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Invited Perspective: Important New Evidence for Glyphosate Hazard Assessment

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Glyphosate is the most widely used pesticide in the world.[1] It is also, arguably, the most controversial. Since being classified as "probably carcinogenic to humans" by the International Agency for Research on Cancer (IARC) in 2015,[2] glyphosate has received close scrutiny from scientists and regulatory bodies. A new study in this issue of *Environmental Health Perspectives* by Chang et al.[3] provides important new evidence to support glyphosate hazard assessment.

The IARC conclusion was driven by the results of animal cancer bioassays and mechanistic studies—mostly produced *in vitro* or, in nonhumans, *in vivo*—indicating DNA and chromosomal damage and oxidative stress induced by glyphosate and glyphosate formulations.[4] The evidence from human studies of cancer was considered "limited" by IARC given that it included positive associations between glyphosate and incidence of non-Hodgkin's lymphoma from several retrospective case–control studies but no such association from the Agricultural Health Study, the only prospective cohort study published at the time of the agency's review.[4] Limitations of the body of evidence and differences in interpretation have influenced subsequent hazard assessments, such as those from the U.S. Environmental Protection Agency[5] and the European Chemicals Agency.[6]

Cited limitations of the previous epidemiologic studies include glyphosate exposure misclassification (due to differential recall in case–control studies or general measurement error), selection bias (introduced because of low participation and missing data), and residual confounding (especially by other pesticides). These issues are difficult to overcome in observational studies, especially when studying cancer outcomes from environmental chemicals, because of the need to characterize an exposure window relevant to carcinogenesis over a number of years and with a potentially long latency period. Furthermore, because glyphosate is readily excreted from the human body,[7] biological measurement of glyphosate or its metabolites to reflect chronic or lifetime exposure is not possible.

The new study by Chang et al. fills important gaps in the epidemiologic literature on glyphosate by quantifying associations between lifetime occupational use and mosaic loss of chromosome Y (mLOY) as a marker of genotoxicity. mLOY is a chromosomal alteration that is commonly detected in the blood cells of adult male humans and has been associated with hematopoietic malignancies.[8] Results from the study by Chang et al., which included licensed pesticide applicators in Iowa and North Carolina, suggest that greater lifetime glyphosate use (reported as number of days) was associated with higher prevalence of expanded mLOY, or mLOY affecting $\geq$10% of cells.[3] Associations were strongest among applicators who were $\geq$70 years of age, those who were never smokers, and those who were not obese. Particularly compelling is that the authors observed a dose–response relationship, with incrementally higher odds of mLOY as total lifetime days of glyphosate use increased ($p_{trend} = 0.03$). This work provides important mechanistic support for genotoxicity of glyphosate in an observational, population-based context. Strengths of the study are avoidance of exposure recall issues by its prospective design, as well as consideration of multiple pesticides as potential confounders. It is also the largest human study of its kind, with 1,606 participants, of whom 343 had mLOY.

Research on biomarker end points, like that conducted by Chang et al., can indicate intermediate effects of exposure that lead to development of cancer. Studies of intermediate effects have several advantages over traditional epidemiologic studies of cancer end points. Intermediate effects, by definition, occur sooner after exposure than do incident cancers, so studies can reduce uncertainty by capturing exposures closer to the time of data collection. In addition, intermediate effects are generally more common than cancers because only a fraction go on to develop cancer. A relatively large proportion of the study population with the biomarker end point of interest may translate into adequate statistical power to estimate associations. Case in point, Chang et al. detected expanded mLOY in 9.8% of farmers.[3] This provides substantial study power compared with studies of incident cancers, especially rare cancers of interest such as specific types of lymphomas and leukemias. Finally, identification of biomarkers of effect in human populations can support causal inference by enhancing biological plausibility of carcinogenicity. This is important for hazard assessment, especially when faced with conflicting findings from epidemiologic studies of cancer end points or when considering novel findings, such as the reported association between glyphosate use and acute myeloid leukemia from the most recent analysis of Agricultural Health Study cohort data.[9]

Evidence for intermediate effects from studies like that by Chang et al.—of humans in real-world exposure settings—is especially valuable; it avoids uncertainties from extrapolating effects found in nonhumans or from *in vitro* experiments. Furthermore, studies of intermediate effects can be performed sooner after the introduction of a new pesticide to the consumer and commercial markets, as compared with studies of cancer incidence, thus allowing more rapid identification of carcinogens. Therefore, supplementing the body of evidence with human studies of biomarkers of effect can go a long way toward improving hazard assessments. However, equally important will be studies demonstrating the risks of cancer development and progression, subsequent to the intermediate effect.

Chang et al. were not able to completely rule out concerns about exposure misclassification.[3] Furthermore, the study results—based on a U.S. population of predominantly European ancestry—may not generalize to lower- and middle-income country populations or to other U.S. populations (such as migrant or seasonal farmworkers) with different patterns of exposure coupled with social environmental stressors that may have implications for cancer incidence.[10,11] Nevertheless, this new work represents a critical step forward in filling knowledge gaps about the mechanisms of glyphosate carcinogenicity in humans, and it will surely inform future hazard assessments. There is a critical need for further population-based

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research studies of this kind for glyphosate, as well as for other pesticides currently in use, particularly in lower- and middle- income countries, where pesticide use is often greater than in the United States and the use of personal protective equipment may be limited.[12]

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