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Glyphosate, the Most Widely Used Herbicide.
Health and safety issues. Why scientists differ in their evaluation of its adverse health effects

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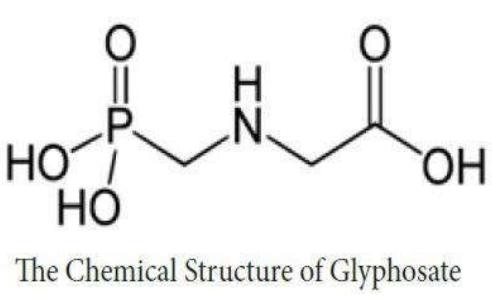
Abstract. Glyphosate, is an herbicide that was introduced by Monsanto under the trade name Roundup in 1974 and in the last decade became the most widely used agricultural pesticide worldwide. It allows farmers to kill weeds but not the crops that will grow there. Glyphosate comes in many forms, including an acid and several salts. There are over 750 products containing glyphosate for sale. It is registered in 130 countries and has been approved for weed control in more than 100 crops. Glyphosate has excellent environmental features such as rapid soil binding, biodegradation and extremely low toxicity to mammals, birds and fish. The most important aspect of pesticide safety is the adverse health effects to farmers and people working and living in agricultural areas. Many epidemiological studies in the last years and various toxicological data were accumulated for glyphosate but the majority found no correlation with any kind of cancer or adverse health effects.
Glyphosate had over the years many environmental critics. There were many claims that glyphosate was linked to increase risk for autism, cancer, gluten allergies, 'leaky gut' syndrome and other disorders. Concerns about glyphosate's possible health impacts increased in 2015 after the International Agency for Research on Cancer (IARC), a research arm of the World Health Organization (WHO), classified glyphosate as "probably carcinogenic," (Group 2A) using what is called a hazard evaluation. The IARC classification was widely circulated by anti-chemical and environmental advocacy groups, which argued for bans or tighter restrictions of the herbicide. In the last decade experimental and epidemiological evidence was accumulated that glyphosate has no significant toxicity in acute, subchronic, and chronic studies. The genotoxicity and carcinogenicity studies for glyphosate and its commercial products (Roundup) were assessed. There was no convincing evidence for direct DNA damage *in vitro* or *in vivo*, and it was concluded that Roundup and its components do not pose a risk for various types of cancer in humans. So, the decision of IARC in 2015 to classify as Group 2A carcinogen came as a big surprise, at the time that a big epidemiological study in the USA (published finally in 2018) with farmers established that there was no risk for development of cancer after long-time exposure to glyphosate. This review presents the most important studies, the dispute among scientists on the IARC decision for the carcinogenicity. Also, an assessment for the differences among toxicologists and other evaluators and regulators for glyphosate adverse health effects and environmental risks.

Introduction: Glyphosate the most widely used herbicide

Glyphosate is an herbicide. It is applied to the leaves of plants to kill both broadleaf plants and grasses. The sodium salt form of glyphosate is used to regulate plant growth and ripen fruit. Glyphosate was first registered for use in the U.S. in 1974 by Monsanto (Roundup). Glyphosate is one of the most widely used herbicides in the USA and in other developed countries. Farmers apply glyphosate in agriculture and forestry, and also it can be applied on lawns and gardens, and for removing weeds in industrial areas. Some products containing glyphosate can be used to control aquatic plants. Glyphosate comes in many forms, including an acid and several salts. There are over 750 products containing glyphosate for sale in the US (commercial bane Roundup, Monsanto). Glyphosate is a non-selective herbicide, meaning it will kill most plants. It prevents the plants from making certain proteins that are needed for plant growth. Glyphosate stops a specific enzyme pathway, the shikimic acid pathway. The shikimic acid pathway is necessary for plants and some microorganisms.[1]



The Chemical Structure of Glyphosate

Figure 1. Glyphosate was registered in 1974 by Monsanto (Roundup) and has been a breakthrough in herbicide chemicals for farming helping farmers to grow crops more sustainably.

According to Monsanto, glyphosate has been a breakthrough for farming. Not only do glyphosate products work really well on weeds, but they also help farmers grow crops more sustainably. For example, it has helped farmers adopt what is called "conservation tillage." With conservation tillage, farmers can disturb less soil and drive their tractors less. As a result, farmers can reduce soil erosion and carbon emissions, which is great for the environment. In fact, conservation tillage can reduce soil erosion by up to 90% and, in 2014 alone, reduced carbon emissions by an amount equivalent to removing nearly 2 million cars from the road.[2]

The success of Monsanto's glyphosate resulted in the last decade to be registered in 130 countries and to be approved for weed control in more than 100 crops. Glyphosate has excellent environmental features such as rapid soil binding, biodegradation and extremely low toxicity to mammals, birds and fish. Glyphosate is non-volatile, stable in sunlight, completely water soluble and easy for applications on crops. The herbicidal action of glyphosate is very crucial. It inhibits an essential plant enzyme called 5- enolpyruvyl-shikimate-3-phosphate synthase (EPSPS) which prevents the production of aromatic amino acids required for protein synthesis. The herbicide enters a plant through foliage and the speed of entry depends on plant species and the delivery system. When in the plant, glyphosate moves in the phloem with sugar and is transported to the growing points within 4 hours, then slows down and stops by 48 hours. The uptake is affected by plant stress, dust and extreme weather.[3]

The original Roundup® herbicide allowed farmers to kill almost every weed that emerged from the soil, thus decreasing the need for tilling to control weeds and suffering soil erosion in the process. The herbicide was decomposing into natural products — carbon dioxide, phosphoric acid, and ammonia — and was also proved to be safe for humans and wildlife. In the early 1980s, Monsanto began to invest heavily in a new science called biotechnology. The company built new labs, hired new scientists, performed year upon year of research and spent billions of dollars chasing a dream. The Farm Chemicals Magazine (1994) called glyphosate as one of the "*Top Ten Products that Changed the Face of Agriculture*." In 1996 Roundup Ready Canola was introduced in Canada. This technology changed the face of Western Canadian agriculture and was a catalyst in the success of the Canadian canola industry.

Canola oil, or canola for short, is a vegetable oil derived from rapeseed (ελαιοκράμβη) that is low in erucic acid, as opposed to colza oil. There are both edible and industrial forms produced from the seed of any of several cultivars of the plant family Brassicaceae, namely cultivars of *Brassica napus* L., *Brassica rapa* subsp. *oleifera*, syn. *B. campestris* L. or *Brassica juncea*, which are also referred to as "canola". Canola oil is produced mainly in Canada and China. Since its commercial introduction in 1974, glyphosate [*N*-[(phosphonomethyl) glycine] has become the dominant herbicide worldwide [4,5]

Figure 2. A canola oil crop in full bloom on the Canadian prairie near Fort Macleod, Alberta. Canola oil is a healthier choice for cooking because it's low in saturated fat and has been shown to reduce cholesterol. Roundup Ready Canola was introduced in Canada and was a catalyst in the success of the Canadian canola industry.

The commercial success and dominance of Glyphosate

Since its commercial introduction in 1974, glyphosate [*N*-(phosphonomethyl) glycine] has become the dominant herbicide worldwide, off patent since 2000, is often paired with herbicide tolerant genetically modified crops. There are several reasons for its success. Glyphosate is a highly effective broad-spectrum herbicide, yet it is very toxicologically and environmentally safe. Glyphosate translocates well, and its action is slow enough to take advantage of this. Glyphosate is the only herbicide that targets 5-enolpyruvyl-shikimate-3-phosphate synthase (EPSPS), so there are no competing herbicide analogs or classes. Since glyphosate became a generic compound, its cost has dropped dramatically. Perhaps the most important aspect of the success of glyphosate has been the introduction of transgenic, glyphosate-resistant crops in 1996. Almost 90% of all transgenic crops grown worldwide are glyphosate resistant, and the adoption of these crops is increasing at a steady pace. Glyphosate/glyphosate-resistant crop weed management offers significant environmental and other benefits over the technologies that it replaces. The use of this virtually ideal herbicide is now being threatened by the evolution of glyphosate-resistant weeds. Adoption of resistance management practices will be required to maintain the benefits of glyphosate technologies for future generations. Since 1974 in the USA over 1.6 billion kg of

glyphosate active ingredient have been applied, or 19 % of estimated global use of glyphosate (8.6 billion kg). Globally, glyphosate use has risen almost 15-fold since so-called "Roundup Ready," genetically engineered glyphosate-tolerant crops were introduced in 1996.[6,7]

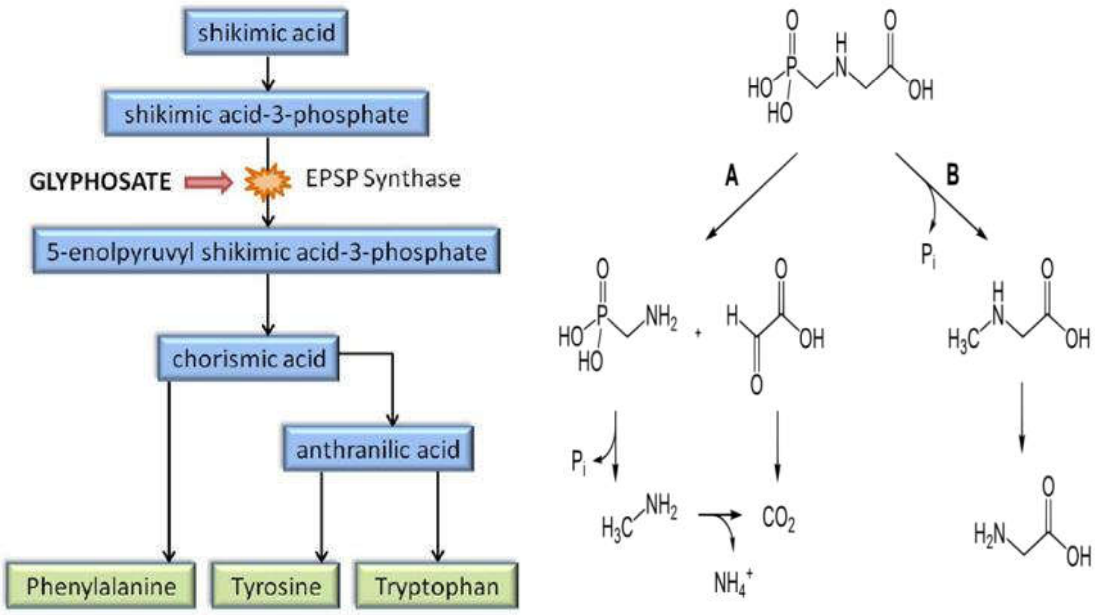


Figure 3. Glyphosate binds to and blocks the activity of the enzyme enolpyruvylshikimate-3-phosphate synthase (EPSPS) which comes at the start of the shikimic acid pathway that converts simple carbohydrate precursors derived from glycolysis and the pentose phosphate pathway to aromatic amino acids and many other important plant metabolites. The active site of the EPSPS enzyme is highly consistent in higher plants, glyphosate affects a broad spectrum of weeds inhibiting the function of the shikimic acid pathway causes a deficiency in aromatic amino acids, eventually leading to the plant's death by starvation [Glyphosate Facts, http://www.glyphosate.eu/glyphosate-mechanism-action].On the right degradation pathway of glyphosate in the ground.

In the last decades, the majority (more than 95%) of maize, cotton, soybean and sugarbeet acres in the USA are treated with herbicides for weed control, improving the economic profitability for farmers. Since their introduction in 1996, over 75 million acres of genetically engineered glyphosate-resistant crops have been planted, making up 80% of soybean acres and 70% of cotton acres in the USA. These genetically engineered crops have been adopted by farmers because they are perceived to offer greater economic benefits than conventional crop and herbicide programs. It is estimated that the adoption of glyphosate-resistant crops has saved USA farmers $1.2 billion (cost of conventional herbicide purchases), application,

tillage and hand weeding. The adoption of glyphosate-resistant crops by US agriculture has reduced herbicide use by around 17 million kg.[8,0]

Studies on toxicity of Glyphosate and human health

The most important aspect of pesticide safety is the adverse health effects to farmers and people working and living in agricultural areas. Health and safety research focuses on acute toxicity and chronic toxicity. Studies on skin exposure to ready-to-use glyphosate formulations showed that can cause irritation, and photocontact dermatitis has been occasionally reported. These effects are probably due to the preservative benzisothiazolin-3-one. Inhalation of glyphosate is a minor route of exposure, but spray mist may cause oral or nasal discomfort, an unpleasant taste in the mouth, or tingling and irritation in the throat. Eye exposure may lead to mild conjunctivitis. Superficial corneal injury is possible if irrigation of the sprayed crops is delayed or inadequate.

In 2000 a review was undertaken to evaluate the health risk of glyphosate (Roundup) for humans. The review included assessments of glyphosate, its major breakdown product [aminomethylphosphonic acid (AMPA)], its Roundup formulations, and the predominant surfactant [polyethoxylated tallow amine (POEA)] used in Roundup formulations worldwide. Experimental evidence has shown that neither glyphosate nor AMPA bioaccumulates in any animal tissue. No significant toxicity occurred in acute, subchronic, and chronic studies. Direct ocular exposure can result in transient irritation, while normal spray dilutions cause, at most, only minimal effects. The genotoxicity data for glyphosate and Roundup were assessed using a weight-of-evidence approach and standard evaluation criteria. There was no convincing evidence for direct DNA damage *in vitro* or *in vivo*, and it was concluded that Roundup and its components do not pose a risk for the production of heritable/somatic mutations in humans. Multiple lifetime feeding studies have failed to demonstrate any tumorigenic potential and it was concluded that glyphosate is non-carcinogenic. There were no effects on fertility or reproductive parameters in two multigeneration reproduction studies with glyphosate. Reviewers concluded that "under present and expected conditions of

new use, there is no potential for Roundup herbicide to pose a health risk to humans".[10]

A 2002 review by the European Union reached the same conclusion. The EU review identified several acceptable exposure scenarios for operators, workers and bystanders, which require however to be confirmed for each plant protection product in accordance with the relevant sections of the above mentioned uniform principles. The review has also concluded that under the proposed and supported conditions of use there are no unacceptable effects on the environment, as provided for in Article 4 (1) (b) (iv) and (v) of Directive 91/414/EEC, provided that certain conditions are taken into account.[11]

Many epidemiological studies in the last years and a series of data were accumulated for glyphosate. A 2012 meta-analysis of all epidemiological studies of exposure to glyphosate formulations found no correlation with any kind of cancer. Meta-analysis is a quantitative, formal, epidemiological study design used to systematically assess previous research studies to derive more precise estimates. The reviewers examined data from the epidemiologic literature to evaluate whether exposure to glyphosate is associated causally with cancer risk in humans, as well as relevant methodological and biomonitoring studies. They identified 7 cohort and 14 case-control studies for the association between glyphosate and one or more cancer outcomes. The results found no consistent pattern of positive associations indicating a causal relationship between total cancer (in adults or children) or any site-specific cancer and exposure to glyphosate.[12]

In 2013 there was a systematic review by the **German Institute for Risk Assessment** (Bundesinstitut für Risikowertung, BfR) of epidemiological studies of workers who use pesticides, exposed to glyphosate formulations. The institute found no significant risk, stating that "the available data are contradictory and far from being convincing". The report was re-evaluated. Several competent authorities in Germany were involved in the re- writing the report (*i.e.,* the German Federal Institute for Risk Assessment -BfR-, the Federal Environment Agency, the Julius Kuehn-Institute and the Federal Office of Consumer Protection and Food Safety). In 2015 the draft re-assessment report this report was send to the European Food Safety Authority (EFSA).[13]

The German Federal Institute for Risk Assessment (BfR) prepared a re-assessment report on health risk assessment for glyphosate. For this purpose, more than 150 new toxicological studies were evaluated for the first time and were described in detail in the draft report by BfR. In addition, all available toxicological studies (nearly 300) were re-assessed from the point of view of compliance with actual quality standards in study conduction and confirmation of interpreted results. Furthermore, about 900 publications from scientific journals have been considered in the draft report and more than 200 publications were reviewed in detail. In conclusion of this re-evaluation process of the active substance glyphosate by BfR the available data do not show carcinogenic or mutagenic properties of glyphosate nor that glyphosate is toxic to fertility, reproduction or embryonal/fetal development in laboratory animals. As a result of the re-assessment for the active substance BfR proposes slight amendments of the reference values. BfR believed that there is convincing evidence that the measured toxicity of some glyphosate containing herbicides is the result of the co-formulants in the plant protection products (*e.g.,* tallowamines used as surfactants). Therefore BfR calls special attention to the co-formulants and incorporated a toxicological assessment of tallowamines in its draft report. A research project initiated by BfR and performed by the University of Veterinary Medicine in Hanover investigated the influence of a glyphosate containing herbicide on microbial metabolism and communities in ruminants. The results of this study were summarised in the draft suggesting that there is no negative impact on the microflora in the rumen. In particular, there was no indication that *Clostridium* bacteria might multiply under the influence of glyphosate.[14,15]

The picture changed in 2015 when the International Agency for Research on Cancer (IARC, Lyon, France), a research arm of the World Health Organization, classified glyphosate as "probably carcinogenic," (Group 2A) using what is called a hazard evaluation. The IARC classification was widely circulated by anti-chemical and anti-GMO advocacy groups, which argued for bans or tighter restrictions of Glyphosate.[16]

The scientific report of IARC for Glyphosate.

The report of IARC stated "….For the herbicide glyphosate, there was limited evidence of carcinogenicity in humans for non-Hodgkin lymphoma (note: *this was the type of cancer mostly connected with exposure to glyphosate in other studies*). The evidence in humans is from studies of exposures, mostly agricultural, in the USA, Canada, and Sweden published since 2001. In addition, there is convincing evidence that glyphosate also can cause cancer in laboratory animals". The IARC Working Group mentioned "…the basis of tumours in mice, the United States Environmental Protection Agency (US EPA) originally classified glyphosate as possibly carcinogenic to humans (Group C) in 1985. After a re-evaluation of that mouse study, the US EPA changed its classification to evidence of non-carcinogenicity in humans (Group E) in 1991. The US EPA Scientific Advisory Panel noted that the re-evaluated glyphosate results were still significant using two statistical tests recommended in the IARC Preamble. IARC stated that "…Glyphosate also caused DNA and chromosomal damage in human cells, although it gave negative results in tests using bacteria. One study in community residents reported increases in blood markers of chromosomal damage (micronuclei) after glyphosate formulations were sprayed nearby…".[16]

The evaluation system of IARC for carcinogenicity

In 1969, the International Agency for Research on Cancer (IARC, a research branch of World Health Organization, WHO) initiated a programme to evaluate the carcinogenic risk of chemicals and other factors to humans (published in monographs). The Monographs programme has since been expanded to include consideration of exposures to complex mixtures of chemicals, occupations and human habits (smoking, diet) and of exposures to other agents, such as radiation and viruses. Relevant biological and epidemiological data are collected by the Carcinogen Identification and Evaluation Unit of IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems such as MEDLINE and TOXLINE. The evaluation of carcinogenicity is subdivided into 4 groups.[17,18]

Group 1 —The agent (mixture) is carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans. This category is used when there is sufficient evidence of carcinogenicity in humans.

Group 2A—The agent (mixture) is probably carcinogenic to humans. The exposure circumstance entails exposures that are **probably** carcinogenic to humans. This category is used when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals.

Group 2B—The agent (mixture) is possibly carcinogenic to humans. The exposure circumstance entails exposures that are **possibly** carcinogenic to humans. This category is used for agents for which there is limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals.

Group 3—The agent (mixture or exposure circumstances) **is not classifiable as to its carcinogenicity** to humans. This category is used most commonly for agents for which the evidence of carcinogenicity is **inadequate** in humans and **inadequate** or limited in experimental animals.

Group 4—The agent (mixture) is probably not carcinogenic to humans. This category is used for agents or mixtures for which there is evidence suggesting lack of carcinogenicity in humans and in experimental animals

Inclusion of an agent in the IARC Monographs does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that an agent has not yet been evaluated in a monograph does not mean that it is not carcinogenic. The evaluations of carcinogenic risk are made by international working groups of independent scientists and are qualitative in nature. No recommendation on carcinogens is given for national regulation or legislation.[17,18]

International dispute for the results of glyphosate's carcinogenicity

On 19th October 2017 the news agency Reuters (reporter Kate Kelland) filled a report "Glyphosate battle. According to the report for Glyphosate by IARC, the working group (WG) edited out "non-carcinogenicity. "…Documents seen by Reuters show how a draft of a key section of IARC assessment of glyphosate - a

report that has prompted international disputes and multi-million-dollar lawsuits - underwent significant changes and deletions before the report was finalised and made public. IARC wields huge influence as a semi-autonomous research unit of the WHO. It issued a report on its assessment of glyphosate - a key ingredient in Monsanto Corp's top-selling weedkiller Roundup - in March 2015. It ranked glyphosate a Group 2A carcinogen, a substance that probably causes cancer in people. That conclusion was based on its experts' view that there was "sufficient evidence" glyphosate causes cancer in animals and "limited evidence" it can do so in humans. The Group 2A classification has prompted mass litigation in the USA against Monsanto and could lead to a ban on glyphosate sales across the European Union. The edits identified by Reuters occurred in the chapter of IARC's review focusing on animal studies. This chapter was important in IARC's assessment of glyphosate, since it was in animal studies that IARC decided there was "sufficient" evidence of carcinogenicity. One effect of the changes to the draft, reviewed by Reuters in a comparison with the published report, was the removal of multiple scientists' conclusions that their studies had found no link between glyphosate and cancer in laboratory animals. In one instance, a fresh statistical analysis was inserted - effectively reversing the original finding of a study being reviewed by IARC. In another, a sentence in the draft referenced a pathology report ordered by experts at the U.S. EPA. It noted the report "firmly" and "unanimously" agreed that the "compound" – glyphosate – had not caused abnormal growths in the mice being studied. In the final published IARC monograph, this sentence had been deleted…".[19]

IARC's results were discussed among the scientific community and were various comments on the differences of opinion in the carcinogenicity of glyphosate. It has to be emphasized here that in the IARC's summary statement there was no finding of a link between glyphosate traces of food and cancer. The group found "limited evidence" of carcinogenicity in agricultural workers exposed to glyphosate for non-Hodgkin lymphoma and prostate cancer. But the panel of the working group found "sufficient evidence" of carcinogenicity in experimental animals. This is a section of the scientific evaluation that is disputed by other scientists. IARC's working group did not determine a specific cancer-causing

mechanism or what level of exposure to glyphosate may be harmful. According to IARC researcher Aaron Blair, a scientist at the US National Cancer Institute, "'Probable' means that there was enough evidence to say it is more than possible, but not enough evidence to say it is a carcinogen … It means you ought to be a little concerned about." Emeritus Professor Aaron Blair, is an internationally acclaimed specialist on pesticides exposure and cancer in farmers and epidemiologist from the U.S. National Cancer Institute). According to the report, the IARC's Working Group knew about unpublished, at the time, experimental results data that showed no link between the weed killer and cancer. But Prof. Aaron Blair, never mentioned this new data to the study group examining whether glyphosate causes cancer. So the IARC made its decision without all of the available evidence. According to Blair, the data was not published in a timely manner because there was too much data to fit into one scientific paper (which seems like a lame excuse to this writer). *Reuters* actually asked whether "he deliberately did not publish it to avoid it being considered by IARC." Of course, Blair denied it. Furthermore, the National Cancer Institute also stated that "space constraints" was one of the reasons why the new data on glyphosate was not published in a timely manner. Of course, the absence of Blair's data was a critical oversight – the IARC ended the meeting by concluding that the weed killer is a "probably human carcinogen (2A)". [19]

Agricultural workers and health issues with Glyphosate

The results of the research that Aaron Blair did not mentioned came from the **Agricultural Health Study (AHS)**, a primarily National Institutes of Health (NIH, USA)-run project that looks at cancer prevalence and other health issues in over 89,000 farmers and their spouses in Iowa and North Carolina. The AHS is a prospective study of cancer and other health outcomes in a cohort of licensed pesticide applicators and their spouses. It began in 1993 with the goal of answering important questions about how agricultural lifestyle and genetic factors affect the health of farming populations. The study is a collaborative effort involving investigators from National Cancer Institute (NCI), the National Institute of

Environmental Health Sciences (NIEHS), the Environmental Protection Agency (EPA), and the National Institute for Occupational Safety and Health (NIOSH). These are the most prestigious institutions in the USA with highly specialized researchers on subjects of epidemiology, toxicology, genetics and environmental health effects on humans exposed in working and physical environmental conditions. The farmers and spouses participation has provided, and continues to provide, the data that researchers need to help the current and future generations of farmers and their families live healthier lives. [NIH, https://aghealth.nih.gov/about/index.html].[20]

The researchers of the AHS examined farmers who were exposed to various agricultural chemicals, including glyphosate. Prof. Aaron Blair himself agreed that the unpublished data showed "no evidence of an association" between exposure to glyphosate and non-Hodgkin lymphoma. The results were published finally in the prestigious cancer *Journal of National Cancer Institute* (JNCI, 2018). The study followed for many years 54,251 pesticide applicators, of which 44,932 (82.8%) used glyphosate. This was a prospective cohort of licensed pesticide applicators from North Carolina and Iowa, USA. The study since the early 1990s, has gathered and analyzed detailed information on the health of participants and their families, and their use of pesticides, including glyphosate. The study strengths included the prospective cohort study design of the AHS and the large number of study participants (n = 54,251). Furthermore, this follow-up study provided a large amount of additional data for glyphosate relative to several types of cancers. In addition, sensitivity analyses were conducted to evaluate the impact of various different analyses and assumptions. The results of these sensitivity analyses were similar to the main analysis.[21]

The abstract of the paper stated: "Glyphosate is the most common used herbicide worldwide, with both residential and agricultural uses. In 2015, the International Agency for Research on Cancer (IARC) classified glyphosate as "probably carcinogenic to humans," noting strong mechanistic evidence and positive association for non-Hodgkin lymphoma (NHL) in some epidemiologic studies. A previous evaluation in the Agricultural Health Study (AHS) with follow-up through 2001 found no statistically significant associations with glyphosate use and cancer at any site. The study concluded that "large, prospective cohort study, no

association was apparent between glyphosate and any solid tumors or lymphoid malignancies overall, including NHL, and its subtypes.[21]

Another review and meta-analysis by Acquavella *et al*. (2016), examined the body of research regarding glyphosate and non-Hodgkin lymphoma. The authors concluded that, "overall, our review did not find support in the epidemiologic literature for a causal association between glyphosate and non-Hodgkin lymphoma or multiple myeloma." The scientists conducted a systematic review of the epidemiologic literature for glyphosate focusing on non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) - two cancers that were the focus of a recent review by the IARC Working Group. They evaluated each relevant study according to a priori criteria for study quality: adequacy of study size, likelihood of confounding, potential for other biases and adequacy of the statistical analyses. Their evaluation included 7 unique case-control studies for NHL and 4 for MM, and all of them had some limitations. Only the Agricultural Health (cohort) Study met their a priori quality standards and this study found no evidence of an association between glyphosate and NHL. For MM, the case control studies shared the same limitations as noted for the NHL case-control studies and, in aggregate, the data were too sparse to enable an informed causal judgment. The scientists concluded that overall the review did not find support in the epidemiologic literature for a causal association between glyphosate and NHL or MM.[22]

Additionally, Dr. Robert Tarone (International Epidemiology Institute in Rockville, Maryland, retired in 2016) also published a paper in 2016 that took IARC's decision regarding glyphosate to task. In his paper concluded that, "…The recent classification by IARC of the herbicide glyphosate as a probable human carcinogen has generated considerable discussion. The classification is at variance with evaluations of the carcinogenic potential of glyphosate by several national and international regulatory bodies. The basis for the IARC classification is examined under the assumptions that the IARC criteria are reasonable and that the body of scientific studies determined by IARC staff to be relevant to the evaluation of glyphosate by the Monograph Working Group is sufficiently complete. It is shown that the classification of glyphosate as a probable human carcinogen was the result of a flawed and incomplete summary of the experimental evidence evaluated by

the IARC Working Group. In the review R. Tarone discussed also the "implications of the erroneous classification of glyphosate with respect to the IARC Monograph Working Group deliberative process".[23]

Conflicting results on Glyphosate for adverse health effects

As one of the best worldwide used broad-spectrum herbicide, glyphosate attracted broad scientific interest for toxicological, epidemiological studies, numerous evaluation reviews and meta-analyses. Most of these studies in the USA and by various regulatory agencies (such as EPA) and scientific bodies, found that glyphosate have no carcinogenic potential, based primarily on results of carcinogenicity studies of rats and mice.

A meta-analysis in 2012 (see reference 12) indentified 7 cohort studies and 14 case-control studies for the association between glyphosate and one or more cancer outcomes. The review found no consistent pattern of positive associations indicating a causal relationship between total cancer (in adults or children) or any site-specific cancer and exposure to glyphosate. Data from biomonitoring studies underscore the importance of exposure assessment in epidemiologic studies, and indicate that studies should incorporate not only duration and frequency of pesticide use, but also type of pesticide formulation.[12]

Another systematic review and meta-analysis (2016) rigorously examined the relationship between glyphosate exposure and risk of lymphohematopoietic cancer (LHC) including non-Hodgkin Lymphoma (NHL), Hodgkin lymphoma (HL), multiple myeloma (MM), and leukemia (LE). Meta-relative risks (meta-RRs) were positive and marginally statistically significant for the association between any versus no use of glyphosate and risk of NHL (meta-RR = 1.3, 95% confidence interval (CI) = 1.0–1.6, based on six studies) and MM (meta-RR = 1.4, 95% CI = 1.0–1.9; four studies). Associations were statistically null for HL (meta-RR = 1.1, 95% CI = 0.7–1.6; two studies), leukemia (meta-RR = 1.0, 95% CI = 0.6–1.5; three studies), and NHL subtypes except B-cell lymphoma (two studies each). Researchers concluded that bias and confounding may account for observed associations. Meta-analysis was

constrained by few studies and a crude exposure metric, while the overall body of literature is methodologically limited and findings are not strong or consistent. The final conclusion was that “a causal relationship has not been established between glyphosate exposure and risk of any type of LHC”.[24]

Figure 4. The scientific debate over the safety of Glyphosate, one of the world’s most widely-used weed-killers, has taken another turn after IARC classified the herbicide as probably carcinogenic (2A). In contrast the European Chemicals Agency’s (ECHA’s) Committee for Risk Assessment has concluded that the available scientific evidence “did not meet the criteria to classify glyphosate as a carcinogen, as a mutagen or as toxic for reproduction. The National Farmers Union (NFU) in England welcomed the EU decision (December 2017) to reauthorise the use of glyphosate for 5 years after lobbying MEPs (members of European Parliament) over its safety and benefits.

The first report on results of the Agricultural Health Study appeared in 2005 publication. The group of researchers evaluated associations between glyphosate exposure and cancer incidence (prospective cohort study of 57,311 licensed pesticide applicators). Detailed information on pesticide use and other factors was obtained from a self-administered questionnaire completed at time of enrollment (1993-1997). Glyphosate exposure was defined as: a) ever personally mixed or applied products containing glyphosate; b) cumulative lifetime days of use, or "cumulative exposure days" (years of use times days/year); and c) intensity-weighted cumulative exposure days (years of use times days/year times estimated intensity level). Poisson regression was used to estimate exposure-response

relations between glyphosate and incidence of all cancers combined and 12 relatively common cancer subtypes. Glyphosate exposure was not associated with cancer incidence overall or with most of the cancer subtypes studied.[25]

Developmental and reproductive problems in humans and animals through exposure to glyphosate (and its active ingredients) was another safety issue that scientists investigated through assessment of epidemiologic and animal studies. The review (2012) examined a number of studies on mechanisms of action related to possible developmental and reproductive effects. Evaluation of this database found no consistent effects of glyphosate exposure on reproductive health or the developing offspring. Furthermore, no plausible mechanisms of action for such effects were elucidated. Although toxicity was observed in studies that used glyphosate-based formulations, the data strongly suggest that such effects were due to surfactants present in the formulations and not the direct result of glyphosate exposure. Scientists concluded that there is no solid evidence linking glyphosate exposure to adverse developmental or reproductive effects at environmentally realistic exposure concentrations. Also, to estimate potential human exposure concentrations to glyphosate as a result of working directly with the herbicide, available biomonitoring data were examined in the review. Data demonstrated extremely low human exposures as a result of normal application practices. The estimated exposure concentrations in humans were >500-fold less than the oral reference dose for glyphosate of 2 mg/kg/d set by the U.S. EPA in 1993.[26]

In 2016 the case of glyphosate and the conflicting scientific results of the various reviews on health and safety prompted a statement of concern over use of glyphosate-based herbicides (GBHs) by a group of scientists (USA, England, Canada). According to their extensive report the scientists stated: "…Initial industry toxicity testing suggested that GBHs (glyphosate-based herbicides) posed relatively low risks to non-target species, including mammals. To accommodate changes in GBH use patterns associated with genetically engineered, herbicide-tolerant crops, regulators have increased tolerance levels in maize, oilseed (soybeans and canola), and alfalfa crops and related livestock feeds. Animal and epidemiology studies published in the last decade, however, point to the need for a fresh look at

glyphosate toxicity. Furthermore, the WHO'S IARC recently concluded that glyphosate is "probably carcinogenic to humans (Group 2A)." In response to changing GBH use patterns and advances in scientific understanding of their potential hazards, scientists have produced a **Statement of Concern** drawing on emerging science relevant to the safety of GBHs". "…Our Statement of Concern considers current published literature describing GBH uses, mechanisms of action, toxicity in laboratory animals, and epidemiological studies. It also examines the derivation of current human safety standards. We conclude that: (1) GBHs are the most heavily applied herbicide in the world and usage continues to rise; (2) Worldwide, GBHs often contaminate drinking water sources, precipitation, and air, especially in agricultural regions; (3) The half-life of glyphosate in water and soil is longer than previously recognized; (4) glyphosate and its metabolites are widely present in the global soybean supply; (5) Human exposures to GBHs are rising; (6) glyphosate is now authoritatively classified as a probable human carcinogen (IARC report); (7) Regulatory estimates of tolerable daily intakes for glyphosate in the USA and EU are based on outdated science. We offer a series of recommendations related to 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. We suggest that common commercial formulations of GBHs should be prioritized for inclusion in government-led toxicology testing programs such as the U.S. National Toxicology Program, as well as for biomonitoring as conducted by the U.S. Centers for Disease Control and Prevention".[27]

Birth defects, abortions, etc., were investigated by various epidemiological studies for exposure to glyphosate in agricultural activities. These studies was the increasing concern among scientists for teratogenic potential on glyphosate. A systematic review of the epidemiological studies searched and found 10 studies testing associations between glyphosate and birth defects, abortions, pre-term deliveries, small for gestational date births, childhood diseases or altered sex ratios. Two additional studies examined changes of time-to-pregnancy in glyphosate-exposed populations. These studies found no significant associations between glyphosate and adverse pregnancy outcomes. The reviewing scientists concluded

that current epidemiological evidence, albeit limited to a few studies using non-quantitative and indirect estimates and dichotomous analysis of exposures, does not lend support to public concerns that glyphosate-based pesticides might pose developmental risks to the unborn child. Nonetheless, owing to methodological limitations of existing analytical observational studies, and particularly to a lack of a direct measurement (urine and/or blood levels), or an indirect estimation of exposure that has proven valid, these negative findings cannot be taken as definitive evidence that glyphosate, at current levels of occupational and environmental exposures, brings no risk for human development and reproduction.[28]

In 2015 another review examined 14 carcinogenicity studies (9 in rats and 5 in mouse) which examined the evidence for carcinogenic effects of Glyphosate, These carcinogenicity data were submitted to regulatory agencies. The review evaluated each study, followed by a weight of evidence of tumour incidence data. There was no evidence of a carcinogenic effect related to glyphosate treatment. The lack of a plausible mechanism, along with published epidemiology studies, which fail to demonstrate clear, statistically significant, unbiased and non-confounded associations between glyphosate and cancer of any single etiology, and a compelling weight of evidence, support the conclusion that glyphosate does not present concern with respect to carcinogenic potential in humans.[29]

In 2018 a detailed overview of the scientific literature on glyphosate toxicity and environmental pollution was published. The overview examined scientific data on residues of glyphosate and its breakdown product aminomethyl phosphonic acid (AMPA) in soil and water, their toxicity to macro- and microorganisms, their effects on microbial compositions and potential indirect effects on plant, animal and human health. Although the acute toxic effects of glyphosate and AMPA on mammals are low, there are some toxic animal data raising the possibility of health effects associated with chronic, ultra-low doses related to accumulation of these compounds in the environment. The study found that Intensive glyphosate use has led to the selection of glyphosate-resistant weeds and microorganisms. Research on a link between glyphosate and antibiotic resistance is scarce. The research group recommend interdisciplinary research on the associations between low level

chronic glyphosate exposure, distortions in microbial communities, expansion of antibiotic resistance and the emergence of animal, human and plant diseases.[30]

Detectable concentrations of glyphosate in human milk was another concern. It has been known that glyphosate does not result in bioaccumulation in biological tissues. So scientists examined mothers; milk for breastfed infants. Researchers collected 41 milk and 40 urine samples from healthy lactating women living in and around Moscow, Idaho and Pullman (Whitman County, Washington). Samples were analysed for glyphosate and AMPA (break down metabolite) with LC-MS. The results showed not they were not detectable, suggesting that dietary exposure in not a health concern for infants.[31]

In the last years there has been another scientific debate over the possibility that glyphosate is an endocrine disruptor. Studies in cell culture showed that glyphosate induces endocrine-mediated effects on end points relevant to toxicity, as well as cell proliferation. These results are contrasting results by EPA. The EPA in their Endocrine Disruptor Screening Program (EDSP) with glyphosate dismissed statistically significant differences consistent with oestrogenic activity in some assays (e.g. altered vitellogenin levels in a fish short-term reproduction assay) because they followed a non-monotonic dose response. The final conclusion of the US EPA was that 'there was no convincing evidence' that glyphosate interacts with endocrine pathways. Significant criticisms of the EDSP assays have been raised by endocrinologists. Also, other scientists have expressed concern about the failure of the EPA to acknowledge non-monotonic dose responses, which have been documented for other endocrine disruptors. Other agencies including the European Food Safety Authority (EFSA) have used the EDSP data to suggest that there is not sufficient evidence to conclude that glyphosate is an endocrine disruptor, but the 2015 EFSA report does note that 'signs of endocrine activity… could not be completely ruled out' in some of these assays.[32-35]

Decisions on Glyphosate by regulating agencies for food and the environment

A Joint Meeting of the Food and Agriculture Organization of the United Nations (FAO) Panel of Experts on Pesticide Residues in Food and the Environment and the World Health Organization (WHO) Core Assessment Group on Pesticide Residues (JMPR) in Geneva . **FAO/WHO**. JOINT FAO/WHO MEETING ON PESTICIDE RESIDUES Geneva, 9–13 May 2016. The Summary of the report: "…The Meeting concluded that glyphosate is not carcinogenic in rats but could not exclude the possibility that it is carcinogenic in mice at very high doses. In view of the absence of carcinogenic potential in rodents at human-relevant doses and the absence of genotoxicity by the oral route in mammals, and considering the epidemiological evidence from occupational exposures, the Meeting concluded that glyphosate is unlikely to pose a carcinogenic risk to humans from exposure through the diet. The Meeting reaffirmed the group **ADI** [Acceptable daily intake or ADI is a measure of the amount of a specific substance, food additive, a residue of a veterinary drug or pesticide, in food or drinking water that can be ingested (orally) on a daily basis over a lifetime without an appreciable health risk and is expressed usually in milligrams (mg) per Kilograms (kg) of body weight per day. The ADI for the sum of glyphosate and its metabolites of 0–1 mg/kg body weight on the basis of effects on the salivary gland. The Meeting concluded that it was not necessary to establish an **ARfD** (Acute Reference for Dose) for glyphosate or its metabolites in view of its low acute toxicity…". [36]

A lengthy report (270 pages) of EPA's Office of Pesticide Programs (12/9/2016) exposed all the available data on glyphosate. In the introduction the EPA report notes: "….Most recently, in September 2015, a third review was done by the Cancer Assessment Review Committee (CARC, USA). Relevant glyphosate data available to EPA at that time for glyphosate were reevaluated, including studies submitted by the registrant and studies published in the open literature. The agency performed this evaluation in support of Registration Review in accordance with the 2005 Guidelines for Carcinogen Risk Assessment, classified glyphosate as "Not Likely to be Carcinogenic to Humans" (CARC, 2015; TXR #0057299). Recently,

several international agencies have evaluated the carcinogenic potential of glyphosate. In March 2015, the International Agency for Research on Cancer (IARC), a subdivision of the World Health Organization (WHO), determined that glyphosate was a probable carcinogen (group 2A) (IARC, 2015). Later, in November 2015, the European Food Safety Authority (EFSA) determined that glyphosate was unlikely to pose a carcinogenic hazard to humans (EFSA, 2015). In May 2016, the Joint Food and Agriculture Organization (FAO)/WHO Meeting on Pesticide Residues (JMPR), another subdivision of the WHO, concluded that glyphosate was unlikely to pose a carcinogenic risk to humans from exposure through the diet (JMPR, 2016). Some individual countries (e.g., France, Sweden) have been moving to ban glyphosate based on the IARC decision, while other countries (e.g., Japan, Canada) have continued to support their conclusion that glyphosate is unlikely to pose a carcinogenic risk to humans.

In the final chapter of EPA's conclusions: "… An extensive database exists for evaluating the carcinogenic potential of glyphosate, including 23 epidemiological studies, 15 animal carcinogenicity studies, and nearly 90 genotoxicity studies for the active ingredient of glyphosate. These studies were evaluated for quality and results were analyzed across studies within each line of evidence. The modified Bradford Hill criteria were then used to evaluate multiple lines of evidence using such concepts as strength, consistency, dose response, temporal concordance and biological plausibility. The available data at this time do no support a carcinogenic process for glyphosate. Overall, animal carcinogenicity and genotoxicity studies were remarkably consistent and did not demonstrate a clear association between glyphosate exposure and outcomes of interest related to carcinogenic potential. In epidemiological studies, there was no evidence of an association between glyphosate exposure and numerous cancer outcomes; however, due to conflicting results and various limitations identified in studies investigating NHL, a conclusion regarding the association between glyphosate exposure and risk of NHL cannot be determined based on the available data. Increases in tumor incidence were not considered treatment-related in any of the animal carcinogenicity studies. In 7 of these studies, no tumors were identified for

detailed evaluation. In the remaining studies, tumor incidences were not increased at doses.[37]

A review in 2017 presented the scientific basis for the health assessment of glyphosate. Since glyphosate was introduced in 1974 and all regulatory assessments have established that glyphosate has low hazard potential to mammals, however, the IARC concluded in March 2015 that it is probably carcinogenic. The IARC conclusion was not confirmed by the EU assessment or the recent joint WHO/FAO evaluation, both using additional evidence. Glyphosate is not the first topic of disagreement between IARC and regulatory evaluations, but has received greater attention. This review presents the scientific basis of the glyphosate health assessment conducted within the European Union (EU) renewal process, and explains the differences in the carcinogenicity assessment with IARC. Use of different data sets, particularly on long-term toxicity/carcinogenicity in rodents, could partially explain the divergent views; but methodological differences in the evaluation of the available evidence have been identified. The EU assessment did not identify a carcinogenicity hazard, revised the toxicological profile proposing new toxicological reference values, and conducted a risk assessment for some representatives uses. Two complementary exposure assessments, human-biomonitoring and food-residues-monitoring, suggests that actual exposure levels are below these reference values and do not represent a public concern.[38]

The European Food and Safety Authority (EFSA) on the controversy for the assessment of Glyphosate

In January 2018 (Nature Briefing. Url B. *Don't attack science agencies for political gain*, *Nature* 553:381, 23.1.2018) Bernhard Url, an officer of EFSA, published a short discussion article on the decision of EFSA on glyphosate. In his article Url warns that: "…Eroding trust in regulatory agencies will not improve democratic accountability…". The article continues "…The job of the European Food Safety Authority (EFSA) is to assess what might make food unsafe. That's hard enough. It is even harder when the agency is at the centre of a public debate that goes far beyond science. This has happened with artificial sweeteners, genetically

modified (GM) organisms and glyphosate, the world's most ubiquitous herbicide. When questions about a society's values are thrust onto scientific agencies rather than elected officials, scientific assessment suffers.[39]

The glyphosate controversy began in earnest two-and-a-half years ago, when EFSA and experts designated by European Union members concluded that the product is unlikely to be carcinogenic. In late 2017, the European Commission renewed a licence allowing the herbicide's sale. EFSA's conclusion contradicted that of the International Agency for Research on Cancer (IARC), which had classified the chemical as "probably carcinogenic" months earlier, bringing its own share of controversy. That the agencies reached different conclusions is not surprising: each considered different bodies of scientific evidence and methodologies. Other independent assessments — by the European Chemicals Agency (ECHA) and regulatory bodies in the United States, Canada, Japan and Australia — agreed with EFSA. So did an expert body on pesticide residues convened by the Food and Agriculture Organization (FAO) of the United Nations and the World Health Organization (WHO). Even so, the divergence between EFSA's conclusion and the IARC's has been debated by legislators from Brussels to Berlin and beyond. We have seen scare stories about trace levels of glyphosate residues in German beer or Italian pasta — but these fail to mention that observed amounts of herbicide residues would pose risks only if a person consumed roughly 1,000 litres of beer or their body's weight in dry pasta in one day.

Why the frenzy? Agencies that find low risk of regulated products are often accused of undue industry influence. We at EFSA believe that some campaigners are unwilling to accept any evidence that certain regulated substances are safe, and will tout weak scientific studies showing the opposite. The same groups applauded EFSA for reviews on other pesticides, such as neonicotinoids, that it deemed dangerous. It seems to us that some campaigners contest the science of safety assessments in pursuit of greater political arguments. These arguments deserve airing — but they belong with policymakers. In the past two years, EFSA has faced multiple allegations over its evaluation of glyphosate. The most pernicious of these is that the agency violated good scientific practice by plagiarizing information from industry. It is true that the document in question, the

Renewal Assessment Report produced by German authorities (refers here to The German BfR, an agency that does evaluations for the European Commission, issued an assessment on glyphosate in March 2016), includes a section summarizing published toxicology literature that contains text compiled by a committee of some 20 companies, including glyphosate's original manufacturer, Monsanto. But this is standard practice, and EFSA peer-review panels vetted the material that appeared. The section brought forward as allegedly copied from industry also highlights concerns over products that contain glyphosate. In fact, it was used to support a recommendation by EFSA in November 2015 to further evaluate the safety of plant-protection products containing glyphosate. This section was made publicly available for comment in 2014, but complaints of copied text by regulatory agencies came in late 2017, after other complaints were raised about Monsanto's possible influence over published scientific literature.

So, when campaigners allege that EFSA did not follow due scientific process when assessing glyphosate, we believe that they are really railing against bigger issues: the role of modern agricultural practices and multinational biotech firms in our food supply. A broader societal discussion about these issues is essential, but it won't be achieved by picking on regulatory science. It is the role of politicians to represent the values, needs and expectations of their constituents through democratic processes. This is outside the responsibility of organizations such as EFSA, which were created to advise EU policymakers on scientific matters. Three changes would help elected officials and regulatory agencies to do their separate jobs. First, questions about societal values should be framed ahead of and outside scientific work. The EU must equip itself with a legal and regulatory framework for food production that accounts for citizens' opinions on intensive agriculture, pesticide use, GM organisms and other biotechnology, and the importance of biodiversity. This will provide a forum for open, honest debate. Second, regulatory and legal guidelines should be drawn up to govern how regulatory bodies interact with industry and handle transparency of the data that they use. Finally, politicians need to decide whether they are willing to allow risk assessment of regulated products, such as glyphosate and food additives, to continue to be based on safety studies commissioned and paid for by the industry, as has been the case for

decades. If so, politicians must have the courage to support the regulatory bodies charged with implementing these rules. If not, they must find funding for these studies elsewhere. Only once these steps have been taken will regulatory agencies be free from allegations of bias when their scientific conclusions are at odds with the political agenda of one interest group or another".[39]

Evaluation and re-evaluation of Glyphosate in Canada.

In June 2015 re-review of glyphosate by **Health Canada** concluded: " *An evaluation of available scientific information found that products containing glyphosate do not present unacceptable risks to human health or the environment when used according to the proposed label directions…..".* In 2015, the PMRA published the outcome of its extensive re-examination of glyphosate for public comment (PRVD2015-01), which concluded that the products containing glyphosate do not present unacceptable risks to human health or the environment when used according to the revised product label directions.

Also, **The Canadian Pest Management Regulatory Agency** on 28 April 2017 announced the re-evaluation of Glyphosate [ISSN: 1925-1025 (PDF version) Catalogue number: H113-28/2017-1E-PDF (PDF version)] [https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-...].[40]

The Executive Summary was as follows: "….Health Canada's primary objective in regulating pesticides is to protect Canadians' health and their environment. Pesticides must be registered by Health Canada's Pest Management Regulatory Agency (PMRA) before they can be imported, sold, or used in Canada. Pesticides must go through rigorous science-based assessments before being approved for sale in Canada. All registered pesticides must be re-evaluated by the PMRA on a cyclical basis to make sure they continue to meet modern health and environment safety standards and continue to have value. In 2015, the PMRA published the outcome of its extensive re-examination of glyphosate for public comment (PRVD2015-01), which concluded that the products containing glyphosate do not present unacceptable risks to human health or the environment when used according to the revised product label directions. During this re-

examination, the PMRA assessed the potential human health risk of glyphosate from drinking water, food, occupational and bystander exposure, as well as the environmental risk to non-target organisms. Both the active ingredient and formulated products were included in the re-evaluation. The assessment was carried out based on available information provided by the manufacturer of the pesticide, as well as a large volume of published scientific literature, monitoring information (for example, ground water and surface water) and reviews conducted by other regulatory authorities.

The overall finding from the re-examination of glyphosate is highlighted as follows:

- Glyphosate is not genotoxic and is unlikely to pose a human cancer risk.
- Dietary (food and drinking water) exposure associated with the use of glyphosate is not expected to pose a risk of concern to human health.
- Occupational and residential risks associated with the use of glyphosate are not of concern, provided that updated label instructions are followed.
- The environmental assessment concluded that spray buffer zones are necessary to mitigate potential risks to non-target species (for example, vegetation near treated areas, aquatic invertebrates and fish) from spray drift.
- When used according to revised label directions, glyphosate products are not expected to pose risks of concern to the environment.
- All registered glyphosate uses have value for weed control in agriculture and non-agricultural land management.

All comments received during the consultation process were taken into consideration. These comments and new data/information resulted in only minor revisions to the proposed regulatory decision described in PRVD2015-01. Therefore, the PMRA is granting continued registration of products containing glyphosate with requirements of additional label updates to further protect human health and the environment.[40]

Re-evaluation of Glyphosate by the German Federal Institute for Risk Assessment (BfR)

The Institute was set up in November 2002 to strengthen consumer health protection. It is the scientific agency of the Federal Republic of Germany which is responsible for preparing expert reports and opinions on food and feed safety as

well as on the safety of substances and products. In this context, the Institute plays an important role in improving consumer protection and food safety. BfR reports to the Federal Ministry of Food and Agriculture (BMEL). It enjoys independence in respect of its scientific assessments and research.

The re-evaluation of Glyphosate by BfR (2/4/2015). During this re-evaluation procedure Germany evaluates glyphosate and a sample formulation of a plant protection product containing glyphosate. In this framework Germany acts as Rapporteur Member State (RMS) writing a draft re-assessment report. Several competent authorities in Germany are involved in the writing process (*i.e.,* the German Federal Institute for Risk Assessment -BfR-, the Federal Environment Agency, the Julius Kuehn-Institute and the Federal Office of Consumer Protection and Food Safety). After the establishment of a draft re-assessment report this report will be send to the European Food Safety Authority (EFSA).

The German Federal Institute for Risk Assessment (BfR) has already completed the draft re-assessment report on health risk assessment. For this purpose, more than 150 new toxicological studies were evaluated for the first time and are described in detail in the draft report by BfR. In addition, all available toxicological studies (nearly 300) were re-assessed from the point of view of compliance with actual quality standards in study conduction and confirmation of interpreted results. Furthermore, about 900 publications from scientific journals have been considered in the draft report and more than 200 publications were reviewed in detail. In conclusion of this re-evaluation process of the active substance glyphosate by BfR the available data do not show carcinogenic or mutagenic properties of glyphosate nor that glyphosate is toxic to fertility, reproduction or embryonal/fetal development in laboratory animals. As a result of the re-assessment for the active substance BfR proposes slight amendments of the reference values. BfR believes that there is convincing evidence that the measured toxicity of some glyphosate containing herbicides is the result of the co-formulants in the plant protection products (*e.g.,* tallowamines used as surfactants). Therefore BfR calls special attention to the co-formulants and incorporated a toxicological assessment of tallowamines in its draft report. A research project initiated by BfR and performed by the University of Veterinary Medicine in Hanover

investigated the influence of a glyphosate containing herbicide on microbial metabolism and communities in ruminants. The results of this study are summarised in the draft suggesting that there is no negative impact on the microflora in the rumen. In particular, there was no indication that *Clostridium* bacteria might multiply under the influence of glyphosate.

After sending the draft re-assessment report of glyphosate to EFSA, it will constitute the basis for the public consultation with all interested stakeholders as well as for the so-called "peer review procedure" by experts from other EU member states. After commenting of the draft, the RMS will incorporate all final comments and remarks. EFSA is steering the re-assessment procedure and will establish an "EFSA conclusion" on basis of the German draft re-assessment report and the comments of the other stakeholders by the end of 2014. The Commission will then take a decision on the future approval of the active ingredient glyphosate on the basis of the EFSA conclusion. All re-assessment reports and scientific opinions which are intended for the public consultation will become publicly available on the EFSA website.[41]

Opinion of European Chemicals Agency (ECHA) on Glyphosate

The European Chemicals Agency sent its opinion to the European Commission on 15 June 2017. On 15 March 2017, the Risk Assessment Committee (RAC) of the European Chemicals Agency concluded by consensus that:[42]

[ECHA's opinion on classification of glyphosate published, ECHA/NI/17/21
Helsinki, 15 June 2017 - The Committee for Risk Assessment's opinion regarding the harmonised classification of glyphosate has now been sent to the European Commission. The opinion is also available on ECHA's website.
[https://echa.europa.eu/-/echa-s-opinion-on-classification-of-glyphosate-published].

a) There is no evidence to link glyphosate to cancer in humans, based on the available information,

b) Glyphosate should not be classified as a substance that causes genetic damage (mutagen) or disrupts reproduction.

The same conclusion was also reached by the following organisations:

i) European Food Safety Authority (EFSA), supported by experts from 27 EU Member State competent authorities

ii) National authorities outside the EU (e.g. Canada, Japan, Australia, New Zealand)

iii) Joint Food and Agriculture Organization (FAO) of the United Nations – World Health Organisation (WHO) Meeting on Pesticide Residues (JMPR)

The International Agency for Research on Cancer (IARC) remains, therefore, the only agency with a divergent view.

European Commission's current proposal to the member states On 16 May 2017 the Commission agreed that the discussions with the Member States about the possible renewal of the approval of glyphosate could restart. The Commission is proposing a renewal of the approval of glyphosate for 10 years. It is now up to the Member States to decide on the Commission's proposal. After the possible renewal of the approval of glyphosate, member states are actually responsible for the authorisation of plant protection products containing glyphosate (e.g. Roundup).

On 20 July 2017 the Commission restarted the discussions with Member States. The objective is to have them finalised in autumn before proceeding to vote. The proposal put forward by the Commission includes:

- Specific provisions that Member States have to take into account when considering applications for glyphosate-based products, namely:
    - protection of groundwater
    - protection of terrestrial animals and non-target plants
- Certain elements that Member States must ensure during assessment and decision making for authorisation (e.g. use in public areas should be minimised)
- The ban of POE-tallowamine (a 'co-formulant' that was previously used in glyphosate-based products) that was put in place in 2016

On 5-6 October 2017 a further round of discussions with the Member States took place. The Commission has made available to the Member States an updated version of the proposal that takes into account the EFSA Conclusion on the potential endocrine disrupting properties of glyphosate that was published on 7 September 2017. On 25 October 2017 the Commission held another round of discussions with the Member States on the proposal for the renewal of approval of glyphosate for 10 years at the Standing Committee on Plants, Animals, Food and Feed. All Member States took the floor and expressed their views on which the Commission took note. On 9 November 2017 at the Standing Committee on Plants, Animals, Food and Feed, Member States voted on the Commission's proposal

(revision 3) for the renewal of approval of glyphosate for 5 years. The Committee delivered a no opinion on this proposal (see minutes of the meeting below for further details). On 27 November 2017 a qualified majority in favour of the proposal by the European Commission to renew the approval of glyphosate for a period of 5 years was reached by the Appeal Committee. Some modifications were made to the draft Implementing Regulation during the meeting (see revision 4 below for the text voted in the Appeal Committee). On 12 December 2017: the European Commission has adopted the act to renew the approval of glyphosate for 5 years.[42]

European Citizens' Initiative on glyphosate

On Friday 6 October the European Commission officially received the submission of the 4th successful European Citizens' Initiative (ECI). By supporting the 'Stop Glyphosate' European Citizens' Initiative, over 1 million citizens from at least 7 Member States have called on the European Commission "to propose to Member States a ban on glyphosate, to reform the pesticide approval procedure, and to set EU-wide mandatory reduction targets for pesticide use". A total of 1,070,865 statements of support have been received from 22 Member States so far, and have been checked and validated by national authorities. The European Commission met with the organisers on 23 October 2017. The organisers presented the citizens' initiative at a public hearing in the European Parliament on 20 November 2017. 12 December 2017: the Commission adopted its response to the ECI .

Why there are differences in the evaluation of carcinogenicity risk of IARC expert report and EFSA

The IARC's decision to classify glyphosate as "probable carcinogen" (Group 2A) in contrast to other scientific groups negative assessment, prompted scientists to explain the differences between hazard assessment and risk assessment regarding exposures for farmers and risk for food consumption. The group of scientists stated in their paper " …In the Monograph No. 112, the Working Group (WG) of IARC's 17 expert scientists evaluated the carcinogenic hazard for four insecticides and the herbicide glyphosate. The WG concluded that the data for glyphosate meet the criteria for classification as a *"probable human carcinogen"*. The definition encompasses chemical substances and exposure (occupational or environmental) circumstances that pose a risk to human health in the long term.

This designation is applied when there is limited evidence of carcinogenicity in humans for a variety of exposures. IARC WG takes into account carcinogenicity evidence from animal studies. Some of these studies are known to use high concentrations of the substance under investigation…".[43]

"….Regarding food safety by residues of glyphosate, The European Food Safety Authority (EFSA) evaluated the risk for residues of glyphosate in foods consumed by humans. The risk is related to concentrations and how much consumes a person per day or per year. In October 2015, EFSA reported on their evaluation of the Renewal Assessment Report (RAR) for glyphosate that was prepared by the Rapporteur Member State, the German Federal Institute for Risk Assessment (BfR). EFSA concluded that 'glyphosate is unlikely to pose a carcinogenic hazard to humans and the evidence does not support classification with regard to its carcinogenic potential'. Addendum 1 (the BfR Addendum) of the RAR discusses the scientific rationale for differing from the IARC Working Group conclusion. In contrast, the IARC WG concluded there is *limited evidence of carcinogenicity in humans* which means "A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence." The finding of *limited evidence* by the IARC WG was for NHL (non-Hodgkin lymphoma), based on high-quality case–control studies, which are particularly valuable for determining the carcinogenicity of an agent because their design facilitates exposure assessment and reduces the potential for certain biases. The Agricultural Health Study (AHS) was the only cohort study available providing information on the carcinogenicity of glyphosate. The study had a null finding for NHL (RR 1.1, 0.7–1.9) with no apparent exposure–response relationship in the results. Despite potential advantages of cohort versus case–control studies, the AHS had only 92 NHL cases in the unadjusted analysis as compared to 650 cases in a pooled case–control analysis from the USA. In addition, the median follow-up time in the AHS was 6.7 years, which is unlikely to be long enough to account for cancer latency ...".

The Summary of expert's report was. "The IARC WG concluded that glyphosate is a 'probable human carcinogen', putting it into IARC category 2A due to *sufficient evidence* of carcinogenicity in animals, *limited evidence* of carcinogenicity in humans and *strong* evidence for two carcinogenic mechanisms.

- The IARC WG found an association between NHL and glyphosate based on the available human evidence.
- The IARC WG found significant carcinogenic effects in laboratory animals for rare kidney tumours and hemangiosarcoma in two mouse studies and benign tumours in two rat studies.
- The IARC WG concluded that there was strong evidence of genotoxicity and oxidative stress for glyphosate, entirely from publicly available research, including findings of DNA damage in the peripheral blood of exposed humans. The RAR concluded that 'classification and labelling for carcinogenesis is not warranted' and 'glyphosate is devoid of genotoxic potential'.
- EFSA classified the human evidence as 'very limited' and then dismissed any association of glyphosate with cancer without clear explanation or justification.
- Ignoring established guidelines cited in their report, EFSA dismissed evidence of renal tumours in three mouse studies, hemangiosarcoma in two mouse studies and malignant lymphoma in two mouse studies. Thus, EFSA incorrectly discarded all findings of glyphosate-induced cancer in animals as chance occurrences.
- EFSA ignored important laboratory and human mechanistic evidence of genotoxicity.
- EFSA confirmed that glyphosate induces oxidative stress but then, having dismissed all other findings of possible carcinogenicity, dismissed this finding on the grounds that oxidative stress alone is not sufficient for carcinogen labelling.

The most appropriate and scientifically based evaluation of the cancers reported in humans and laboratory animals as well as supportive mechanistic data is that glyphosate is a *probable human carcinogen*. On the basis of this conclusion and in the absence of evidence to the contrary, it is reasonable to conclude that

glyphosate formulations should also be considered likely human carcinogens. The CLP Criteria allow for a similar classification of Category 1B when there are 'studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals'.

In the RAR (renewal assessment report), almost no weight is given to studies from the published literature and there is an over-reliance on non-publicly available industry-provided studies using a limited set of assays that define the minimum data necessary for the marketing of a pesticide. The IARC WG evaluation of *probably carcinogenic to humans* accurately reflects the results of published scientific literature on glyphosate and, on the face of it, unpublished studies to which EFSA refers. Most of the authors of this commentary previously expressed their concerns to EFSA and others regarding their review of glyphosate to which EFSA has published a reply. This commentary responds to the EFSA reply. The views expressed in this editorial are the opinion of the authors and do not imply an endorsement or support for these opinions by any organisations to which they are affiliated.[43]

Politics and science in decision making for pesticides in the EU

The European Union has various scientific committees to deal with scientific problems, such the regulation and licensing of pesticides used in agriculture, in coordination with other international agencies (like FAO and WHO). In November 2017 the European Commission proposed to 28 member states to renew the licence of glyphosate for another 5 years. The glyphosate licence in the EU countries was ending in the EU on 15 December 2017. In the vote that followed only half of the 28 member states backed a European Commission proposal to renew the licence of glyphosate for five years. An EU appeal committee tried to rule on the issue. This decision came out at a time that there were negative reactions in various countries and demands by environmental organization for a total ban, after the IARC decision to classified as "probably carcinogenic". The Commission supported it own scientists and organizations supporting glyphosate as safe to use. The UK was among the 14 states backing the Commission position on glyphosate.

Nine voted against - including France and Italy. Germany was among the five who abstained.[44]

A report by Reuters in Brussels commented for the November 2017 vote in EU on glyphosate renewal. The comments were: "… Germany defeated its key EU ally France in a very tight vote on Monday to clear the use of weed-killer glyphosate for the next five years after a heated debate over whether it causes cancer. After months of indecisive votes among the 28 member states in Brussels, Germany, whose Chancellor Angela Merkel has yet to form a new coalition after a September election (2016), came off the fence after abstaining in previous meetings. It said it backed a European Commission (that was the minister of agriculture) proposal against the wishes of France. The Commission, the European Union's executive, said in a statement that 18 countries had backed its proposal to renew the chemical's license. Nine countries were against and one abstained, giving a "positive opinion" by the narrowest possible margin under rules requiring more than a simple majority. The extension was opposed by Germany's center-left Social Democrats (SPD), with which Merkel is expected to launch exploratory talks this week on renewing their "grand coalition" after plans for an alliance with two other parties failed. French President Emmanuel Macron, who was elected in May on a platform of pursuing deeper EU integration alongside Germany, had wanted a shorter extension (up to 3 years) and a rapid phasing out of glyphosate, which is a mainstay of farming across the continent. After the vote, he said (in a tweet) he would take all necessary measures to ban the product, originally developed by Monsanto, as soon as an alternative is available and at the latest within three years. Monsanto declined to comment.[45]

Another problem with pesticides that was controversial in the last decade and caused disputes among EU members, were the neonicotinoid insecticides. In a long-awaited assessment, the European Union's food-safety agency (EFSA) has concluded that three controversial neonicotinoid insecticides pose a high risk to wild bees and honeybees. The findings by the European Food Safety Authority (EFSA) in Parma, Italy, raise the chances that the EU will soon move to ban all uses of the insecticides on outdoor crops. In 2013, the EU prohibited applications of the three chemicals on crops attractive to bees — such as sunflowers, oilseed rape and

maize (corn) — after an EFSA assessment raised concern about the insecticides' effects. Since then, researchers have amassed more evidence of harm to bees, and the European Commission last year (2017) proposed banning all outdoor uses, while still allowing the pesticides in greenhouses. The latest EFSA assessment strengthens the scientific basis for the proposal. The EU member states could vote on the issue as soon as 22 March 2018. The EFSA assessment covered the 3 neonicotinoids of greatest concern to bee health — clothianidin, imidacloprid and thiamethoxam. The agency considered more than 1,500 studies, including all the relevant published scientific literature, together with data from academia, chemical companies, national authorities, non-governmental organizations (NGOs) and beekeepers' and farmers' associations. The assessment found that each of the three chemicals posed at least one type of high risk to bees in all outdoor uses.

The EFSA found that foraging bees are exposed to harmful levels of pesticide residues in pollen and nectar in treated fields and contaminated areas nearby, as well as in dust created when treated seeds are planted. It also concluded, on the basis of more limited evidence, that neonicotinoids can sometimes persist and accumulate in the soil, and so can affect generations of planted crops and the bees that forage on them. "EFSA's advice is often criticized by interested parties such as NGOs and companies, but this is a good demonstration of how EFSA gives scientifically sound and impartial advice," says José Tarazona, head of the agency's pesticides unit. A spokesperson for the global biotechnology firm Syngenta, which produces neonicotinoids, says that EFSA's conclusions are overly conservative. "When regulators make decisions about crop-protection products, what should matter is science, data and that the processes in place are respected and that the public interest is served," the spokesperson says. EU member states were scheduled to vote on the proposal to outlaw outdoor uses on 13 December, but postponed it partly because many wanted to wait until EFSA completed its evaluation. Member states will discuss the EFSA assessment at a meeting of the commission's Standing Committee on Plants, Animals, Food and Feed sometime in March 2018.[46]

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