Glyphosate: Evaluation of Carcinogenic Potential

Charge to the FIFRA SAP for October 18-21, 2016 Meeting

Glyphosate is a non-selective, phosphonomethyl amino acid herbicide registered to control weeds in various agricultural and non-agricultural settings. Labeled uses of glyphosate include over 100 terrestrial food crops as well as other non-agricultural sites, such as greenhouses, aquatic areas, and residential areas. Use of glyphosate in the United States and globally has increased overtime, particularly with the introduction of glyphosate-resistant crops; however, usage has stabilized in recent years due to the increased number of weed species becoming resistant to glyphosate. Glyphosate is currently undergoing Registration Review, which reviews all registered pesticides at least every 15 years as mandated by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

Recently, EPA collected and analyzed a substantial amount of data informing the carcinogenic potential of glyphosate and utilized the draft "Framework for Incorporating Human Epidemiological & Incident Data in Health Risk Assessment". The draft framework provides the foundation for evaluating multiple lines of scientific evidence. A comprehensive analysis of data on glyphosate from submitted guideline studies and the open literature was performed. This includes epidemiological, animal carcinogenicity, genotoxicity, and absorption, distribution, metabolism, and excretion (ADME) studies. Guideline studies were collected for consideration from the toxicological databases for glyphosate and glyphosate salts. A fit-for-purpose systematic review was executed to obtain relevant and appropriate guideline and open literature studies with the potential to inform the human carcinogenic potential of glyphosate. Furthermore, the list of studies obtained from the toxicological databases and systematic review was cross-referenced with recent internal reviews, review articles from the open literature, international agency evaluations, and a list of studies provided by registrants.

Available data from epidemiological, animal carcinogenicity, and genotoxicity studies were reviewed and evaluated for study quality and results to inform the human carcinogenic potential of glyphosate according to the 2005 Guidelines for Carcinogen Risk Assessment. A total of 58 epidemiological studies, 20 animal carcinogenicity studies, and almost 200 genotoxicity assays were considered in the current evaluation. Additionally, multiple lines of evidence were integrated in a weight-of-evidence analysis using the modified Bradford Hill Criteria considering concepts, such as strength, consistency, dose response, temporal concordance, and biological plausibility. The totality of the data has been used by the agency to inform cancer classification descriptors according to the 2005 Guidelines for Carcinogen Risk Assessment. Although there are studies available on glyphosate-based pesticide formulations, the agency is soliciting advice from the FIFRA Scientific Advisory Panel (SAP) on this evaluation of human carcinogenic potential for the active ingredient glyphosate only at this time.

1. The agency has collected a multitude of studies that may inform the human carcinogenic potential of glyphosate through a systematic review of the open literature and toxicological databases for glyphosate and glyphosate salts as described in Section 2.0. Please comment on the agency's methods to collect references for this evaluation, including the completeness, transparency, and appropriateness of these methods. Please

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also comment on whether there are additional relevant studies that could inform the human carcinogenic potential of glyphosate that were not included in the current evaluation.

2. As part of its analysis, the agency has considered 58 individual epidemiological studies investigating the potential for an association between glyphosate exposure and numerous cancer outcomes. Detailed study evaluations were performed to determine overall quality rankings for relevant studies. These evaluations took into consideration study characteristics, including study design, exposure assessment, outcome assessment, control for confounders, statistical analyses, and risk of bias. Twenty-three studies were considered informative with regard to the carcinogenic potential of glyphosate.

    a. Please comment on the agency's review and evaluation process of relevant epidemiology studies to inform the human carcinogenic potential of glyphosate.
    b. Please comment on the strengths and limitations of the available studies to inform the association between glyphosate and solid tumors, leukemia, and Hodgkin lymphoma and the agency's conclusion regarding these cancer types described in Section 3.6.
    c. Please comment on the strengths and limitations of the available studies to inform the association between glyphosate and multiple myeloma. Please comment on the agency's conclusion as described in Section 3.6
    d. Please comment on the strengths and limitations of the available studies to inform the association between glyphosate and non-Hodgkin lymphoma (NHL). Please comment on the agency's conclusion as described in Section 3.6.

3. The agency has followed the 2005 EPA Guidelines for Carcinogen Risk Assessment to evaluate laboratory animal carcinogenicity studies for glyphosate. As described in Sections 4.5 and 4.6, a total of 9 acceptable rat and 6 acceptable mouse carcinogenicity studies were evaluated and considered in the weight-of-evidence analysis. Consistent with the 2005 Guidelines, this analysis took into consideration statistical evidence of a dose-response, the occurrence of corroborating pre-neoplastic lesions or related non-neoplastic lesions to support tumor findings, evidence of progression to malignancy, concurrent and historical control information, and statistical and biological significance of increase tumor incidence, as well as the reproducibility of tumor findings.

    a. Please comment on the agency's review and evaluation process of relevant laboratory animal carcinogenicity studies to inform the human carcinogenic potential of glyphosate.
    b. For some of the available animal studies, statistically significant trends in tumor incidence were observed with a lack of statistically significant pairwise comparisons when adjusted for multiple comparisons[1]. Please comment on the agency's methodology and interpretation of statistical analyses to evaluate a linear

[1] Individual studies include Stout and Rueckerf (1990), Brammer (2001), Wood et al. (2009a), Atkinson (1993b), Wood et al. (2009b), Sugimoto (1997). Results are summarized in Table 4.11 and Table 4.18.

dose-response (trend test) and increased tumor incidence as compared to controls (pairwise comparisons).

c. Unusually low incidences in concurrent controls in comparison with historical controls were noted in Lankas (1981), Stout and Rueckerf (1990), and Wood et al. (2009b) and considered as part of the weight-of-evidence for tumor findings. Please comment on the agency's use and interpretation of historical control data as a line of evidence to inform the statistical and biological significance of tumor findings for glyphosate.
d. Please comment on the agency's conclusion that there is an absence of corroborating preneoplastic lesions or related non-neoplastic lesions. Please also comment on the agency's conclusion that there is a lack of progression to malignancy to support tumor findings.
e. In the case of glyphosate, there are multiple carcinogenicity studies available for the evaluation of carcinogenic potential. The agency looked across all of the studies and found that tumor findings were not consistent or reproduced in other studies conducted in the same species and strain at similar or higher doses. Please comment on the interpretation of conflicting evidence and reproducibility for these studies.
f. As described in Section 1.4, high-end estimates of exposure based on the currently registered uses for glyphosate in the United States have been calculated as 0.47 mg/kg/day and 7 mg/kg/day for potential residential and occupational exposures, respectively. As a result, the agency concluded that tumors observed at high-doses (approaching or exceeding 1,000 mg/kg/day) following glyphosate administration are not relevant for human health risk assessment. Please comment on the conclusions regarding the relevance of high-dose tumors to the human health risk assessment for glyphosate.
g. Please comment on the strengths and uncertainties associated with the agency's overall weight-of-evidence and conclusions based on the available animal carcinogenicity studies, as described in Section 4.8.

4. As part of its analysis, the agency has considered almost 200 assays investigating the genotoxic potential of glyphosate. Of these, 107 were performed with the active ingredient glyphosate. These included *in vitro* and *in vivo* studies from the open literature, as well as studies submitted to the agency that were conducted according to Office of Chemical Safety and Pollution Prevention (OCSPP)/ Organization for Economic Cooperation and Development (OECD) guidelines. Non-mammalian studies were excluded from this analysis unless the assays were generally recognized to inform the human carcinogenic potential of glyphosate (e.g., bacterial reverse mutation assays). Studies evaluated genotoxic endpoints, such as gene mutations in bacteria and mammalian cells, chromosomal aberrations, micronuclei formation, and other assays measuring DNA damage.

   a. Please comment on the agency's review and evaluation process of relevant genotoxicity studies to inform the human carcinogenic potential of glyphosate, including the decision to exclude non-mammalian studies (e.g., reptiles, plants,

worms, fish), except those generally recognized to inform human carcinogenic potential.

b. Consistent with the OECD guidance (2015), *in vivo* findings in genetic toxicology testing are generally considered as having a greater relevance to humans than *in vitro* findings. Consistent with the 2005 Cancer Guidelines, all available data were considered in the weight-of-evidence evaluation of the genotoxic potential for glyphosate. The relevant studies are summarized in Tables 5.1-5.7. Please comment on the agency's approach for evaluating the genotoxicity data.
c. As described in Section 1.4, oral exposure is considered the primary route of concern for glyphosate and high-end estimates of exposure range from 0.47-7 mg/kg/day. Please comment on the human health relevance of the genotoxicity findings with respect to the doses where effects were observed and the route of administration.
d. Please comment on the strengths and uncertainties associated with the agency's overall weight-of-evidence and conclusions based on the available genotoxicity studies, as described in Section 5.7.

5. The modified Bradford Hill criteria were used to evaluate multiple lines of evidence using such concepts as strength, consistency, dose response, temporal concordance, and biological plausibility. In accordance with the 2005 Cancer Guidelines, the agency used a weight-of-evidence analysis to characterize the human carcinogenic potential of glyphosate and determine which cancer descriptor is supported by the data. The agency has described the strengths and uncertainties associated with the choice of various cancer descriptors with a focus on "suggestive evidence of carcinogenic potential" and "not likely to be carcinogenic to humans". Please comment on the completeness, transparency, and scientific quality of the agency's characterization of the carcinogenic potential.