Glyphosate: useful, dangerous? To license or to phase out?

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ABSTRACT

Glyphosate, a herbicide blocking an enzyme essential for all plants, but not for animals and humans, has certain advantages as compared to other plant protection products. It is not persistent. Due to the production and application of more than 700,000 tons per year, large portions of mankind are exposed. The International Agency on Research on Cancer (IARC) of the World Health Organisation (WHO) has looked more closely on glyphosate and has classified it as “probably carcinogenic for humans (2A)” The German Bundesamt für Risikobewertung (BfR) and the European Food Safety Authority (EFSA) have analysed the data and contradict the IARC classification. In this paper, the process of decision finding and essential arguments for the contradictory classification are commented. In the ensuing public discussions, conflicts could have been rationalized if the BfR and the EFSA had offered more transparency regarding their evaluation and had restricted their opinions and their proposals to their genuine task: to propose regulations concerning the risks (which follow from possible hazards).

Key words: Glyphosate – Risk Communication

INTRODUCTION

Should the European Union (EU) renew the license for the herbicide glyphosate, or should its use be phased out? The recently omnipresent debate touches several aspects: toxicity and carcinogenicity of this compound, credibility of results published by official and semi-official agencies, deficiencies in the communication of hazards and risks, and finally society’s opinions and attitudes on agricultural techniques.
PROPERTIES AND EFFECTS
OF GLYPHOSATE

Glyphosate, synthesized in 1950, was recognized to be a potent and useful herbicide in the early seventies of the last century. Monsanto acquired the patent – meanwhile expired – in 1974 and has marketed glyphosate in combination with surfactants as Roundup®. Today, some 100 producers sell, and farmers and garden owners apply, more than 700,000 tons of glyphosate per year.

Glyphosate is odorless, water soluble and not volatile. It blocks the enzyme 5-enol-pyruvylshikimate-3-phosphate-synthetase (EPSPS). This enzyme is present in practically all plants and is essential for the synthesis of the aromatic amino acids phenylalanine, tryptophane, and tyrosine. Animals and man have no EPSPS, and do not depend for their amino acid synthesis on the function of this enzyme; therefore glyphosate in its biochemical mode of action is toxic for plants, as well as to fungi and other microorganisms, but not for animals and mankind. Only few plants, among them genetically modified plants, are resistant to glyphosate. Glyphosate is metabolized and degraded by bacteria, and half life in soils is 2 to 7 weeks.

Glyphosate is usually applied in combination with surfactants, shortly before sowing, and again after harvest, to suppress unwanted plant growth. Furthermore, maize, rape and leguminoses can be treated until 7 days before harvesting in order to enhance maturation and desiccation. In agriculture, 1–2.5 (up to 4) kg per hectare are applied.

CONTROVERSIES ON THE RENEWAL
OF LICENSING

EC regulation 1107/2009 requires the renewal of licenses for pesticides in ten year intervals. Producers (“applicants”), having formed a Glyphosate Task Force (GTF), must present newly created scientific data in a dossier to one of the EU member states (Reporting Member State, RMS) to produce a Renewal Assessment Report (RAR) that is to be presented to the European Food Safety Agency (EFSA). EFSA evaluates the RAR and proposes actions to the European Commission (Directorate General for Health and Food Safety).

Germany has asked the Bundesinstitut für Verbraucherschutz und Lebensmittelsicherheit (Federal Office for Consumer Protection and Food Safety, BVL) to evaluate the glyphosate dossier; the Bundesinstitut für Risikobewertungen (Federal Institute for Risk Assessment, BfR) has been asked to report on aspects relevant for human health.

Both BfR and EFSA reports are not accessible for the public, neither authors nor details on uses or evaluations of scientific literature are visible or open for discussion. However, one author has held in hands the BfR report (as of march 2015) and has commented it [1,2]. EFSA has asked for comments and organised a hearing in March, 2016; and a summary – without many details – of the EFSA report has been published in 2015 [3].

During these processes, in 2015, the International Agency for Research of Cancer (IARC), a World Health Organisation (WHO) agency, has published their Monography 112 [4] resuming: There is limited evidence in humans for the carcinogenicity of glyphosate. A positive association has been observed for non-Hodgkin lymphoma. There is sufficient evidence in experimental animals for the carcinogenicity of glyphosate. Glyphosate is probably carcinogenic to humans (Group 2A).

The Joint Meeting FAO/WHO Meeting on Pesticide Residues (JPMR), however, declared in may 2016, that there was no risk for humans, considering the real exposure rates.

Based on such informations and judgements and possibly on own convictions, the European Parliament voted for a time limited licensing, giving a temporary allowance for 7 years, and to restrict the use of glyphosate to professional agriculture. Furthermore, the parliament suggested an open and independent reevaluation of all scientific data used by EFSA.

The European Commission has, after deliberations in May 2016, not issued a judgement, but postponed its decisions because apparently there existed no qualifying majority, not for, nor against prolongation of the license. By June 30, 2016, the Commission prolonged the license for 18 further months. Foreseeably, the glyphosate debate will arise anew in 2017.

CANCEROSTICITY IN EXPERIMENTAL
ANIMALS, EVALUATION BY IARC

Much of the scientific literature reviewed by IARC on long term application of glyphosate to experimental animals, often including high doses (several gram per kilogram of food) has not revealed any cancerogenic effects. Some „positive“ studies evaluated by IARC are:

Groups of each 50 male and female CD-1-mice were fed for two years glyphosate, 0, 1.000, 5.000,
and 30,000 ppm. Ureteral adenomas were observed in male animals in 1/49, 0/49, 0/50, and 2/50, which was interpreted as “positive trend, p < 0.034”. Ureteral carcinomas occurred in 0/49, 0/49, 0/50, and 1/50. There were no reports on the results in female mice. Summarily, the authors judged that there was a “significant increase in the incidence of rare tumors.” [5]

In another long time study, groups of each 50 CD-1-mice received 0, 100, 300, and 1,000 mg of glyphosate per kilogram of body weight. This was without effects on survival or body weight. Haemangiosarcomas were seen in male animals in a frequency of 0/50, 0/50, 0/50, and 4/50, however not in female animals. Histiocytic sarcoma occurred in 0/100, 5/100, 3/100, and 3/100 animals. The comment was: “There was an increase in the incidence of haemangiosarcoma in males... and an increase in histiocytic sarcoma.” [6]

The following table (table 1) from the BfR-report has been cited by Clausing [1].

<table>
<thead>
<tr>
<th>Strain/Study Code</th>
<th>Control</th>
<th>Low Dose</th>
<th>Mid Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD1/ASB2012-11 492</td>
<td>Incidence</td>
<td>0 ppm</td>
<td>500 ppm</td>
<td>1,500 ppm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0/51</td>
<td>1/51</td>
<td>2/51</td>
</tr>
<tr>
<td>Swiss-Albino/ASB2012-11 491</td>
<td>Incidence</td>
<td>0 ppm</td>
<td>100 ppm</td>
<td>1,000 ppm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10/50</td>
<td>15/50</td>
<td>16/50</td>
</tr>
<tr>
<td>CD1/ASB2012-11 493</td>
<td>Incidence</td>
<td>0 ppm</td>
<td>1,600 ppm</td>
<td>8,000 ppm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2/50</td>
<td>2/50</td>
<td>0/50</td>
</tr>
<tr>
<td>CD1/Tox9552382</td>
<td>Incidence</td>
<td>0 ppm</td>
<td>100 ppm</td>
<td>300 ppm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4/50</td>
<td>2/50</td>
<td>1/50</td>
</tr>
</tbody>
</table>

Table 1. Incidence of malignant lymphomas in male mice. *statistically significant dose-dependent increase according to Cochran-Armitage trend test; ** statistically significant according to RAR

For the results, both from IARC as those cited in table 1, significances are calculated and taken as indication for dose dependency, although all groups are quite small. Moreover, and more importantly, it has to be questioned whether consequences of such high dose exposure (0.1 to 4% in food, daily intake of up to grams of glyphosate per kg of body weight) really are of any practical relevance.

Epidemiologic Studies

IARC considers that there is limited evidence for the carcinogenicity of glyphosate in humans ([7], pages 16-30). Their report cites one study in cohorts and many case-control studies. Most studies show an over-all relative risk (RR) for carcinogenicity of 1.0. Several studies have found an elevated RR for non-Hodgkin lymphoma and multiple myeloma. All case-control investigations have been retrospective studies and always have considered the effects of mixtures of multiple herbicides and pesticides, and thus have many inherent uncertainties.

Risk-Benefit Considerations

Agriculture could be managed without glyphosate in humans ([4], just as it has been possible several decades ago. If glyphosate should be phased out, possibly more toxic, and more persistent other herbicides would be used by farmers; or deep ploughing would disturb the microbiotic architecture of our fields and – just as after glyphosate spraying – result in weed-free, “sterile” soils. Grubbing, instead of ploughing, is considered to be protective for the nature. Ploughing would also result in markedly higher fuel consumption. The glyphosate debate thus touches more fundamental aspects: what kind of agriculture do we wish to have in future, intensive and yield oriented, or “ecologic”? Whether the use of glyphosate is licensed or forbidden, will not decide this question. With, or without, glyphosate, we will continue to have a weed-free, “sterile” agriculture. Inherent is, of course, also the question of how we can supply sufficient food for the ever growing number of men on earth.

HAZARD VS. RISK; DIFFICULTIES IN RISK COMMUNICATION

IARC decisions often are taken as ultimate wisdom. However, one must know that IARC judgements sometimes are based on majority votes of the commission, with opposite appraisals of some or several of committee members (e.g. decision on carcinogenicity of electromagnetic fields Monography
102/2013); and there is reason properly read the reasonings and to question some votes of IARC, e.g. for nitrates in food (Monography 94/2010), when inadequate evidence for carcinogenicity in humans of nitrate and nitrite is seen, and when all the same a 2A-classification is the result: ingested nitrate and nitrite under conditions that result in endogenous nitrosation is probably carcinogenic to humans.

Much of the difficulties, of the controversies in the debate on glyphosate licensing results from the fact, that the meaning of hazard and risk are not well understood or mediated. This is true for the general public, for media and politicians, and often also for “experts”.

Hazard describes the potential to inflict a damage, disease, adverse effect. Risk stands for the probability that such an adverse effect will result from exposure. Political decisions should be based on risk evaluations, and these should be as solidly based as possible.

Therefore, it is important to properly read what the IARC states [7]: A cancer ‘hazard’ is an agent that is capable of causing cancer under some circumstances, while a cancer ‘risk’ is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. The Monographs are an exercise in evaluating cancer hazards, despite the historical presence of the word ‘risks’ in the title. The distinction between hazard and risk is important, and the Monographs identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.

The Monographs are used by national and international authorities to make risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes and decide among alternative options for public health decisions. The evaluations of IARC Working Groups are scientific, qualitative judgements on the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which public health decisions may be based. Public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations.

From editor

IARC classification of some organophosphate pesticides*

<table>
<thead>
<tr>
<th>Activity (current status)</th>
<th>Evidence in humans (cancer sites)</th>
<th>Evidence in animals</th>
<th>Mechanistic evidence</th>
<th>Classification*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetrachlorvinphos</td>
<td>Insecticide (restricted in the EU and for most uses in the USA)</td>
<td>Inadequate</td>
<td>Sufficient</td>
<td>2B</td>
</tr>
<tr>
<td>Parathion</td>
<td>Insecticide (restricted in the USA and (EU)</td>
<td>Inadequate</td>
<td>Sufficient</td>
<td>2B</td>
</tr>
<tr>
<td>Malathion</td>
<td>Insecticide (currently used; high production volume chemical)</td>
<td>Limited (non-Hodgkin lymphoma, prostate)</td>
<td>Sufficient</td>
<td>Genotoxicity, oxidative stress, inflammation, receptor-mediated effects, and cell proliferation or death</td>
</tr>
<tr>
<td>Diazinon</td>
<td>Insecticide (restricted in the USA and EU)</td>
<td>Limited (non-Hodgkin lymphoma, leukaemia, lung)</td>
<td>Limited</td>
<td>Genotoxicity and oxidative stress</td>
</tr>
<tr>
<td>Glyphosate</td>
<td>Herbicide (currently used; highest global production volume herbicide)</td>
<td>Limited (non-Hodgkin lymphoma)</td>
<td>Sufficient</td>
<td>Genotoxicity and oxidative stress</td>
</tr>
</tbody>
</table>

LITERATURE


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