Misleading glyphosate-cancer study Part 2: ‘Symptom of a widespread problem’—Concerns about ideological activism in science research and communications

geneticliteracyproject.org/2021/02/10/misleading-glyphosate-cancer-study-part-2-symptom-of-a-widespread-problem-concerns-about-ideological-activism-in-science-research-and-communications/

Geoffrey Kabat | February 10, 2021

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For the better part of five years, a coalition of environmental groups and tort lawyers (aided by the mainstream press) has relentlessly asserted that the weedkiller glyphosate poses a serious cancer risk. A team of respected epidemiologists poured gasoline on this already raging fire in 2018, when they published a meta-analysis (which I’ll refer to as “the Zhang paper” after the first author) that found a significant association between glyphosate exposure and the risk of non-Hodgkin’s lymphoma (NHL).

In part one of this series, I detailed how the authors of what appeared to be an important paper made some highly questionable decisions in order to reach their conclusion, namely selecting certain data points and excluding others from the studies they considered. Despite

the serious defects that I and a few other scientists pointed out soon after the paper appeared online, the paper's conclusion —that relatively heavy exposure to glyphosate was associated with a 41 percent increased risk of NHL —ensured that it would get widespread publicity.

Editor's note: This is part two of a two-part series. Read part one: The glyphosate debacle: How a misleading study about the alleged risks of the weedkiller Roundup and gullible reporters helped fuel a cancer scare
Read Dr. Kabat's February 2019 article 41% glyphosate-cancer increase claim under fire: Did authors of new meta-study deliberately manipulate data or just botch their analysis?

But there were still other indications of bias in the paper that provide insight into the authors' thinking. In this follow-up piece, I want to examine some of the other instances of bias, then address three crucial questions. How could this paper, flawed as it is, have passed peer review and largely escaped serious criticism in the two years following publication? What does the Zhang paper reveal about the authors' mindset, and about standards of scholarship in the field of environmental epidemiology? And, finally, what are the implications for efforts to produce reliable science that can guide policy makers and consumers?

Other indications of bias

Well before I got to the heart of the Zhang paper, I picked up signals that put my critical antennae on guard. On page three, the authors stated, "GBHs [glyphosate-based herbicides] have recently undergone a number of regional, national, and international evaluations for carcinogenicity in humans [20-23], resulting in considerable controversy regarding glyphosate and GBH's overall carcinogenic potential."

In order to support their claim of "considerable controversy," the authors provided two references to agencies that found that glyphosate is not a health concern (US Environmental Protection Agency, EPA; Joint FAO/WHO Meeting on Pesticide Residues, JMPR) and two that found it to be a "probable carcinogen" (The International Agency for Research on Cancer, IARC; and California's Office of Environmental Health Hazard Assessment, OEHHA), thus implying that opinion is evenly divided and balanced.

In fact, roughly a dozen national and international agencies have found glyphosate to be safe and non-carcinogenic (EPA, Health Canada, the European Food Safety Authority, the European Chemicals Authority, the UN's Food and Agriculture Organization, and the health agencies of France, Germany, Australia, New Zealand, Japan, and Brazil). The fact is that IARC is the only major agency that has found glyphosate to be problematic, and its analysis has been deemed defective by many independent experts. As for OEHHA, it mechanically

follows IARC in its designation of carcinogens under California's Proposition 65, a byzantine law approved by voters in 1986 that has led the Golden State to list garlic bread and, for a time, coffee as possible carcinogens.

A Proposition 65 sign in a San Francisco Starbucks warns of acrylamide in coffee and baked goods. Credit: Robert Alexander/Getty Images

Whatever controversy over glyphosate there is, then, is the product of political and legal considerations, not evidence that the weedkiller causes cancer. However, the assertion that there is "considerable controversy" is important to the Zhang authors because, in their telling, it is what motivated their meta-analysis, as the following sentence makes clear: "Hence, addressing the question of whether or not GBHs are associated with NHL has become *even more critical*" (emphasis mine).

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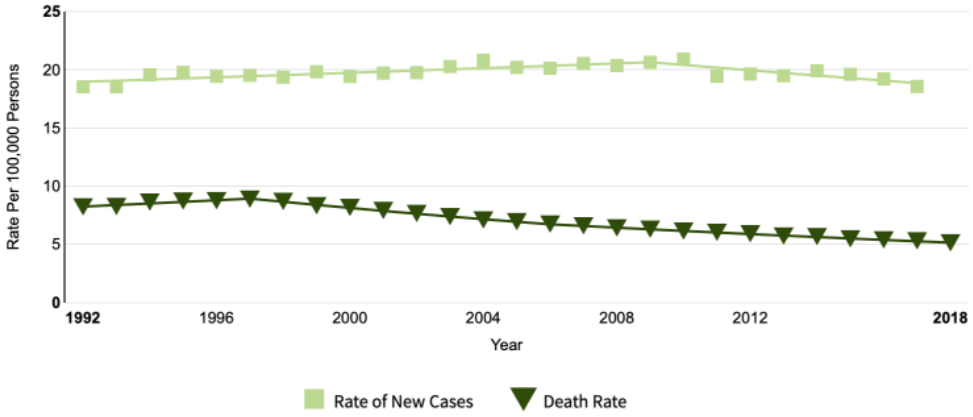
Throughout the paper, there are other similarly one-sided characterizations of the evidence on specific topics.

First, in their introduction, the authors emphasized the amount of glyphosate used in the past decade and noted that it has been detected in various foods and baby formula, concluding that glyphosate "may be considered ubiquitous in the environment." However,

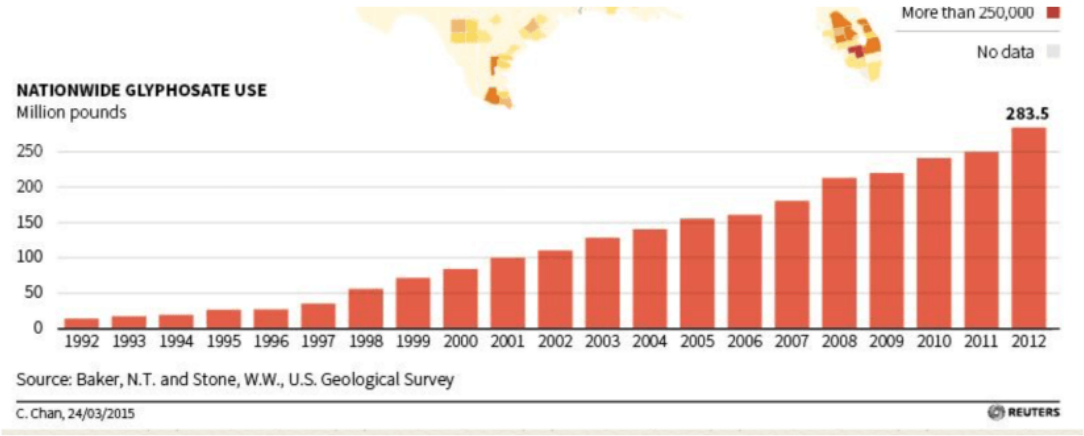
they omitted that glyphosate has relatively low acute and chronic toxicity compared to other pesticides and that the levels detected in foods are well below the level at which any adverse effects would be expected.

They observed that use of glyphosate increased roughly 16-fold between 1992 and 2009, but they failed to note that the incidence of NHL has remained unchanged over the past thirty years.



New cases come from SEER 13. Deaths come from U.S. Mortality.
All Races, Both Sexes. Rates are Age-Adjusted.
Modeled trend lines were calculated from the underlying rates using the Joinpoint Trend Analysis Software.

New cases are also referred to as incident cases in other publications. Rates of new cases are also referred to as incidence rates.



Second, they articulated criticisms of the Agricultural Health Study (AHS) at length based on secondary considerations, but failed to note its strengths. The AHS is, in fact, the best epidemiological investigation of glyphosate's cancer-causing potential, and it poses a

significant challenge to Zhang's conclusion. It is striking that the authors failed to note the much more serious problems with the case-control studies they inappropriately combined with the AHS (Read part one for a full analysis of this issue).

Third, to supplement the results of the meta-analysis of human studies, Zhang et al. summarized the results of studies of lymphomas in mice following the administration of glyphosate, which they interpreted as providing additional evidence of the carcinogenicity of glyphosate. However, the evidence appears mixed and, where increasing trends were seen in the tumor yield with increasing doses of glyphosate, they were modest. Researchers have evaluated glyphosate rodent studies for all tumor sites and found more instances of tumor decreases with increasing glyphosate exposure levels than tumor increases.

Finally, the authors pointed to a number of biological mechanisms that may play a role in the development NHL in humans and of lymphoma in animals. While such mechanisms are worthy of study, it is generally recognized that the results of laboratory studies are less directly relevant to risk assessment than epidemiologic studies and, secondarily, animal experiments.

Thus, there is a pattern throughout the Zhang paper of what I call "motivated reasoning." Rather than evaluating the evidence on its merits, the authors constructed a narrative designed to support their a priori hypothesis. In other words, their critical faculties served to imprison them in their motivated thinking, always a danger in science that physicist Richard Feynman addressed in his 1974 commencement address at Caltech titled "Cargo Cult Science." Feynman emphasized that when you formulate a hypothesis, you must list all the observations and facts that support it, but you must also list all of the observations and facts that do not agree with it. This is the only way not to "fool yourself"—and, Feynman added, "you are the easiest person to fool."

What about peer review and the response from the wider community?

Given the Zhang paper's unjustified assumptions and methodological flaws, how did it survive peer review? Peer review is a lottery, by which I mean the quality of the review depends very much on the individuals who perform the review, as well as the editor who oversees the review. Some reviewers are tough minded and the study author senses they miss nothing in evaluating a paper.

At the other extreme, reviewers who are less alert or less methodologically astute may feel that the authors have made a convincing case. I would argue that Zhang et al. wrote their paper with an emphasis on justifying their choices and judgments rhetorically, if not scientifically. One almost feels snowed by their arguments. And their style of argumentation

appears to have been very effective. What is clear is that neither the editors nor the reviewers noticed the pattern of motivated reasoning, selective attention to facts, and unsupported assumptions that I have described.

The fact that the Zhang paper was published in *Mutation Research,* a publication with a broad focus on genetic toxicology, rather than in an epidemiology journal may have increased the likelihood of an inadequate review of a paper reporting on a meta-analysis of observational epidemiology studies.

How do the authors respond to criticism?

The authors' response to substantive criticism has been revealing. Rather than acknowledging criticism and presenting valid arguments to support their position or modifying it, they doubled down on their hypothesis and tried to divert attention from the key issues, while asserting the transparency and quality of their work. In addition, they implied that their critics must have some conflict of interest.

I will give just one example among many. In her February 2020 Forbes piece, responding after a full year to my critique published in February 2019, Lianne Sheppard, the Zhang paper's senior author, wrote that "cherry-picking of data to achieve particular results is never acceptable scientific practice, and in the case of our meta-analysis, this claim is not true." But, based on her a priori hypothesis, she defended her selection of the one relative risk out of five from the AHS (relative risk 1.12) that ensured a statistically significant result.

Forbes

Feb 20, 2020, 02:56pm EST | 3,094 views

Glyphosate Science Is Nuanced. Arguments About It On The Internet? Not So Much

The Lab Bench Contributor ⓘ

Science

Perspectives from the cutting edge of science

POST WRITTEN BY

Lianne Sheppard

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This was not the main analysis presented by the AHS researchers in their paper – that was the unlagged relative risk of 0.87. And, as I made clear in part one, there are two glaring facts that should have motivated Sheppard to reconsider her choice. First, the AHS, by far the largest and most careful study, showed no support for her a priori hypothesis that the highest exposure group would show the strongest association – and demonstrated this point in all five analyses! Second, as the Zhang authors themselves acknowledged, the latency period for NHL to develop is uncertain, and could be as short as two years, although their conclusion is based on the assumption that it is 20 years. Recognition of both these facts should have made the authors reconsider the justification for their analysis.

After this evasion of the science, Sheppard went on to raise further diversions, arguing that publications in the popular media are not appropriate for the serious business of evaluating risks scientifically. Only the sacred precincts of academic journals–where my colleagues and I have recently published a thorough critique of the Zhang paper – are suitable venues for such discussion. Sheppard seems unaware of the flourishing, real-time discussions of critical issues in science and medicine by the likes of Eric Topol, Peter Hotez, Vinay Prasad, and many others on Twittter. True scientists are happy to engage with an interested audience, whatever the forum.

The Zhang paper is a symptom of a widespread problem

I have devoted time to examining this paper because I believe it is symptomatic of a state of mind that is prevalent in environmental and lifestyle epidemiology. This area is challenging due to the difficulty of measuring human exposure to low-level environmental agents—often

measured at a single point in time—and gauging their long-term health effects against the background of exposures that are often orders of magnitude stronger (smoking, alcohol consumption, diet, body mass index, postmenopausal hormones, etc). Nevertheless, numerous papers continue to be published examining the association of self-reported exposures to trace levels of chemicals in urine or blood with risk of some chronic disease.

There are those working in this area who appear to feel that, in spite of the limitations of the studies—or, perhaps, because of these limitations—one has to take seriously results that are suggestive of an association. In a sense, because of the difficulty of documenting low-level exposures, scientists may feel that they have to give them the "benefit of the doubt." Given the limitations of the data, the findings of such studies need to be interpreted with an allowance for the fact that the studies can't tell us what we want to know.

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The science policy scholar Daniel Sarewitz has used the term "trans-science" to refer to the study of complex questions that can't be answered by present-day science. In the absence of definitive data, what seems to be most important to these people is their *interest* in the question regarding the effects of a particular chemical agent. This is how results from weak studies that appear to point to a risk can be seized on, and this is what appears to have happened in the Zhang paper. What is lacking in high-quality evidence is compensated for by ideological and moral zeal.

Researchers are keenly aware that the media, the public, and even journal editors and reviewers are sensitive to findings that appear to implicate a common exposure in chronic disease. Where strong data are lacking but the issue is one that will resonate with the public and the media, scientists know that their message will get picked up and get traction. We've seen many examples of this in research on electromagnetic fields, endocrine disrupting chemicals and BPA, DDT and other pesticides, e-cigarettes, and many other issues.

A number of agencies and institutions have been associated with this type of motivated science—the International Agency for Research on Cancer (IARC) regarding glyphosate, cell phones, and other exposures; the National Institute for Environmental Health Sciences (NIEHS) regarding BPA; and the Endocrine Society regarding endocrine-disrupting chemicals generally.

In contrast to the kind of science exemplified by the Zhang paper, there are examples of sober and careful work by scientists who are trying to advance knowledge in their field by building on firm results and framing new hypotheses. This work, however, is unlikely to attract media attention.

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A recent paper by Moubadder et al. has reviewed environmental exposures in relation to NHL. With regard to environmental exposures, they noted that several infectious agents have been causally linked to NHL. However, with regard to chemical exposures, they concluded that numerous studies have attempted to link NHL risk to chemical exposures, but in spite of many reported associations, "causality has not been established."

Review > Cancer Epidemiol Biomarkers Prev. 2020 Oct;29(10):1844-1855.
doi: 10.1158/1055-9965.EPI-20-0228. Epub 2020 Jul 29.

Linking Environmental Exposures to Molecular Pathogenesis in Non-Hodgkin Lymphoma Subtypes

Leah Moubadder [1], Lauren E McCullough [1], Christopher R Flowers [2], Jean L Koff [3]

Affiliations + expand

PMID: 32727723 PMCID: PMC7541593 (available on 2021-04-01)
DOI: 10.1158/1055-9965.EPI-20-0228

Commenting on the Zhang meta-analysis, they had this to say:

> "A recent meta-analysis that included the 2018 Agricultural Health Study (AHS), a cohort of pesticide applicators that have been followed prospectively, and five case–control studies found the relative risk of NHL to increase by 41% among those highly exposed to glyphosate-based herbicides [meta-risk ratio (RR) = 1.41; 95% CI, 1.13–1.75; ref. 20]. However, studies on the AHS population alone, which includes 515 incident NHL cases, have consistently observed no association between reported glyphosate exposure and NHL risk, regardless of the latency period (i.e., 5-, 10-, 15-, and 20-year lag times; refs. 21, 22)."

Taking a broad view of the role of environmental exposures in the etiology of NHL, Moubadder considered glyphosate specifically, but still came to the conclusion that causality has not been shown for any chemical.

In contemplating the contrast between the Moubadder paper and the Zhang paper, I was reminded of interviewing the reproductive expert Richard Sharpe about the huge amount of fruitless research that had been devoted to BPA as a cause of adverse reproductive events. In the early 1990s Sharpe had been one of the originators of the so-called "environmental estrogen hypothesis" and had seen it grow into a huge academic bandwagon, which he dissociated himself from. Sharpe shifted his attention to studying the effects of pharmaceuticals taken by pregnant women on the fetus and the developing child, as well as other exposures. The shift away from studying trace exposures to BPA to more significant exposures has already led to evidence of real effects.

Explaining why he went his own way, he said, "... I was lucky that the question that drove me was 'what causes these disorders?' not 'how do EDCs [endocrine disrupting chemicals] cause these disorders?' Such a simple difference, but it takes your thought processes in a very different direction."

Geoffrey Kabat is a cancer epidemiologist and the author of *Getting Risk Right: Understanding the Science of Elusive Health Risks*. Find Geoffrey on Twitter @GeoKabat

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