Evaluation of the IARC Monograph on Glyphosate

INTRODUCTION

Regulatory authorities and scientific programs within the World Health Organization (WHO) have consistently concluded that glyphosate is not carcinogenic. The International Agency for Research on Cancer’s (IARC) classification of glyphosate as a Group 2A, “probable human carcinogen”, is inconsistent with the conclusions reached by other WHO expert committees and with decades of reviews by regulatory agencies around the world.

ANIMAL CARCINOGENICITY DATA


IARC’s conclusion conflicts with the overwhelming consensus because it: (1) considers only a small subset of the available carcinogenicity studies of glyphosate in rats and mice, (2) disregards the conclusions of the scientists and pathologists who actually conducted the studies and reviewed the slides; and (3) interprets findings in a manner inconsistent with generally accepted scientific principles. In short, IARC did not conduct a weight-of-evidence evaluation or follow standard toxicological practice and evaluation frameworks that are the foundation of hazard assessment (Adami et al., 2011 and Lewis et al., 2002).

Due to the lack of effective mechanisms for the sharing of company-owned study data, and to guarantee the safety of glyphosate obtained from different processes of synthesis, several manufacturers of glyphosate initiated their own toxicological testing programs over the past four decades. Occasionally, regulatory studies were repeated to reflect major changes in the underlying government regulatory test guidelines. This has led to an unprecedented number of studies addressing the same toxicological endpoints, resulting in an extraordinarily robust scientific study database (which is unique among pesticides, industrial chemicals, and pharmaceuticals). The large volume of studies—addressing the same endpoints, conducted over a 40-year period by several independent companies and laboratories, and applying continually evolving toxicology test guidelines—provides a unique opportunity to evaluate potential human health hazards from glyphosate.

Glyphosate has been evaluated for potential carcinogenicity in an extraordinarily large number of studies. Most of these studies were not evaluated in depth by IARC. In fact, there are five carcinogenicity studies in mice and nine carcinogenicity studies in rats for glyphosate. IARC based its conclusion on only two carcinogenicity studies in mice and two carcinogenicity studies in rats. The studies that were not relied upon by IARC were of similar quality, were universally negative, and demonstrate that the limited evidence of carcinogenicity observed in a small subset of studies is almost certainly due to chance, and not due to treatment with glyphosate.

For example, IARC reviewed a study by Atkinson et al., 1993. In relying on this study as support for its Group 2A classification of glyphosate, IARC focused on a 4/50 incidence of hemangiosacroma in male mice at the highest dose level (1 g/kg/day). However, IARC did not consider the results of four additional
carcinogenicity studies in male mice; each of these studies observed no cases of hemangiosarcoma at doses of glyphosate as much as five times higher than the high dose in the Atkinson et al., study. These studies have sufficient power to demonstrate that glyphosate does not cause hemangiosarcoma in male mice.

Greim et al., 2015 evaluated all fourteen carcinogenicity studies and 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 published epidemiology studies that fail to demonstrate clear, statistically significant, unbiased and non-confounded associations between glyphosate and cancer of any single etiology, support the conclusion that glyphosate is not carcinogenic. These fourteen studies were also recently evaluated by the Rapporteur Member State for the Annex 1 renewal process for glyphosate in the European Union (EU 2015). The European Union similarly concluded that “glyphosate is unlikely to pose a carcinogenic risk in humans”.

IARC (Guyton et al., 2015) highlighted three separate “carcinogenic effects” as the basis for its conclusion that there is “sufficient evidence in animals”, even though none of these was replicated: (1) “a positive trend in the incidence of renal tubule carcinoma and of renal tubule adenoma and carcinoma (combined) in males in one feeding study in CD-1 mice”, (2) “a significant positive trend in the incidence of haemangiosarcoma in male CD-1 mice” in a different study, and (3) “a significant increase in the incidence of pancreatic islet cell adenomas” in male Sprague-Dawley rats in two studies. Each of these will be discussed in the sections below.

HAEMANGIOSARCOMAS IN MICE

IARC conclusion: “There was a significant positive trend in the incidence of haemangiosarcoma in male CD-I mice.”

- IARC relies on the Atkinson et al., 1993 study for this conclusion. The JMPR/WHO (2004) was the only group to discuss the haemangiosarcomas seen in mice in this study; they concluded that the haemangiosarcomas were not caused by administration of glyphosate because of (i) the lack of a dose-response relationship, (ii) the lack of statistical significance, and (iii) the fact that the incidences recorded in this study fell within the historical ranges for controls. The JMPR/WHO concluded that “administration of glyphosate to CD-1 mice for 104 weeks produced no signs of carcinogenic potential at any dose. The NOAEL was 1000 mg/kg bw per day, [which was] the highest dose tested.”

- As discussed above, IARC also ignored the results of four other carcinogenicity studies in male mice, each of which observed no cases of hemangiosarcoma at doses of glyphosate as much as five times higher than the high dose in the Atkinson study.

KIDNEY TUMORS IN MALE MICE

IARC conclusion: “There was a positive trend in the incidence of renal tubule carcinoma and of renal tubule adenoma or carcinoma (combined) in males in one feeding study in CD-I mice”.

- IARC relies on the Knezevich and Hogan (1983) study for this conclusion. However, the US EPA (1993) and others (JMPR/WHO 1986; WHO IPCS 1994; EU 2002,2015; Canada PMRA 1991, 2015; Williams et al., 2000; and Greim et al., 2015) have reviewed this same study and
have repeatedly determined that the renal tubule tumors found in male mice were not related to glyphosate treatment.

- The original study pathologist for the Knezevich and Hogan (1983) study noted that the tumors observed were not significantly elevated, were within the historical control range, and were not seen in females. The pathologist also noted that no preneoplastic lesions were observed. Therefore, the study authors concluded that the kidney tumors were spontaneous and not related to treatment, and thus were not evidence of the carcinogenicity of glyphosate. The leading kidney pathologist in the United States and other members of an expert Pathology Working Group (PWG), as well as group of biometricians and EPA scientists, reached the same conclusion (US EPA 1991).

- Furthermore, the four other carcinogenicity studies in mice show no statistically significant increase in this tumor type, further suggesting that kidney tumors were unrelated to glyphosate.

- In the Monograph (IARC 2015), IARC presents information about the US EPA evaluation, (US EPA 1985), as support for its conclusion that the kidney tumors were treatment-related. However, EPA’s evaluations do not actually support IARC’s conclusion. EPA’s evaluation of these tumors was thorough and included a PWG (Sauer et al., 1985) and EPA Science Advisory Panel (SAP) Review (US EPA 1991). The PWG scientists concluded: “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” (Sauer, et al., 1985). In short, the conclusion in the Monograph is counter to that of the PWG, EPA, EPA’s SAP and all other regulatory Agencies globally and other WHO programs who have evaluated all the data.

**PANCREATIC TUMORS IN MALE RATS**

*IARC conclusion: “Two studies in the Sprague-Dawley strain showed a significant increase in the incidence of pancreatic islet cell adenoma in males.”*

- IARC relies on the Stout and Ruecker (1990) and Lankas (1981) studies for this conclusion. However, the US EPA (1993; 2012; 2013) and others (JMPR/WHO 1986, 2004; WHO IPCS 1994; EU 2002, 2015; Canada PMRA 1991, 2015; Williams et al., 2000; and Greim et al., 2015) have reviewed these and other studies and have repeatedly determined that the pancreatic islet cell adenomas found in male rats were not related to treatment with glyphosate.

- In Stout and Ruecker (1990), there was a slightly increased incidence of pancreatic islet cell adenomas in the low-dose and high-dose males. However, there was no significant positive dose-related trend in the occurrence of the adenomas; there was no progression to carcinomas; and the incidence of pancreatic hyperplasia (non-neoplastic lesion) was not dose-related. As a result, the authors concluded that the adenomas were not treatment related. The JMPR/WHO (2004) also reviewed this study and concluded “administration of glyphosate to Sprague-Dawley rats for 24 months produced no signs of carcinogenic potential.” Specifically, the JMPR/WHO concluded that there was no evidence of dose-related pancreatic damage or preneoplastic lesions, and that the only pancreatic islet cell carcinoma in the study occurred in the male control group, indicating a lack of treatment-
induced neoplastic progression. JMPR/WHO concluded: “Taken together, the data support the conclusion that the occurrence of pancreatic islet cell adenomas in male rats was spontaneous in origin and unrelated to administration of glyphosate.”

- In the Lankas (1981) study, tumors were observed in 0/50 of the control group, 5/49 of the low dose group, 2/50 of the mid dose group, and 2/50 of the high dose group. Because these results deviate substantially from a typical dose-response trend, no regulatory agency considers these findings to be treatment related. The JMPR/WHO (1987), for example, reviewed this study and concluded “there were no increases in tumors that were treatment-related.”

- There are also a number of other rat carcinogenicity studies in addition to those cited by IARC. Greim et al. (2015) combined data from all nine rat carcinogenicity studies with doses ranging from 3-1,290 mg/kg/day and found no dose-response relationship between pancreatic tumors and treatment with glyphosate.

- In conclusion, pancreatic islet cell tumors are common in rats and occur with a variable incidence, results are not consistent between studies, there is no dose-response relationship, and the incidences were within the normal historical control range.

**GENOTOXICITY, MECHANISTIC AND OTHER RELEVANT DATA**

The IARC Monograph (IARC 2015) reported there is strong evidence that glyphosate and commercial formulations can be genotoxic and produce oxidative damage. This conclusion is in stark contrast to the conclusions of regulatory authorities (US EPA 1993, 2012, 2013; Canada PMRA 1991, 2015; EU 2002, 2015), scientific bodies (JMPR/WHO 1986, 2004, WHO IPCS 1994, WHO Water Quality 2005) and third party experts (Williams et al., 2000; Mink et al., 2012; Kier and Kirkland, 2013; Kier 2015; and Greim et al., 2015) around the world that glyphosate is not genotoxic or carcinogenic.

In reaching its conclusion, IARC disregarded a plethora of relevant data and the opinions of numerous scientists who have carefully considered all the available data. There is an expansive database of studies conducted by several glyphosate registrants for regulatory purposes (EU 2015) as well as those reported by other scientists in the open literature that assess the genotoxicity potential of glyphosate and glyphosate-based formulations. IARC did not consider many of these studies. For instance, IARC did not consider a review publication (Kier & Kirkland, 2013) that provided in-depth summaries of 66 regulatory studies conducted according to well-accepted and validated testing guidelines. Moreover, IARC ignored a recent publication by Kier (2015) that critically reviewed an additional 40 genotoxicity biomonitoring studies, including a study singled-out by IARC as showing evidence of genotoxicity (discussed below).

IARC did not conduct a well-reasoned weight-of-evidence evaluation or follow standard practice and frameworks that are the foundation of risk assessments (Adami et al., 2011 and Lewis et al., 2002). Further, IARC focused on the limited number of studies reporting adverse findings and did not use a weight-of-evidence hierarchical organization for evaluating genotoxicity (see Appendix 1). IARC interpreted findings differently, and the studies relied upon are compromised by various deficiencies and limitations such as: non-validated methodologies; non-conformance with internationally recognized guidelines and Good Laboratory Practices (GLP); use of in vitro studies with immortalized human cell lines or other types of modified cells that are not appropriate for hazard assessment; use of inappropriately high concentrations (in vitro) or dose levels (in vivo) of test materials; and use of irrelevant routes of exposure for humans (e.g., intraperitoneal injection).
IARC cited a large number of studies that examined a wide range of endpoints relevant to genotoxicity, oxidative stress, receptor mediated effects, cell proliferation/death and immunosuppressive effects with glyphosate alone, glyphosate-based formulations and aminomethylphosphonic acid (“AMPA”) (a degradation product of glyphosate). These studies included in vivo and in vitro, mammalian and non-mammalian experimental systems. However, IARC’s main conclusion in this area that factored into its overall evaluation was that there is strong evidence for genotoxicity and oxidative stress. Therefore, only these endpoints are discussed in this document.

Although IARC evaluated genotoxicity and oxidative stress separately in the Monograph, there is significant overlap in how IARC addressed these two phenomena, likely because the two processes can be inter-related. IARC focused on a variety of studies in which cells were exposed to extremely high concentrations of test material or animals were inappropriately exposed to high doses (e.g., intraperitoneal injection). Such high doses can damage the cells/membranes that are directly exposed, leading to severe cytotoxicity, including oxidative stress; these primary toxic effects can, in turn, produce effects on the cells’ DNA that are secondary to the stress induced by the unrealistic dosing method. As such, this document does not differentiate between the studies IARC relied upon as evidence of genotoxicity and those that it relied upon as evidence of oxidative stress.¹

Two of the studies IARC relied on to make claims of genotoxicity/oxidative were Bolognesi et al. (1997) and Peluso et al. (1998).

- Bolognesi et al. (1997) reported that intraperitoneal (ip) injection of mice with glyphosate and a glyphosate-based formulation could result in DNA damage in kidney and liver. Williams et al. (2000) also reviewed this study and concluded there are several reasons to question the results from this assay. Most notably, as was the case in the Peluso et al. (1998) study, the effects reported were only observed at doses close to or in excess of the ip LD₅₀ for mice. Again, effects observed only at a near-lethal dose level using an irrelevant route of exposure are of no relevance for purposes of human hazard identification.

- Peluso et al. (1998) like Bolognesi et al., directly injected test material into the abdomens of mice at near-lethal doses. When mice were injected with a glyphosate-based formulation which contained a surfactant, the authors reported what they described as evidence for DNA adducts in the kidneys and livers of these animals.

- Williams et al. (2000) reviewed the Bolognesi et al. (1997) and Peluso et al. (1998) studies and identified a number of problems with their procedures that led to erroneous conclusions. First, there is no evidence for a dose-response relationship over the narrow range of doses examined. Second, the level of adducts reported is so low that it is well within the range reported for normal endogenous adducts. In addition, Peluso et al. (1998) were unable to provide any chemical characterization of the product(s) that they identified as adducts. As such, the observations of Peluso et al. (1998) are not supportive of a biologically relevant response. The route of administration is unusual, since injections of an herbicide into the abdomen is not a relevant route of exposure for humans.

- Heydens et al. (2008) conducted a series of mode-of-action investigations to understand the results of the Peluso et al. (1998) and Bolognesi et al. (1997) studies. The authors demonstrated that exposure by ip injection produced marked liver and kidney toxicity, but

¹ Further, it should be noted that Henderson et al. (2015) concluded that, in contrast to the current models, their data suggests that oxidative stress is not a key determinant in the mechanism of non-genotoxic carcinogenesis.
oral administration did not. The results suggest that high-dose ip injections of a formulated product may induce secondary effects mediated by local toxicity rather than genotoxicity. The large increases in 8-OHdG (a marker of oxidative stress) reported by Bolognesi et al. (1997) were not reproduced by Heydens et al. (2008). Because of the more robust nature of the Heyden et al. (2008) investigation, the results of the Bolognesi et al. (1997) study do not provide sufficient evidence to conclude that high-dose ip administration of glyphosate causes oxidative damage to DNA. Heydens et al. (2008) concluded that their results continue to support the conclusion that glyphosate and glyphosate-based products are not genotoxic under exposure conditions that are relevant to animals and humans. IARC did not consider Heydens et al. (2008) in reaching its conclusions in the Monograph.

IARC also relied on Bolognesi et al. (2009) to support its finding of genotoxicity.

- More specifically, the IARC summary published in *The Lancet Oncology* states in reference to the Bolognesi et al. (2009) study: “One study reported increases in blood markers of chromosomal damage (micronuclei) in residents of several communities after spraying glyphosate formulations”. The IARC Monograph refers to the same study as follows: “One of these studies examined chromosomal damage (micronucleus formation) in circulating blood cells before and after aerial spraying with glyphosate-based formulations and found a significant increase in micronucleus formation after exposure in three out of four different geographical areas” (IARC 2015).

- The Bolognesi et al. (2009) study attempted to evaluate possible DNA damage in people living near areas where glyphosate was used aerially to eradicate illicit crops. It is extremely difficult to draw meaningful conclusions from this study, however, because there were so many uncontrolled variables. In addition, the study relied on self-reporting, which inherently leads to inaccuracies and/or information that cannot be verified.

- It is important to note that Dr. Keith Solomon, one of the authors of the publication, has stated that he does not know how IARC came to its conclusion because IARC’s conclusion conflicts with the conclusion reached by the authors of the study (http://www.producer.com/daily/toxicologist-pans-un-glyphosate-report/). Dr. Solomon stated that there was no difference in micronuclei between those subjects that self-reported exposure to glyphosate compared to those that self-reported no exposure to glyphosate.

- There are various inconsistencies in the Bolognesi et al. (2009) study that raise significant questions; for example:
  1. The degree of DNA damage observed immediately after the glyphosate spraying was not consistent with the application rates used.
  2. There was no association between self-reported direct contact with eradication sprays and DNA damage in two sprayed regions.
  3. The largest increase in DNA damage was reported in the region where only 1 of 25 people from this population self-reported contact with spray exposure.

- The clear lack of correlations led the study authors themselves to be cautious in drawing conclusions. For example:
In the Abstract, the authors stated that the data suggest that damage is small and appears to be transient; the evidence indicates that the genotoxic risk is low.

In the Discussion, the authors concluded that genotoxic damage is small and transient, and that genotoxic risk is of low biological relevance.

- A more defensible conclusion that appears to be supported by the self-reported exposure information is that this study does not clearly demonstrate an association between glyphosate exposure and the endpoint.

IARC also overlooked that glyphosate has no “structural alerts” to indicate that it would be carcinogenic or mutagenic. Structural alerts are molecular substructures or reactive groups that are related to the carcinogenic and mutagenic properties of the chemicals, and represent a sort of “codification” of a long series of studies aimed at highlighting the mechanisms of action of the mutagenic and carcinogenic chemicals. The identification of the structural alerts has had a great value both in terms of understanding mechanisms and of assessing the carcinogenic hazard posed by chemicals (Benigni and Bossa, 2006).

**EPIDEMIOLOGY**

There are no epidemiology data to support IARC’s assertion that there is limited evidence of carcinogenicity in humans. IARC classified the epidemiological data as “limited evidence in humans for the carcinogenicity of glyphosate. A positive association has been observed for non-Hodgkin lymphoma”. However, the epidemiological results for non-Hodgkin lymphoma (“NHL”) were inconsistent across several case-control studies, where recall bias is an important concern. In addition, there was no association between glyphosate and NHL in the one large prospective cohort study in which exposure was documented before follow-up for cancer outcomes and bias was minimized. Accordingly, the weight of the epidemiological evidence does not support the conclusion of an association between NHL and glyphosate, much less a causal relationship.

IARC minimized the relevance of the largest and single most important epidemiological study of the health of pesticide applicators (the Agricultural Health Study or AHS), which found no link between glyphosate and NHL or any another cancer (De Roos et al., 2005). The AHS evaluated approximately 60,000 licensed pesticide applicators and was undertaken in the 1990s to provide a large, unbiased set of data to examine cancer and other health risks to pesticide applicators. In the AHS, information on pesticide use was collected first before follow-up for cancer and other outcomes. The results of the AHS showed: (i) no greater risk of NHL in pesticide applicators as compared to average incidence rates of cancer in the state (Koutros et al., 2010), (ii) no greater risk of NHL in glyphosate users compared to non-users (De Roos et al, 2005), and (iii) no increase in NHL risk with amount of glyphosate use (De Roos et al., 2005). It is interesting to note that while the use of glyphosate has dramatically increased over the past 25 years in the US, the new cases of NHL have not (see Figure 1).
Agricultural Health Study

The Agricultural Health Study (AHS) began in 1993. It is a collaboration of the US EPA, the National Institute of Environmental Health Sciences (NIEHS), the National Cancer Institute (NCI), and the National Institute for Occupational Safety and Health (NIOSH). EPA plans to use the results from the AHS in their registration reviews.²

Laura Freeman, a current Co-Principal Investigator of the AHS who works at the Division of Cancer Epidemiology and Genetics, National Cancer Institute, was a member of the President’s Cancer Panel on October 21, 2008. In her 2009 follow-up publication, she reported on the AHS findings to date and explained that there were no findings of an association between glyphosate and cancer (the reference in her publication was De Roos et al., 2005).

In summarizing AHS publications, Weichenthal et al. (2010) noted that increased rates in the following cancers were not associated with glyphosate use: overall cancer incidence, lung cancer, pancreatic cancer, colon or rectal cancer, lymphohematopoietic cancers, leukemia, NHL, multiple myeloma, bladder cancer, prostate cancer, melanoma, kidney cancer, childhood cancer, oral cavity cancers, stomach cancer, esophagus cancer and thyroid cancer. Other available studies have looked at the full range of human cancers and there was no association for cancer overall for any of the major cancers.

IARC’s conclusion stands in stark contrast to the conclusions reached by numerous regulatory authorities. It is apparent that one of the differences between IARC and the regulatory agencies is one of orientation – IARC appears to be using a relatively uncritical signal detection perspective versus weighing the quality of the various findings to arrive at an overall conclusion, as is done by regulatory agencies. In conducting a weight-of-the-evidence evaluation, it is critical to evaluate the quality of the underlying epidemiological studies.

It appears that IARC did not consider the quality and limitations of the case-control studies (De Roos, et al., 2003; McDuffie et al., 2001) and Eriksson et al., 2008) it relied upon. In particular, the absence of an

association between glyphosate and NHL in a large, prospective study like the AHS raises serious questions about the results of the smaller, less powerful case-control studies that IARC relied upon to find a causal relationship.

In an article published in February of 2015, Aaron Blair (the chair of the IARC Meeting 112 panel and member of the Epidemiology Workgroup, a Co-Principal Investigator that started the AHS study, a current member of its Executive Committee and co-author on De Roos et al, 2005) wrote that “Prospective cohort studies are perceived by many as the strongest epidemiologic design.” ……“Occupational epidemiologists should seek opportunities to initiate prospective cohorts to investigate high priority, occupational exposures”. (Blair et al., 2015).

From an interview with Aaron Blair:

“This is the work Dr. Blair is proudest of after decades of cancer research. This sequence of carefully planned studies eventually led to the extraordinarily productive Agricultural Health Study, which followed more than 89,000 individuals living on farms or applying pesticides commercially in North Carolina and Iowa, and resulted in dozens of articles published in major scientific journals. The great strength of this project is that unlike much other important research on cancer, it does not depend on individuals’ ability to recall exposures. It surveys those with a high likelihood of exposure and moves forward through time, asking questions and recording disease as it occurs. This type of experimental design is called a cohort study, and where it is possible, it is able to eliminate many types of bias and confounding factors that plague other experimental designs.” ³

De Roos et al. 2005 (Cohort Study)

Prospective study of private and commercial applicators in Iowa and North Carolina. Participants completed a 21-page questionnaire. Among the 54,315 participants, 41,035 (75.5%) had reported using glyphosate and 13,280 (24.5%) had not. Of the 41,035 there 92 cases of NHL or 0.2%. There was no statistically significant association between glyphosate and “all cancers” or any cancer site in analyses of ever versus never-exposed to glyphosate, in analyses of tertiles of cumulative exposure days of glyphosate exposure, or in analyses of tertiles of intensity-weighted exposure days.

Case-Control Studies

IARC relied upon case-control studies. The number of people with NHL that said they had used glyphosate were 36 in De Roos et al. (2003), 51 in McDuffie et al. (2001), and 29 in Eriksson et al. (2008), 29 exposed. The AHS study (De Roos et al., 2005), had the largest number of 92.

These studies also used diverse methods to estimate exposure to glyphosate from questionnaires and/or interviews and to classify estimated glyphosate exposure for epidemiologic analyses. The most detailed exposure-response analysis was in the AHS performed by De Roos et al. (2005).

Qualitative review indicated that two (De Roos et al., 2003, Eriksson et al., 2008) of the three studies had rate ratio estimates that rose with increasing exposure. In contrast, the large and important Agricultural Health Study (De Roos et al., 2005) found no evidence of such a trend.

The epidemiology data do not support IARC’s assertion that there is limited evidence of carcinogenicity in humans. Regulatory authorities and scientific bodies have reached the same conclusion, and have cautioned about the use of case-control studies to support a finding of carcinogenicity:

- **JMPR/WHO (2004):** “Widely used pesticides, like glyphosate, have recently become a focus of epidemiological research. In the past few years several epidemiological studies have been published that reported weak associations of glyphosate with lymphopoeitic cancers (Nordstrom et al., 1998; Hardell & Erikson, 1999; McDuffie et al., 2001). . . . However, the results of these studies do not meet generally accepted criteria from the epidemiology literature for determining causal relationships. Generally, the associations were rather weak and rarely statistically significant. Control for potential confounding factors, including other pesticides, was not possible owing to limited available information and small numbers of subjects. It was not measured whether there actually was any internal exposure or the extent of such exposure and, accordingly, a possible dose–response relationship could not be evaluated.”

- **Annex 1 Renewal - European Union (2015) (reviewing De Roos 2003, McDuffie 2001, Eriksson 2008, and De Roos et al., 2005, among others):** “In epidemiological studies in humans, there was no evidence of carcinogenicity and there were no effects on fertility, reproduction and development or of neurotoxicity that might be attributed to glyphosate.”

As discussed herein, an examination of the animal carcinogenicity, genotoxicity and human epidemiologic data reveals a number of inconsistencies, discrepancies and misstatements in IARC’s classification of glyphosate. In addition, IARC’s glyphosate classification contradicts assessments of other WHO programs and evaluations conducted by regulatory bodies such as the Australian Pesticides and Veterinary Medicines Authority, the German Federal Institute for Risk Assessment, Health Canada, the U.S. EPA, and even OEHHA itself. All of these agencies have consistently concluded that glyphosate is not carcinogenic.

Respectfully,

**Monsanto Company**

By: [Signature]
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When evaluating data for genotoxicity, a primary goal is to determine (a) the likelihood of occurrence of a key event; and (b) whether that event might lead to heritable changes associated with any adverse effect \textit{in vivo}, including cancer. The basis upon which a weight-of-evidence evaluation can be constructed include the following:

- Any statistically significant observations should be reproducible and biologically significant.
- A dose–response relationship should exist for effects.
- The effects should be permanent and progressive, as opposed to reversing upon cessation of chemical dosing.
- The nature of DNA effects should be characterized.
- The database should be consistent or inconsistencies adequately explained.
- The effects produced in the assay should be relevant to humans.

A central objective of the weight-of-evidence is to avoid a situation that could permit one experimental test result to be accorded greater weight than others. A conceptual approach to the relative weighting of genotoxicity testing data in the final assessment of mutagenic or carcinogenic potential is shown in Figure 1 below (Williams et al. 2000).

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\caption{Weight-of-evidence data hierarchy organization for evaluation for genotoxicity.}
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The key features of the weight-of-evidence scheme described in Figure 1 are its ability to accommodate results from multiple testing protocols and its requirement to place a premium on consistency and coherence of results. Greater weight is given to results from laboratories using accepted, well-validated protocols employing GLP procedures. The scheme can also function as a tool for analysis of a specific protocol, evaluating internal consistency of results from testing for similar endpoints. On the other hand, a result from a novel procedure might be acceptable because it is deemed to provide important
evidence of a chemical mode of action. The weight-of-evidence analysis is also significantly affected by the relevance of the data available. Short term assays disclose evidence of genotoxic events in vitro or in vivo that can be compared to more comprehensive examinations of animals such as by the 2-year rodent cancer bioassay. For purposes of human risk assessment, greater confidence should be placed in those test systems that examine possible genetic effects from chemical exposure of animals than in tests that rely on selected homogeneous cell populations raised and tested in vitro. Chemical exposures of biological systems carried out in vitro are much less realistic, and results of such tests can be determined by the effects of toxicity. Such toxicity can occur at unusually high exposure concentrations and/or be dependent on metabolic and detoxification capabilities. Finally, a weight-of-evidence evaluation seeks to establish a dose–response relationship. Greater attention should be given wherever there is a clear association between increased exposure and a genetic effect.
REFERENCES


