On the International Agency for Research on Cancer classification of glyphosate as a probable human carcinogen

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The recent classification by International Agency for Research on Cancer (IARC) of the herbicide glyphosate as a probable human carcinogen has generated considerable discussion. The classification is at variance with evaluations of the carcinogenic potential of glyphosate by several national and international regulatory bodies. The basis for the IARC classification is examined under the assumptions that the IARC criteria are reasonable and that the body of scientific studies determined by IARC staff to be relevant to the evaluation of glyphosate by the Monograph Working Group is sufficiently complete. It is shown that the classification of glyphosate as a probable human carcinogen was the result of a flawed and incomplete summary of the experimental evidence evaluated by the Working Group. Rational and effective cancer prevention activities depend on scientifically sound and unbiased assessments of the carcinogenic potential of suspected agents. Implications of the erroneous classification of glyphosate with respect to the IARC Monograph Working Group deliberative process are discussed. European Journal of Cancer Prevention 00:000–000 Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

In March 2015, the International Agency for Research on Cancer (IARC) convened a Monograph Working Group to assess the carcinogenicity of five organophosphate pesticides. As a result of this Working Group for volume 112 of the IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, the herbicide glyphosate was assigned a 2A classification, indicating that glyphosate is ‘probably carcinogenic to humans’ (Guyton et al., 2015; IARC, 2015a). The IARC classification is at variance with other recent evaluations of the carcinogenic potential of glyphosate (Bundesinstitut für Risikobewertung, 2015), and has been criticized widely for a variety of reasons, including the makeup of the Working Group, the selection of studies to be considered in the evaluation process, and the IARC goal of evaluating carcinogenic hazard (defined by IARC as the ‘capability of causing cancer under some circumstances’) rather than carcinogenic risk (e.g. the likelihood of causing cancer under actual exposure conditions) (Academics Review, 2015; Science Media Centre, 2015; Porterfield, 2016).

Subsequent to the IARC classification, an evaluation of glyphosate by the European Food Safety Authority (EFSA) concluded that glyphosate was unlikely to pose a carcinogenic threat to humans (European Food Safety Authority, 2015). Although there are differences in the evaluation criteria resulting in the two conflicting conclusions of carcinogenic potential, an open letter with 96 signees was sent to the EFSA commissioner strongly opposing the EFSA decision on glyphosate and endorsing the IARC classification (Portier et al., 2015), with subsequent publication of a related 94-author commentary (Portier et al., 2016). The corresponding author, Christopher Portier, was an ‘Invited Specialist’ for the IARC Monograph 112 Working Group that evaluated glyphosate (Guyton et al., 2015; IARC, 2015b). Portier’s participation in the Working Group evaluating glyphosate has been questioned because of his affiliation with the advocacy group, Environmental Defense Fund, particularly as researchers with ties to industry are usually excluded from participation on IARC Working Groups (IARC, 2015b; Porterfield, 2016; Zaruk and Entine, 2016).

A recent joint meeting of the United Nations and WHO panels on the health effects of pesticide residues (JMPR) reviewed the potential carcinogenicity of glyphosate at levels consumed in food (World Health Organization, 2016a). The JMPR review concluded that glyphosate was unlikely to pose a carcinogenic risk to humans from dietary exposure (World Health Organization, 2016a). This conclusion was not considered to be contradictory to the IARC classification because of the possibility that glyphosate might cause cancer at higher exposure levels or through nondietary routes of exposure (World Health Organization, 2016b). The controversy surrounding the IARC classification of glyphosate as a probable carcinogenic hazard, however, remains unresolved.

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Criticisms noted previously of the IARC Monograph 112 Working Group and the IARC glyphosate classification all have some merit, but it has not been generally recognized that IARC’s 2A classification for glyphosate is based on an incomplete and flawed evaluation of those studies determined by the IARC staff to be relevant to assessing the carcinogenic potential of glyphosate. This is particularly true for the evaluation of animal carcinogenicity studies.

Animal studies
For studies discussed below, the strength of the dose–response in tumor rates with increasing glyphosate exposure level will be measured using two-sided \( P \)-values on the basis of the exact Cochran–Armitage trend test (Gart et al., 1986). IARC concluded that there was sufficient evidence that glyphosate caused cancer in animals, primarily on the basis of two studies in CD-1 mice (IARC, 2015a). In the first study, groups of 50 male and female CD-1 mice were fed diets containing 0, 1000, 5000, and 30 000 ppm glyphosate. This study reported a positive trend in renal tubule adenomas in male CD-1 mice (0/49, 0/49, 1/50, and 3/50; \( P = 0.019 \)). Despite the small numbers of tumors, this finding was deemed consequential because of the relative rarity of renal tubule tumors in CD-1 mice. The United States (US) Environmental Protection Agency requested additional pathological examination of renal tumors in this study, including the convening of a Pathology Working Group (IARC, 2015a). As a result of the additional pathology, one new renal tubule adenoma was discovered in a control animal and three of the four original renal tubule tumors were upgraded from adenoma to carcinoma. This resulted in conventionally nonsignificant positive trends in carcinomas (0/49, 0/49, 1/50, and 2/50; \( P = 0.063 \)) and in adenomas and carcinomas combined (1/49, 0/49, 1/50, and 3/50; \( P = 0.065 \)). On the basis of these marginal findings, the IARC Working Group concluded that this study showed that glyphosate caused renal tubule tumors in male CD-1 mice.

Immediately after the sentence in the IARC Monograph 112 glyphosate chapter reporting the original renal tubule adenoma findings in the first CD-1 mouse study for males comes the following remarkable sentence: ‘No data on tumours of the kidney were provided for female mice.’ Unstated is who exactly was supposed to provide these data on female mice to IARC. IARC has been evaluating the potential for carcinogenicity of agents for 40 years and the IARC staff is certainly aware of how rodent carcinogenicity studies are routinely carried out and reported (e.g. pathology findings are reported for a variety of organs and systems, including the kidneys, for both male and female animals). Yet, despite the allegedly rigorous, transparent, thorough, and careful evaluation process followed by Monograph Working Groups (Pearce et al., 2015), IARC apparently made no effort to obtain the kidney pathology findings for female CD-1 mice. In fact, the tumor summaries for this and the other rodent carcinogenicity studies of glyphosate relied upon by the Working Group were made available to IARC before the Monograph 112 Working Group meeting in a review paper (Greim et al., 2015; IARC, 2015a). A supplement to the review paper contains the summary pathology tables for each of the rodent studies reviewed. The CD-1 mouse study in question is mouse study 10 in the Greim et al. (2015) review, and the pathology table reports no renal tubule tumors in female CD-1 mice (0/50, 0/50, 0/50, and 0/50). Thus, there is no support in female mice for the marginal findings in male mice with respect to kidney tumors.

Even if the female CD-1 mouse data had been included in the IARC deliberations, the Working Group might still have concluded that there was evidence of a sex-specific carcinogenic effect. An even more disturbing omission from the Working Group deliberations, however, argues against this interpretation. The second CD-1 mouse study reported in the IARC Monograph glyphosate chapter is mouse study 11 in the Greim et al. (2015) review. Inexplicably, particularly in view of the significance given to the marginal kidney tumor findings in the previously evaluated CD-1 mouse study, the paragraph in the IARC glyphosate chapter reporting on the second CD-1 mouse study does not even mention kidney pathology. In the second CD-1 mouse study, groups of male and female mice were fed diets with glyphosate at doses calibrated to result in exposure levels of 0, 100, 300, and 1000 mg/kg of body weight. No renal tubule tumors were observed in female mice in this study (0/50, 0/49, 0/50, and 0/50). Kidneys were examined for 50 male mice in each of the four exposure groups in this study, and two renal tubule adenomas (one in the control group and one in the lowest dose group) and two renal tubule carcinomas (again, one in the control group and one in the lowest dose group) were observed. That is, although a few of these relatively rare renal tubule tumors were observed in males in the first CD-1 mouse study, primarily in the two highest dose groups, the few such tumors in males in the second CD-1 mouse study were observed only in the control and the lowest dose groups. It is apparent that these two studies together provide no evidence whatsoever to support the hypothesis that glyphosate causes renal tubule tumors in male CD-1 mice.

The paragraph on the second CD-1 mouse study in the IARC glyphosate chapter reports an increase in hemangiosarcomas in male mice (0/50, 0/50, 0/50, 4/50; \( P = 0.0036 \)). As was the case with kidney tumors in the first CD-1 mouse study, there was no supporting evidence of increased hemangiosarcoma risk in female mice at the highest exposure levels in this study (0/50, 2/49, 0/50, and 1/50). Similar to the situation with kidney tumors, however, there is no mention of hemangiosarcomas in the discussion of the first CD-1 mouse study.

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in the glyphosate chapter despite the reported hemangiosarcoma increase in the second study. A few hemangiomas and hemangiosarcomas (reported as hemangioendotheliomas in the summary pathology tables) were reported in the first CD-1 mouse study. For male mice, one hemangioma was reported in the lowest dose group and one hemangiosarcoma was reported in the middle dose group, providing no support for the increased rate of hemangiosarcomas at the highest glyphosate exposure level among males in the second CD-1 mouse study. More of these blood vessel tumors were reported for females than for males in the first CD-1 mouse study. They were reported by organ site in the summary pathology tables for the first study, but assuming that no mouse had more than one such tumor, the summary incidence rates in female mice for hemangiomas and hemangiosarcomas are 1/50, 1/50, 6/50, and 4/50 ($P=0.302$) and for hemangiosarcomas, these are 1/50, 0/50, 5/50, and 4/50 ($P=0.130$). All except one of the hemangiomas and hemangiosarcomas in the two studies were observed in organs or tissues in which they most often occur in control CD-1 mice (i.e. spleen, liver, mesentry, and uterus). The evaluation of both mouse studies together does not provide credible evidence that glyphosate causes blood vessel tumors in CD-1 mice.

Only two statistically significant tumor increases were observed in the two CD-1 mouse experiments relied upon by the IARC Working Group in arriving at the glyphosate carcinogen classification; they were observed only among male mice, involved a small number of animals, and were not supported by increased tumor rates among female mice in the same study or male mice in the other study. The first increase was for renal tubule adenomas in the original pathology report in the first study and the second increase was for hemangiosarcomas in the second study. The claim that significant increases in malignant tumors were observed in both CD-1 mouse studies evaluated by the IARC glyphosate Working Group (Portier et al., 2015) is incorrect, and a reasonable synthesis of the evidence from both mouse studies does not support a conclusion that glyphosate is a mouse carcinogen.

Although the rat carcinogenicity studies reviewed by the IARC Working Group provide no evidence that glyphosate causes malignant tumors, the IARC glyphosate chapter concluded that there was some evidence that glyphosate caused adenomas, particularly pancreatic islet cell adenomas in male Sprague–Dawley rats. Such tumors are not particularly rare in Sprague–Dawley rats, and the evaluation of the three Sprague–Dawley rat studies relied upon by IARC does not provide evidence of a dose–response relation with glyphosate exposure. Tumor rates were reported in the glyphosate chapter for only two of the Sprague–Dawley rat studies. In one study, the observed incidence rates for pancreatic islet cell adenomas in a control group and three groups exposed to increasing glyphosate levels among male rats are 1/58, 8/57, 5/60, and 7/59. There is no evidence of a dose–response in the three glyphosate-exposed groups, and as noted in an earlier review of this study by the World Health Organization (1994) the control group rate appears to be unusually low. In a second study, the observed incidence rates for pancreatic islet cell adenomas in male rats are 0/50, 5/49, 2/50, and 2/50, again providing little evidence of increased tumor rates with increasing glyphosate exposure. The pancreatic islet cell adenoma rates are not reported in the IARC glyphosate chapter for the third Sprague–Dawley rat study evaluated by the Working Group, but it is rat study 3 in the Greim et al. (2015) review. The rates for male rats in this study in the control group and four increasing glyphosate exposure levels are 7/50, 1/24, 2/17, 2/21, and 1/49. This is a mirror image of the tumor pattern in the first Sprague–Dawley rat study, which the Working Group considered to provide evidence that glyphosate might induce tumors, in that it is the highest glyphosate exposure level for which the pancreatic islet cell adenoma rate appears to be unusually low, and there is no evidence of a dose–response in the other four exposure groups. A synthesis of the data from all three rat studies does not support the conclusion that glyphosate is associated with increased pancreatic islet cell adenoma rates in male Sprague–Dawley rats.

The IARC Working Group concluded that increased incidence rates in one of the three Sprague–Dawley rat studies of liver adenomas in males (2/44, 2/45, 3/49, and 7/48; $P=0.035$) and thyroid C-cell adenomas in females (2/57, 2/60, 6/59, and 6/55; $P=0.068$) also provided evidence that glyphosate is an animal carcinogen. The other two Sprague–Dawley studies relied upon by the Working Group, however, provided no evidence that glyphosate increased the risk of liver or thyroid C-cell adenomas, and none of the three Sprague–Dawley studies provided evidence that glyphosate was associated with increased incidence of liver carcinomas or thyroid C-cell carcinomas (Greim et al., 2015). The highlighting of selective marginally significant tumor increases in a single study without noting the complete absence of supporting evidence of tumor increases in two other studies using the same rat strain is a highly questionable scientific practice. Once again, a synthesis of the data from all three rat studies does not provide evidence in support of the hypothesis that glyphosate is associated with increased liver or thyroid C-cell tumor rates in Sprague–Dawley rats.

Glyphosate would not have been classified by IARC as a probable human carcinogen except for the Working Group’s conclusion that there was sufficient evidence of carcinogenicity in animals. When all relevant data from the rodent carcinogenicity studies of glyphosate relied upon by the Working Group are evaluated together, it is clear that the conclusion that there is sufficient evidence...
that glyphosate is an animal carcinogen is not supported empirically. Even a conclusion that there is limited evidence of animal carcinogenicity would be difficult to support on the basis of the rodent carcinogenicity assays of glyphosate reviewed by the IARC Working Group.

Epidemiology

There is general agreement among various national and international agencies and groups that have evaluated glyphosate, including IARC, that the evidence for human carcinogenicity is limited. The IARC Monograph 112 Working Group focused on non-Hodgkin’s lymphoma (NHL), but the case made by IARC for a possible role of glyphosate in the etiology of NHL is quite weak (Science Media Centre, 2015). For example, the only significant finding reported for NHL and glyphosate in a US study (De Roos et al., 2003) is of questionable epidemiological weight. Glyphosate was one of 47 different pesticides evaluated for associations with NHL in this pooled analysis of case-control studies, and each pesticide was assessed using two different statistical methods. A significant association was reported between glyphosate and NHL for only one of the statistical methods applied (standard logistic regression). As is common practice with IARC Working Groups, the relative risk estimate and confidence interval from the logistic regression that are reported in the IARC glyphosate chapter are reproduced exactly as presented in the published paper (De Roos et al., 2003), without any adjustment for the large number of pesticides evaluated and the multiple statistical comparisons performed in the study. This practice exaggerates the significance of the reported risk estimate.

The sporadic positive findings for NHL and glyphosate observed in case-control studies were not confirmed in a large US cohort study, the Agricultural Health Study (AHS) (De Roos et al., 2005), and this appeared to temper somewhat the IARC Working Group conclusion on the evidence for human carcinogenicity of glyphosate. Portier et al. (2015, 2016) discount the AHS glyphosate finding because of the small number of NHL cases included in the 2005 analysis, but this raises a question about the investigation of a possible association between glyphosate exposure and NHL in the AHS. An updated assessment of NHL risk within the AHS was published recently (Alavanja et al., 2014). This study was based on follow-up through 2010 in North Carolina and through 2011 in Iowa, so that it would have added a decade of additional NHL cases to the earlier evaluation of glyphosate in the AHS (De Roos et al., 2005). Inexplicably, although previous studies evaluating associations between a single disease and multiple pesticides in the AHS have included pesticides from all four classes, insecticides, herbicides, fungicides, and fumigants (Alavanja et al., 2003, 2004; Engel et al., 2005; Lee et al., 2007; Andreotti et al., 2009; Landgren et al., 2009; Dayton et al., 2010; Dennis et al., 2010; Kamel et al., 2012; Koutros et al., 2013; Starling et al., 2014), the NHL update excluded all herbicides (Alavanja et al., 2014). The NHL update excluded all herbicides (Alavanja et al., 2014). The Overall Chair of the March 2015 Working Group for IARC Monograph 112 was a coauthor on the NHL update paper (Alavanja et al., 2014). In view of the potential value of an updated analysis of glyphosate and NHL risk within the AHS in the 2015 IARC Working Group deliberations on glyphosate, the exclusion of herbicides from the 2014 paper is difficult to comprehend or justify. Updated analyses in the AHS of herbicides using the NHL cases and statistical methods of the recent paper (Alavanja et al., 2014) should be published as soon as possible to provide for a more complete evaluation of the possible association between glyphosate exposure and NHL risk in humans.

IARC Working Group composition and deliberative process

The incomplete and flawed synthesis of experimental data resulting from the glyphosate deliberations of the Monograph 112 Working Group is difficult to reconcile with the recent unconditional defense of the IARC Monograph Program evaluation process by 124 researchers from around the world (Pearce et al., 2015). Despite questions that have been raised about IARC Working Group composition and certain dynamics of consensus decision making in ad-hoc deliberative bodies that can result in a considerable potential for error (Brown, 2000; Sunstein, 2006; Boffetta et al., 2009; McLaughlin et al., 2010a, 2010b, 2011; Erren, 2011; McLaughlin and Tarone, 2013), IARC officials and defenders apparently see no reason to consider modifications to what they consider to be ‘the best approach available’ (Wild and Cogliano, 2011; Pearce et al., 2015). Evidence from recent Working Groups suggests that steps taken in 2005 to ‘increase transparency’ in the IARC Monograph process because of a perceived undue influence of ‘industrial stakeholders’ (Samet, 2015) may have gone too far. The current process seems at times to be akin to a criminal trial with a prosecutor and a biased jury, but no defense counsel. It is not uncommon for epidemiologists in a Working Group to be selected on the basis of having published positive findings about cancer risk associated with an exposure being evaluated. Participants with dissenting opinions should be sought for inclusion on Working Groups, with conflicts of interest clearly identified, but not used to automatically exclude potential participants (May, 2011). Furthermore, all types of conflicts of interest should be recognized, including those arising as a result of pursuit of professional advancement, future funding opportunities, personal recognition, and public policy activism or advocacy (PLoS Medicine Editors, 2008; McLaughlin et al., 2010a, 2011; Erren, 2011; Brown et al., 2014; Curry, 2016; Trinquart et al., 2016).

The role of IARC staff in guaranteeing that all relevant information is made available to a Working Group is critically important, as is the responsibility of Working
Group members to evaluate and report on all relevant data in the final Monograph text. The selective omission of data from IARC Working Group deliberations is not restricted to the evaluation of rodent studies or to the glyphosate deliberations. For example, an embalmer case-control study played a major role in the question-able IARC conclusion that formaldehyde causes leukemia in humans (Hauptmann et al., 2009; IARC, 2012), but the odds ratio of 0.1 (95% confidence interval, 0.01–1.2) for nasopharyngeal carcinoma among embalmers in this study (Hauptmann et al., 2009) was ignored by the same IARC Working Group in its deliberations on the alleged association between formaldehyde and nasopharyngeal carcinoma (McLaughlin and Tarone, 2013). Continuing to disregard numerous specified difficulties that can adversely affect decision making by IARC Working Groups, including the role played by nonfinancial and nonindustry conflicts of interest, will only serve to undermine the scientific credibility of the IARC Monographs Program (McLaughlin and Tarone, 2013). Rational and effective cancer prevention activities depend on scientifically sound and unbiased assessments of the carcinogenic potential of suspected agents by international agencies and national regulatory bodies. Arguing by authority in large numbers (Pearce et al., 2015), without dealing empirically with the many specific questions and issues that have been raised, will not serve the goal of improving either the IARC deliberative process or the integrity of the carcinogen classifications arrived at by Monograph Working Groups.

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Conflicts of interest

There are no conflicts of interest.

References


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