hazard classifications made by the IARC Monographs are the result of scientific deliberations of Working Groups of independent scientists, free from conflicts of interest. The resulting Monograph represents the Working Group's consensus conclusions, based on their critical review of the published scientific literature, agreed upon by all Working Group members in plenary sessions. The principles, procedures and scientific criteria that guide the evaluations are described in the Preamble to the IARC Monographs.

Although IARC is not in a position to provide witnesses for any potential hearing, I welcome this opportunity to respond to your various points and in so doing to correct repeated misrepresentations of the Monographs promoted by some sections of the media over an extended period of time. You would also both be welcome to visit the Agency and to pose your questions directly to me and my staff.

The Agency remains committed to its work to reduce the ever growing burden of cancer worldwide.

Yours sincerely,

Christopher P. Wild, PhD
Director

IARC response to criticisms of the Monographs and the glyphosate evaluation

Prepared by the IARC Director

January 2018

Background

Since the evaluation of glyphosate by the IARC Monographs Program in March 2015, the Agency has been subject to unprecedented, coordinated efforts to undermine the evaluation, the program and the organization. These efforts have deliberately and repeatedly misrepresented the Agency's work. The attacks have largely originated from the agro-chemical industry and associated media outlets. They have taken place in the context of major financial interests relating to: a) the relicensing of glyphosate by the European Commission; b) hundreds of litigation cases in the USA brought by cancer patients against Monsanto, claiming that their malignancies were caused by glyphosate use; c) and the decision by the Californian Environmental Protection Agency to label glyphosate as a carcinogen.

In response to the misrepresentations, the Agency has sought to provide a clear account of its actions, including keeping its governing bodies informed of developments. Many of the relevant documents have been posted in the public domain on the IARC Governance website[1] and on dedicated glyphosate webpages[2]. IARC scientists have responded to industry-funded critiques appearing in scientific journals by published letters to journal editors. Given its limited capacity, IARC has not tried to develop an extensive media campaign to present its position, or to counter all industry-sponsored attacks in the media. However, in selected and important cases, IARC has addressed the false claims in the media[2].

IARC response to criticisms of the Monographs and the glyphosate evaluation

A number of quite specific and other more general criticisms have been aimed repeatedly at the glyphosate evaluation and the wider Monographs program. Many criticisms in the media originate from one Reuters journalist; another source is a March 2015 article that

[1] http://governance.iarc.fr/ENG/infocouncils.php

[2] http://www.iarc.fr/en/media-centre/iarcnews/2016/glyphosate_IARC2016.php

Forbes[3] since removed from their website, ending their relationship with the author amid revelations in the New York Times that the article was ghostwritten by Monsanto. A number of these criticisms were included subsequently in two letters to the IARC Director from the US House of Representatives Committee on Science, Space and Technology[4].

IARC did not edit parts of the glyphosate Monograph to achieve a particular outcome

- The Reuters journalist[5] obtained a draft of parts of the glyphosate Monograph from Monsanto and compared the draft with the final, published version of the Monograph. On this basis the journalist claimed IARC had selectively edited the text to favor an evaluation of glyphosate as *"probably carcinogenic to humans"*. The majority of the highlighted differences were related to a review article co-authored by a Monsanto scientist, which has been the subject of investigative reporting concerning "ghost-writing". The Agency rejected the false claims published by Reuters[6].
- The Working Group considered that information contained in the review article was insufficient to allow independent scientific evaluation. As a result, the draft text was revised by the Working Group; the text in the published Monograph is its consensus opinion.
- For all Monograph evaluations, the drafts prepared over the months prior to a meeting form the basis of open and detailed scientific debate during the eight-day evaluation meeting in Lyon and are modified by the Working Group as a result.
- Changes made to the draft documents are the result of deliberation between Working Group members and are not attributable to any particular scientist.
- IARC staff (secretariat to the meeting) do not draft or revise the Monograph text, which is the preserve of Working Group members.

Data from the Agricultural Health Study (AHS) were not deliberately excluded from the Monograph

[3] https://www.nytimes.com/2017/08/01/business/monsantos-sway-over-research-is-seen-in-disclosed-emails.html
[4] http://governance.iarc.fr/ENG/Docs/CLSBiggs-IARC_01112017.pdf; http://governance.iarc.fr/ENG/Docs/CPWild-LSmith&ABiggs.pdf; http://governance.iarc.fr/ENG/Docs/SST_IARC12082017.pdf http://governance.iarc.fr/ENG/Docs/CPWild_Smith_Biggs_Lucas_20180111.pdf
[5] https://www.reuters.com/investigates/special-report/who-iarc-glyphosate/
[6] http://www.iarc.fr/en/media-centre/iarcnews/pdf/IARC_Response_Reuters_October2017.pdf

- One suggestion made in media reports is that results from the AHS were withheld from the IARC Monograph evaluation and that recent results would have led to a different evaluation[7]. Monsanto lawyers obtained draft scientific manuscripts of the AHS as a result of calling the Principal Investigator of the AHS, Dr Aaron Blair to testify in litigation hearings in the US. IARC rejected the claims publicly[8].
- The AHS is a prospective study that has been ongoing since the 1990s and publications date back more than 20 years, with incremental updates published periodically. For the 2015 classification of glyphosate, several peer-reviewed publications from the AHS were available and included in the evaluation. At the time of the Monograph evaluation the latest AHS publication did not report an association between non-Hodgkin lymphoma and glyphosate. However, this null finding did not outweigh the positive associations found in other epidemiological studies.
- The most recent analysis from the AHS only became available in 2017 - 30 months after the Monograph evaluation - and was consistent with the prior results included in the Monograph, except that new data on increased leukemia risk with glyphosate exposure were not available to the Working Group in 2015.
- Because the Monograph classification reflects the consensus view of the Working Group, based on a systematic review of all publicly available studies, it is inappropriate to speculate about how new data from one study might change that expert opinion.
- The lengthy court testimony given by Dr. Blair does not support any change in the classification of glyphosate consequent to the latest AHS publication. To the contrary, when asked, *"Has anything you've been shown by Monsanto's lawyers in the 3 hours and 40 minutes that he questioned you changed the opinions that you had at the IARC meeting about glyphosate and non-Hodgkin lymphoma?"*, Dr. Blair answered, *"No"*.[9]

<u>IARC Monograph evaluations are transparent and open to scrutiny</u>

- The suggestion has been made that IARC's Monograph evaluations lack transparency[10] because the draft documents are not made available and changes to drafts are not ascribed to specific Working Group members.

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[7] https://www.reuters.com/investigates/special-report/glyphosate-cancer-data/
[8] http://governance.iarc.fr/ENG/Docs/IARC_responds_to_Reuters_15_June_2017.pdf
[9] Videotaped deposition of Aaron Earl Blair, PhD. March 20, 2017. MDL No. 2741, Case No. 16-md-0271-VC. United States District Court, Northern District of California.
[10] https://www.reuters.com/article/us-health-cancer-iarc-exclusive/exclusive-who-cancer-agency-asked-experts-to-withhold-weedkiller-documents-idUSKCN12P2FW

- Draft and deliberative materials are not made public, in order to protect the Working Group scientists from interference by vested interests. The position of IARC and WHO concerning the public release of deliberative documents, or records of deliberative scientific discussions, is consistent with standard practice in scientific committees.
- For example, the Monographs approach is in line with the US National Research Council; reports from the US National Research Council routinely indicate that, *"the review comments and draft manuscript remain confidential to protect the integrity of the deliberative process."* [11]
- IARC's practices are also consistent with the Joint Meeting on Pesticide Residues (JMPR) (jointly administered by the FAO and WHO), which evaluated glyphosate in 2016, in particular with regard to the confidentiality of draft and deliberative documents, the determination of conclusions and decisions by consensus from all participants, and the adoption of the final report by the *"entire Meeting"*.[12]
- It is noteworthy that Monograph meetings are open to scientific stakeholders in order to balance participation *"from constituencies with differing perspectives"*[13]. All participants have full access to the draft documents and discussions. For example, the meeting on glyphosate included an Observer from Monsanto and a Representative from the US Environmental Protection Agency (EPA). The Monsanto Observer was quoted in the media as saying: *"The meeting was held in accordance with IARC procedures. Dr Kurt Straif, the director of the Monographs, has an intimate knowledge of the rules in force and insisted that they be respected."*[14]

IARC has a strong rationale for inclusion of only publicly available studies in Monograph evaluations

- The Monographs have been accused of selective use of scientific studies ("cherry-picking"[15]) because Working Groups consider only reports available in the public domain, identified and documented through the systematic assembly and review of all publicly available and pertinent studies, as specified in the Monographs Preamble. This practice is

[11] Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde (2011) https://www.ncbi.nlm.nih.gov/books/NBK208227/; Review of EPA's Integrated Risk Information System (IRIS) Process (2014) https://www.ncbi.nlm.nih.gov/books/NBK230074/
[12] http://www.who.int/foodsafety/publications/jmpr_guidance_document_1.pdf?ua=1
[13] http://monographs.iarc.fr/ENG/Preamble/currenta5participants0706.php
[14] http://www.lemonde.fr/planete/article/2017/10/18/glyphosate-monsanto-tente-une-derniere-man-uvre-pour-sauver-le-roundup_5202606_3244.html
[15] https://www.nature.com/news/widely-used-herbicide-linked-to-cancer-1.17181

criticized because it excludes studies conducted by industry when these are publicly unavailable.

- The Monographs do not exclude research conducted by industry *per se*. Where industry-conducted studies are published in scientific journals they are considered, if available in sufficient detail to allow independent scientific review. Under the same conditions, the Monographs also take account of industry-conducted research in summary form or if placed in the public domain by national regulatory agencies.
- The need for industry-conducted studies to be publicly accessible is in line with the existing (e.g. European Medicines Agency) or developing (e.g. European Food Standards Agency) policies of other international agencies.
- Consistent with the above principles and as required by its Preamble, the glyphosate Monograph did not consider any unpublished information on the AHS (see above). However, as already mentioned, the Working Group did include published reports from the AHS.
- IARC follows its current practice in order to enable others to scrutinize the basis of its decisions rather than relying on appeals to authority or trust. This transparency is fundamental to the scientific process.

Monograph Working Group members who evaluated glyphosate were free from conflict of interests

- Another suggestion is that the Working Group evaluation of glyphosate was unduly influenced by Dr Christopher Portier[16], who was an Invited Specialist at the meeting[17]. It is suggested that Dr Portier had contractual commitments to US law firms involved in glyphosate litigation at the time of the Monograph meeting.
- IARC is not aware of any contractual relationship existing between Dr. Portier and litigation lawyers relating to glyphosate at the time of the Monograph meeting in March 2015, when glyphosate was evaluated. However, IARC did take account of other real or apparent conflict of interests declared by Dr. Portier, specifically his part-time role with the Environmental Defense Fund. On this basis, IARC invited his participation in the meeting as an Invited Specialist and his declared conflict of interest was made public on the IARC Monograph website two months in advance of the glyphosate evaluation.

[16] https://www.reuters.com/investigates/special-report/health-who-iarc/
[17] http://governance.iarc.fr/ENG/Docs/SST_IARC12082017.pdf

- Dr. Portier had full access to draft documents and discussions during the meeting, and was recognized to speak at the meeting. However, as an Invited Specialist, Dr. Portier was not a member of the Working Group that was responsible for the critical reviews and evaluations developed during the meeting, including the work performed in sub-groups assessing the epidemiology, animal bioassays or other relevant mechanistic data.
- None of the 16 Working Group members - or any other meeting participant (including the Observer from Monsanto, other Observers, and the US EPA Representative) - signaled any attempt at undue influence by Dr. Portier.
- A related suggestion has been that Dr Portier influenced the original decision to evaluate glyphosate[18] through chairing the April 2014 meeting of the "Advisory Group to Recommend Priorities for IARC Monographs during 2015-2019". However, this Advisory Group comprised 21 members from 13 countries and recommended over 80 different agents for IARC to consider for evaluation over the five-year period mentioned, one of which was glyphosate. The IARC Secretariat took the decision on the five agents to be reviewed at the Monograph meeting in March 2015.

IARC evaluates only agents that have some evidence of carcinogenicity

- Some critics say the Monographs program finds "everything causes cancer"[19] because of nearly 1000 agents evaluated only one has been categorized in Group 4, "probably not carcinogenic to humans".
- The criticism is misleading because the Monographs do not select at random the agents evaluated for carcinogenicity. Instead, in the interest of efficiency and according to the Preamble to the Monographs, "Agents are selected for review on the basis of two main criteria: (a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity."
- IARC puts out a public call for agents to be reviewed and establishes the "Advisory Group to Recommend Priorities for IARC Monographs" to propose priorities for evaluation of agents based on the criteria mentioned above.
- Despite this careful selection of agents, in reality around half (502 of 1003) of the Monograph evaluations resulted in agents being classified in Group 3 ("not classifiable as to its carcinogenicity to humans"); just 12% of all agents evaluated (120 of 1003) are

[18] https://www.reuters.com/investigates/special-report/health-who-iarc/
[19] Ibid.

Group 1 ("carcinogenic to humans") and a further 38% (380 agents) fall into Group 2B ("possibly carcinogenic to humans") or 2A ("probably carcinogenic to humans"). This is far from the finding everything is carcinogenic.

Monograph evaluations take account of "real-world" exposures by evaluation of epidemiological studies

- A charge levelled at the Monographs is that evaluations are divorced from the "real world" i.e. are made without taking account of realistic human exposures.
- However, epidemiological studies are a central part of Monograph evaluations and, by definition deal with people exposed in daily life, including at work. The studies frequently consider the gradient of risk observed with different levels of exposure. One part of the Monograph evaluation is specifically dedicated to describing the circumstances under which human exposure occurs and at what levels.
- In addition, when considering scientific evidence of carcinogenicity including biological mechanisms, the Working Groups place special emphasis on whether the observations are relevant to humans.
- In light of occurring ("real world") human exposures, Working Groups synthesize evidence in humans, animals and other model systems in reaching overall conclusions.

The Monographs program re-evaluates an agent when a substantial additional body of scientific evidence becomes available

- As a science-driven process, the Monographs program has a responsibility to re-evaluate an agent when a significant additional body of evidence becomes available. However, this has led to updates being labelled as a "retraction"[20] if the classification changes, as when coffee was re-evaluated in 2016. The implication that if an evaluation changes then all evaluations are open to doubt not only misrepresents the Monographs but misunderstands science. Science is not static; evidence accumulates and understanding evolves, thus enabling updated evaluations.

[20] https://oversight.house.gov/wp-content/uploads/2016/09/2016-09-26-JEC-to-Collins-NIH-IARC-Funding-due-10-10.pdf

- In practice, by far the most frequent change in classification after re-evaluation is that the agent goes into a higher group (e.g. Group 2A to 1). The fact that most re-classifications move into a higher group is an objective indicator that the Monographs do not overstate the strength of available evidence but are in fact conservative in nature.
- A scientifically updated classification is not, therefore, equivalent to a retraction. Rather, re-evaluation is the sign of a strong, science-driven program responding to scientific progress.

The Monograph evaluations group agents according to the strength of evidence of carcinogenicity, not their potency

- The Monograph evaluation results in a classification based on the strength of evidence that an agent causes cancer or not. In other words, it is a measure of how confident the Working Group is that this agent causes cancer in humans.
- The Monograph evaluations do include consideration of the level of exposure (dose) associated with the risk of developing cancer (response) and strong dose-response relationships corroborate the confidence that a particular agent is a cause of the cancers observed. However, this potency of the agent i.e. how many cancers it causes at certain exposure levels, is not the basis of classification.
- Consequently agents with different potencies can be placed in the same classification group. For example, various forms of tobacco, plutonium, diesel engine emissions, hepatitis viruses and processed meat all have sufficiently strong evidence to classify them in Group 1. The distinction between strength of evidence and magnitude of effect is highlighted in media communications and on the Monographs website in order to make this distinction clear[21].

IARC Monographs identify carcinogenic hazards and do not include a risk assessment

- The IARC Monographs identify carcinogenic hazards i.e. those agents having the potential to cause cancer under some circumstances. This has led some to downplay the relevance of hazard identification[22] and even to suggest the exercise is without value.

[21] http://monographs.iarc.fr/ENG/News/Q&A_ENG.pdf

[22] See internet archive (https://web.archive.org/web/20170220012554/https://www.forbes.com/sites/henrymiller/2015/03/20/march-madness-from-the-united-nations/#6d6581212e93, best viewed with Microsoft Edge

- The IARC Monographs program is explicit about the difference between hazard identification and risk assessment on its website[23].
- In fact, identifying carcinogenic hazards is a crucially important and necessary first step in risk assessment and management; it should be a "red flag" to those charged with protecting public health.
- Revealing that an exposure is a threat (or hazard with a Group 1, 2A or 2B classification) should trigger either immediate remedial action (e.g. bans, as with asbestos or access to artificial tanning salons for young people, or labelling of carcinogenic hazards) or further evaluation of the scale of the risk (risk assessment) in order to set the levels of exposure a particular society is willing to accept (e.g. control measures in occupational settings; acceptable levels of airborne pollutants, or food contamination by pesticides, etc.).
- In contrast to hazard identification, the specific exercise of risk assessment typically involves extrapolation beyond the observed data, employs a variety of statistical models and is based on anticipated levels of exposure and background cancer incidence rates that are often specific to a population or region.
- Following risk assessment, decisions on managing risk encompass social, economic and political considerations. For the above reasons, IARC defers risk assessment and risk management to national and international bodies, restricting itself to provision of hazard identification as a scientific foundation to those subsequent steps.
- This area of debate brings into sharp relief the different and often imprecise ways the word risk is used and understood. A quantitative examination of the elevated risk associated with a given exposure is an integral part of hazard identification, as a support to causal inference. But this differs from the statistical exercises of quantitative risk assessment described above.
- There is clear value in IARC and WHO liaising closely in future exercises of hazard identification and risk assessment and as mentioned in Section II of this document, discussion is in progress.

IARC evaluations make use of the latest scientific data and methodologies

- The IARC Monographs pioneered and continue to be a leader worldwide in objective, systematic cancer hazard evaluations.

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and Safari browsers), as cited in https://www.nytimes.com/2017/08/01/business/monsantos-sway-over-research-is-seen-in-disclosed-emails.html.

[23] http://monographs.iarc.fr/ENG/News/Q&A_ENG.pdf

- Authoritative reviews, including by the National Research Council of the US (NRC, 2011, 2014, 2018)[24], have heralded IARC's review and evaluation methodology, citing it as exemplary and recommending it as one potential model for adoption by US national risk assessment programs.
- Additionally, the IARC Monographs data integration process has been adapted to other systematic review methodologies[25].
- The Monographs Program has received funding from the NCI/NIH USA for over thirty years. The most recent proposal received a score close to the best possible in the current NIH evaluation system. This rating therefore reflects a very high scientific esteem for the programme on the side of the independent reviewers.
- The Monographs program undergoes scientific review by a Review Panel (composed of IARC Scientific Council members and external experts), most recently (in 2014) receiving the highest possible rankings for performance (Outstanding) and fit with the Agency's mission (Perfect).
- A subsequent IARC Monographs Advisory Group concurred with the Scientific Review Panel in supporting the current system of selection and use of experts for the cancer hazard evaluations, accompanied by strict management of conflict of interests. The Advisory Group also encouraged the Program to disseminate the findings of the evaluations as broadly as possible to the scientific and technical community, policymakers and the general public.
- In consideration of this valuable peer review input, and also taking into account positive peer review by the US NCI, the Programme remains committed to conducting reviews that are scientifically rigorous, respected, and free of conflict of interests.

[24] Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde (2011). https://www.ncbi.nlm.nih.gov/books/NBK208227/; Review of EPA's Integrated Risk Information System (IRIS) Process (2014). https://www.ncbi.nlm.nih.gov/books/NBK230074/; Using 21st Century Science to Improve Risk-Related Evaluations (2018). https://www.ncbi.nlm.nih.gov/books/NBK424983/

[25] Environ Health Perspect. 2014 Oct; 122(10): 1007–1014. doi: 10.1289/ehp.1307175; Environ Health Perspect. 2014 Jul;122(7):711-8. doi: 10.1289/ehp.1307972

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Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA)

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The International Agency for Research on Cancer (IARC) Monographs Programme identifies chemicals, drugs, mixtures, occupational exposures, lifestyles and personal habits, and physical and biological agents that cause cancer in humans and has evaluated about 1000 agents since 1971. Monographs are written by ad hoc Working Groups (WGs) of international scientific experts over a period of about 12 months ending in an eight-day meeting. The WG evaluates all of the publicly available scientific information on each substance and, through a transparent and rigorous process,[1] decides on the degree to which the scientific evidence supports that substance's potential to cause or not cause cancer in humans.

For Monograph 112,[2] 17 expert scientists evaluated the carcinogenic hazard for four insecticides and the herbicide glyphosate.[3] The WG concluded that the data for glyphosate meet the criteria for classification as a *probable human carcinogen*.

The European Food Safety Authority (EFSA) is the primary agency of the European Union for risk assessments regarding food safety. In October 2015, EFSA reported[4] on their evaluation of the Renewal Assessment Report[5] (RAR) for glyphosate that was prepared by the Rapporteur Member State, the German Federal Institute for Risk Assessment (BfR). 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[5] discusses the scientific rationale for differing from the IARC WG conclusion.

Serious flaws in the scientific evaluation in the RAR incorrectly characterise the potential for a carcinogenic hazard from exposure to glyphosate. Since the RAR is the basis for the European Food Safety Agency (EFSA) conclusion,[4] it is critical that these shortcomings are corrected.

THE HUMAN EVIDENCE

EFSA concluded 'that there is very limited evidence for an association between glyphosate-based formulations and non-Hodgkin lymphoma (NHL), overall inconclusive for a causal or clear associative relationship between glyphosate and cancer in human studies'. The BfR Addendum (p. ii) to the EFSA report explains that 'no consistent positive association was observed' and 'the most powerful study showed no effect'. The IARC WG concluded there is *limited evidence of carcinogenicity in humans* which means "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 finding of *limited evidence* by the IARC WG was for NHL, based on high-quality case–control studies, which are particularly valuable for determining the carcinogenicity of an agent because their design facilitates exposure assessment and reduces the potential for certain biases. The Agricultural Health Study[6] (AHS) was the only cohort study available providing information on the carcinogenicity

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of glyphosate. The study had a null finding for NHL (RR 1.1, 0.7–1.9) with no apparent exposure–response relationship in the results. Despite potential advantages of cohort versus case–control studies, the AHS had only 92 NHL cases in the unadjusted analysis as compared to 650 cases in a pooled case–control analysis from the USA.[7] In addition, the median follow-up time in the AHS was 6.7 years, which is unlikely to be long enough to account for cancer latency.[8]

The RAR classified all of the case–control studies as 'not reliable,' because, for example, information on glyphosate exposure, smoking status and/or previous diseases had not been assessed. In most cases, this is contrary to what is actually described in the publications. Well-designed case–control studies are recognised as strong evidence and routinely relied on for hazard evaluations.[9 10] The IARC WG carefully and thoroughly evaluated all available epidemiology data, considering the strengths and weaknesses of each study. This is key to determining that the positive associations seen in the case–control studies are a reliable indication of an association and not simply due to chance or methodological flaws. To provide a reasonable interpretation of the findings, an evaluation needs to properly weight studies according to quality rather than simply count the number of positives and negatives. The two meta-analyses cited in the IARC Monograph[11] are excellent examples of objective evaluations and show a consistent positive association between glyphosate and NHL.

The final conclusion[5] (Addendum 1, 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 cancer data.[1] *Sufficient evidence* means 'that a causal relationship has been established' between glyphosate and NHL. BfR's conclusion is equivalent to deciding that there is not *sufficient evidence*. Legitimate public health concerns arise when 'causality is credible', that is, when there is *limited evidence of carcinogenicity*.

EVIDENCE FROM ANIMAL CARCINOGENICITY STUDIES

EFSA concluded 'No evidence of carcinogenicity was confirmed by the majority of the experts (with the exception of one minority view) in either rats or mice due to a lack of statistical significance in pairwise comparison tests, lack of consistency in multiple animal studies and slightly increased incidences only at dose levels at or above the limit dose/maximum tolerated dose (MTD), lack of preneoplastic lesions and/or being within historical control range'. The IARC WG review found a significant positive trend for renal tumours in male CD-1 mice,[12] a rare tumour, although no comparisons of any individual exposure group to the control group were statistically significant. The WG also identified a significant positive trend for hemangiosarcoma in male CD-1 mice,[13] 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 male Sprague-Dawley rats.[14–16] In one of these rat studies, thyroid gland adenomas in females and liver adenomas in males were also increased. By the IARC review criteria,[1] this constitutes *sufficient evidence* in animals.

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]). On the basis of the BfR Addendum, it seems there were three additional mouse studies and two additional rat studies that were unpublished and available to EFSA. Two of the additional studies were reported to have a significant trend for renal tumours, one in CD-1 mice (Sugimoto. *18-Month Oral Oncogenicity Study in Mice*. Unpublished, designated ASB2012–11493 in RAR. 1997), and one in Swiss-Webster mice (Unknown. *A chronic feeding study of glyphosate (roundup technical) in mice*. Unpublished, designated ABS2012–11491 in RAR. 2001). One of these studies (Sugimoto. Unpublished, 1997) also reported a significant trend for hemangiosarcoma. The RAR also reported two studies in CD-1 mice showing significant trends for malignant lymphoma (Sugimoto. Unpublished, 1997; Unknown. *Glyphosate Technical: Dietary Carcinogencity Study in the Mouse*. Unpublished, designated ABS2012–11492 in RAR. 2009).

The RAR dismissed the observed trends in tumour 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,[1 17 18] scientific reports[19] and publications[20–23] on this issue, the recommended first choice is the use of concurrent controls and trend tests, even in the EC regulations cited in the RAR[18] (see p.375). Trend tests are more powerful than pairwise comparisons, particularly for rare tumours where data are sparse. Historical control data should be from studies in the same time frame, for the same animal strain, preferably from the same laboratory or the same supplier and preferably reviewed by the same pathologist.[17 18] While the EFSA final peer review[4] mentions the use of historical control data from the original laboratory, no specifics are provided and the only referenced historical control data[24] are in the BfR addendum.[5] One of the mouse studies[12] was clearly done before this historical control database was developed, one study (Sugimoto. Unpublished, 1997) used Crj:CD-1 mice rather than Crl:CD-1 mice, and one study[13] did not specify the substrain and was reported in 1993 (probably started prior to 1988). Hence, only a single study (Unknown. Unpublished, 2009) used the same mouse strain as the cited historical controls, but was reported more than 10 years after the historical control data set was developed.

The RAR dismissed the slightly increased tumour incidences in the studies considered because they occurred "only at dose levels at or above the limit dose/maximum tolerated dose (MTD)", and because there was a lack of preneoplastic lesions. Exceeding the MTD is demonstrated by an increase in mortality or other serious toxicological findings at the highest dose, not by a slight reduction in body weight. No serious toxicological findings were reported at the highest doses for the mouse studies in the RAR. While some would argue that these high doses could cause cellular disruption (eg, regenerative hyperplasia) leading to cancer, no evidence of this was reported in any study. Finally, a lack of preneoplastic lesions for a significant neoplastic finding is insufficient reason to discard the finding.

MECHANISTIC INFORMATION

The BfR Addendum dismisses the IARC 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 reviewed studies were not done under guideline principles, they should get less weight. To maintain transparency, IARC reviews only publicly available data. The use of confidential data submitted to the BfR makes it impossible for any scientist not associated with BfR to review this conclusion. Further weakening their interpretation,

the BfR did not include evidence of chromosomal damage from exposed humans or human cells that were highlighted in Tables 4.1 and 4.2 of the IARC Monograph [3]

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 minimise 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. In contrast, 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 play a key role in distinguishing between the effects of mixtures, pure substances and metabolites.

Finally, we strongly disagree that data from studies published in the peer-reviewed literature should automatically receive less weight than guideline studies. Compliance with guidelines and Good Laboratory Practice does not guarantee validity and relevance of the study design, statistical rigour and attention to sources of bias.[25 26] The majority of research after the initial marketing approval, including epidemiology studies, will be conducted in research laboratories using various models to address specific issues related to toxicity, often with no testing guidelines available. 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, not just on compliance with guideline rules.

GENERAL COMMENTS

Science moves forward on careful evaluations of data and a rigorous review of findings, interpretations and conclusions. An 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 elements of transparency do not exist for the RAR.[5] For example, citations for almost all references, even those from the open scientific literature, have been redacted. The ability to objectively evaluate the findings of a scientific report requires a complete list of 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 where financial support, conflicts of interest and affiliations of authors are fully disclosed. 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.[27]

Several guidelines have been devised for conducting careful evaluation and analysis of carcinogenicity data, most after consultation with scientists from around the world. Two of the most widely used guidelines in Europe are the OECD guidance on the conduct and design of chronic toxicity and carcinogenicity studies[17] and the European Chemicals Agency Guidance on Commission Regulation (EU) No 286/2011;[18] both are cited in the RAR. The methods used for historical controls and trend analysis are inconsistent with these guidelines.

Owing to the potential public health impact of glyphosate, which is an extensively used pesticide, it is essential that all scientific evidence relating to its possible carcinogenicity is publicly accessible and reviewed transparently in accordance with established scientific criteria.

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* evidence for two carcinogenic mechanisms.

- The IARC WG found an association between NHL and glyphosate based on the available human evidence.
- The IARC WG found significant carcinogenic effects in laboratory animals for rare kidney tumours and hemangiosarcoma in two mouse studies and benign tumours in two rat studies.
- The IARC WG concluded that there was 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.

The RAR concluded[5] (Vol. 1, p.160) that 'classification and labelling for carcinogenesis is not warranted' and 'glyphosate is devoid of genotoxic potential'.

- EFSA[4] classified the human evidence as 'very limited' and then dismissed any association of glyphosate with cancer without clear explanation or justification.
- Ignoring established guidelines cited in their report, EFSA dismissed evidence of renal tumours in three mouse studies, hemangiosarcoma in two mouse studies and malignant lymphoma in two mouse studies. Thus, EFSA incorrectly discarded all findings of glyphosate-induced cancer in animals as chance occurrences.
- EFSA ignored important laboratory and human mechanistic evidence of genotoxicity.
- EFSA confirmed that glyphosate induces oxidative stress but then, having dismissed all other findings of possible carcinogenicity, dismissed this finding on the grounds that oxidative stress alone is not sufficient for carcinogen labelling.

The most appropriate and scientifically based evaluation of the cancers reported in humans and laboratory animals as well as supportive mechanistic data is that glyphosate is a *probable human carcinogen*. On the basis of this conclusion and in the absence of evidence to the contrary, it is reasonable to conclude that glyphosate formulations should also be considered likely human carcinogens. The CLP Criteria[18] (Table 3.6.1, p.371) allow for a similar classification of Category 1B when there are 'studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals'.

In the RAR, almost no weight is given to studies from the published literature and there is an over-reliance on non-publicly available industry-provided studies using a limited set of assays that define the minimum data necessary for the marketing of a pesticide. The IARC WG evaluation of *probably carcinogenic to humans* accurately reflects the results of published scientific literature on glyphosate and, on the face of it, unpublished studies to which EFSA refers.

Most of the authors of this commentary previously expressed their concerns to EFSA and others regarding their review of glyphosate[28] to which EFSA has published a reply.[29] This commentary responds to the EFSA reply.

The views expressed in this editorial are the opinion of the authors and do not imply an endorsement or support for these opinions by any organisations to which they are affiliated.

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JECH

Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA)

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Commentary

IARC Monographs: 40 Years of Evaluating Carcinogenic Hazards to Humans

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[illegible]

Background: Recently, the International Agency for Research on Cancer (IARC) Programme for the Evaluation of Carcinogenic Risks to Humans has been criticized for several of its evaluations, and also for the approach used to perform these evaluations. Some critics have claimed that failures of IARC Working Groups to recognize study weaknesses and biases of Working Group members have led to inappropriate classification of a number of agents as carcinogenic to humans.

Objectives: The authors of this Commentary are scientists from various disciplines relevant to the identification and hazard evaluation of human carcinogens. We examined criticisms of the IARC classification process to determine the validity of these concerns. Here, we present the results of that examination, review the history of IARC evaluations, and describe how the IARC evaluations are performed.

Discussion: We concluded that these recent criticisms are unconvincing. The procedures employed by IARC to assemble Working Groups of scientists from the various disciplines and the techniques followed to review the literature and perform hazard assessment of various agents provide a balanced evaluation and an appropriate indication of the weight of the evidence. Some disagreement by individual scientists to some evaluations is not evidence of process failure. The review process has been modified over time and will undoubtedly be altered in the future to improve the process. Any process can in theory be improved, and we would support continued review and improvement of the IARC processes. This does not mean, however, that the current procedures are flawed.

Conclusions: The IARC Monographs have made, and continue to make, major contributions to the scientific underpinning for societal actions to improve the public's health.

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Introduction

Important advances in human health have come from the recognition of health hazards and the development of policy actions to address them (Brownson et al. 2009; Espina et al. 2013; Samet 2000). Government and nongovernmental organizations use expert panels to review the scientific literature and to assess its relevance to public health policies. Scientific experts are charged with reviewing the quality and quantity of the scientific evidence and providing scientific interpretations of the evidence that underpin a range of health policy decisions.

The *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* of the International Agency for Research on Cancer (IARC) are a prominent example of such an expert review process. The goal of the Monograph Programme is to assess carcinogenic hazards from occupational, environmental, and lifestyle exposures and agents, thus providing an essential step in the societal decision-making process to identify and then control carcinogenic hazards. For these evaluations, IARC assembles groups of scientists with a range of relevant scientific expertise (called "Working Groups") to review and assess the quality and strength of evidence from informative publications and perform a hazard evaluation to assess the likelihood that the agents of concern pose a cancer hazard to humans (Tomatis 1976). IARC has used this approach for four decades, since the first Monograph in 1972 (IARC 1972). Although widely accepted internationally, there have been criticisms of the classification of particular agents in the past, and more recent criticisms have been directed at the general approach adopted by IARC for such evaluations (Boffetta et al. 2009; Epidemiology Monitor 2012; Ioannidis 2005; Kabat 2012; McLaughlin et al. 2010, 2011).

The Monographs are widely used and referenced by governments, organizations, and the public around the world; therefore, it is critical that Working Group conclusions be clear and transparent. In addition to the actual evaluation, a major contribution of the Monographs is the assembly of relevant literature and its dissemination to the public. We recognize that no system of evaluation is perfect. It is important to foster continuing improvement of the methods used by IARC and other bodies that review scientific evidence. The IARC process itself has been modified from time to time (e.g., addition of specific evaluation of mechanistic data and greater use of formal meta-analyses and data-pooling approaches). Indeed, as recently as April 2014, the IARC Monographs program has been a subject of a review by the Advisory Group to recommend priorities for IARC Monographs during 2015–2019 (Straif et al. 2014). The Advisory Group has made a number of recommendations on further improvements in the Monographs process specifically related to conflict of interest, transparency, and the use of the systematic review procedures in data gathering and evaluation. Thus, possible changes to the process are periodically considered by IARC

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governing groups (Scientific Council and Governing Council) and Advisory Groups.

Here, we focus on current IARC processes and practices because these have been the focus of recent criticisms. The authors of this Commentary are scientists from a wide range of disciplines who are involved in designing and conducting studies that provide data used in hazard evaluations, such as those performed by IARC. Many (but not all) of us have served on IARC Monograph Working Groups, but none are current IARC staff. We first discuss the history of IARC, and describe how the IARC evaluations are performed in order to foster evidence-based policy. We then describe why unbiased evaluations, based on the evidence and free of conflicts of interest, are necessary for public health decision making. Finally, we discuss the recent criticisms of the IARC approach.

The IARC Monographs

History of the IARC Monographs. Shortly after IARC's establishment, its parent entity, the World Health Organization (WHO), asked IARC to prepare a list of agents known to cause cancer in humans. IARC recognized the need for a systematic process to determine which agents should be listed. Such a process was launched in 1972 by Lorenzo Tomatis, then Chief of the Division of Carcinogenicity of IARC (Tomatis 1976). IARC is funded by the governments of 24 countries that have decided to become members, in addition to competitive grants from funding agencies. The IARC Monograph Programme is mainly funded by the U.S. National Cancer Institute through a renewable grant subject to peer review of the program. Other sources of external funding have included the European Commission Directorate-General of Employment, Social Affairs and Equal Opportunities; the U.S. National Institute of Environmental Health Sciences; and the U.S. Environmental Protection Agency.

The IARC process antedates current systematic review methods, but anticipated some of them, for example, with regard to transparent literature identification. In the IARC process, agents are assessed for carcinogenic hazard and assigned to one of five categories, ranging from carcinogenic to humans to probably not carcinogenic to humans (Appendix 1). The classification categories are described in the preamble to the Monographs (IARC 2006). Carcinogenic hazard identification refers to an assessment of whether an agent causes cancer. Hazard identification does not predict the magnitude of cancer risks under specific conditions; this can be determined only with appropriate exposure–response information (National Research Council 2009).

The IARC Monograph process. The process for the preparation of an IARC Monograph is clearly described in the Preamble, which is published as part of each Monograph (e.g., IARC 2014a). It starts with the nomination of candidate agents. Nominations come from national regulatory agencies, scientists, and stakeholders, including public health professionals, experts in environmental or occupational hygiene, industry representatives, and private citizens. It is important to note that anyone (including private citizens) can participate in the nomination process. The Monograph Programme convenes meetings of special Advisory Groups (composed of external scientists that possess a broad range of relevant professional skills) to review agents nominated for evaluation and to suggest IARC priorities for such reviews (Ward et al. 2010). Announcements of a review are made on the IARC website (http://monographs.iarc.fr/ENG/Meetings/). For example, in 2013 IARC sought nominations for agents to be evaluated in 2015–2019 (IARC 2014b). An Advisory Group reviewed the nominated agents and exposures, added several new ones, and discussed the priorities for each.

The IARC staff makes the final selection of agents for review by taking into account the prevalence and intensity of exposure (of both occupational groups and the general population) and availability of sufficient literature for an evaluation of carcinogenicity, as well as advice from the Advisory Groups. The large majority of evaluations concern specific compounds, but there are also monographs on various occupations or industries, for example, aluminum production, insecticide applicators, firefighters, manufacture of leather goods, leather tanning and processing, welding, painters, petroleum refining, and pulp and paper manufacturing. Some individual exposures that occur in these settings have also been evaluated.

The next step is the selection of members of the Working Group (WG). IARC staff review the literature to identify Working Group candidates and specialists in relevant areas of expertise; they also seek names of possible candidates from the scientific community and advisory groups. The list of potential members, including disclosure of relevant conflicts of interest, is posted on the IARC website (http://monographs.iarc.fr/ENG/Meetings/) before the WG is convened, and anyone can send comments. Members are typically scientists who have conducted research relevant to the agent under review, but not necessarily on the specific agent. Selection procedures are evaluated yearly by the Scientific and the Governing Councils. The IARC Section of Monographs also has an external Advisory Board, made up of independent scientists, that periodically peer reviews its activities. In addition to Working Group members, invited specialists, representatives of health agencies, stakeholder observers, and the IARC Secretariat also attend meetings.

The responsibility of the Working Group is to review the literature before the Monograph meeting, discuss the literature at the meeting, and then classify whether an agent is carcinogenic, probably carcinogenic, possibly carcinogenic, not classifiable, or probably not carcinogenic to humans (see Appendix 1). Working Group members are also responsible for writing the IARC Monograph, which must both review the literature and explain why the Working Group came to their specific conclusions.

The procedures used to evaluate the scientific evidence are described in the Preamble to the Monographs (IARC 2006). It is important to stress that only Working Group members conduct the actual evaluation (Wild and Cogliano 2011; Wild and Straif 2011). IARC staff facilitate the evaluation process and ensure that the procedures described in the Preamble are followed; however, they do not determine the outcomes.

IARC assessments of carcinogenicity are based on, and necessarily limited to, scientific evidence available at the time of the review. The evidence comes from epidemiologic studies, animal bioassays, pharmacokinetic/mechanistic experiments, and surveys of human exposure. The aim is to include all relevant papers on cancer in humans and experimental animals that have been published, or accepted for publication, in peer-reviewed scientific journals and also any publicly available government or agency documents that provide data on the circumstances and extent of human exposure. To that end, the search of the literature takes a comprehensive approach. Papers that are found not to provide useful evidence can be excluded later in the process. IARC staff first use previous IARC Monographs (if available), database searches using relevant text strings, and contact with investigators in the field to identify potentially relevant material. Thus, the initial assembly of the literature is performed by individuals who are not engaged in the actual evaluation. Working Group members are then assigned various writing tasks and are instructed to perform their own literature searches to identify any further papers that might have been missed. In addition, all of the papers assembled by IARC are made available to the full Working Group before they meet, and any member can recommend other papers not previously identified that they think should be considered. Finally, papers can be recommended by stakeholder representatives before or during the Working Group meeting.

At the meeting of the Working Group, the assembled documents are reviewed and summarized by discipline-related subgroups.

However, any member of the Working Group has access to all of the assembled literature. The summaries are distributed to all subgroups, and information from all disciplines is discussed in plenary sessions prior to assigning the agents to a specific carcinogenicity category.

Because new findings continually emerge in the literature, agents are reconsidered when IARC and IARC Advisory Groups judge that there is sufficient additional information that might alter a previous evaluation. Thus, conclusions regarding human carcinogenicity of particular substances may change as new evidence becomes available. For some agents, this reevaluation has resulted in progression toward greater certainty regarding their human carcinogenicity, whereas for others the progress has been moved toward less certainty. Such movements are expected in an open, transparent, and evidence-based process. A comprehensive update of all Group 1 carcinogens was recently accomplished in Volume 100 A through F (http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php).

Usually, several agents are evaluated in a single meeting lasting more than 1 week. After discussing the evidence fully, the Working Group members follow the published IARC procedures for combining information from epidemiologic studies and bioassays to arrive at a preliminary classification (IARC 2014a). Mechanistic data are then considered in order to determine whether they warrant a change from the preliminary classification. The Working Group then votes on the final determination. Many votes are unanimous, but on occasion some reviewers may favor a higher or lower ranking than the majority. When there is dissent, alternative interpretations and their underlying reasoning are sometimes reported in the rationale for the evaluation if the dissenters feel their point of view is not sufficiently addressed in the monograph.

Consideration of the totality of the evidence. IARC Working Groups make every effort to provide full and transparent documentation of what evidence was assembled, how it was evaluated, and which papers were most important for the hazard evaluation. Consequently, the monographs are often quite lengthy, containing many evidence tables [see, for example, the recent monograph on trichloroethylene (IARC 2014c)]. Evaluations involve consideration of all of the known relevant evidence from epidemiologic, animal, pharmacokinetic/mechanistic, and exposure studies to assess cancer hazard in humans. Information on human exposure is not formally graded as part of the overall assessment of carcinogenic hazard; however, these data make a critical contribution to the process by characterizing the timing, duration, and levels of exposure in the population, and in evaluating the quality of the exposure assessment in epidemiologic studies.

Doubts and criticisms have sometimes been expressed about the relative weights attributed to evidence from individual disciplines to the assessment of cancer hazards to humans; however, each discipline provides important evidence toward the overall evaluation of causality according to the Bradford Hill considerations (Hill 1965). Because the totality of the evidence is considered, deficiencies in one discipline are often offset by strengths in another. For example, epidemiologic studies may focus on population-relevant exposures, whereas findings from animal experiments usually involve higher exposures but are less susceptible to confounding.

Long-term animal bioassays and mechanistic studies provide critical information on the capacity of an agent to produce cancer in mammalian systems, including humans, and to contribute to decisions that would lead to better protection of human health. Bioassays are the backbone of regulatory science because they provide the opportunity to rigorously evaluate potential hazards before there is widespread human exposure. Bioassays and mechanistic studies are sometimes criticized for employing exposure routes and doses that in most instances humans would not experience, although experimental dose categories sometimes approach exposure levels found in occupational situations. There is evidence that carcinogenicity in human and animal studies is often concordant, although data may differ as to the affected cancer site (Haseman 2000; Maronpot et al. 2004; Tomatis 2002). A major effort to evaluate the concordance between animal and human results is currently under way; two Working Groups were convened at IARC in 2012, and a systematic evaluation of the correspondence between human and animal data was undertaken (a report is not yet publicly available).

Criticisms of the IARC Process

IARC Monographs are widely used to identify potential carcinogenic hazards to humans and serve as reference documents summarizing the literature on many different agents. In recent years, however, individuals have criticized both the classification of individual agents as well as the general evaluative approach (Boffetta et al. 2009; Epidemiology Monitor 2012; Kabat 2012; McLaughlin et al. 2010, 2011). We discuss four of these criticisms below.

Criticisms of epidemiology. Some of the criticisms of the IARC process have occurred in the context of more general criticisms of epidemiology as a science (Kabat 2008); these were discussed in detail by Blair et al. (2009). Potential methodological weaknesses for observational epidemiologic studies are well recognized and can be found in any epidemiologic textbook (Checkoway et al. 2004; Rothman et al. 2008). Most studies are subject to one or more methodological limitations, but this does not necessarily invalidate their findings (Blair et al. 2009). In fact, the value of epidemiologic studies has been shown by the identification of a number of well-established human carcinogens, including tobacco, asbestos, benzene, hexavalent chromium, and some viruses, in multiple studies. Some critics also argue that small or nonexistent health risks are unjustifiably highlighted and hyped by researchers who have a vested interest in continued research funding and the need to publish to benefit their careers (Boffetta et al. 2008; Kabat 2008; McLaughlin et al. 2010, 2011; Taubes 1995). However, such overstated results are unlikely to exert much of an influence in a Monograph because IARC evaluations are based on the totality of the evidence. The problem would have to occur in multiple studies, and the Working Group would have to be unable to identify it or be unwilling to weigh such studies appropriately. Incorrect positive conclusions regarding carcinogenicity may also occur in reviews of multiple studies because of publication bias, which may selectively populate the literature only with "positive" findings. However, once a topic is recognized as scientifically important, reports on relevant studies will be published regardless of the findings, so publication bias is mainly a concern for newly arising issues. To evaluate the potential for publication bias, Working Groups consider whether stronger negative studies (both in terms of design and sample size) have emerged after publication of an initial cluster of smaller and/or weaker positive studies. Funnel plots help in the assessment of bias relating to sample size and publication bias (Borenstein et al. 2009). In contrast, there are no established statistical techniques to clearly characterize strength of design.

One of the distinctive features of epidemiology is that criticism and self-criticism are firmly embedded in the discipline. A great deal of work has been done on developing methods for critical appraisal (Elwood 2007) and for assessing the likely strength and direction of possible biases (Rothman et al. 2008). Epidemiologists and other members on Working Groups routinely use various approaches to assess possible bias in study design and analysis when weighing the strengths of different studies.

The issue of false positives. Epidemiology specifically has been criticized for a tendency to produce false-positive results (i.e., individual study associations not borne out by the weight of the evidence) or to preferentially report positive findings over negative

or inconclusive findings (i.e., publication bias) (Boffetta et al. 2008, 2009; Ioannidis 2005; Kabat 2012; McLaughlin and Tarone 2013). This criticism has been most often applied to potential false positives from individual studies, but it has been inferred that this problem may also apply to overall hazard evaluations, which use findings from multiple studies. We will consider each of these issues in turn.

False-positive findings may occur by chance, particularly when many combinations of exposures and health outcomes have been examined in a single study without strong prior expectations of association; this happens often, for example, in genome-wide association studies where thousands of gene–disease associations are evaluated. Chance, of course, operates in all disciplines and in both observational and experimental studies. However, there are well-known statistical techniques to reduce the probability of declaring chance findings as "positive" (Rothman et al. 2008). Independent replication, however, is the most convincing way of checking for "chance" findings; hazard evaluations, such as those conducted by IARC Working Groups, rely heavily on reproducibility in independent studies and also interpret data following Bradford Hill principles (Hill 1965).

False negatives are more difficult to address, and perhaps they occur more frequently than false positives because of low statistical power, nondifferential misclassification of exposure and/or outcome, and incomplete follow-up, which tends to reduce the observed difference in risk between the exposed and nonexposed populations (Ahlbom et al. 1990; Blair et al. 2009; Grandjean 2005; Rothman et al. 2008). A new positive association stimulates research, whereas studies finding no associations tend to stifle further work.

There are difficulties in conducting epidemiologic studies of agents that are relatively "weak" carcinogens, or for stronger carcinogens where exposure is very low because bias and confounding can obscure weak positive associations (MacMahon et al. 1981). In general, weak carcinogens and low levels of exposure result in a smaller "signal-to-noise" ratio making the real signal more difficult to detect. Although the identification of small relative risks to humans poses special challenges to scientific research, the refinement of study designs, improvements in methods of exposure assessment, and the use of biomarkers have helped to address the problems (e.g., newer studies on the effects of air pollution, the growth in opportunities to examine gene–environment interactions) (Gallo et al. 2011). In some situations, there is less of a problem. For example, in occupational studies, exposures and relative risks may be higher while differences in lifestyle factors between different groups of workers are smaller (Checkoway et al. 2004); thus, any confounding by nonoccupational factors is likely to be weak, even from potent causes of cancer such as cigarette smoking (Siemiatycki et al. 1988). Of course, the interpretation of such studies is enhanced when there is supporting evidence from bioassays and/or mechanistic studies.

False-positive and false-negative findings in individual studies may arise by chance or bias, including bias due to confounding (Rothman et al. 2008). However, the evaluation of multiple independent epidemiologic studies from various geographic locations, involving a variety of study designs, as well as evidence from experimental studies, reduces the possibility that false-positive findings from any individual study influences the overall evaluation process. Some studies may have greater influence than others because of methodological strengths and/or large sample size. The use of information from a variety of study designs reduces the likelihood of false-positive evaluations because it is unlikely that the same biases will occur in multiple studies based on different populations under different study designs. Moreover, apparently conflicting results from epidemiologic studies do not necessarily indicate that some are false positive or false negative. This might, for example, reflect differences in levels of exposure or susceptibility to the effects of exposure (effect modification). Finally, judgment by the Working Group is not based exclusively on epidemiologic studies but usually also on results from laboratory and mechanistic studies that provide further evidence and biological coherence. For the Monographs that evaluate carcinogenic hazards associated with specific occupations or industries, the exposures of interest usually involve a complex mixture of chemicals. For these evaluations, most information comes from epidemiologic studies, although exposures to individual agents occurring at these workplaces may have been evaluated in experimental studies.

Discontent with IARC Monograph processes. The IARC Monograph evaluation process has been criticized and it has been alleged that "a number of scientists with direct experience of IARC have felt compelled to dissociate themselves from the agency's approach to evaluating carcinogenic hazards" (Kabat 2012). This is a serious charge. However, the author of this claim provided no evidence to support the charge that a "number of scientists" have dissociated themselves from the process, nor has there been any indication of how many scientists have taken this step, or for what reason. In science, we expect sweeping statements such as this to be appropriately documented. We have not been able to identify any credible support for this contention.

There is an IARC Governing Council and a Scientific Council to provide oversight and guidance to the agency. The Governing Council represents the participating states and sets general IARC policy. It appoints the IARC Director and members of the Scientific Council. The latter are independent scientists who are selected to provide scientific expertise and not as representatives of the member states. They serve for 4 years and serve without pay. The voting members of Monograph Working Groups are not employed by IARC, and they perform this task without financial compensation. There have been 111 volumes, including six separate documents under Volume 100, and three Supplements. Over the years, as the number of publications for each agent to be evaluated increased, the size of Working Groups has increased. Early in the process they were sometimes as small as 10, but now they sometimes include as many as 30 scientists. We estimate that over the entire Monograph series, approximately 1,500 scientists have served as Working Group members, and of course many scientists have also served on the Advisory Groups, Scientific Council, and Governing Council. Thus, if even a small percentage of these scientists were disenchanted with the IARC process, it would result in a considerable number of such individuals and should be easy to document. To be taken seriously, the "dissociation" criticism needs to be supported by documented information describing the number of scientists who have taken this action.

Criticisms of specific evaluations. Some criticisms of the IARC process relate to specific agents, where it is asserted that the hazard evaluations of category 2B, 2A, or 1 are not supported by the scientific literature. In the 111 volumes of the Monographs produced over the four decades since 1971, 970 agents have been considered, 114 (12%) have been classified as carcinogenic to humans (Group 1), 69 (7%) as probably carcinogenic (Group 2A), 283 (29%) as possibly carcinogenic (Group 2B), 504 (52%) as not classifiable regarding their carcinogenicity (Group 3), and 1 (< 1%) as probably not carcinogenic to humans (Group 4). Thus, even for this highly select group of agents (i.e., those selected for evaluation because there was some concern that they might be carcinogenic), more than one-half were "not classifiable" or "probably not carcinogenic," and a further 29% were placed into the category of possibly carcinogenic to humans. This distribution, based on nearly 1,000 evaluations in which fewer than one in five agents were classified as carcinogenic or probably carcinogenic to humans, does not support a conclusion that the process is heavily biased

toward classifying agents as carcinogenic (Boffetta et al. 2009; Kabat 2012).

The monographs for formaldehyde, coffee, DDT, and radiofrequency electromagnetic radiation have been cited as examples of problematic evaluations by some (Kabat 2012) [among these, only formaldehyde was classified as known to be carcinogenic to humans (Group 1) by an IARC Working Group]. These are important agents. However, to accept the charge that IARC evaluations are fundamentally biased, one has to assume that the scientists who were members of the Working Groups were incapable of appropriately evaluating weaknesses in the data, or that they distorted the evaluative process because of personal biases. In our experience, neither of these assertions is correct. Dissent among scientists is not unusual in any area of science. It is a strength of the scientific process. The IARC process capitalizes on this by bringing scientists from different disciplines together in one room to evaluate the literature and to reach a reasoned conclusion. Differences of opinion occur among Working Group members. These differences, however, typically involve disputes related to assignment to adjacent classification categories. It is instructive that there are no instances in which a carcinogen classified at the Group 1 level by one Working Group has been reversed by another. The recent review of all Group 1 agents for Volume 100 provided ample opportunity to reverse such previous classifications, but none occurred. Every scientist could probably name a substance that has been reviewed by IARC that they might personally place in a different category from that assigned by the Working Group, but this is one opinion against the collective wisdom and process of the Working Group.

Criticisms of the composition of the working groups. The composition of the Working Groups has also been criticized (Erren 2011; McLaughlin et al. 2010, 2011); it has been argued that members of the Working Groups who have conducted research on the agents under evaluation have a vested interest in advancing their own research results in the deliberations. This criticism has been addressed directly by Wild and colleagues (Wild and Cogliano 2011; Wild and Straif 2011) from IARC, and we know of no evidence to support this contention. Even if some scientists on the Working Group have performed research on some of the agents being considered, they make up a minority of the Working Group because several agents are usually evaluated in a single meeting, so the number of Working Group members who have conducted research on any one agent is typically small. Our experience has been that having some scientists who are knowledgeable about the studies of the agent under evaluation (and can therefore answer technical queries) and others from different, but related, fields provides a knowledgeable and balanced mix of scientific backgrounds for a thoughtful evaluation of the literature.

Working Group members do not receive any fee for their work, but they are paid travel expenses, and there is some prestige associated with service on an IARC Monograph. However, most scientists asked to serve on IARC Working Groups have already achieved some measure of scientific stature, and there is no reason why this should bias their evaluation in one direction or the other. In addition,

Appendix 1: Classification Categories for the Overall Evaluation for the IARC Monographs (IARC 2006)

Group 1: The agent is *carcinogenic to humans.*
This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.
This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic.*

Group 2A: The agent is *probably carcinogenic to humans.*
This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Group 2B: The agent is *possibly carcinogenic to humans.*
This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is *not classifiable as to its carcinogenicity to humans.*
This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.
Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of noncarcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4: The agent is *probably not carcinogenic to humans.*
This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

IARC strictly requires that any conflict of interests be divulged, and does not allow those with conflicts of interest to serve on Working Groups, although nonvoting observers who may have conflicts of interest are able to attend the Working Group meetings.

Conclusions

For more than four decades the IARC Monograph Programme has provided evaluations of cancer hazards to humans from many different exposures and agents. These are often the first evaluations of new and emerging threats to public health and, consequently, are subject to intense scrutiny. Although these evaluations are widely respected and used by many organizations, institutions, companies, and government agencies to improve the public's health, IARC has recently been subject to criticism over conclusions on specific agents, the process that leads to such conclusions, and membership of the Working Groups. Debate and criticism facilitate self-correction and a check on the validity in science. We are concerned, however, that the criticisms expressed by a vocal minority regarding the evaluations of a few agents may promote the denigration of a process that has served the public and public health well for many decades for reasons that are not supported by data.

There has been very broad involvement of the scientific community in the IARC Monograph Programme through participation in the Working Groups and service on the IARC Governing and Scientific Councils and ad hoc Advisory Board for the Monograph Programme. The long list of scientists who are coauthors of this paper attests to the strong support that IARC has in the scientific community. Many exposures that IARC has evaluated have also been independently evaluated by other institutions, such as the U.S. National Toxicology Program (https://ntp.niehs.nih.gov/); U.S. Environmental Protection Agency (http://www.epa.gov/); National Academy of Sciences (http://www.nasonline.org/); the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values and Biological Exposure Indices (http://www.acgih.org/); the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (http://www.av.se/arkiv/neg/); Institute of Occupational Medicine (http://www.iom-world.org/); World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Expert Reports; European Chemicals Agency (https://echa.europa.eu); Swedish Criteria Group for Occupational Standards (2013); California Office of Environmental Hazard Assessment (Proposition 65; http://oehha.ca.gov/prop65/background/p65plain.html); Health Canada Bureau of Chemical Safety (http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/fd-da/bcs-bsc/index-eng.php); Scientific Committee on Occupational Exposure Limits (SCOEL), European Commission, Employment, Social Affairs and Inclusion (http://ec.europa.eu/social/main.jsp?catId=1488&langId=en&intPageId=684); European Food Safety Authority (EFSA 2013); and European Chemicals Agency (ECHA; http://echa.europa.eu/). Assessments from these groups typically come to conclusions similar to those from IARC. This further indicates broad agreement within the scientific community regarding evidence on carcinogenicity in the scientific literature and expands the number of scientists who do not have a "vested interest" but who have generally agreed with those conclusions.

Disagreement with the conclusions in an IARC Monograph for an individual agent is not evidence for a failed or biased approach. Some disagreement about the carcinogenic hazard of important agents seems inherent to the scientific enterprise and is unavoidable at early stages of the hazard evaluation, where IARC usually operates. Because the evaluations are not—and should not be—static, it is difficult to see how such assessments could be addressed any differently. Substances now universally recognized as human carcinogens (e.g., tobacco, asbestos) at one time went through a quite lengthy period of contentious debate (Michaels 2006, 2008). Any process can in theory be improved with fair and constructive criticism; appropriate reviews may take place from time to time, and we would support continued review and improvement of the IARC processes. However, as a group of international scientists, we have looked carefully at the recent charges of flaws and bias in the hazard evaluations by IARC Working Groups, and we have concluded that the recent criticisms are unfair and unconstructive.

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COMMENTARY

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Commentary: IARC Monographs Program and public health under siege by corporate interests

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The International Agency for Research on Cancer (IARC) evaluates causes of cancer with help from independent international experts in an open and transparent manner. Countries, research and regulatory agencies, and other organizations adopt IARC evaluations for communication of human cancer hazards, and for strategies to prevent cancer. Scientists worldwide endorse IARC cancer evaluations and process. Those with economic interests, however, challenge IARC's cancer evaluations, most recently for glyphosate and red and processed meats, and are conducting a campaign including intervention from US Congressional Representatives to discredit IARC's review process and to undermine financial support—a campaign intimidating to IARC and Working Group members. Challenges to scientific interpretations serve to advance science and should be resolved by scientific experts who do not have conflicts of interest. Such interference does not bode well for the free flow of scientific information that informs and protects the public from risks of cancer.

KEYWORDS
cancer prevention, corporate influence, glyphosate, IARC monographs, monsanto, roundup

1 | INTRODUCTION

The International Agency for Research on Cancer (IARC) was established in Lyon, France in 1965 as a specialized cancer research agency of the World Health Organization, with founding members Germany, France, Italy, United Kingdom, and United States. Currently, IARC has 25 member countries. Since 1970 the IARC Monographs Program, created by Lorenzo Tomatis, MD, has been evaluating chemical substances, agents, exposure circumstances, and lifestyle factors for evidence of carcinogenicity. IARC Monographs provide a unique and valuable objective international health service to evaluate and inform the public about cancer hazards. IARC Working Group (WG) meetings held in Lyon, France, thrice a year, are comprised of independent scientists from throughout the world, providing a truly international perspective. Meetings are openly transparent and members are vetted for conflicts of interest. The primary objective of the Program is to publish in the form of agent/substance-oriented Monographs, critical reviews and scientific evaluations written by an international WG of experts on evidence of carcinogenicity for a wide range of human exposures. IARC staff coordinates the process and provides scientific and material support to WGs. The authors of this commentary have participated in the IARC Monographs Program meetings. Also, Harri Vainio and James Huff have served as Chiefs of the IARC Monographs Program.

Levels of evidence for an agent causing cancer are agreed upon by WG members as detailed in IARC Monographs,[1,2] and shortly after WG meetings are concluded, summary evaluations with supporting evidence are published in Lancet Oncology. Monographs report on human cancers observed with available measures of exposures as an integral part of hazard characterization, the initial step in the risk assessment process, but do not ordinarily perform quantitative dose-response risk assessments that extend beyond the range of observed data. Countries and research and regulatory agencies adopt IARC classifications for communication of potential human cancer hazards,[3] and for developing strategies to control and prevent cancer.

Institution at which the work was performed: The work was not performed at an institution.

In Monographs Volumes 1-120, IARC evaluated available experimental, epidemiological, and mechanistic evidence of carcinogenicity for IARC's 1003 agents.[1] The selection process for agents relies upon published scientific findings indicating human exposures and potential cancer risk based on studies in humans and experimental animals along with information on mechanism.[4,5] Agents without evidence of carcinogenicity and human exposure are not selected for review. Centered on these selection factors, one would a priori expect a significant percentage of agents reviewed and evaluated to provide evidence of carcinogenicity. Categorical results for 1003 evaluations are:[6] Group 1 "carcinogenic to humans," 120 agents; Group 2A "probably carcinogenic to humans," 81; Group 2B "possibly carcinogenic to humans," 299; Group 3 "not classifiable as to its carcinogenicity to humans," 502; Group 4 "probably not carcinogenic to humans, 1. Based on selection criteria, it is thus surprising that only ~20% of agents/exposure circumstances reviewed are classified as human carcinogens or probable human carcinogens.

Likewise, selection of chemicals for animal cancer testing by the US National Toxicology Program based on widespread human exposure, and not suspicion of carcinogenic activity,[7] resulted in only 6.8% of substances giving positive cancer results in two species (one requirement for IARC sufficient evidence of cancer in experimental animals). These results further support the observation that the slightly higher percentage of carcinogens identified in IARC reviews is a reflection of the chemical selection criteria. Yet, despite this selection bias for agents that demonstrate evidence of carcinogenicity, only 120 of 1003 IARC agents (12%) evaluated were considered unequivocally carcinogenic to humans; adding those 81 agents evaluated by IARC WGs as "probably carcinogenic to humans" still results in only 20%; while 50% of agents evaluated by IARC were not classifiable as to their carcinogenicity to humans. Nonetheless, in light of this low percentage of agents reviewed, evaluated, and considered to be carcinogenic by IARC, the American Chemistry Council (ACC), a trade association which promotes the interests of US chemical companies has voiced its opinion that IARC is "dubious and misleading" in classifying potential carcinogens.[8] ACC and its consultants further criticize IARC for misleading the public by over-evaluating agents that cause cancer in humans.[9,10]

We mention two IARC Monographs that have recently received considerable attention: red and processed meats[11] and glyphosate (two other chemicals evaluated at the same meeting as 2A, diazinon and malathion, engendered no criticism).[12] In October 2015, after an 8-day meeting, an independent IARC WG of 22 scientists from ten countries concluded consumption of "processed meat" is "carcinogenic to humans" based on sufficient evidence for colorectal cancer from epidemiology studies; and "consumption of red meat" is "probably carcinogenic to humans" based on credible studies showing associations with colorectal, pancreatic, and prostate cancers. Differences in these evaluations center on strength of available epidemiological evidence: consumption of processed meat was classified as Group 1 on sufficient evidence in humans, whereas consumption of red meat was classified as Group 2A on substantial epidemiological data and strong mechanistic evidence. Significantly, the IARC WG "assessed more than 800 epidemiological studies that investigated the association of cancer with consumption of red meat or processed meat in many countries, from several continents, with diverse ethnicities and diets."[11,13] [Note: the IARC definition of *sufficient evidence of carcinogenicity* to humans signifies "a causal relationship has been established between exposure to the agent and human cancer." *Limited evidence of carcinogenicity* to humans means that "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."[1,6]

Glyphosate was discovered in 1970 and brought to the market in 1974 by Monsanto under the trade name Roundup. Glyphosate, a broad-spectrum herbicide, currently the highest production volume of all herbicides, is promoted and sold worldwide by many agrochemical companies, in different solution strengths and with various adjuvants, under dozens of trade names, as more than 750 glyphosate products.[12] In March 2015, after an 8-day meeting, an independent IARC WG of 17 scientists from 11 countries concluded glyphosate, an herbicide widely used to control weeds in non-agricultural and agricultural settings primarily on genetically-engineered crops, was "probably carcinogenic to humans" [2A] based on sufficient evidence of carcinogenicity in experimental animals and limited evidence of cancer in humans for non-Hodgkin lymphoma. In addition, there was strong evidence that glyphosate operates through two key characteristics of known human carcinogens: exposure to glyphosate or glyphosate-based formulations is genotoxic based on studies in human cells in vitro and studies in experimental animals, and strong evidence that glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid (major metabolite) induces oxidative stress in experimental animals, and in studies of humans cells in vitro.[12,14] Some have questioned this conclusion,[15,16]whereas 94 international independent scientists agreed with and support IARC's evaluation for glyphosate[17] as do others.[18,19] Further, IARC, the German Federal Institute for Risk Assessment (BfR), and the European Food Safety Authority (EFSA) found increases of tumors in seven carcinogenicity studies in mice and rats.[20]However, BfR and EFSA opined five reasons for dismissing these carcinogenic effects, using a "weight of evidence" (WOE) approach. Clausing[20] and Clausing et al,[21] however, have adequately challenged the validity of the BfR and EFSA approach, and their five WOE reasons for dismissing evidence of carcinogenicity.

Regarding the worldwide credibility and public health value of IARC Monographs, 124 scientists with expertise in chemical carcinogenesis have praised and endorsed the IARC Monographs for the transparency of their review process and IARC's impartial high quality evaluations in identifying cancer hazards in the environment and workplace.[22] IARC allows observers and representatives from government agencies, industry and other organizations to attend and participate in WG meetings; however, they are not permitted to vote on evaluations of carcinogenicity.

For the past 47 years, IARC Monographs have contributed to improving public health by providing evidence-based unbiased expert evaluations to identify carcinogens and to support cancer prevention

and control.[22] Nonetheless, vested-interest criticisms of IARC cancer evaluations,[10] supported by pro-industry consultants,[23–25] have centered particularly on the scientific credibility of IARC evaluations. Pointedly, in response to IARC evaluations for red and processed meat and glyphosate, the ACC initiated a Campaign for Accuracy in Public Health Research (CAPHR) with the proclaimed aim "to promote credible, unbiased, and transparent science" to assist public health and policy makers in their evaluation and interpretation of evidence for cancer causation.[9] The ACC further states "IARC's Monographs Program suffers from persistent scientific and process deficiencies that result in public confusion and misinformed policy-making." Yet, most of the authoritative sources cited in an article critical of the IARC Monographs Program[10] appear to have conducted research or consultations that has been supported by industry.[23,24] Monsanto, through membership in the ACC, has lobbied extensively, and paid scientists to author papers on the safety and continued use of glyphosate,[25–28] and that contradict the findings of IARC despite recognized human health hazards. McClellen,[27] as editor of Critical Reviews in Toxicology, has published 10 articles dealing with glyphosate and health effects; most dispute IARC's conclusions in its evaluation of glyphosate or otherwise conclude that glyphosate's risk is minimal, or non-existent.[26,29–37] These authors have been supported/funded directly or indirectly by Monsanto, the primary producer of glyphosate and products containing this active ingredient. Additionally, Monsanto has sent a threatening letter of intimidation to IARC staff.[38] Ominously, EPA staff has been accused of collusion with Monsanto to downgrade the health hazards of glyphosate.[39–41]

Ironically, from recently released documents, Monsanto thought their herbicide would indeed fit into the IARC category of either "possibly," or "probably carcinogenic to humans" long before the IARC Monographs review meeting and yet mounted a campaign to criticize IARC's evaluation.[42,43] Further, a Monsanto internal confidential memorandum states "And while we have vulnerability in the area of epidemiology, we also have potential vulnerabilities in the other areas that IARC will consider, namely, exposure, genetox, and mode of action … If there is a force working against glyphosate, there is ample fodder to string together to help the cause [presumably to make glyphosate/Roundup viewed as safe] even though it is not scientifically justified in its purest form."[42]

The ACC has lobbied US Congress to investigate IARC's review of glyphosate.[44] Now, because of successful lobbying, US Congressional Republicans are questioning the credibility of IARC Monographs and funding from the US National Institutes of Health (NIH). They further question the ability of EPA to objectively evaluate the carcinogenicity of glyphosate because one staff member participated in the IARC review as a WG member. A six-page letter from the Chairman of the Committee on Oversight and Government Reform[45] to Francis Collins, Director, NIH, questions NIH support for IARC Monographs, and requests a briefing on NIH funding to such "foreign" entities in light of IARC's cancer evaluations being inconsistent with other entities, particularly on red meats, processed meats, and glyphosate.

Additionally, an eight-page letter[46] from the chair of The Committee on Science, Space, and Technology to Gina McCarthy, Administrator, US Environmental Protection Agency, admonishers her for EPA staff members apparent role in the IARC Monograph WG's evaluation of glyphosate. Congressman Smith expressed concern that "activists" working both within and outside of EPA might derail the EPA preliminary evaluation of glyphosate[16]-an evaluation not yet finalized that is contradictory to the IARC conclusion on the probable carcinogenicity of glyphosate. Further, Kelland,[47] a defender of Monsanto, has contacted IARC glyphosate Working Group members and has accused IARC of altering the Working Group's evaluation. IARC[48] has rebutted these accusations. Further, congressional hearings are being considered to investigate IARC and the Monographs Program evaluation process and requests have been made for IARC to provide names of potential witnesses.[49] The Director of IARC has responded to the inquiry of Smith and Biggs,[50] but declined to provide witnesses for any potential congressional hearing. The response from IARC[50] apparently did not satisfy Congressman Smith et al[51] who continue to question the integrity of the IARC Monographs Program, US funding for the program, and to again request that IARC provide names of potential witnesses. Such tactics are intimidating to IARC, to IARC Working Group members, and to research and regulatory agencies reliant on IARC's science-based cancer causation evaluations.

Potential inconsistencies or relevant challenges in scientific interpretation often serve to advance science and should be resolved by scientific experts who do not have a conflict of interest in these evaluations, and certainly not by politicians with vested interests who lack understanding of the strength of scientific evidence supporting or opposing a particular scientific determination.

The interferences by economic interests in cancer evaluations conducted by public health institutions[52,53] do not bode well for the free flow of scientific information that informs and protects the public and workers from clear risks of cancer.

AUTHORS' CONTRIBUTIONS

All authors participated in the conception, design, analysis, interpretation of the work and in the revision of drafts, and all authors agreed with the final version of the commentary. PFI and JH participated in the acquisition of the documents included in the analysis and the first draft, and are accountable for the accuracy and integrity of the documents cited in the report.

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Dr. James Huff reports that he has been retained as expert consultant on long-term animal bioassays of glyphosate in litigation for plaintiffs. All other authors report no conflicts of interest.

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DISCLAIMER

None.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND POLLUTION
PREVENTION

MAR 16 2017

MEMORANDUM

SUBJECT: Transmission of Meeting Minutes and Final Report of the December 13-16, 2016 FIFRA SAP Meeting Held to Consider and Review Scientific Issues Associated with EPA's Evaluation of the Carcinogenic Potential of Glyphosate

TO: Riek P. Keigwin, Jr.
Acting Director
Office Pesticides Programs

FROM: Steven M. Knott, M.S.
Acting Executive Secretary
FIFRA SAP Staff
Office of Science Coordination and Policy

THRU: Stanley Barone, Ph.D.
Acting Director
Office of Science Coordination and Policy

Please find attached the meeting minutes and final report of the December 13-16, 2016 Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) open public meeting held in Arlington, Virginia. This report addresses a set of scientific issues associated with EPA's evaluation of the carcinogenic potential of glyphosate.

Attachment

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FIFRA Scientific Advisory Panel
Meeting Minutes and Final Report
No. 2017-01

A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

EPA's Evaluation of the Carcinogenic Potential of Glyphosate

December 13-16, 2016
FIFRA Scientific Advisory Panel Meeting
Held at the EPA Conference Center,
One Potomac Yard
Arlington, Virginia

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NOTICE

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP) is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act and established under the provisions of FIFRA as amended by the Food Quality Protection Act (FQPA) of 1996. The FIFRA SAP provides advice, information, and recommendations to the Agency Administrator on pesticides and pesticide-related issues regarding the impact of regulatory actions on health and the environment. The Panel serves as the primary scientific peer review mechanism of the Environmental Protection Agency (EPA), Office of Pesticide Programs (OPP) and is structured to provide balanced expert assessment of pesticide and pesticide-related matters facing the Agency. Food Quality Protection Act (FQPA) Science Review Board members serve the FIFRA SAP on an *ad hoc* basis to assist in reviews conducted by the Panel. These meeting minutes and final report have been written as part of the activities of the FIFRA SAP and represent the views and recommendations of the FIFRA SAP and do not necessarily represent the views and policies of the EPA, or of other agencies in the Executive Branch of the Federal government. Mention of trade names or commercial products does not constitute an endorsement or recommendation for use. The meeting minutes and final report do not create or confer legal rights or impose any legally binding requirements on the EPA or any party. In preparing the meeting minutes and final report, the FIFRA SAP carefully considered all information provided and presented by the EPA, as well as information presented in public comments.

These meeting minutes and final report of the December 13-16, 2016 FIFRA SAP meeting held to consider and review scientific issues associated with EPA's evaluation of the carcinogenic potential of glyphosate were certified by James McManaman, Ph.D., FIFRA SAP Chair and Steven Knott, M.S., Designated Federal Official. The minutes and final report are publicly available on the SAP website (https://www.epa.gov/sap) under the heading of "Scientific Advisory Panel Meetings" and in the public e-docket, Docket Identification Number: EPA-HQ-OPP-2016-0385, accessible through the docket portal: https://www.regulations.gov. Further information about FIFRA SAP reports and activities can be obtained from its website at https://www.epa.gov/sap. Interested persons are invited to contact Steven Knott, Designated Federal Official, via email at knott.steven@epa.gov.

SAP Minutes and Final Report No. 2017-01

A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

EPA's Evaluation of the Carcinogenic Potential of Glyphosate

December 13-16, 2016
FIFRA Scientific Advisory Panel Meeting
Held at the EPA Conference Center
One Potomac Yard
Arlington, Virginia

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FIFRA SAP Chair
FIFRA Scientific Advisory Panel

Date: MAR 16 2017

Steven Knott, M.S.
Designated Federal Official
Office of Science Coordination and Policy, EPA

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Date: MAR 16 2017

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TABLE OF ACRONYMS

ACRONYMS	DESCRIPTION
AAF	2-Acetylaminoflourene
AHS	Agricultural Health Study
AIDS	Acquired Immunodeficiency Syndrome
AOP	Adverse Outcome Pathway
ATS	Academy of Toxicological Sciences
BW	Body Weight
CASAC	Clean Air Science Advisory Committee
CDK	Cyclin-dependent kinase
CI	Confidence Interval
CNV	Gene Copy Number Variation
DABT	Diplomate of the American Board of Toxicology
DNA	Deoxyribonucleic Acid
EFSA	European Food Safety Authority
FACE	Fellow of the American College of Epidemiology
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	Food Quality Protection Act of 1996
FRSC	Fellow of the Royal Society of Chemistry
GM	Genetically Modified
HIV	Human Immunodeficiency Virus
HL	Hodgkin's Lymphoma
IARC	International Agency for Research on Cancer
IP	Intraperitoneal
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
MM	Multiple Myeloma
MOA	Mode of Action
MRID	EPA OPP Master Record Identification Number
MTD	Maximum Tolerated Dose
NHL	Non-Hodgkin's lymphoma
NIOSH	National Institute for Occupational Safety and Health
NRC	National Research Council
NTP	National Toxicology Program
OCSPP	EPA Office of Chemical Safety and Pollution Prevention

ACRONYMS	DESCRIPTION
OECD	Organization for Economic Cooperation and Development
OPP	Office of Pesticide Programs
OR	Odds Ratio
OSHA	Occupational Safety and Health Administration
RR	Relative Risk
SAP	FIFRA Scientific Advisory Panel
SAS	Statistical Analysis System
SCE	Sister Chromatid Exchanges
USDA	United States Department of Agriculture
US EPA or EPA	United States Environmental Protection Agency
WHO	World Health Organization
8-OH-dG	8-hydroxy-2' -deoxyguanosine

INTRODUCTION

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed the meeting minutes and final report of the SAP meeting regarding scientific issues associated with **EPA's evaluation of the carcinogenic potential of glyphosate.** Advance notice of the SAP meeting was published in the *Federal Register* on July 26, 2016 (81 FR 48794).

Glyphosate is a non-selective, phosphonomethyl amino acid herbicide registered to control weeds in various agricultural and non-agricultural settings. Labeled uses of glyphosate include over 100 terrestrial food crops as well as other non-agricultural sites, such as greenhouses, aquatic areas, and residential areas. Use of glyphosate in the United States and globally has increased over time, particularly with the introduction of glyphosate-resistant crops; however, usage has stabilized in recent years due to the increased number of weed species becoming resistant to glyphosate. Glyphosate is currently undergoing Registration Review, which is a program where all registered pesticides are reviewed at least every 15 years as mandated by the Federal Insecticide, Fungicide, and Rodenticide Act.

Recently, several international agencies have evaluated the carcinogenic potential of glyphosate. In March 2015, the International Agency for Research on Cancer (IARC), a subdivision of the World Health Organization (WHO), concluded that glyphosate was "probably carcinogenic to humans" (Group 2A). Later, in November 2015, the European Food Safety Authority (EFSA) concluded that glyphosate was unlikely to pose a carcinogenic hazard to humans. In May 2016, the Joint Food and Agriculture Organization (FAO) / WHO Meeting on Pesticide Residues (JMPR), another subdivision of the WHO, concluded that glyphosate was unlikely to pose a carcinogenic risk to humans from exposure through the diet.

Recently, EPA collected and analyzed a substantial amount of data informing the carcinogenic potential of glyphosate and utilized its draft "*Framework for Incorporating Human Epidemiological & Incident Data in Health Risk Assessment*" (EPA, 2010) to assess its potential carcinogenic hazard. The draft framework provides the foundation for evaluating multiple lines of scientific evidence and includes two key components: (i) Problem formulation and (ii) Use of the mode of action/adverse outcome pathway (MOA/AOP) frameworks. A comprehensive analysis of data on glyphosate from submitted guideline studies and the open literature was performed. This included epidemiological, animal carcinogenicity, genotoxicity, metabolism, and mechanistic studies. Guideline studies were collected for consideration from the toxicological databases for glyphosate and glyphosate salts. A fit-for-purpose systematic review was conducted to obtain relevant and appropriate open literature studies with the potential to inform the human carcinogenic potential of glyphosate. Furthermore, the list of studies obtained from the toxicological databases and systematic review was cross-referenced with recent internal reviews, review articles from the open literature, and international agency evaluations (i.e., IARC, EFSA, and JMPR).

Available data from epidemiological, laboratory animal carcinogenicity, and genotoxicity studies were reviewed and evaluated for study quality and results to inform the human carcinogenic potential of glyphosate. Additionally, as described in the draft "*Framework for Incorporating Human Epidemiological & Incident Data in Health Risk Assessment,*" the

multiple lines of evidence were integrated in a weight-of-evidence analysis using the modified Bradford Hill Criteria considering concepts such as strength of association, consistency of observations, dose response, temporal concordance, and biological plausibility.

The focus of this SAP meeting was on soliciting advice from the Panel on the evaluation and interpretation of the available data for each line of evidence and the weight-of-evidence analysis, as well as how the available data inform cancer classification descriptors per the Agency's 2005 *Guidelines for Carcinogen Risk Assessment.* The Agency's evaluation is summarized in an Issue Paper entitled: Glyphosate Issue Paper: Evaluation of Carcinogenic Potential, EPA's Office of Pesticide Programs, September 12, 2016 (EPA, 2016a).

During the FIFRA SAP meeting, US EPA personnel provided the following presentations (listed in order of presentation):

Welcome and Opening Remarks – Jack Housenger, Director, Office of Pesticide Programs

Introduction – Dana Vogel, Director, Health Effects Division, Office of Pesticide Programs

Overview of Glyphosate Registration and Carcinogenic Potential Evaluation – Monique Perron, ScD, Health Effects Division, Office of Pesticide Programs

Systematic Review and Data Collection Methods – Gregory Akerman, PhD, Health Effects Division, Office of Pesticide Programs

Data Evaluation of Epidemiology Studies – Monique Perron, ScD, Health Effects Division, Office of Pesticide Programs

Data Evaluation of Animal Carcinogenicity Studies – Anwar Dunbar, PhD, Health Effects Division, Office of Pesticide Programs

Data Evaluation of Genetic Toxicity – Gregory Akerman, PhD, Health Effects Division, Office of Pesticide Programs

Data Integration and Weight-of-evidence Analysis Across Multiple Lines of Evidence – Monique Perron, ScD, Health Effects Division, Office of Pesticide Programs

To view the entire FIFRA Scientific Advisory Panel Meeting Minutes and Final Report (No. 2017-01), visit https://www.epa.gov/sites/production/files/2017-03/documents/december—13-16—2016—final—report—03162017.pdf

WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

PREAMBLE

LYON, FRANCE
2006

CONTENTS

Amended January 2006

Last update September 2015

PREAMBLE

The Preamble to the *IARC Monographs* describes the objective and scope of the programme, the scientific principles and procedures used in developing a *Monograph*, the types of evidence considered and the scientific criteria that guide the evaluations. The Preamble should be consulted when reading a *Monograph* or list of evaluations.

A. GENERAL PRINCIPLES AND PROCEDURES

1. Background

Soon after IARC was established in 1965, it received frequent requests for advice on the carcinogenic risk of chemicals, including requests for lists of known and suspected human carcinogens. It was clear that it would not be a simple task to summarize adequately the complexity of the information that was available, and IARC began to consider means of obtaining international expert opinion on this topic. In 1970, the IARC Advisory Committee on Environmental Carcinogenesis recommended ' . . . that a compendium on carcinogenic chemicals be prepared by experts. The biological activity and evaluation of practical importance to public health should be referenced and documented.' The IARC Governing Council adopted a resolution concerning the role of IARC in providing government authorities with expert, independent, scientific opinion on environmental carcinogenesis. As one means to that end, the Governing Council recommended that IARC should prepare monographs on the evaluation of carcinogenic risk of chemicals to man, which became the initial title of the series.

In the succeeding years, the scope of the programme broadened as *Monographs* were developed for groups of related chemicals, complex mixtures, occupational exposures, physical and biological agents and lifestyle factors. In 1988, the phrase 'of chemicals' was dropped from the title, which assumed its present form, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*.

Through the *Monographs* programme, IARC seeks to identify the causes of human cancer. This is the first step in cancer prevention, which is needed as much today as when IARC was established. The global burden of cancer is high and continues to increase: the annual number of new cases was estimated at 10.1 million in 2000 and is expected to reach 15 million by 2020 (Stewart & Kleihues, 2003). With current trends in demographics and exposure, the cancer burden has been shifting from high-resource countries to low- and medium-resource countries. As a result of *Monographs* evaluations, national health agencies have been able, on scientific grounds, to take measures to reduce human exposure to carcinogens in the workplace and in the environment.

The criteria established in 1971 to evaluate carcinogenic risks to humans were adopted by the Working Groups whose deliberations resulted in the first 16 volumes of the *Monographs* series. Those criteria were subsequently updated by further ad-hoc Advisory Groups (IARC, 1977, 1978, 1979, 1982, 1983, 1987, 1988, 1991; Vainio *et al.*, 1992; IARC, 2005, 2006).

The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been

established as being effective during previous *Monograph* meetings but remain, predominantly, the prerogative of each individual Working Group.

2. Objective and scope

The objective of the programme is to prepare, with the help of international Working Groups of experts, and to publish in the form of *Monographs*, critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures. The *Monographs* represent the first step in carcinogen risk assessment, which involves examination of all relevant information in order to assess the strength of the available evidence that an agent could alter the age-specific incidence of cancer in humans. The *Monographs* may also indicate where additional research efforts are needed, specifically when data immediately relevant to an evaluation are not available.

In this Preamble, the term 'agent' refers to any entity or circumstance that is subject to evaluation in a *Monograph*. As the scope of the programme has broadened, categories of agents now include specific chemicals, groups of related chemicals, complex mixtures, occupational or environmental exposures, cultural or behavioural practices, biological organisms and physical agents. This list of categories may expand as causation of, and susceptibility to, malignant disease become more fully understood.

A cancer 'hazard' is an agent that is capable of causing cancer under some circumstances, while a cancer 'risk' is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. The *Monographs* are an exercise in evaluating cancer hazards, despite the historical presence of the word 'risks' in the title. The distinction between hazard and risk is important, and the *Monographs* identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.

In the *Monographs*, an agent is termed 'carcinogenic' if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The induction of benign neoplasms may in some circumstances (see Part B, Section 3a) contribute to the judgement that the agent is carcinogenic. The terms 'neoplasm' and 'tumour' are used interchangeably.

The Preamble continues the previous usage of the phrase 'strength of evidence' as a matter of historical continuity, although it should be understood that *Monographs* evaluations consider studies that support a finding of a cancer hazard as well as studies that do not.

Some epidemiological and experimental studies indicate that different agents may act at different stages in the carcinogenic process, and several different mechanisms may be involved. The aim of the *Monographs* has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms. Information on mechanisms may, however, be used in making the overall evaluation (IARC, 1991; Vainio *et al.*, 1992; IARC, 2005, 2006; see also Part B, Sections 4 and 6). As mechanisms of carcinogenesis are elucidated, IARC convenes international scientific conferences to determine whether a broad-based consensus has emerged on how specific mechanistic data can be used in an evaluation of human carcinogenicity. The results of such conferences are reported in IARC Scientific Publications, which, as long as they still reflect the current state of scientific knowledge, may guide subsequent Working Groups.

Although the *Monographs* have emphasized hazard identification, important issues may also involve dose–response assessment. In many cases, the same epidemiological and experimental studies used to evaluate a cancer hazard can also be used to estimate a dose–

response relationship. A *Monograph* may undertake to estimate dose–response relationships within the range of the available epidemiological data, or it may compare the dose–response information from experimental and epidemiological studies. In some cases, a subsequent publication may be prepared by a separate Working Group with expertise in quantitative dose–response assessment.

The *Monographs* are used by national and international authorities to make risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes and decide among alternative options for public health decisions. The evaluations of IARC Working Groups are scientific, qualitative judgements on the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which public health decisions may be based. Public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations.

3. Selection of agents for review

Agents are selected for review on the basis of two main criteria: (a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity. Mixed exposures may occur in occupational and environmental settings and as a result of individual and cultural habits (such as tobacco smoking and dietary practices). Chemical analogues and compounds with biological or physical characteristics similar to those of suspected carcinogens may also be considered, even in the absence of data on a possible carcinogenic effect in humans or experimental animals.

The scientific literature is surveyed for published data relevant to an assessment of carcinogenicity. Ad-hoc Advisory Groups convened by IARC in 1984, 1989, 1991, 1993, 1998 and 2003 made recommendations as to which agents should be evaluated in the *Monographs* series. Recent recommendations are available on the *Monographs* programme website (http://monographs.iarc.fr). IARC may schedule other agents for review as it becomes aware of new scientific information or as national health agencies identify an urgent public health need related to cancer.

As significant new data become available on an agent for which a *Monograph* exists, a re-evaluation may be made at a subsequent meeting, and a new *Monograph* published. In some cases it may be appropriate to review only the data published since a prior evaluation. This can be useful for updating a database, reviewing new data to resolve a previously open question or identifying new tumour sites associated with a carcinogenic agent. Major changes in an evaluation (e.g. a new classification in Group 1 or a determination that a mechanism does not operate in humans, see Part B, Section 6) are more appropriately addressed by a full review.

4. Data for the *Monographs*

Each *Monograph* reviews all pertinent epidemiological studies and cancer bioassays in experimental animals. Those judged inadequate or irrelevant to the evaluation may be cited but not summarized. If a group of similar studies is not reviewed, the reasons are indicated.

Mechanistic and other relevant data are also reviewed. A *Monograph* does not necessarily cite all the mechanistic literature concerning the agent being evaluated (see Part B, Section

4). Only those data considered by the Working Group to be relevant to making the evaluation are included.

With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed. The same publication requirement applies to studies originating from IARC, including meta-analyses or pooled analyses commissioned by IARC in advance of a meeting (see Part B, Section 2c). Data from government agency reports that are publicly available are also considered. Exceptionally, doctoral theses and other material that are in their final form and publicly available may be reviewed.

Exposure data and other information on an agent under consideration are also reviewed. In the sections on chemical and physical properties, on analysis, on production and use and on occurrence, published and unpublished sources of information may be considered.

Inclusion of a study does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results, and limitations are clearly outlined in square brackets at the end of each study description (see Part B). The reasons for not giving further consideration to an individual study also are indicated in the square brackets.

5. Meeting participants

Five categories of participant can be present at *Monograph* meetings.

(a) The Working Group is responsible for the critical reviews and evaluations that are developed during the meeting. The tasks of Working Group Members are: (i) to ascertain that all appropriate data have been collected; (ii) to select the data relevant for the evaluation on the basis of scientific merit; (iii) to prepare accurate summaries of the data to enable the reader to follow the reasoning of the Working Group; (iv) to evaluate the results of epidemiological and experimental studies on cancer; (v) to evaluate data relevant to the understanding of mechanisms of carcinogenesis; and (vi) to make an overall evaluation of the carcinogenicity of the exposure to humans. Working Group Members generally have published significant research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts. Working Group Members are selected on the basis of (a) knowledge and experience and (b) absence of real or apparent conflicts of interests. Consideration is also given to demographic diversity and balance of scientific findings and views.

(b) Invited Specialists are experts who also have critical knowledge and experience but have a real or apparent conflict of interests. These experts are invited when necessary to assist in the Working Group by contributing their unique knowledge and experience during subgroup and plenary discussions. They may also contribute text on non-influential issues in the section on exposure, such as a general description of data on production and use (see Part B, Section 1). Invited Specialists do not serve as meeting chair or subgroup chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations.

(c) Representatives of national and international health agencies often attend meetings because their agencies sponsor the programme or are interested in the subject of a meeting. Representatives do not serve as meeting chair or subgroup chair, draft any part of a *Monograph,* or participate in the evaluations.

(d) Observers with relevant scientific credentials may be admitted to a meeting by IARC in limited numbers. Attention will be given to achieving a balance of Observers from constituencies with differing perspectives. They are invited to observe the meeting and

should not attempt to influence it. Observers do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations. At the meeting, the meeting chair and subgroup chairs may grant Observers an opportunity to speak, generally after they have observed a discussion. Observers agree to respect the Guidelines for Observers at *IARC Monographs* meetings (available at http://monographs.iarc.fr).

(e) The IARC Secretariat consists of scientists who are designated by IARC and who have relevant expertise. They serve as rapporteurs and participate in all discussions. When requested by the meeting chair or subgroup chair, they may also draft text or prepare tables and analyses.

Before an invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests to report financial interests, employment and consulting, and individual and institutional research support related to the subject of the meeting. IARC assesses these interests to determine whether there is a conflict that warrants some limitation on participation. The declarations are updated and reviewed again at the opening of the meeting. Interests related to the subject of the meeting are disclosed to the meeting participants and in the published volume (Cogliano *et al.*, 2004).

The names and principal affiliations of participants are available on the *Monographs* programme website (http://monographs.iarc.fr) approximately two months before each meeting. It is not acceptable for Observers or third parties to contact other participants before a meeting or to lobby them at any time. Meeting participants are asked to report all such contacts to IARC (Cogliano *et al.*, 2005).

All participants are listed, with their principal affiliations, at the beginning of each volume. Each participant who is a Member of a Working Group serves as an individual scientist and not as a representative of any organization, government or industry.

6. Working procedures

A separate Working Group is responsible for developing each volume of *Monographs*. A volume contains one or more *Monographs*, which can cover either a single agent or several related agents. Approximately one year in advance of the meeting of a Working Group, the agents to be reviewed are announced on the *Monographs* programme website (http://monographs.iarc.fr) and participants are selected by IARC staff in consultation with other experts. Subsequently, relevant biological and epidemiological data are collected by IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems such as PubMed. Meeting participants who are asked to prepare preliminary working papers for specific sections are expected to supplement the IARC literature searches with their own searches.

Industrial associations, labour unions and other knowledgeable organizations may be asked to provide input to the sections on production and use, although this involvement is not required as a general rule. Information on production and trade is obtained from governmental, trade and market research publications and, in some cases, by direct contact with industries. Separate production data on some agents may not be available for a variety of reasons (e.g. not collected or made public in all producing countries, production is small). Information on uses may be obtained from published sources but is often complemented by direct contact with manufacturers. Efforts are made to supplement this information with data from other national and international sources.

Six months before the meeting, the material obtained is sent to meeting participants to prepare preliminary working papers. The working papers are compiled by IARC staff and sent, prior to the meeting, to Working Group Members and Invited Specialists for review.

The Working Group meets at IARC for seven to eight days to discuss and finalize the texts and to formulate the evaluations. The objectives of the meeting are peer review and consensus. During the first few days, four subgroups (covering exposure data, cancer in humans, cancer in experimental animals, and mechanistic and other relevant data) review the working papers, develop a joint subgroup draft and write summaries. Care is taken to ensure that each study summary is written or reviewed by someone not associated with the study being considered. During the last few days, the Working Group meets in plenary session to review the subgroup drafts and develop the evaluations. As a result, the entire volume is the joint product of the Working Group, and there are no individually authored sections.

IARC Working Groups strive to achieve a consensus evaluation. Consensus reflects broad agreement among Working Group Members, but not necessarily unanimity. The chair may elect to poll Working Group Members to determine the diversity of scientific opinion on issues where consensus is not readily apparent.

After the meeting, the master copy is verified by consulting the original literature, edited and prepared for publication. The aim is to publish the volume within six months of the Working Group meeting. A summary of the outcome is available on the *Monographs* programme website soon after the meeting.

B. SCIENTIFIC REVIEW AND EVALUATION

The available studies are summarized by the Working Group, with particular regard to the qualitative aspects discussed below. In general, numerical findings are indicated as they appear in the original report; units are converted when necessary for easier comparison. The Working Group may conduct additional analyses of the published data and use them in their assessment of the evidence; the results of such supplementary analyses are given in square brackets. When an important aspect of a study that directly impinges on its interpretation should be brought to the attention of the reader, a Working Group comment is given in square brackets.

The scope of the *IARC Monographs* programme has expanded beyond chemicals to include complex mixtures, occupational exposures, physical and biological agents, lifestyle factors and other potentially carcinogenic exposures. Over time, the structure of a *Monograph* has evolved to include the following sections:

1. Exposure data
2. Studies of cancer in humans
3. Studies of cancer in experimental animals
4. Mechanistic and other relevant data
5. Summary
6. Evaluation and rationale

In addition, a section of General Remarks at the front of the volume discusses the reasons the agents were scheduled for evaluation and some key issues the Working Group encountered during the meeting.

This part of the Preamble discusses the types of evidence considered and summarized in each section of a *Monograph*, followed by the scientific criteria that guide the evaluations.

1. Exposure data

Each *Monograph* includes general information on the agent: this information may vary substantially between agents and must be adapted accordingly. Also included is information on production and use (when appropriate), methods of analysis and detection, occurrence, and sources and routes of human occupational and environmental exposures. Depending on the agent, regulations and guidelines for use may be presented.

(a) General information on the agent

For chemical agents, sections on chemical and physical data are included: the Chemical Abstracts Service Registry Number, the latest primary name and the IUPAC systematic name are recorded; other synonyms are given, but the list is not necessarily comprehensive. Information on chemical and physical properties that are relevant to identification, occurrence and biological activity is included. A description of technical products of chemicals includes trade names, relevant specifications and available information on composition and impurities. Some of the trade names given may be those of mixtures in which the agent being evaluated is only one of the ingredients.

For biological agents, taxonomy, structure and biology are described, and the degree of variability is indicated. Mode of replication, life cycle, target cells, persistence, latency, host response and clinical disease other than cancer are also presented.

For physical agents that are forms of radiation, energy and range of the radiation are included. For foreign bodies, fibres and respirable particles, size range and relative dimensions are indicated.

For agents such as mixtures, drugs or lifestyle factors, a description of the agent, including its composition, is given.

Whenever appropriate, other information, such as historical perspectives or the description of an industry or habit, may be included.

(b) Analysis and detection

An overview of methods of analysis and detection of the agent is presented, including their sensitivity, specificity and reproducibility. Methods widely used for regulatory purposes are emphasized. Methods for monitoring human exposure are also given. No critical evaluation or recommendation of any method is meant or implied.

(c) Production and use

The dates of first synthesis and of first commercial production of a chemical, mixture or other agent are provided when available; for agents that do not occur naturally, this information may allow a reasonable estimate to be made of the date before which no human exposure to the agent could have occurred. The dates of first reported occurrence of an exposure are also provided when available. In addition, methods of synthesis used in past and present commercial production and different methods of production, which may give rise to different impurities, are described.

The countries where companies report production of the agent, and the number of companies in each country, are identified. Available data on production, international trade and uses are obtained for representative regions. It should not, however, be inferred that those areas or nations are necessarily the sole or major sources or users of the agent. Some identified uses may not be current or major applications, and the coverage is not necessarily

comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their therapeutic efficacy.

(d) Occurrence and exposure

Information on the occurrence of an agent in the environment is obtained from data derived from the monitoring and surveillance of levels in occupational environments, air, water, soil, plants, foods and animal and human tissues. When available, data on the generation, persistence and bioaccumulation of the agent are also included. Such data may be available from national databases.

Data that indicate the extent of past and present human exposure, the sources of exposure, the people most likely to be exposed and the factors that contribute to the exposure are reported. Information is presented on the range of human exposure, including occupational and environmental exposures. This includes relevant findings from both developed and developing countries. Some of these data are not distributed widely and may be available from government reports and other sources. In the case of mixtures, industries, occupations or processes, information is given about all agents known to be present. For processes, industries and occupations, a historical description is also given, noting variations in chemical composition, physical properties and levels of occupational exposure with date and place. For biological agents, the epidemiology of infection is described.

(e) Regulations and guidelines

Statements concerning regulations and guidelines (e.g. occupational exposure limits, maximal levels permitted in foods and water, pesticide registrations) are included, but they may not reflect the most recent situation, since such limits are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that that country does not have regulations with regard to the exposure. For biological agents, legislation and control, including vaccination and therapy, are described.

2. Studies of cancer in humans

This section includes all pertinent epidemiological studies (see Part A, Section 4). Studies of biomarkers are included when they are relevant to an evaluation of carcinogenicity to humans.

(a) Types of study considered

Several types of epidemiological study contribute to the assessment of carcinogenicity in humans — cohort studies, case–control studies, correlation (or ecological) studies and intervention studies. Rarely, results from randomized trials may be available. Case reports and case series of cancer in humans may also be reviewed.

Cohort and case–control studies relate individual exposures under study to the occurrence of cancer in individuals and provide an estimate of effect (such as relative risk) as the main measure of association. Intervention studies may provide strong evidence for making causal inferences, as exemplified by cessation of smoking and the subsequent decrease in risk for lung cancer.

In correlation studies, the units of investigation are usually whole populations (e.g. in particular geographical areas or at particular times), and cancer frequency is related to a summary measure of the exposure of the population to the agent under study. In correlation studies, individual exposure is not documented, which renders this kind of study more prone

to confounding. In some circumstances, however, correlation studies may be more informative than analytical study designs (see, for example, the *Monograph* on arsenic in drinking-water; IARC, 2004).

In some instances, case reports and case series have provided important information about the carcinogenicity of an agent. These types of study generally arise from a suspicion, based on clinical experience, that the concurrence of two events — that is, a particular exposure and occurrence of a cancer — has happened rather more frequently than would be expected by chance. Case reports and case series usually lack complete ascertainment of cases in any population, definition or enumeration of the population at risk and estimation of the expected number of cases in the absence of exposure.

The uncertainties that surround the interpretation of case reports, case series and correlation studies make them inadequate, except in rare instances, to form the sole basis for inferring a causal relationship. When taken together with case–control and cohort studies, however, these types of study may add materially to the judgement that a causal relationship exists.

Epidemiological studies of benign neoplasms, presumed preneoplastic lesions and other end-points thought to be relevant to cancer are also reviewed. They may, in some instances, strengthen inferences drawn from studies of cancer itself.

(b) Quality of studies considered

It is necessary to take into account the possible roles of bias, confounding and chance in the interpretation of epidemiological studies. Bias is the effect of factors in study design or execution that lead erroneously to a stronger or weaker association than in fact exists between an agent and disease. Confounding is a form of bias that occurs when the relationship with disease is made to appear stronger or weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease. The role of chance is related to biological variability and the influence of sample size on the precision of estimates of effect.

In evaluating the extent to which these factors have been minimized in an individual study, consideration is given to a number of aspects of design and analysis as described in the report of the study. For example, when suspicion of carcinogenicity arises largely from a single small study, careful consideration is given when interpreting subsequent studies that included these data in an enlarged population. Most of these considerations apply equally to case–control, cohort and correlation studies. Lack of clarity of any of these aspects in the reporting of a study can decrease its credibility and the weight given to it in the final evaluation of the exposure.

Firstly, the study population, disease (or diseases) and exposure should have been well defined by the authors. Cases of disease in the study population should have been identified in a way that was independent of the exposure of interest, and exposure should have been assessed in a way that was not related to disease status.

Secondly, the authors should have taken into account — in the study design and analysis — other variables that can influence the risk of disease and may have been related to the exposure of interest. Potential confounding by such variables should have been dealt with either in the design of the study, such as by matching, or in the analysis, by statistical adjustment. In cohort studies, comparisons with local rates of disease may or may not be more appropriate than those with national rates. Internal comparisons of frequency of disease among individuals at different levels of exposure are also desirable in cohort studies, since

they minimize the potential for confounding related to the difference in risk factors between an external reference group and the study population.

Thirdly, the authors should have reported the basic data on which the conclusions are founded, even if sophisticated statistical analyses were employed. At the very least, they should have given the numbers of exposed and unexposed cases and controls in a case–control study and the numbers of cases observed and expected in a cohort study. Further tabulations by time since exposure began and other temporal factors are also important. In a cohort study, data on all cancer sites and all causes of death should have been given, to reveal the possibility of reporting bias. In a case–control study, the effects of investigated factors other than the exposure of interest should have been reported.

Finally, the statistical methods used to obtain estimates of relative risk, absolute rates of cancer, confidence intervals and significance tests, and to adjust for confounding should have been clearly stated by the authors. These methods have been reviewed for case–control studies (Breslow & Day, 1980) and for cohort studies (Breslow & Day, 1987).

(c) Meta-analyses and pooled analyses

Independent epidemiological studies of the same agent may lead to results that are difficult to interpret. Combined analyses of data from multiple studies are a means of resolving this ambiguity, and well-conducted analyses can be considered. There are two types of combined analysis. The first involves combining summary statistics such as relative risks from individual studies (meta-analysis) and the second involves a pooled analysis of the raw data from the individual studies (pooled analysis) (Greenland, 1998).

The advantages of combined analyses are increased precision due to increased sample size and the opportunity to explore potential confounders, interactions and modifying effects that may explain heterogeneity among studies in more detail. A disadvantage of combined analyses is the possible lack of compatibility of data from various studies due to differences in subject recruitment, procedures of data collection, methods of measurement and effects of unmeasured co-variates that may differ among studies. Despite these limitations, well-conducted combined analyses may provide a firmer basis than individual studies for drawing conclusions about the potential carcinogenicity of agents.

IARC may commission a meta-analysis or pooled analysis that is pertinent to a particular *Monograph* (see Part A, Section 4). Additionally, as a means of gaining insight from the results of multiple individual studies, ad-hoc calculations that combine data from different studies may be conducted by the Working Group during the course of a *Monograph* meeting. The results of such original calculations, which would be specified in the text by presentation in square brackets, might involve updates of previously conducted analyses that incorporate the results of more recent studies or de-novo analyses. Irrespective of the source of data for the meta-analyses and pooled analyses, it is important that the same criteria for data quality be applied as those that would be applied to individual studies and to ensure also that sources of heterogeneity between studies be taken into account.

(d) Temporal effects

Detailed analyses of both relative and absolute risks in relation to temporal variables, such as age at first exposure, time since first exposure, duration of exposure, cumulative exposure, peak exposure (when appropriate) and time since cessation of exposure, are reviewed and summarized when available. Analyses of temporal relationships may be useful in making causal inferences. In addition, such analyses may suggest whether a carcinogen

acts early or late in the process of carcinogenesis, although, at best, they allow only indirect inferences about mechanisms of carcinogenesis.

(e) Use of biomarkers in epidemiological studies

Biomarkers indicate molecular, cellular or other biological changes and are increasingly used in epidemiological studies for various purposes (IARC, 1991; Vainio *et al.*, 1992; Toniolo *et al.*, 1997; Vineis *et al.*, 1999; Buffler *et al.*, 2004). These may include evidence of exposure, of early effects, of cellular, tissue or organism responses, of individual susceptibility or host responses, and inference of a mechanism (see Part B, Section 4b). This is a rapidly evolving field that encompasses developments in genomics, epigenomics and other emerging technologies.

Molecular epidemiological data that identify associations between genetic polymorphisms and interindividual differences in susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. If the polymorphism has been demonstrated experimentally to modify the functional activity of the gene product in a manner that is consistent with increased susceptibility, these data may be useful in making causal inferences. Similarly, molecular epidemiological studies that measure cell functions, enzymes or metabolites that are thought to be the basis of susceptibility may provide evidence that reinforces biological plausibility. It should be noted, however, that when data on genetic susceptibility originate from multiple comparisons that arise from subgroup analyses, this can generate false-positive results and inconsistencies across studies, and such data therefore require careful evaluation. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent being evaluated, data on this phenotype may be useful in making causal inferences.

(f) Criteria for causality

After the quality of individual epidemiological studies of cancer has been summarized and assessed, a judgement is made concerning the strength of evidence that the agent in question is carcinogenic to humans. In making its judgement, the Working Group considers several criteria for causality (Hill, 1965). A strong association (e.g. a large relative risk) is more likely to indicate causality than a weak association, although it is recognized that estimates of effect of small magnitude do not imply lack of causality and may be important if the disease or exposure is common. Associations that are replicated in several studies of the same design or that use different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (such as differences in exposure), and results of studies that are judged to be of high quality are given more weight than those of studies that are judged to be methodologically less sound.

If the risk increases with the exposure, this is considered to be a strong indication of causality, although the absence of a graded response is not necessarily evidence against a causal relationship. The demonstration of a decline in risk after cessation of or reduction in exposure in individuals or in whole populations also supports a causal interpretation of the findings.

A number of scenarios may increase confidence in a causal relationship. On the one hand, an agent may be specific in causing tumours at one site or of one morphological type. On the other, carcinogenicity may be evident through the causation of multiple tumour types. Temporality, precision of estimates of effect, biological plausibility and coherence of the

overall database are considered. Data on biomarkers may be employed in an assessment of the biological plausibility of epidemiological observations.

Although rarely available, results from randomized trials that show different rates of cancer among exposed and unexposed individuals provide particularly strong evidence for causality.

When several epidemiological studies show little or no indication of an association between an exposure and cancer, a judgement may be made that, in the aggregate, they show evidence of lack of carcinogenicity. Such a judgement requires firstly that the studies meet, to a sufficient degree, the standards of design and analysis described above. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results should be considered and excluded with reasonable certainty. In addition, all studies that are judged to be methodologically sound should (a) be consistent with an estimate of effect of unity for any observed level of exposure, (b) when considered together, provide a pooled estimate of relative risk that is at or near to unity, and (c) have a narrow confidence interval, due to sufficient population size. Moreover, no individual study nor the pooled results of all the studies should show any consistent tendency that the relative risk of cancer increases with increasing level of exposure. It is important to note that evidence of lack of carcinogenicity obtained from several epidemiological studies can apply only to the type(s) of cancer studied, to the dose levels reported, and to the intervals between first exposure and disease onset observed in these studies. Experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.

3. Studies of cancer in experimental animals

All known human carcinogens that have been studied adequately for carcinogenicity in experimental animals have produced positive results in one or more animal species (Wilbourn *et al.*, 1986; Tomatis *et al.*, 1989). For several agents (e.g. aflatoxins, diethylstilbestrol, solar radiation, vinyl chloride), carcinogenicity in experimental animals was established or highly suspected before epidemiological studies confirmed their carcinogenicity in humans (Vainio *et al.*, 1995). Although this association cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there is *sufficient evidence of carcinogenicity* in experimental animals (see Part B, Section 6b) also present a carcinogenic hazard to humans. Accordingly, in the absence of additional scientific information, these agents are considered to pose a carcinogenic hazard to humans. Examples of additional scientific information are data that demonstrate that a given agent causes cancer in animals through a species-specific mechanism that does not operate in humans or data that demonstrate that the mechanism in experimental animals also operates in humans (see Part B, Section 6).

Consideration is given to all available long-term studies of cancer in experimental animals with the agent under review (see Part A, Section 4). In all experimental settings, the nature and extent of impurities or contaminants present in the agent being evaluated are given when available. Animal species, strain (including genetic background where applicable), sex, numbers per group, age at start of treatment, route of exposure, dose levels, duration of exposure, survival and information on tumours (incidence, latency, severity or multiplicity of neoplasms or preneoplastic lesions) are reported. Those studies in experimental animals that are judged to be irrelevant to the evaluation or judged to be inadequate (e.g. too short a

duration, too few animals, poor survival; see below) may be omitted. Guidelines for conducting long-term carcinogenicity experiments have been published (e.g. OECD, 2002).

Other studies considered may include: experiments in which the agent was administered in the presence of factors that modify carcinogenic effects (e.g. initiation–promotion studies, co-carcinogenicity studies and studies in genetically modified animals); studies in which the end-point was not cancer but a defined precancerous lesion; experiments on the carcinogenicity of known metabolites and derivatives; and studies of cancer in non-laboratory animals (e.g. livestock and companion animals) exposed to the agent.

For studies of mixtures, consideration is given to the possibility that changes in the physicochemical properties of the individual substances may occur during collection, storage, extraction, concentration and delivery. Another consideration is that chemical and toxicological interactions of components in a mixture may alter dose–response relationships. The relevance to human exposure of the test mixture administered in the animal experiment is also assessed. This may involve consideration of the following aspects of the mixture tested: (i) physical and chemical characteristics, (ii) identified constituents that may indicate the presence of a class of substances and (iii) the results of genetic toxicity and related tests.

The relevance of results obtained with an agent that is analogous (e.g. similar in structure or of a similar virus genus) to that being evaluated is also considered. Such results may provide biological and mechanistic information that is relevant to the understanding of the process of carcinogenesis in humans and may strengthen the biological plausibility that the agent being evaluated is carcinogenic to humans (see Part B, Section 2f).

(a) Qualitative aspects

An assessment of carcinogenicity involves several considerations of qualitative importance, including (i) the experimental conditions under which the test was performed, including route, schedule and duration of exposure, species, strain (including genetic background where applicable), sex, age and duration of follow-up; (ii) the consistency of the results, for example, across species and target organ(s); (iii) the spectrum of neoplastic response, from preneoplastic lesions and benign tumours to malignant neoplasms; and (iv) the possible role of modifying factors.

Considerations of importance in the interpretation and evaluation of a particular study include: (i) how clearly the agent was defined and, in the case of mixtures, how adequately the sample characterization was reported; (ii) whether the dose was monitored adequately, particularly in inhalation experiments; (iii) whether the doses, duration of treatment and route of exposure were appropriate; (iv) whether the survival of treated animals was similar to that of controls; (v) whether there were adequate numbers of animals per group; (vi) whether both male and female animals were used; (vii) whether animals were allocated randomly to groups; (viii) whether the duration of observation was adequate; and (ix) whether the data were reported and analysed adequately.

When benign tumours (a) occur together with and originate from the same cell type as malignant tumours in an organ or tissue in a particular study and (b) appear to represent a stage in the progression to malignancy, they are usually combined in the assessment of tumour incidence (Huff *et al.*, 1989). The occurrence of lesions presumed to be preneoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed. If an agent induces only benign neoplasms that appear to be end-points that do not readily undergo transition to malignancy, the agent should nevertheless be suspected of being carcinogenic and requires further investigation.

(b) Quantitative aspects

The probability that tumours will occur may depend on the species, sex, strain, genetic background and age of the animal, and on the dose, route, timing and duration of the exposure. Evidence of an increased incidence of neoplasms with increasing levels of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms.

The form of the dose–response relationship can vary widely, depending on the particular agent under study and the target organ. Mechanisms such as induction of DNA damage or inhibition of repair, altered cell division and cell death rates and changes in intercellular communication are important determinants of dose–response relationships for some carcinogens. Since many chemicals require metabolic activation before being converted to their reactive intermediates, both metabolic and toxicokinetic aspects are important in determining the dose–response pattern. Saturation of steps such as absorption, activation, inactivation and elimination may produce non-linearity in the dose–response relationship (Hoel *et al.*, 1983; Gart *et al.*, 1986), as could saturation of processes such as DNA repair. The dose–response relationship can also be affected by differences in survival among the treatment groups.

(c) Statistical analyses

Factors considered include the adequacy of the information given for each treatment group: (i) number of animals studied and number examined histologically, (ii) number of animals with a given tumour type and (iii) length of survival. The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto *et al.*, 1980; Gart *et al.*, 1986; Portier & Bailer, 1989; Bieler & Williams, 1993). The choice of the most appropriate statistical method requires consideration of whether or not there are differences in survival among the treatment groups; for example, reduced survival because of non-tumour-related mortality can preclude the occurrence of tumours later in life. When detailed information on survival is not available, comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the time the first tumour was discovered) can be useful when significant differences in survival occur before tumours appear. The lethality of the tumour also requires consideration: for rapidly fatal tumours, the time of death provides an indication of the time of tumour onset and can be assessed using life-table methods; non-fatal or incidental tumours that do not affect survival can be assessed using methods such as the Mantel-Haenzel test for changes in tumour prevalence. Because tumour lethality is often difficult to determine, methods such as the Poly-K test that do not require such information can also be used. When results are available on the number and size of tumours seen in experimental animals (e.g. papillomas on mouse skin, liver tumours observed through nuclear magnetic resonance tomography), other more complicated statistical procedures may be needed (Sherman *et al.*, 1994; Dunson *et al.*, 2003).

Formal statistical methods have been developed to incorporate historical control data into the analysis of data from a given experiment. These methods assign an appropriate weight to historical and concurrent controls on the basis of the extent of between-study and within-study variability: less weight is given to historical controls when they show a high degree of variability, and greater weight when they show little variability. It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls, particularly when historical controls show high between-study variability and are, thus, of little relevance to the

current experiment. In analysing results for uncommon tumours, however, the analysis may be improved by considering historical control data, particularly when between-study variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, gender and strain, as well as other factors such as basal diet and general laboratory environment, which may affect tumour-response rates in control animals (Haseman *et al.*, 1984; Fung *et al.*, 1996; Greim *et al.*, 2003).

Although meta-analyses and combined analyses are conducted less frequently for animal experiments than for epidemiological studies due to differences in animal strains, they can be useful aids in interpreting animal data when the experimental protocols are sufficiently similar.

4. Mechanistic and other relevant data

Mechanistic and other relevant data may provide evidence of carcinogenicity and also help in assessing the relevance and importance of findings of cancer in animals and in humans. The nature of the mechanistic and other relevant data depends on the biological activity of the agent being considered. The Working Group considers representative studies to give a concise description of the relevant data and issues that they consider to be important; thus, not every available study is cited. Relevant topics may include toxicokinetics, mechanisms of carcinogenesis, susceptible individuals, populations and life-stages, other relevant data and other adverse effects. When data on biomarkers are informative about the mechanisms of carcinogenesis, they are included in this section.

These topics are not mutually exclusive; thus, the same studies may be discussed in more than one subsection. For example, a mutation in a gene that codes for an enzyme that metabolizes the agent under study could be discussed in the subsections on toxicokinetics, mechanisms and individual susceptibility if it also exists as an inherited polymorphism.

(a) Toxicokinetic data

Toxicokinetics refers to the absorption, distribution, metabolism and elimination of agents in humans, experimental animals and, where relevant, cellular systems. Examples of kinetic factors that may affect dose–response relationships include uptake, deposition, biopersistence and half-life in tissues, protein binding, metabolic activation and detoxification. Studies that indicate the metabolic fate of the agent in humans and in experimental animals are summarized briefly, and comparisons of data from humans and animals are made when possible. Comparative information on the relationship between exposure and the dose that reaches the target site may be important for the extrapolation of hazards between species and in clarifying the role of in-vitro findings.

(b) Data on mechanisms of carcinogenesis

To provide focus, the Working Group attempts to identify the possible mechanisms by which the agent may increase the risk of cancer. For each possible mechanism, a representative selection of key data from humans and experimental systems is summarized. Attention is given to gaps in the data and to data that suggests that more than one mechanism may be operating. The relevance of the mechanism to humans is discussed, in particular, when mechanistic data are derived from experimental model systems. Changes in the affected organs, tissues or cells can be divided into three non-exclusive levels as described below.

(i) Changes in physiology

Physiological changes refer to exposure-related modifications to the physiology and/or response of cells, tissues and organs. Examples of potentially adverse physiological changes include mitogenesis, compensatory cell division, escape from apoptosis and/or senescence, presence of inflammation, hyperplasia, metaplasia and/or preneoplasia, angiogenesis, alterations in cellular adhesion, changes in steroidal hormones and changes in immune surveillance.

(ii) Functional changes at the cellular level

Functional changes refer to exposure-related alterations in the signalling pathways used by cells to manage critical processes that are related to increased risk for cancer. Examples of functional changes include modified activities of enzymes involved in the metabolism of xenobiotics, alterations in the expression of key genes that regulate DNA repair, alterations in cyclin-dependent kinases that govern cell cycle progression, changes in the patterns of post-translational modifications of proteins, changes in regulatory factors that alter apoptotic rates, changes in the secretion of factors related to the stimulation of DNA replication and transcription and changes in gap–junction-mediated intercellular communication.

(iii) Changes at the molecular level

Molecular changes refer to exposure-related changes in key cellular structures at the molecular level, including, in particular, genotoxicity. Examples of molecular changes include formation of DNA adducts and DNA strand breaks, mutations in genes, chromosomal aberrations, aneuploidy and changes in DNA methylation patterns. Greater emphasis is given to irreversible effects.

The use of mechanistic data in the identification of a carcinogenic hazard is specific to the mechanism being addressed and is not readily described for every possible level and mechanism discussed above.

Genotoxicity data are discussed here to illustrate the key issues involved in the evaluation of mechanistic data.

Tests for genetic and related effects are described in view of the relevance of gene mutation and chromosomal aberration/aneuploidy to carcinogenesis (Vainio *et al.*, 1992; McGregor *et al.*, 1999). The adequacy of the reporting of sample characterization is considered and, when necessary, commented upon; with regard to complex mixtures, such comments are similar to those described for animal carcinogenicity tests. The available data are interpreted critically according to the end-points detected, which may include DNA damage, gene mutation, sister chromatid exchange, micronucleus formation, chromosomal aberrations and aneuploidy. The concentrations employed are given, and mention is made of whether the use of an exogenous metabolic system *in vitro* affected the test result. These data are listed in tabular form by phylogenetic classification.

Positive results in tests using prokaryotes, lower eukaryotes, insects, plants and cultured mammalian cells suggest that genetic and related effects could occur in mammals. Results from such tests may also give information on the types of genetic effect produced and on the involvement of metabolic activation. Some end-points described are clearly genetic in nature (e.g. gene mutations), while others are associated with genetic effects (e.g. unscheduled DNA synthesis). In-vitro tests for

tumour promotion, cell transformation and gap-junction intercellular communication may be sensitive to changes that are not necessarily the result of genetic alterations but that may have specific relevance to the process of carcinogenesis. Critical appraisals of these tests have been published (Montesano *et al.*, 1986; McGregor *et al.*, 1999).

Genetic or other activity manifest in humans and experimental mammals is regarded to be of greater relevance than that in other organisms. The demonstration that an agent can induce gene and chromosomal mutations in mammals *in vivo* indicates that it may have carcinogenic activity. Negative results in tests for mutagenicity in selected tissues from animals treated *in vivo* provide less weight, partly because they do not exclude the possibility of an effect in tissues other than those examined. Moreover, negative results in short-term tests with genetic end-points cannot be considered to provide evidence that rules out the carcinogenicity of agents that act through other mechanisms (e.g. receptor-mediated effects, cellular toxicity with regenerative cell division, peroxisome proliferation) (Vainio *et al.*, 1992). Factors that may give misleading results in short-term tests have been discussed in detail elsewhere (Montesano *et al.*, 1986; McGregor *et al.*, 1999).

When there is evidence that an agent acts by a specific mechanism that does not involve genotoxicity (e.g. hormonal dysregulation, immune suppression, and formation of calculi and other deposits that cause chronic irritation), that evidence is presented and reviewed critically in the context of rigorous criteria for the operation of that mechanism in carcinogenesis (e.g. Capen *et al.*, 1999).

For biological agents such as viruses, bacteria and parasites, other data relevant to carcinogenicity may include descriptions of the pathology of infection, integration and expression of viruses, and genetic alterations seen in human tumours. Other observations that might comprise cellular and tissue responses to infection, immune response and the presence of tumour markers are also considered.

For physical agents that are forms of radiation, other data relevant to carcinogenicity may include descriptions of damaging effects at the physiological, cellular and molecular level, as for chemical agents, and descriptions of how these effects occur. 'Physical agents' may also be considered to comprise foreign bodies, such as surgical implants of various kinds, and poorly soluble fibres, dusts and particles of various sizes, the pathogenic effects of which are a result of their physical presence in tissues or body cavities. Other relevant data for such materials may include characterization of cellular, tissue and physiological reactions to these materials and descriptions of pathological conditions other than neoplasia with which they may be associated.

(c) Other data relevant to mechanisms

A description is provided of any structure–activity relationships that may be relevant to an evaluation of the carcinogenicity of an agent, the toxicological implications of the physical and chemical properties, and any other data relevant to the evaluation that are not included elsewhere.

High-output data, such as those derived from gene expression microarrays, and high-throughput data, such as those that result from testing hundreds of agents for a single end-point, pose a unique problem for the use of mechanistic data in the evaluation of a carcinogenic hazard. In the case of high-output data, there is the possibility to overinterpret changes in individual end-points (e.g. changes in expression in one gene) without considering the consistency of that finding in the broader context of the other end-points (e.g. other genes

with linked transcriptional control). High-output data can be used in assessing mechanisms, but all end-points measured in a single experiment need to be considered in the proper context. For high-throughput data, where the number of observations far exceeds the number of end-points measured, their utility for identifying common mechanisms across multiple agents is enhanced. These data can be used to identify mechanisms that not only seem plausible, but also have a consistent pattern of carcinogenic response across entire classes of related compounds.

(d) Susceptibility data

Individuals, populations and life-stages may have greater or lesser susceptibility to an agent, based on toxicokinetics, mechanisms of carcinogenesis and other factors. Examples of host and genetic factors that affect individual susceptibility include sex, genetic polymorphisms of genes involved in the metabolism of the agent under evaluation, differences in metabolic capacity due to life-stage or the presence of disease, differences in DNA repair capacity, competition for or alteration of metabolic capacity by medications or other chemical exposures, pre-existing hormonal imbalance that is exacerbated by a chemical exposure, a suppressed immune system, periods of higher-than-usual tissue growth or regeneration and genetic polymorphisms that lead to differences in behaviour (e.g. addiction). Such data can substantially increase the strength of the evidence from epidemiological data and enhance the linkage of in-vivo and in-vitro laboratory studies to humans.

(e) Data on other adverse effects

Data on acute, subchronic and chronic adverse effects relevant to the cancer evaluation are summarized. Adverse effects that confirm distribution and biological effects at the sites of tumour development, or alterations in physiology that could lead to tumour development, are emphasized. Effects on reproduction, embryonic and fetal survival and development are summarized briefly. The adequacy of epidemiological studies of reproductive outcome and genetic and related effects in humans is judged by the same criteria as those applied to epidemiological studies of cancer, but fewer details are given.

5. Summary

This section is a summary of data presented in the preceding sections. Summaries can be found on the *Monographs* programme website (http://monographs.iarc.fr).

(a) Exposure data

Data are summarized, as appropriate, on the basis of elements such as production, use, occurrence and exposure levels in the workplace and environment and measurements in human tissues and body fluids. Quantitative data and time trends are given to compare exposures in different occupations and environmental settings. Exposure to biological agents is described in terms of transmission, prevalence and persistence of infection.

(b) Cancer in humans

Results of epidemiological studies pertinent to an assessment of human carcinogenicity are summarized. When relevant, case reports and correlation studies are also summarized. The target organ(s) or tissue(s) in which an increase in cancer was observed is identified. Dose–response and other quantitative data may be summarized when available.

(c) Cancer in experimental animals

Data relevant to an evaluation of carcinogenicity in animals are summarized. For each animal species, study design and route of administration, it is stated whether an increased incidence, reduced latency, or increased severity or multiplicity of neoplasms or preneoplastic lesions were observed, and the tumour sites are indicated. If the agent produced tumours after prenatal exposure or in single-dose experiments, this is also mentioned. Negative findings, inverse relationships, dose–response and other quantitative data are also summarized.

(d) Mechanistic and other relevant data

Data relevant to the toxicokinetics (absorption, distribution, metabolism, elimination) and the possible mechanism(s) of carcinogenesis (e.g. genetic toxicity, epigenetic effects) are summarized. In addition, information on susceptible individuals, populations and life-stages is summarized. This section also reports on other toxic effects, including reproductive and developmental effects, as well as additional relevant data that are considered to be important.

6. Evaluation and rationale

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms. The strength of the mechanistic evidence is also characterized.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency). A classification may change as new information becomes available.

An evaluation of the degree of evidence is limited to the materials tested, as defined physically, chemically or biologically. When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of the degree of evidence.

(a) Carcinogenicity in humans

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the

Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

When the available epidemiological studies pertain to a mixture, process, occupation or industry, the Working Group seeks to identify the specific agent considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.

(b) Carcinogenicity in experimental animals

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals.

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence.*

A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.

Limited evidence of carcinogenicity: The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

Inadequate evidence of carcinogenicity: The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

Evidence suggesting lack of carcinogenicity: Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied.

(c) Mechanistic and other relevant data

Mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is highlighted. This may include data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–activity relationships, metabolism and toxicokinetics, physicochemical parameters and analogous biological agents.

The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated, using terms such as 'weak', 'moderate' or 'strong'. The Working Group then assesses whether that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans derive from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

The conclusion that a mechanism operates in experimental animals is strengthened by findings of consistent results in different experimental systems, by the demonstration of biological plausibility and by coherence of the overall database. Strong support can be obtained from studies that challenge the hypothesized mechanism experimentally, by demonstrating that the suppression of key mechanistic processes leads to the suppression of tumour development. The Working Group considers whether multiple mechanisms might contribute to tumour development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals and whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumours observed in experimental animals are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating a favoured mechanism.

For complex exposures, including occupational and industrial exposures, the chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The Working

Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(d) Overall evaluation

Finally, the body of evidence is considered as a whole, in order to reach an overall evaluation of the carcinogenicity of the agent to humans.

An evaluation may be made for a group of agents that have been evaluated by the Working Group. In addition, when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of agents if the strength of the evidence warrants it.

The agent is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent is a matter of scientific judgement that reflects the strength of the evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data.

Group 1: The agent is *carcinogenic to humans.*

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

Group 2A: The agent is *probably carcinogenic to humans.*

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Group 2B: The agent is *possibly carcinogenic to humans.*

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is *not classifiable as to its carcinogenicity to humans.*

This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4: The agent is *probably not carcinogenic to humans.*

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

(e) Rationale

The reasoning that the Working Group used to reach its evaluation is presented and discussed. This section integrates the major findings from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic and other relevant data. It includes concise statements of the principal line(s) of argument that emerged, the conclusions of the Working Group on the strength of the evidence for each group of studies, citations to indicate which studies were pivotal to these conclusions, and an explanation of the reasoning of the Working Group in weighing data and making evaluations. When there are significant differences of scientific interpretation among Working Group Members, a brief summary of the alternative interpretations is provided, together with their scientific rationale and an indication of the relative degree of support for each alternative.

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LETTER FROM UN SPECIAL RAPPORTEUR

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Mandate of the Special Rapporteur on the implications for human rights of the environmentally sound management and disposal of hazardous substances and wastes

REFERENCE: SPS/SHD/MDV/fl

29 January 2018

Dear Sirs,

I have the honor to address you in my capacity as Special Rapporteur on the implications for human rights of the environmentally sound management and disposal of hazardous substances and wastes, pursuant to Human Rights Council resolution 36/15. I write in reference to your letter of 17 January 2018 addressed to the Inspector General and the Acting Secretary of the U.S. Department of Health & Human Services.[1]

In this letter, you inform that the Congressional Committee on Science, Space and Technology is conducting oversight of the activity of Dr. Linda Birnbaum, director of the U.S. National Institute of Environmental Health Sciences (NIEHS). The oversight relates to an article co-authored by Dr. Birnbaum and Dr. Liza Gross, in the scientific journal PLOS Biology, a highly selective peer-reviewed publication. You indicated your suspicion that Dr. Birnbaum might have violated the U.S. Anti-Lobbying Act by encouraging citizens "to petition the Government to make certain policy decisions." The letter underlines this statement: "Closing the gap between evidence and policy will require that engaged citizens, both scientists and nonscientists, work to ensure our government officials pass health-protective policies based on the best available scientific evidence."

In this regard, I would like to take this opportunity to express my deep concern regarding what I believe may be an attempt to intimidate a highly respected scientist for her contribution to a scientific journal. The article in question contained no specific policy guidance that could suggest lobbying or any signal of conflict of interest. Rather, it simply insisted on the need for policies and norms to be fully grounded in the best possible scientific evidence, and for the public to engage in debates regarding how the U.S. Government fulfills its obligation to protect the public from exposures to toxic chemicals, pollution and other hazardous substances.

Encouraging citizen engagement, as done by Drs. Birnbaum and Gross, does not articulate a "certain" policy outcome. Rather, it promotes fundamental human rights,

[1] Available at http://bit.ly/2E5qRnS and http://bit.ly/2GfOk6E

The Honorable Lamar Smith
U.S. House of Representatives
Chairman of the U.S. House Committee on Science, Space and Technology

The Honorable Andy Biggs
U.S. House of Representatives
Chairman of the U.S. House Sub-Committee on Environment

including the right to take part in the conduct of public affairs, which the United States of America has recognized. Public participation is core component of democracy, and central to environmental governance. Indivisible from the right to participation is the right to information and freedom of expression, which Drs. Birnbaum and Gross promote and exercise in their article.

Last year, I reported to the U.N. Human Rights Council that "the ability to protect the human rights to life and to health [from hazardous substances] and to realize the right to the benefits of scientific progress and its applications hinges upon the ability to translate evidence into protective laws and policies."[2] I noted that extreme delays in the translation of evidence of hazard and risk into protective measures have harmed the public, drawing on well-documented examples from the United States of America. I emphasize to you that State's duty to protect the rights to life, health and physical integrity from toxic and otherwise hazardous substances must be reflected in the adoption, implementation and enforcement of adequate laws and policies regarding such substances.[3]

The work of NIEHS is essential to protecting human rights, including the rights of children, who are arguably the most at risk of health impacts from exposure to toxic chemicals and pollution. In 2016, I reported to the U.N. Human Rights Council on the urgent need of all States to better protect children from exposure to pollution and toxic chemicals.[4] The gap between what is required under international human rights law, and the protections afforded by Governments based on current scientific knowledge continues to diverge. And, race and poverty continues to be major factor in the disproportionate levels of exposure by children of color and low-income communities.

I encourage you and your Congressional colleagues to explore opportunities to support the crucial work of NIEHS in advancing human rights. Ensuring laws and policies adequately protect everyone—rich or poor, young or old—from exposure to hazardous substances an obligation of States, which flows naturally from international human rights law.[5] While the United States of America remains the only country in the world that is not Party to the U.N. Convention on the Rights of the Child, it is a signatory and thus obligated not to defeat its object and purpose.

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[2] A/HRC/36/41 available at: http://www.ohchr.org/EN/Issues/Environment/ToxicWastes/Pages/Annual.aspx

[3] I note two ongoing cases of delayed implementation of U.S. toxic chemical laws https://earthjustice.org/sites/default/files/files/Pet%20for%20Rev-Prioritization%20Rule.pdf and https://earthjustice.org/sites/default/files/files/Pet%20for%20Rev-Risk%20Eval%20Rule.pdf

[4] A/HRC/33/41 available at: http://www.ohchr.org/EN/Issues/Environment/ToxicWastes/Pages/Annual.aspx

[5] See e.g. human rights to life and to the highest attainable standard of health, which are enshrined at the Universal Declaration of Human Rights (respectively articles 3 for and 25), and further developed by the U.N. Convention on the Right of the Child (respectively articles 6 and 24).

Considering the public relevance of this debate and its direct relation to the work I conduct as a Special Rapporteur, I have decided to send this open letter in a spirit of cooperation. The letter will be posted in the webpage of the mandate.

I remain at your disposal to further discuss the reasons for the concerns stated in this letter and my work on the implications for human rights of the environmentally sound management and disposal of hazardous substances and wastes.

Please accept, dear Sirs, the assurances of my highest consideration.

Baskut Tuncak
Special Rapporteur on the implications for human rights of the environmentally sound management and disposal of hazardous substances and wastes

cc: Hon. E. D. Hargan, Acting Director, U.S. Dept. of Health and Human Services
Hon. D. R. Levinson, Inspector General, U.S. Dept. of Health and Human Services
Hon. E. Bernice Johnson, Ranking Member, U.S. House Committee on Science, Space and Technology
Hon. P. D. Ryan Jr., Speaker of the U.S. House of Representatives

LIST OF PARTICIPANTS IN GLYPHOSATE PROGRAM

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans
VOLUME 112: SOME ORGANOPHOSPHATE INSECTICIDES AND HERBICIDES: DIAZINON, GLYPHOSATE, MALATHION, PARATHION, AND TETRACHLORVINPHOS
Lyon, France: 3-10 March 2015

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Working Group Members and Invited Specialists served in their individual capacities as scientists and not as representatives of their government or any organization with which they are affiliated. Affiliations are provided for identification purposes only.

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[1] Peter P Egeghy received "in kind" support and reimbursement of travel expenses of on average less than US $2.000 per year during the last 4 years from participation in meetings sponsored by the American Chemistry Council, an industry trade association for American chemical companies, and the Health and Environmental Sciences Institue (HESI), a nonprofit scientific research organization based in Washington and funded by corporate sponsors.

[2] Christopher J Portier receives a part-time salary from the Environmental Defense Fund, a United States–based nonprofit environmental advocacy group.

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[3] Mette Kristine Boye Kristensen is employed by Cheminova A/S, Denmark, a global company developing, producing and marketing crop protection products.

[4] Tom Sorahan is a member of the European Glyphosphate Toxicology Advisory Panel, and received reimbursement of travel cost from Monsanto to attend EuroTox 2012.

[5] Christian Strupp is employed by ADAMA Agricultural Solutions Ltd, Israel, a producer of Diazinone and Glyphosphate.

[6] Patrice Sutton's attendance of this Monographs meeting is supported by the Clarence E. Heller Charitable Foundation, a philanthropic charity with a mission to protect and improve the quality of life through support of programs in the environment, human health, education and the arts.

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Jiri Zavadil, Section of Mechanisms of Carcinogenesis

NOTE REGARDING CONFLICTS OF INTERESTS: Each participant submitted WHO's Declaration of Interests, which covers employment and consulting activities, individual and institutional research support, and other financial interests. Participants identified as Invited Specialists did not serve as meeting chair or subgroup chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations. The Declarations were updated and reviewed again at the opening of the meeting.

NOTE REGARDING OBSERVERS: Each Observer agreed to respect the Guidelines for Observers at *IARC Monographs* meetings. Observers did not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations. They also agreed not to contact participants before the meeting, not to lobby them at any time, not to send them written materials, and not to offer them meals or other favours. IARC asked and reminded Working Group Members to report any contact or attempt to influence that they may have encountered, either before or during the meeting.

Posted on 26 January 2015, updated 19 October 2016

Monsanto's IARC Battle Plan

The two documents attached have been referred to jointly by the media as Monsanto's IARC Battle Plan. Monsanto, based on the publicly available scientific evidence, assumed that glyphosate would receive a "*possible*" (2B Classification) or "*probable*" (2A Classification) rating from IARC. On March 20, 2015, IARC released its Glyphosate Monograph labelling the chemical "probably carcinogenic to humans," a Class 2A rating.

The first document was produced on February 23, 2015 and outlines various tasks to combat the upcoming release of the IARC Monograph on Glyphosate.

The second document is dated February 17, 2015 and is titled: ***"Preparedness and Engagement Plan for IARC Carcinogen Rating of Glyphosate."*** It provides a list for Pre-IARC and Post-IARC activities coordinated by Monsanto for the chemical industry, non-profit groups widely reported to be front groups for industry, and other third-party experts to combat the IARC rating for Glyphosate. Notably, the documents suggest a social media campaign against IARC through Facebook, Twitter and third-party expert blogs, op-eds, links, tweets and retweets. These documents made available through litigation against Monsanto regarding its glyphosate-containing herbicide Roundup provide a window on the tactics used to combat scientific evidence that is unfavorable to glyphosate.[1]

[1] The two documents attached were obtained via the law firm of Baum Hedlund Aristei Goldman and can be found here: http://baumhedlundlaw.com/pdf/monsanto-documents/72-Document-Details-Monsantos-Goals-After-IARC-Report.pdf

Draft Feb 23, 2015

Glyphosate: IARC

The International Agency for Research on Cancer (IARC), part of the World Health Organization, coordinates and conducts both epidemiological and laboratory research into the causes of human cancer. It also evaluates the carcinogenic potential of individual substances based only on publicly available information. While glyphosate has been a low priority for evaluation by IARC for more than two decades, it was nominated for review in mid-April 2014.

After learning of the ~~nomination~~ selection of glyphosate for review in September, the regulatory team's initial focus was publishing safety studies that were not yet in the public domain. All research had to be published or accepted for publication by Feb. 3, 2015 to be considered in the IARC review. Regulatory Affairs has shared these recent publications with IARC and is continuing to share directly with [illegible] and observers.

Comment [vp1]: [illegible]

Comment [vp2]: [illegible]

IARC has a history of questionable and politically charged rulings on the carcinogenic properties of products such as cell phones, coffee and caffeine. We should assume and prepare for the outcome of a 2B rating (*possible* human carcinogen); a 2A rating (*probable* human carcinogen) is possible but less likely.

It is possible that IARC's decision will impact future regulatory decision making. Regulatory is not aware of a situation where a regulatory body took a different position than IARC. Competent authorities for regulating pesticides and assessing chemical hazard typically evaluate a broader range of studies and make their own decisions. They also use the most protective hazard classification system, the Globally Harmonized System, which differs significantly from that used by IARC. Thus IARC classifications can readily differ from those of other regulatory bodies. This could further delay the U.S. EPA review.

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Comment [k4]: and EU? Canada? Japan?

The IARC meeting where glyphosate will be reviewed and the decision will be made will occur March 3-10, 2015. IARC will post its decision soon after on its website ({ HYPERLINK "http://www.iarc.fr/" }). We are already seeing activists increase allegations against the Roundup brand (ie glyphosate) and link those allegations directly to GM crops. We anticipate this will increase with the IARC decision. CLI seems to be willing to develop high-level communications around the IARC process to prepare for the publication of the IARC decision. To date, CLA and ECPA have not been engaged; we will need industry support specific to the glyphosate rating.

Comment [k5]: [illegible]

International Agency for Research on Cancer
World Health Organization

"The International Agency for Research on Cancer (IARC) is the specialized cancer agency of the World Health Organization"

Jen Listello	Reg Affairs – US	LEAD
Kelly Clauss	Issues Preparedness and Engagement	
Linda Dudenhoeffer	Stakeholder Outreach	
Richard Garnett	Regulatory Affairs – Global	
Bill Heydens	Regulatory Product Safety Assessment / Strategy	
Dan Jenkins	U.S. Agency Regulatory Affairs	
Kim Link	Issues Preparedness and Engagement	
Kim Magin	Industry Affairs	
John Vicini	Regulatory Policy / Scientific Affairs	

Monsanto Company Confidential Page [PAGE] of [NUMPAGES]

Draft Feb 23, 2015

Glyphosate: IARC

[redacted]

Due Date	Who/What	Objective	MON Owner	Status
Pre-Decision/Posting				
Feb 3, 2015	Deadline for data submission	Update public record with most current and complete data	Bill Heydens	Complete
	Monsanto.com/glyphosate	Update to include gly not [redacted]	Bill Reeves Kyel Richard	
Week of Feb. 23-27	Planning and Preparation			
	Engage Henry Miller	Inoculate / establish public perspective on IARC and reviews	Eric Sachs	
	Blog post to reiterating gly not carcinogen/tweets	Establish SM content and amplify scientific studies	Aimee Hood Kim Link Heather McClurg	
	Outreach to EPA / IARC participants	Ensure awareness of scientific studies	Dan Jenkins	
Prior to March 3	Contact journals to inquire about press releases for 6 new publications	Amplification of scientific studies	David Saltmiras	
	Inform/ Engage Industry Associations	Lead voice in "who is IARC" plus 28 outrage	Kim Link Kelly Clauss Richard Garnett Kim Magin	Ongoing
	Engage CLI and regional industry associations in communications	Communicate the perspective of the IARC process	Kelly Clauss Richard Garnett	Ongoing
	Address new allegations	Neutralize impact	Kim Link Charla Lord	Ongoing
	Outreach to / collaboration with DAS (2,4D scheduled for IARC review in June 2015)	Maximize efforts / coordinated industry response	Bill Heydens Donna Farmer	Ongoing
	Global Reg Affairs (Canada, US, EU, LAS, Brazil, Asia Pacific, India)	Inform ongoing activities for regulator outreach	Richard Garnett	Ongoing
Week of March 2-6	Implement Inoculation Plan / Continue Preparations			
	Engage with experts to plan for publications and other activities in case IARC classification is unfavourable	Respond to the classification and defend at global regulatory	Bill Heydens, Donna Farmer John Acquavella	

[redacted]

Draft Feb 23, 2015

Glyphosate: IARC

		authorities		
	Share SM messages (Twitter, Facebook)	Amplify positive gly content	Kim Link Heather McClurg	
	Prepare key Monsanto spokespeople	Ensure strong, consistent MON messaging	FH Kelly Clauss	
	Communicate to employees via ET email and Connection article	Raise awareness and inoculate employees	Jaclyn Pollnow	
Post-Decision/Posting				
Week of March 9-13	Implementation of Crisis Plan, as necessary			
March 10	Outreach to key stakeholders (utilize discussion guide)	Neutralize impact of decision / gain active support	Linda Dudenhoeffer	
March 10	Outreach to grower groups (utilize discussion guide, provide key talking points)	Neutralize impact of decision / gain active support	Kim Magin IA colleagues	
	Outreach to regional regulators	Neutralize impact of decision / gain active support	Dan Jenkins Regional RA	
@ Posting	Publish / amplify blog post on the meaning of the IARC ruling	Ensure MON POV / neutralize SM	Kim Link Charla Lord Heather McClurg	
@ Posting	Add IARC statement to web	Ensure MON POV / neutralize SM	Kyel Richard	
@ Posting	Publish Connection article for employees	Ensure MON POV	Jaclyn Pollnow	
@ Posting	Outreach to ag media	Ensure MON POV in coverage	John Combest	

See Attachment A: Communications Plan

Reading

EXTERNAL (Glyphosate is not carcinogenic)

- @EPA concluded in 2013 that "glyphosate does not pose a cancer risk to humans" [HYPERLINK "http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2012-0132-0009"]
- @EPA groups glyphosate in the lowest category E, indicating glyphosate does not pose a cancer risk to humans http://www.epa.gov/oppsrrd1/reregistration/REDs/factsheets/0178fact.pdf
- FAQ #7 Does glyphosate cause cancer? [HYPERLINK "http://www.monsanto.com/glyphosate/pages/glyphosate-frequently-asked-questions.aspx" \l "seven"]
- Backgrounder Glyphosate: No evidence of carcinogenicity[HYPERLINK "http://www.monsanto.com/glyphosate/Documents/no-evidence-of-carcinogenicity.pdf"]
- Discover.com [HYPERLINK "http://discover.monsanto.com/conversation/question/are-you-ready-to-be-held-accountable-for-the-many-diseases-which-are-caused-by-your-poison-such-as-leaky-gut-syndrome-and-cancer"]

Comment [k7]: Ensure Mink link is fixed

Draft Feb 23, 2015

Glyphosate: IARC

- GMOAnswers, Does glyphosate cause cancer? [HYPERLINK "http://gmoanswers.com/ask/does-glyphosate-cause-cancer"]
- GMOAnswers, Breast cancer from glyphosate? [HYPERLINK "http://gmoanswers.com/ask/how-can-you-say-they-are-safe-when-recent-studies-not-conducted-monsanto-show-direct-link-breast"]
- Science Direct, Epidemiologic studies of glyphosate and non-cancer health outcomes: [HYPERLINK "http://www.sciencedirect.com/science/article/pii/S0273230011001516"]
- Regul Toxicol Pharmacol. Epidemiologic studies of glyphosate and cancer: a review.
  - http://www.ncbi.nlm.nih.gov/pubmed/[redacted]

INTERNAL

- xxx

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Draft Feb 23, 2015

ATTACHMENT A: PREPAREDNESS AND ENGAGEMENT PLAN
FOR IARC CARCINOGEN RATING OF GLYPHOSATE
Last Updated: February 17, 2015

OBJECTIVES FOR PREPAREDNESS & ENGAGEMENT

- Protect the reputation and FTO of Roundup by communicating the safety of glyphosate
- Amplify science-based information to prevent unfounded claims from becoming popular opinion
- Provide cover for regulatory agencies to continue making re-registration decisions based on science

AUDIENCES

- IARC Panelists and Observers
- Regulators
- Stakeholders
- Farmer Customers

STRATEGIES/TACTICS

PRE-IARC

1. Amplification of Scientific Studies
   - Support the development of three new papers on glyphosate focused on epidemiology and toxicology
   - Work with RPSA and Strategic Communications to amplify existing studies and new papers
     - Authors work directly with scientific journals to issue alerts and news releases on new bodies of work
     - RPSA posts blog from first-person viewpoint of Monsanto's David Saltmiras, co-author of one of the glyphosate cancer papers
     - Share resources and content with Monsanto key regions to amplify the message globally

2. Inform / Inoculate / Engage Industry Partners
   - Develop a "toolkit" containing key information and resources
     - Identify any message shortcomings and address through updates to monsanto.com/glyphosate and through US and EU blog posts
   - Work with RPSA, Stakeholder Outreach Team, Industry Affairs, Government Affairs, US Business, Global CE and Regulatory teams, etc. to engage industry partners
     - Tier 1: Crop Life International / European Crop Protection Association / GMO Answers / BIO – identify committees that are best to engage
     - Tier 2: Academics (AgBioChatter), Biofortified, Sense About Science, Genetic Literacy Project, Academics Review
     - Tier 3: Alert food companies via Stakeholder Engagement team (IFIC, GMA, CFI) for "inoculation strategy" to provide early education on glyphosate residue levels, describe science-based studies versus agenda-driven hypotheses
     - Tier 4: Inoculate key grower associations

3. Address New Allegations
   - Respond quickly and publically to new pseudoscience cancer studies
   - Identify / request third-party experts to blog, op/ed, tweet and/or link, repost, retweet, etc.

POST-IARC

4. Orchestrate Outcry with IARC Decision ~ March 10, 2015
   - Industry conducts robust media / social media outreach on process and outcome
     - [Sense About Science?] leads industry response and provides platform for IARC observers and industry spokesperson
     - CU and other associations issue press releases

- Joint Glyphosate Taskforce pubitshes press release, letter signed by leaders of each manufacturer in North America and Europe
- Push opinion leader letter to key daily newspaper on day of IARC ruling with assistance of Potomac Group

- Monsanto responds with strong reactive statement
  - Distribute video and audio responses to IARC decision
  - Address media inquiries with company glyphosate spokesperson
  - Utilize Monsanto channels (web, FB, Twitter, blog, etc) to provide Monsanto POV
  - Corporate Engagement team packages industry and Monsanto responses, then distributes via email to ~20 most influential ag media outlets across print, radio and TV

5. Engage Regulatory Agencies
   - Grower associations / growers write regulators with an appeal that they remain focused on the science, not the politically charged decision by IARC

ARTICLE SUBMITTED BY REPRESENTATIVE JERRY MCNERNEY

Reply-To: POLITICO subscriptions <reply-fe8b137376620c7a77-1163473_HTML-637934647-1376319-0@politicoemail.com>

By Simon Marks

02/06/2018 08:24 AM EDT

The European Parliament today agreed to create a special committee to investigate potential failings in the EU's system for renewing pesticides such as glyphosate.

Approved during a plenary session in Strasbourg, the committee will present recommendations to the European Commission on how to change EU law to ensure that the science used to prove a substance's safety is not aligned too closely with industry. The move comes after the U.S. agri-giant Monsanto was accused last year by activists and lawmakers of undue influence over the scientific literature that went into proving the safety of glyphosate, the active ingredient in its Roundup herbicide.

Policymakers are also looking at the possibility of creating a special fund — financed by industry but run by the European Food Safety Authority — in order to increase the independence of scientific research on the safety of pesticide substances.

The committee will investigate conflicts of interest "at all levels" and look at whether the Commission followed regulations when making the decision to renew glyphosate's license for another five years.

This article first appeared on POLITICO.EU on Feb. 6, 2018.

DOCUMENTS SUBMITTED BY REPRESENTATIVE DONALD S. BEYER, JR.

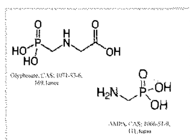
APAMT POSTER GERONA)

Biomonitoring of glyphosate across the United States in urine and tap water using high-fidelity LC-MS/MS method

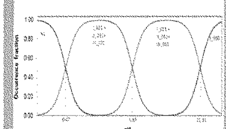
Axel Adams[1,2], Matthew Friesen[1], Alex Olson[1], Roy Gerona[1]
1. University of San Francisco, San Francisco, CA. 2. UCSF-UC-Berkeley Joint Medical Program, Berkeley, CA.

Introduction

•Glyphosate (N-(phosphonomethyl)glycine) is arguably the most important herbicide ever discovered[1] and is the most widely used herbicide in the world with U.S. of 185 million pounds in 2007[2]
•Its mode of action as a herbicide is via inhibition of synthesis of aromatic amino acids in plants[3]
•Main breakdown product is (aminomethyl)phosphonic acid (AMPA)



•March 2015, IARC ruled glyphosate as a Group 2A carcinogen based upon a meta-analysis linking glyphosate exposure to Non-Hodgkin's Lymphoma (OR: 1.5, 95%CI 1.1-2.0, I^2=32.7%)[4,5]
•Glyphosate is a notoriously difficult analyte
- Small, polar, and amphoteric (pKa's of pH 0.47, 5.69, and 11.81)[6]
- No fluorophore or chromophore
- Structurally similar to many small polar molecules in biological matrices (e.g. glycine)
- Strong chelator of divalent metal cations[7]



Charge Distribution of Glyphosate as a Function of pH[6]

•Aims:
1.Develop a direct method for analysis of glyphosate in urine and tap water for future use in both biomonitoring studies and assessment of acute intoxication.
2.Demonstrate utility of method in a public glyphosate testing in the United States.

Analysis

- LC: Agilent binary 1260 Infinity LC pump and autosampler injector
- MS: AB Sciex Triple Quad 5500 LC-MS/MS
- Column: Obelisc N column (100mm x 2.1mm x 5 m, SILIC Technologies)
- Quantitation in urine done using standard addition with IS of ^{13}C-2-glyphosate with spike concentrations at 0.2, 1, and 2ppb
- Quantitation in tap water done using stable isotope dilution method using peak area ratios[8]

MRM Transitions

Analyte	MRM Transition	DP	CE	CXP
Glyphosate	168.071/62.900	-40V	-32V	-11V
	168.071/81.000	-40V	-22V	-7V
Glyphosate-2-^{13}C	169.400/63.000	-30V	-40V	-9V

LC-MS Conditions

LC Conditions		
Autosampler Temp.	4°C	
Column Temp.	40°C	
Elution Gradient	Isocratic	
Mobile Phase	1% Formic Acid/HPLC-Grade H_2O	
Mobile Phase pH	2.2	
Flow Rate	1000µL/min	
Injection Volume	25µL	
MS Conditions		
MS Mode	Negative	
Curtain Gas	20.0bar	
Collision Gas	9.0bar	
Ion Spray Voltage	-4500V	
Temperature	700°C	
Ion Source Gas 1	60.0bar	
Ion Source Gas 2	60.0bar	
Method Duration	6.00 min	
Validation	Matrix	Concentration
LOD	Urine	0.2ppb
LLOQ		0.5ppb
LOD	Water	0.01ppb
LLOQ		0.005ppb

Results from Public Testing[ŧ]

Matrix	Population	n	Avg. Glyphosate Conc. (ppb)	Standard Error
Urine	Overall	131	3.096	0.186
	Women	75	2.941	0.214
	Men	56	3.304	0.329
	Children (confirmed <18years old)*	7	3.586	0.300
	Adults*	124	3.069	0.196
	Region			
	Northeast	21	3.000	0.343
	Midwest	19	3.050	0.289
	South	16	2.313	0.828
	West	75	3.053	0.275

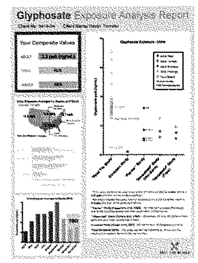
ŧGlyphosate residues were not observed in any tap water samples – as would be expected due to phosphorus removal during water treatment
*Only 60/131 participants included age on requisition forms

Limitations:

-Selection bias: people likely to pay for this service are not representative of general U.S. population and the West is represented disproportionately
-Consistency of sample collection; urine concentrations were corrected based upon urine osmolality

Public Testing Reports

- Public Testing offered as a fee for service
- Participants received a summary report of the glyphosate levels in urine along with infographics comparing their results to results obtained for different regions of the U.S.



Conclusions:

•Glyphosate residues were observed in 93% of urine samples in voluntary public testing in the U.S. general population; this is higher than the frequency observed in Europe using GC-MS (43.9%)[9]
•Tap water obtained was free of glyphosate residues as expected; exposure is likely due to dietary intake or environmental exposure

Future Directions:

•Develop method for AMPA in urine
•Develop direct LC-MS method not requiring standard addition
•Develop method for glyphosate and AMPA in other biological matrices such as serum and breast milk

References:

UCSF University of California San Francisco — Berkeley UCSF Joint Medical Program

HRI GLYPHOSATE STUDY SUMMARY RESULTS

Health Research Institute
Laboratories

February 2, 2018

The Honorable Donald S. Beyer, Jr.
Ranking Member
Subcommittee on Oversight
Committee on Science, Space & Technology

Dear Representative Beyer,

Health Research Institute is collaborating with researchers at the University of California San Diego to measure human environmental exposure to glyphosate. We test urine samples provided by participants using LC/MS instrumentation, the gold standard in analytical chemistry.

Our analytical capacities are routinely evaluated by a third-party, independent proficiency testing program. We passed the most recent proficiency test with a high degree of accuracy.

We plan to submit the results of our glyphosate environmental exposure study for peer-reviewed publication later this year. Results, to date, that you may find of interest include:

1078 people have been tested, from October 2016 to today.

923 people (86%) had detectable levels of glyphosate.

155 people (14%) had no detectable levels relative to our limit of detection of 0.03 parts per billion.

The average level of glyphosate in the urine of study participants is 0.46 parts per billion.

The top 10 percentile had an average of 2.74 parts per billion.

The levels in North Americans tested in the study are 120% higher than levels found in a similar study in Europe (Hoppe, 2013).

People who consume non-organic oats had twice the glyphosate levels as those who do not. This may be due to the agricultural practice of desiccation, or drying, of the oat crop with glyphosate prior to harvest.

People who consume the most organic foods have one quarter the glyphosate levels as those who consume the least organic foods.

P.O. Box 370 • Fairfield, IA 52556
www.HRILabs.org
641-552-6258

People who consume the most vegetables per day have half the glyphosate levels as those who consume the least vegetables.

People who consume the most meals outside of their homes had the same glyphosate levels as those who consume most of their meals at home.

People who use glyphosate on their yards or farms have 80% higher glyphosate levels than those who do not use glyphosate.

We hope you find these statistics helpful. Please let us know if you have any questions.

Sincerely,

John Fagan

John Fagan, PhD
Chief Scientist

GLYPHOSATE TEST RESULTS

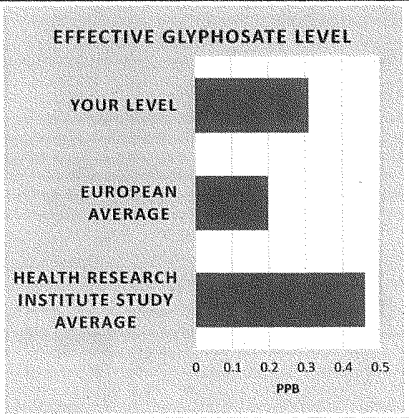
Health Research Institute Laboratories

Report Number S0002386- 20180202
Report Date 2018-02-02

Certificate of Analysis

Specimen Type:	urine	HRI Labs Sample No.:	S0002386
Client:	Don Beyer	Receipt Date:	2018-02-01
Authorized Person:	Don Beyer	Test Date:	2018-02-01
Sample Weight / Volume:	30 ml	Shipment Temp:	Ambient
		Storage Temp:	4°C

Analysis:	Results:	
Residue:	Level:	Units:
Glyphosate	**0.31**	ppb (ng/mL)
AMPA	**Trace**	ppb (ng/mL)
Effective Glyphosate Level	**0.31**	ppb (ng/mL)



Methods

Sample Analysis: HRI TM #6 "Glyphosate in water and urine, Cation H method"

Glyphosate	LOQ = 0.25 ppb, LOD = 0.03 ppb	Terms: "Trace" is between LOD and LOQ
AMPA	LOQ = 0.25 ppb, LOD = 0.04 ppb	"Not Detected" is less than LOD

Effective Glyphosate Level calculated according to Food and Agriculture Organization (FAO) method where total glyphosate residue is the sum of the weight of glyphosate + 1.5 × the weight of its metabolite AMPA. Effective glyphosate levels above the LOQ are normalized using specific gravity.

Released on Behalf of HRI Laboratories by:

Dr. John Fagan, Chief Scientist

P.O. Box 370
Fairfield, IA 52556
+1 641-552-6258

CLIA ID #16D2122655

v.1.1

Letters

RESEARCH LETTER

Excretion of the Herbicide Glyphosate in Older Adults Between 1993 and 2016

The herbicide Roundup is sprayed onto genetically modified crops and applied as a desiccant to most small nongenetically modified grains. Use of this herbicide has increased since 1994 when genetically modified crops were introduced in the United States. Glyphosate, the primary ingredient in the herbicide, is found in these crops at harvest.[1] Environmental exposure through dietary intake of these crops has potential adverse health effects and can be assessed by measuring urinary excretion.[2-4] We measured excretion levels of glyphosate and its metabolite aminomethylphosphonic acid (AMPA) in participants from the Rancho Bernardo Study (RBS) of Healthy Aging.

Methods | The RBS, established in 1972, is a prospective study of 6629 adults older than 50 years residing in Southern California.[5] As of 2016, approximately 1000 participants were active (the primary reason for loss to follow-up was mortality). Of those 1000 participants, 112 had routine morning spot urinary biospecimens obtained at each of 5 clinic visits that took place from 1993 to 1996 and from 2014 to 2016. One hundred of these 112 were randomly selected for this study, which was approved by the University of California, San Diego, institutional review board. All participants gave written informed consent.

Samples were analyzed using high-performance liquid chromatography coupled with mass spectrometry. Limits of detection (LOD) were 0.03 µg/L for glyphosate and 0.04 µg/L for AMPA; assays were linear up to 50 µg/L. Analyses were normalized to each sample's specific gravity, thereby accounting for dilution or concentration effects due to variability in water intake and age-related or other differences in renal function. Changes over time in the proportion of samples above the LOD were assessed using generalized estimating equation models to account for the dependency of observations in repeated measures. A 2-sided significance threshold was set at less than .05. Statistical analyses were performed using R (R Foundation), version 3.3.2.

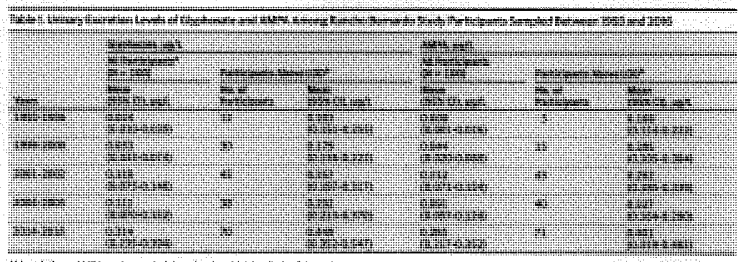
Results | Among the 100 participants in this study, the mean age in 2014-2016 was 77.7 years (SD, 6.6) and 60% were women. These values were not different from the 112 with urine specimens but were older than the entire group of 1000 active participants in the RBS (mean age, 71.7 years [SD, 12.0]) ($P < .001$).

The mean glyphosate level increased from 0.024 µg/L in 1993-1996 to 0.314 µg/L in 2014-2016, and reached 0.449 µg/L in 2014-2016 for the 70 participants with levels above the LOD (**Table 1**). Mean AMPA levels increased from 0.008 µg/L in 1993-1996 to 0.285 µg/L in 2014-2016, and reached 0.401 µg/L in 2014-2016 for the 71 participants with levels above the LOD.

The prevalence rates of glyphosate samples above the LOD increased significantly over time, from 0.120 (95% CI, 0.064-0.200) in 1993-1996 to 0.700 (95% CI, 0.600-0.788) in 2014-2016 (Wald statistic = 80.5; $P < .001$) (**Table 2**). The prevalence of AMPA samples above the LOD increased significantly from 0.050 (95% CI, 0.016-0.113) in 1993-1996 to 0.710 (95% CI, 0.611-0.796) in 2014-2016 (Wald statistic = 103; $P < .001$).

Discussion | Mean glyphosate and AMPA levels and the proportion of samples with detectable levels increased over

Table 1. Urinary Concentrations Levels of Glyphosate and AMPA Among Rancho Bernardo Study Participants Sampled Between 1993 and 2016



Abbreviations: AMPA, aminomethylphosphonic acid; LOD, limit of detection.

[a] Participants with levels below the LOD had values set at 0.

[b] The LOD was 0.03 µg/L for glyphosate and 0.04 µg/L for AMPA.

Table 2. Urinary Excretion Prevalence Rates of Glyphosate and AMPA Among Rancho Bernardo Study Participants Sampled Between 1993 and 2016

Years	Prevalence Rate (95% CI)[a]	
	Glyphosate	AMPA
1993-1996	0.120 (0.064-0.200)	0.050 (0.016-0.113)
1999-2000	0.300 (0.212-0.400)	0.150 (0.086-0.235)
2001-2002	0.430 (0.331-0.533)	0.430 (0.331-0.533)
2004-2005	0.390 (0.294-0.493)	0.400 (0.303-0.503)
2014-2016	0.700 (0.600-0.788)	0.710 (0.611-0.796)

Abbreviation: AMPA, aminomethylphosphonic acid.

[a] *P* value was less than .001.

time. A 2015 review of nonfarmer US and European adults reported mean urinary glyphosate levels of 1.35 µg/L and 0.215 µg/L, respectively.[6] The values observed in this study fall within this range and were higher than in European adults. Animal and human studies suggest that chronic exposure to glyphosate-based herbicides can induce adverse health outcomes.[3] Animals consistently fed an ultra-low dosage of the herbicide with a 50-ng/L glyphosate concentration show hepatotoxicity consistent with nonalcoholic fatty liver disease and its progression to steatohepatosis.[4] In July 2017, in accordance with the Safe Drinking Water and Toxic Enforcement Act of 1986, the state of California listed glyphosate as a probable carcinogen.

Limitations of this study include that the cohort lived in Southern California, which might have different exposures than other states, only a subset of RBS participants were studied, urinary levels represent recent exposure, urinary-specific gravity is reduced with age, and data on clinical outcomes were not evaluated. Future studies of the relationships between chronic glyphosate exposure and human health are needed.

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Author Contributions: Dr Mills had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Mills, Laughlin.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Mills, Fagan.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Mills, Fagan.
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Supervision: Mills, Fagan, Barrett-Connor.

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COMMENT & RESPONSE

Prediabetes Prevalence in China

To the Editor Mr Wang and colleagues[1] estimated that the overall prevalence of prediabetes was 35.7% among Chinese adults in 2013 and concluded that the difference from previous estimates may be due to an alternate method of measuring hemoglobin A_{1c} (HbA_{1c}). The previous estimate by Xu et al[2] in 2010 was 50.1% (52.1% in men and 48.1% in women).

However, the study by Wang and colleagues might still have overestimated the prevalence of prediabetes in China. In a nationally representative sample of 46 239 adults in 2008, the prevalence of prediabetes was 15.5% (16.1% among men and 14.9% among women).[3] In contrast, the prevalence of diabetes in the 2008 study was 9.8%, which is close to the 10.2% in the current study. Wang and colleagues used HbA_{1c} levels as the criterion for prediabetes. Although the increased prediabetes prevalence could be due to improved sensitivity of screening with HbA_{1c} measurement, the increase from 15.5% in 2008 to 35.7% in 2013 is suspect.

Wang and colleagues used HbA_{1c} levels of 5.7% to 6.4% to diagnose prediabetes, as recommended in the United States. However, this criterion, developed in the US population, has not been validated in a Chinese population. In addition, a study on the relationship between HbA_{1c} level and the oral glucose tolerance test among Chinese adults found that the accuracy of HbA_{1c} measurement for detecting diabetes

LETTER SUBMITTED BY CHAIRMAN LAMAR SMITH

CAMPAIGN FOR ACCURACY IN
PUBLIC HEALTH RESEARCH
COALITION

February 19, 2018

The Honorable Lamar Smith
Chairman
Committee on Science, Space, & Technology
2409 Rayburn House Office Building
Washington, DC 20515

The Honorable Frank D. Lucas
Vice Chairman
2405 Rayburn House Office Building
Washington, DC 20515

The Honorable Eddie Bernice Johnson
Ranking Member
2468 Rayburn House Office Building
Washington, DC 20515

Re: House Science, Space, & Technology Committee hearing – "In Defense of Scientific Integrity: Examining the IARC Monograph Programme and Glyphosate Review"

Dear Chairman Smith, Vice Chairman Lucas, and Ranking Member Johnson:

The Campaign for Accuracy in Public Health Research (CAPHR) Coalition[1] applauds the House Science, Space, & Technology Committee (Committee) for holding a hearing on the International Agency for Research on Cancer's (IARC) troubled Monographs Program (or Program) on February 6, 2018. The Coalition commends the Committee for acknowledging that fundamental changes need to be made to address the Program's flawed scientific approach and lack of transparency. The CAPHR Coalition fully supports the Committee's continued oversight of the IARC Monographs Program, especially given ongoing U.S. funding.[2]

We recognize much of IARC's work makes important contributions to public health. However, we have serious concerns with the Monograph Program's processes for gathering and analyzing studies, evaluating various lines of evidence, integrating evidence from mechanistic studies

[1] Members of the CAPHR Coalition are: American Chemistry Council, American Petroleum Institute, Chemistry Industry Association of Canada, CropLife America, National Association of Manufacturers, Society of Chemical Manufacturers & Affiliates, Styrene Information & Research Center, and United States Council for International Business.

[2] The U.S. government funds most of the IARC Monographs Program, providing it with approximately $1 million each year, which is in addition to the $1.8 million for the U.S.'s IARC membership contribution and other U.S. grants.

including determining human relevance of animal studies, peer engagement, public engagement, peer review processes and the practices IARC uses to promote Monograph conclusions. We also reinforce the active role the U.S. government plays in promoting sound science and evidence-based policy at home and abroad. In particular, we note the Resolution from the 70th World Health Assembly in May 2017 "*to enhance the coordination between IARC and other parts of WHO on assessments of hazards and risks, and on the communication of those assessments.*"

The CAPHR Coalition advocates for modernizing IARC's Monographs Program through greater transparency and balanced assessments that produce credible conclusions. The Monographs Program – which evaluates cancer hazards, not risks – has been criticized by leading scientists and regulators for its lack of transparency, frequent conflicts of interest, questionable carcinogen classifications, and misleading communications. Additional concerns regarding the Program have been raised and reinforced by numerous credible and independent experts, including efforts to suppress and omit relevant data and manipulation of outcomes when designating carcinogenic classifications.

Recent announcements from IARC have caused confusion for the general public. IARC's classifications of some substances have contradicted the U.S. government's own findings or have resulted in the need for explanatory communications to concerned members of the public. Such discrepancies result from IARC's limited assessment of cancer hazard, unlike the practices of most regulators worldwide, including the U.S. Environmental Protection Agency (EPA) that conduct thorough risk-based assessments. Due to their focus on hazard assessment, IARC's assessments can also contradict those of other WHO entities – such as the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) – further contributing to public confusion.

The Coalition believes that the six principles for reform delineated below, if implemented, would strengthen the integrity of the Monographs Program's processes and ensure that IARC updates the methods and assumptions of the Monographs Program to reflect modern scientific practices, rather than the outdated approaches it has relied on since the program was established in 1969.

The following are the CAPHR Coalition Principles for Reform of the Monographs Program:

1. **Consider a Substance's Risk, Not Just Hazard**

Though IARC uses the word "risk" in its monograph titles, it does not consider the actual risk of developing cancer based on exposure under real world circumstances. Rather, the Monographs Program considers only a substance's hazard: whether the substance could cause cancer in humans under any circumstances, such as doses and exposure levels far beyond what is typical. Unfortunately, this distinction is not widely known or understood, leading to significantly misinterpreted conclusions. Instead, the Program's identification of substances as carcinogens must no longer ignore the essential elements of dose and exposure. Without this context, IARC's monograph conclusions are of little value in real world settings, and instead create

potential adverse consequences in areas including health, safety, and nutrition in both developed and developing countries. This context should be provided when IARC publishes and promotes its findings to the media and other stakeholders to prevent confusion.

2. **Require Reliance on Weight of Evidence**

Currently, IARC monographs do not consider the full weight of the scientific evidence. Currently, the Program which considers only selected findings, ignores conflicting evidence, and fails to fully consider the quality of individual studies. Instead, when making determinations in its monographs, the Monographs Program should give the most weight to those studies that are of the highest quality and greatest relevance to humans. A weight of the evidence approach evaluates each relevant study for its strengths and limitations before its conclusions are used as part of the review.

3. **Establish Standard Criteria for Selecting Studies**

IARC monographs also regularly rely on poor quality studies as the basis of conclusions. To remedy this, the Monographs Program should establish clearly defined, transparent criteria for assessing the quality and reliability of studies for its monographs. It is currently unclear how the Program determines which studies it will consider and which it will disregard.

4. **Increase Transparency, Utilize Input from Stakeholders, and Employ Independent Scientific Peer Review**

The IARC Monographs Program consistently lacks transparency. The Program can address this concern by openly engaging with and allowing participation from stakeholders during monograph development, including meetings with industry experts. IARC should clearly articulate in its monographs how it considered stakeholder input and provide stakeholders an opportunity to comment on a draft monograph.

Currently, each Monograph is developed by a Working Group comprised of scientists appointed by IARC. The Working Group reviews studies and data, conducts analyses, and then relies on their expert opinion to arrive at their conclusions, which are then published. This process, which may have been permissible in the 1960's when the Monograph Program was initiated, allows the Working Group to both conduct and review their own scientific work. In 2018, this process does not comport with best scientific practices, wherein independent scientific peer review is now a fundamental precept of credible and transparent scientific analyses, even for analyses, conclusions and reports generated by expert groups, such as those of the U.S. National Academies.[3] Therefore IARC should develop and implement an independent scientific peer review process for the Monographs.

[3] http://national-academies.org/studyprocess/index.html#st4

5. Explain Conflicts of Interest

The IARC Monographs Program has a history of suffering from conflicts of interest. To rectify this recurring issue, IARC should disclose all conflicts of interest among the Monograph Program participants and advisors to its working groups, not just those affiliated with industry. For example, IARC has not disclosed instances when its advisors and monograph working group members from the academic or NGO community may have a personal or professional stake in the outcome of the monograph.

6. Improve Monograph Releases

Currently, IARC releases a summary of a new monograph immediately after the Program makes a carcinogenic determination; however, the full monograph with supporting evidence is not immediately released and may not be released for years. Rather, IARC should release all monograph information at one time and do away with its current practice of releasing short summaries of the Monograph Program's findings months before supporting information is made public. IARC's current publication practice fails to provide the evidence and exposure levels used to support its classifications of substances as carcinogenic, causing misunderstanding by media and the public.

In conclusion, IARC monographs cause significant public confusion, unwarranted marketplace de-selection, and regulatory action despite being of questionable relevance, as the monographs do not reflect actual risks. Therefore, IARC must make key improvements to its Monographs Program to enhance the credibility and utility of its findings and prevent further public misunderstanding of its conclusions.

We appreciate the opportunity to provide comments. If the CAPHR Coalition can provide any additional information, please contact Alexa Burr (Alexa_Burr@americanchemistry.com or 202-249-6425).

Sincerely,

Alexa Burr
CAPHR Coalition