Message

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Subject: Draft / Sample Glyphosate Manuscript
Attachments: Manuscript_Expert Panel.docx

Donna, Kimberly,

Here is my **1st shot** at starting the Manuscript for the Panel report. The Intro is a little long, but I am trying to do 2 things: first, show that IARC is in stark contrast to EVERYBODY else; second, since IARC made such a big deal of the mouse kidney story, I thought it was important to tell the WHOLE, REAL story of how many people looked at this and came to the conclusion that is opposite of IARC's conclusion.

If you get a chance, please take a look and offer any suggestions.

Thanks,

Bill

EXHIBIT 30
WIT: McClellan
DATE: 2/6/19
D. Srebrenick, CRR, CLR

Expert Panel report on the carcinogenic potential of glyphosate

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Address for Correspondence: *WHO SHOULD THIS BE ???*

Keywords
Carcinogenicity, epidemiology, exposure, glyphosate, genotoxicity, herbicide, mouse, rat, regulatory, tumor

Abstract

The carcinogenic potential of the herbicide glyphosate has been the subject of numerous reviews by health and regulatory agencies for the last 30 years. All of these reviews have concluded that glyphosate does not pose a carcingenic risk to humans. However, the International Agency for Research on Cancer (IARC) recently reached a different conclusion and classified glyphosate as a probable human carcinogen (Group 2A). Because this classification caused confusion for various stakeholders, an Expert Panel was assembled to review the basis for IARC's decision and to critically exam glyphosate's carcinogenic potential. Examination of exposure data revealed that dietary and occupational exposure to glyphosate is extremely low; this leads to the conclusion that glyphosate would need to be an extremely potent carcinogen, which is not consistent with all the human and animal data. – and does not support – is not consistent with --
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Table of Contents

Introduction

Glyphosate is a active ingredient that is widely used in a variety of herbicide formulations to control annual and perennial grasses and broadleaf weeds. It is a non-selective herbicide that inhibits plant growth by interfering with the production essential aromatic amino acids; specifically, this interference is accomplished by inhibition of the enzyme 5-enolpyruvylshikimate 3-phosphate synthase, which is responsible for the synthesis of chlorismate, an intermediate in the synthesis of phenylalanine, tyrosine and tryptophanthose amino acids. This enzymatic pathway for synthesizing aromatic amino acids is not shared by members of the animal kingdom. The herbicidal properties of glyphosate were discovered in 1970, and the first glyphosate product was introduced in 1974 for weed control (Franz *et al.*, 1997).

Glyphosate is a relatively simple molecule which consists of the amino acid glycine and a phosphonomethy moiety (Figure **1**). As such, glyphosate has no structural alerts for chromosomal damage, genotoxicity, mutagenicity, or carcinogenicity when analyzed by Derek (Kier and Kirkland, 2013). It is a polar molecule that is incompletely (15-36%) absorbed orally, undergoes very little biotransformation, and is rapidly excreted unmetabolized (Williams *et al.*, 2000). A molecule with these characteristics would be expected to exhibit, at most, only a low order of toxicity. The results from toxicity studies and regulatory risk assessments have been consistent with that expectation (JMPR, 1986, 2006; US EPA 1993; WHO IPCS 1994; Williams *et al.*, 2000; EU, 2002).

The first rodent chronic toxicity/carcinogenicity studies with glyphosate were conducted in the late 1970s/early 1980s timeframe, and the first assessment of the molecule's carcinogenic potential was conducted by the US Environmental Protection Agency (EPA) in 1985. This review was done by an EPA panel that then was called the Toxicology Branch Ad Hoc Committee, which was comprised of members of the Toxicology Branch of the Hazard Evaluation Division. At that time, two chronic animal bioassays were available: a combined chronic toxicity/carcinogenicity study in Sprague-Dawley rats (26 months) and a carcinogenicity study in CD-1 mice (18 months). The Agency concluded that the data did not

demonstrate a carcinogenic response in rats. However, EPA also concluded that the dose levels used in that study were inadequate for assessing glyphosate's carcinogenic potential in this species. EPA concluded that there was limited evidence of an increased incidence of renal tubule adenomas in male mice at the high dose level (4,841 mg/kg/day), a dose that greatly exceeds the limit dose level (1000 mg.kg/day) for carcinogenicity testing with pesticides. Based on this information, the Agency initially classified glyphosate as a group C carcinogen (see US EPA, 1991).

The kidney slides from the mouse study were subsequently re-examined by a consulting pathologist, and three other well-established experts scientists also reviewed the slides and/or the chronic toxicity data. All these scientists concluded that there was no relationship to treatment. A Pathology Working Group (PWG) was also conducted and issued the following conclusion: "This PWG firmly believes and unanimously concurs with the original pathologist and reviewing pathologist that the incidences of renal tubular cell neoplasms in this study are not compound related" (US EPA, 1986a).

All available information was presented to an EPA FIFRA Science Advisory Panel (SAP) in February, 1986. The SAP determined that the carcinogenic potential of glyphosate could not be determined from the existing data and proposed that a chronic rat and/or mouse study be conducted in order to clarify these unresolved questions ; the panel also proposed that glyphosate be categorized as Group D or having "inadequate animal evidence of oncogenicity" (US EPA, 1986b).

After considering the SAP's conclusions and recommendations, EPA requested that a new 2-year rat oncogenicity study be conducted. In 1991, after the new rat study was completed, EPA re-convened its Carcinogenicity Peer Review Committee to review the results of this study as well as all of the relevant scientific data on glyphosate. The Committee concluded that glyphosate should be classified in Group E (evidence of non-carcinogenicity) based upon the lack of a carcinogenic response in two animal species. Subsequent re-evaluations by EPA (1993, 2012, 2013) have re-affirmed the Agencies earlier conclusion.

The carcinogenic potential of glyphosate has been reviewed by other major national regulatory agencies. Canada's Pesticide Management Regulatory Agency (PMRA) review of glyphosate concluded that there was no evidence that glyphosate causes mutations or cancer (Canada PMRA, 1991). The Australian Pesticides and Veterinary Medicines Authority (APVMA) evaluated the active ingredient and concluded that the evidence shows that glyphosate is not genotoxic or carcinogenic (APVMA, 2013) [NEED REFERENCE]. Most recently, the complete genotoxicity, carcinogenicity and human epidemiology databases were evaluated by the German Federal Institute for Risk Assessment (BfR) for the European Commission on the Annex 1 renewal of glyphosate. The BfR concluded that glyphosate is unlikely to pose a carcinogenic risk to humans (European Union, 2015). This conclusion was supported by the peer review evaluation conducted by the European Food Safety Authority (EFSA, 2015) [NEED REFERENCE].

Glyphosate has also been evaluated for carcinogenic potential by expert scientists and scientific groups within the World Health Organization (WHO). Williams *et. al.* (2000) concluded that lifetime feeding studies with the herbicide did not demonstrate any tumorigenic potential. Greim et al (2015) recently evaluated fourteen rodent carcinogenicity studies (nine with rats and five with mice) conducted with glyphosate by various pesticide manufacturers for regulatory purposes. The authors concluded that there was no evidence of a carcinogenic effect related to glyphosate treatment. The authors further stated that the lack of a plausible mechanism, along with epidemiology studies which fail to demonstrate a clear statistically significant, unbiased and non-confounded associations between glyphosate and cancer, support the conclusion that glyphosate does not present concern with respect to carcinogenic potential in humans. The WHO International Programme on Chemical Safety (WHO IPCS, 1994) concluded that the available studies with glyphosate did not indicate that glyphosate is mutagenic or carcinogenic. A Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group concluded that there was an absence of

carcinogenic potential in animals and a lack of genotoxicity in standard tests; thus, "the Meeting concluded that glyphosate is unlikely to pose a carcinogenic risk to humans" (JMPR, 2006).

Despite these numerous reviews done by a wide variety of scientists and regulatory/health agencies spanning three decades, the International Agency for Research on Cancer (IARC) decided in 2014 to initiate an additional evaluation of glyphosate oncogenic potential as part of it's Monograph Programme. Glyphosate, along with 4 other pesticides (the insecticides diazinon, malathion, parathion and tetrachlorvinphos) , was considered by an IARC panel which met in March, 2015 at the International Agency for Cancer in Lyon, France. A brief summary of IARC's conclusions was initially published in The Lancet Oncology on March 20, 2015 (Guyton *et. al.*, 2015), and the full IARC Monograph (Volume 112) was published online on July 29, 2015 (IARC, 2015). IARC concluded that glyphosate is "*probably carcinogenic to humans (Group 2A)*" based on *limited evidence* in humans and *sufficient evidence* in experimental animals; it was also concluded that there was strong evidence of genotoxicity and oxidative stress (IARC, 2015).

[NOTE: BY EARLY OCTOBER, WE SHOULD HAVE SEEN THE RESULTS OF RE-EVALAUTIONS FROM EU, EFSA AND US EPA, AND THIS INFO CAN BE ADDED IF WE DECIDE TO DO SO].

Because these conclusions are in such stark contrast to those from all other assessments of carcinogenic potential, it was decided that IARC's processes and conclusions should be subjected to a thorough review by highly qualified & experienced scientists. Toward that end, Intertek Scientific & Regulatory Consultancy Services was commissioned by Monsanto Company to assemble a panel of scientific experts in the 4 areas considered by IARC: Exposure data; Studies of cancer in humans; Studies of cancer in experimental animals; Mechanistic and other relevant data.

Expert Panel and evaluation procedures

Thirteen scientific experts were selected and recruited by Intertek to participate on this Expert Panel. Panelists were assigned to one of the four areas considered by the IARC Panel (Exposure, Studies of cancer in humans, Studies of cancer in experimental animals, Mechanistic and other relevant data) based on their areas of expertise; two panelists participated in two areas. The scientists who participated in the Mechanistic and other relevant data section were experts in genetic toxicology because genotoxicity data was the primary focus of that IARC Working Group.

Prior to the meeting, all key studies/publications cited by IARC were made available to the panelists for their review; panelists could request any additional information they felt was necessary for them to conduct a thorough evaluation. The scientists were asked to closely examine the studies/data that IARC used to come to their conclusions; however panelists were also advised to examine any and all information needed to come to overall conclusions in their respective areas.

Based on the scope of the information to be evaluated, it was decided that the panel would meet over a two-day period to discuss all relevant information and make appropriate conclusions regarding the carcinogenic potential of glyphosate. The expert scientists held pre-meeting phone conferences and communicated via email to establish and plan how they would prepare for and conduct their review at the Expert Panel review meeting. Because the amount, nature and quality of the data used by IARC varied considerably across the four areas, the approach used by the expert panelists in those areas varied somewhat as well. The approach taken in each area is described below.

<u>Exposure</u>

The primary conclusion that IARC made was that glyphosate can be found in soil, air, water and food. There was no meaningful attempt to describe/quantitate (mg/kg/day) possible human exposures or put

such exposure values in perspective. Therefore, it was decided that the primary need in this area was a more thorough assessment of the scientific literature than that presented by IARC so that more meaningful operator/applicator and dietary exposure assessments could be conducted. One of the panelists was charged with developing such assessments so that they could be presented to the rest of panel and considered in plausibility discussions.

Studies of cancer in humans

IARC concluded that there was *limited evidence* in humans based on two case-control studies of NHL from Canada and the USA, and two case-control studies from Sweden. IARC also noted that there were excesses reported for multiple myeloma in three studies, but they did not weight this information as strongly because: of the possibility that chance could not be excluded; risk estimates were not statistically significant nor were they adjusted for other pesticide exposures.

It was decided that panelists in this area would be asked at the review meeting to arrive at a consensus on the following questions separately for NHL and MM:

1. Based on your review of the epidemiologic literature for glyphosate do you agree or disagree with the following statements:
    a. The epidemiologic evidence is strong enough to conclude that there is a causal association between glyphosate exposure and NHL/MM.
    b. There is strong epidemiologic evidence for a causal relationship between glyphosate and NHL/MM – though not quite strong enough to be conclusive.
    c. Though the evidence is not conclusive, there are several high quality epidemiologic studies that have found an association between glyphosate and NHL/MM.

d. The available studies are of insufficient quality or consistency to permit a conclusion regarding the presence or absence of a causal association between glyphosate exposure and NHL/MM.

e. The epidemiologic evidence, on balance, suggests that glyphosate is unlikely to be causally related to NHL/MM in the circumstances that have been studied epidemiologically.

2. Develop a brief consensus statement that describes the epidemiologic evidence for glyphosate and cancer. If a consensus cannot be reached, majority and minority views can be developed.

Studies of cancer in experimental animals

IARC concluded that there was *sufficient evidence* in experimental animals based on: a positive trend in the incidence of renal tubule tumors in males in one feeding study with mice; a significant positive trend in the incidence of haemangiosarcoma in male mice in a single study; increased incidence of pancreatic islet cell adenomas in male rats from two studies; a significant positive trend in the incidences of benign hepatocellular tumors in males and benign C-cell adenomas in females from the same study. IARC had also previously concluded that a glyphosate-based formation promoted skin tumors in an initiation-promotion study (Guyton *et al.*, 2015), but in the Monograph, it was stated that the study was "considered inadequate to evaluate the carcinogenicity of glyphosate alone" (IARC, 2015). Given the ambiguity of the significance of this finding to the overall IARC conclusion, it was decided that this finding should be included in the Expert Panel's evaluation.

The approach utilized by the expert panelists evaluating the experimental animal section was quite straightforward - individually evaluate each tumor type cited by IARC with an appropriate overall weight-of-evidence evaluation to determine if any of the tumors were related-to-treatment with glyphosate. Weight-of-evidence considerations included: dose-response, historical control information,

reproducibility, progression to malignancy, tumor multiplicity, tumor latency, and existence of associated preneoplastic lesions (*e.g.*, hyperplasia, cell death). This sub-group was also asked if the animal results cited by IARC reasonably support a conclusion that there is sufficient evidence of carcinogenicity in experimental animals. If not, the experts would be asked to provide an appropriate Weight-of-Evidence conclusion regarding glyphosate's oncogenic potential based on results from animal bioassays.

This group of experts also decided to address an issue that arose regarding published information that IARC decided not to consider in its review. Prior to the IARC meeting, Greim *et. al.* (2015) published a detailed review article which contained information from fourteen chronic/carcinogenicity rodent studies. The original tumor incidence data from the study reports were presented in an online data supplement. Further, the studies discussed in the publication had been submitted to and evaluated by a number of regulatory agencies globally over time. However, the IARC Working Group decided that it was unable to use those studies because the information provided was insufficient. The Expert Panel decided that it would comment on the appropriateness of IARC's decision to exclude this information from its review.

Mechanistic and other relevant data

IARC concluded that there is strong evidence that glyphosate and glyphosate-based formulations cause genotoxicity; for AMPA (aminomethyl-phosphonic acid - an environmental metabolite of glyphosate), IARC concluded that the evidence moderate. One study, which examined chromosomal damage (micronucleus formation) in community residents living near sprayed agricultural areas, was highlighted by IARC as evidence that glyphosate-based formulations cause genotoxicity. IARC also stated there is strong evidence that glyphosate, glyphosate-based formulations and AMPA can induce oxidative stress.

Similar to the issue regarding use of published information in the area of rodent carcinogenicity studies, IARC also decided not to consider a key genotoxicity publication, Kier and Kirkland (2013). This publication was a comprehensive review of more than 100 genotoxicity publications and regulatory studies of glyphosate and glyphosate-based formulations which incorporated all the results into a weight of evidence evaluation; this review was accompanied by extensive "online supplementary material" which included extensive information and data tables. And like the rodent carcinogenicity studies, 66 of the studies in the review had been submitted to and evaluated by a number of regulatory agencies globally. Nevertheless, the IARC Working Group decided not to include this information in its evaluation.

The Expert Panel members in this area decided that the following questions should be considered by the group:

Genotoxicity

1. Does the panel agree that the regulatory studies presented in Kier and Kirkland (2013) with individual study information and data in the supplement should be considered in evaluation the genotoxicity of glyphosate and glyphosate-based formulations?
2. What is the overall weight of evidence evaluation for genotoxicity and DNA-reactive genotoxicity of glyphosate, glyphosate-based formulations (GBF's) and aminomethylphosphonic acid (AMPA)?
3. Does the panel agree with IARC's conclusions that there is strong evidence that glyphosate causes genotoxicity, strong evidence for genotoxicity of GBF's and moderate evidence for genotoxicity of AMPA?

Oxidative Stress

4. What is the overall weight of evidence evaluation for oxidative stress induction by glyphosate, GBF's and AMPA?
5. Is induction of oxidative stress a plausible explanation for non DNA-reactive genotoxic effects observed in some genotoxicity studies?
6. Does the panel agree with IARC's conclusion that there is strong evidence that glyphosate, GBF's and AMPA can induce oxidative damage?

Cancer Mechanisms

7. What is the overall weight of evidence that genotoxicity or oxidative stress of glyphosate or GBF's might be a mechanism for carcinogenesis in experimental animals or humans?
8. Does the panel agree with IARC's rationale statement that "There is strong evidence that glyphosate can operate through two key characteristics of known human carcinogens and that these can be operative in humans" and that this supports their overall evaluation that glyphosate is *probably carcinogenic to humans*.

Summary of exposure to glyphosate

Results and conclusions

Studies of cancer in humans

Studies of cancer in experimental animals

Mechanistic and other relevant data

Discussion and overall conclusions

Acknowledgements

Declaration of interest

The employment affiliation of the authors is as shown on the cover page. Panel members received compensation from Intertek according to their standard fees for service; Intertek, in turn, was reimbursed by Monsanto Company. Tom Sorahan, Helmut Greim, and David Kirkland have received compensation from Monsanto Company for other work on glyphosate. Monsanto Company is the original producer and marketer of glyphosate formulations. The authors had sole responsibility for the content of the paper and the interpretations and opinions expressed in the paper are those of the authors.

The authors have sole responsibility

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