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Asian Journal of Organic & Medicinal Chemistry

Volume: 5 Year: 2020
Issue: 4 Month: October–December
pp: 340–347
DOI: <https://doi.org/10.14233/ajomc.2020.AJOMC-P301>

Received: 2 December 2020
Accepted: 24 December 2020
Published: 31 December 2020

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Available online at: <http://ajomc.asianpubs.org>

ARTICLE

Glyphosate and Non-Hodgkin Lymphoma

Alberto Boretti 

ABSTRACT

The herbicide “glyphosate” known with the trade name of “Round-Up” has been using for 50 years and it is the world’s most widely used herbicide. It has helped to increase the agricultural yields of crops around the world, thus assisting to feed billions of peoples. After Round-Up was declared “probable carcinogen” in 2015 by the International Agency for Research on Cancer (IARC), there has been a growing number of claims that glyphosate is the cause of the types of cancer of the most poorly understood origin, such as non-Hodgkin lymphoma. From an analysis of the available literature, the link between non-Hodgkin lymphoma and “Round-Up” is shown to be extremely weak.

KEYWORDS

Glyphosate, Environmental epidemiology, Agriculture production, Non-Hodgkin lymphoma, Toxicology.

INTRODUCTION

Glyphosate is the world’s most used herbicide [1-3] with a total 8.6 million tons sprayed worldwide since 1974 and a dramatic increment of use in recent years (15-fold increased use since 1996). Glyphosate is an organophosphorus compound, a phosphonate. Fig. 1 is the chemical structure of glyphosate, of formula $C_3H_8NO_5P$. Glyphosate acts by inhibiting the plant enzyme 5-enolpyruvylshikimate-3-phosphate synthase, which is essential to plant growth. This enzyme is not found in humans or animals. Glyphosate was designed to have effects on plants and not humans.

Even if every chemical can cause toxicity *via* a variety of modes of action, this toxicity must be proven for the specific amounts that could reach humans. It is obvious that the glyphosate could cause non-Hodgkin lymphoma (NHL), which is the subject of this review.

The use of glyphosate has been beneficial to the growth of agricultural yields. Since 1974, glyphosate has contributed to the growth of the agricultural yields. As shown by Ritchie [4], in Fig. 2, over the last 50 years, the global population has more than doubled. The land available per person to grow food has reduced. Feeding of the rapidly growing population with shrinking land resources has only been made possible mostly by increasing the yield output with improvements of water use and farming practices, the use of higher-yielding crops, fertilizers and pesticides (that include herbicides). Thus, the use of glyphosate has provided significant societal advantages. With the excuse of being carcinogenic, glyphosate is now likely

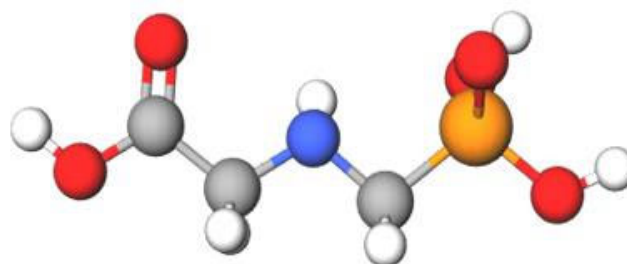
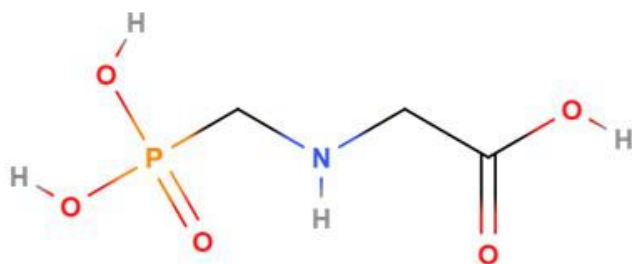


Fig. 1. Glyphosate molecule. Left, structural formula. Right, 3d model. From molview.org/?cid=3496

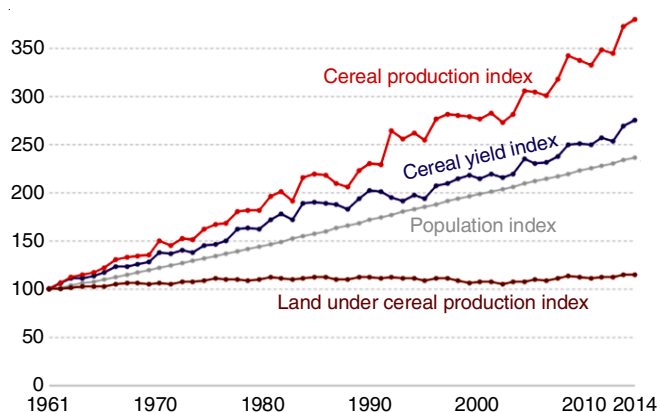


Fig. 2. Index of cereal production, yield and land use, 1961-2014, World, ourworldindata.org/yields-vs-land-use-how-has-the-world-produced-enough-food-for-a-growing-population. Accessed January 15, 2020

to be removed from the market. This can have profound impacts on agricultural yields.

The cause of NHL is not known with certainty. NHL is associated with the production of too many abnormal lymphocytes that do not die but grow and divide. NHL can begin in the B cells, which are the cells producing antibodies neutralizing infection agents and the T cells, that are the cells acting directly on the infection agents. While countless narratives are claiming the existence of numerous factors increasing the risk of NHL, in most people with NHL, there is no trace of these alleged risk factors and many people with the alleged risk factors do not develop NHL [5]. The most popular risk factors for NHL include a weak immune system, immunosuppressive therapies, infections, chemicals, older age, etc. [5].

Because of the wide use of glyphosate globally, glyphosate has been one of the most studied pesticides by researchers from industry, agencies and academia. A search for “glyphosate” on Google Scholar, a database that includes not only medical works, returns about 295,000 results, while a search for “Round-Up” returns about 159,000 results.

While some of these papers speculate about the most various negative consequences of the use of glyphosate, so far, none of the detailed reviews by scientific expert panels in several countries on a multiplicity of hypothetical apprehensions, have found reasons to outlaw the use of glyphosate. Because of the widespread use of glyphosate, over now almost 50 years, there should have been many cases showing eventual side effects. This mass impact is still missing. The link between glyphosate and NHL is discussed hereafter.

EXPERIMENTAL

To prove the hypothesis that glyphosate causes NHL, what is needed is: (a) an environmental correlation. In the specific, it must be shown that there is an increment of cases of NHL phased with the increased use of glyphosate; (b) laboratory experiments and trials demonstrating causality between the presence of glyphosate and abnormal function of lymphocytes; and (c) definition of mechanisms explaining the effects.

The available literature is sourced to answer these three questions.

RESULTS AND DISCUSSION

Published works on glyphosate indexed in PubMed:

As shown in Fig. 3, laboratory experiments and trials demonstrating the causality are missing in the specific subject.

A search on a more reliable medical database than google scholar such as Pubmed by keyword “*glyphosate*” (pubmed.ncbi.nlm.nih.gov/?term=glyphosate) returns 3,581 results (Fig. 3a). These 3,581 works include 11 clinical trials (Fig. 3b); 12 meta-analyses, (Fig. 3c); 7 randomized controlled trials (Fig. 3d); 190 reviews (Fig. 3e); 9 systematic reviews (Fig. 3f) and 3,458 journal articles (Fig. 3g). A negligibly small number of clinical trials, meta-analysis and randomized controlled trials, performed mostly in the past, is coupled to an exponentially growing number of journal articles speculating on the matter.

A more specific search for “*glyphosate*” and “*non-Hodgkin Lymphoma*” (pubmed.ncbi.nlm.nih.gov/?term=(glyphosate)+AND+(non-hodgkin+lymphoma)) provides an even more speculative background. The search only returns 19 results (Fig. 3h), of which 17 are journal articles, with the two most relevant ref. [6,7], and then another ref [8], i.e. a very subjective review of Andreotti *et al.* [6] done by reanalyzing the same data to come to a different conclusion. Zhang *et al.* [8] is also the top of relevance for the other two categories, meta-analyses, that have other 3 entries and systematic reviews, with the other 2 entries. The number of clinical trials is 0, the same as the number of randomized clinical trials.

Thus, without any clinical trials or randomized controlled trials, there are of relevance two environmental works [6,7], plus a subjective reexamination of Andreotti *et al.* [6] proposed in Zhang *et al.* [8] and the exponentially growing number of journal articles speculating on the matter.

A search for “non-Hodgkin lymphoma” (pubmed.ncbi.nlm.nih.gov/?term=non-hodgkin+lymphoma) returns very different background information. There are 115,395 results (Fig. 3i), while clinical trials are 5,202 (Fig. 3j). Randomized

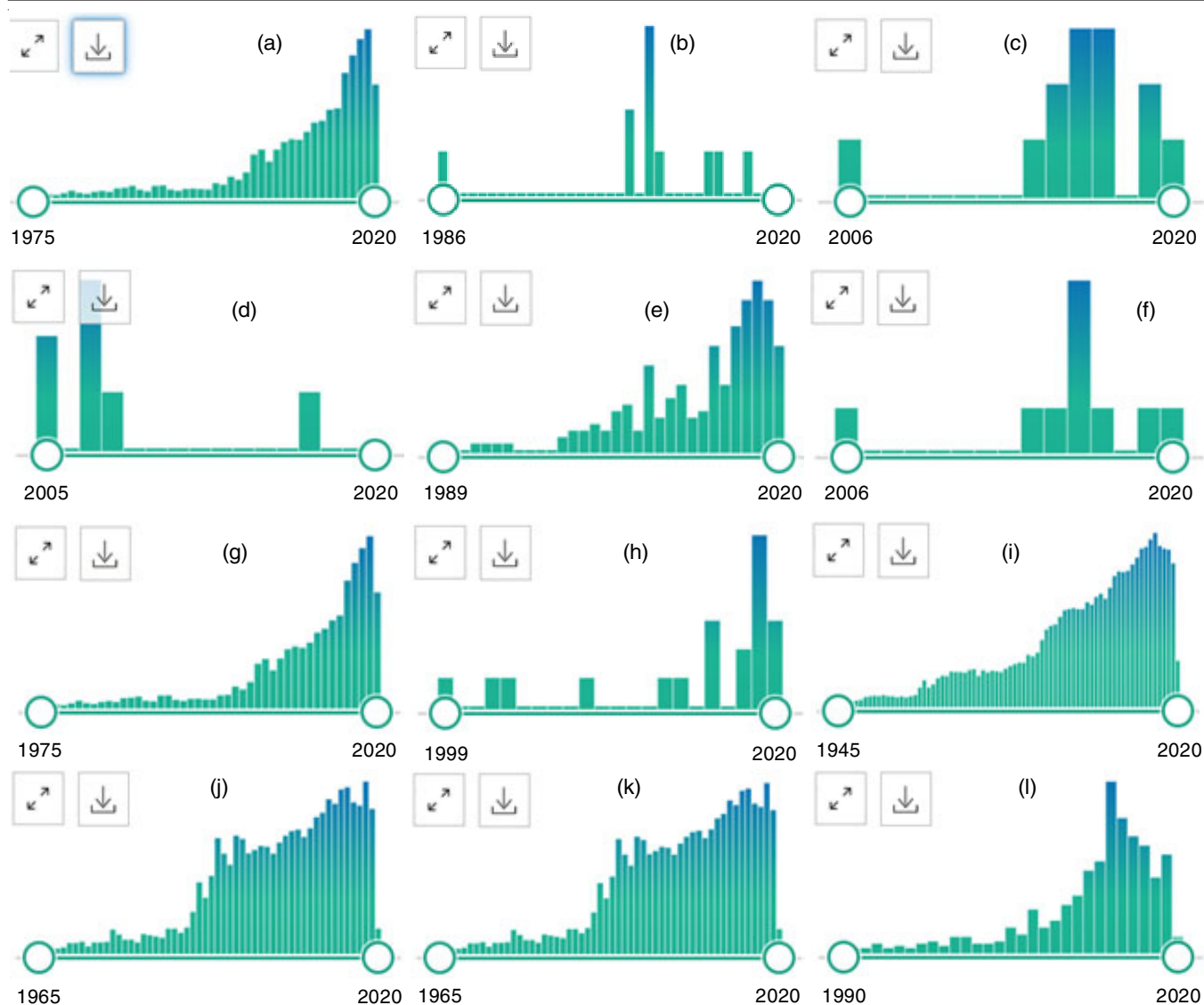


Fig. 3. Classification of published articles indexed in PubMed on **glyphosate**: (a) total; (b) clinical trials; (c) meta-analysis; (d) randomized controlled trials; (e) reviews; (f) systematic reviews; (g) journal articles. Classification of published articles indexed in PubMed on **glyphosate and non-Hodgkin lymphoma** (h) the total. The number of clinical trials is 0, the same as the number of randomized clinical trials. There are only two relevant works and one subjective reanalysis of one of them, to provide material for the discussion. Classification of published works in PubMed on non-Hodgkin lymphoma. Fig. (i) total; (j) clinical trials; (k) randomized controlled trials; and (l) meta-analyses

controlled trials are 1,224 (Fig. 3k). All these numbers are increasing in recent years. The number of meta-analyses is 462 (Fig. 3l). Reviews are 14,614 and systematic reviews are 348. The number of journal articles is 106,073 results.

Opposite to the study of NHL, i.e. a proper medical subject, the study of the effect of glyphosate on NHL is not a subject that has been based so far on medical hard work, but only a few environmental studies and then speculations.

Attribution of probable carcinogen to glyphosate: The first attribution worth mention of “probable carcinogen” to glyphosate comes in a statement by the International Agency for Research on Cancer (IARC) in 2015. The IARC is an inter-governmental agency focused on hazard assessments. They are well-known for classifying as “carcinogenic” substances classified by other regulatory agencies as “safe”. Of the 1,000 carcinogenic factors that the IARC has evaluated, only one has been able to escape its label of carcinogenic.

For IARC, 2019 [8], “Known human carcinogen” are alcoholic beverages, estrogen-progestogen, ethanol in alcoholic beverages, processed meat (consumption of), or salted fish (but only Chinese-style), while their “Known to be human carcinogen” also include alcoholic beverage consumption or analgesic mixtures having phenacetin. In between other “Probable carcinogen” besides glyphosate, the IARC includes frying, emissions from high-temperature, red meat (consumption), hairdresser or barber (workplace exposure) and hot beverages (< 65 °C). Hence, the IARC, that labels “carcinogen” almost everything, considers glyphosate less carcinogenic than alcoholic beverages, processed meat (consumption of), or salted fish (but only Chinese-style).

This labeling is not based on any scientific evidence. There should have been no issue with that. However, the search for carcinogenic side effects of Round-Up has gone viral since then. The IARC itself noted that there was limited evidence

for a link to cancer in humans [10]. Although several studies have shown that people who work with this herbicide seem to be at increased risk of NHL, their report also notes that a separate huge US study, the Agricultural Health Study [6] found no link between glyphosate and NHL. That study followed thousands of farmers and looked at whether they had an increased risk of cancer. This study found no connection.

Role of glyphosate for non-Hodgkin lymphoma (NHL):

Among carcinogenic concerns, the possibility that glyphosate could cause the NHL is the most popular, likely because the reasons why tumors develop from lymphocytes in patients with NHL are obscure. As written by Mayo clinic [5], “in most cases, doctors don’t know what causes non-Hodgkin’s lymphoma. In some cases, it’s due to a weakened immune system” and Health line [11] admits doctors and researchers don’t know what causes NHL.

Not later than 2016, in partial response to the IARC claims of 2015 [7] found that only the agricultural health (cohort) study met our a priori quality standards and this study found no evidence of an association between glyphosate and NHL. The companion paper [12] also found that the overall weight of evidence from the genetic toxicology data supports a conclusion that glyphosate (including GBFs and AMPA) does not pose a genotoxic hazard and therefore, should not be considered support for the classification of glyphosate as a genotoxic carcinogen and the assessment of the epidemiological data found that the data do not support a causal relationship between glyphosate exposure and non-Hodgkin lymphoma.

The carcinogenic properties of glyphosate in general and the role of glyphosate in NHL development, is anything but proven. Not even the US EPA presently believes glyphosate is causing cancer [13] as they say, EPA continues to find that there are no risks to public health when glyphosate is used following its current label and that glyphosate is not a carcinogen. The lack of correlation is confirmed by other studies. Recently, Andreotti [6] wrote that in this large, prospective cohort study, **no association was apparent between glyphosate and any solid tumors or lymphoid malignancies overall, including NHL and its subtypes.**

Looking at the available scientific literature, if a majority decision could be drafted, then glyphosate should be declared non-carcinogenic and certainly not influential for the development of NHL. However, the manufacturing of consent through the Mainstream media (MSM) is supporting a different verdict.

Several works such as Acquavella *et al.* [7] and Williams *et al.* [12] were accompanied by “Expression of Concern” published by the editorial board following messages by “anonymous” readers. In several journals, there are statements such as “We, the Editor-in-Chief and Publisher of the journal, have been informed of concerns over the completeness of acknowledged contributions to the above supplement and in the declarations of interest provided by the named contributors”, were thus used to delegitimize the conclusions of the inconvenient science, not questioning the works, but their authors.

There are also contrarian works, however flawed. Andreotti *et al.* [6] also wrote, “there was some evidence of increased risk of AML (acute myeloid leukemia) among the highest exposed group that requires confirmation”. A very subjective review

of Andreotti *et al.* [6] was done by Zhanget *al.* [8] that reanalyzed the same data to come to a different conclusion. The relative risks of cancer in the group exposed to glyphosate [6] reduced in 3 of 4-time intervals at 5, 10 and 15 years, while it increased in 1 of 4-time intervals at 20 years. Zhang *et al.* [8] forgot to mention the reduced risk at 5, 10 and 15 years, building up their story with the 20 years’ results. While the positive outcome at 5, 10 and 15 years in the environmental study by Andreotti *et al.* [6] is certainly not a reason to cure cancer with glyphosate, the negative outcome at 20 years coupled with the positive outcome at 5, 10 and 15 years may only be interpreted as lack of any evidence against glyphosate in the specific study. The flaws of Zhang *et al.* [8] are very well discussed in several articles [14-16]. Regretfully, the last word in Wikipedia is the flawed paper of Zhang *et al.* [8] with no mention of the works Salzberg *et al.* [15] and EPA [16], showing the flaws of the study.

It is an unfortunate circumstance that some compounds such as glyphosate are declared harmful to humans by MSM although the association is far from obvious, before an environmental correlation suggesting causality is shown and before further studies through detailed experiments in a laboratory to identify the mechanisms have only been thought of. Opposite, there are other cases, for example, aluminum adjuvants, with aluminum a well-known neurotoxic substance, where there is an environmental correlation, there are animal models, mechanisms and measurements of aluminum concentration in brain tissues of subjects with an autism spectrum disorder, just to name a few of the works in the literature [17-20] and nevertheless, the MSM does not believe it may be harmful to humans.

Environmental correlations: While the use of glyphosate has increased over the last 24 years, there is no clear growth in the incidence of NHL associated with glyphosate in countries with large agricultural outputs. Fig. 4 presents the incidence of NHL in Australia, the UK and the US over this century. The incidence is stable at 23/100,000 for males and 15/100,000 for females in Australia, it is stable at slightly less than 20/100,000 men and women in the US, but it has increased 23 to 28/100,000 for males and 16 to 20/100,000 for females in the UK. As the use of glyphosate per capita in Australia and the US is exceeding the use of glyphosate per capita in the UK, it is hard to believe that there is a link between NHL and glyphosate, with likely other factors much more relevant than glyphosate for the development of NHL.

Roser and Ritchie [21] show an interesting map of the prevalence of cancer in general. Fig. 5 presents the number of people with cancer across all countries of the world. Fig. 6 presents the concentration in soil of glyphosate and AMPA [22]. AMPA is the recalcitrant metabolite aminomethyl-phosphonic acid of glyphosate [23]. Fig. 7 finally presents the watershed-aggregated runoff potential expressed in glyphosate [22]. While some countries such as the US have high numbers for both, most of the other countries do not have this correlation.

Many causes are biasing environmental studies, as many parameters may affect the result and not all of them are under control. Hence, a sharp increasing incidence rate of NHL could have been not necessarily correlated to the sharply increasing use of glyphosate. A lack of growth should be considered an

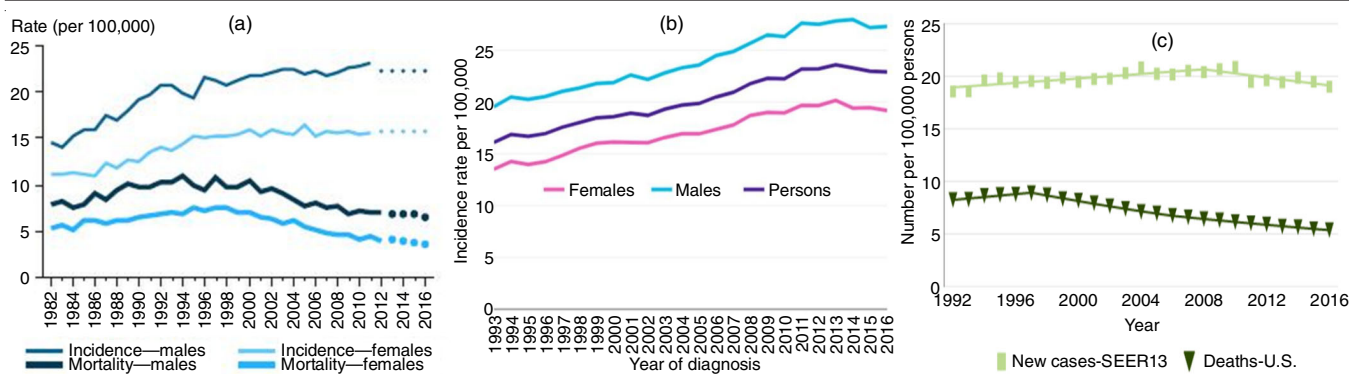
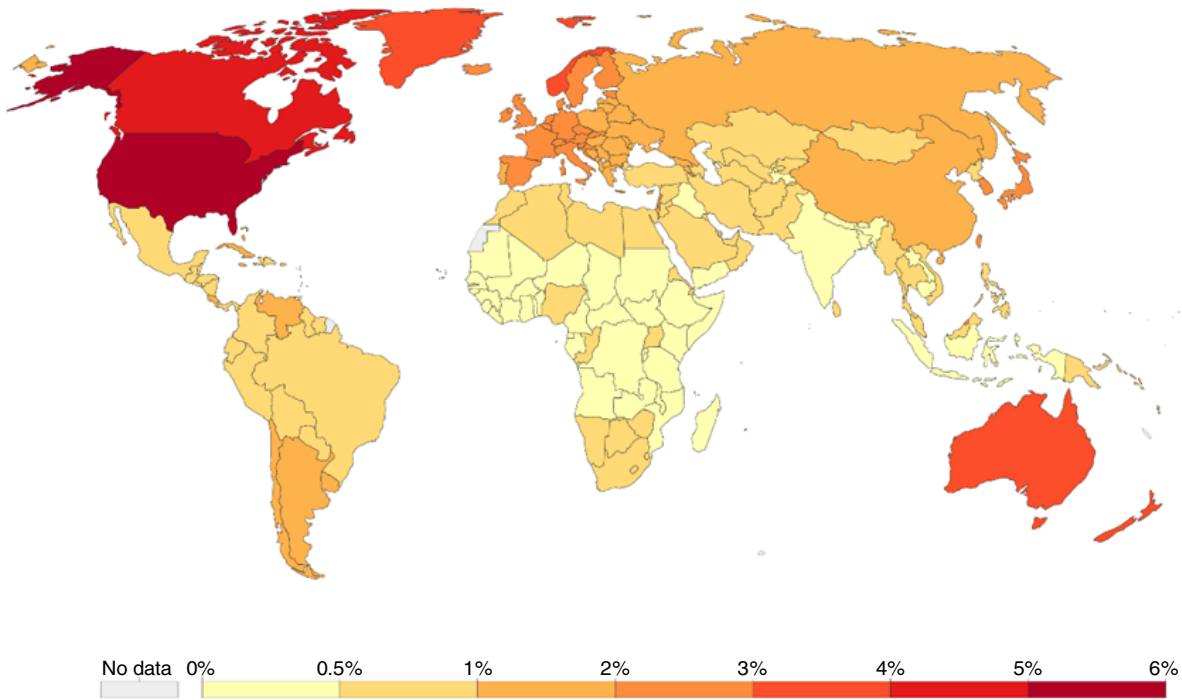


Fig. 4. (a) Incidence and mortality of NHL in Australia, 1982-2016. Copyright © Commonwealth of Australia 2020, cancer australia.gov.au/sites/default/files/statistics/summary/89982cca-9c13-4be9-b9e3-d65f25cfcde.jpg?n=9187, Accessed January 15, 2020. (b) incidence of NHL in UK, 1993-2016. Cancer Research UK, www.cancerresearchuk.org/sites/default/files/cancer-stats/inc_asr_mfp_nonhodgkinlymphoma_i16/inc_asr_mfp_nonhodgkinlymphoma_i16.xlsx, Accessed January 15, 2020. (c) Incidence of NHL in the US, 1992-2016. US National Cancer Institute, seer.cancer.gov/statfacts/html/nhl.html, Accessed January 15, 2020

Share of population with cancer, 2017



Share of total population with any form of cancer, measured as the age-standardized percentage. This share has been age-standardized assuming a constant age structure to compare prevalence between countries and through time.



Source: IHME, Global Burden of Disease

OurWorldInData.org/cancer · CC BY

Fig. 5. Cancer incidence across countries globally [Ref. 21]

indication that glyphosate is most likely not influential. The rate of NHL is stable in this century of further increasing use of glyphosate in countries of heavier agriculture such as Australia or the US, while the rate of NHL is higher and further increase in this century in the UK, where the use of glyphosate per capita is certainly less than in Australia. Thus, Fig. 4 suggests that other factors may be more dangerous for NHL than glyphosate. Similarly, the map of general cancer incidence, Fig. 5, does not correlate with the map of the concentration of glyphosate, Figs. 6 and 7.

If environmental studies are not conclusive against Round-Up, it has not been demonstrated so far how Round-Up may affect the abnormal production of lymphocytes that characterizes NHL. There are no studies that have proven a mechanism according to which this specific compound is acting on the lymphocytes. Nevertheless, the manufacturing of consent is further progressing through MSM and court actions to determine the end of the glyphosate era.

If glyphosate is more likely harmless to humans than carcinogenic, while it helps to feed the world, this is not relevant.

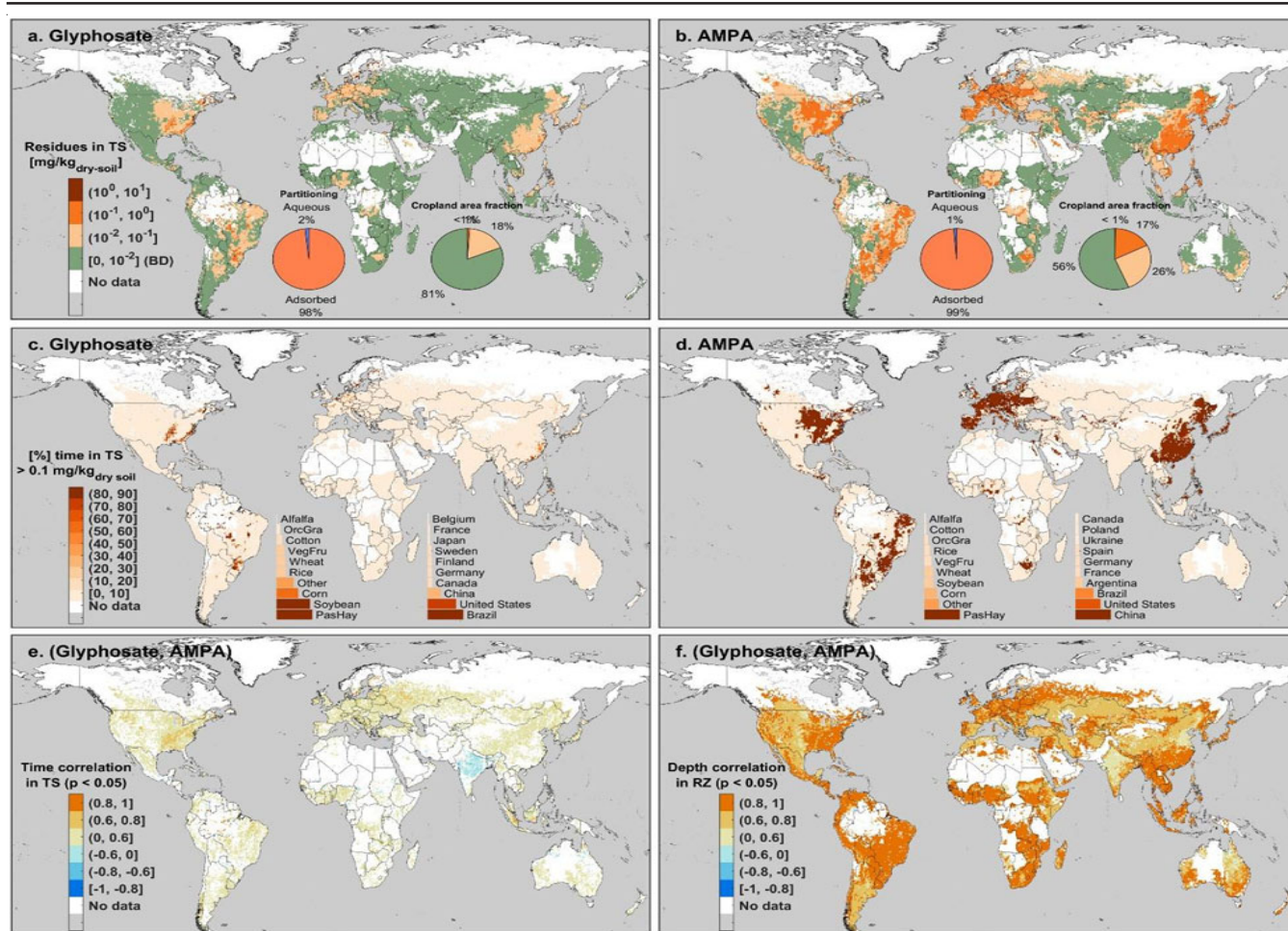


Fig. 6. Geographic distribution of (a) and (b) time-averaged glyphosate, GLP and recalcitrant metabolite aminomethyl-phosphonic acid of glyphosate, AMPA, residue mass fraction in the topsoil (TS, upper 30 cm), respectively; (c) and (d) percent time during which time-resolved GLP and AMPA mass fractions exceed 0.1 mg/kg_{dry-soil} in TS, respectively; and (e) and (f) time correlation of GLP and AMPA residue in TS and depth correlation of time-resolved residue in the root zone (RZ, upper 100 cm), respectively. Reprinted from Maggi *et al.* [22], Copyright (2020), with permission from Elsevier

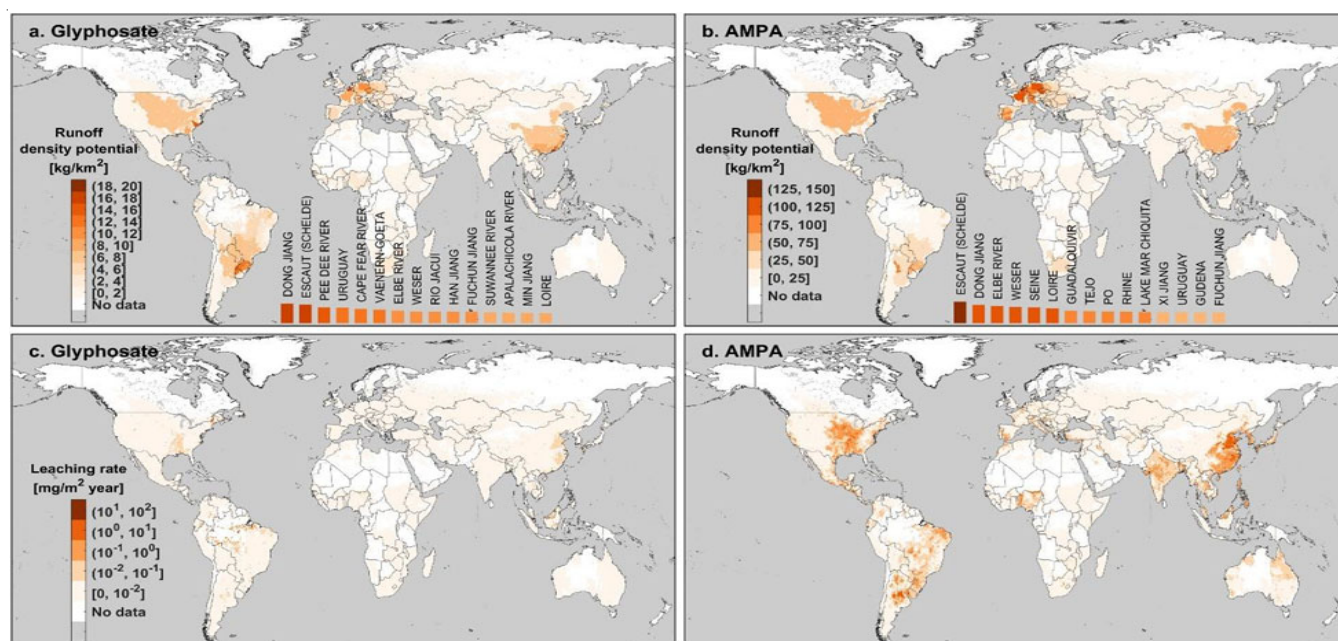


Fig. 7. Geographic distribution of (a) and (b) watershed-aggregated runoff potential expressed in glyphosate, GLP and recalcitrant metabolite aminomethyl-phosphonic acid of glyphosate, AMPA, residue in the topsoil (TS, upper 30 cm) per unit area, respectively; and (c) and (d) time-averaged annual leaching rate below the root zone (RZ, upper 100 cm) per unit area. Reprinted from Maggi *et al.* [22], Copyright (2020), with permission from Elsevier

A jury in California [24], has found that “Round Up weed killer is (a) a major factor in man’s cancer” and more specifically “Round Up caused non-Hodgkin lymphoma”. Many similar cases are being proposed.

Starting from the International Agency for Research on Cancer (IARC) subjective “likely carcinogenic” attribution, glyphosate has been transformed into an evil compound. NHL is the type of cancer most associated with glyphosate. The cause-effect is however still unproven.

For a causality, it would be necessary to confirm a correlation suggested by environmental studies by finding which are the mechanisms affecting the anomalous lymphocytes production in humans by this herbicide and prove them. We are at the stage where the environmental correlations are missing.

The consensus about the non-carcinogenic state of glyphosate is overwhelming [6,7,12,13,25-30]. There is no evidence of human carcinogenicity in the labeled uses of glyphosate. When a statistical association of glyphosate with cancer has been found, this has been the result of biases and confounding in correlational studies due to exposure to other carcinogens, as commented by Chang and Delzell [31], or cherry-picking of the information of past studies, as commented by several researchers [14-16].

The study of Zhang *et al.* [8] as also here commented, was wrongly proposing as evidence the likely increased carcinogenic in one group of four, neglecting to report the reduced carcinogenicity in three groups of four, that could have suggested the opposite conclusion. Glyphosate does not reduce the risk of cancer, nor increase.

Unproven is the claim that glyphosate causes DNA/chromosomal damage in human cells, or the many other claims linking glyphosate to every other health issue, from Birth Defects to Colitis, from Heart Disease to Parkinson’s Disease, from Alzheimer’s Disease to Autism. The hard facts supporting these claims are missing.

There is a growing concern, properly expressed by Kaiser [24] about one judge and few jurors with little or no scientific ability deciding if a compound is guilty or innocent of bringing benefits or damages to humanity. Civil Courts should not be the venue for deciding questions of science [24]. Similarly, this should not be a matter in the hand of the mainstream media. As concluded by Salzberg [15] even in those with very high exposures to glyphosate, the evidence that it causes any type of cancer is very weak. And for ordinary consumers, there’s nothing to worry about.”

The latest work by EPA [16] similarly concludes that the a priori hypothesis that higher/longer exposures produce larger effect sizes advanced by Zhang *et al.* [8] in their analysis does not appear to be supported by the new AHS data from Andreotti *et al.* [6], which is the largest, best-designed high quality study examined. EPA [16] clearly state the strongest support based on the weight-of-evidence is for glyphosate being categorized as not likely to be carcinogenic to humans.

A similar conclusion is also found by properly reading the work of Leon *et al.* [32]. Their AGRICOH survey combined three cohorts from France (AGRICAN), from Norway (CNAP) and the US (AHS). They did not find a statistically significant relationship between ever-exposure to glyphosate and NHL

overall. This analysis benefited from a large cohort of farmers and farmworkers, but only one of the three cohorts used actual measurement instruments (self-administered questionnaire) for glyphosate exposure. McFarland *et al.* [17] concluded that the additional information provided in Leon *et al.*’s work [32] combining the AGRICAN, CNAP and AHS studies do not impact the EPA conclusions that are again the strongest support based on the weight-of-evidence is for glyphosate being categorized as not likely to be carcinogenic to humans. Another recent meta-analysis showing little evidence of the association of glyphosate and NHL is proposed in Donato *et al.* [33]. The lack of any correlation between glyphosate and NHL is also proposed in Barukèic’s work [34].

There is a growing population in the world and a growing demand for food, water and energy. Science should work for the benefit of all mankind, making things better, rather than worse. The study of better herbicides is always welcomed, as well as welcomed is the study of what causes NHL and the way to cure NHL.

There are many worrying cases of manufacturing of consent through the Mainstream Media (MSM) biasing scientific debates of what is beneficial or not to the humanity. For what concerns glyphosate, the MSM is working towards a “guilty” verdict, no matter the charge, with NHL, or something else the crime. Scientific works suggesting glyphosate is more likely not harmful than carcinogenic [6,7,12,13,15,16,29,33] are all downplayed by the MSM. If the Wikipedia page for glyphosate censors, the US EPA statement of this January 6, 2020, leaving the “last word” to the discredited paper of Zhang *et al.* [6], this is certainly something, we should be worried about.

The causes of NHL are not known with certainty. Environmental studies do not show any association between NHL and glyphosate. There is no proven mechanism proposed to correlate the behaviour of lymphocytes with glyphosate. Among the hypotheses for NHL, glyphosate is one of the most unlikely causes of NHL. National and international agencies have found that glyphosate is not carcinogenic. It is not the single anomalous judgment, based on a hazard assessment, by a politicized organization such as the IARC, that should change everything. This singular view has fueled the demonization of glyphosate by activists, politicians and the organic food industries. This campaign may result in banning this herbicide *i.e.* environmentally benign and has no documented adverse effects on humans. This ban will result in a decline in productivity, deterioration of soil, increased labor for farmers and increased prices.

There are substantial benefits from the use of glyphosate and the best scientific evidence does not support the claim that glyphosate is carcinogenic. More specifically, there is no evidence that glyphosate is the cause of NHL, the subject of this review. There is however, a campaign in the media and in the courts that gives currency to the narrative that glyphosate is carcinogenic in general and causes NHL in particular.

Glyphosate has very likely nothing to do with the NHL. There are many sufferings of NHL without having had any contact with the herbicide. Billions of people around the world will be left without food, if glyphosate is suddenly eliminated without replacement. The glyphosate that causes the NHL is likely a minority narrative to harm the majority.

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