

An earlier review of the toxicity of glyphosate and the original Roundup™ formulation concluded that neither glyphosate nor this formulation pose a risk for the production of heritable/somatic mutations in humans (Williams *et al.*, 2000, ASB2012-12053). An addendum of the RMS to the previous DAR (2000, ASB2013-2748, a slightly amended version may be found in Volume 3 under B.6.4.7) provided strong evidence that positive results obtained with different formulations in some test systems were likely due to cytotoxicity and perhaps even DNA reactivity of certain co-formulants but certainly not attributable to glyphosate itself.

A new review of more recent (since 2001) genotoxicity publications was submitted in this EU re-evaluation and included analysis of study methodology and incorporation of all the findings into a weight of evidence approach for genotoxicity (for details, see Volume 3, B.6.4.8).

As reviewed by Williams *et al.* (2000, ASB2012-12053), most gene mutation studies for glyphosate and glyphosate-based formulations were negative. Of fifteen gene mutation assays reported, there were only two positive observations. Subsequent to this review, only two new gene mutation studies have been published, both with negative or inconclusive results. These publications on gene mutation provided only limited additional information that was suitable for assessment of genotoxicity of glyphosate.

A large number of publications addressed chromosome aberrations. The weight of evidence from *in vitro* and *in vivo* mammalian studies supports the earlier conclusion that glyphosate and glyphosate-based formulations are predominantly negative for this endpoint category. Exceptions were mostly observed in unusual test systems but there are also some unexplained discordant positive results in more widely used mammalian systems. However, these occasional findings are by far outweighed by the negative high quality studies reported above.

Likewise, several reports of positive results for DNA damage endpoint by means of the SCE (sister chromatid exchange), the alkaline SCGE (single cell gel electrophoresis) and the comet assay have been published for glyphosate and certain formulations. The data suggest that these effects were likely due to cytotoxic effects (*e.g.*, of surfactants) at high concentrations rather than to DNA reactivity.

A new comprehensive review on genotoxicity studies of glyphosate and glyphosate-based formulations was submitted by Kier and Kirkland (2013, ASB2014-9587). The authors concluded that an overwhelming preponderance of negative results in well-conducted bacterial reversion and *in vivo* mammalian micronucleus and chromosomal aberration assays indicates that glyphosate and its formulations were not genotoxic in these core assays. Negative results for *in vitro* gene mutation and a majority of negative results for chromosomal effect assays in mammalian cells add to the weight of evidence that glyphosate was not genotoxic. Mixed results were observed for micronucleus assays of formulations in non-mammalian systems. Reports of positive results for DNA damage endpoints indicate that some formulations tend to elicit DNA damage effects at high (toxic) dose levels but the data suggest that this is due to cytotoxicity rather than to DNA interaction, perhaps associated with the surfactants present in many products.

Taking a weight of evidence approach, it may be concluded that there is no *in vivo* genotoxicity and mutagenicity potential of glyphosate or its formulations to be expected under normal exposure scenarios, *i.e.*, below toxic dose levels.