# MAIN REPORT: GLYPHOSATE – THE EVIDENCE

## WORLDWIDE USE OF GLYPHOSATE

Glyphosate, also called N-(phosphonomethyl)glycine as well as the different products in which it appears as an active agent (Roundup, Rodeo, etc.), is a biologically active substance used as a broad spectrum, post-emergent, non selective (kills all vegetation), systemic herbicide. It is the most widely used herbicide in the world, with an estimated 720,000 tonnes produced globally in 2012 (IARC 2017; Glyphosate Task Force, 2013a). An increase in production is linked to the widespread adoption of no-till practices (to reduce soil erosion) and the use of genetically modified crops engineered to be glyphosate resistant (post-harvest use only in EU due to restrictions on genetically modified crops) as well as its broad spectrum, non-selective nature (IARC, 2017; Duke & Powles, 2009; Glyphosate Task Force, 2014). When applied at low concentrations, it can act as a desiccant or plant growth regulator.

A search of the Garden Pesticides Search facility offered by the HSE (2019a) reveals that there are 276 individual products containing glyphosate currently authorised for use by amateurs in UK: these include products such as retailer own brand weed-killers, ready-to-use formations such as path and patio sprays, concentrated formulations from a range of chemical producers, and products aimed at specific weeds/ plants such as brambles, tree stumps, and ivy. Names vary with many recognisable such as 'Roundup' or names including 'weed-killer', with one brand from Monsanto called 'Ecoplug Max Garden' or 'Roundup Ecoplug' which, despite its 'green' sounding name contains 720g/kg of glyphosate. Many of the ready-to-use formulations contain 7.2 g/l glyphosate while many concentrated forms are 60 g/l – 120 g/l glyphosate with 72-90 g/l most common but can be up to 360 g/l glyphosate, sometimes with other herbicides added (e.g. diflufenican, pyraflufen-ethyl, diquat and sulfosulfuron). In granular form, 680 g/kg upward of glyphosate are not unknown. It is one of the most commonly used pesticides in the home and garden sector (IARC, 2017).

For professional users, there are a further 170 products available (HSE, 2019b). Concentration in these products tends to be >360 g/l or equivalent in granule form but ready-to-use formulas of 144 g/l glyphosate are also available. While the amateur-use products are largely licenced for use on unwanted vegetation, professional-use products are aimed more at the agricultural sector with licencing for destruction of edible crops as well as use in and around cereal crops. Horticultural crops might also be cited e.g. apple and pear, as well as amenity vegetation use, forestry and land adjacent to aquatic areas.

Given that glyphosate is used as an herbicide in mixtures containing other chemicals (adjuvants, surfactants etc.), the term glyphosate-based herbicides or GBHs will be used when referring to the herbicide mixture to distinguish it from the active ingredient glyphosate.

## MODE OF ACTION

Glyphosate's mode of action is to inhibit plant growth by preventing the formation of amino acids crucial to the growth and development of the plant in meristematic cells. More specifically, glyphosate interferes with the metabolism of chorismic acid in the aromatic amino acid biosynthetic pathway (Jaworski, 1972) by binding to and blocking the activity of the enzyme enolpyruvylshikimate-3-phosphate synthase (EPSPS) in chloroplasts, preventing the biosynthesis of phenylalanine, tyrosine and tryptophan which are involved in the formation of hormones, vitamins and other essential plant metabolites. Ultimately, EPSPS blocking prevents carbohydrates from forming amino acids leading the plant to starve to death (Glyphosate Task Force, 2013b). EPSPS is found in plants, many bacteria, fungi and other microorganisms and is hence a focus of research for new herbicides, antibiotics and antiparasitics (Schönbrunn et al., 2001): Schönbrunn et al., (2001) report that glyphosate inhibits the growth of a number of pathogens including the malaria-causing *Plasmodium falciparum*. A result of this particular biological activity does raise concern for soil biota and microbiome health (Druille et al., 2016) but does indicate that animals are less likely to display a biological response when exposed to glyphosate.

As animals do not possess EPSPS, glyphosate is mainly excreted unmetabolized in the urine although gut microbes might have a role in metabolism (IARC, 2015: Motojyuku et al. 2008). Levels have been detected in those exposed to glyphosate, with glyphosate identified in urine and blood. Dermal absorption and ingestion (accidental and deliberate) are considered the main routes of exposure, with evidence indicating that the use of gloves reduces urinary levels (Curwin et al. 2007). Addition of other substances (adjuvants, surfactants etc.) might increase the uptake/intake of glyphosate during exposure to herbicide formulations and might also alter how glyphosate is metabolised (Benbrook, 2019).

## LEGISLATION AFFECTING GLYPHOSATE IN EUROPE

A recent research paper by Sosa et al. (2019) analysed the peer-reviewed research submitted to science journals from 1974 (the year Monsanto launched glyphosate to market) to 2016 (as discussion on the health impacts of glyphosate was escalating), finding that the first 30 years was dominated by research in the US and by the producers Monsanto. Sosa et al. (2019) report that it wasn’t until around the year 2000 that research into the toxicological and environmental impacts of glyphosate was first seriously addressed, a delay of around 25 years since the herbicide was first introduced to the market. The original patent expired in the USA in the year 2000 but earlier, in 1991, around the rest of the world (Székács & Darvas, 2018).

While much of the earlier research attempted to elucidate the mode of action of glyphosate, as discussed by Schönbrunn et al., (2001), later research has focused on the environmental and health impacts of glyphosate. It is a common misconception that all the chemicals we use have been exhaustively tested for toxicological and environmental impact – this is not the case. In the EU, the REACH Regulation (EC No 1907/2006) was introduced in 2007 to improve the protection of human health and the environment from risks posed by chemicals. REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) sets out procedures for collecting and assessing the properties and potential hazards of chemicals manufactured or imported into the EU in quantities of one tonne or more (HSE, 2019c; EU, 2016). It meant that, for the first time, detailed analysis of many widely used chemicals was required and has resulted, in combination with a range of other substance specific legislation, in the restriction, withdrawal or substitution of a number of chemicals considered by the EU to possess unacceptable levels of health or environmental risk. Herbicides have long been covered by plant protection products legislation with the first pan-EU legislation coming into force in 1993 following the implementation of the Plant Protection Products Directive 91/414/EEC which was subsequently replaced by Plant Protection Products Regulation (EC 1107/2009). This regulation determines whether glyphosate can be used as an herbicide in the EU and hence the UK. It is expected that under Brexit, this will remain the case, at least initially.

The European Chemical Agency (ECHA) compiles a chemicals database which contains data required by REACH and other legislation (although not Plant Protection Products Regulation information) and lists glyphosate as a substance that is ‘toxic to aquatic life with long lasting effects and causes serious eye damage' (ECHA, 2019). It is listed in Annex III of REACH as 'Substances predicted as likely to meet criteria for category 1A or 1B carcinogenicity, mutagenicity, or reproductive toxicity'.

In the EU Pesticides database, reports and findings of tests and studies used to evaluate approval of glyphosate are available together with the most recent renewal report: the approval for glyphosate was renewed in December 2017 until December 2022 (EU Pesticides Database, 2019). The renewal is subject to a number of requirements including protection of groundwater in vulnerable areas, protection of operators and amateur users, protection of biodiversity/non-target organisms, and compliance with pre-harvest good agricultural practice. Despite being approved for use, the renewal report does state that 'Member States shall ensure that the genotoxic potential of formulations containing glyphosate is addressed before granting authorisations for plant protection products containing glyphosate'. This statement indicates that the while the EU is not explicitly banning glyphosate, it is leaving it to members states to determine whether or not to take steps to withdraw approval. A number of European countries, together with other countries around the world, have made the decision to ban glyphosate use/withdraw approval/restrict use, as reported by the attorneys Baum, Hedland, Aristei, Goldman PC (2019), the law company behind two of the most recent court cases.

## INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

In July 2015, the International Agency for Research on Cancer (IARC), a highly respected organisation within the World Health Organization, first published IARC Monographs Volume 112: Some Organophosphate Insecticides and Herbicides; the volume has since been updated and made available online (Guyton et al., 2015; IARC, 2017). The volume included a monograph on glyphosate, and this became a focus of attention. The IARC Working Group reviewed the evidence collected and determined that glyphosate was 'probably carcinogenic to humans' (Group 2A).

The classification made headlines around the world, particularly with regard to the court cases that resulted. So far (as of May 2019), there have been three successful jury verdicts in favour of the plaintiffs against Bayer, the chemical manufacturer who bought the original developers of glyphosate, Monsanto, in 2018. The compensation awarded is substantial, with the last court case resulting in $87 million awarded to a couple who had been diagnosed with non-Hodgkin lymphoma attributed to glyphosate use (Los Angeles Times, 2019). All cases so far have been brought in California, the only US state to issue a warning on glyphosate by adding it to the Proposition 65 List (OEHHA, 2019). A court case is due to start in August 2019 in St Louis, Missouri, the home of Monsanto, the results of which will be carefully watched around the world as there are over 13,000 cases in the US alone waiting to go to trial (Reuters, 2019). Two of the three cases heard so far and the case in Missouri relate to glyphosate use at home: the first case was the only one to involve use in an occupational context (school groundsman).

## IARC EVIDENCE

Although IARC has classified glyphosate as 'probably carcinogenic to humans' (Group 2A) – a category that also includes anabolic (androgenic) steroids, lead, red meat and occupational exposure of hairdressers to hair colourants – this is a summary evaluation that overlays more subtle interpretations of the data currently available. This decision was based on "limited" evidence of cancer in humans (from real-world exposures that actually occurred as shown in epidemiological studies) and "sufficient" evidence of cancer in experimental animals (from studies of "pure" glyphosate in toxicological studies). IARC also concluded that there was "strong" evidence for genotoxicity, both for "pure" glyphosate and for glyphosate formulations (IARC, 2017).

All IARC monographs follow a particular format, analysing publicly available, peer-reviewed studies to assess exposure data (levels of use, exposure pathways and evidence of exposure such as levels in the environment, food and in biomarkers), reports of cancer in humans (epidemiological studies), cancer in experimental animals (using toxicological testing) and information from other sources such as work to indicate potential mode of carcinogenic action. Exposure studies have identified glyphosate in urine in both urban and rural populations as well as chromosome damage in blood samples from GBH-exposed individuals (MLHB, 2013; Varona et al., 2009; Bolognesi et al. 2009). One of the strongest types of epidemiological study is the cohort study which compares exposures in a given population (the cohort) to particular health outcomes over time. Such populations or cohorts tend to be large, many thousands of people, and so provide a reliable measure of risk. The Agriculture Health Study is a cohort study carried out in the Midwest USA 1993-2001 which considered health risks arising from glyphosate exposure. It did not report an association with non-Hodgkin lymphoma or all cancers combined but did identify a two-fold increase in risk for multiple myeloma, a subtype of non-Hodgkin lymphoma, in a subgroup of the cohort associated with exposure to glyphosate (RR= 2.6; 95% CI, 0.7–9.4). Due to perceived limitations of the multiple myeloma subgroup and concerns with other studies reporting a link to multiple myeloma, the IARC Working Group did not consider this outcome in their final decisions. Case-control studies in the USA, Canada and Sweden, which match cases of a particular health outcome with a control group which is free of the health outcome to understand the causal factors behind the health outcome, did find an increased risk for non-Hodgkin lymphoma associated with glyphosate exposure. The odds for developing no-Hodgkin lymphoma were 1.51 to 2.1 times greater for those exposed to glyphosate (i.e. odds ratios were 2.1 (95% CI, 1.1–4.0); 1.85 (95% CI, 0.55–6.2); and 1.51 (95% CI, 0.77–2.94)). Meta-analyses are the very best evidence base and yet there is only one such study currently available for glyphosate. This meta-analysis indicates that glyphosate exposure might increase risk by 30% (RR = 1.3; 95% CI, 1.03–1.65). Animal tests indicate a link between cancer and glyphosate, operating through oxidative stress. One study of exposed individuals identified a significant relationship between chromosomal damage and glyphosate exposure (Bolognesi et al., 2009) which is supported by the more extensive animal data identifying DNA damage, providing strong support for genotoxicity.

## USEPA AND EFSA – A DIFFERENT CONCLUSION?

Following the publication of the IARC report, the United States Environmental Protection Agency (USEPA) published a review of the carcinogenicity of glyphosate (USEPA, 2016). The conclusion of the report was that glyphosate was "not likely to be carcinogenic to humans." A similar conclusion was reached by the European Food Safety Authority (EFSA, 2015) in carrying out a risk assessment as part of the glyphosate pesticide renewal application consideration. EFSA reported that "glyphosate is unlikely to pose a carcinogenic hazard to humans and the evidence does not support classification with regard to its carcinogenic potential according to Regulation (EC) No 1272/2008". Nevertheless, the approval renewal decision does contain a note of caution (as seen above). It is therefore worth exploring the different conclusions reached by EFSA and the USEPA compared to IARC.

The simple explanation is that the different organisations considered different evidence bases and assigned different weights to studies included in both assessments. This does not necessarily mean that one conclusion is necessarily superior to another. According to a study of the different analyses carried out by the different organisations, Benbrook (2019) has suggested that IARC considered a greater number of studies, with more weight given to epidemiological studies and toxicological studies of GBHs, and gave greater weight to occupational exposure, particularly in farming communities. The USEPA and EFSA looked at the chemical glyphosate (rather than GBHs), different toxicological reports and population-level dietary exposures assuming legal levels of residue in food.

A key aspect, therefore, is the different targets considered by the USEPA and IARC in their investigations: IARC looked at occupational exposure and the exposure of communities exposed to directly to GBH spraying activities while the USEPA looked at dietary exposure at the population level. It can therefore be argued that it is the degree of exposure – or dose - that is important, as long understood through the much-used quote attributed to Paracelsus: "All things are poison and nothing is without poison; only the dose makes a thing not a poison." While there is disagreement concerning the particular hazard posed by glyphosate and GBHs, they are undoubtedly biologically active and therefore capable of exerting an influence on a living organism. It is possible to reduce any risk by minimising exposure: hazard + exposure = risk. Small doses obtained via dietary exposure, for instance, pose little risk. Larger doses, for instance large scale aerial spraying, are of greater concern.

A further consideration is the potential difference between the risk posed by glyphosate compared to GBHs. Hollert and Backhaus (2019) emphasise that GBHs are more toxic than glyphosate alone, as borne out by the IARC review compared to the USEPA work, but there has been little work on the different GBH formulations although recent work indicates that the toxicity of ingredients other than glyphosate in GBHs are of greater concern than the active ingredient (Mesnage et a;., 2019).

## WHAT DOES THIS MEAN FOR HORTICULTURISTS?

As with all evidence-based work, more studies are required to enable a better understanding of the link between glyphosate, GBHs and cancer. The high profile of the IARC classification combined with the court cases will have initiated more studies into glyphosate and more epidemiological studies will be expected in the coming years (a very recently meta-analysis, for instance, found an increased risk of non-Hodgkin lymphoma in individuals with high GBH exposure (Zhang et al., 2019)). It is a highly politicised area and so is likely to be discussed and debated for many years, as was the case for the tobacco industry. While tobacco smoking is now classified as a definite carcinogen (Group 1: carcinogenic to humans), it is still legal and widely practiced. Other Group 1 carcinogens are processed meat (consumption of), Chinese-style salted fish, solar radiation and outdoor air pollution – all still widely consumed/major exposures. For comparison, other IARC Group 2A carcinogens include consumption of red meat, emissions from high temperature frying and drinking very hot beverages.

A pragmatic approach is therefore suggested to GBHs. Reducing exposure through the use of personal protection equipment (PPE), ensuring full compliance with regulations and following the recommendations of manufacturers will reduce overall risk. The UK has long required professional users of pesticides to undergo courses to ensure awareness of the environmental and health consequences of incorrect pesticide use (Safe Use of Pesticides courses and qualifications: PA 1 and beyond): all professional horticulturists should have completed PA1 and so will be aware of the need for PPE and correct storage, use and disposal of these chemicals. Amateur users of GBHs who do not follow the guidelines on packaging are potentially at more risk of exposure – a factor seen in the recent court cases in the USA. Use of an integrated weed management strategy and use of alternatives to herbicide application will also reduce exposure and hence risk, with the added benefit of reducing the amount of chemical released to the wider environment (see below). A growing acceptance of 'untidy' gardens and the benefits of certain weeds for biodiversity should also help reduce use of herbicides more generally.

Horticulture as an occupation has not been assessed by IARC although a number of occupations have been considered, with some classified as Group 1: carcinogenic to humans (painter; chimney sweep, iron and steel founding) and Group 2A: probably carcinogenic to humans (hairdressers). For horticulturists, the main risks are probably sun exposure (solar radiation is a Group 1 carcinogen) and musculo-skeletal issues due to the physical nature of the occupation.

## ENVIRONMENTAL IMPACTS

Glyphosate is considered an aquatic toxin and has been identified in most environmental compartments. There are a plethora of studies that indicate the negative impacts of glyphosate and GBHs on the environment, many from over the last few years, considering depletion of soil microorganisms (e.g. Druille et al. 2016; Helander et al. 2018) to long-term impacts on soil macro fauna (e.g. Jacques et al., 2019), impacts on fish and other aquatic organisms (Ma et al., 2019; Matozzo et al., 2019; Smith et al., 2019) and even damage to non-target plants (Soares et al., 2019) and bees (Eler Seide et al., 2018). As biologically active substances, herbicides have long been recognised as environmental pollutants and this is one of the key considerations in training courses aimed at the safe use of pesticides. Correct use of GBHs and other herbicides reduces risk of environmental damage but as many of these studies show, it does not prevent it. The impact of long-term application will not be understood for many years as glyphosate and GBHs have been used for less than 50 years.

Levels in food are reassuringly found in most studies to be below MRLs (maximum residue levels) (Xu et al., 2019).

## OVERALL CONCLUSION

Glyphosate is still an essential chemical for use in weed control, particularly in large-scale food production. Technological innovations are increasingly allowing for spot weeding on large-scale production facilities which will reduce use although GM plants with glyphosate resistance are of concern with regard to volumes used as well as potential glyphosate resistance in wild populations. Environmental issues alone would warrant caution with regard to over-use of GBHs, with glyphosate a recognised aquatic toxin and also demonstrating potential long-term damage to soil organisms, non-target plants and terrestrial invertebrates. All studies, by USEPA, EFSA and IARC, would indicate that while there is some disagreement concerning the hazard posed to human health – whether it poses genotoxicity or not – there is little risk posed by residues on food. The most significant evidence for a health impact is associated with large exposures to GBHs, a particular concern for occupational users. Given that more evidence is required to fully assess the degree of risk posed by glyphosate, a pragmatic approach is to ensure that PPE is worn at all times during preparation, use and disposal of GBHs, and that regulations and good practice are followed at all times. Considering whether the use of GBHs are really needed in any given situation or whether an alternative weed control method, including use of interpretation in public gardens to develop a better acceptance of weeds, is more suitable offers another approach to reducing exposure.

## RECOMMENDATIONS

Suggestions for public gardens:

- Follow all manufacturers guidelines for use, storage and disposal of glyphosate including accurate recording all glyphosate use by volume and application type;
- Ensure that all PPE is effective and used properly to minimise operational exposure;
- Assess how much glyphosate is being used in your garden, where it is applied and for what reason – are current usage patterns strictly necessary?
- Develop a clear policy brief on the use of glyphosate in your garden defining when, where and how it is to be used including restrictions on use such as where alternative approaches exist and where bystander exposure might be an issue (gardens or areas with high visitor numbers/engagement). Implement this policy across your garden.

- Accept weedy areas – consider use of interpretation to explain to visitors why the area might not be pristine. Perhaps we need to be more accepting of the 'messy garden' look?

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