Summary

Glyphosate and Oxidative Stress: ECHA’s superficial approach neglects existing hazards

Background

The EU regulation on the placing of pesticides (plant protection products) on the market (EC) 1107/2009 has established rules to ensure that pesticide active substances and products cause no adverse effects on human and animal health, and the environment. This includes the assessment of studies sponsored by the company interested in placing a pesticide product on the market, and all peer-reviewed scientific literature on the active substance and its relevant metabolites “dealing with side-effects on health, the environment and non-target species” published within the last 10 years (Article 8.5). These are assessed first by national agencies (acting as Rapporteur Member States) and thereafter by the European Chemicals Agency (ECHA) and the European Food Safety Authority (EFSA), who coordinate the hazard classification and peer review of the risk assessment\(^1\) respectively. The authorities are obliged to ensure that no studies are missing, and if so, to incorporate them in the assessment.

The assessment of glyphosate, the most widely used herbicide in the world, has been re-initiated in the EU within the context of its market license renewal before the end of the year, 2023. A key step in this procedure was the hazard assessment and classification of glyphosate, which was conducted by member state experts in ECHA’s Risk Assessment Committee (RAC) and was finalised in May 2022. Based on the available evidence, ECHA concluded that a classification of glyphosate as genotoxic or carcinogenic “is not warranted”. During the hazard assessment, certain scientists were invited by civil society groups to participate as observers in the RAC discussions, and provided information supporting the classification of glyphosate as a presumed carcinogen (may cause cancer) and/or genotoxic (damages the DNA), similar to the classification made by the International Agency for Research on Cancer (IARC) in 2015.

In their paper “Glyphosate and Oxidative Stress: ECHA’s superficial approach neglects existing hazards”, these scientists highlight the failure of EU agencies to acknowledge this potential mechanism of glyphosate’s carcinogenicity. They explain how this mechanism could contribute, directly or indirectly, to the observed cancer incidents in both industry-provided animal studies as well as those from peer-reviewed scientific literature. Furthermore, oxidative stress may also lead to damage of the nervous system, which could partly explain the observed neurodegenerative effects associated with glyphosate exposure.

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\(^1\) In toxicology, a hazard is – if applicable - the harmful property of a chemical (e.g. carcinogenic, genotoxic or toxic to reproduction). A risk is the chance that harmful effects will occur (following exposure to the chemical).
Oxidative Stress- the underlying mechanism induced by glyphosate that can lead to disease

"Reactive oxygen species" (ROS) are molecules produced during normal cellular processes and play important roles in cell functions. When the production of ROS exceeds the capacity of the cell’s defence system to deactivate them, it can lead to "oxidative stress,” which may cause cellular damage. Oxidative stress has been linked to serious diseases such as cancer and nervous system damage.

The authors provide an overview on how ROS are formed, how they are measured by a range of methods and how certain pollutants may interfere with their production or their deactivation, resulting in oxidative stress. Excess ROS can cause direct DNA damage but may also interfere with signalling molecules and networks (e.g., calcium signalling cascade), or epigenetics (change in DNA processes without directly altering the DNA sequence itself), leading to carcinogenesis. Depending on the levels of production, ROS may also cause cell death.

It is crucial for the assessment of glyphosate to recognise that only a small portion of the adverse effects caused by ROS is associated with DNA damage. This implies that the standard genotoxicity tests commonly employed in regulatory assessments, which primarily focus on direct DNA damage, cannot capture the broad spectrum of adverse effects induced by ROS. Therefore, given that biomarkers of oxidative stress are not included in the standard test guidelines, it is essential (and a legal requirement) to properly integrate the results of such studies published in the peer-reviewed scientific literature into the hazard assessment. However, as argued by the authors, the ECHA failed to do so, as evident in its Opinion on glyphosate released in May 2022. Initially, ECHA considered a limited number of studies from the scientific literature (11 out of 32 available), and even when these were later included, it refrained from acknowledging the findings on oxidative stress as important. Moreover, it referred to them as equivocal without scientific justification and based its conclusions on the standard genotoxicity tests provided by the pesticide companies, which – as explained – fail to detect the full range of adverse effects. EFSA too supports this flawed approach.

Next, the authors dive into the evidence that exposure to glyphosate causes oxidative stress and describe how this may explain the adverse effects reported in scientific literature. Starting by referring to the first evidence from 40 years ago, the authors examine the most relevant recent publications showing that glyphosate consistently induces oxidative stress in rodents, pigs, and human cells.

As an example, two studies have shown evidence of oxidative stress in the kidneys of mice. Interestingly, in three out of the five animal carcinogenicity studies submitted by the glyphosate companies, animals had developed an increased incidence of renal tumours. At the same time, it is standard knowledge of tumour biology that particularly in the development of kidney tumours, ROS play a role.

In human populations, an epidemiology study called the Agricultural Health Study, which is considered by regulatory agencies of high quality, showed that the increase in oxidative stress markers in agricultural workers was associated with exposure to glyphosate-based herbicides.

The paper also indicates that oxidative stress induction by glyphosate may lead to cancer via epigenetic mechanisms. Similarly, to oxidative stress, there are no standard tests to measure epigenetic changes, the evidence must come from the scientific literature.
Overall, this significant body of work clearly demonstrates that despite consistent results across different studies and species, the EU regulatory agencies have neglected the important mechanistic evidence indicating that glyphosate induces oxidative stress. It is scientifically perplexing why these agencies continue to disregard this toxic mechanism of glyphosate, which could potentially explain the various adverse effects observed in animal studies and humans. Furthermore, this failure to acknowledge the adverse effects caused by glyphosate is not only scientifically questionable but also a violation of the law. Considering the widespread use of glyphosate-based products, neglecting these adverse effects poses a health risk to both farm workers and the general population, a risk that could be easily avoided by banning the use of glyphosate.

Read the full paper: Glyphosate and Oxidative Stress: ECHA’s superficial approach neglects existing hazards