

Genetic Literacy Project

SCIENCE NOT IDEOLOGY

WHO's IARC under fire for ignoring exculpatory data on glyphosate: Should it be reformed or abolished?

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Editor's note: A controversial assessment of the cancer risks presented by the glyphosate has again brought unwanted attention to the World Health Organization's International Agency for Research on Cancer (IARC). An investigation by [Reuters](#) revealed that the scientist leading the review failed to mention fresh data showing there was no cancer link -- meaning the agency never took the information into account before categorizing the herbicide as "[probably carcinogenic](#)" in its report in 2015.

Over four decades, the organization has assessed 989 substances and activities, ranging from arsenic to red meat to working as a painter to sunlight, and found all but one of them were likely to cause cancer in humans. Ranked among the "Group 1 Carcinogens" are wood dust and Chinese salted fish.

The findings are used by many global agencies to inform regulators. But they have caused consternation, particularly among scientists who believe the evaluation standards, established decades ago, are out of touch with modern toxicological knowledge. At stake are judgments that can affect the lives of millions of people and the economic activities of states and multinational companies. IARC's rulings influence many things, from whether chemicals are licensed for use in industry to whether consumers accept certain products or lifestyles.

Concerns about glyphosate's health impacts increased in 2015 after IARC called glyphosate a [likely carcinogen](#). The IARC classification was widely circulated by anti-chemical and anti-GMO advocacy groups, which argued for bans or tighter restrictions.

More recent controversies over classification of red meat and processed meat as cancer-causing have spurred scientists and regulators to re-examine IARC's methodologies and mandate. Ten leading scientists authored a paper for [Regulatory Toxicology and Pharmacology](#) calling for reform of IARC's mandate and techniques, which most dramatically impact European regulations but also oversight in North America. Three of those scientists who co-authored the journal article discuss the reforms necessary to bring IARC's practices into the 21st century. The authors:

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The IARC monograph program on Evaluation of Carcinogenic Risks must be reformed and brought into the 21st century – or it should be abolished

Summary

The IARC monograph program is an outmoded cancer classification scheme that has remained fundamentally unchanged since the monograph program was established in the early 1970s. In the intervening 45+ years, scientific understanding of cancer causation has deepened and provided decision makers with an evolving appreciation of how effects seen in laboratory animals should be used to protect human health. Conceptual and experimental breakthroughs in cancer causation have been incorporated by the WHO IPCS, the US EPA, the United Kingdom's Committee on Carcinogenicity, and others. In contrast, IARC has continued to apply its classification system largely as if the last half-century of scientific research hadn't happened, completely ignoring issues of dose and exposure that are fundamental to risk assessment as it has been practiced around the world for several decades. The result is an unhelpful, even absurdist, scheme, in which chemicals with orders of magnitude differences in cancer potency are placed in the same group. The IARC monograph program is a historical artifact that no longer serves the function for which it was established. It must be reformed to be brought into the 21st century – or it should be abolished.

Analysis

The objective of the IARC monograph (“IARC Monographs on the Evaluation of Carcinogenic Risks to Humans”) process has not changed fundamentally since it was started 45 years ago and represents a scientific viewpoint that is now decades out of date. Science has progressed dramatically in the last half century, but the IARC cancer classification system remains frozen in time, sometimes producing results that have little scientific rationale, defy common sense and can have disruptive practical consequences.

Recently, agencies tasked with protecting health – and the public at large – have had to contend with IARC assessments that place substances such as bacon and plutonium in the same group as to their potential to cause cancer (carcinogenic to humans). In another instance, IARC cleared coffee, which they had previously labeled as possibly carcinogenic, but only if the coffee is not consumed above a certain temperature, otherwise it is considered probably carcinogenic. At the same time, IARC retained caffeic acid, which is found in coffee, as a 2B (possible) carcinogen (1). What are the public and policy makers supposed to do with such conflicting information?

Out of the more than 900 agents examined over the course of the IARC monograph program's history, only one chemical has ever been classified as probably not carcinogenic. A process that concludes for almost everything either there is evidence it is a carcinogen and should be treated as such or it is “not classifiable” (it is not possible to reach any conclusion on the available evidence – an example in this group is saccharin) provides little value to those engaged in the complex process of public health protection through chemical regulation.

Recent examinations of IARC's controversial findings on glyphosate (2A: probably carcinogenic to humans) have also raised serious questions about the scientific basis and objectivity of IARC's scientific reviews (2, 3). In addition, it appears that the process for many evaluations has become highly politicized, with several of those associated with the review campaigning in the EU to have glyphosate banned and putting themselves in open conflict with regulatory agencies that have done more extensive and scientifically rigorous reviews.

Simple “hazard identification” schemes, such as those used by IARC, were originally developed in the 1960’s and ‘70’s based on human epidemiological data, evolving in the 1980’s to include the results of long term bioassays in laboratory rodents. In these studies, animals were dosed daily with a Maximum Tolerated Dose and one or two lower doses of the test substance over the course of their lifetimes. The studies were designed to answer a simple binary question: can a substance cause cancer, or can’t it, based on whether there was any increase in the incidence of tumors over the lifetime of the animals?

But as more and more chemicals were tested, approximately 50 percent were found to be capable of causing tumors in laboratory rodents – including many “natural” chemicals found in fruits and vegetables that are part of a healthy diet. Quite obviously, the basic tenet of toxicology – that dose is important – wasn’t suspended when it came to carcinogenicity. Clearly, one complication was that the toxic effects of large doses of chemicals were themselves involved in producing tumors in animals.

Chemicals that are part of the natural make up of fruits and vegetables were carcinogenic at high doses in such studies. Foods containing such chemicals include apples, carrots, celery, tomatoes, pears, grapes, citrus (d-limonene), herbs and spices (methyl eugenol), coffee and lettuce (caffeic acid), carrots (aniline), bread (acetaldehyde), arugula broccoli and mustard (allyl isothiocyanate), jasmine tea (benzyl acetate) and many more. One might also note that both ginkgo biloba and aloe vera have been found by IARC to be group 2B, “possibly carcinogenic to humans” (4).

As the scientific understanding of cancer causation deepened, researchers in the 1990’s began to develop frameworks for assessing the many different mechanisms – or modes of action – in cancer formation. These allowed scientists to differentiate between effects in laboratory animals (particularly rodents) and humans, with their different physiologies and responses to chemical insults and to distinguish effects operative only at certain dose levels and/or certain routes of exposure. Knowledge of mode of action also provided a means to understand the relevance of adverse effects seen in animal studies for application to assessing possible impact on human health.

In the early years of the 21st century, these conceptual and experimental breakthroughs were incorporated by the WHO IPCS into a framework for analyzing the relevance of a cancer mode of action for humans (5). The US EPA Cancer Risk Assessment Guidelines included a similar framework, and later so too did the United Kingdom’s Committee on Carcinogenicity decision tree approach, among others.

In contrast, the IARC monograph program has continued to apply its classification system largely as if the last half-century of scientific research hadn’t happened, while completely ignoring issues of dose and exposure that are fundamental to real risk assessment as it has been practiced around the world for several decades. It is not just that the IARC process is hazard-based and therefore it is for others to conduct a risk assessment, but rather the premise that if a substance can cause cancer, regardless of the circumstances, it should be ‘labelled’ carcinogenic, which is flawed. The result is an unhelpful, even absurdist, scheme in which chemicals with

multiple orders of magnitude difference in the dose required to cause cancer are placed in the same group.

IARC's "hazard identification" scheme might have some value if it were used as originally intended – to flag new or untested chemicals for further study. As we saw with the unfortunate recent example of glyphosate, however, the organization has not been content with such a limited and circumscribed role. Now, it often reviews substances after they have been thoroughly evaluated by more extensively and more mechanistically informed scientific regulatory bodies such as EPA, BfR, EFSA and even the FAO/WHO JMPR. In contrast to IARC, these expert bodies review *all* of the available, scientifically-acceptable, literature, both published and unpublished, and have access to the raw data of the unpublished studies, allowing them to conduct their own, independent analyses.

There are fundamental deficiencies in the IARC process and in the statements by IARC staff and Working Group members (6, 7). For example, a number of those involved in the IARC review of glyphosate have sought not only to portray the IARC finding as alarming, but have also attempted to discredit and undermine thorough reviews conducted by credible agencies and organizations, often under a legal mandate.

Meanwhile, scientists who examined the IARC monograph itself found themselves taken aback, even shocked, at the way in which some of the findings had been presented. Indeed, as one leading scientist said, they got this "totally wrong" and pointed to the clearly biased selection of studies IARC reviewed (8).

Instead of using institutional positions to excite "chemophobia" in the broader public, those placed in positions of public trust should note that both overall cancer mortality and cancer incidence adjusted for age, as well as those for most major sites, are falling (9). Not only can cancers often be cured or abated, but fewer people are developing cancer to begin with. This is true despite the widespread use of chemicals – both natural and synthetic – in our modern economy.

We know today that the biggest controllable factors influencing cancer causation are life-style issues, such as smoking, obesity, lack of education and poverty, and infections (e.g. hepatitis virus, human papilloma virus). We can also be reassured by the fact that national regulatory systems, as they've been developed and modernized over the last half century, have been highly successful in protecting public health from those substances that might cause harm, as judged by any reasonable standard of evidence.

While the IARC monograph program may once have been relevant, it is no longer serving its intended purpose nor is it useful for public health based decision-making. As presently constituted, the IARC monograph program represents a regressive force in regulatory science, unnecessarily disrupting a system that works well in protecting public health. In addition, it causes political turmoil and public anxiety that has no societal benefit. The results of its outdated classification scheme reflect unsound science, create unnecessary fear and uncertainty, undermine the integrity of the public health regulatory system, and divert research funds and other resources from more useful endeavors.

It's time that the global scientific, regulatory and political community assess the value of continuing the IARC monograph program, and openly – with complete transparency -- examine the legitimate questions that have been raised concerning the organization's conflicts of interest, scientific rigor and evidential standards. The IARC monograph program needs to be fundamentally reformed to reflect advances in knowledge of mechanisms of chemical carcinogenicity and other areas of biology if it is to provide value. If that reform can't be accomplished, it should be relegated to the regulatory museum where it belongs, along with other historical artifacts like the Model T Ford, the biplane, and the rotary dial telephone that no longer serve an important function in our society today.

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