CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 4.6, 4.9 **CAC/44 CRD/40**

Original Language Only

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Forty-fourth Session

Comments of CropLife International

CropLife International on behalf of Bayer Crop Science, the data sponsor for glyphosate, offers this comment on antimicrobial resistance, raised in CAC/44 CRD/37 under agenda items 4.6 and 4.9. CropLife International kindly asks that a reference to this CRD be included in the report if other CRDs are also referenced under agenda items 4.6 or 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. In other words, a highly artificial test system using a very high concentration of glyphosate that does not reflect real-world glyphosate practices was used support these study claims. 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 the CAC, 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 CAC 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.