

Exhibit 22

Safety Evaluation and Risk Assessment of the Herbicide Roundup¹ and Its Active Ingredient, Glyphosate, for Humans

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Reviews on the safety of glyphosate and Roundup herbicide that have been conducted by several regulatory agencies and scientific institutions worldwide have concluded that there is no indication of any human health concern. Nevertheless, questions regarding their safety are periodically raised. This review was undertaken to produce a current and comprehensive safety evaluation and risk assessment for humans. It includes assessments of glyphosate, its major breakdown product [aminomethylphosphonic acid (AMPA)], its Roundup formulations, and the predominant surfactant [polyethoxylated tallow amine (POEA)] used in Roundup formulations worldwide. The studies evaluated in this review included those performed for regulatory purposes as well as published research reports. The oral absorption of glyphosate and AMPA is low, and both materials are eliminated essentially unmetabolized. Dermal penetration studies with Roundup showed very low absorption. Experimental evidence has shown that neither glyphosate nor AMPA bioaccumulates in any animal tissue. No significant toxicity occurred in acute, subchronic, and chronic studies. Direct ocular exposure to the concentrated Roundup formulation can result in transient irritation, while normal spray dilutions cause, at most, only minimal effects. The genotoxicity data for glyphosate and Roundup were assessed using a weight-of-evidence approach and standard evaluation criteria. There was no convincing evidence for direct DNA damage *in vitro* or *in vivo*, and it was concluded that Roundup and its components do not pose a risk for the production of heritable/somatic mutations in humans. Multiple lifetime feeding studies have failed to demonstrate any tumorigenic potential for glyphosate. Accordingly, it was concluded that glyphosate is noncarcinogenic. Glyphosate, AMPA, and POEA were not teratogenic or developmentally toxic. There were no effects on fertility or reproduc-

tive parameters in two multigeneration reproduction studies with glyphosate. Likewise there were no adverse effects in reproductive tissues from animals treated with glyphosate, AMPA, or POEA in chronic and/or subchronic studies. Results from standard studies with these materials also failed to show any effects indicative of endocrine modulation. Therefore, it is concluded that the use of Roundup herbicide does not result in adverse effects on development, reproduction, or endocrine systems in humans and other mammals. For purposes of risk assessment, no-observed-adverse-effect levels (NOAELs) were identified for all subchronic, chronic, developmental, and reproduction studies with glyphosate, AMPA, and POEA. Margins-of-exposure for chronic risk were calculated for each compound by dividing the lowest applicable NOAEL by worst-case estimates of chronic exposure. Acute risks were assessed by comparison of oral LD₅₀ values to estimated maximum acute human exposure. It was concluded that, under present and expected conditions of use, Roundup herbicide does not pose a health risk to humans. © 2000 Academic Press

Key Words: glyphosate; Roundup; herbicide; human exposure; risk assessment.

INTRODUCTION

History of Glyphosate and General Weed Control Properties

The herbicidal properties of glyphosate were discovered by Monsanto Company scientists in 1970. Glyphosate (Fig. 1) is a nonselective herbicide that inhibits plant growth through interference with the production of essential aromatic amino acids by inhibition of the enzyme enolpyruvylshikimate phosphate synthase, which is responsible for the biosynthesis of chorismate, an intermediate in phenylalanine, tyrosine, and tryptophan biosynthesis (Fig. 2). This pathway for biosynthesis of aromatic amino acids is not shared by members of the animal kingdom, making blockage of this pathway an effective inhibitor of amino acid biosynthesis exclusive to plants. Glyphosate expresses its herbi-

¹ Roundup is a registered trademark of Monsanto.

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Acute exposure. Estimates of aggregated acute exposure in adult applicators (0.163 mg/kg body wt/day) and children (0.0911 mg/kg body wt/day) were substantially higher than those for chronic exposure. In children, this increase was primarily due to contributions from reentry exposure and, to a lesser degree, the ingestion of wild foods. The acute oral LD₅₀ of POEA is approximately 1200 mg/kg. The estimated acute exposure values are 7360 to 13,200 times lower than this value.

OVERALL CONCLUSIONS AND SUMMARY STATEMENT

This assessment was conducted for adult applicators and children (age 1 to 6 years) because they have the highest potential exposures. Estimates of exposure described for these two subpopulations and used in these risk calculations are considered excessive compared to those likely to result in the general population from the use of Roundup herbicide. MOE analyses compare the lowest NOAELs determined from animal studies to worst-case levels of human exposure. MOEs of greater than 100 are considered by authoritative bodies to indicate confidence that no adverse health effects would occur (WHO, 1990). The MOEs for worst-case chronic exposure to glyphosate ranged from 3370 to 5420; the MOEs for AMPA ranged from greater than 269 to 83,300; and for POEA the MOEs ranged 461 to 1380. Based on these values, it is concluded that these substances do not have the potential to produce adverse effects in humans. Acute exposures to glyphosate, AMPA, and POEA were estimated to be 7360–1,730,000 times lower than the corresponding LD₅₀ values, thereby demonstrating that potential acute exposure is not a health concern. Finally, under the intended conditions of herbicide use, Roundup risks to subpopulations other than those considered here would be significantly lower. It is concluded that, under present and expected conditions of new use, there is no potential for Roundup herbicide to pose a health risk to humans.

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