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Review

Does exposure to glyphosate lead to an increase in the micronuclei frequency? A systematic and meta-analytic review

Nédia de Castilhos Ghisi [a, b, *], Elton Celton de Oliveira [b], Alberto José Prioli [b]

[a] Programa de Pós-graduação em Ecologia de Ambientes Aquáticos e Continentais (PEA)/Nupélia, Universidade Estadual de Maringá (UEM), Av. Colombo, 5790, Zona 7, 87020-900, Maringá (PR), Brazil
[b] Universidade Tecnológica Federal do Paraná (UTFPR), Estrada para Boa Esperança, km 4, 85660-000, Dois Vizinhos (PR), Brazil

HIGHLIGHTS

- Systematic meta-analytical review correlating glyphosate exposure and micronuclei.
- Groups exposed to glyphosate formulations have increased formation of micronuclei.
- Significant difference among glyphosate (GLY) and its commercial formulations.
- Difference in MN formation among different exposure routes of GLY.
- Difference in MN formation among different groups of vertebrates.

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ABSTRACT

Glyphosate-based herbicides are among the most used pesticides worldwide. Reviews on the safety of glyphosate have been conducted by several regulatory agencies and researches centers, many times with contradictory results. This study is a systematic meta-analytical review of experimental studies on the relationship between exposure to the glyphosate (GLY) and its formulations with the formation of micronuclei (MN) to establish a quantitative estimate of the environmental risks. The natural logarithm (ln) of the estimated response ratio was calculated from 81 experiments. A meta-analysis was performed on the complete data set, and individual meta-analyses were conducted after stratification by test system, class of vertebrate, exposure route, gender, endpoints, type of literature, formulation, GLY dose and exposure time. A forest plot showed an overall positive association between GLY exposure and its formulations and MN, corroborated by the cumulative effects size. Different responses were observed on mammalian and non-mammalian. Interesting results was noticed in exposure route where oral administration of GLY presented no significance. Exposure by intraperitoneal injection presented the highest MN formation. Pure GLY caused fewer effects than to commercial mixtures, but both presented mutagenic effects. The studies with males presented significant responses, while studies with females were not significant. The cumulative effects size was not clearly related to GLY dose, and was negatively related to exposure time. It can be attributed to different test systems, exposure routes and protocols analyzed. In conclusion, our results support the hypothesis that exposure to GLY and its formulations increases the frequency of MN formation.

Contents

* Corresponding author. UTFPR (Universidade Tecnológica Federal do Paraná), Campus Dois Vizinhos, Estrada para Boa Esperança, Km 04, Comunidade de São Cristóvão, ZIP CODE: 85660-000, Dois Vizinhos (PR), Brazil.
E-mail addresses: nediaghisi@gmail.com (N.C. Ghisi), elton.c.oliveira2@gmail.com (E.C. Oliveira), ajprioli@nupelia.uem.br (A.J. Prioli).

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1. Introduction

Glyphosate [N-(phosphonomethyl) glycine] (GLY) is one of the main pesticides that have been discovered to date and is the most globally commercialized pesticide for the non-selective control of weeds (Baylis, 2000; Monsanto, 2005). This systemic herbicide inhibits the growth of plants by interfering in the production of the aromatic amino acids phenylalanine, tyrosine and tryptophan, which causes a reduction in protein synthesis (Faus et al., 2015).

Current agricultural activities are highly dependent on the use of glyphosate-based commercial formulations, and this has become even more true in recent years because more than 75% of genetically modified plants have been formulated to tolerate high levels of glyphosate (Vera-Candioti et al., 2013). The formulations of glyphosate-based herbicides are complex and variable mixtures – adjuvants and surfactants are added to the active ingredient (GLY) with the objective of increasing its absorption and effectiveness (Baylis, 2000). Unfortunately, surfactants can present toxicity many times greater than GLY, making the formulated product much more toxic than the isolated active ingredient (Vera-Candioti et al., 2013). The specific original Roundup® (RU) formulation was composed by 41% isopropylamine glyphosate salt and surfactant (15.4% a polyethoxylated tallowamine). Nowadays, it is no longer sold in many markets, and other glyphosate formulations with different compositions are sold under the Roundup® brand name, with different glyphosate forms, concentrations and surfactant systems (Kier and Kirkland, 2013a). Despite the great number of benefits of the use of pesticides in agriculture, such as GLY, these agrochemicals can be dangerous if not used appropriately, and many of them pose a potential risk due to their contamination of foods, water and air (WHO, 1994). The great use and ubiquity of this GLY-based products increases the need for toxicological studies that determine the level of environmental risks of these products and their effects on non-target organisms (Borggaard and Gimsing, 2008). In this regard, numerous studies have been performed in recent years with different test systems to evaluate the harmful effects of GLY, both alone and in its commercial formulations, but the results of these studies are highly conflicting.

On the one hand, glyphosate-based herbicides are very effective in the control of undesired vegetation and are described by their manufacturers as having low toxicity and good environmental compatibility (Cox, 1998), and they are believed to be less toxic than other pesticides. Nonetheless, other studies have shown that GLY is moderately persistent in water under low light conditions and it is also highly persistent in the dark (Mercurio et al., 2014). It can potentially contaminate rivers, surface waters and soil, in which the detection levels of the herbicide is increased proportionally to the dosage of applications. Likewise, the flow increased by rain causes the transport of the herbicide from the direct area of influence to downstream sites (Peruzzo et al., 2008). A recent study shows that GLY can induce the growth of human breast cancer cells via estrogen receptors, and also tumor promoting activity in mice (George et al., 2010; Thongprakaisang et al., 2013).

Pesticide and its residues are subjected to chemical reactions with environmental reagents from the very beginning. The main reactions in the environment include oxidation, reduction, and nucleophilic displacements in biomolecules such as DNA (Crosby, 1982), and for this reason the genotoxicity of pesticides is a worldwide concern. The genotoxic and mutagenic effects of GLY and RU have been studied in different manners (Grisolia, 2002; Li and Long, 1988; Mañas et al., 2009; Poletta et al., 2009; Seiler, 1977 among many others), and these studies have generated some contradictory results. According to Williams et al. (2000), there is no *in vitro* or *in vivo* evidence that RU causes direct damage to DNA, indicating that it and its components do not present risks in regard to somatic or heritable mutations in humans. Similar results were obtained in a genetic mutation test with *Salmonella typhimurium* and in a mammalian cell culture study (Wildeman, 1982). Additionally, Li and Long (1988) performed an *in vitro* DNA synthesis test in rat hepatocytes to examine the genotoxicity of GLY and reported no DNA damage; they also reported that GLY did not cause DNA damage in the bone marrow of rats using a chromosome aberration test. In the same manner, other studies have found that neither GLY nor RU caused an increase in the frequency of micronuclei and chromosomal aberrations in rats after *in vivo* exposure to these pesticides (Dimitrov et al., 2006; Rank et al., 1993). Many interesting results from several databases were compiled in the recent review paper from Kier and Kirkland (2013a). As pointed by authors, negative results for *in vitro* gene mutation and a majority of negative results for chromosomal effect assays in mammalian cells have provided evidences that glyphosate is not typically genotoxic for these endpoints in mammalian systems. Mixed