PRELIMINARY TECHNICAL ANALYSIS OF THE IARC MONOGRAPH

NOTE

EXPOSURE DATA

There are no new exposure data or studies in the IARC Monograph on glyphosate released on July 29, 2015. Regulatory agencies and other organizations like the JMPR (FAO/WHO) go to greater lengths to evaluate available literature and model dietary, occupational and/or residential exposures. Regulators have determined large margins of exposure, meaning that glyphosate can be safely used according to label directions and does not pose a risk when ingested as a residue in trace amounts in the diet.

In the Monograph section *1.4 Occurrence and exposure* IARC cites old references where more recent ones exist, and appears to selectively use references and data. Additionally, IARC cites detections of glyphosate in different matrices (urine, serum, soil, air, water, and food) without putting the levels and potential exposures into the proper context. Regulatory authorities and the JMPR establish ADIs and/or AOELs to account for potential human exposures and establish safe exposure levels. When these exposure values are put into the proper context it is consistently concluded that there are no health concerns with exposure to glyphosate.

For example, a recent publication by Niemann et al., (2015) describes a critical review of seven studies from Europe and the US where traces of glyphosate were found in human urine samples from farmers and the general public. The authors then compared the estimates of internal human exposure from these studies to an appropriate reference value – i.e. an acceptable daily intake (ADI) or acceptable operator exposure level (AOEL). It is important to point out that the Niemann et al. was an article published on line January 8, 2015 and was included in a list of references Monsanto submitted to IARC for the glyphosate review. The Nieman et al. publication was not included in the IARC review.

Niemann et al. critically concluded on glyphosate that:

- "All measured values, even the highest, were of no health concern. The calculated human exposures were at least one order but mainly two or more orders of magnitude lower than ADI (allowable daily intakes) and AOEL (allowable operator exposure levels)."

Human exposure to glyphosate can occur via the diet and application of glyphosate-based formulations for vegetation control (residential and commercial). According to the American Council on Science and Health in "BIOMONITORING: Measuring Levels of Chemicals in people – and What the Results Mean," biomonitoring surveys run the "risk of misinterpreting the data from these programs." They state that

"perhaps the most common misperception is that the mere detection of a chemical in our bodies suggests a health hazard rather than simply providing a measure of exposure."

Regulatory authorities and the JMPR establish ADIs and/or AOELs to account for human exposures. So it is not surprising to see traces of glyphosate in human urine samples. Because glyphosate is not metabolized in humans, does not bioaccumulate, and is excreted unchanged in urine, measuring urine levels can provide reliable estimates of actual internal human exposure.

In this regard, relevant conclusions by Niemann et al. include:

- "Current analytical techniques allow the detection and determination of trace amounts of glyphosate in human urine more today than in the past however the results obtained with different methods do not differ much and, to some extent, confirm each other."
- "…findings in human urine may result from dietary intake, residential and/or occupation exposure…"
- "Urinary concentrations in operators after application of plant protection products tend to be higher than those resulting from dietary intake of glyphosate by consumers."
- "All measured values, even the highest, were of no health concern."

The highest concentration (0.004 mg/kg/day) reported in the Niemann et al., paper was from a farmer in the Farm Family Exposure Study (FFES) (Acquavella et al., 2004). To put the value of 0.004 mg/kg/day into perspective (see Figure 1): the US EPA ADI is 1.75 mg/kg/day (2013), the JMPR/WHO (2004) ADI is 1.0 mg/kg/day and 0.5 mg/kg/day is the ADI set recently for the EU Annex 1 Renewal (EU 2015). It should be noted that based on scientific evaluation of the available data, the JMPR/WHO in 2004 raised their ADI to 1.0 mg/kg/day from 0.3 mg/kg/day and the EU in 2015 raised its ADI to 0.5 mg/kg/day from 0.3 mg/kg/day from the one established in the Annex 1 listing in 2002.

It appears IARC's literature review was critically incomplete, failing to represent the wealth of information available. For example in *1.4.1 Exposure (b) Community exposure*, IARC stated that "despite extensive worldwide use, there are relatively few studies on the environmental occurrence of glyphosate (Kolpin et al., 2006)". The abstract from the Koplin et al. reference, however, states: "Thus, compared to other herbicides (e.g. atrazine) there are relatively few studies on the environmental occurrence of glyphosate and AMPA". It is unclear why IARC quotes an older literature reference while, there were 91 articles on environmental monitoring of glyphosate published between 2001 and 2014 included in the European Annex I literature review (EU 2015), with 68 articles published after 2006.

Further, it appears IARC selectively quoted from certain references they cited and omitted to provide broader context on exposure. For example, in the section *1.4.1 Exposure (b) Community exposure*, IARC states that "in surface water, glyphosate is not readily broken down by water or sunlight (EPA, 1993a)." The reference cited is the US EPA Reregistration Eligibility Document, which states that "if glyphosate were to reach surface water it would be resistant to hydrolysis and aqueous photolysis." It is accurate that glyphosate is not readily broken down by water (hydrolysis), however that does not mean it is not degraded in water - it is degraded by microbes over time. The half-life of glyphosate has a range of 7-22 days across 6 systems, with a geometric mean of about 10 days (EU 2015). It appears IARC quoted the US EPA to imply glyphosate is persistent in surface water, but omitted the broader context that glyphosate does degrade due to microbial action, a fact well know to the US EPA and other global risk assessors.

In section *1.4.1 (b) (ii) Water*, IARC states that "Glyphosate in soil can leach to groundwater, although the rate of leaching is believed to be low (Borggaard and Gimsing, 2008." This implies that glyphosate has the potential to leach from any soil type into groundwater. However Borggaard and Gimsing had stated more comprehensively "Although sorption and degradation of glyphosate can be very different in different soils, it seems clear that glyphosate leaching is limited in uniform, non-structured soils without macropores, e.g. many sandy soils, and the risk of surface and groundwater pollution with glyphosate (and AMPA) is considered to be low."

Since glyphosate and AMPA can readily be removed from water by conventional drinking water treatment methods (which include sand filtration and chlorination), it is highly unlikely that they would be detected in finished drinking water (Jönsson et al., 2013; Speth 1994).

The World Health Organization reviewed water quality data for glyphosate and AMPA and stated in its in WHO Guidelines for Drinking-water (2005) that "because of their low toxicity, the health-based value derived for AMPA alone or in combination with glyphosate is orders of magnitude higher than concentrations of glyphosate or AMPA normally found in drinking-water. Under usual conditions, therefore, the presence of glyphosate and AMPA in drinking-water does not represent a hazard to human health. For this reason, the establishment of a numerical guideline value for glyphosate and AMPA is not deemed necessary."

In section *1.4.1 (b) (iii) Residues in food and dietary intake*, IARC cites an EFSA report from 2009 that they accessed in November of 2014 and a Danish study from 2001 (Granby and Vahl). These are older references, while more recent reports providing a more comprehensive context were omitted from consideration by IARC. EFSA reports are provided on an annual basis and the 2012 report (published on December 11, 2014) was included in a reference list submitted to IARC by Monsanto for the glyphosate review. In the 2012 report more than 78390 samples of more than 750 different food products were tested for approximately 800 different pesticides (http://www.efsa.europa.eu/en/efsajournal/pub/3942.htm). Of the 635 samples analyzed for glyphosate 78 (12.2%) had detectable residues but none contained residues in excess of the Maximum Residue Limits (MRL). The estimated long-term dietary exposure for glyphosate accounted for 0.63% of the ADI. It was concluded based on the current scientific knowledge that no long-term risk is expected.

While the study by Granby and Vahl demonstrated the low level of glyphosate intake from cereals (for an adult at 60 kg, it is 0.007 mg /day representing 0.04% of the ADI), IARC failed to consider other more recent information. For example, the Danish National Food Institute (Technical University of Denmark) prepared its more recent report presenting the results from the 2004-2011 period of the monitoring programs conducted by The Danish Veterinary and Food Administration. The number of samples with detected residues of glyphosate for fruits and vegetables and cereals were 12.2 and 1.5%, respectively. The report concluded that: "The risk assessment of the cumulative exposure was performed by the Hazard Index method. The Hazard Quotient was calculated for each pesticide and then summed into a so-called Hazard Index, (HI). The HQs for the individual pesticides range from 0.00001% to 2.4% with most of the HQs (98%) being below 1% (see 7.9) indicating that there is no risk of adverse effects following exposure to the individual pesticides."

7.9 Exposure and Hazard Quotients for individual pesticides (consumer group "Adults").

Model 1: No correction for non-detects
Model 3: Non-detects assumed to be ½LOR; correction factor limited to 25.
Corrected for peeling.

Pesticide	Exposure (µg/kg bw/day)		Exposure (µg/day)		Hazard Quotient	
	Model 1	Model 3	Model 1	Model 3	Model 1	Model 3
Glyphosate	0.013	0.11	0.95	8.4	0.0042%	0.037%

In addition the yearly Danish National Food Institute reports are also available on line: http://www.food.dtu.dk/Publikationer/Foedevaresikkerhed/Kemiske_forureninger/Pesticidrester.

In *Section 1.4.1 (b) (iv) Household exposure*, IARC cites a reference by Guha et al., 2013. There was no analytical determination of real world exposure. Just because someone owns or uses a product does not necessarily mean they are "exposed". This report only represents the findings of a home interview of 500 residentially stable households enrolled in the Northern California Childhood Leukemia Study during 2001–2006. Trained interviewers inventoried residential pesticide products and queried participants about their storage and use. The analyses were restricted to 259 participating control households.

Regarding household exposures, Niemann et al. (2015) discussed the findings of Curwin et al. 2007. Curwin et al. analyzed urine samples from farm and non-farm households in Iowa. The range of urine concentrations was 1.1-2.7 µl (across fathers, mothers and children). Niemann et al. determined this represented 0.1% of the Annex I renewal ADI of 0.5 mg/kg/day.

Conclusion:
When human exposure values are put into the proper context it is consistently concluded that there are no health concerns with exposure to glyphosate.

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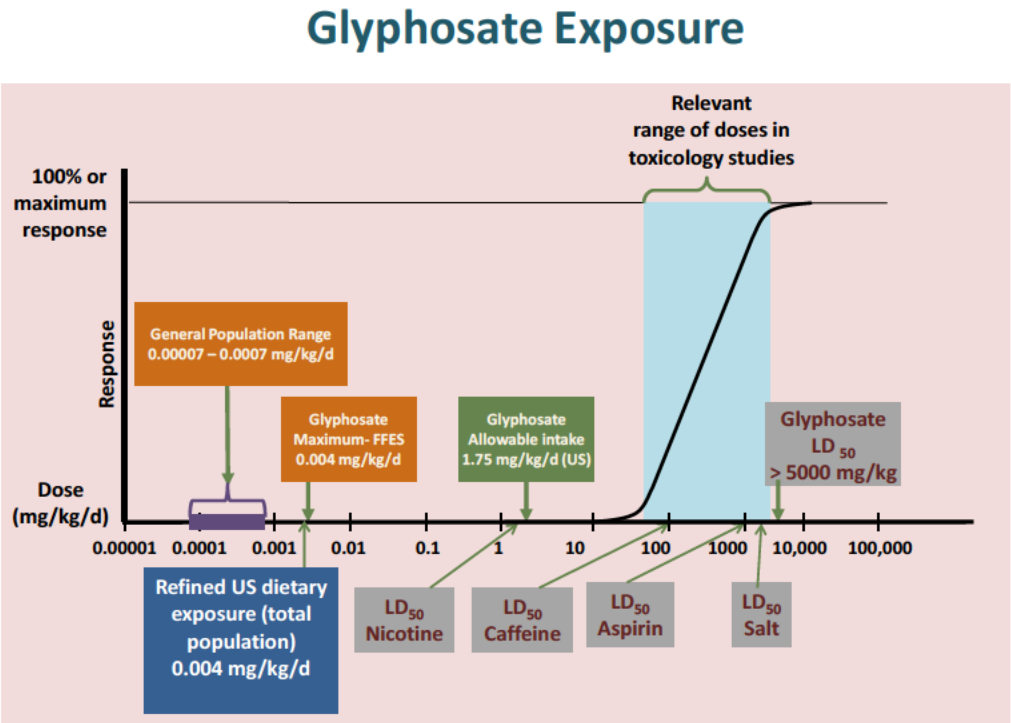
Figure 1.



On this logarithmic scale in mg/kg/d note the urinary concentrations in the orange boxes, the US ADI in the green box, the LD_{50s} for glyphosate and other substances in the gray boxes, a refined US dietary exposure assessment for the total population in the blue box and the range of dose levels in the mammalian toxicology studies with glyphosate.

EPIDEMIOLOGY

There is no new epidemiology data or studies in the IARC Monograph that was released on July 29, 2015, and Monsanto Company does not agree that there is credible evidence that glyphosate use can cause non-Hodgkin lymphoma (NHL).

IARC confirmed its classification on the epidemiological data as "limited evidence in humans for the carcinogenicity of glyphosate. A positive association has been observed for non-Hodgkin lymphoma". The conclusion could just as easily have been that the results for NHL were inconsistent across several case-control studies where recall bias is an important concern and there was no association for glyphosate and NHL in the one large prospective cohort study where exposure was documented before follow-up for cancer outcomes and bias was minimized to the greatest extent possible among all the studies. Accordingly, on balance, the data do not support the conclusion of an association between NHL and glyphosate.

IARC continues to minimize the relevance of the largest and single most important study into the health of pesticide applicators (the Agricultural Health Study (AHS) or Ag Health Study) that found no link between glyphosate and NHL or any another cancer (De Roos et al., 2005). The AHS is the largest prospective cohort study conducted of approximately 60,000 licensed pesticide applicators that was set up in the 1990s to provide a large unbiased set of data to examine cancer and other health risks in pesticide applicators. In the Ag Health Study, information on pesticide use was collected before follow-up for cancer and other outcomes. In this study, there was no greater risk of NHL in all applicators when their cancer experience was compared to State cancer incidence rates (Koutros et al., 2010), no greater risk of NHL in glyphosate users compared to non-users (De Roos et al, 2005), and NHL risk did not increase with amount of glyphosate use (De Roos et al., 2005). It is interesting to note (see Figure 1) that while the use of glyphosate use has continued to increase over the past decade in the US, the new cases of NHL have not.

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). The EPA plan to use the results from the AHS in their registration reviews. http://www.epa.gov/pesticides/health/ag-health.html

Laura Freeman, a current Co-Principal Investigator of the AHS and with 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 where no cancer sites were associated with glyphosate (the reference in her publication was De Roos et al., 2005).

As there was no increased risk in any cancer, it is quite surprising that the results of the AHS findings of no excess of NHL as discussed in the DeRoos et al., 2005 publication didn't drive a conclusion of no evidence of NHL, particularly since Aaron Blair, the chair of the IARC panel and member of the

Epidemiology Workgroup, was one of the Co-Principal Investigators that started the AHS study, is on its Executive Committee and was a co-author with De Roos on the 2005 publication.

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."

(https://poisoningourchildren.wordpress.com/2014/03/13/interview-with-aaron-blair-phd-mph-scientist-emeritus-at-the-national-cancer-institute-nci/

Again, it is difficult to understand why the findings of the AHS—reported to be the largest, most comprehensive study of agricultural health ever conducted in the United States—were not given sufficient weight to overshadow the weaker case-control studies.

Given that an effect could not been seen in a sample size that large says the biologic effect being proposed is too small to be detected in this study and the findings found in the other smaller studies raise serious questions as to the applicability to a large population and more important that there is any cause and effect relationship.

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.

It is difficult to understand how IARC came to such a different conclusion regarding NHL and glyphosate compared to regulatory authorities. While the in-depth evaluation of the Monograph is ongoing, it is apparent that one of the differences between IARC's and regulatory agencies' conclusions 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 determining a definition of limited evidence, IARC has no requirement that the few positive epidemiology studies be of high quality.

Comment on Cohort Study

De Roos et al.. 2005 – 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.

Comments on Case-Control Studies

The studies IARC chose as limited evidence were 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.

The 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.

De Roos et al., 2003 (Interviews with subjects or next-of kin to assess pesticide use)

Of 650 people with NHL 36 said they had used glyphosate (5.5%). 1933 people without NHL 61 said they had used glyphosate (3.2%). The association between glyphosate and NHL was estimated by De Roos et al. (2003) in a standard logistic regression model and in a hierarchical regression model that specified prior distributions for individual pesticides. As described by De Roos et al. (2003), the standard logistic regression model can yield imprecise estimates when modeling multiple pesticides, especially when their use is infrequent and reporting is susceptible to error. To overcome this limitation, they used hierarchical regression models “with the objective of obtaining increased precision and accuracy for the ensemble of estimates.” Moreover, De Roos et al. noted that more conservative prior assumptions specified in the hierarchical models “seemed appropriate in a largely exploratory analysis of multiple exposures for which there is little prior knowledge about how pesticide exposures interact in relation to the risk of NHL. **A statistically significant association based on a pooled analysis of case-control studies of NHL and glyphosate was reported in a standard logistic regression model, but the pooled odds ratio was not significant in the hierarchical regression**. It is not clear why IARC choose the results of the standard logistic regression model over the hierarchical model that De Roos used to overcome limitations with the other method.

McDuffie et al., 2001 (Mailed, self-reported questionnaire was administered to capture lifetime exposure history and follow up phone call if necessary)

This was a Canadian population-based case-control study of NHL in men. Of 517 men with NHL, 51 said they had used glyphosate or 9.9%. 1506 men without NHL 133 said they had used glyphosate or 8.8%. Glyphosate, which did not show a significant association with NHL in individual chemical analyses, showed odds ratios of 1.0 for use one to two days per year and 2.1 with reported use for three or more days per year. The authors characterized this pattern of odds ratios (ORs) as a dose response. However, this characterization was not supported by a trend analysis. Inspection of the data shows only an association in the highest frequency of use category, not a trend of increasing ORs with increasing reported days of use. The study found a slightly elevated OR for any exposure to glyphosate and reported a statistically significant OR of 2.1 for >2 days/year of exposure compared to no exposure, based on 23 cases and 36 controls. The latter OR was **not adjusted for potential confounding by other pesticides**. The results for glyphosate are weak, they lack external support, and they could easily be due to chance, confounding or bias because of the methodologic problems. McDuffie et al. did not consider time since first reported exposure in any of their analyses of glyphosate or other pesticides.

Eriksson 2008 (Self-reported questionnaire determining total work history with detailed questions regarding exposure to pesticides, organic solvents, and other chemicals)

This Swedish case-control study evaluated the association between glyphosate, including duration of exposure (days) and latency (years), and NHL, including histopathologic type. Of 995 people with NHL, 29 (3%) said they used glyphosate; and of the 1016 without NHL, 18 said they had used glyphosate (1.8%). The statistically significant ‘‘univariate’’ association between glyphosate and NHL was attenuated and **no longer significant** after adjustment for age, sex, year of diagnosis or study enrollment, and additional pesticides.

Comments on Epidemiology Literature by European Authoritative Sources

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

"In epidemiological studies in humans, there was no evidence of carcinogencity and there were no effects on fertility, reproduction and development or of neurotoxicity that might be attributed to glyphosate. "

This review included the case-control studies of De Roos 2003, McDuffie 2001 and Eriksson 2008, as well as the cohort of De Roos et al., 2005.

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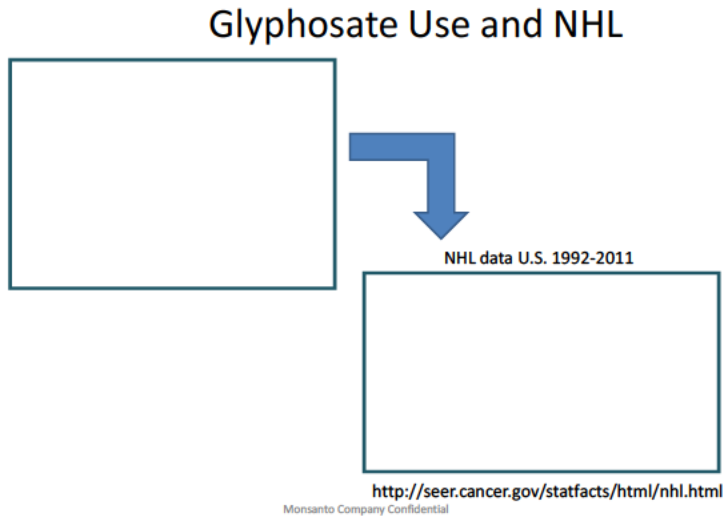
Figure 1.


Glyphosate Use and NHL
NHL data U.S. 1992-2011
http://seer.cancer.gov/statfacts/html/nhl.html
Monsanto Company Confidential

ANIMAL CARCINOGENICITY DATA

There are no new animal bioassays in the IARC Monograph that was released on July 29, 2015 (IARC 2015). Likewise, there was no significant new information in that document. Compared to the summary of IARC's opinion on glyphosate in the *News* section of *The Lancet Oncology* of March 20, 2015 (Guyton et al., 2015), IARC did expand the discussion regarding kidney tumors in male mice in the monograph, but they did not introduce any new information, and the additional discussion does not impact the overwhelming evidence supporting the conclusion that glyphosate does not produce kidney tumors in male mice. IARC also added a discussion of rat liver and thyroid tumors to the Monograph, but the analyses leading to their conclusions suffer from the same flaws and deficiencies as noted previously (e.g., lack of dose response, within historical control range, and not reproducible in other studies).

Regulatory authorities (US EPA 1993, 2012, 2013; Canada PMRA 1991, 2015; EU 2002, 2015), scientific bodies (JMPR/WHO 2004; WHO IPCS 1994; WHO Water 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 for decades have concluded that glyphosate is not genotoxic or carcinogenic. In the Monograph published on July 29, 2015, IARC concluded "There is *sufficient evidence* in experimental animals for the carcinogenicity of glyphosate" (IARC 2015).

It appears that IARC came to an opinion which conflicts with the overwhelming consensus by: (1) disregarding the opinions of all the other scientists and pathologists who conducted the actual studies; (2) interpreting findings differently/incorrectly; and (3) relying on non-standard studies with adverse effects where the methods have not been validated, not conducted according to international guidelines, and not relevant for humans based on exposure conditions. Clearly, IARC did not conduct a weight-of evidence evaluation or follow standard toxicological practice and evaluation frameworks that are the foundation of hazard and risk assessment (Adami et al., 2011 and Lewis et al., 2002).

Due to the lack of effective legal and regulatory provisions for the sharing of company-owned study data in the past, and to guarantee the safety of technical glyphosate obtained from different processes of synthesis, several manufacturers of glyphosate had to initiate toxicological testing programs of their own over the past four decades. Occasionally, regulatory studies had to be repeated to reflect major changes in the underlying government regulatory test guidelines. In the case of glyphosate, this has given rise to a multitude of studies for the same toxicological endpoints, leading to the availability of an extraordinarily robust scientific study database that can be considered unique among pesticides, industrial chemicals, and pharmaceuticals. Such a remarkable volume of studies addressing the same endpoints, conducted over the last 40 years by several independent companies and laboratories while toxicology test guidelines have evolved, provides a unique opportunity to evaluate potential human health hazards to glyphosate.

Greim et al., 2015 evaluated fourteen carcinogenicity studies (nine rat and five mouse). They concluded 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, which fail to demonstrate clear, statistically significant, unbiased and non-confounded associations between glyphosate and cancer of any single etiology, and a compelling weight of evidence, support the conclusion that glyphosate does not present concern with respect to carcinogenic potential in humans. These fourteen studies were also recently evaluated by the German Rapporteur Member State for the positive list Annex 1 renewal process for glyphosate in the European Union (EU 2015). They concluded that "glyphosate is unlikely to pose a carcinogenic risk in humans".

Now that the Monograph (IARC 2015) has been published online, it is apparent how the animal subgroup of the IARC panel came to the conclusion of "*sufficient evidence in animals"*, a conclusion that contradicts the overwhelming conclusions of other regulatory agencies. In fact when it comes to glyphosate, regulatory agencies have been clear for decades that all labeled uses of glyphosate are safe for human health.

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-l mice.

- IARC relies on the Knezevich and Hogan (1983) study for this conclusion. The US EPA (1993) and others since (JMPR/WHO 1986; WHO IPCS 1994; JMPR/WHO 2004; EU 2002 and 2015; Canada PMRA 1991, 2015; Williams et al., 2000; and Greim et al., 2015), however, have long determined that the renal tubule tumors found in male mice in this study (Knezevich and Hogan 1983) were not related to treatment.
- The original study pathologist noted that these tumors were not significantly elevated, were within the historical control range, were not seen in females, and no preneoplastic lesions were observed. Therefore, it was concluded that the kidney tumors were spontaneous and not related to treatment and glyphosate was not considered to be carcinogenic in the study. 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.
- Furthermore, there are four additional carcinogenicity studies in mice with glyphosate and this tumor type has not been observed in any of them, further suggesting that kidney tumors were unrelated to glyphosate.
- In the Monograph (IARC 2015), IARC presents considerable information about details of the U.S.US EPA evaluation, (EPA 1985), which then lead to IARC's conclusion that the kidney tumors were treatment-related. This could be misinterpreted to indicate that EPA's evaluations actually supported such a conclusion; this is not the case. EPA's evaluation of these tumors was thorough and included a Pathology Working Group (PWG; Sauer et al., 1985) and EPA Science Advisory Panel (SAP) Review. Ultimately, the PWG, SAP and EPA did not reach the conclusion that IARC did. Rather, the PWG scientists concluded that "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 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. The US EPA (1993; 2012; 2013) and others since (JMPR/WHO 1986; WHO IPCS 1994; JMPR/WHO 2004; EU 2002 and 2015; Canada PMRA 1991, 2015; Williams et al., 2000; and Greim et al., 2015), however, reviewed these and other studies and have long determined that the pancreatic islet cell adenomas found in male rats are not related to treatment.
- In one study (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 their occurrence; there was no progression to carcinomas; and the incidence of pancreatic hyperplasia (non-neoplastic lesion) was not dose-related. It As such, the authors concluded that these were not treatment related.
    - The JMPR/WHO (2004) reviewed this study and concluded "administration of glyphosate to Sprague-Dawley rats for 24 months produced no signs of carcinogenic potential."
    - Specifically, JMPR/WHO noted that: there was no evidence of dose-related pancreatic damage or preneoplastic lesions; 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, the incidence for the tumor is 0/50 in control, 5/49 in low dose, 2/50 in mid dose and 2/50 in high dose. Because of the remarkable lack of a dose response these findings are not considered by any regulatory agency to be treatment related.
    - The JMPR/WHO (1987) reviewed this study and concluded "there were no increases in tumors that were treatment-related."
- There are also a number of additional rat carcinogenicity studies beyond those cited by IARC. Greim et al. (2015) combined data from all the studies with doses ranging from 3-1290 mg/kg/day and found no dose-response.
- In conclusion, this is a common tumor in rats that occurs with a variable incidence, results are not consistent between studies, there is no dose-response, and the incidences were within the normal historical control range.

LIVER & THYROID TUMORS IN RATS

IARC conclusion: There was also a statistically significant positive trend in the incidence of hepatocellular adenoma in males and of thyroid follicular cell adenoma in females.

- IARC again relies on the Stout and Ruecker (1990) to support this conclusion. As noted above, the authors concluded that these were not treatment related, and the JMPR/WHO (2004) similarly found that administration of glyphosate to rates produced no signs of carcinogenic potential.

- As is the case with pancreatic tumors in rats (discussed above), these are common tumors in rats that occur with a variable incidence; thus all factors must be taken into account to determine if the occurrence of tumors is treatment-related or spontaneous.
- The US EPA provided a detailed evaluation of the liver and thyroid tumors, including the Stout and Ruecker (1990) study, as part of its Second Peer Review of Glyphosate (1991).
    - For the liver tumors, EPA noted that the incidence of tumors was not significant in the pair-wise comparison and was within the range of historical controls; furthermore, there was no progression from adenoma to carcinoma, and there was no treatment-related occurrence of preneoplastic lesions. Therefore the occurrence of liver adenomas was not considered compound-related.
    - For the thyroid tumors, EPA noted that the incidence of tumors was not significant in the pair-wise comparison; there was no progression to carcinoma and no significant dose-related increase in severity or incidence of hyperplasia (pre-neoplastic precursor). Therefore, the thyroid tumors were not considered compound-related.
- Interestingly, the IARC Working Group noted in the Monograph that "there was no apparent progression to carcinoma for either tumor type." As noted above by the US EPA, this is evidence that the tumors are not related to glyphosate treatment. So this piece of evidence, pointed out by IARC itself, actually contradicts its own conclusion.
- It should also be noted that the hepatocellular adenoma in males and thyroid follicular cell adenoma in females did not appear in the IARC assessment published in The Lancet Oncology (Guyton et al., 2015); no explanation was given for why these tumors were added to the Monograph published on July 29, 2015.

HAEMANGIOSARCOMAS IN MICE

IARC conclusion: "There was a significant positive trend in the incidence of haemangiosarcoma in male CD-l mice."

- IARC relies on Atkinson (1993) to support this conclusion. The JMPR/WHO (2004) was the only group to discuss the haemangiosarcomas seen in mice in this study (Atkinson, 1993); they did not consider them to be caused by administration of glyphosate due to the lack of a dose-response relationship, the lack of statistical significance, and the fact that the incidences recorded in this study fell within the historical ranges for controls. Their conclusion was "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."

SKIN-TUMOUR PROMOTER

IARC conclusion: "A glyphosate-based formulation was found to be a skin-tumour promoter in the initiation-promotion study in male Swiss mice."

- IARC relies on George et al. (2010) study to support this conclusion. IARC concluded "the glyphosate formulation tested appeared be a tumour promoter." However, this study does not show that glyphosate has carcinogenic potential. The most logical explanation for the results reported is that it is an artifact of the way in which the test material was

administered in this particular study. Ultimately, IARC concluded that "this was an inadequate study for the evaluation of glyphosate."

- Doses in this study are not representative of human exposures to glyphosate-based formulations. Mice received topical applications of concentrated glyphosate formulated product three times per week for 32 weeks without washing. Given the repeated exposure to an irritating material which is not washed off over the course of 32 weeks, the tumor promotion is likely a physical response to substantial localized dermal irritation over a prolonged period of time. It is a well established toxicological phenomenon that prolonged cellular irritation/destruction from various sources can lead to increased cell proliferation and ultimately tumor formation. This is an exposure scenario/regimen that is not relevant to humans.
- Epidemiological studies reviewed by Mink et al. (2012) reported neither an association with glyphosate, nor an association between glyphosate and skin or lip cancers.

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GENOTOXICITY, MECHANISTIC AND OTHER RELEVANT DATA

The IARC Monograph released on July 29, 2015 (IARC 2015) reported there is strong evidence that glyphosate and commercial formulations can be genotoxic and produce oxidative damage. This is in stark contrast to what regulatory authorities (e.g., US EPA 1993, 2012, 2013; Canada PMRA 1991, 2015; EU 2002, 2015; Japan 1999), scientific bodies (JMPR/WHO 2004, WHO IPCS 1994, WHO Water 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 for decades have concluded that glyphosate is not genotoxic or carcinogenic.

The only way IARC could have come to an opinion so completely opposite regarding glyphosate and glyphosate-based formulations was to disregard a plethora of more relevant data and the opinions of numerous other scientists who have carefully considered all the available data. There is an expansive data-base with studies conducted by several glyphosate registrants for regulatory purposes (most recently in 2015 by the German Rapporteur Member State reviewing glyphosate for the European Union Annex 1 Renewal process; 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, which have all concluded that glyphosate and glyphosate-based products are not genotoxic. For instance, IARC did not consider a review publication (Kier & Kirkland, 2013) which 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) which critically reviewed an additional 40 genotoxicity biomonitoring studies, including a study singled-out by IARC as showing evidence of genotoxicity (discussed below).

It appears 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 has clearly focused on the 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 such as: non-validated methodologies; not conducted according to internationally recognized guidelines; not conducted under 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; using inappropriately high concentrations (*in vitro*) or dose levels (*in vivo*) of test materials; and use of irrelevant routes of exposure for humans (*e.g*., direct injection into the abdominal cavity).

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 AMPA. The 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 these two phenomena were discussed. This most likely stems from the fact that 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.*, direct injection into the abdomen). 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. Thus, the current document does not differentiate between the studies IARC relied upon as evidence of genotoxicity or and those relied upon as evidence of oxidative stress.[1]

IARC relied on two studies that have been used to make claims of genotoxicity/oxidative damage in the past: 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 Pelusa 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 do not demonstrate any significant risk to humans.
- Peluso et al. (1998) directly injected test material into the abdomens (intraperitoneal or ip administration) of mice at near-lethal doses. When mice were injected with a glyphosate-based formulation which contained a surfactant, they 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 the procedure that led to erroneous conclusions. First, there is no evidence for a dose response 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, and it should be concluded that 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 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 appear to provide sufficient evidence to conclude that high-dose ip administration of

[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.

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. It should be noted that Monsanto included the Heydens et al. (2008) publication in a list of reference provided to IARC for the review of glyphosate, but IARC did not include it in the Monograph.

- Furthermore, Levine et al. (2007) demonstrated that surfactants can elicit cytotoxic effects such as perturbation of the mitochondrial membrane and disruption of mitochondrial membrane potential in cultured mammalian cells. The EU review concluded surfactant effects provide a plausible mechanism for observations of glyphosate-based formulations inducing DNA damage responses (EU 2015). Such responses would be expected to be associated with cytotoxicity-inducing exposures and exhibit a threshold. It should again be noted that Monsanto included the Levine et al. (2007) publication in a list of references provided to IARC for the review of glyphosate, but IARC did not include it in the Monograph.

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

- More specifically, the following statement in the IARC summary published in *The Lancet Oncology* is 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*".* This same study is referred to in the Monograph as "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).
- IARC claimed that the Bolognesi et al. (2009) study showed evidence of chromosomal damage (micronucleus formation) in circulating blood cells. This is a study that 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 because there were so many uncontrolled variables and problems that come with such a study, most notably, self-reporting (inaccuracies and/or information cannot be verified).
- It is important to note that Dr. Keith Solomon, one of the authors of the publication, has stated he does not know how IARC came to its conclusion because that is not the conclusion the authors had reached (personal communication). 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 this study that raise significant questions; for example:
    - The degree of DNA damage observed immediately after the glyphosate spraying was not consistent with the application rates used.
    - There was no association between self-reported direct contact with eradication sprays and DNA damage in two sprayed regions.
    - 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 with drawing conclusions; they made somewhat different conclusions in different places in the publication:
    - In the Abstract, they stated the data suggest that damage is small and appears to be transient; the evidence indicates that the genotoxic risk is low.
    - In the Discussion, they also 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.

A key feature overlooked by IARC is that glyphosate has no structural alerts to indicate that it would be carcinogenic or mutagenic. The 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 risk posed by chemicals (Benigni and Cecilia Bossa, 2006).

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APPENDIX 1.

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 any adverse effect *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 over 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. (Williams et al. 2000).

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.

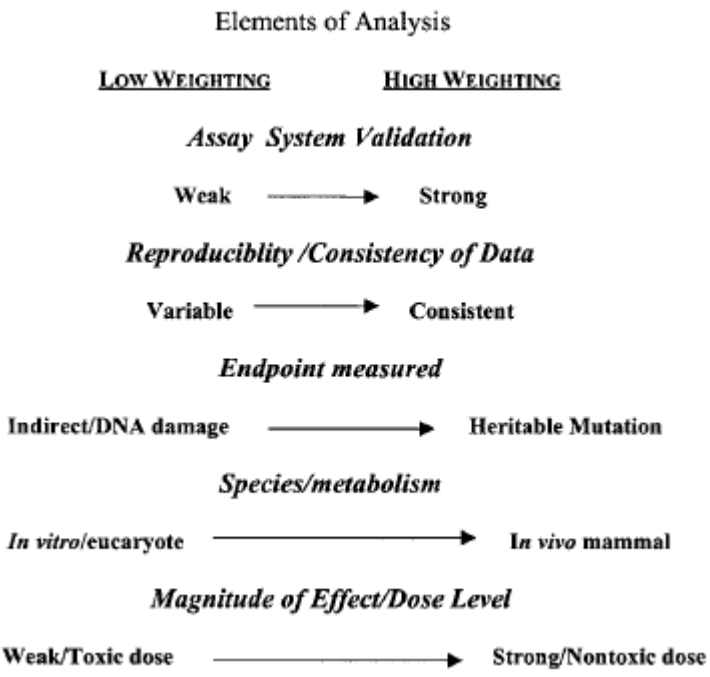

Figure 1. Weight-of-evidence data hierarchy organization for evaluation for genotoxicity.