UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

000256

DATE: December 5, 1979

SUBJECT: EPA Reg.#524-308; 90-Day Subacute Toxicity Test with Aminomethylphosphonic Acid (CP50435); a plant metabolite of glyphosate.
Accession No. 241351 CASWELL#661A

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Registrant: Monsanto Agricultural Products Co.
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Recommendations:

1. The submitted 90-day rat toxicology study is acceptable as Core-Minimum Data and supports the registrations and tolerances for glyphosate. The NOEL is 400 mg/kg/day for aminomethylphosphonic acid in the rat.

Review:

1. 90-Day Subacute Toxicity Study with CP 50435 in Rats (Monsanto; IR-78-174; IRDC No. 401-050)

Test Material: Aminomethylphosphonic acid; plant metabolite of glyphosate.

Eighty male (70 to 93 grams) and 80 female (67 to 90 grams) weanling Charles River CD rats were assigned to groups as shown below:

Dosage Level mg/kg/day	Number of Rats Male	Female
0 (control)	20	20
400	20	20
1200	20	20
4800	20	20

The rats were observed twice a day 7 days a week for mortality and overt toxicity. Detailed observations of each rat, individual body weights and food consumption were recorded weekly. 10 male and 10 female per group were selected for clinical laboratory tests at 45 and 88 days of study. The blood samples were collected by theorbital sinus technique from fasted rats. The urine was collected while the rats were fasting.

The hematological determinations included hematocrit value, hemoglobin concentration, RBC count, WBC count (total and differential, platelet count and reticulocyte count.

The blood chemistry determinations included fasting blood sugar, BUN, total cholesterol total protein, albumin, globulin (calculated), direct and total bilirubin and the activities of SAP, LDH, SGOT, and SGPT.

Urinanlysis included description of color and appearance, determination of volume, specific gravity and pH, qualitative tests for glucose, protein, ketones, bilirubin and urobilinogen; and microscopic examination of the sediment. All statistical analyses compared the treatment groups with the control group by sex appropriate methods.

At the completion of the compound feeding period, all suriviving rats were sacrificed by CO_2 asphyxiation and necropsied. The liver, testes, heart and brain from each rat sacrificed at termination were weighed and the ovaries were weighed after fixation. Hematoxylin and eosin stained paraffin sections of the following tissues from all rats from the control and 4800 mg/kg/day groups were examined microscopically

brain (3 sections)	spleen	large intestine (colon, cecum)
spinal cord	lymph nodes (mes.)	
peripheral (sciatic) nerve	thymus	pancreas
eye (optic nerve)	sternum (bone marrow)	liver
pituitary	salivary gland	kidneys
thyroid (parathyroid)	esophagus	testes/ovaries
adrenals	stomach (3 sections)	prostate/uterus
trachea	small intestine	skeletal muscle
lung/bronchi	heart	

and other tissues with gross lesions, H&E stained paraffin sections of kidneys, liver, heart, urinary bladder, and any other tissues with gross lesions were prepared and examined from all rats from the 400 and 1200 mg/kg/day groups.

Results

One male rat and five female rats at the 4800 mg/kg/day dosage level were found dead on day 45 following the collection of blood. Similarly, one female rat in the control group and two female rats at the 1200 mg/kg/day dosage level were found dead after the collection of blood on study day 88.

In addition, one male rat in moribund condition was sacrificed in week 12.

Survival after 90 days was as follows:

Dosage Level mg/kg/day	No. surviving/No. Initiated Male	Female
0 (control)	19/20	19/20
400	20/20	20/20
1200	20/20	18/20
2400	19/20	15/20

For both male and female rats at the 4800 mg/kg/day dosage level and the male rats at the 1200 mg/kg/day dosage level, a statistically significant decrease in body weight occurred. Male rats at 4800 mg/kg/day had decreased food consumption. No changes considered to be related to the compound were seen in the hematological determinations.

The LDH values of the blood from rats at the 4800 mg/kg/day dosage level were higher than that of control rats. For male rats at 4800 mg/kg/day, the mean LDH acitivity was 48 and 145% greater than controls at 45 and 88 weeks, respectively. Similarly, for the female rats at the 4800 mg/kg/day dosage group, the mean LDH activity was 29 and 171% greater than the control values at 45 and 88 days, respectively.

A statistical increase in LDH activity was observed after 88 days in both the 400 and 1200 mg/kg/day females when compared to the controls. However, the control values obtained were below normal while these values from both treated groups were within a range considered normal. Statistically significant decreases in glucose concentration were observed after 88 days in males and females of the high-dose group. Similarly, at 88 weeks, both sexes at 4800 mg/kg/day exhibited statistically elevated SGOT.

A reduction in the pH was noted in urine obtained from both sexes of the high-dose group at 45 days (females only) and 88 days. Increases in the amount of calcium oxalate crystals was seen in the urine of both sexes of the high-dose after both 45 and 88 days of treatment.

No treatment related gross necropsy lesions were noted in any of the rats. Several statistical variations in absolute and relative organs weights were observed but could not be related to treatment since no dose-response or microscopic changes could be detected. Microscopic pathological lesions considered related to treatment were limited to the urinary tract of rats from the 1200 mg/kg/day and 4800 mg/kg/day groups. Urinary bladder from rats of the 400 mg/kg/day group were comparable to those of control rats.

These signs of irritation corresponded to observations of hyperplasia of the urinary bladder in rats from both the 1200 and 4800 mg/kg/day groups, with an increase in incidence and severity noted at the higher level.

The lesion was reportedly relatively uniform in nature over the circumference of theurinary bladder and did not exhibit papillarity. Epithelial hyperplasia was also reported in the pelvic kidney section of several rats from the 4800 mg/kg/day dosage group only. This lesion was not uniform over the epithelial pelvic surface area, which is itself irregular in texture. Several of these hyperlasia epithelial cells contained a hyaline-like cytoplasmic inclusion.

CONCLUSION:

The NOEL is considered to be 400 mg/kg/day dosage group. The LEL is 1200 mg/kg/day and the effects consisted of weight loss and histopathological lesions in the urinary bladder.

Classification: Core-Minimum DATA

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