Scientific Advice Mechanism High Level Group

Explanatory note on scientific advice for the regulatory assessment of glyphosate in plant protection products

This note is addressed to the Commissioner for Research, Science and Innovation following the Scientific Advice Mechanism High Level Group (SAM HLG) second plenary meeting (16th, 17th March 2016), the minutes[1] of which record that SAM HLG will provide a *"short explanatory note on the {glyphosate} situation".*

Glyphosate is at present approved for use as an active substance[2] in plant protection products[3] in all Member States of the EU and is labelled with the hazard classifications "*corrosive (causes serious eye damage)*" and "*hazardous to the environment (toxic to aquatic life with long lasting effects)*". Renewal of this approval is sought by the European Glyphosate Task Force[4] (GTF), a consortium of companies, in an application to an EU regulatory process involving the European Commission, EU Member States and the European Food Safety Authority (EFSA).

Current debate about the safety of glyphosate arises mainly from differences in recent classifications of its human carcinogenic hazard potential by EFSA and by the World Health Organisation's International Agency for Research on Cancer (WHO-IARC). In its November 2015 'conclusion on pesticide peer review'[5] (hereafter, EFSA Conclusions), EFSA declares that glyphosate is "*unlikely to pose a carcinogenic hazard to humans"*, while WHO-IARC's March 2015 Monograph[6] declares that glyphosate is "*probably carcinogenic to humans"*.

This note does not take a position on the carcinogenic hazard[7] potential of glyphosate. This is in line with the minutes of the abovementioned meeting and the mandate of the SAM HLG in which it is stated that SAM HLG "*does not duplicate advice being provided by existing bodies"*[8].

WHO-IARC's classification of glyphosate as probably carcinogenic for humans means that WHO-IARC found *limited evidence* in humans and *sufficient evidence* in experimental animals of carcinogenicity, and *strong* mechanistic and other evidence

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[1] https://ec.europa.eu/research/sam/index.cfm?pg=library

[2] The term 'active substance' is defined (in Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market) as chemical elements and their compounds, as they occur naturally or by manufacture, including any impurity inevitably resulting from the manufacturing process, which have general or specific action against harmful organisms or on plants, parts of plants or plant products.

[3] Also known as pesticides or herbicides

[4] http://www.glyphosate.eu/

[5] http://www.efsa.europa.eu/en/efsajournal/pub/4302

[6] http://monographs.iarc.fr/ENG/Monographs/vol112/

[7] A hazard is a source of potential harm. The risk that the hazard will be harmful depends on the dose at which such harm occurs and the likelihood to be exposed to such a dose

[8] https://ec.europa.eu/research/sam/index.cfm?pg=library

that exposure to glyphosate and glyphosate based formulations is genotoxic[9] or induces oxidative stress, characteristic of known human carcinogens.

EFSA by contrast classified the evidence as *very limited* in humans, stated also that there is "*no evidence of carcinogenicity… in either rats or mice*" and that the mechanistic evidence shows that glyphosate is *"unlikely to be genotoxic in vivo[10] and does not require hazard classification regarding mutagenicity[11] according to the CLP regulation[12]".*

Why these findings are different and what this really means have been discussed at length in correspondence[13] between interested parties and in the media, drawing public concern. Uncertainty about the understanding and interpretation of these differences in classification has raised questions about the EU decision-making process for the approval of glyphosate as an active substance. If a decision is not taken by June 30th 2016, glyphosate containing products will be banned from sale in the EU from 2017.

While both EFSA and WHO-IARC deliver a carcinogenicity hazard assessment for glyphosate, the scope and purpose of the EFSA Conclusions are different from those of the WHO-IARC Monograph. EFSA is tasked to conduct a full risk assessment of the active substance only, considering all aspects of human and environmental safety. As part of that process EFSA also conducts a hazard assessment and a comparison with the hazard approval criteria, to be considered by the European Chemicals Agency (ECHA) if a Member State submits a proposal for harmonised classification and labelling (CLP). The EFSA assessment thus represents one step in the EU regulatory process. The WHO-IARC Monograph is by contrast a stand-alone assessment concerning the carcinogenic potential of glyphosate and of glyphosate-based formulations.

1. Consequently, the parameters of the regulatory process of which the EFSA Conclusions form a part differ from those applicable to the WHO-IARC Monograph:

    - To obtain a renewed approval of glyphosate, the GTF provided the EC, all Member States and EFSA with a file containing proprietary studies and peer-reviewed scientific studies published in the previous 10 years. Germany, as the EU Rapporteur Member State (RMS), conducted a first assessment in the form of a draft Review Assessment Report, which was peer-reviewed by EFSA in cooperation with the other Member States[14], a

[9] The term is generally understood to refer to agents which damage genetic information which may lead to mutation, cancer, or cell death

[10] The term *in vivo* is commonly understood to refer to experiments conducted on living organisms, or parts thereof. Strictly speaking, animal experiments are conducted *in vivo*, but both EFSA and WHO-IARC separate whole animal carcinogenicity studies from mechanistic (including genotoxicity) *in vivo* and *in vitro* studies (where *in vitro* is here understood to refer to experiments performed on cells or cellular components alone). In the quoted text, the implication (supplied by the non-quoted context) to the reader is therefore that while there may be some *in vitro* mechanistic evidence, this is not substantiated by *in vivo* mechanistic evidence

[11] A mutagen is generally understood to be an agent which causes direct or indirect damage to genetic information, which is retained in cell division, and which may consequently lead to cancer. Not all genotoxins are mutagens, and not all mutagens cause cancer

[12] Regulation 1272/2008 on the classification, labelling and packaging of substances and mixtures (the CLP regulation)

[13] http://www.efsa.europa.eu/en/press/news/160113

[14] It is noted that Sweden presented a dissenting minority opinion on the eventual EFSA conclusion

process which resulted in the EFSA Conclusions. WHO-IARC used publicly available information only, either published in peer-reviewed journals or in the form of summaries from industry proprietary studies made available through previous regulatory assessments by other bodies [for glyphosate: the 2006 Joint FAO/WHO Meeting on Pesticide Residues (FAO/WHO-JMPR) risk assessment and 1985, 1986, and 1991 U.S. Environmental Protection Agency (EPA) assessments]. It is noted that some proprietary studies were not available to WHO-IARC and that recent correspondence[15,16] between Commissioner Andriukaitis and the GTF may result in these being made available.

- In line with its mandate, EFSA has not taken into account some evidence reviewed by WHO-IARC dealing with formulations, *i.e.* mixtures of glyphosate and other chemicals. Differences between the observed effects for pure glyphosate and glyphosate formulations are reported in the WHO-IARC monograph. EFSA nevertheless assessed one co-formulant considered of particular concern, despite this not being part of its mandate. The document[17] accompanying the EFSA Conclusions indicates that "*the toxicity of formulations and in particular their genotoxic potential should be further considered and addressed*".

- The EU and the WHO-IARC classification schemes are different. The EU Classification, Labelling and Packaging (CLP) criteria[18], as implemented in the ECHA guidance (ECHA, 2013 and 2015), are based on the United Nations' Global Harmonised System (UN-GHS) criteria[19] and follow a 'weight of evidence' approach. WHO-IARC has developed its own classification system, criteria and methodology. However, it is understood that there is a strong link between the WHO-IARC and the CLP hazard classes.

2. Furthermore, when reviewing the common database of carcinogenicity studies, EFSA and WHO-IARC have in some cases developed different interpretations or attributed different values or weight to these. It is beyond the scope of this note to detail all of the commonly examined studies, and the various conclusions. The main divergences may however be summarised as follows:

   - Having employed different statistical methodologies in their analyses, EFSA and WHO-IARC differ in their assessment of the statistical significance of findings from animal model carcinogenicity studies. The same data are found to be statistically significant or not depending on the method employed by either EFSA (pairwise comparison with untreated

[15] http://ec.europa.eu/commission/2014-2019/andriukaitis/announcements/my-letter-dr-richard-p-garnett-chair-board-glyphosate-task-force-04-april-2016_en
[16] http://www.glyphosate.eu/system/files/sidebox-files/letter_to_commissioner_andriukaitis.pdf
[17] http://www.efsa.europa.eu/sites/default/files/4302_glyphosate_complementary.pdf
[18] Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures (the CLP regulation).
[19] http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html

controls) or WHO-IARC (test for a trend). EFSA and WHO-IARC differ in their assessments of the legitimate use of these methods in these cases.

- EFSA and WHO-IARC differ in their interpretation of the biological relevance of these statistical findings in animal model carcinogenicity studies, and accordingly attribute different weight to these findings. EFSA contends that:
  - there is a lack of a clear dose-response relationship;
  - incidences of tumour development are not different from those which are observed in control groups (not exposed to glyphosate);
  - there was a lack of consistency in responses between male and female experimental animals within the same studies and for similar dose groups between studies; and
  - there was a lack of pre-neoplastic lesions[20].
- According to EFSA, the finding by WHO-IARC of glyphosate-alone genotoxicity *in vivo* in rats and mice is not valid. EFSA contend that these studies did not follow the OECD guidelines for good laboratory practice and one is given no weight as EFSA assesses it as having "major flaws" in the study design. In the other study, differences in interpretation relate to whether observed DNA damage is due to secondary cytotoxic or to direct genotoxic effects. According to EFSA, secondary cytotoxicity (due to high intraperitoneal doses[21]) should be excluded from the assessment of the intrinsic genotoxicity potential.
- Finally, EFSA and WHO-IARC attribute different weight to findings from human epidemiological case-control[22] and cohort[23] studies as EFSA and WHO-IARC have a different view on whether these studies indicate a causal relationship between exposure to the active substance and an increased risk for cancer. EFSA and WHO-IARC also differ in their assessment of the statistical significance of a meta-analysis of mostly case-control studies, where a link is made between exposure to various pesticide formulations, including glyphosate-based formulations, and the development of Non-Hodgkin Lymphoma (a form of cancer).

In addition to the performance of a carcinogenic hazard assessment by both EFSA and WHO-IARC, EFSA also undertook a full risk assessment of glyphosate. EFSA concluded that the highest level of glyphosate intake at which no adverse effects for human health are to be expected is 50 mg/kg body weight/day. According to EFSA, this limit is determined on the basis of adverse effects, other than carcinogenicity, to human health. Using a safety factor of 100, EFSA then proposes an acceptable daily intake (ADI)

[20] Pre-neoplastic lesions are characteristic cellular changes that are a good indicator for carcinogenicity

[21] This refers to high doses of glyphosate being injected into the peritoneum (abdomen/body cavity)

[22] These compare patients with disease (cases) to matching (age, gender, etc.) persons without disease (controls) and look back to determine if there is an association between exposure and disease

[23] These follow groups of persons over time and look for associations between exposure and disease

of 0.5 mg/kg body weight/day and an acute reference dose[24] (ARfD) of 0.5mg/kg body weight.

The FAO/WHO-JMPR published its full risk (re-)assessment of glyphosate, May 16th, 2016[25]. It concludes that "*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 … that glyphosate is unlikely to pose a carcinogenic risk to humans from exposure through the diet*". FAO/WHO-JMPR therefore recommends an ADI for glyphosate and metabolites of 0–1 mg/kg body weight (the EFSA ADI is within this range). FAO/JMPR did not however consider an ARfD necessary for glyphosate or its metabolites in view of its "*low acute toxicity*".

It is understood that the US Environmental Protection Agency is also in the process of conducting such a full re-assessment.

In the course of its risk assessment, EFSA also assessed a proposal for classification and labelling of glyphosate using the ECHA CLP guidance. As the responsibility for that assessment is with the European Chemicals Agency (ECHA), the latter has been requested to consider the classification and labelling of glyphosate[26]. According to the information available at this time ECHA will assess glyphosate only. Its assessment is likely to be based on the same studies that were available to EFSA.

[24] The amount which can safely be consumed in a single dose

[25] http://www.who.int/foodsafety/jmprsummary2016.pdf?ua=1

[26] http://echa.europa.eu/en/view-article/-/journal_content/title/echa-e-news-19-august-2015