Chapter 15
Glyphosate Toxicology: What We Can Learn From the Current Controversy

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ABSTRACT

This chapter explores the glaring scientific differences in the human health assessment of the popular herbicide glyphosate between European and American institutions. The International Agency for Research on Cancer (IARC) classified glyphosate as a probable human carcinogen, while the U.S. Environmental Protection Agency (EPA) concluded that glyphosate is not likely to be carcinogenic to humans. Both IARC's and the EPA's carcinogenic risk assessment processes are discussed. This work reveals uncertainties in the sciences of toxicology and epidemiology, as well as assumptions made in their applications for evaluating glyphosate. These uncertainties, along with the political context of chemical risk assessment, are at the root of the divergent findings on the carcinogenic risks of glyphosate.

INTRODUCTION

By now it is widely understood that determining the safety of a chemical has become a heavily politicized activity. Notwithstanding the claims of regulatory bodies, that science-based evidence guides their health and environmental assessments of a chemical, we continue to see a significant divergence in the toxicological profiles among different sectors of the scientific community and between the agencies of different countries.

The battlegrounds over the safety of chemicals occur between non-profit groups and government regulatory agencies as well as between groups of scientists who position themselves on one side or the other on whether a chemical is safe enough or too dangerous to keep in commercial use.

What can explain the differences in the assessment of chemical safety? The published science behind any chemical assessment is available to all. The science of toxicology is not, at least overtly, embedded in an ideology. It is taught throughout the world utilizing principles and textbooks that are widely shared.

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Since the Enlightenment empiricism has been the cornerstone of the physical and social sciences. We perform experiments and allow the data to determine whether a hypothesis has been confirmed or falsified. Sometimes it takes one elegant, well executed experiment to bring consensus to a community of scientists. That was the case when evidence from an eclipse confirmed Einstein's General Theory of Relativity that the path of light can be altered by a massive body.

In the science of chemical toxicology there are not *experimentum crucis* [crucial experiments] capable of bringing consensus to a problem. Every experimental result in toxicology can be dissected for the gaps in reaching a definitive conclusion that the chemical is hazardous. There are always more experiments to perform to reduce the uncertainties. Commercial interests exploit the uncertainties to derail any regulations by demanding more studies.

Of course, even if there were a consensus on how a substance affects the human body, there remains the normative question, "what is acceptable risk?" These decisions are made every time a new drug is introduced for approval by the U.S. Food and Drug Administration. (FDA). When there is a consensus on the drug's efficacy against a disease, there must be a decision on whether its benefits are worth the risks of the side effects that will accrue to some patients. And even when a drug is licensed by the regulatory body, individuals can decide for themselves whether the risk of side effects are worth the benefits claimed for the drug.

Industrial and agricultural chemicals once approved expose countless people who cannot easily protect themselves or opt out of being exposed to the chemical. As an example, the law regulating industrial chemicals in the United States, first passed in 1976 as the Toxic Substances Control Act (TSCA) had a forty-year run before it was amended in 2016. Within those forty years about 85,000 chemicals were introduced into consumer products, yet only five chemicals were highly regulated or banned (Krimsky, 2017). I will leave to the final section why it has been so difficult for regulatory agencies in the United States to fully evaluate, regulate and ban toxic chemicals.

In this chapter I shall focus on the agricultural herbicide glyphosate. After a brief discussion of its path to commercial use and its special role in genetically engineered crops, I shall examine the cancer hazard assessment carried out by the International Agency for Research on Cancer (IARC) and compare that with the similar assessment by the U.S. Environmental Protection Agency (EPA). While they had access to the same published science, their conclusions were vastly different. IARC found that glyphosate is a probable human carcinogen, while the EPA concluded that it was not a human carcinogen. I will be exploring the reasons for this divergence of views on glyphosate toxicology. Did they use different criteria for determining human carcinogenicity? Did they employ different models of carcinogenesis? Did they select the relevant studies differently? Were there political and economic forces affecting the decision? I shall also discuss the efforts by one of the leading manufacturers of glyphosate, Monsanto, through its product Roundup, to influence a finding that it was safe to use as labeled. My analysis is based largely on two documents, IARC's *Monograph on the Evaluation of Carcinogenic Risks to Humans* and EPA's *Revised Glyphosate Issue Paper* both released in 2017.

DISCOVERY OF GLYPHOSATE

In 1950 a Swiss chemist, Henri Martin, while working for a small pharmaceutical company, developed a new (phosphonomethyl) derivative of an amino acid glycine. Failing to find any pharmaceutical applications, it was left in storage and in the log books. After the company (Cilag) was sold, the research

samples, including the glycine derivative, was passed on to a chemical company and eventually ended up at Monsanto. As reported by Dill et al (2010):

In its Inorganic Division, Monsanto was developing compounds as potential water-softening agents and over 100 related aminomethylphosphonic acid (AMPA) analogs were synthesized. When these compounds were tested as herbicides by Dr. Phil Hamm, two showed some herbicidal activity on perennial weeds.

When water has high concentrations of calcium, iron and magnesium it is said to be hard. Calcium and magnesium have two positive charges and iron has three. Since glyphosate is a negatively charged molecule, it can bond with the other molecules and pull them out of solution. In 1961 glyphosate was patented by the Stauffer Chemical Company as a descaling (metal binders) and chelating agent and was used to clean mineral deposits in pipes and boilers of residential and commercial hot water systems.

While Monsanto scientists were investigating glyphosate's potential water-softening properties, which were too weak to be commercially useful, they learned that it was a phytotoxicant and could kill weeds. A Monsanto chemist, John Franz, made analogs of AMPA to get a more potent herbicide. He synthesized the current form of glyphosate in 1970. It was first described by Franz and colleagues in the *Proceedings of the North Central Weed Science Society* (Baird et al., 1971). Monsanto gave the compound the trade name of Roundup. Franz received U.S. patent 3,799,758 on March 26, 1974 for glyphosate, which he assigned to Monsanto. The patent states:

In accordance with the invention it has been found that the growth of germinating seeds, emerging seedlings, maturing and established woody and herbaceous vegetation and aquatic plants can be controlled by exposing the emerging seedlings or above ground portions of maturing and established vegetation, or the aquatic plants to the action of an effective amount of glycines of the present invention...These compounds are effective as post-emergent phytotoxicants or herbicides... (John, 1974)

Glyphosate's herbicidal property is based on its inhibition of the enzyme EPSPS (present in plants, fungi and bacteria), which is necessary for the plants to synthesize amino acids, without which they cannot survive. Vertebrates, including humans, do not possess the same enzyme pathway. In the next development, Monsanto found that some bacteria survived in the presence of Roundup. Recombinant DNA technology had been in development for about a decade. Monsanto scientists worked on splicing the genes that made the bacteria tolerant to Roundup in plants. When that was achieved, a new class of genetically engineered herbicide-resistant crops was introduced into agriculture under the moniker "Roundup-ready seeds."

ROUNDUP'S COMMERCIAL APPLICATIONS

Monsanto received a license for Roundup on the basis of studies that classified it as a relatively safe herbicide. The fact that the chemical pathway (shikimate) that the herbicide disrupted in plants and bacteria does not exist in humans was a point in its favor. Through the 1970s and 1980s hundreds of products containing glyphosate were marketed in the United States for use in agriculture, forestry, home lawn care, and gardens. Today, an estimated 750 farm and garden products contain glyphosate (Landrigan and Belpoggi, 2018).

In 1985 an EPA panel classified glyphosate as a Class C chemical, which stipulates that there is suggestive evidence of carcinogenic potential, based on kidney adenomas in male mice. In 1991 the EPA downgraded its classification to Class E, which means "evidence of non-carcinogenic for humans."

Through an unexpected discovery in 1989 a Monsanto plant in Louisiana that manufactured Roundup released glyphosate residues into waste ponds. Monsanto' waste cleanup division discovered that the bacteria in the ponds developed a resistance to the herbicide. The genes that made the bacteria herbicide resistant became a subject of interest to the seed developers who sought a method of introducing them into soybeans.

After a set of agreements were reached among Monsanto, Agracetus, and Asgrow (later acquired by Monsanto), the method of transferring herbicide-resistant genes into soybeans proved successful and a major distributor of soybeans agreed to take on the genetically engineered seed. In 1992, Monsanto struck a deal with the giant seed company Pioneer to commercialize GMO soybeans and corn. By 1996 the first herbicide resistant seeds entered the U.S. market.

Monsanto heralded the herbicide-resistant crop technology as a breeding mechanism that would establish a new era of sustainable agriculture introducing high quality and safe herbicides (Kishore, G.M. et al., 1992). Charles Benbrook studied the use of herbicides before and after the introduction of herbicide-resistant seeds. He found that glyphosate applications rose globally nearly 15-fold since herbicide-resistant seeds were introduced into agriculture (Benbrook, 2016). Partly as a result of its expanded use, more attention was focused on the toxicology of glyphosate. This resulted in more laboratory studies and new agency reviews.

IARC'S ASSESSMENT OF GLYPHOSATE

The International Agency for Research on Cancer (IARC), an independent research arm of the World Health Organization (WHO), issued its evaluation on whether the herbicide glyphosate was a human carcinogen in 2015. Its report concluded: Glyphosate is probably carcinogenic to humans. That finding ignited a controversy among scientists and across national boundaries.

IARC was established as a world cancer agency in 1965 through a resolution of the World Health Assembly. It began its chemical monograph program in 1971. The stated aim of the program was to develop an instrument capable of evaluating the best evidence available at a given time on carcinogenic agents, in order to provide a sound scientific basis for cancer prevention (Saracci and Wild, 2015). The agency has strict procedures for developing a monograph on the carcinogenicity of a chemical that includes its choice of panelists, observers, conflicts of interest, and the choice of scientific studies.

For the monograph on glyphosate IARC established a Working Group of 18 scientists from nine countries including France, Chile, Italy, Australia, Canada, Finland, The Netherlands, New Zealand and the United States. Five categories of participants were invited to its meeting: the Working Group; additional specialists; representatives of national and international health agencies, such as the U.S. Centers for Disease Control; observers with relevant scientific credentials; and the IARC staff. It even had an observer from Monsanto.

Each participant including the IARC staff had to disclose any relevant financial interests covering four years related to the subject matter of the meeting. The declarations of interest are evaluated by IARC officials, who decide whether changes should be made in an individual's participation. The monograph panel reviews different types of studies that can reveal evidence for human carcinogenicity including:

cohort studies, case control studies, correlation or ecological (epidemiological) studies; intervention studies, and case reports.

IARC does not conduct studies, rather it reviews studies in the scientific literature. It will only accept data from studies in the public domain and available to independent scientific review. The panel will not accept studies from industry that has not gone through peer review and have been published. Evidence of human carcinogenicity is classified into one of five categories: carcinogen; probable carcinogen; possible carcinogen; not classifiable; and probably not a carcinogen. The IARC Working Group on glyphosate met on Lyon, France on March 3-10, 2015. Its carcinogenic assessment of glyphosate, along with several other pesticides, was published in a monograph in 2017 titled *Some Organic Phosphate Insecticides and Herbicides* (IARC, 2017).

The majority of IARC's report on glyphosate is devoted to the review and summary of relevant studies selected by the Working Group. The *Monograph* consisted of detailed charts with key characteristics of each study listed including organ sites, risk estimates and exposure categories. Their reviews include studies classified as case control, cohort, occupational, food residue, human excretion, and *in vitro* with human cells.

One of the main sources of evidence for IARC was a prospective cohort study conducted in IOWA and North Carolina called the Agricultural Health Study. The National Institutes of Health administered a survey to pesticide users (insecticides and herbicides), which questioned participants about crops grown, livestock raised, pesticide application methods, and protective equipment used. This type of survey is designed to acquire human exposure data, which are then correlated positively or negatively with disease outcomes. This population study is highly valued as the only published findings on people's exposure to glyphosate correlated with cancer for different sites. The total cohort assembled in 1997 comprised 75,000 adult study subjects. IARC cites seven reports from the Agricultural Health Study and several case control reports as central to its evaluation of the human carcinogenic potential of glyphosate.

At the beginning of its *Monograph,* IARC states that it uses the term "carcinogenic risk" to mean that an agent is capable of causing cancer and that the evaluation of such risks are made by international working groups of independent scientists and are qualitative in nature. While the Working Group found no correlation between exposure to glyphosate and prostate, breast, colorectal, skin, and pancreatic cancers, it did find an association between glyphosate and non-Hodgkin's lymphoma (NHL). The IARC monograph stated: Two large case-control studies of NHL [non-Hodgkin's lymphoma] from Canada and he USA, and two case-control studies from Sweden reported statistically significant increased risks of NHL in association with exposure to glyphosate (IARC, 2017). Even when adjusted for exposure to other pesticides, the risk of NHL persisted.

IARC referenced 269 scientific studies for its glyphosate monograph. It included both positive and negative findings in its assessment. The working group found limited evidence in humans for the carcinogenicity of glyphosate, and found sufficient evidence in animal studies to declare glyphosate a carcinogen. Based largely on the animal data and with limited human data, IARC reported that the weight of evidence convinced the Working Group that glyphosate was a probable human carcinogen.

"Weight of evidence" is generally not quantifiable. There are no scales to "weigh" the evidence. The "weighing of evidence" is a committee process that depends on the collective experience of panel members when they review the body of toxicology studies, the types and quality of studies, and the plausibility of cancer outcomes. Thus, the "weight of evidence" is the outcome of a consensus of panel members based on their collective experience. That is why it is critically important for panel members to be unbiased and non-conflicted by financial interests. Some panels may have a preference for human data and will

not classify a chemical as a carcinogen unless the human epidemiological data, on its own, is convincing. Other toxicologists will use whatever human data is available and combine it with animal data.

There was no indication from its report that IARC departed from standard criteria or models of carcinogenicity or genotoxicity as it based its assessment on peer-reviewed and established toxicological assessments. Also, the *Monograph* provided no algorithm for "weighing the evidence" or for the integration of the diverse studies into a conclusion.

EPA'S ASSESSMENT OF GLYPHOSATE

The EPA has been engaged in the assessment of glyphosate at least as early as 1985, when it classified the chemical as a possible human carcinogen. In 1986 the EPA asked its FIFRA [Federal Insecticide, Fungicide, Rodenticide Act] Scientific Advisory Panel (SAP) to evaluate the carcinogenic potential of glyphosate. With the available evidence at the time the SAP listed glyphosate as a Group D chemical, which signifies that it is not classifiable as to its carcinogenicity. It recommended that the EPA undertake new studies. In 1991, when new rodent studies of glyphosate became available, the EPA's Carcinogenicity Peer Review Committee classified glyphosate as a Group E chemical (evidence of non-carcinogenicity in humans), thereby downgrading its risk. And in 2015, the EPA's Cancer Assessment Review Committee found that glyphosate is not likely to be carcinogenic to humans.

The EPA's Office of Pesticide Programs issued its revised assessment of glyphosate on December 12, 2017 in a 216-page document. After an introduction that discusses their systematic review of the literature, data collection and studies submitted to the agency, the report proceeds with an examination of the existing science on glyphosate and cancer sites. Since IARC only identified NHL as the only cancer site associated with glyphosate exposure, I shall focus on EPA's review of glyphosate and NHL and seek to understand why IARC and EPA differed on that association.

The EPA's lengthy study provided greater detail than that of IARC on how it evaluated individual studies, how it generated a literature review, and on the rating of studies as low, moderate or high quality. Like IARC, the EPA provided summary tables of individual studies. There are a few general comments that can be made about EPA's review of the science linking glyphosate and NHL. EPA considered the sample sizes used by IARC as too small. They also questioned the meta-analyses that combined data from different studies.

The EPA review committee looked at nine studies related to NHL published between 1990 and 2013, some that pooled data from other studies, a multi-center population-based study, a hospital-based case control study using questionnaire data, and meta-analyses. Some of EPA's evaluation of the quality of the data are as follows:

Many of the evaluated studies were limited by small sample sizes, which resulted in large confidence intervals and reduced the reliability of the results to demonstrate a true association (EPA, 2017).

Analyses were performed with 6 studies, which many would consider small for performing meta-analyses. Rarely will meta-analyses synthesize data from studies with identical study designs and methods (EPA, 2017).

The EPA report also was dubious about confounding factors in the studies that IARC used in its analysis. The report stated that: lack of adjustment for co-exposure to other pesticides in these analyses could partially explain the conflicting results between the cohort and the case-control studies (EPA, 2017). This is just a speculation. It is not at all generally expected that different study methods will yield identical results. You have to look at the trend lines. They also noted that the meta-analyses that were statistically significant were borderline. They argued that each study carries over "confounding issues inherent in each individual study" into the meta-analysis. Unless each study used in the meta-analysis are identical in method with no confounding factors, it will be subject to the criticism. However, rarely will meta-analyses claim there is such parity between studies, yet their results are widely accepted. Also cited was that publication bias may have played a role because positive results (adverse findings) are more likely to be published than results that show no effect.

The EPA review makes no reference to bias from studies by the pesticide and chemical industries. Those effects are well documented in the literature. The EPA also criticized the exposure data from individuals surveyed. It argued that investigators used proxy respondents for exposure assessment in the major agricultural study, which has the potential to increase recall bias.

The EPA report found deficiencies in each of the nine studies. For example, it stated: none of the studies in this evaluation of glyphosate exposure and risk of NHL accounted for other potential confounders, such as diesel exhaust fumes, solvents, animals, and UV radiation (EPA, 2017). The entire analysis can be likened to a "Devil's Advocate" position against claims of glyphosate associated with NHL. The EPA report concludes the section on NHL with the statement:

Based on the weight-of-evidence, the agency cannot exclude chance and/or bias as an explanation for observed associations in the database. Due to study limitation and contradictory result across studies of at least equal quality, a conclusion regarding the association between glyphosate exposure and risk of NHL cannot be determined based on the available data (EPA, 2017).

EXTERNAL INFLUENCES OF TOXICOLOGICAL SCIENCES

Whenever scientific groups exhibit substantial disagreement on the toxicological assessment of a chemical it is important to consider non-scientific factors that may have influence on the assessments. In the case of glyphosate, a chemical in commerce since the 1970s, which has been extremely lucrative to herbicide manufacturers, there has been a strong corporate lobbying effort to protect its regulatory approval in the United States and elsewhere throughout the world.

After IARC reported its finding that glyphosate was a probable human carcinogen, hundreds of lawsuits were filed in the United States against Monsanto on behalf of individuals who had contracted Non-Hodgkin's lymphoma, alleging glyphosate as the cause. Several hundred cases were consolidated by one judge in the U.S. District Court in San Francisco, California. Many other lawsuits are making their way through state courts. As part of the legal process, plaintiffs may request internal documents from Monsanto, called discovery documents. A substantial trove of these discovery documents has been placed on a publicly accessible database. Two French journalists, Stéphane Foucart and Stéphane Horel

Table 1. Comparison of EPA and IARC Assessment of Glyphosate

	EPA Report	IARC Monograph
Year Published	2017	2017
International Panel	No	Yes
Review of existing studies only	Yes	Yes
Number of specific articles referenced	114	269
Unpublished studies cited	Yes (30)	No (0)
Use of "weight of evidence"	Yes	Yes
Characterization of "weight of evidence"	Yes	No
Categorize quality of studies	Yes	No
Finding	Non-carcinogenic in humans	Probable human carcinogen

received the Varenne Award for their series published in *Le Monde* (Foucart and Horel, 2017). The Monsanto litigation documents were posted on an open access public website titled US Right to Know (US Right to Know, n.d.) One book has already been published citing the documents (Gillam, 2017).

The documents reveal an intense lobbying effort on the part of Monsanto that includes ghostwriting articles for scientific journals allegedly showing that glyphosate is safe for humans, undue influence on EPA regulators (Gillam, 2017a) and efforts to gain journal retractions on papers that are unfavorable to glyphosate health risks. The company hired contract researchers to write journal articles favorable to glyphosate that did not include Monsanto's funding source or its input. What we have found from these documents is that the regulatory process in the United States has been replete with corporate lobbying at the regulatory agencies, at journals, and at the Executive Branch of government to penalize the World Health Organization by withholding funds because of the IARC finding.

There have been studies published about ghostwriting in medical journals largely associated with pharmaceutical companies (McHenry, 2010; Sismondo, 2007). Also, much has been written about the efforts of the tobacco and lead industries to influence science. Lawsuits against pesticide manufacturers have generally not unshielded internal documents, which are placed under protective order, putatively to protect trade secrets. The glyphosate case is the exception. When the Roundup litigation documents were released to the public, we begin to see scholarly articles analyzing them for what they reveal about corporate influence on science. (McHenry, 2018; Krimsky and Gillam, 2018).

Among the things we learn from the internal documents from Monsanto is that the company ghost-wrote journal articles as a standard business practice. In addition, they cultivated relationships with journal editors by engaging them as consultants and expecting favors at the appropriate time. Monsanto also provided lecture notes for scientists who presented talks at scientific meetings. Their strategy was to seed the scientific and regulatory communities with a constructed consensus on the safety of glyphosate and in particular its product Roundup.

IMPEDIMENTS TO CONSENSUS OVER CHEMICAL RISK

As a field, toxicology's primary focus is to study the effects of chemicals on humans and other living things. There is no single test or methodology for obtaining such knowledge. Human population studies, when possible, provide the most direct evidence. Clinical trials, which are rarely acceptable for industrial chemicals, are used for pharmaceuticals that are designed for therapeutic purposes. The gold standard methodology for drug safety and efficacy is the randomized controlled trial with human subjects. In animal studies, randomization is not necessary because the animals are bred to be genetically similar. While animal studies offer great control for exposure and confounding variables, the results are often discounted by some stakeholders, courts and regulators because of the physiological differences between humans and animals.

EPA's "Revised Glyphosate Issue Paper" stated that there was insufficient evidence to establish glyphosate as a human carcinogen. In the EPA's glyphosate file, it refers to a general fact sheet that was produced by Oregon State University (Oregon State University, n.d.). The fact sheet stated: The U.S. EPA classified glyphosate as Group E, evidence of non-carcinogenicity in humans. The U.S. EPA does not consider glyphosate to be a human carcinogen based on studies of laboratory animals that did not produce compelling evidence of carcinogenicity. It then added: Researchers reviewed the scientific literature on glyphosate, its major metabolite AMPA, formulated Roundup products manufactured by Monsanto, and the surfactant POEA. They found that Roundup and its components did not cause mutations or tumor formation. The researchers concluded that glyphosate is not carcinogenic. The reference given for this claim is: Williams, Kroes and Munro. Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans. This paper is now known from the Monsanto litigation internal documents as a ghostwritten paper. Yet, it was never retracted by the journal. After the publisher reviewed the allegations against so-called ghost-written or Monsanto-influenced papers, the journal published an "expression of concern" that proper disclosures were not made in the published articles.

Another edition of the fact sheet referred to in the EPA Internet site stated:

Is glyphosate likely to contribute to the development of cancer? When high doses were administered to laboratory animals, some studies suggest that glyphosate has carcinogenic potential. Studies on cancer rates in people have provided conflicting results on whether the use of glyphosate containing products is associated with cancer. Some studies have associated glyphosate use with non-Hodgkin lymphoma (http://npic.orst.edu/factsheets/glyphogen.html)

EPA's updated review of glyphosate is largely focused on showing every conceivable limitation of each study that has shown any positive association of glyphosate with NHL. The agency criticized the exposure data of the human studies, small sizes of animal studies, incommensurability of metadata, and the possible confounding effects from exposure to other pesticides. Animal experiments or human epidemiological studies involving low-dose exposures are vulnerable to all types of limitations, which are exploited by pesticide manufacturers who ask for consistent, replicable, dose-dependent and definitive results (Krimsky, 2014; Lanphear, 2017). There is no indication from the EPA analysis of what evidence it would accept to demonstrate that glyphosate exposure is associated with NHL. What we do know, is what evidence they would not accept.

The scientific assessment of the data on glyphosate, is not straight forward and requires lots of presuppositions such as "we assume glyphosate is safe unless proven unsafe" or "we assume glyphosate is unsafe unless proven safe." The assumption we begin with determines the relevant evidence.

Beyond the science, there are also the impediments from the politics. The appointment by President Donald Trump of Scott Pruitt to head the U.S. EPA has set a new goal for the agency. As reported by the *Guardian* in 2018, Pruitt promised polluters EPA will value their profits over American lives (Nuccitelli, 2018). Agency scientists would be given a signal that any chemical must be reviewed with the goal of demonstrating that the scientific evidence is not sufficient to declare the chemical unsafe. The agency can always appeal to the "weight of evidence." Most uses of "weight of evidence" (WOE) are subjective and do not reveal a methodology. One commentator notes:

...the frequent lack of definition of the term "weight of evidence," multiple uses of the term and a lack of consensus about its meaning, and the many different kinds of weights, both qualitative and quantitative, which can be used in RA [risk assessment]. A practical recommendation emerges: the WOE concept and its associated methods should be fully described when used. A research agenda should examine the advantages of quantitative versus qualitative weighting schemes, how best to improve existing methods, and how best to combine those methods (e.g., epidemiology's causal criteria with toxicology's quality criteria (Weed, 2005).

In an unusual consensus statement signed by fourteen scientists provides a list of uncertainties in the current state of knowledge on the toxicology of glyphosate (Myers et al., 2016). Concerns over use of glyphosate-based herbicides and risks associated with exposures: a consensus statement. These scientists were not emphasizing these uncertainties to dismiss the potential health effects. They understand that the uncertainties they raise are exploited by the commercial glyphosate interests, who argue against imposing any but the most minimal regulations on the herbicide. The consensus statement concludes that glyphosate should be given a high priority for full assessment.

Among the uncertainties cited in the consensus statement are:

- Because glyphosate is used in conjunction with other agricultural chemicals including insecticides, herbicides and fungicides, it is difficult to distinguish its effects from the effects of other substances in human studies. Since chemicals are not studies in mixtures, the synergistic effects of glyphosate with other chemicals is unknown.
- Adjuvants in glyphosate formulations are not tested independently. Either acting alone or in conjunction with other chemicals, the adjuvants might have unanticipated and untested effects.
- The vast majority of glyphosate toxicology studies used in regulatory assessments do not cover a sufficiently wide range of dose levels; some exclude low but environmentally relevant doses.
- Biomonitoring of glyphosate and its metabolites in the blood and urine of people have not been conducted. Without this information, you cannot estimate exposure risk.
- There is limited data on glyphosate pharmacokinetics in vertebrates, such as how it behaves in the organs, tissues and fluids and whether and where bioaccumulation occurs.

The EPA's classification of human carcinogens stated in its 2005 *Guidelines for Carcinogen Risk Assessment*, lists five categories: 1) carcinogenic to humans; 2) likely to be carcinogenic to humans; 3)

suggestive evidence of carcinogenic potential; 4) inadequate information to assess carcinogenic potential; 5) not likely to be carcinogenic to humans. These categories closely match IARC's five categories, where its second category is a "probable human carcinogen."

The EPA report states that choosing one of the five categories is a matter of judgment and cannot be reduced to a formula, since each category is applicable to "a wide variety of potential data sets and weights of evidence." The report spends considerably more time on "weight of evidence" than is found in the IARC *Monograph.* The agency report concludes that, based on all the available data, the "weight of evidence" does not support the conclusion that glyphosate is either "carcinogenic to humans" or "likely to be carcinogenic to humans." Referring to its 2005 *Cancer Guidelines*, the criteria for a chemical to be "carcinogenic to humans" only when there is convincing epidemiological evidence of a causal association between human exposure to the chemical and cancer. And for the second category, "likely to be carcinogenic to humans," the weight of evidence must be adequate to reach carcinogenic potential to humans.

One can use this information in two ways. Because of the uncertainties, there is no definitive evidence of glyphosate cancer risk and therefore let the product remain in commerce as it has been. Or, as the consensus scientists state: a fresh and independent examination of GBH [glyphopsate-based herbicides] should be undertaken… accompanied by systematic efforts by relevant agencies to monitor GBH levels in people and in the food supply, none of which is occurring today (Myers et al., 2016).

As in the IARC study, the EPA analysis did not apply non-traditional models of carcinogenesis. They did select and emphasized different studies and it is likely, although not definitive, they used different criteria for human carcinogenicity than that of IARC, whose criteria was not as transparent as that of the EPA.

What we learn from this exercise is that glyphosate's commercial stakeholders accept the phrase "no evidence of risk" means allow the herbicide to remain on the market. In contrast, others may say "no evidence of risk" is not tantamount to "evidence of no risk." The standoff is between those individuals who believe a substance is safe unless you have conclusive evidence it is not safe and those who consider a substance unsafe until it can be proven safe. Unlike U.S. environmental law, the European Union has adopted the "Precautionary Principle" whereby a nation can (and perhaps should) take action if there is a chemical risk that remains inconclusive.

CONCLUSION

The current scientific controversy over glyphosate toxicology cannot be de-contextualized from the political circumstances in which it is embedded. Those groups and scientists that have a professional or financial interest in the continued use of glyphosate select the science that supports that conclusion and dismiss or discount the studies that do not. For example, a study that shows glyphosate is a chelating agent that can affect the micronutrients of plants and ultimately of humans has been ignored by regulators (Mertens et al., 2018). Another study found that glyphosate exposure in pregnancy shortened gestational length (Parvez et al., 2018). And when a non-peer reviewed report indicates that glyphosate was found to bioaccumulate in mother's breast milk, a peer-reviewed counter report by a pro-glyphosate consultant disputes the results (Bus, 2015). Of course, these studies do not demonstrate that glyphosate causes human cancer. IARC relied on animal studies that did find cancer and human studies that raised important suspicions that glyphosate could be the cause of non-Hodgkin's lymphoma. But the accumulation of

studies, including one in rodents that shows glyphosate can impact the microbiome of vertebrates (Mao et al., 2018), or the teratogenic effects of glyphosate on frog embryos (Bonfanti et al., 2018) begin to build a case against the chemical.

This analysis shows that human toxicology, in the best of circumstances, has its own problematic features. When we add the uncertainties of low doses, difficulty of finding long-term effects, singling out one substance from cluster exposures to the financial interests that have become embedded in the practice of science, the results are understandably divergent across communities. Even the best and politically unencumbered toxicology will endure uncertainties. The question is whether the uncertainties should justify keeping a chemical in commerce, or prevent the chemical from entering commerce in the first place. After forty-four years in use, public health officials are asking for independent toxicological studies on the health effects of glyphosate-based herbicides. This fact alone underscores the failure of the "approve first, test later" principle of regulation. The toxicological debates are best resolved before a chemical has become part of the human diet, which is emblematic of the European Precautionary Principle.

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