Case Study #1 Summary

Title: Does Glyphosate Cause Cancer? A Debate

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1. **Provide a few sentences summarizing the method illustrated by the case study.**

   Glyphosate was classified as a probable carcinogen by IARC (2017). This position is in contrast to all other national and international health organizations, including EFSA (2023), JMPR (2017), and US EPA (2017, 2020), and has been questioned by expert panels (Williams et al., 2016). This case study is structured as an open debate in front of a science panel in order to lay out and discuss the data relevant to IARC's classification.

2. **Describe the problem formulation(s) the case study is designed to address. How is the method described in the case useful for addressing the problem formulation?**

   The problem formulation addresses the specific concern that glyphosate causes cancer, and the more general question on whether the hazard identification approach used by IARC is preferred to that used by others which includes both hazard identification and dose response assessment.

3. **Comment on whether the method is general enough to be used directly, or if it can be extrapolated, for application to other chemicals and/or problem formulations. Please explain why or why not.**

   The structure of this case study as a debate is consistent with other hot button topics debated by other organizations, such as whether the Delaney Cause[1] should be sunset due to improved understanding on how chemicals cause cancer by the Society of Toxicology in 2019[2] and published as Krishan et al. (2021).

4. **Discuss the overall strengths and weaknesses of the method.**

   Debates in general can be helpful in undercovering strengths and weaknesses in opposing positions. This debate is perhaps somewhat more refined than others in that the debate is conducted in front of a panel of erudite risk assessment scientists and also open to observer

[1] The Delaney Clause of the Federal Food, Drug, and Cosmetic Act became law in 1958 because of concerns that potentially harmful chemicals were finding their way into foods and causing cancer. It states, "[n]o additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal."

[2] "The Delaney Clause, from 1958 to 2019: Making the Model Relevant: A Pro Delany Perspective, Society of Toxicology. Baltimore, MD. March 12, 2019.

comments. Furthermore, the debate and ensuing discussion and comments will also be captured in workshop report.

5. **Outline the minimum data requirements and describe the types of data sets that are needed.**

   Glyphosate was approved by EPA in 2017 with the database appropriate for a food use pesticide. The database for glyphosate's potential carcinogenicity is now much more extensive in terms of epidemiology investigations, experimental animal studies, and mode of action (MOA) information. Debates regarding the carcinogenicity of other chemicals will rarely have this extensive information.

Does your case study:

A. Describe the dose-response relationship in the dose range relevant to human exposure?

This debate will focus on weight of the evidence (WOE) for glyphosate's potential carcinogenicity, and whether risk assessment for any cancer findings for glyphosate is appropriate. Aspects of dose response is an active part of the hazard identification and ensuing WOE, but a dose response assessment is not envisioned.

B. Address human variability and sensitive populations?

Human variability is addressed to some extent in available epidemiological studies. It is also addressed through the use of dose response models in the hazard identification using experimental animal data.

C. Address background exposures or responses?

Glyphosate does not naturally occur. So background exposures are either not relevant or are subsumed in the available epidemiology and toxicology data reviewed as part of the evaluation of glyphosate's potential carcinogenicity.

D. Address incorporation of existing biological understanding of the likely mode of action?

The mode of action (MOA) for glyphosate's desired effect on plants is not relevant to humans. However, understanding the MOA for toxic effects of excess doses in humans will be discussed, especially as it relates to glyphosate's potential carcinogenicity.

E. Address other extrapolations, if relevant – insufficient data, including duration extrapolations, interspecies extrapolation?

The database for glyphosate's potential carcinogenicity is extensive. It includes many long term studies in experimental animals and sufficient understanding of interpecies differences to allow reasonable extrapolations. Robust epidemiological studies are also available.

F. Address uncertainty?

This debate is expected to highlight uncertainties in the science, if any, on either or both sides of the potential carcinogenicity of glyphosate.

G. Allow the calculation of risk (probability of response for the endpoint of interest) in the exposed human population?

The development of risks is not anticipated in this debate. Instead, this debate will focus on glyphosate's hazard identification.

H. Work practically? If the method still requires development, how close is it to practical implementation?

Structured debates are a normal part of the overall scientific process. This debate is not unusual in the overall scientific enterprise.

References

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