Gylphosate is a Carcinogen

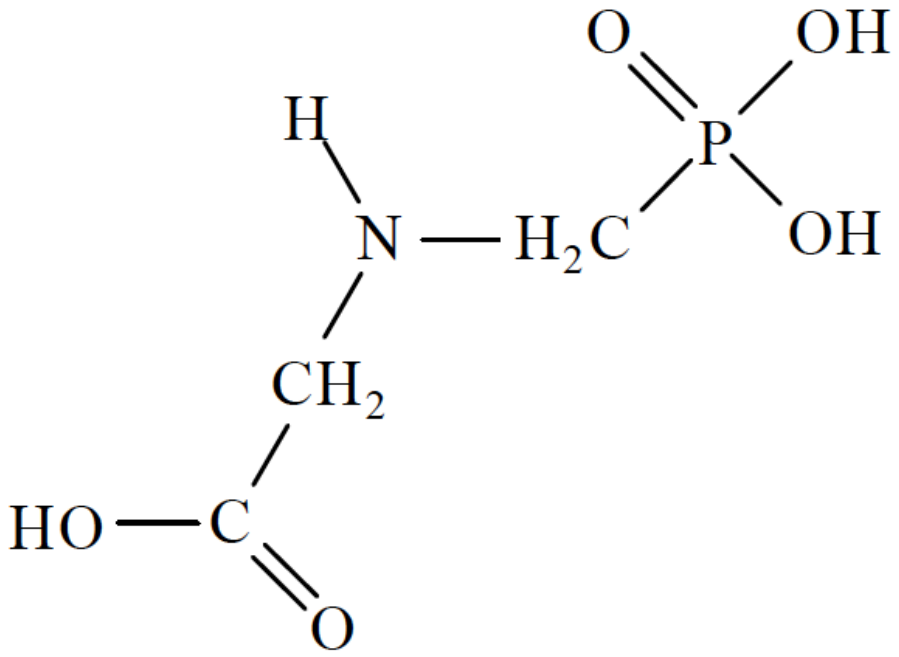
Michael L. Dourson, PhD, DABT, FATS, FSRA

Standing in lieu of the International Agency for Research on Cancer (IARC)

Structure of Glyphosate

- IARC, 2017, page 321

1.1.2 *Structural and molecular formulae and relative molecular mass*



Molecular formula: $C_3H_8NO_5P$
Relative molecular mass: 169.07

Discussions with IARC (summer, 2025)

From: Michael Dourson <dourson@tera.org>
Sent: Thursday, August 14, 2025 4:11 PM
To: epic.dis <epic@iarc.who.int>; Véronique Terrasse terrassev@iarc.who.int

Dear Colleagues

We invite one of your esteemed colleagues to speak at a debate in Workshop XV of the Beyond Science and Decisions series that will be held virtually on November 19 and 20, 2025. The debate will center on whether or not glyphosate and its formulations are carcinogenic, which as you know is a position that your organization espouses whereas others do not.

A draft of the agenda are brochure are attached. Registration is available at: https://www.tera.org/Alliance%20for%20Risk/ARA_Dose-Response.htm.

You may be aware that since 2010, the Alliance for Risk Assessment (*ARA*) has sponsored this workshop series building on the ideas of the National Academy of Sciences' (NAS) Science & Decisions: Advancing Risk Assessment (2009). Fourteen previous workshops brought together over 60 organizations seeking to advance the NAS recommendations. Over 60 presented case studies have thus far contributed to an expanding compendium of practical, problem-driven approaches for "fit for purpose" risk assessments. Links to publications of workshop reports can be found at: https://tera.org/Alliance%20for%20Risk/ARA_Dose-Response.htm.

Please feel free to contact any of us for details or further questions. We look forward to your active participation.

Sincerely,

James Bus, Exponent
Michael Dourson, Toxicology Excellence for Risk Assessment
Neeraja Erraguntla, American Chemistry Council
Suzanne Fitzpatrick, US Food and Drug Administration
Tracie Phillips, Texas Commission on Environmental Quality
Marc Williams, US Defense Health Agency
Pamela Williams, E Risk Sciences, LLP

Discussions with IARC (summer, 2025) continued

From: Véronique Terrasse <terrassev@iarc.who.int>
Date: Tuesday, August 19, 2025 at 7:59 AM
To: Michael Dourson <dourson@tera.org>
Subject: Re: Invitation to speak on Glyphosate

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From: Michael Dourson <dourson@tera.org>
Date: Tuesday, August 19, 2025 at 9:25 AM
To: Véronique Terrasse <terrassev@iarc.who.int>
Cc: James Bus <jbus@exponent.com>, et al.

Subject: Re: Invitation to speak on Glyphosate

Dear Veronique

No worries. We will find a scientist who is willing to argue your position. If you do not mind, we will send you their presentation prior to the debate so that you can suggest modifications. Alternatively, please feel free to send us your presentation.

The debate will follow the usual arrangements for 20-30 minutes to lay out each side of the argument, and then a 10-minute rejoinder by each side. A unique feature of this debate is that we will have a science panel listening in and who will offer comments, suggestions and critiques. Of course we will send you a report of the meeting…

Discussions with IARC (fall, 2025)

From: Michael Dourson <dourson@tera.org>
Date: Friday, November 7, 2025 at 10:07 AM
To: Véronique Terrasse <terrassev@iarc.who.int>

Cc: James Bus <jbus@exponent.com>, 'Erraguntla, Neeraja' <neeraja_erraguntla@americanchemistry.com>, Suzanne_Fitzpatrick <suzanne.fitzpatrick@fda.hhs.gov>, Tracie Phillips <tracie.phillips@tceq.texas.gov>, WILLIAMS, MARK ADRIAN CIV DHA DHA PUB HEALTH - A (USA) <mark.a.williams804.civ@health.mil>, Pamela Williams <pwilliams@eriskciences.com>
Subject: Glyphosate Debate Slides

Dear Veronique

As promised, attached is a set of draft slides for your review. The debate is on November 19 at 10 am Eastern Time in the US. I will strive to incorporate any of your comments and suggestions submitted to me by next Thursday, November 13th. Afterwards the presentations are loaded to the website for general distribution.

Please note that I have included our correspondences as part of my presentation, since folks at the workshop will want to know whether you were contacted. Please let me know if this is not welcome. I have no problem just mentioning this without the slides.

Cheers!

Michael

Meta-analyses of Epidemiology Studies
IARC, 2017, page 350

- "Schinasi & Leon (2014) conducted a systematic review and meta-analysis of NHL [*non-Hodgkin's lymphoma*] and occupational exposure to agricultural pesticides, including glyphosate."

- "The meta-analysis for glyphosate included six studies (McDuffie et al., 2001; Hardell et al., 2002; De Roos et al., 2003; 2005a; Eriksson et al., 2008; Orsi et al., 2009) and yielded a meta risk-ratio of 1.5 (95% CI, 1.1–2.0)."

- "[The Working Group noted that the most fully adjusted risk estimates from the articles by Hardell et al. (2002) and Eriksson et al. (2008) were not used in this analysis.]"

- "After considering the adjusted estimates of the two Swedish studies in the meta-analysis, the Working Group estimated a meta risk-ratio of 1.3 (95% CI, 1.03–1.65)."

IARC (2017) Summary of Human Carcinogenicity Data (pages 395-6)

5.2.1 NHL and other haematopoietic cancers

"In summary, case–control studies in the USA, Canada, and Sweden reported increased risks for NHL [*Non-Hodgkin's Lymphoma*] associated with exposure to glyphosate. The increased risk persisted in the studies that adjusted for exposure to other pesticides. [*However,*]The AHS [*Agricultural Health Study*] cohort did not show an excess of NHL. The Working Group noted that there were excesses reported for multiple myeloma in three studies; however, they did not weight this evidence as strongly as that of NHL because of the possibility that chance could not be excluded; none of the risk estimates were statistically significant nor were they adjusted for other pesticide exposures."

5.2.2 Other cancer sites

"No association of glyphosate with cancer of the brain in adults was found in the Upper Midwest Health case–control study. No associations in single case–control studies were found for cancers of the oesophagus and stomach, prostate, and soft-tissue sarcoma. For all other cancer sites (lung, oral cavity, colorectal, pancreas, kidney, bladder, breast, prostate, melanoma) investigated in the large AHS, no association with exposure to glyphosate was found."

IARC (2017) Summary of Experimental Animal Carcinogenicity Data (page 396)

Male and Female Mice

- 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-1 mice.
- No significant increase in tumour incidence was seen in female mice in this study.
- In the second feeding study, there was a significant positive trend in the incidence of haemangiosarcoma in male CD-1 mice.
- No significant increase in tumour incidence was seen in female mice in this study.

Male and Female Rats

- Two studies in the Sprague-Dawley strain showed a significant increase in the incidence of pancreatic islet cell adenoma in males at the lowest dose.*
- One of these two studies also showed a significant positive trend in the incidences of hepatocellular adenoma in males and of thyroid C-cell adenoma in females.
- Two studies (one in Sprague-Dawley rats, one in Wistar rats) found no significant increase in tumour incidence at any site.

* In males at the lowest dose, there was a statistically significant increase in the incidence of pancreatic islet cell adenoma compared with controls: 8/57 (14%) versus 1/58 (2%), $P \leq 0.05$ (Fisher exact test). Additional analyses by the EPA (1991a) (using the Cochran–Armitage trend test and Fisher exact test, and excluding rats that died or were killed before week 55) revealed a statistically significant higher incidence of pancreatic islet cell adenoma in males at the lowest and highest doses compared with controls: lowest dose, 8/45 (18%; $P = 0.018$; pairwise test); intermediate dose, 5/49 (10%); highest dose, 7/48 (15%; $P = 0.042$; pairwise test) versus controls, 1/43 (2%). The range for historical controls for pancreatic islet cell adenoma reported in males at this laboratory was 1.8–8.5%. [The Working Group noted that there was no statistically significant positive trend in the incidence of these tumours, and no apparent progression to carcinoma.] (IARC, 20177, page 356)

Genotoxicity and Mutagenicity (IARC, 2017, page 397)

- There is strong evidence that glyphosate causes genotoxicity. The evidence base includes largely positive results, but generally only at highest doses:
  - human cells in vitro (concentrations up to 12,680 ug/mL),
  - mammalian model systems in vivo (doses up to 2000 mg/kg-day i.p. and in vitro (concentrations up to 22,500 ug/L), and
  - studies in other non-mammalian organisms.
- In-vivo studies in mammals gave generally positive results in the liver, with mixed results for the kidney and bone marrow
- The end-points that have been evaluated in these studies comprise biomarkers of DNA adducts and various types of chromosomal damage.
- Tests in bacterial assays [*for mutagenicity*] gave consistently negative results.

Key Characteristics
(IARC, 2017, pages 398-399)

- In addition to limited evidence for the carcinogenicity of glyphosate in humans and sufficient evidence for the carcinogenicity of glyphosate in experimental animals, there is strong evidence that glyphosate can operate through two key characteristics of known human carcinogens, and that these can be operative in humans.
- Specifically, there is strong evidence that exposure to glyphosate or glyphosate-based formulations is genotoxic based on studies in humans in vitro and studies in experimental animals.
- There is strong evidence that glyphosate, glyphosate-based formulations, and amino-methyl-phosphonic acid (*a principal metabolite of glyphosate*) can act to induce oxidative stress based on studies in experimental animals, and in studies in humans in vitro.

IARC (2017) Risk Characterization Determination (page 398)

- “There is limited evidence in humans for the carcinogenicity of glyphosate. A positive association has been observed for non-Hodgkin lymphoma.”

- “There is sufficient evidence in experimental animals for the carcinogenicity of glyphosate.”

- “Glyphosate is probably carcinogenic to humans (Group 2A).”

Portier, 2020 (page 1)

- A comprehensive analysis of the animal carcinogenicity data for glyphosate from chronic exposure rodent carcinogenicity studies. Environmental Health.19:18

- One-sided trend analyses identify 37 significant tumor findings in 13 studies demonstrate consistency across studies in the same sex/species/strain for many of these tumors.

- The strongest evidence shows that glyphosate causes:
  - hemangiosarcomas, kidney tumors and malignant lymphomas in male CD-1 mice,
  - hemangiomas and malignant lymphomas in female CD-1 mice,
  - hemangiomas in female Swiss albino mice,
  - kidney adenomas, liver adenomas, skin keratoacanthomas and skin basal cell tumors in male Sprague-Dawley rats,
  - adrenal cortical carcinomas in female Sprague-Dawley rats and
  - hepatocellular adenomas and skin keratocanthomas in male Wistar rats.

Portier, 2020 (continued, page 13)

- “EPA discussed only 7 of the 21 statistically significant tumor increases in rats and 5 of the 16 significant tumor increases in mice. Similar comments apply to the EFSA review and all of the other regulatory reviews.”
- “To be fair to the regulatory agencies, it should be noted that the original study reports from the laboratories that did these studies also failed to identify many of the significant trends discussed in this review because they relied predominantly on pairwise evaluations like Fisher’s exact test and failed to do any trend analyses.”

Panzacchi et al., 2025

- Carcinogenic effects of long-term exposure from prenatal life to glyphosate and glyphosate-based herbicides in Sprague–Dawley rats

- “Glyphosate and GBHs at exposure levels corresponding to the EU ADI and the EU NOAEL caused dose-related trend increases in incidence of multiple benign and malignant tumors in SD rats of both sexes. Early-life onset and mortality were observed for multiple tumors.” (page 2)

- “These results provide robust evidence supporting IARC’s conclusion that there is “sufficient evidence of carcinogenicity [of glyphosate] in experimental animals”. (page 2)

Benign and malignant tumors at multiple anatomic sites		Glyphosate	Roundup Bioflow	RangerPro
Leukemia males & females	Lymphoblastic leukaemias	Upward trend	Upward trend	Upward trend
	Monocytic leukaemias	Upward trend	Upward trend	Upward trend
Benign and malignant tumors of the skin males & females (Fisher exact: 0.059 for total)	Squamous cell papilloma	Upward trend	-	-
	Keratoacanthoma	Upward trend	-	Upward trend
	Benign tumors	Upward trend	Upward trend	-
	Trichoepithelioma	-	Upward trend	-
	Basal cell carcinoma	-	Upward trend	-
Bone tumors males & females	Chondroma	Upward trend	-	-
	Osteoma	Upward trend	-	Upward trend
	Osteosarcoma	-	Upward trend	-
Other tumors in males	Mammary gland: Benign tumors	Upward trend	Upward trend	-
	Kidney: Malignant tumor	-	Upward trend	-
	Urinary bladder carcinoma	-	Upward trend	-
	Thyroid gland carcinoma	Upward trend	-	-
	Adrenal gland Carcinoma	-	-	Upward trend
	Endocrine Pancreas carcinoma	-	-	Upward trend
	Spleen: Hemangiosarcoma	-	-	Upward trend
	Central Nervous System tumor	Upward trend	-	-
	Nervous System Schwannoma	-	Upward trend	-
Other tumors in females	Thyroid gland: C-cell carcinoma	-	-	Upward trend
	Ovary: Fibroma	Upward trend	-	-
	Ovary: Malignant cell tumor	-	Upward trend	-
	Uterus: Benign Schwannoma	Upward trend	-	-
	Uterus: Hemangiosarcoma	-	-	Upward trend

Panzacchi et al., 2025
32 Positive trends

NEOPLASMS BY SITE IN MALE SD RATS	Glyphosate	Roundup Bioflow	RangerPro
Skin: Subcutaneous tissue, Fibrosarcoma	Downward trend	Downward trend	Downward trend
Zymbal glands: Carcinoma, sebaceous or squamous	Downward trend	-	Downward trend
Forestomach: Squamous cell Papilloma	-	Downward trend	Downward trend
Pancreas: Exocrine carcinoma	-	Downward trend	Downward trend
Pelvis: Papilloma, transitional cell	Downward trend	Downward trend	Downward trend
Thyroid gland: C-cell adenoma	Downward trend	Downward trend	-
Adrenal glands: Pheochromocytoma	Downward trend	Downward trend	Downward trend
Brain: Astrocytoma malignant	Downward trend	Downward trend	-
Haemolymphoreticular tissues: Histiocytic sarcoma	Downward trend	Downward trend	Downward trend
NEOPLASMS BY SITE IN FEMALE SD RATS			
Skin: Subcutaneous tissue, Fibroma	Downward trend	Downward trend	Downward trend
Oral cavity: Squamous cell carcinoma	Downward trend	Downward trend	Downward trend
Stomach (forestomach): Squamous cell Papilloma	-	Downward trend	Downward trend
Intestine: Adenomatous polyp	Downward trend	Downward trend	Downward trend
Liver: Hemagiosarcoma	Downward trend	Downward trend	Downward trend
Ovary: Adenocarcinoma	Downward trend	Downward trend	Downward trend
Uterus: Polyp (glandular or stromal)	Downward trend	Downward trend	Downward trend
Uterus: Leiomyosarcoma	Downward trend	Downward trend	Downward trend
Vagina: Benign granular cell tumor	Downward trend	Downward trend	Downward trend
Endocrine Pancreas: Islet cell carcinoma	Downward trend	Downward trend	Downward trend
Central nervous system (Meninges) cell tumour	Downward trend	Downward trend	Downward trend
Central nervous system Malignant tumour	Downward trend	Downward trend	Downward trend
Bones (Head): Osteoma	Downward trend	Downward trend	Downward trend
Soft tissues: Lipoma	Downward trend	Downward trend	Downward trend

Panzacchi et al., 2025
62 Negative trends

Rana et al., 2023

Mapping the key characteristics of carcinogens for glyphosate and its formulations: A systematic review

- "The greatest strength of our comprehensive systematic literature review was the exhaustive means of data collection and analysis: we assessed and compared the results of every assay reported within each study.
- The totality of evidence from mechanistic studies in human and animal systems suggests that glyphosate and its formulations possess several of the ten key characteristics of carcinogens (graphical abstract).
- Overall, as depicted in Fig. 5, our findings of strong evidence of glyphosate's ability to cause genotoxicity, epigenetic alterations, oxidative stress, chronic inflammation, and endocrine disruption, as well as its demonstrated perturbation of the gut microbiota outline several avenues implicated in lymphomagenesis."
- Greatest weakness? Doses in the various studies were not generally stated so that matching study concentrations to expected human exposures was not possible.

Becker et al. (2025)

Beyond key characteristics of carcinogens: an archetypal MOA-based evidence system for hypothesis testing to advance carcinogenrisk assessment

- Are the IARC key characteristics to cancer hazard identification a robust new approach to organizing and evaluating the mechanistic data that avoid the need to identify modes of action and underlying hypotheses?
- From one vantage point, perhaps. Because KCCs are based on empirical observations of characteristics associated with known carcinogens, they can assist the organization of the mode of action literature.
- Yet, as much as 50% of carcinogens classified by IARC do not exhibit any key characteristics, while other chemicals, not known to evoke cancer by both EPA and IARC, often do.
- Furthermore, many other toxicities, unrelated to cancer, may be mediated by similar toxicity pathways and biological responses and show similar key characteristics.

Conclusions

- IARC judges that glyphosate is probably carcinogenic to humans and places this in their Group 2A, based on:
  - Statistically significant positive trends for non-Hodgkin lymphoma in some human studies.
  - Statistically significant positive trends for a variety of tumors and a pair-wise comparison for one tumor, pancreatic adenomas, in rats.
- Portier (2020) supports the IARC position with an analysis of one-sided statistically significant positive trends in experimental animals.
- Panzacci et al. (2025) supports the IARC position with an experiment in rats showing 32 statistically significant positive trends…but also shows 61 negative trends.
- Rana et al. (2023) supports the IARC position through an analysis of key characteristics of carcinogens; Becker et al. (2025) would disagree.