

Current Status of Glyphosate Registrations Worldwide

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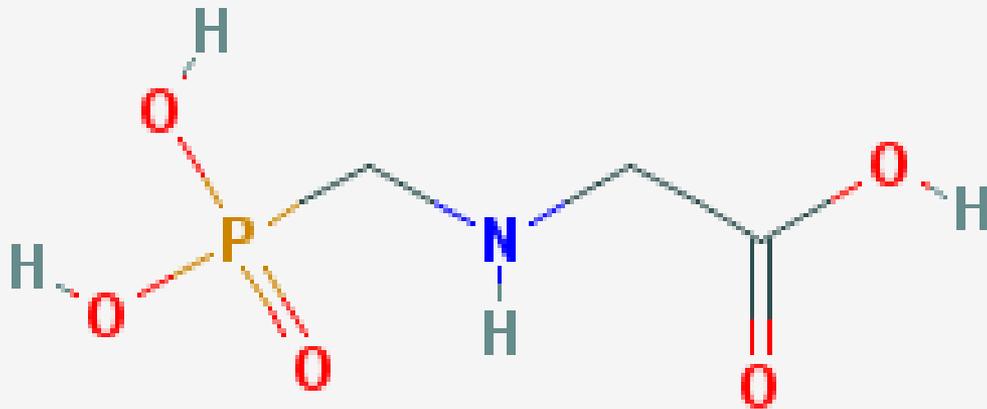
Glyphosate

- First registered in 1974 under the trade name Roundup
- Foliar-applied herbicide that is both phloem and xylem mobile
- Is tightly bound to phosphate sorption sites in soil, so soil activity is very rare
- Widely used in vineyards, orchards, fallow fields, and Roundup Ready crops

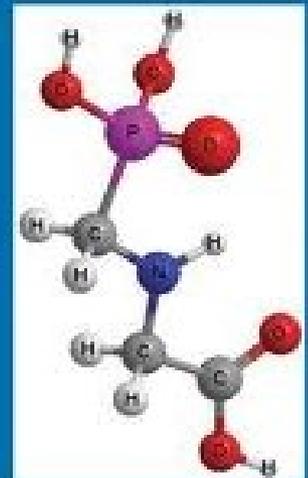


In This Session:

- Does Glyphosate Cause Cancer?



GLYPHOSATE



Is Glyphosate Safe??

- Recent events have clouded the view!
- In particular, the finding by the International Agency for Research on Cancer (IARC, an agency within the World Health Organization) that glyphosate is a Group 2A Carcinogen was announced in March, 2015
- *Many thanks to Dr. Len Ritter, Professor Emeritus of Toxicology with University of Guelph, for much of the following timeline information*

Pesticide Registrations

- In the US and Canada, all pesticides must undergo a re-registration process every 13 to 15 years
 - Registrants must address all concerns brought out in the science, especially regarding toxicological effects
- The last re-registration of glyphosate was in 1993, so the process for this herbicide began again a few years ago
 - US EPA began its re-registration process for glyphosate in 2009
 - Canada's PMRA (equivalent to US EPA) released its finding in April, 2015

Enter the IARC

- The IARC was born in 1965 in effort to “better understand the occurrence, natural history, causes, and prevention of cancer”
- March, 2015: Glyphosate were classified as “probably carcinogenic to humans (Group 2A)”
- What does this mean?

The IARC Selects Agents for Review Based on Two Criteria:

- The evidence of human exposure
- There is some evidence or suspicion of carcinogenicity

- Risk = Toxicity x Exposure
 - So cancer risk is based on the inherent toxicity of the agent and a human's exposure to that agent (frequency, duration, and intensity)

The IARC's Rating Scale

- Group 4: Probably not carcinogenic to humans (1 agent)
- Group 3: Not classifiable as to its carcinogenicity to humans (505 agents)
- Group 2B: Possibly carcinogenic to humans (292 agents)
- Group 2A: Probably carcinogenic to humans (81 agents)
- Group 1: Carcinogenic to humans (119 agents)



WHAT DOES
“PROBABLY
CAUSES CANCER”
ACTUALLY MEAN?

<https://www.youtube.com/watch?v=CbBkB81ySxQ>

What Does The Record Say?

- 1974: EPA registered glyphosate
- 1993: EPA re-registered glyphosate
 - “Based on the results of its re-registration review, EPA has concluded that all registered uses of glyphosate are eligible for re-registration.”
 - “The Agency has classified glyphosate as a Group E carcinogen (signifies evidence of noncarcinogenicity in humans).”

An Updated Review of Glyphosate at the Advent of Roundup Ready

- Comprehensive review of glyphosate was conducted by Williams et al. (1998-2000)
 - Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient glyphosate for humans. *Regulatory Toxicology and Pharmacology* 31:117-165
 - “Multiple lifetime feeding studies have failed to demonstrate any tumorigenic potential for glyphosate. Accordingly, it was concluded that glyphosate is noncarcinogenic.”
 - Further, “It was concluded that, under present and expected conditions of use, Roundup herbicide does not pose a health risk to humans.”

WHO's Other Arm:

Joint Meeting on Pesticide Residues, 2004

- “Administration of glyphosate for two years produced no evidence of a carcinogenic response to treatment in rats. The NOAEL was 6000 ppm (= 361 mg/kg bw per day).”
 - “No statistically significant increases in the incidence of any tumours, either benign and malignant, in either sex when compared with the control groups.”

The Agricultural Health Study

- Joint project by EPA, National Cancer Institute, National Institute of Environmental Health Sciences, National Institute for Occupational Safety and Health
 - Since 1993, over 89,000 farmers and spouses in IA and NC have participated
- DeRoos et al. 2005. Cancer incidence among glyphosate-exposed pesticide applicators in the AHS. *Environmental Health Perspectives* 113:49-54
 - “Glyphosate exposure was not associated with cancer incidence overall or with most of the cancer subtypes we studied. There was a suggested association with multiple myeloma incidence that should be followed up as more cases occur in the AHS.”

Another Review, 2012

- Mink et al. Epidemiologic studies of glyphosate and cancer: a review. *Regulatory Toxicology and Pharmacology* 63:440-452
 - “To examine potential cancer risks in humans, we reviewed the epidemiologic literature to evaluate whether exposure to glyphosate is associated causally with cancer risk in humans. We also reviewed relevant methodological and biomonitoring studies of glyphosate. Seven cohort studies and fourteen case control studies examined the association between glyphosate and one or more cancer outcomes.”

The Mink et al. Review

- “Our review of the currently available epidemiologic literature on glyphosate and cancer found no evidence of a consistent pattern of positive associations that would be indicative of a causal relationship between any site-specific cancer and exposure to glyphosate.”

Let's Get Back To EPA

- 2013: “Based on the data summarized in Unit III.A,” *(the Mink et al. review)* “EPA has concluded that glyphosate does not pose a cancer risk to humans. Therefore, a dietary exposure assessment for the purpose of assessing cancer risk is unnecessary.”

Do You Remember DeRoos' Myeloma Question in 2005?

- Sorohan. 2015. Multiple myeloma and glyphosate use: a re-analysis of US Agricultural Health Study (AHS) Data. *International Journal of Environmental Research and Public Health* 12:1548-1559
 - “There were no statistically significant trends for multiple myeloma risks in relation to reported cumulative days (or intensity weighted days) of glyphosate use. The doubling of risk reported previously arose from the use of an unrepresentative restricted dataset and analyses of the full dataset provides no convincing evidence in the AHS for a link between multiple myeloma risk and glyphosate use.”

Germany Assesses Glyphosate

- January, 2015: Germany, on behalf of the European Union, issued a renewal assessment report for glyphosate
 - “Classification and labeling for carcinogenicity is not warranted. This is based on a large number of long-term studies in rats (that) did not reveal any evidence of carcinogenicity. In the mouse, a higher incidence of malignant lymphoma was observed in one out of five carcinogenicity studies at an exaggerated dose level in a strain with high background incidence of this tumor type.”
 - “Epidemiological studies in the whole did not provide evidence of carcinogenicity in man.”

IARC's Report, March, 2015

- “For the herbicide glyphosate, there was limited evidence of carcinogenicity in humans for non-Hodgkin’s lymphoma.”
- “In addition, there is convincing evidence that glyphosate also can cause cancer in laboratory animals.”
- “The IARC Working Group that conducted the evaluation considered the significant findings from the USEPA report” (*EPA in 1985 had initially classified glyphosate as possibly carcinogenic to humans from data in a mouse study*) “and several more recent positive results in concluding that there is sufficient evidence of carcinogenicity in experimental animals.”

Germany Responds in April, 2015

- “In its recent evaluation, IARC...came to the conclusion that glyphosate should now be classified as a carcinogenic substance in Group 2A (probably carcinogenic to humans), based on ‘limited evidence’ in human experiments and ‘sufficient evidence’ in animal experiments. As the ‘Rapporteur Member State’ for the active substance glyphosate, the German Federal Institute for Risk Assessment (BfR) was responsible for the human health risk assessment and has assessed glyphosate as noncarcinogenic.”
- “The current report of BfR to the EU based on the evaluation of over 30 epidemiological studies came to the overall assessment that there is no validated or significant relationship between exposure to glyphosate and an increased risk of non-Hodgkin lymphoma or other types of cancer.”

Canada Weighs In, April, 2015

- “In consideration of the strength and limitations of the large body of information on glyphosate, which included multiple short and long term (lifetime) animal toxicity studies, numerous *in vivo* and *in vitro* genotoxicity assays, as well as the large body of epidemiological information, the overall weight of the evidence indicates that glyphosate is unlikely to pose a human cancer risk.”
- “An evaluation of available scientific information found that products containing glyphosate do not present unacceptable risks to human health or the environment when used according to label directions.”

One More Point by PMRA in Canada

- Remember Risk = Toxicity x Exposure?
- “The IARC recently assigned a hazard classification for glyphosate as ‘probably carcinogenic to humans.’ It is important to note that a hazard classification is not a health risk assessment. The level of exposure, which determines the actual risk, was not taken into account by IARC. Pesticides are registered in Canada only if the level of exposure to Canadians does not cause any harmful effects, including cancer.”
- “Products containing glyphosate are unlikely to affect your health when used according to label directions.”
- “When used according to proposed label directions, glyphosate products do not pose an unacceptable risk to the environment. Labelled risk-reduction measures mitigate potential risks posed by glyphosate formulations to non-target plants and freshwater/marine/estuarine organisms.”

Oh, and Remember That Other WHO Committee?

- Joint Meeting on Pesticide Registration, that in 2004 set NOAELs of 361 mg/kg bw per day (based on rat data)
- In June, 2015 WHO pointed out that these two committees have different functions
 - JMPR to perform risk assessment for regulatory purposes
 - IARC to deal with hazard identification
- Proposed an *ad hoc* task force be formed to advise JMPR on the studies IARC used to come to their opinion
 - In September, 2015 the Task Force found that IARC had access to newer studies than JMPR had available in 2004, and that JMPR would then re-evaluate their finding of noncarcinogenicity

JMPR Reports Again

- The Joint Meeting on Pesticide Registration announced in May 2016 that it has concluded that “glyphosate is unlikely to pose a carcinogenic risk to humans from exposure through the diet”

European Food Safety Authority

- The EFSA released a report in November, 2015:
 - Concluded that glyphosate is unlikely to be genotoxic (i.e. damaging to DNA) or to pose a carcinogenic threat to humans
 - Glyphosate is not proposed to be classified as carcinogenic under the EU regulation for classification, labelling and packaging of chemical substances
 - In particular, all the Member State experts but one agreed that neither the epidemiological data (i.e. on humans) nor the evidence from animal studies demonstrated causality between exposure to glyphosate and the development of cancer in humans
 - EFSA set the acceptable operator exposure level at 0.1 mg/kg bw per day and an acceptable daily intake for consumers was set in line with the ARfD (the German report) at 0.5 mg/kg bw per day

What About The Surfactant?

- The EFSA also reported on the potential “genotoxicity, long-term toxicity, carcinogenicity, reproductive/developmental toxicity, and endocrine disrupting potential” of the polyethoxylated tallowamine (POEA) surfactant in Roundup formulations
- The group cited no available information on the residues in plants and livestock and concluded that “the available data are insufficient to perform a risk assessment” for the surfactant

Fast Forward to 2016

- Europe's Commission for Health and Food Safety had taken up the glyphosate re-registration issue, but could not come to consensus
- Recommended:
 - Continued use of glyphosate until December, 2017
 - Removal of POEA from all herbicide formulations until full risk assessment is possible
 - Pay "particular attention to protection of groundwater in vulnerable areas, in particular with respect to noncrop uses"
- In July, 2016, EU member states voted to accept these recommendations (22 in favor, 6 abstentions)

What About Down Under?

- The Australian Pesticides and Veterinary Medicine Authority states that it has completed its assessment of the IARC report and other recent assessments of glyphosate, and “has concluded that glyphosate does not pose a cancer risk to humans”
 - “The current assessment by the APVMA is that products containing glyphosate are safe to use as per the label instructions”
- In August 2016, New Zealand’s Environmental Protection Authority (EPA) published a review of the evidence for carcinogenicity as a result of exposure to glyphosate
 - “Using a weight-of-evidence approach, the EPA concluded that glyphosate was unlikely to cause cancer in humans”

Is Glyphosate Used Anywhere Else?

- Yup, pretty much everywhere
- Glyphosate is registered for use in over 160 countries world-wide
- To date, no international regulator has banned the use of glyphosate in any country, following the IARC re-classification
- In some countries retailers have made the commercial decisions to stop supplying glyphosate or to restrict sales for certain uses, such as the homeowner market

The Most Recent AHS Study

- Andreotti et al. 2017. Glyphosate Use and Cancer Incidence in the Agricultural Health Study. *Journal of the National Cancer Institute*, djx233, <https://doi.org/10.1093/jnci/djx233>
- “In this large, prospective cohort study, no association was apparent between glyphosate and any solid tumors or lymphoid malignancies overall, including non-Hodgkins lymphoma and its subtypes. There was some evidence of increased risk of acute myeloid leukemia among the highest exposed group that requires confirmation.”

Right Now In Europe

- The EU voted in November, 2017 to extend registration for glyphosate until 2022 (instead of the typical 15-year re-registration)
 - Led by Germany, 18 countries (representing 65.7% of the EU's population) voted in favor (EU required affirmative votes representing at least 65% of the population in order to pass this measure)
 - 9 countries were opposed (Belgium, Greece, France, Croatia, Italy, Cyprus, Luxembourg, Malta, and Austria)
 - 1 abstention (Portugal)
- In a tweet after the vote, French President Emmanuel Macron said he will order a ban on the use of glyphosate in France "as soon as alternatives are found, and within three years at the latest"

EPA Draft Risk Assessment

- In December, 2017, USEPA concluded that “...glyphosate is not likely to be carcinogenic to humans. The Agency’s assessment found no other meaningful risks to human health when the product is used according to the pesticide label. The Agency’s scientific findings are consistent with the conclusions of science reviews by a number of other countries as well as the 2017 National Institute of Health Agricultural Health Survey.”

Bottom Line For Now

- IARC's assessment stands in sharp contrast to global assessment of the lack of carcinogenicity by glyphosate
- EPA's draft risk assessment stands in agreement with the EU (Germany), Canada, Australia, and New Zealand in assessing glyphosate as being noncarcinogenic to humans
- EPA is scheduled to release its draft re-registration decision in the fourth fiscal quarter (April to September, 2018)
- Stay tuned...



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