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Safety Evaluation and Risk Assessment of the Herbicide Roundup[1] 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 reproductive 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 LD_{50} 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.

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-

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formed for regulatory purposes and, thus, comply with accepted protocols and Good Laboratory Practices (GLP), according to standards of study conduct in effect at the time. Published research reports available in the general scientific literature range in quality from well-conducted investigations to those containing serious scientific deficiencies. Other sources of information, primarily reviews from regulatory agencies and international organizations, have also been used to develop this risk assessment. In this effort, the authors have had the cooperation of Monsanto Company that has provided complete access to its database of studies and other documentation. Glyphosate-based products are currently manufactured by a variety of companies worldwide. Some sources of information, including studies produced by manufacturers of glyphosate-based products other than Monsanto, are not generally available and as such were not considered for this risk assessment. Data for such products are proprietary and not readily available and therefore were not evaluated for inclusion in this risk assessment.

PRINCIPLES OF THE RISK ASSESSMENT PROCESS

The risk assessment process involves the characterization of toxicities and estimation of possible adverse outcomes from specific chemical exposures (CCME, 1996; Environment Canada, 1997; NRC, 1983; U.S. EPA, 1995, 1997a). The NRC (1983) and U.S. EPA Draft Cancer Risk Assessment Guidelines (1996) define risk characterization as the step in the risk assessment process that integrates hazard identification, dose–response assessment, and exposure assessment, using a combination of qualitative and quantitative information. Risk assessment can provide a comprehensive estimate of the potential effect in specific, well-defined, and described circumstances.

Hazard identification assesses the capacity of an environmental agent to cause adverse effects in experimental systems or humans. This is a qualitative description based on several factors such as availability of human data, data from laboratory animals, and any ancillary information (e.g., structure–activity analysis, genetic toxicity, pharmacokinetics) from other studies. Finally, a weight-of-evidence is prepared based on data accumulated from many sources, where a mode of action is suggested, responses in experimental animals are evaluated, and the relevance of these to human outcomes is discussed (U.S. EPA, 1995).

The determination of hazard is often dependent on whether a dose–response relationship is available (U.S. EPA, 1991). Hazard identification for developmental toxicity and other noncancer health effects is usually done in conjunction with an evaluation of dose–response relationships. The dose–response assessment evaluates what is known about the biological mode of action of a chemical and assesses the dose–response relationships on any effects observed in the laboratory. At this stage, the assessment examines quantitative relationships between exposure (or the dosage) and effects in the studies used to identify and define effects of concern.

The exposure assessment addresses the known principal paths, patterns, and magnitudes of human exposure and numbers of persons who may be exposed to the chemical in question. This step examines a wide range of exposure parameters including the scenarios involving human exposure in the natural environment. Monitoring studies of chemical concentrations in environmental media, food, and other materials offer key information for developing accurate measures of exposure. In addition, modeling of environmental fate and transport of contaminants as well as information on different activity patterns of different population subgroups can produce more realistic estimates for potential exposures. Values and input parameters used for exposure scenarios should be defensible and based on data. Any assumptions should be qualified as to source and general logic used in their development (e.g., program guidance, analogy, and professional judgment). The assessment should also address factors (e.g., concentration, body uptake, duration/frequency of exposure) most likely to account for the greatest uncertainty in the exposure estimate, due either to sensitivity or to lack of data.

A fundamental requirement for risk characterization for humans is the need to address variability. Populations are heterogeneous, so heterogeneity of response to similar exposures must also be considered. Assessments should discuss the dosage received by members of the target population, but should retain a link to the general population, since individual exposure, dosage, and risk can vary widely in a large population.

In addition to variability, uncertainty arises from a lack of knowledge about factors that drive the events responsible for adverse effects. Risk analysis is characterized by several categories of uncertainty including measurement uncertainty, uncertainties associated with modeled values, and uncertainties that arise from a simple lack of knowledge or data gaps. Measurement uncertainty refers to the usual error that accompanies scientific measurements as expected from statistical analysis of environmental sampling and monitoring. The assumptions of scientific models for dose–response or models of environmental fate and transport also have some uncertainty. Finally, in the absence of data, the risk assessor should include a statement of confidence that estimates or assumptions made in model development adequately fill the data gap.

Chemical Characterization and Technical Aspects of Roundup Formulations Addressed in This Review

Glyphosate is an amphoteric compound with several pK_a values. The high polarity of the glyphosate mole-

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 LD_{50} 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 LD_{50} 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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REFERENCES

Acquavella, J. F., Weber, J. A., Cullen, M. R., Cruz, O. A., Martens, M. A., Holden, L. R., Riordan, S., Thompson, M., and Farmer D. R. (1999). Human ocular effects from self-reported exposures to Roundup herbicides. *Hum. Exp. Toxicol.* **18**, 479–486.

Adam, A., Marzuki, A., Abdul Rahman, H., and Aziz, M. A. (1997). The oral and intratracheal toxicities of Roundup and its components to rats. *Vet. Hum. Toxicol.* **39**, 147–151.

Allin, J. C. (1989). *Glyphosate Residues in Wheat Grain and Straw after Preharvest Treatment with Roundup herbicide.* Unpublished report, Monsanto Company.

Anderson, D., Francis, A. J., Godbert, P., Jenkinson, P. C., and Butterworth, K. R. (1991). Chromosomal aberrations (CA), sister-chromatid exchanges (SCE) and mitogen-induced blastogenesis in cultured peripheral lymphocytes from 48 control individuals sampled 8 times over 2 years. *Mutat. Res.* **250**, 467–476.

Auletta, C. S. (1983a). *A Dermal Sensitization Study In Guinea Pigs—Test Material: Glyphosate.* Unpublished report, Bio/Dynamics Inc., East Millstone, NJ.

Auletta, C. S. (1983b). *A Dermal Sensitization Study in Guinea Pigs.* Unpublished report, Bio/Dynamics, Inc., East Millstone, NJ.

Auletta, C. S. (1985a). *Acute Oral Toxicity Study in Rats.* Unpublished report, Bio/Dynamics, Inc., East Millstone, NJ.

Auletta, C. S. (1985b). *Acute Dermal Toxicity Study in Rabbits.* Unpublished report, Bio/Dynamics, Inc., East Millstone, NJ.

Auletta, C. S. (1985c). *Primary Dermal Irritation Study in Rabbits (4-Hour Exposure).* Unpublished report, Bio/Dynamics, Inc., East Millstone, NJ.

Auletta, C. S. (1985d). *Eye Irritation Study in Rabbits.* Unpublished report, Bio/Dynamics, Inc., East Millstone, NJ.

Baba, Y., Takeda, M., Yosino, K., Sagara, E., Tai, T., and Yamashita, M. (1989). Acute toxicity of the herbicide "Roundup" in the rat. *Jpn. J. Toxicol.* **2**, 397–400.

Bakke, J. P. (1991). *Evaluation of the Potential of AMPA to Induce Unscheduled DNA Synthesis in the In Vitro Hepatocyte DNA Repair Assay Using the Male F344 Rat.* Unpublished report, SRI International, Menlo Park, CA.

Bechtel, C. L. (1987). *Acute Toxicity of Roundup Herbicide Administered by Inhalation to Male and Female Sprague-Dawley Rats.* Unpublished report, Monsanto Environmental Health Laboratory, St. Louis, MO.

Bender, M. A., Preston, R. J., Leonard, R. C., Pyatt, B. E., Gooch, P. C., and Shelby, M. D. (1989). Chromosomal aberration and sister-chromatid exchange frequencies in peripheral blood lymphocytes of a large human population sample. *Mutat. Res.* **204**, 421–433.

Birch, M. D. (1973). *Toxicological Evaluation of Glyphosate.* Unpublished report Younger Laboratories, Inc., St. Louis, MO.

Birch, M. D. (1977). *Toxicity Studies on POEA.* Unpublished report, Younger Laboratories, Inc., St. Louis, MO.

Blaszcak, D. L. (1987a). *Eye Irritation Study in Rabbits.* Unpublished report, Bio/Dynamics, Inc., East Millstone, NJ.

Blaszcak, D. L. (1987b). *Primary Dermal Irritation Study in Rabbits (4-Hour Exposure/Semi-occlusive Covering).* Unpublished report, Bio/Dynamics, Inc., East Millstone, NJ.

Blaszcak, D. L. (1987c). *A Dermal Sensitization Study in Guinea Pigs.* Unpublished report, Bio/Dynamics, Inc., East Millstone, NJ.

Blaszcak, D. L. (1987d). *Acute Oral Toxicity Study in Rats.* Unpublished report, Bio/Dynamics, Inc., East Millstone, NJ.

Blaszcak, D. L. (1987e). *Acute Dermal Toxicity Study in Rabbits.* Unpublished report, Bio/Dynamics, Inc., East Millstone, NJ.