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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: ***GLYPHOSATE*** - Report of the Hazard Identification Assessment Review Committee.

FROM: William Dykstra, Toxicologist. William Dykstra 4/20/98
Registration Action Branch 1
Health Effects Division (7509C)
and
Jess Rowland, Executive Secretary 4/20/98
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THROUGH: K. Clark Swentzel, Chairman, K. Clark Swentzel 4/21/98
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Mike Metzger, Co-Chairman
Hazard Identification Assessment Review Committee 4/21/98
Health Effects Division (7509C)

TO: Melba Morrow, Branch Senior Scientist
Registration Action Branch 1
Health Effects Division (7509C)

PC Code: 417300

On March 26, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee evaluated the toxicology data base of **GLYPHOSATE,** re-assessed the Reference Dose (RfD) established in 1992 as well as the toxicological endpoints selected for acute dietary and occupational/residential exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to glyphosate as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented in this report.

Committee Members in Attendance

Members present were: Mike Metzger (Co-Chairman), Clark Swentzel (Chairman), Bill Burnam, Sue Makris, Melba Morrow, Karen Hammernik, Karl Baetcke, Robert Fricke, John Redden, and Jess Rowland (Executive Secretary) . Member(s) in absentia: None. Data was presented by William Dykstra of the Registration Action Branch 1.

In attendance was also Julianna Cruz of Registration Action Branch 1.

Data Presentation:
and
Report Presentation

William Dykstra.
Toxicologist

Report Concurrence:

Jess Rowland
Executive Secretary

I. INTRODUCTION

On March 26, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee evaluated the toxicology data base of Glyphosate, re-assessed the Reference Dose (RfD) established in 1992 as well as the toxicological endpoints selected for acute dietary and occupational/residential exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to glyphosate as required by the Food Quality Protection Act (FQPA) of 1996.

II. HAZARD IDENTIFICATION

A. Acute Reference Dose (RfD)

Study Selected: None §

MRID No.: None

Executive Summary:

Dose and Endpoint for Risk Assessment: Not Applicable

Comments about Study/Endpoint: A review of the rat and rabbit developmental studies did not provide a dose or endpoint that could be used for acute dietary risk purposes. Additionally, there were no data requirements for acute or subchronic rat neurotoxicity studies since there was no evidence of neurotoxicity in any of the toxicology studies at very high doses and glyphosate lacks a leaving group. Therefore, it would not seem likely to inhibit esterases, which is the presumptive neurotoxic mechanism of concern for all organophosphates.

Uncertainty Factor (UF): None

This Risk Assessment is **NOT** required.

B. Chronic RfD

Study Selected: Rabbit Developmental study § 83-3(b)

MRID No.: 00046363

Executive Summary: Groups of 16/dose Dutch Belted rabbits were dosed with technical glyphosate at doses of 0, 75, 175, or 350 mg/kg/day between gestation days 6 to 27. Maternal effects were seen at only the high dose and consisted of diarrhea, nasal discharge and death [10/16]. Developmental effects were not seen at any dose tested. Therefore, the NOEL and LOEL for maternal toxicity were 175 mg/kg/day and 350 mg/kg/day, respectively.

Dose and Endpoint for Establishing RfD: NOEL = 175 mg/kg/day based on death, diarrhea, and nasal discharge at 350 mg/kg/day (LOEL).

Uncertainty Factor(s): 100 (10 x for interspecies extrapolation and 10 x for intraspecies variation).

$$\textbf{Chronic RfD} = \frac{\text{175 mg/kg/day (NOEL)}}{\text{100 (UF)}} = \textbf{2.0 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor: The NOEL for maternal toxicity in the rabbit developmental study was the lowest NOEL of all the major studies which include the 24-month mouse carcinogenicity study [NOEL = 750 mg/kg/day], the 1-year dog study [NOEL = 500 mg/kg/day], 2-year chronic/onco rat study [NOEL = 400 mg/kg/day], 2-generation rat reproduction study [NOEL = 500 mg/kg/day] and rat developmental study [NOEL = 1000 mg/kg/day]

This risk assessment is required.

C. Occupational/Residential Exposure

1. Dermal Absorption

Dermal Absorption Factor: A dermal absorption factor is not applicable since dermal risk assessments are not required.

2. Short-Term Dermal - (1-7 days)

Study Selected: None §

MRID No.: None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not Applicable.

Comments about Study/Endpoint:. No systemic or dermal toxicity was seen following repeated dermal applications of technical glyphosate at 0, 100, 1000 or 5000 mg/kg/day, 6 hours/day, 5 days/week for three consecutive weeks to male and female New Zealand rabbits. The NOEL was 1000 mg/kg/day and the LOEL was 5000 mg/kg/day based on decreased food consumption in females [MRID No. 00098460]. In addition, the use of a 3% dermal absorption rate (estimated) in conjunction with the oral NOEL of 175 mg/kg/day established in the rabbit developmental study yields a dermal equivalent dose of > 5000 mg/kg/day.

This risk assessment is **NOT** required.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: None

MRID No.: None

Executive Summary: None

Dose/Endpoint for Risk Assessment: Not Applicable

Comments about Study/Endpoint: See short term

This risk assessment is **NOT** required.

4. Long-Term Dermal (Several Months to Life-Time)

Study Selected: None

MRID No.: None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not Applicable

Comments about Study/Endpoint:. See short term

This risk assessment is **NOT** required.

5. Inhalation Exposure (Any Time period).

Study Selected: None

MRID No.: None

Executive Summary: None

Dose/Endpoint for Risk Assessment: Not Applicable

Comments about Study/Endpoint: Based on the low toxicity of the formulation products (Toxicity Category III or IV) and the physical characteristics of the technical product (wetcake) there is minimal concern for potential inhalation exposure or risk. The acute inhalation study was waived for technical glyphosate.

This risk assessment is **NOT** required.

D. Recommendation for Aggregate Exposure Risk Assessments

There are no registered residential uses at the present time. Therefore, aggregate exposure risk assessments will be limited to food + water.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

Executive Summary : Randomized groups of 60/sex/dose Sprague-Dawley rats were fed glyphosate at dietary levels of 0, 2000, 8000, or 20,000 ppm [male: 0, 89, 362, or 940 mg/kg/day; female: 0, 113, 457, or 1183 mg/kg/day]. The NOEL was 8000 ppm [362 mg/kg/day for males and 457 mg/kg/day for females] and the LOEL was 20,000 ppm [940 mg/kg/day for males and 1183 mg/kg/day for females] based on decreased weight gain in females, decreased urinary pH in males, increased incidence of cataracts and lens abnormalities in males, and increased absolute and relative liver weight in males. The carcinogenic potential was negative.

MRID No. 41643801

Discussion of Tumor Data: The study showed a slightly increased incidence of pancreatic islet cell adenomas in the low and high dose males; hepatocellular adenomas in the low and high dose males; and thyroid C-cell adenomas in the mid and high dose males and females. The Agency concluded that these adenomas were not treatment-related and glyphosate was not considered to be carcinogenic in this study. The pancreatic islet cell adenomas did not display a positive dose-trend in their occurrence; there was no progression to carcinoma and the incidence of pancreatic hyperplasia was not dose-related. The hepatocellular adenomas were not statistically significant by pair-wise comparison; the incidence was within the range of historical controls; there was no progression to carcinoma and the hyperplasia was not compound-related. The C-cell adenomas were statistically significant by pair-wise comparison and were not dose-related; there was no progression to carcinoma and there was no significant dose-related increase in severity or incidence of hyperplasia in either sex.

Adequacy of the Dose Levels Tested: The highest dose tested was the limit dose of 20,000 ppm in both sexes.

2. Carcinogenicity Study in Mice

Executive Summary: Randomized groups of 50/sex/dose CD-1 mice were fed glyphosate in the diet for 2 years at doses of 0, 1000, 5000, or 30,000 ppm [0, 150, 750, or 4500 mg/kg/day]. The systemic NOEL was 5000 ppm and the LOEL was 30,000 ppm based on decreased weight gain in both sexes, hepatocyte necrosis and interstitial nephritis in males and increased incidence of proximal tubule epithelial basophilia and hypertrophy in females. The carcinogenic potential was negative.

MRID No. 00130406, 00150564

Discussion of Tumor Data The incidence in males of renal tubular adenomas, a rare tumor, was 1, 0, 1, and 3 in the control, low, mid, and high dose groups, respectively. Although the trend was significant, there was no statistical significance by pairwise comparison of the control and high dose group. The incidence at the high dose exceeded the occurrence of historical controls from the testing laboratory. The non-neoplastic findings in the male kidney did not occur in a increased dose-related manner and the tumorigenic findings in the kidney were considered to occur by chance rather than as a result of treatment.

Adequacy of the Dose Levels Tested: The highest dose tested [30,000 ppm] exceeded the limit dose of 7000 ppm for both sexes of mice.

3. Classification of Carcinogenic Potential The OPP Cancer Peer Review Committee classified glyphosate as a "Group E " pesticide [no evidence for carcinogenicity in two acceptable species].

IV. FQPA CONSIDERATIONS

1. Neurotoxicity:

There were no data requirements for acute or subchronic rat neurotoxicity studies since there was no evidence of neurotoxicity in any of the toxicology studies at very high doses and glyphosate lacks a leaving group. Therefore, it would not seem likely to inhibit esterases, which is the presumptive neurotoxic mechanism of concern for all organophosphates.

2 Developmental Toxicity

In a prenatal developmental toxicity study , pregnant Sprague-Dawley rats received oral administration of glyphosate (98.7%) in 0.5% aqueous methocel at 0, 300, 1000 or 3500 mg/kg/day during gestation days 6 through 19. For maternal toxicity, the NOEL was 1000 mg/kg/day and the LOEL was 3500 mg/kg/day based on diarrhea, decreased mean body weight gain, breathing rattles, inactivity, red matter around the nose and mouth, and on forelimbs and dorsal head, decreases in total implantations/dam and inviable fetuses/dam, and death (24% of the group). For developmental toxicity, the NOEL was 1000 mg/kg/day and the LOEL was 3500 mg/kg/day based on increased number of litters and fetuses with unossified sternebrae, and decreased mean fetal body weights (MRID # 00046362).

In a prenatal developmental toxicity study, pregnant New Zealand white rabbits received oral administration of glyphosate (98.7%) in 0.5% aqueous methocel at 0, 75, 175 or 350 mg/kg/day during gestation days 6 through 27. For maternal toxicity, the NOEL was 175 mg/kg/day and the LOEL was 350 mg/kg/day based on diarrhea, nasal discharge, and death (62.5% of does died by gestation day 21). Developmental toxicity was not observed at any dose tested. For developmental toxicity, the NOEL was ≥ 175 mg/kg/day (insufficient litters were available at 350 mg/kg/day to assess developmental toxicity) (MRID # 00046363).

3. Reproduction Toxicity

In a three-generation reproduction study, Sprague-Dawley rats received diets containing glyphosate at 0, 3, 10 or 30 mg/kg/day for three generations. For parental systemic toxicity, the NOEL was 30 mg/kg/day (highest dose tested). The only effect observed was an increased incidence of focal tubular dilation of the kidney (both unilateral and bilateral combined) in the high-dose male F_{3b} pups. However, this effect (focal tubular dilation of the kidneys) was not observed at the 1500 mg/kg/day level in a 2-generation rat reproduction study discussed below. Therefore, the OPP Developmental Peer Review Committee concluded that the effect seen in the three generation study was a spurious rather than glyphosate-related effect. No reproductive or offspring toxicity was observed; NOELs was ≥30 mg/kg/day (MRID # 00105995).

In a two-generation reproduction study, Sprague-Dawley rats received diets containing glyphosate at 0, 2000, 10,000 or 30,000 ppm for two generations. Treatment-related effects observed at 30,000 ppm included soft stools, very frequent, in the F_0 and F_1 males and females, decreased food consumption and body weight gain of the F_0 and F_1 males and females during the growth (premating) period, and decreased body weight gain of the F_{1a}, F_{2a} and F_{2b} male and female pups during the second and third weeks of lactation. Focal tubular dilation of the kidneys, observed in the 3-generation study, was not observed at any dose level in this study. Based on the above findings, the parental and developmental (pup) NOEL's are 500 mg/kg/day and the parental and developmental (pup) LOEL's are 1500 mg/kg/day. The reproductive toxicity NOEL is ≥1500 mg/kg/day (MRID # 41621501).

4. Additional information from the literature No studies were available

5. Determination of Susceptibility

The data provided no indication of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to glyphosate. In the prenatal developmental toxicity study in rats, developmental toxicity was seen in the presence of maternal toxicity at the highest dose tested. No developmental toxicity was seen in the rabbits. In reproductions toxicity studies, effects in the offspring were observed only at or above treatment levels which resulted in evidence of parental toxicity.

6. Recommendation for a Developmental Neurotoxicity Study

i. Evidence that suggest requiring a developmental neurotoxicity study:

There was no evidence to suggest that a developmental neurotoxicity study was needed.

ii. Evidence that do not support a need for a developmental neurotoxicity study: Rat and rabbit developmental studies and 2-generation rat reproduction study.

7. Determination of the FQPA Safety Factor:

The application of an FQPA factor for the protection of infants and children from exposure to glyphosate required by FQPA, will be determined during risk characterization by the FQPA Safety Committee. However, the HIARC, based on hazard assessment, recommends to the FQPA Safety Factor Committee that the additional 10 x factor should be removed because:

(i) The data provided no indication of increased susceptibility of rats or rabbits to in utero and/or postnatal exposure to glyphosate.

(ii) No evidence of developmental anomalies, including abnormalities in the development of fetal nervous system was observed in the pre-and/or postnatal studies.

(iii) The toxicology data base is complete and there are no data gaps.

V. DATA GAPS none

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VI SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	None	No toxicological endpoint attributable to a single dose was identified in oral studies including the rat and rabbit developmental toxicity studies.	
	Acute RfD = None		
Chronic Dietary	NOEL = 175 UF = 100	Mortality, diarrhea, and nasal discharge	Developmental - Rabbit
		Chronic RfD = 2.0 mg/kg/day	
Short-, Intermediate and Long-Term (Dermal)	None	No systemic toxic effects seen at doses up to 1000 mg/kg/day in the 21 day dermal toxicity study. Risk assessment is not required.	
Inhalation (Any Time Period)	None	Based on low toxicity of formulations and technical material [wet cake] inhalation study was waived. Risk assessment is not required.	

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