UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

DATE: December 12, 2017

SUBJECT: Response to the Final Report of the Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (FIFRA SAP) on the Evaluation of the Human Carcinogenic Potential of Glyphosate

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Introduction:

As part of Registration Review, the Agency reevaluated the human carcinogenic potential of glyphosate. 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. 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 was used by the Agency to inform cancer classification descriptors according to the 2005 Guidelines for Carcinogen Risk Assessment. In December 2016, the Agency convened the FIFRA SAP to review this evaluation and the final report with comments from the SAP panel was published in March 2017[1].

The Agency has reviewed the final report from the SAP panel and considered their recommendations in order to update the Issue Paper. It was noted that the panel did not reach consensus on the majority of the recommendations provided. As a result, revisions to the Issue Paper focused on statements where consensus appeared to be reached and are identified in this response document. Additional revisions to the Issue Paper were made to address errors and further details on approaches taken for the evaluation. Other panel recommendations where consensus was not reached are also addressed in this response document.

The responses in this document are generally grouped by charge question topics. In some cases, recommendations and/or topics span across different charge questions; however, they will only be addressed once in this document under the most appropriate topic.

Systematic Review & Data Collection:

Summary of Recommendation: The panel found that EPA's literature review methods were, in general, transparent and appropriate. There were several recommendations regarding updates to the literature search terms or supplementary suggested searches (e.g., not excluding the search term 'water', including terms for glyphosate salts, adding a search for glyphosate and immunotoxicity, and conducting a search for manufacturing data). Some panel members also suggested adding a cut-off date for the search. Additionally, specific articles were identified by some panel members for consideration. Lastly, some panel members noted that at least two people should independently select, review, and score studies and that the Issue Paper was not clear regarding this process.

EPA Response: The Agency appreciates the suggestions for improving the search terms for the systematic review of the open literature. At this time, the Agency does not believe an updated search is warranted, but if an updated search is conducted in the future, the search term recommendations will be considered at that time. A cut-off date of May 6, 2016 was used for this evaluation and referenced in Section 2.1.1 of the Issue Paper. The studies obtained for the

[1] https://www.epa.gov/sap/meeting-materials-december-13-16-2016-scientific-advisory-panel

Agency's evaluation were cross-referenced with recent internal reviews and review articles in the open literature to ensure all available and relevant studies were included. Furthermore, the Agency also cross-referenced with reviews by international agencies. The Agency considered all of the studies in these international reviews, as well additional studies identified in the systematic review. As a result, the Agency does not believe an updated search will yield additional studies that would greatly impact the overall conclusions; however, as described later in this document, an analysis of the Agricultural Health Study (AHS) cohort was recently published (Andreotti et al., 2017) with an extended follow-up period of 17.5 years. Given this analysis directly informs concerns raised by some panel members regarding the earlier analysis of the AHS cohort (De Roos et al., 2005), particularly with respect to the follow-up period necessary to evaluate risks associated with non-Hodgkin lymphoma (NHL), the findings of this study have been incorporated into the revised Issue Paper. The draft human health risk assessment for glyphosate and the revised Issue Paper will be available for public comment and additional studies may be suggested at that time for the Agency to consider.

With respect to the suggested supplementary searches, the Agency believes that it is unlikely they would alter the overall conclusions of the evaluation of human carcinogenic potential of glyphosate. There is no evidence of immunotoxicity in the glyphosate toxicological database, including a guideline immunotoxicity study (MRID 48934207). Subsequent to the SAP meeting, the Agency requested data from the registrants regarding exposure during manufacturing processes. The data submitted indicated there were very low glyphosate exposures (MRID 50463501), such that it was concluded by the registrant that follow-on studies were not warranted. This is consistent with the oral description provided by the registrant for the manufacturing process at the SAP meeting, which indicated that glyphosate is not produced until late in the process and most of the process is automated.

Lastly, we appreciate the panel's comments on the number of staff that should be involved in selecting, reviewing, and scoring studies. For the EPA's evaluation, three EPA staff members independently evaluated all of the studies and came to consensus on which studies would be considered relevant to the issue of concern (i.e., human carcinogenic potential of glyphosate). Since this was not clear in the Issue Paper, a statement has been added to Section 2.1.1.

Data Evaluation of Epidemiology:

Summary of Recommendation: The panel concluded that, overall, the Agency's review and evaluation chose relevant epidemiology studies that inform the assessment of the human carcinogenic potential of glyphosate. However, the SAP panel noted that the epidemiological data may not align with the other toxicological findings since the epidemiological studies concerned subjects exposed to glyphosate formulations, rather than glyphosate only.

EPA Response: The Agency recognizes that the epidemiological data represents human exposure to glyphosate formulations. In the absence of glyphosate only exposure data, the Agency believes these data should still be considered in this evaluation since they represent the best available data for evaluating human exposures and potential risk of cancer. As described in Section 7.0, the Agency has been collaborating with the National Toxicology Program (NTP) to

evaluate potential differences in formulation toxicity and the results of this research will be considered when available.

Summary of Recommendation: There were several suggestions from panel members related to the study quality rankings assigned to individual studies. In some of these cases, there were panel members who did not agree with the study quality ranking given by the Agency to particular studies. In other cases, some panel members thought the process should be altered, such that studies assigned a high or moderate ranking would be combined into a single group.

EPA Response: The Agency appreciates the suggestions provided by some panel members; however, studies with moderate and high rankings were treated similarly in this evaluation; therefore, shifting studies between these rankings would not impact the overall conclusions. Furthermore, there were contradictory recommendations from panel members regarding individual study quality rankings in many instances and, without consensus on these, EPA has not made any changes to the study quality rankings at this time.

OPP's Framework for Incorporating Human Epidemiologic and Incident Data in Risk Assessments for Pesticides was finalized in December 2016. This document incorporated improvements recommended by the SAP, public comments, and the experience gained since drafting the original framework. It is considered a document that will be updated from time-to-time as the Agency progresses and on as-needed basis; therefore, suggestions and recommendations from this panel on how to improve the study quality evaluation of epidemiological studies may be considered for future updates.

Summary of Recommendation: The panel noted that the choice of the "unexposed" or reference group could be a source of differences in study findings and recommended that a discussion of reference groups should be added as a point for consideration.

EPA Response: The Agency agrees that the choice of "unexposed" or referent group could contribute to differences observed between studies. Discussion has been added to Section 3.6.

Summary of Recommendation: The panel stated the Agency assumed the direction of confounding is to inflate any true effect of glyphosate in the absence of statistical adjustment and recommended that the discussion not assume the direction of confounding. It was also noted that exposure to farm animals and viruses was not considered in the evaluation as a potential confounder in NHL studies, while also noting that it is well documented that farmers are at increased risk of leukemia and lymphoma and this risk existed prior to the introduction of glyphosate.

EPA Response: As the Agency stated in Section 3.2.4 of the Issue Paper, "the direction and magnitude for confounders are, in general, difficult to determine because they are dependent upon the relationship of each confounding factor with glyphosate and the cancer under investigation." The direction of confounders was not assumed for all potential confounders; however, an analysis of the available studies for NHL that adjusted for co-exposures to other pesticides was detailed in Section 3.6 and it indicated that the direction for this confounder would be to inflate any true effect in the absence of statistical control. This analysis underscored

the importance for adjusting for this plausible confounder. The Agency agrees that exposure to farm animals and viruses is also a potential confounder for the NHL studies and that it should be noted that farmers have an increased risk of NHL, which existed prior to the introduction of glyphosate. Text has been added in Sections 3.2.4 and 3.6 to address these points.

Summary of Recommendation: The panel discussed the possibility that recall bias in retrospective case-control studies can result in over-estimation of the risk of NHL associated with pesticide exposure. Some panel members felt that key studies show evidence of recall bias, exacerbated in some cases by selection bias. One member demonstrated that the studies potentially subject to recall bias were more likely to report risk estimates greater than 1 as compared to studies that were not subject to recall bias. Other panel members felt that the necessary data to appropriately evaluate whether recall bias is present or not in the reviewed studies are not available and, in any case, the potential impacts of recall bias on the findings could not be reliably separated from those of other potential biases. Additionally, the panel noted that statistical bias was not considered in the Agency's evaluation.

EPA Response: The Agency agrees that recall bias, and in limited cases selection bias, may have played a role in the elevated risk estimates reported in case-control studies and discussed this in detail for the NHL studies in Section 3.6 of the Issue Paper. The Agency appreciates the points made by several panel members; however, the Agency does not believe any additional revisions to the Issue Paper are warranted at this time that would impact the overall conclusion. The Agency acknowledges that there was no discussion of statistical bias in the Issue Paper. There is potential for statistical bias when fitting models with too many parameters and, as noted by some panel members, the challenge of statistical bias may be present in many of the studies; however, it is unknown which direction this bias impacted the risk estimates and reanalysis of the data is not possible without access to the underlying raw data for these studies. Therefore, no additional text has been added to the Issue Paper.

Summary of Recommendation: Some panel members expressed concerns with the AHS cohort study. These concerns included a brief follow-up period, use of a relatively young cohort, utilization of a prevalent cohort, and exclusion of applicators exposed prior to 1993-1997.

EPA Response: The Agency recognized in Section 3.6 that some have argued that the follow-up period in De Roos et al. (2005) is not sufficiently long to account for the latency of NHL; however, the discussion also provides additional details that indicated that members of the cohort likely experienced a longer exposure time beyond the follow-up and that the follow-up time may not be a substantial concern for this study. Furthermore, an analysis of the AHS cohort was recently published (Andreotti et al., 2017) with an extended follow-up period of 17.5 years showed no association between glyphosate exposure and all lymphohematopoietic cancers, NHL, or any of its subtypes across exposure metrics. No association was observed in unlagged or lagged analyses, after adjustment for pesticides linked to NHL in previous AHS analyses, and after exclusion of multiple myeloma from the NHL grouping. Given the availability of this updated analysis of the AHS cohort, the discussion of latency concerns has been reduced in the in Section 3.6 of the Issue Paper.

The AHS is not considered a young cohort. Based on the data from the enrollment questionnaire, subjects <40 years old comprised only 17% or less of each exposure group (i.e., never exposed, lowest exposed, higher exposed). As stated in De Roos et al. (2005), the study identified incident, not prevalent, cases. Additionally, applicators were recruited between 1993 and 1997, but were not excluded if they were exposed prior to that time.

Other Notable Revisions/Clarifications:

- Kachuri et al. (2013) has been identified as an extended analysis of Pahwa et al. (2012). Notations have been made in Tables 3.2 and 3.4. Additionally, this has been reflected in the text of Section 3.5.2 and Section 3.6.
- Koutros et al. (2013) was incorrectly listed as a nested case-control study. Tables 3.2 and 3.3 have been updated to identify the study as a prospective cohort study. Additionally, this correction has been reflected in the text of Sections 3.3.1 and 3.4.
- Sorahan (2015) has been noted as a reanalysis of De Roos et al. (2005) in Table 3.4 and this has been further reflected in the text in Section 3.6
- A meta-risk ratio has been added to Figure 3.2.
- Text has been changed to the beginning of Section 3.6 to clarify the total number of individual studies identified and the number of studies that were used in pooled analyses by other studies.
- The discussion of expected risk estimates with respect to timing of studies and relative use across countries was removed. Although the Agency believes the discussion was incorrectly interpreted by the panel as a comparison of sales and estimated effect estimates, we believe this discussion did not strongly contribute to the overall conclusion and agreed to remove the text for simplicity.
- As suggested by the panel, the term "adjust" was used instead of "control" when referring to confounders.
- As suggested by the panel, the sample size rather than power of a study was referenced in discussions.
- The panel also suggested adding ranges of effect estimates to tables, discussion of the timing of studies, and dose-response information for NHL to Section 3.6. No revisions were made based on the comments since the range of effect estimates is provided in the discussion of each study, the timing of studies is already reported in Table C.1 of Appendix C, and a discussion of the dose-response information for NHL was already included in Section 3.6.

<u>Data Evaluation of Animal Carcinogenicity Studies:</u>

Summary of Recommendation: Overall, the panel was divided with regard to its interpretation of the rodent bioassays of glyphosate. In particular, some panel members focused on individual, statistically significant increases in tumor-responses within individual bioassays, while others focused on the lack of consistency among these responses within the unusually large dataset as a whole. Those in the latter, suggested a more holistic presentation and discussion of each tumor type.

EPA Response: The Agency considers many factors when interpreting the results of carcinogenicity studies. The 2005 EPA Guidelines for Carcinogen Risk Assessment are intended

as a guidance only and does not provide a checklist for determining whether tumor findings are related to treatment. These guidelines emphasize the importance of weighing multiple lines of evidence in reaching conclusions regarding human carcinogenic potential of chemicals. Evaluation of observed tumor findings takes into consideration both biological and statistical significance. There are several factors in the 2005 EPA Guidelines for Carcinogen Risk Assessment used in the weight-of-evidence evaluation of individual studies. The Agency's approach is consistent with the panel members that suggested a more holistic presentation and discussion of each tumor type. As a result, Section 4.8 has been revised to reflect this recommendation.

Summary of Recommendation: The panel provided numerous comments and recommendations regarding the statistical analyses and interpretation of the results by the Agency. These included the interpretation of pairwise comparisons and trend tests, suggested methods for multiple comparisons, adjustments for survival disparities, and significance levels to be applied.

EPA Response: The panel thought that the Agency gave more weight to pairwise comparisons than trend analyses and cited the following language from the 2005 Guidelines for Carcinogen Risk Assessment:

> "Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result".

However, the full paragraph is as follows:

> "Trend tests and pairwise comparison tests are the recommended tests for determining whether chance, rather than a treatment-related effect, is a plausible explanation for an apparent increase in tumor incidence. A trend test such as the Cochran-Armitage test (Snedecor and Cochran, 1967) asks whether the results in all dose groups together increase as dose increases. A pairwise comparison test such as the Fisher exact test (Fisher, 1950) asks whether an incidence in one dose group is increased over that of the control group. By convention, for both tests a statistically significant comparison is one for which p is less than 0.05 that the increased incidence is due to chance. Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result."

When read in the context of the full paragraph, the statement is referring generally to the fact that in all statistical analyses a hypothesis is rejected when statistical significance occurs. This does not imply that statistical significance alone in an individual test is sufficient to determine that observed tumors are treatment-related. As discussed above, the Agency evaluated the animal carcinogenicity data using a weight of evidence approach, which included both the trend and pairwise analyses.

The panel noted that the Sidak adjustment to account for multiple comparisons is not appropriate when multiple comparisons are not independent, such as when several different groups at different exposures are compared to the same control group, and suggested reanalyzing the data

using another multiple comparisons correction method. The Agency agrees with the panel and has reanalyzed the data using the Benjamini-Hochberg correction method, one of the suggested methods (M. Perron; 12-DEC-2017; TXR# 0057690). As part of this reanalysis, it was also noted that some of the statistical analyses included animals sacrificed at an interim time point and animals that died prior to the interim sacrifice (Lankas, 1981; Wood et al., 2009a; Brammer, 2001; Sugimoto, 1997; Wood et al., 2009b). To be consistent across all of the studies, these animals have now been excluded from the statistical analyses. Additional text has been added to Section 4.3 of the Issue Paper describing the approach taken for these analyses.

The SAP panel suggested that survival adjustments should be made in the statistical analyses of tumor incidences. The Agency routinely adjusts for survival when significant mortality differences are observed between control and treatment groups. However, in the case of glyphosate, there was no need to incorporate survival adjustments into the analyses since no significant mortality differences were observed. It was noted by the panel that some studies had low survival at termination; however, these studies were conducted according to the OCSPP carcinogenicity test guidelines, such that survival did not fall below 25% at 18 months for mice and 24 months for rats. Again, there were no mortality differences between control and treatment groups in these studies to warrant survival adjustments.

The EPA acknowledges that other comments were made in the SAP report regarding statistical analyses of tumor findings in the animal carcinogenicity studies; however, there was no consensus for these suggestions and were often made by only one member or a very small subset of members. For example, there was a suggestion to pool data across all of the studies and conduct a meta-analysis for a tumor type. EPA does not feel this type of analysis is appropriate for this data set and numerous issues were raised during public comment that would discourage using this approach. Another suggestion was made to adjust for all multiple comparisons that would be made in a single study, as demonstrated in one of the public comments. Although EPA recognizes the utility of this approach to further support our conclusions, an inordinate amount of time and resources would be required to perform these analyses across the large database of glyphosate animal carcinogenicity studies. The Agency cannot devote these resources to perform this task given the results of these analyses would not impact the overall conclusions. Lastly, one panel member noted that the Food and Drug Administration (FDA) does not require analysts to use multiple comparison procedures to adjust comparison-wise significance levels, but instead sets a small p-value of 0.005 as its cutoff level for establishing significance. This approach is not consistent with the 2005 Guidelines for Carcinogen Risk Assessment and some panel members stated that they did not agree with applying a “conservative test” since it is not necessarily an appropriate scientific goal when evaluating the potential carcinogenicity of glyphosate.

Summary of Recommendation: The panel recommended that EPA clearly explain why historical control rates were used in some analyses and not in others. The panel thought historical controls were used subjectively only in situations where concurrent control incidence levels were low, which may potentially introduce biases. As part of their discussion, the panel cited language from the 2005 Guidelines for Carcinogen Risk Assessment that states that “the most relevant historical data come from the same laboratory and the same supplier and are gathered within two or three years one way or the other of the study under review”. They further

stated that given the genetic drift observed in animal breeding populations, "historical control data that is more than three to five years old may not be representative of the animals currently being supplied".

EPA Response: In the original Issue Paper, the Agency only discussed historical controls if the concurrent control incidence appeared to be low as compared to historical control incidence; however, the Agency recognizes the concerns raised by the panel. As a result, historical control data have been presented for those studies where historical control data are available from the performing laboratory for the same species and strain for a study. These data were primarily generated within 3 years and in limited cases within 5 years of the date the study was conducted.

Summary of Recommendation: Panel members believed that the selection of 1,000 mg/kg/day as a limit dose *a priori* appeared to be an *ad hoc* decision that was not well-justified and not justified on the basis of the 2005 Guidelines for Carcinogen Risk Assessment. Some panel members did not believe that responses should be disregarded at any dose above a pre-selected "limit dose" when the maximum tolerated dose (MTD) has not been exceeded.

EPA Response: The Agency did not disregard or exclude high dose data from its evaluation. The 2005 Guidelines for Carcinogen Risk Assessment states that "practical upper limits have been established to avoid the use of excessively high doses in long-term carcinogenicity studies of environmental chemicals". The limit dose of 1,000 mg/kg/day is based on OCSPP harmonized test guidelines for carcinogenicity studies (OCSPP 870.4200 and OCSPP 870.4300), which state that the high dose need not exceed 1,000 mg/kg/day. As a result, when studies exceeded the limit dose, it was noted in the Agency's evaluation.

Summary of Recommendation: The panel noted that monotonic dose response is not identified as a criterion for a positive rodent response in the EPA's 2005 Guidelines for Carcinogen Risk Assessment. Many panel members believed that four positive tumor responses were discounted due to lack of monotonicity, with some members believing excessive weight was given to lack of a monotonic dose response in the overall weight of evidence evaluation.

EPA Response: The Agency does not believe excessive weight was given to the lack of a monotonic dose response. In the evaluation of the animal carcinogenicity studies, lack of a monotonic dose response was one line of evidence evaluated and was only noted for 3 tumor responses across 14 animal carcinogenicity studies. Additional lines of evidence were used in the weight of evidence evaluations for each tumor type to conclude that the tumor was not considered treatment-related.

Summary of Recommendation: The panel did not believe it was clear in the Issue Paper how tumors and lesions were selected for evaluation.

EPA Response: Tumors were selected for statistical analyses if the study report identified tumors as statistically significant and/or were identified by reviewers as potentially biologically significant based on the presence of an increasing monotonic dose-response and/or relative increases from concurrent controls. Preneoplastic or related non-neoplastic lesions were investigated if they were present in organs/tissues where tumors were observed and demonstrated

biological significance based on the presence of an increasing monotonic dose-response and/or relative increases from concurrent controls. For toxicological studies submitted to the Agency for pesticide registration, including animal carcinogenicity studies, detailed reviews are performed, which summarize study findings and identify effects, such as lesions and tumors, for evaluation. Text has been added to Section 4.3 of the Issue Paper.

Other Notable Revisions:

- The study by Burnett (1979) in rats was removed from the evaluation. This study was conducted with a contaminant of glyphosate, not the active ingredient glyphosate.

Data Evaluation of Genetic Toxicity:

Summary of Recommendation: The panel generally agreed with the Issue Paper's conclusion regarding the lack of genotoxicity effects of glyphosate. Panel members also agreed that, in the determination of whether glyphosate is likely to be genotoxic in humans, the EPA document focused appropriately on studies conducted in cultured mammalian cells and laboratory animal models.

One panel member recommended that this section of the document should be expanded to indicate that none of the assays employed provides an unbiased (global) measure of small insertions, deletions and rearrangements, which can result in gene copy number variation (CNV). The panel member cited evidence of inhibition of DNA replication in studies conducted in sea urchin embryos (Marc et al., 2002, 2004) and gene amplification reported in plants species undergoing selective genetic pressure (Gaines et al., 2010 and Widholm et al., 2001).

EPA Response: The Agency agrees that the assays evaluated in the Issue Paper do not directly measure CNV. However, in the approach used in the Issue Paper and supported by the panel, the Agency focused on studies conducted in mammalian test systems and internationally recognized validated test systems to determine genotoxic potential of glyphosate in humans. Since the cited studies evaluating gene CNV were not conducted in mammalian systems, the topic was not added to the Issue Paper. Furthermore, the findings do not alter the Agency's overall conclusion that there is no convincing evidence that glyphosate induces mutations *in vivo* via the oral route.

Summary of Recommendation: One panel member encouraged the agency to consider two key human biomonitoring studies in their evaluation of genotoxicity, specifically studies by Bolognesi et al. (2009) and Koureas et al. (2014).

EPA Response: These studies were considered by the Agency in the Issue Paper presented to the SAP and were assigned a low quality ranking (Section 3.3.3 and Appendix D of the Issue Paper). Bolognesi et al. (2009) was assigned a low quality ranking based on the considerations outlined in Figure 3.1. As discussed in Section 3.3.3, Koureas et al. (2014) was assigned a low quality ranking due to questionable sample size, lack of information regarding the number of exposed subjects, the use of an immunoassay that is less specific than other methods for measuring the biomarker of interest, and the outcome evaluated does not measure the consequence of genetic damage. The Agency concluded that studies assigned a low quality

ranking do not provide reliable information to evaluate associations between glyphosate exposure and genotoxic or cancer outcomes.

Data Integration & Weight-of-Evidence Analysis Across Multiple Lines of Evidence

Summary of Recommendation: The Issue Paper presented to the SAP concluded that the strongest support is for glyphosate to be classified as "not likely to be carcinogenic to humans at doses relevant for human health risk assessment". There were concerns with the classification descriptor including "at doses relevant for human health risk assessment" as a condition. Some members agreed with "not likely to be carcinogenic to humans", while others believed it should be "suggestive evidence of carcinogenic potential". An additional suggestion was given to use a different classification descriptor, such as "no credible evidence of carcinogenicity" or "equivocal", as such the panel was not in consensus regarding the Agency's determination.

EPA Response: The Agency agrees with the classification descriptor of "not likely to be carcinogenic to humans" without the condition of "at doses relevant for human health risk assessment". The condition "at doses relevant for human health risk assessment" was removed because the panel believed that the focus of this evaluation of the carcinogenic potential of glyphosate should be hazard identification since it is the first step of a risk assessment. The text has been updated accordingly in the revised Issue Paper. The Agency still believes that the strongest support is for "not likely to be carcinogenic to humans". Suggestions of different classification descriptors, such as "no credible evidence of carcinogenicity" or "equivocal" are not appropriate since these descriptors are not consistent with the 2005 Guidelines for Carcinogen Risk Assessment. The classification descriptors "not likely to be carcinogenic to humans" and "suggestive evidence of carcinogenic potential" both utilize a reference dose approach; therefore, a quantitative cancer risk assessment would not be required for either of these descriptors. The Agency also noted that none of the panel members believed glyphosate should be classified as "likely to be carcinogenic to humans" or "carcinogenic to humans".

Summary of Recommendation: Some panel members hypothesized the rodent bioassay data were consistent with glyphosate acting as a weak tumor promoter and felt that the Issue Paper would benefit from a discussion of the hypothesis that glyphosate may be a weak cancer promoter. Other panel members felt that such a conclusion was speculative and ignored the lack of reproducibility across animal carcinogenicity studies.

EPA Response: The Agency does not believe a discussion of this hypothesis should be added to the Issue Paper since the Agency concluded none of the tumor findings were treatment-related. Furthermore, the Agency is not aware of any mechanistic data to support this hypothesis and, therefore, would not include speculative information in the analysis.

Summary of Recommendation: The panel noted that the 2010 draft "Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment" discusses the utility of incident data and recommended including a discussion of human incident data in the Issue Paper.

EPA Response: A Tier II incident report for glyphosate has been completed by the Agency (S. Recore; 6-FEB-2014; D417808). As stated in this report, the acute health effects reported are

consistent with the previous incident report for glyphosate, and the other databases and medical literature reviewed. These health effects primarily include dermal, ocular, and respiratory effects. Effects are generally mild/minor to moderate meaning the symptoms were minimally traumatic and resolved rapidly. The relatively high (absolute) number of reported glyphosate incidents across the reviewed databases is likely a result of glyphosate being among the most widely used pesticides by volume. It should be noted that most of the incidents reported are minor in severity.

The panel itself recognized in its recommendation that incident data have little direct relevance to cancer outcomes. The Agency does not believe that incorporation of human incident data would contribute to the evaluation of the human carcinogenic potential of glyphosate. Human incident data provides insight on potential acute or short-term effects from single exposures. As such, these data do not have the ability to strongly inform the carcinogenic potential of a chemical following long-term exposures. Incident data can provide useful, complementary information that assists the Agency in evaluating real-world risks of pesticides; however, the role of this data is primarily to inform risk assessment/risk management decisions, such as indicating a potential need for a new risk assessment or new risk management measures, evaluating the success of risk mitigation actions after implementation, and targeting possible enforcement activities.