Glyphosate has become the world's most widely used weed killer, which could well be serious cause for concern

Glyphosate has recently been the subject of a number of articles in newspapers and magazines. Three of them in particular caught my attention: *"Glyphosate presence in honey raises concerns"* in the Canadian weekly The Western Producer [Arnason, 09.03.2017], *"Tribunal Monsanto: la firme américaine reconnue coupable d'atteinte aux droits humains (US firm found guilty of human rights abuses)"* in the French newspaper Le Monde [Barroux, 19.04.2017], and *"Roundup in EU toegestaan omdat Monsanto wetenschappelijke studies beïnvloedde (Roundup allowed in the EU because Monsanto influenced scientific studies)"* in the Flemish weekly Knack [Harmsen 25.04.2017].

Glyphosate, the active ingredient in Monsanto's flagship herbicide Roundup, may have contaminated the honey production because bees forage on corn and soybeans, which are sprayed with the weed killer during the growing season. Glyphosate has been a highly controversial substance since March 2015. The International Agency for Research on Cancer (IARC) classified the herbicide glyphosate and the insecticides malathion and diazinon as probably carcinogenic to humans (Group 2A) — the second worst rating possible[1].

For glyphosate, some evidence of carcinogenicity in humans for non-Hodgkin lymphoma (NHL) is based on several exposure studies, mostly agricultural, since the beginning of the 21st Century [Alexander et al. 2007, and references herein]. In addition, there is convincing proof that glyphosate can cause cancer in laboratory animals [IARC Monograph 112; Guyton et al. 2015]. Not all references of the IARC-report were well received though. For example, Séralini et al. [2012] published a controversial study in *Food and Chemical Toxicology*, but the paper was eventually retracted by the editor and later republished in *Environmental Sciences Europe* [Séralini et al. 2014]. The authors evaluated both the effects of feeding laboratory rats with transgenic corn as well as the effects of exposure to the increasingly common herbicide Roundup, and concluded that pathologies cannot be excluded. They observed severe hepatic and renal disturbances. Moreover, Séralini et al. [2014] called into question the earlier conclusions of a Monsanto team [Hammond et al. 2004], claiming that the initial indicators of organ toxicity were not "biologically meaningful". But the Séralini et al. study suffers from enormous gaps in the number of animals studied and from incorrect statistical interpretation.

Granted, some studies are liable to create controversy. However, in spite of their weaknesses and shortcomings, there is every reason to believe that they will achieve the strategic goal set by the authors, i.e. to endorse the role of whistle-blower.

[1] This category is used when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. In some cases, an agent (mixture) may be classified in this category when there is inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent, mixture or exposure circumstance may be classified in this category solely on the basis of limited evidence of carcinogenicity in humans (http://ec.europa.eu/health).

Monsanto was accused of crimes against humanity and ecocide, and was denounced for the marketing of toxic products that killed people. The “advisory” opinion of the court, under the chairmanship of Françoise Tulkens, former judge of the European Court of Human Rights, was published in The Hague on Tuesday, April 18. The document does not however constitute condemnation in the legal sense of the term as it is not “legally binding”.

Hundreds of internal documents and emails were unsealed by Judge Vince Chhabria, who was presiding over litigation brought by people who claim to have developed NHL as a result of exposure to glyphosate. It would seem that Monsanto has influenced and falsified scientific studies for many years. The documents and internal emails produced in 2015 reveal that Monsanto executives strategise about how to work with academic and independent scientists to convey the company’s message that glyphosate does not increase the risk of cancer. Moreover, the Monsanto documents suggest that company officials “ghost wrote” portions of scientific papers to be submitted to peer-reviewed scientific journals [Cornwall 2017]. One of the emails reveals that the company itself secretly wrote a study, even though it was published in the peer-reviewed journal *Regulatory Toxicology and Pharmacology* under the authorship of “independent” scientists [Williams et al. 2000].

Approval for Roundup in both the European Union and the United States has been Monsanto’s priority target. The company’s strategy sounds very familiar. Industry has clearly understood that debating the science is much easier and more efficient than debating the policy [Michaels 2008]. Williams et al. [2000] concluded that: … *under present and expected conditions of use, Roundup herbicide does not pose health risks to humans*... Today, almost 20 years later, this conclusion seems to me highly implausible. Several recent articles on the link between glyphosate and kidney disease, autism, rheumatoid arthritis and pulmonary problems are now available [Jayasumana et al. 2014, 2015; Beecham et al. 2016; Sealy et al. 2016; Parks et al. 2017; Hoppin et al. 2017]. Even when considering that link and causality are significantly different concepts, great care is recommended.

The European Food Safety Authority (EFSA) carried out an additional evaluation and peer review of the toxicity of glyphosate. Its assessment focused on the active substance and considered the weight of evidence of all available information. In contrast to the IARC evaluation, the EU peer review experts, with one exception, concluded that glyphosate is unlikely to pose a carcinogenic hazard to humans and that the evidence does not support classification with regard to its carcinogenic potential [EFSA 2015a].

And again, several references quoted in the report have given rise to a great deal of uneasiness. In their review paper, Kier & Kirkland [2013] concluded that the lack of genotoxic hazard potential, evidenced by core gene mutation and chromosomal effect studies, and coupled with the very low human and environmental species systemic exposure potential, indicates that glyphosate and typical glyphosate-based formulations present negligible genotoxicity risk. Both Kier & Kirkland, however, were paid consultants of the Glyphosate Task Force for the preparation of their review, and Larry Kier was a former employee of Monsanto Company. Employment by a business or research institute whose funding was significantly derived from commercial sources could possibly have been created a conflict of interest [Robinson et al. 2013].

EFSA's mission is to provide independent scientific advice to risk managers of the European Commission and Member States and to communicate to all interested parties and to the public at large on risks in the food and feed chain. European Member States must act in such a way that they don't fail to meet their commitments, even when the independent scientific advice is extremely expensive.

The EFSA peer review expert group also concluded [EFSA 2015b] that the toxicity of glyphosate needs to be redefined. Pending the completion of gap-filling research, an acute reference dose (ARfD) of 0.5 mg per kg body weight[2] and an acceptable daily intake of 0.5 mg per kg body weight per day were proposed. Moreover, EFSA proposes that the toxicity of each pesticide formulation and in particular its genotoxic potential should be further considered and addressed by Member State authorities while they re-assess uses of glyphosate-based formulations in their own territories.

Carcinogenic or not carcinogenic: this was a textbook example of the paradoxical situation that affected Europe in 2015/2016. Pending a conclusion by the European Chemicals Agency (ECHA), Europe provisionally authorized glyphosate under certain conditions.

After a great deal of procrastination, ECHA concluded that there were no grounds for classifying the controversial herbicide, glyphosate, as a carcinogen, as a mutagen or as a toxic substance for reproduction. ECHA's Committee for Risk Assessment (RAC) agreed to maintain its current harmonised classification of glyphosate as a substance causing serious eye damage and being toxic to aquatic life with long-lasting effects, and 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 [https://echa.europa.eu].

As for EFSA, the classification is based solely on the hazardous properties of the pure substance [EFSA 2015]. Neither does it take into consideration the likelihood of exposure to the substance and so, does not address the risks of exposure.

What chemical substance are we talking about? Glyphosate — its correct IUPAC designation is N-(phosphonomethyl)glycine — is the most heavily-used agricultural chemical in the history of the world. Glyphosate is mainly used as active substance in herbicides or weed killers to prevent unwanted plant growth. It is applied to the leaves of the plants, especially the annual broadleaf weeds and grasses that compete with the crops.

Glyphosate was discovered to be an herbicide by Monsanto chemist John E. Franz in 1970. The company began to market the substance in 1974 under the trade name Roundup [Wikipedia]. Glyphosate is used in agriculture and horticulture to combat weeds before sowing. Moreover, where genetically modified plants with resistance to glyphosate are grown, Glyphosate is sometimes used after sowing to destroy weeds growing among the crops.

The proposed minimum purity of the active substance, as manufactured by the members of the European Glyphosate Task Force, varies between 950 and 983 g per kg. In other words, every kg is

[2] The ARfD of a chemical is the estimated amount of a substance in food or drinking water expressed on a body weight basis that can be ingested over a short period of time, usually during one meal or one day, without appreciable health risk to the consumer on the basis of all known facts at the time of evaluation.

"contaminated" with 17 to 50 g of other chemicals, some of them relevant and others not. N-nitroso-glyphosate and formaldehyde are considered relevant impurities [EFSA 2015].

Widely used herbicides: also where palm trees grow! [source: PIXABAY - https://pixabay.com/]

Why are the opinions of IARC, EFSA, and ECHA fundamentally different? Or maybe they are not so different? The IARC report looked at both the active substance glyphosate as well as glyphosate-based formulations. The EU assessments, on the other hand, only considered glyphosate. IARC and EU adopted different approaches. It is the distinction between the effects of one single active substance and of pesticide formulations (mixtures of several chemicals) that explains how EFSA and IARC could express different opinions on the basis of the available data. For the EU assessment, studies conducted with glyphosate were more relevant than studies conducted with formulated products containing other constituents, particularly when the other constituents could not be clearly identified.

We know for a fact, however, that humans are chronically exposed to multiple exogenous substances, including environmental pollutants, drugs and dietary components, and we suspect that many among these compounds impact human health and that their combination in complex mixtures could significantly exacerbate their individual harmful effects. Delfosse et al. [2015], for example, clearly demonstrate that a pharmaceutical oestrogen and a persistent organochlorine pesticide, both of which exhibit low efficacy when studied separately, cooperatively bind to the pregnane X receptor, leading to synergistic activation.

Why then focus on the effects of the pure chemical rather than assess pesticide formulations? Many scientists have convincingly evidenced that the effects of mixtures differ from the sums of their individual effects [Pape-Lindstrom & Lydy 1997; Laetz et al. 2002; Gore et al. 2015; Delfosse et al. 2015; Krepker et al. 2017]. Today, the "contaminants'cocktail" remains a broadly misunderstood and

insufficiently researched concept with a strong social resonance. Now is the time to invest in studies on the cocktail effects of pollutants.

This is very important, because although some studies suggest that certain glyphosate-based formulations may be genotoxic[3], others that look solely at the active substance glyphosate do not show this effect. It is therefore likely that the genotoxic effects observed in glyphosate-based formulations are caused by exposure to several constituents, such as obligatory ingredients as well as impurities. It also happens that the genotoxic effect of a mixture exceeds the sum of the individual effects since the different compounds work in synergy. It is to be expected that glyphosate-based formulations display higher toxicity than that of the active ingredient, because of the presence of other chemicals.

In its assessment, EFSA suggests that the toxicity of each pesticide formulation and in particular its genotoxic potential should be further investigated and addressed by Member State authorities as they re-assess uses of glyphosate-based formulations in their own territories. This must be done quickly! Inert ingredients can increase the ability of pesticide formulations to affect significant toxicologic end points, including developmental neurotoxicity, genotoxicity, and disruption of hormone function [Cox & Surgan 2006].

It is simply not possible to reach convincing conclusions on the basis of incomplete and poor data, and fabricated or manipulated research results. Professor Jan Tijtgat, a toxicologist at Katholieke Universiteit Leuven, has already suggested starting risk evaluation all over again.

As long as it has not been clearly demonstrated that the product is harmless, large-scale use of glyphosate should be banned by virtue of the precautionary principle that should always be applied by public authorities when managing public health risks. The precautionary principle is relevant in those specific circumstances where risk managers have identified there are reasonable grounds for concern that an unacceptable level of risk to health exists but the supporting information and data may not be sufficiently complete to enable a comprehensive risk assessment to be made. At the end of this year, the European glyphosate license will expire. Hopefully, decision makers will not lend their support to half-baked solutions!

Science moves rapidly and increases our knowledge. New approaches, accounting for chemical similarity and overlaying multiple data sources, will play a future role in risk assesments [Guha et al. 2016]. Moreover, it is now recognized that testing for glyphosate in urine can both help determine the level of exposure to glyphosate and guide towards optimal treatment plans for the patients [Shaw & Pratt-Hyatt 2017].

Premature conclusions have to be avoided, especially since additional analyses are still required by the European Member States [EFSA 2015b].

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[3] In genetics, genotoxicity describes the property of chemical agents that damages the genetic information within a cell causing mutations [Wikipedia].

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May, 2017