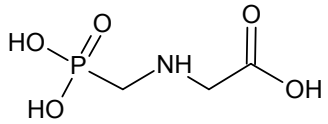
N-(PHOSPHONOMETHYL)-GLYCINE (ROUNDUP, GLYPHOSATE) IN RECENT CONTROVERSIAL OPINIONS

PAVEL DRAŠAR[a] and PAVEL POC[b]

[a] *Department of Chemistry of Natural Compounds, VŠCHT Prague, Technická 5, 166 28 Prague 6,* [b] *European Parliament, Altiero Spinelli Building, 60 rue Wiertz, B-1047 Brussels, Belgium*
pavel.drasar@vscht.cz

N-(Phosphonomethyl)-glycine and its salts, derivatives and formulations containing it – known as GBH (an abbreviation that stands for glyphosate-based herbicides but is interpreted by its opponents as standing for 'Grievous Bodily Harm', a term used in British criminal law) – are increasingly provoking debates that produce no consistent conclusion, for the reason that they are clearly being conducted by two irreconcilable camps that will never agree. On the one hand there are those who hold that there are good reasons to believe that glyphosate may be, and most likely is, linked to a range of diseases observed particularly among workers coming into contact with it, and on the other hand there are those who produce the chemical, of which almost 10 million tonnes have been used on fields worldwide since 1970, making it the most widely used chemical ever made. We will therefore look at some recent opinions.



N-(Phosphonomethyl)-glycine

According to the American Chemical Abstracts Service SciFinder, some 17 000 papers have been written about the chemical itself over the period of its use, while the patent of 1961 describes it as a product useful for suppressing nematodes, rust and mildew[1]. The first paper on its biochemistry states that it inhibits amino acid biosynthetic pathways[2].

Glyphosate broad-spectrum herbicide has been sold to farmers and gardeners (under the common trade name of 'Roundup') since about 1974 (ref.[3]). Volumes of glyphosate herbicide have steadily increased since that time, and some farmers cannot imagine growing their crops without it. This type of herbicide was developed in an effort to replace or reduce reliance on herbicides that cause well-documented problems associated with crop damage, slipping efficacy and human health risks. Initial toxicity tests indicated that it posed a relatively low risk to non-target species, including mammals. As a result, regulatory authorities around the world concluded that acceptable exposure limits had to be established, and it is still recorded in recognised databases as a substance with a relatively low acute toxicity level (e.g. LD_{50} rats and mice 4873, 1568 mg/kg, p.o.)[4]. On the basis of developments and changes in the use of GBH – linked to the use of genetically modified, herbicide-tolerant crops – regulators have dramatically increased tolerance levels in maize, oilseed crops (soybeans and rape) and alfalfa crops and related animal feeds. Animal and epidemiology studies published in the last decade, however, point to the need for a fresh look at glyphosate toxicity. In addition, the World Health Organisation and its International Agency for Research on Cancer (IARC) recently concluded that glyphosate is 'probably carcinogenic to humans'. In response to changing GBH use patterns and advances in scientific understanding of their potential hazards, a working group of experts has issued an opinion that summarises recent studies on GBH use, mechanisms of action, toxicity in laboratory animals and epidemiological studies, but also changes to current safety standards. The group concluded that: (1) GBHs are the most heavily applied herbicides in the world, and their usage continues to rise. (2) Worldwide, GBHs often contaminate drinking water sources, precipitation, and air, particularly in agricultural regions. (3) The half-life of glyphosate in water and soil is longer than previously recognised. (4) Glyphosate and its metabolites are widely present in the global soybean supply. (5) Human exposures to GBH are rising. (6) Glyphosate is now authoritatively classified as a probable human carcinogen. (7) Regulatory estimates for tolerable daily intakes of glyphosate in the United States and European Union are based on outdated science. The group offers a series of recommendations on the need for new investments in epidemiological studies, biomonitoring and toxicology studies that draw on the principles of endocrinology to determine whether the effects of GBHs are due to endocrine disrupting activities. The group suggests that commercial formulations of GBHs should be prioritised for inclusion in government-led toxicology testing programmes, such as the US National Toxicology Programme, as well as for biomonitoring, as conducted in the US by the Centre for Disease Control and Prevention[5].

In the same year as the above paper, a broad-ranging paper was published consisting of five studies by varying combinations of authors who stated, among other things, that they used data from Monsanto. The work assumes that scientific research on the possible carcinogenic risks of glyphosate and its use will continue for some time, as will the associated debate about how science influences political decisions on the regulation of products containing glyphosate. The contents of these five documents, the extensive list of references in each of them, including supplementary material (available online for several of them), should contribute to and pave the way for a continuing scientific debate that leads to political decisions on this widely used chemical[6]. The first study concludes that the known data do not support the IARC conclusions that classified glyphosate as a 'probable human carcinogen' and further concludes, consistent with previous studies, that glyphosate is unlikely to constitute a carcinogenic risk for humans[7]. The second states that only highly exposed population groups can be perceived as threatened[8]. The third states[9] that a review of the data available did not find a basis in the epidemiological literature for a causal link between glyphosate and non-Hodgkin's lymphoma (NHL) or multiple myeloma (MM). The fourth then adds that, with regard to carcinogenicity and mechanism classifications, the authors concluded that the evidence

relating to oxidation stress in the carcinogenicity mechanism was largely unconvincing and the data profiles were not consistent with the characteristics of genotoxic carcinogens[10,11].

So, to complicate matters, the IARC (International Agency for Research on Cancer) working group of nearly one hundred global experts concluded in 2016 that glyphosate is, in contrast to the above, a 'probable human carcinogen', and listed it under its Category 2A owing to sufficient evidence of carcinogenicity in animals but limited evidence of carcinogenicity in humans and strong evidence of two carcinogenic mechanisms; while the European Food Safety Authority (EFSA) concluded in 2015 that 'glyphosate is unlikely to pose a carcinogenic hazard to humans and the evidence does not support classification with regard to its carcinogenic potential'[12].

A further study from 2016 suggests a broader risk of developing skin melanoma in persons exposed to pesticides, especially herbicides (glyphosate) and fungicides (mancozeb, maneb), particularly if subjects are exposed to sunlight while performing their work[13].

A systematic overview and meta-analysis from 2016 examines the relationship between exposure to glyphosate and the risk of lymphohematopoietic cancer (LHC), including NHL, Hodgkin's lymphoma (HL), multiple myeloma (MM) and leukaemia. The authors note, in contrast, that no causation was found between exposure to glyphosate and the risk of any type of HL[14].

Another alarming discovery was the fact that commercial products containing herbicides – such as Dicamba, 2.4-dichlorophenoxyacetic acid and glyphosate – induce a changed response to antibiotics in the case of *Escherichia coli* and *Salmonella enterica* serovar Typhimurium[15]. In addition to this finding, the paper also discusses potential health effects in humans, domestic animals and critical insects. Similarly worrying is the finding that glyphosate, or rather its metabolites such as aminomethylphosphonic acid (AMPA) and methylphosphonic acid, and impurities present, such as *N*-(phosphnomethyl)iminodiacetic acid (PMIDA), *N*-methyl glyphosate, hydroxymethylphosphonic acid and bis-(phosphonomethyl)amin, cause damage to human erythrocytes[16].

But if we look at an 'older' paper from 2013, which vividly describes how glyphosate suppresses cytochrome P450 (CYP) enzymes and the biosynthesis of amino acids in the intestinal microbiome (a microorganism now considered a disease pathway of the modern age)[17], we find that, at least for those amino acids, we have been going round and round this issue since 1972. According to the study, GBH's inhibition of CYP enzymes contributes to poor detoxification of xenobiotics and to inflammatory processes, gastrointestinal problems, obesity, diabetes, heart disease, depression, autism, infertility, cancer and Alzheimer's disease. It is hard to avoid the impression that this paper has somehow been overlooked. Moreover, when we also see that glyphosate can also have a negative effect on grapevine berries by increasing their acidity and reducing their anthocyanin content[18], we must conclude that glyphosate and all GBHs should be regarded as chemicals similar to DDT or thalidomide, which can be used only in exceptional cases and with the utmost caution, and that the use of such chemicals should be avoided wherever possible. It is very likely that some chemicals that are considered relatively harmless to humans and the acute toxicity of which has been shown to be low, may, as endocrine disruptors, cause chronic problems that are hard to predict, even in small doses[19]. Some evidence for this is set out in, for example, a Dutch study which found 196 deaths over 13 years among 1 341 licensed appliers of herbicides, with many different causes, but especially cancer, as shown similarly in an analogous study conducted on 17 000 children whose parents used pesticides[20], and this fact is also supported by another extensive survey[21].

Disregarding long-known uncomfortable facts – for economic reasons, as might be expected – is unjustifiable, and we can therefore only agree with the above study that there is a very pressing need to keep stepping up monitoring of the proven and potential effects of elements of our environment on humans and to draw the scientific, economic and political conclusions from that monitoring in good time.

REFERENCES

1. Toy A. D. F., Uhing E. H.: US 3160632 19641208 (1964).
2. Jaworski E. G.: J. Agricult. Food Chem. *20*, 1195 (1972).
3. Thomas T. M., Burke J.: Irish J. Agricult. Res. *11*, 366 (1972).
4. The Merck Index, 13. vyd., Merck & Co., Inc., Whitehouse Station, New Jersey 2001.
5. Myers J. P., Antoniou M. N., Blumberg B., Carroll L., a spol.: Environ. Health *15*, 19 (2016).
6. McClellan R. O.: Crit. Rev. Toxicol. *46*, sup1, 1 (2016).
7. Williams G. M., Aardema M., Acquavella J., Berry S. C., Brusick D., Burns M. M., a spol.: Crit. Rev. Toxicol. *46*, sup1, 30 (2016).
8. Solomon K. R.: Crit. Rev. Toxicol. *46*, sup1, 21 (2016).
9. Acquavella J., Garabrant D., Marsh G., Sorahan T., Weed D. L.: Crit. Rev. Toxicol. *46*, sup1, 28 (2016).
10. Brusick D., Aardema M., Kier L., Kirkland D., Williams G.: Crit. Rev. Toxicol. *46*, sup1, 56 (2016).
11. http://www.huffingtonpost.com/carey-gillam/iarc-scientists-defend-gl_b_12720306.html , staženo 9. 12. 2016.
12. Portier C. J., Armstrong B. K., Baguley B. C., Baur X., Belyaev I., a spol.: J. Epidemiol. Commun. H. *70*, 741 (2016).
13. Fortes C., Mastroeni S., Segatto M., Hohmann C., Miligi L., Bakos L., Bonamigo R.: J. Occup. Environ. Med. *58*, 370 (2016).
14. Chang E. T., Delzell E.: J. Environ. Sci. Heal. B *51*, 402 (2016).
15. Kurenbach B., Marjoshi D., Amábile-Cuevas C. F., Ferguson G. C., Godsoe W., Gibson P., Heinemann J. A.: mBio *6* (2), e00009-15 (2015).
16. Kwiatkowska M., Huras B., Bukowska B.: Pestic. Biochem. Physiol. *109*, 34 (2014).
17. Samsel A. Seneff S.: Entropy *15*, 1416 (2013).
18. Donnini S., Tessarin P., Ribera-Fonseca A., Di Foggia M., Parpinello G. P., Rombola A. D.: Food Chem. *213*, 26 (2016).
19. Ritter S.: Chem. Eng. News, Oct. *24*, 5 (2016).
20. Flower K. B., Hoppin J. A., Lynch C. F., Blair A., Knott C., Shore D. L., Sandler D. P.: Environ. Health Perspect. *112*, 631 (2004).
21. Weichenthal S., Moase C., Chan P.: Environ. Health Perspect. *118*, 1117 (2010).