

Glyphosate and Glyphosate- Based Herbicides (GBH) are not Carcinogenic*

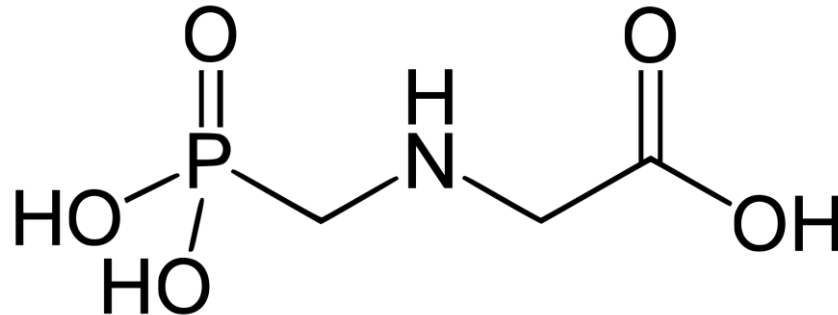
*Despite what you may have heard on television and
from social media

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How did we get here?

Let's start at the beginning...

- glyphosate was developed in the 1970s to be a safe herbicide and was registered by EPA in 1974
- It has become the most widely used herbicide in the US and globally
- Frequently used with GMOs
- Structure is shown below:



Glyphosate toxicity

- Glyphosate interferes with plant-specific enzyme
- Little systemic toxicity in mammals
- RfD = 1 mg/kg bw/day
- No quantitative cancer risk assessment was performed by EPA

Indicators of Potential Carcinogenicity

- Structure activity
- Rodent studies
- Genotoxicity
- Epidemiology



Initial EPA Evaluation of Carcinogenicity

- Standard genotoxicity data were negative
- The rat carcinogenicity study was determined to be negative by EPA
- The carcinogenicity study in mice reported a low incidence of an uncommon renal tumor
unusual tumor

1983 Mouse Carcinogenicity Study (males)

Dose (ppm)	0	1000	5000	30,000
No. Exposed	49	49	50	50
No. of mice with renal tubule adenomas/ carcinomas	1	0	1	3

Rodent Carcinogenicity Studies of Glyphosate

- Many subsequent studies have been conducted
- Six studies were deemed not adequate for use in evaluation of carcinogenicity
- Eight rat and 6 mouse studies are “acceptable” for the WOE determination
- Carcinogenicity data base for glyphosate is unparalleled for a pesticide
- No carcinogenicity demonstrated in the 14 acceptable carcinogenicity bioassays

Is this Evidence of Carcinogenicity?

Table 4.10. Liver Adenomas in Male Wistar Rats (Brammer, 2001) Cochran-Armitage Trend Test and Fisher's Exact Test Results.				
	0 mg/kg/day	121 mg/kg/day	361 mg/kg/day	1214 mg/kg/day
Adenoma Incidence (%)	0/44 ^a (0)	2/48 (4)	0/48 (0)	5/49 (10)
Raw p-value =	0.010*	0.269	1.000	0.037*
Adjusted p-value =	0.029*	0.269	1.000	0.055

Note: Trend test results denoted at control; * denotes significance at $p=0.05$; ** denotes significance at $p=0.01$

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 52 (interim sacrifice).

Not evidence of carcinogenicity because...

1. Not significant by pair-wise comparison after adjustment
2. No dose response
3. High dose exceeds limit dose
4. No evidence of progression
5. Within historical control range
6. Adenomas only
7. Not consistent with other studies

Glyphosate Genotoxicity Studies (Gene mutation and CA Assays)

Study Type	Number of Studies	Positive Studies	Positive and Published
Gene mutation			
Gly	33	1	1
GBH	31	2	2
Chromosomal Aberrations			
Gly	16	3	3
GBH	10	7	7
Total assays (GLY, GBH and metabolite)	217	90	89

DNA Damage Studies

Study Type	Number of Studies	Positive Studies	Positive and Published	
DNA Damage				
Gly	29	23	23	
GBH	38	33	33	

Does glyphosate cause DNA damage?

- EPA reviewed the 59 studies of glyphosate, GBH or the primary metabolite reporting DNA damage and concluded only 9 were useful
- Problems with the others included inappropriate dosing, phylogenetically distant organisms, co-exposures to other agents, poor study descriptions
- 3 of the 9 were reported to be positive
- DNA damage likely to be due to toxicity in positive studies
- **Weight of evidence determination is that glyphosate is not genotoxic**

Agricultural Health Study

- Sponsored by NCI with assistance from EPA, NIEHS and NIOSH
- Detailed survey of 89,000 farmers and families
- Careful characterization of exposure and health status
- Farmers are exposed to much higher levels of glyphosate than consumers
- **No evidence of carcinogenicity in glyphosate-exposed farmers or farm families**

Reviews of Glyphosate by National and International Authorities

- Initially, an ad hoc EPA committee recommended classification as Group C “limited evidence of carcinogenicity”
- 1986 EPA CARC concluded that glyphosate was not classifiable and recommended further testing
- 1991 and 2017 re-evaluations by EPA CARC concluded “not likely to be a human carcinogen”
- JMPR reviewed glyphosate (1986, 1997, 2004, 2011 and 2016) and found no evidence of carcinogenicity
- This was also the conclusion of European Food Safety Agency, European Chemicals Agency, Canadian Pesticide Management and Review Agency and almost all other regulatory Agencies
- **2016 IARC classification- “probably carcinogenic to human” is the outlier**

IARC Peculiarities

- Reliance on published literature (“public domain”)
- Compliance with EPA guidelines and Good Laboratory Practices (GLP) is not important for IARC
- Preamble is rigid and is based on EPA 1986 Cancer Guidelines
- No external review process. The decision made during ten day meeting is final
- Not risk based
- Is it time to update or re-invent IARC monograph process?

Post-IARC Information

More recent data-

- NTP screening showed no activity for glyphosate
- lack of carcinogenicity re-affirmed by JMPR and EPA
- Ramazzini Institute study – unusual study design, ambiguous results, positive trends due to multiple comparisons

In summary...

- Glyphosate has a long history of safe use
- Glyphosate does not have characteristics of a carcinogen
- Glyphosate is not carcinogenic in cancer bioassays
- The Ag Health Study did not show evidence of carcinogenicity
- Glyphosate has been repeatedly reviewed by EPA and other governmental agencies in many countries. The consensus among countries is that it is not carcinogenic.

Are glyphosate formulations carcinogenic?

- Tests for carcinogenicity are required only for the active ingredient
- Inert ingredients may be used in many formulations and are assessed independently
- Not practical to test all formulations for carcinogenicity
- AI testing needed for dietary risk
- Each person's exposure history is unique
- Ag Health study is reassuring for formulation carcinogenicity
- No basis to conclude that any given formulation is carcinogenic

