Glyphosate Issue Paper: Evaluation of Carcinogenic Potential

EPA's Office of Pesticide Programs

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Exerpts

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Proposed Conclusions Regarding the Carcinogenic Potential of Glyphosate

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. Following the introduction of glyphosate-resistant crops in 1996, glyphosate use increased dramatically; however, glyphosate use has stabilized in recent years due to the increasing number of glyphosate-resistant weed species.

Since its registration in 1974, numerous human and environmental health analyses have been completed for glyphosate, which consider all anticipated exposure pathways. Glyphosate is currently undergoing Registration Review. As part of this process, the hazard and exposure of glyphosate are reevaluated to determine its potential risk to human and environmental health using current practices and policies. The human carcinogenic potential of glyphosate has been evaluated by the agency several times. As part of the current evaluation for Registration Review, the agency has performed a comprehensive analysis of available data from submitted guideline studies and the open literature. This includes epidemiological, animal carcinogenicity, and genotoxicity studies.

An extensive database exists for evaluating the carcinogenic potential of glyphosate, including 23 epidemiological studies, 15 animal carcinogenicity studies, and nearly 90 genotoxicity studies for the active ingredient glyphosate. These studies were evaluated for quality and results were analyzed across studies within each line of evidence. (p 140)

For cancer descriptors, ***the available data and weight-of-evidence clearly do not support the descriptors "carcinogenic to humans", "likely to be carcinogenic to humans", or "inadequate information to assess carcinogenic potential"****. For the "suggestive evidence of carcinogenic potential" descriptor, considerations could be looked at in isolation; however, following a thorough integrative weight-of-evidence evaluation of the available data, the database would not support this cancer descriptor.* ***The strongest support is for "not likely to be carcinogenic to humans"*** *at doses relevant to human health risk assessment.* (p 141)

Epidemiology

(studies related with cancer incidence in humans)

> *A total of 24 epidemiological studies from the open literature were identified as appropriate for detailed evaluation. Of these, 23 studies were considered informative with regard to the carcinogenic potential of glyphosate. There was no evidence of an association between glyphosate exposure and solid tumors. There was also no evidence of an association between glyphosate exposure and leukemia, or HL.*) (p 63)

Open questions, insufficient data:

Multiple Myeloma

> *Overall, the available epidemiologic evidence for an association between glyphosate and risk of multiple myeloma is inadequate to assess the carcinogenic potential at this time due to the potential for confounding in three of the four studies, the limited observation of a possible exposure-response relationship in a single study, and concerns whether restricted datasets were representative of the whole cohort.*

NHL (Non-Hodgkin Lymphoma)

> *Due to study limitations and contradictory results across studies of at least equal quality, a conclusion regarding the association between glyphosate exposure and risk of NHL cannot be determined based on the available data.*

Animal Carcinogenicity

> *Glyphosate has been extensively tested in rodents to evaluate its carcinogenic potential. A total of 15 rodent carcinogenicity studies were considered to be adequate for this analysis. Nine studies were conducted in the rat and 6 studies were conducted in the mouse.* (p 95)
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> *…*
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> *In 5 of the 9 rat studies conducted with glyphosate, no tumors were identified for detailed evaluation. Of the remaining 4 rat studies, a statistically significant trend was observed for tumor incidences in the testes, pancreas, liver, thyroid, or mammary gland; however, the agency determined that these tumor findings are not considered to be related to treatment,*
>
> *…*
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> *In 2 of the 6 mouse studies, no tumors were identified for detailed evaluation. In the remaining 4 mouse studies, 3 observed a statistically significant trend in tumor incidences in the hemangiosarcomas, lung adenomas, malignant lymphomas or hemangiomas; however, the agency determined that none of the tumors observed in the mouse are treatment related,*
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> *…*
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> *Based on the weight-of-evidence, the agency has determined that any tumor findings observed in the rat and mouse carcinogenicity studies for glyphosate are not considered treatment-related. Tumor findings observed at the highest doses tested were also not reproduced in studies in the same animal strain at similar or higher doses. Furthermore, even if the high-dose tumors were*

considered treatment-related, these findings are not considered relevant for human health risk assessment based on the use pattern and potential exposures for glyphosate. *(p 96)*

Genotoxicity

(Property of chemical agents that damages the genetic information within a cell causing mutations, which may lead to cancer)

The totality of the genetic toxicology information was evaluated using a weight of evidence approach to determine the genotoxic potential of glyphosate. This involves the integration of in vitro and in vivo results as well as an overall evaluation of the quality, consistency, reproducibility, magnitude of response, dose-response relationship and relevance of the findings. (p 126)

…

Evidence of primary DNA damage
Glyphosate technical is not considered to be electrophilic and did not induce DNA adducts in the liver or kidney at an i.p. dose of 270 mg/kg. However, evidence of DNA strand breaks were reported in a number mammalian cell studies using the comet assay. Additionally, transient increases in alkali labile sites in the liver and kidney of mice and an induction of 8-OHdG in DNA were seen in the livers of mice following i.p. injections with 300 mg/kg glyphosate. These effects were seen at high doses for the i.p. route in mice (LD_{50} for mouse =130 mg/kg; NTP, 1992). However, due to technical limitations identified in a number of these studies (e.g. use of cancer cell lines that have not been well-characterized, atypical exposure protocols and no indication of blind to treatment), caution should be exercised in interpreting the results.

In vitro mutations
Glyphosate technical was negative in all 39 studies for mutagenicity in bacteria. In the four studies that tested for gene mutations in mammalian cells in vitro, no increase in mutations were observed.

In vitro chromosomal alterations
Mixed results were observed in studies evaluating in vitro chromosomal alterations with glyphosate treatment…

Mammalian in vivo chromosomal alterations
All three in vivo mammalian studies evaluating chromosomal aberrations with glyphosate technical were negative… (p 127)

Conclusion for Glyphosate

The overall weight of evidence indicates that there is no convincing evidence that glyphosate induces mutations in vivo via the oral route…
While there is limited evidence genotoxic for effects in some in vitro experiments, in vivo effects were given more weight than in vitro effects particularly when the same genetic endpoint was measured, which is consistent with current OECD guidance. The only positive findings reported in vivo were seen at relatively high doses that are not relevant for human health risk assessment. (p 128)

Cancer Classification

…the available data and weight-of-evidence clearly do not support the descriptors "carcinogenic to humans", "likely to be carcinogenic to humans", or "inadequate information to assess carcinogenic potential"…
It could be argued that the "suggestive evidence of carcinogenic potential" descriptor would be appropriate….
In summary, considering the entire range of information for the weight-of-evidence, the evidence outlined above to potentially support the "suggestive evidence of carcinogenic potential" descriptor are contradicted by other studies of equal or higher quality and, therefore, the data do not support this cancer classification descriptor… (p 137)

…

For the "not likely to be carcinogenic to humans" descriptor, one of the considerations is whether there is "convincing evidence that carcinogenic effects are not likely below a defined dose range". In the case of glyphosate, effects are not likely below 500 mg/kg/day based on oral studies. *(p 139)*

…

Overall, there is not strong support for the "suggestive evidence of carcinogenic potential" cancer classification descriptor based on the weight-of-evidence, which includes the fact that even small, non-statistically significant changes observed in animal carcinogenicity and epidemiological studies were contradicted by studies of equal or higher quality. The strongest support is for "not likely to be carcinogenic to humans" at the doses relevant to human health risk assessment for glyphosate. *(p 140)*