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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: February 9, 1982

SUBJECT: EPA Reg.#524-308; Lifetime Feeding Study in Rats with Glyphosate
CASWELL #661A Accession#246617-21

FROM: William Dykstra, Toxicologist
Toxicology Branch/HED (TS-769)

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

Recommendation:

1) The study is acceptable as Core-Minimum Data. The oncogenic potential is negative. The NOEL for chronic toxicity is the low-dose of 3.0 mg/kg/day.

Review:

1) A Lifetime Feeding Study of Glyphosate in Rats (Bio/dynamics Project No. 77-2062; 9/18/81)

Test Material: Glyphosate (technical); 98.7% a.i.; fine white powder; Lot#XHJ-64

Four groups of 50/sex/group, corresponding to controls, low-dose group, mid-dose group and high-dose group were employed in the study. The dosage level of test-material administered to each group was 0 (controls, Group 1) 30 ppm (low-dose, Group 2) 100 ppm (mid-dose Group 3) and 300 ppm (high-dose, Group 4) during the first week of the study. For the remainder of the study, dose levels of 3.05, 10.30 and 31.49 mg/kg/day for the males and 3.37, 11.22 and 34.02 mg/kg/day for the females were maintained. Termination occurred at 26 months (until survival had decreased to 30% in one group per sex).

All rats were observed twice daily for mortality and toxic signs and given a detailed physical examination each week throughout the study. Body weights and food consumption were determined at pretest, weekly through 14 weeks and biweekly thereafter. Water consumption was determined for 10 rats/sex/group for two separate three-day periods at 18 and 24 months.

The following clinical parameters were determined for 10 rats/sex/group at 4, 8, 12, 18 and 24 months: hematology included hemoglobin, hematocrit, erythrocytes, platelets, and total and differential leucocytes; blood biochemistry parameters included serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, lactic acid dehydrogenase, blood urea nitrogen, fasting glucose, cholesterol, total protein, albumin, globulin, total and direct bilirubin, potassium and calcium; urinalysis included gross appearance, specific gravity, pH, protein, glucose, ketones, bilirubin, occult blood and microscopic analysis.

Complete necropsies were performed on all rats that died or were sacrificed during or at the end of the study. Organ weights were recorded for adrenals, brain, heart, kidneys, liver, testes/ovaries, pituitary, spleen and thyroid. Microscopic examination of the following tissues was performed for all treated and control rats: abdominal aorta, adrenals, blood smear, bone, bone marrow, brain (3 sections), epididymides, esophagus, eyes with optic nerve and harderian glands, gonads, heart, cecum, colon, duodenum, ileum, jejunum, kidneys, liver, lungs (with bronchi), lymph nodes, mammary gland, nerve (sciatic), pancreas, parathyroid, pituitary, prostate, salivary gland, skeletal muscle, seminal vesicles, skin, spinal cord (cervical), spleen, stomach, thymus, thyroid, trachea, urinary bladder, uterus, gross lesions, tissue masses or suspect tumors. Three coronal sections through the head and a section of thoracic spinal cord from ten males and ten females of each group were also examined microscopically.

Results:

Survival was unaffected by treatment. Survival was greater than 50% for each sex of each group at 18 months.

Decreased body weight gains, although not statistically significant, were seen in treated males beginning at week 26 and continuing to week 102. The decreases reached 6% for high-dose males at week 74 and 2-3% for mid- and low-dose males during this growth period. Decreased body weight gains were statistically significantly (10-15%) reduced in the low- and mid-dose female rats from weeks 84 to 92.

No dose-response relationship was present in the decreased body weight gains in female rats. The changes in body weight did not affect survival.

Food consumption showed a few significant changes in males and females, but overall food consumption was unaffected by treatment.

Water consumption for males and females did not show a treatment-related effect.

Hematology, clinical chemistry, and urinalyses values of treated male and female rats were comparable to controls.

Absolute organ weights and relative organ weights of male and female treated rats were comparable to controls.

The results of gross necropsy did not reveal any treatment-related findings.

Microscopic examination revealed lymphocytic hyperplasia of the thymus occurring at statistically significant incidences in the mid- and high-dose female rats.

Another non-neoplastic lesion occurring at increased incidence was focal vacuolation of the liver in high-dose male rats.

Other microscopic findings in male and female treated rats were comparable to their respective controls.

Neoplastic lesions were comparable between the controls and treated groups.

However, the interestitial cell tumor in the testis of male rats was observed in the following groups as showed below:

Group I (control) 0/50
Group II (low-dose) 3/50
Group III (mid-dose) 1/50
Group IV (high-dose) 6/50

The occurrence of testicular interstitial tumors of 12% (6/50) in the high-dose group is statistically significant ($p = 0.013$).

To further examine these results, the historical control data for interstitial cell tumor of the testes were compiled. These control data include only those lifetime feeding studies with Charles River Sprague-Dawley rats conducted by Bio/dynamics Inc. which were tested concurrently with the present study, i.e., were completed within nine months of termination of the present study, and lasted at least 24 months. For all male animals on test (Table IV, page 10, Vol. 1), the high-dose group incidence in the present study of 12% (6/50) was slightly higher than the highest-concurrent control incidence of 7% (5/75) and higher than the overall incidence of 4.5% (24/535).

We agree with the interpretation of the testicular tumors given by Experimental Pathology Laboratories pathologist, Dr. Martin G. Strobl, (Vol. 2, page 4), who states:

"The significance, if any, of the 12% incidence of interstitial cell tumor in the testis in the high dose group of male rats in this study in comparison to the control group is not known. It may represent a biological variation in this strain of rats. The incidence of interstitial cell tumor in the testis in Group II and Group III of this study was similar to the incidence observed in the control groups of male rats in the other concurrent studies and did not appear to be related to the administration of the test compound in this study."

Conclusion:

Oncogenic potential is negative. The NOEL for chronic toxicity is 3.0 mg/kg/day (low-dose).

Classification: Core-Minimum Data

TS-769:th:TOX/HED:WDykstra:2-8-82:card #6

Test for Significance of Differences Between Proportions 2/5/82

Lymphocytic hyperplaasia

Ppm	# RESP	Total	%	+/-2(S.D.)	One Tail P Statistic Fisher's
0.000	5	25	20.00	+/-(17.68)	
30.000	13	32	40.63	+/-(18.58)	0.084
100.000	18	37	48.65	+/-(17.46)	0.020
300.000	17	34	50.00	+/-(18.28)	0.017

Test for a linear trend is not significant

Test for Significance of Differences Between Proportions 2/4/82

Testicular tumors

ppm	# RESP	Total	%	+/-2(S.D.)	One Tail P Statistic Fisher's
0.000	0	50	0.00	+/-(1.00)	
30.000	3	50	6.00	+/-(7.58)	0.121
100.000	1	50	2.00	+/-(4.88)	0.500
300.000	6	50	12.00	+/-(10.01)	0.013

Test for Linear Trend in Proportions P = 0.011