Caswell file

Glyphosate/Tox

(35)

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5 of 10

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAR 27 1985

Detailed material/methods have been removed.

004361

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: 4-Week Subchronic Inhalation in Rats With Roundup 33-1/3% Use-Dilution. EPA Reg. No. 524-308; Accession #252621; CASWELL #661A.

TO: Robert Taylor (25)
Registration Division (TS-767C)

FROM: D. Stephen Saunders Jr., Ph.D. Steve Saunders 3-25-85
Toxicologist, Section V
TOX/HED (TS-769C)

THRU: Laurence D. Chitlik, DABT LDC 3/26/85
Head, Section V
TOX/HED (TS-769C)
and
Theodore M. Farber, Ph.D. 3/27/85
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Chemical: Glyphosate; Roundup 33-1/3% Use-dilution.

Action Requested

Review the rat subchronic inhalation study submitted in support of the registration of the herbicide Glyphosate.

Recommendations

1) The study is classified as Core-Supplementary data. The number of tissues examined in control and high dose animals was not sufficient (see review of methods). Complete histopathology of control and high dose animals, and examination of all target tissues from the intermediate dose groups will be required for the study to be upgraded.

2) Although this study is Supplementary data, a repeat study will not be required at this time. The approved uses, as documented in the Glyphosate Index Entry (memo from Phyllis Johnson of Benefits and Use Division to HED, March 19, 1984), would not seem likely to result in repeated inhalation exposures to large numbers of humans. However, since Glyphosate is a Registration Standard, a more detailed analysis of use patterns as part of the Standard may reveal a need for a subchronic inhalation study. Therefore, any decision as to the need for a repeat inhalation study is tentative pending the completion of the Glyphosate Registration Standard.

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Chemical: Glyphosate.

Test Material: Roundup (33-1/3% use-dilution); 41.56% isopropylamine salt of glyphosate in concentrate; Lot no. LDRP-04-037

Study Type: Rat 4-week subchronic inhalation.

Study Identification: "Four-Week Study of 33-1/3% Use-Dilution of Roundup in Water Administered to Male and Female Sprague-Dawley Rats by Inhalation".

Sponsor:	Monsanto
Contracting Lab.:	Same, Environmental Health Laboratory St. Louis, Missouri
Study No.:	830025
Project No.:	ML-83-015
Report date/submitted:	12-21-83/3-9-84
EPA Accession no.:	252621
Study Director:	David J. Velasquez

Test Animal: Male and Female Sprague-Dawley rats (Crl:CD[SD]BR), obtained from Charles River Labs., Portage, MI; 15/sex/dose

Dose Tested: 0, 0.05, 0.15, and 0.50 mg/L Target doses
0, 0.38, 0.76, and 2.17 mg/L Nominal
0, 0.05, 0.16, and 0.36 mg/L Actual
animals exposed for 6 hrs/day, 5 days/week for 4 weeks, 22 exposures total.

Reviewed by: D. Stephen Saunders Jr., Ph.D.
Toxicologist, Section V
TOX/HED (TS-769C)

Approved by: Laurence D. Chitlik, DABT
Head, Section V
TOX/HED (TS-769C)

Conclusions:

No treatment-related effects were noted. However, the number of tissues examined microscopically was not sufficient to insure that no treatment-related effects were present.

NOEL = Not established

Classification: Core-Supplementary Inadequate number of tissues examined from control and high dose groups.

Methods

A photocopy of the submitted methods is appended. The methods were reviewed and the following point(s) were noted:

1) Inadequate histological examination of tissues from control and high dose rats. Only brain, heart, kidneys, liver, lung, sciatic nerve, nose and turbinates, gonads, spleen, and trachea were examined. The following tissues (recommended by the 1982 Pesticide Assessment Guidelines) were not examined: pituitary, thyroid/parathyroid, thymus, salivary glands, pancreas, uterus, aorta, gastrointestinal tract, urinary bladder, lymph nodes, and eyes.

Results

A. Mortality and Clinical Signs- No deaths were reported during the treatment period.

The only sign noted that appeared to be treatment-related was red coloration around the nose. By the fourth week of exposure, this sign was observed in (out of 15 rats): 1 control, 3 low, 7 mid and 6 high dose males; and 2 control, 1 low, 2 mid and 5 high dose females.

B. Body Weights- No statistically significant effects on body weight gain were noted (table 1). High dose males and females gained about 10% less body weight over the period of treatment compared to controls.

Table 1. Effect of Treatement on Body Weight Gain[a]

Dose[b] (mg/L)	MALES		FEMALES	
	Day 1[c]	Day 28[d]	Day 0[c]	Day 28[d]
0	315.2 ± 13.91	421.2 ± 23.19	206.1 ± 10.66	264.1 ± 15.51
0.05	313.4 ± 16.70	414.4 ± 24.23	207.5 ± 9.06	271.9 ± 11.38
0.16	311.3 ± 16.38	415.7 ± 23.12	205.4 ± 10.65	261.3 ± 14.53
0.36	314.7 ± 21.00	410.2 ± 23.52	205.4 ± 6.39	255.6 ± 12.49

[a]data excerpted from table 2 of submitted study. Values are in g, mean ± std. dev., calculated by investigators.

[b]analytical dose concentrations.

[c]first day of treatment.

[d]final day of treatment.

C. Clinical Pathology: (1) Hematology- This parameter was measured in animals at sacrifice. Statistically significant decreases (about 4% relative to control) were noted in mean corpuscular hemoglobin concentration (MCHC) in mid and low dose males and in mean corpuscular hemoglobin (MCH) in mid dose

males only. These changes were not dose-related since no effects were noted in high dose males, and no effects on total RBC count or on total hemoglobin were noted in low and mid dose males. Therefore, the statistically significant small decreases in MCHC and MCH are considered spurious and of no toxicological significance. No significant changes were noted in females at termination.

C.(2) Serum Chemistry- This parameter was measured in animals at sacrifice. The only apparent treatment-related effect was an increase in albumin and total protein in mid and high dose females. Both parameters were increased by about 10% in these animals. Other parameters were unaffected, and no significant effects were noted in treated males.

D. Necropsy Data: (1) Organ Weights- The only statistically significant change that was noted was a decrease of about 5% in the average organ/body weight ratios of kidney and liver in low dose males. The average absolute organ weights of these tissues were also decreased by about 7% in these animals, however the change was not statistically signficant. No other effects on organ weights were noted.

(2) Gross Observations- No treatment-related changes were noted upon gross examination of tissues at necropsy.

(3) Histopathology- Microscopic examinations were conducted only on heart, kidneys, liver, lymph node, lung, nose/turbinates, spleen, trachea, brain, sciatic nerve, and epididymides from control and high dose animals.

An apparent increase in the incidence of findings related to inflammation or irritation of the lung, nose, and trachea was observed in high dose females. However, chronic lung inflammation is a common finding in rats, and no increase in the incidence of these findings was noted in males. Further, inflammation of the lung, nose, and trachea was noted in control males and females, and although the incidence of inflammation in high dose females was apparently increased, the severity of the finding did not increase in response to treatment. Therefore, these findings are not considered to be toxicologically significant.

No other significant effects were noted upon microscopic examination.

E. Analyses of Test Atmosphere- The concentration of the test material was analytically determined daily. Each daily value was the average of 4 separate determinations. The average daily analytical concentrations of the test material are tabulated in table 3. The Mass Median Aerodynamic Diameter (MMAD) of the high dose atmosphere varied from 1.85 to 2.50 microns. Thus, the majority of the test material would be predicted to penetrate at least into the bronchial tree, although a value of 1 micron is generally accepted as the maximum size that will penetrate into the alveolar airspace of the rat. No significant variations in the concentration of test atmospheres within the test chamber were noted.

Table 3. Analytical Measurements[a]

	DOSE LEVELS (mg/L)		
	Low	Mid	High
Target	0.05	0.15	0.50
Nominal (range)	0.37 ± 0.02 (0.33-0.40)	0.75 ± 0.08 (0.60-0.97)	2.17 ± 0.15 (1.7-2.4)
Actual (range)	0.05 ± 0.01 (0.034-0.600)	0.16 ± 0.04 (0.095-0.223)	0.36 ± 0.08 (0.212-0.491)

[a]data excerpted from Appendix I of submitted study.

Discussion

The only apparent treatment-related effects noted in this study were a slight decrease in body weight gain in high dose (0.36 mg/L analytical) males and females, and a 10% increase in serum albumin and total protein in mid and high dose females. Neither effect is considered toxicologically significant: the differences in average body weights were slight and not statistically significant; and a pathological correlate of increased serum protein has not been described. Further, no histological evidence for injury to the liver, the site of albumin synthesis, was noted.

Although no significant effects were noted in this study, the number of tissues examined microscopically is not adequate to insure that no treatment-related effects occurred. In order to upgrade this study, it will be necessary for the registrant to microscopically examine the tissues from control and high dose rats that were omitted in the original examination (but are recommended by the 1982 Pesticide Assessment Guidelines, see "Methods"), and any target tissues from low and mid dose males and females in order to determine the NOEL for any observed effects.