CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 6

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON PESTICIDE RESIDUES

53rd Session
(Virtual)
4-8 July and 13 July 2022

(Comments of CropLife International)

Statement on Glyphosate (#58)

July 6, 2022

Response to Conference Room Document 28 / CCPR53

CropLife International on behalf of Bayer Crop Science, the data sponsor for glyphosate (compound #58), offers this comment on endocrine disruption, carcinogenicity, and antimicrobial resistance, raised in Conference Room Document 28 and in comments made by observer organizations in the CCPR53 plenary. CropLife International kindly asks that a reference to this CRD be included in the CCPR53 report if CRD 28 or comments in the CCPR53 plenary are also referenced.

Endocrine disruption / carcinogenicity:

Over the last decade comprehensive reviews of glyphosate and glyphosate formulations by leading regulatory authorities have confirmed that they can be used safely according to their label instructions. This includes the WHO evaluation of glyphosate that was completed in May 2016 and the May 2022 classification decision by the European Chemicals Agency (ECHA); for example the ECHA kept the hazard classification unchanged from its previous review and regarding carcinogenicity made this statement: **"***Based on a wide-ranging review of scientific evidence, the committee again concludes that classifying glyphosate as a carcinogen is not justified***."** As stated in CCPR52 and repeated here, in these reviews no regulatory authority in the world has classified glyphosate as an endocrine disruptor.

We invite all the CCPR delegates to take advantage of the Transparency website that can be found at www.glyphosate.eu, where the EU glyphosate submission and other related materials (such as individual study reports) can be accessed.

ECHA: https://echa.europa.eu/-/glyphosate-no-change-proposed-to-hazard-classification

https://www.glyphosate.eu/

https://ec.europa.eu/food/system/files/2021-06/pesticides_aas_agg_report_202106.pdf

https://ec.europa.eu/food/plants/pesticides/approval-active-substances/renewal-approval/glyphosate/assessment-group_en

WHO: https://www.who.int/foodsafety/jmprsummary2016.pdf

Antimicrobial resistance

Please note in November 2021 a similar response was forwarded to a comment in CAC/44 CRD/37 under agenda items 4.6 and 4.9.

Antimicrobial resistance is one of the greatest threats facing humanity. However, critical to mitigating this threat is identifying the causative factors of this crisis. There are many possible hypotheses or correlations that can be associated with the increase in antimicrobial resistance over the last several decades. However, correlation does not equal causation, and to suggest that glyphosate is a key factor in this crisis of antimicrobial resistance based on correlations or unproven hypotheses is not sound scientific practice, and, perhaps more importantly, distracts from the well-documented drivers of antimicrobial resistance and associated actions to mitigate them.

Antimicrobial resistance is a complex, multifactorial problem. However, it is now well-regarded that the misuse of antibiotics particularly in rapidly growing animal production systems in Asia and Africa plays a key role in antimicrobial resistance development (Holmes et al. 2016). Antimicrobial stewardship systems and practices therefore remain a key component in the responsible use of antibiotics.

- It is also important to clarify that glyphosate is not an "antibiotic drug", has not been registered for this use, and it is therefore misleading to represent it as such. Glyphosate is an herbicide and is commercialized for its herbicidal use. While some microbes naturally possess a similar target enzyme than that found in plants, there are naturally occurring sensitive and resistant versions of the enzyme, and sensitivity or resistance to glyphosate abides by the same toxicological principles of any substance, where the dose of the molecule in the context of real-world usage practices must be accounted for in consideration of toxicological effects. For example, from the vast glyphosate database of risk assessment studies it is known that "the maximum glyphosate and AMPA concentrations in soil (PEC_{soil}) assuming application to permanent crops (tillage depth 5 cm) at the maximum cumulative annual application rate of 4.32 kg glyphosate a.e./ha, each year for 10 years, are reported to be 6.62 mg a.e./kg dry soil for glyphosate". "By way of comparison, initial predicted environmental concentrations ($PEC_{initial}$) of glyphosate and AMPA directly following a single application of 4.32 kg a.e./ha to bare soil are 5.76 mg a.e./kg soil and 2.04 mg a.e./kg soil, respectively." (von Mérey et al., 2016).
- By contrast, a concentration of 1240 mg/L of glyphosate in an *in vitro* study of a single bacterium in pure culture was used to support a study's claims of a glyphosate-antibiotic resistance connection, via the activation of the inducer of the AcrAB efflux pump. The AcrAB-TolC efflux system is a type of bacterial sump pump that responds to a wide variety of substances far beyond antimicrobials used for therapeutic reasons, including bile, pH changes, cationic peptides, salicylic acids, other medications, and other substances present in excess, that could harm the cell. It would be expected that very high doses of multiple compound – including herbicides, including formulated ingredients that include surfactants and other substances - would elicit a response, such as upregulation of an efflux pump, or other stress responses from bacteria. It does not appear that the authors in this study have controlled for pH effects or ionic strengths of using these high concentrations of herbicides. High doses of glyphosate, for example, can lead to significant pH changes, which on its own may induce efflux pumps. (Tsui &Chu, 2003).
- Additionally, a recent *in vitro* study selected for glyphosate resistant mutants of animal clinical isolates of *Salmonella enterica* by subjecting the bacteria to very high doses of glyphosate (> 20,000 ppm). They then analyzed the mutants and found that glyphosate resistance evolution is a "slow" process that neither results in a sustained stress response (e.g., overexpression of efflux pumps is transient) nor imparts a fitness cost, and it also does not result in cross tolerance or cross resistance to clinically relevant antibiotic (Pöppe et al., 2020).

- In summary, in the context of real-world usage practices and the expected levels in the environment when applied according to according to label instructions, it is very unlikely that herbicides have a significant "additive" role in the evolution of antimicrobial resistance. Highly artificial test systems, such as *in vitro* systems, using very high doses of any compounds including herbicides to elicit stress responses, and even herbicide resistant mutants, should be interpreted with caution. Such effects are elicited at high doses, up to several thousand-fold greater than found in realistic exposure scenarios. There is no well-substantiated mechanism by which real world glyphosate usage practices could induce antimicrobial resistance.

Antimicrobial Activity Patent

As a matter of record there are existing patents for glyphosate for potential use as an antimicrobial. Like many patent claims based on *in vitro* information or a case built only on the mode of action of the active ingredient, the specific patent owned by the data sponsor was based on consideration that microbes may have a glyphosate-sensitive target enzyme. As stated above there are no approved or registered uses of glyphosate as an antimicrobial due to numerous limitations of translating a theoretical use into a practical one. The existence of this patent has no or very limited relevance to the work of Codex, as environmental concentrations of glyphosate resulting from its use as an herbicide are far below the level that shows antimicrobial activity in an *in vitro* system.

In summary, glyphosate is not a key driver of antimicrobial resistance development. We hope the Codex system remains focused on effective interventions to combat antimicrobial resistance globally.

References:

Holmes, A. H., Moore, L. S., Sundsfjord, A., Steinbakk, M., Regmi, S., Karkey, A., ... & Piddock, L. J. (2016). Understanding the mechanisms and drivers of antimicrobial resistance. *The Lancet*, *387*(10014), 176-187.

von Mérey, G., Manson, P. S., Mehrsheikh, A., Sutton, P., & Levine, S. L. (2016). Glyphosate and aminomethylphosphonic acid chronic risk assessment for soil biota. *Environmental toxicology and chemistry*, *35*(11), 2742-2752.

Tsui, Martin TK, and L. M. Chu. "Aquatic toxicity of glyphosate-based formulations: comparison between different organisms and the effects of environmental factors." *Chemosphere* 52.7 (2003): 1189-1197.

Pöppe, Judith, et al. "Selection for resistance to a glyphosate-containing herbicide in Salmonella enterica does not result in a sustained activation of the tolerance response or increased cross-tolerance and cross-resistance to clinically important antibiotics." *Applied and environmental microbiology* 86.24 (2020): e01204-20.