Comments on the IARC classification of glyphosate as a probable human carcinogen

Committee on Science, Space and Technology

February 6, 2018

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The IARC Monograph Working Groups evaluate three types of evidence in assessing the potential carcinogenicity of an agent; animal carcinogenicity studies, epidemiologic studies of cancer risk in humans, and "mechanistic and other relevant data". For each of the first two categories (animal and human studies) the evaluation leads to a conclusion that there is sufficient evidence of carcinogenicity, limited evidence of carcinogenicity, inadequate evidence of carcinogenicity, or evidence suggesting lack of carcinogenicity. The evaluation of mechanistic and other relevant data is not as formalized, and there is some subjectivity in how this evaluation contributes to the final carcinogen classification. The overall classification of an agent depends largely on the summary conclusions regarding the strength of evidence from the animal studies and the human studies. Of particular importance with regard to my European Journal of Cancer Prevention paper on the glyphosate classification, if the Working Group concludes that there is sufficient evidence that the agent is an animal carcinogen then the agent will be assigned to Group 2B (possibly carcinogenic to humans), Group 2A (probably carcinogenic to humans), or Group 1 (carcinogenic to humans).

In explaining occasional differences between IARC classifications and those of other regulatory bodies worldwide, IARC often notes that its Monograph Program evaluates cancer hazard rather than cancer risk. The following paragraph is from page 2 of the current Preamble to every published Monograph.

> A cancer 'hazard' is an agent that is capable of causing cancer under some circumstances while a cancer 'risk' is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. The *Monographs* are an exercise in evaluating cancer hazards, despite the historical presence of the word 'risks' in the title. The distinction between hazard and risk is important, and the *Monographs* identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could endanger risks that are significantly higher.

This distinction could provide a plausible explanation for why the conclusion in IARC Monograph 112 on the carcinogenic potential of glyphosate differed from

that of other bodies (e.g., the EFSA and JMPR, both of which concluded that glyphosate exposure from food consumption was not likely to be carcinogenic), but my paper points out a more basic problem with the IARC glyphosate classification.

Additional questions have been raised about the IARC glyphosate deliberations, including the selection of studies IARC chose to rely upon in evaluating glyphosate (IARC has stricter criteria for selecting studies than many regulatory bodies) and the makeup of the Working Group (e.g., the inclusion of an invited specialist affiliated with the Environmental Defense Fund). These issues are not considered in my paper. My paper critiques the deliberations of the Working Group that evaluated glyphosate on IARC's terms. I accept that IARC is evaluating hazard rather than risk, that the IARC criteria for determining carcinogenic hazard are reasonable, and that the body of studies relied upon by IARC is sufficiently complete to provide a valid assessment of the carcinogenic potential of glyphosate. My critique concludes that the IARC classification of glyphosate as a probable carcinogen was the result of a flawed and incomplete evaluation of the very rodent cancer studies that IARC relied upon. Although the Working Group concluded that there was sufficient evidence that glyphosate was an animal carcinogen, I conclude that a proper summary of the rodent studies relied upon by IARC would not even support the conclusion that there is limited evidence that glyphosate is an animal carcinogen. Without the conclusion that there is sufficient evidence that glyphosate is animal carcinogen, the IARC criteria would not have supported the overall classification of glyphosate as a probable human carcinogen.

IARC concluded that there was sufficient evidence that glyphosate caused cancer in animals, primarily on the basis of two studies in CD-1 mice. In the first study, groups of 50 male and female CD-1 mice were fed diets containing 0, 1000, 5000, and 30000 parts per million glyphosate over a two year period. The original study report noted a positive trend in renal tubule adenomas in male CD-1 mice. The tumor rates were 0/49, 0/49, 1/50, and 3/50 at increasing dose levels ($p=0.019$). The US EPA requested additional pathological examination of renal tumors in this study, including the convening of a Pathology Working Group. One

additional renal tubule adenoma was discovered in the unexposed control group, and three of the original renal tubule tumors were upgraded from adenomas to carcinomas. Thus the final tumor rates after the pathological review for carcinomas were 0/49, 0/49, 1/50, and 2/50 (p=0.063), and for carcinomas and adenomas combined were 1/49, 0/49, 1/50, and 3/50 (p=0.065). These marginally significant findings were considered particularly consequential by the IARC Working Group because of the alleged rarity of such renal tumors in CD-1 mice, and it was concluded that this study showed that glyphosate caused renal tubule tumors in male CD-1 mice.

There was no *a priori* expectation that glyphosate should cause kidney tumors, and ordinarily such a small increase in tumors with increasing dose level would not be considered especially noteworthy, particularly since around 20 organs and tissues are typically evaluated pathologically in rodent carcinogenicity studies. Nonetheless, even the small observed increase would be of concern if there was also evidence of an increase in renal tubule tumors for female mice in the same study or for male or female mice in the second CD-1 mouse study relied upon by IARC. Thus, the following sentence from the glyphosate chapter of Monograph 112 in the discussion of the first CD-1 mouse study is remarkable: "No data on tumours of the kidney were provided for female mice." IARC has been evaluating rodent carcinogenicity studies for over 40 years, and is aware that the renal tumor rates for female mice would have been provided in the original study report that provided the male tumor rates. IARC staff should have been able to acquire the female tumor rates. In fact, they should have been motivated to acquire the female renal tumor rates because of the male results. I obtained the female renal tubule tumor rates for the first CD-1 mouse study from a review of glyphosate rodent studies published in Critical Reviews in Toxicology (Greim et al., 2015). For females the tumor rates were 0/50, 0/50, 0/50, and 0/50. That is, there was no evidence from female mice exposed to the same high levels of glyphosate for an increase in kidney tumors. The review paper by Greim et al. was discussed briefly in the summary of the Working Group deliberations in Monograph 112, but the review and its accompanying supplemental material were, for the most part, discounted.

Even though there was no evidence that glyphosate caused tumors in female CD-1 mice in this study, the Working Group still might have argued for a sex-specific carcinogenic effect, particularly if there was evidence of such an effect in the second CD-1 mouse study relied upon by IARC. Inexplicably, however, in spite of devoting two paragraphs to the discussion of renal tubule tumors observed in first CD-1 mouse study, there is no mention whatsoever of kidney pathology in the one paragraph of the Monograph 112 glyphosate chapter devoted to the second CD-1 mouse study. Again, IARC staff should have been motivated to acquire the renal tumor rates from the second study because of the male results from the first study. No explanation has been offered by IARC for this disturbing omission of relevant kidney tumor data. The renal tubule tumor rates from the second study were also provided in the supplemental material of the Greim et al. review paper. Male and female mice were exposed to dose levels slightly lower than those in the first CD-1 mouse study, and for males the renal tubule tumor rates at increasing glyphosate exposure level were 2/50, 2/50, 0/50, and 0/50 ($p=0.042$ for an ***inverse*** association with glyphosate dose level). That is, while a marginally significant increase in renal tubule tumors was observed for males in the first mouse study based on small numbers of tumors, a marginally significant decrease in renal tubule tumors was observed in the second mouse study based on small numbers. It should also be noted that two of the supposedly extremely rare renal tumors were observed in the unexposed mice in this study. Taken together these two studies provide no evidence whatsoever to support the conclusion that glyphosate causes renal tumors in male mice. For female mice in the second study the tumor rates were 0/50, 0/49, 0/50, and 0/50. Thus, there is no evidence from the two mouse studies relied upon by the Working Group that glyphosate causes renal tumors in male or female mice.

My published paper notes other instances in which rodent tumor rates which might support a conclusion that glyphosate is associated with tumor risk were included in the Monograph 112 glyphosate deliberations, while tumor rates from the same studies that do not support an association between glyphosate exposure and tumor risk were excluded. Such systematic exclusion of exculpatory evidence is outrageous, particularly when it is practiced by an influential source

such as the IARC Monograph Program. My paper was published online in August of 2016, and not one of the claims in the paper has been refuted. In addition to critiquing the Monograph 112 Working Group summary of rodent studies I also raised questions about the summary of epidemiologic studies by the Working Group. Publications since August 2016 and depositions of key Working Group members relating to lawsuits filed against Monsanto after the IARC glyphosate classification was announced in March of 2015 have substantiated the facts presented, and questions raised, in my paper.

I have no conflict of interest whatsoever with regard to glyphosate or Monsanto. Since my retirement in June of 2016 I have received no payment for any of my continued scientific efforts. No payment was received for writing the European Journal of Cancer Prevention paper, nor was I requested by anyone to write the paper. The decision to write the paper was mine alone, after I discovered the serious scientific errors made by IARC in the glyphosate deliberations. Nobody else contributed in any way to the writing of the paper.

References

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