Glyphosate /Tox

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

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

THRU: Orville E. Paynter, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: Review of an "abbreviated" report of "A Twelve Month Oral Toxicity Study of CP76100 In Hamsters" June 29, 1979, Bio/dynamics Inc. Project #76-1401; EPA Reg.#524-308, Glyphosate, Caswell #661A

Recommendation:

This "abbreviated" report on the oral toxicity of CP76100 (sodium salt of N-nitrosoglyphosate), an impurity in Roundup® herbicide, is inadequate for evaluating the carcinogenic potential and oral toxicity of this chemical.

The cover letter, dated August 10, 1982, from Robert W. Street, Monsanto Co., enclosed with the abbreviated report, stated that the full report is being printed and would be filed with the Agency by September 30, 1982. Surely it is available by now. The full report is necessary for a proper review.

Review:

The data package from Monsanto Company (report R.D. #437) consisted of the first section (pp 1-13: abstract, introduction, methods, results and discussion, and summary) and Table 1 (providing mortality data) of the Bio/dynamics final report and a comprehensive summary of the final report by Dr. Richard C. Dirks, Senior Product Toxicologist, Monsanto Company.

CP76100, Lot T-701, was administered orally in distilled water to Syrian Golden Hamsters at dose levels of 3, 10 and 30 mgs. active ingredient/kg/day. Control hamsters received an equivalent amount of sodium in distilled water to that given to the high dose group. Groups initially consisted of 70 hamsters/sex; due to high mortality, animals dying within the first two months were replaced and 5/sex/group were added after approximately two months of the study.

Although the study was intended to last 18 months, with interim sacrifices (10/sex/level) at 6 and 12 months, it was terminated 3 weeks after the 12th month due to high mortality, which had reached 63% for control females.

Animals were observed daily for mortality and gross signs of toxicity and were given weekly physical examinations for signs of toxicity and pharmacologic effects and palpated for masses. An ophthalmology examination was made pretest, and at 6 and 12 months.

Body weights and food consumption were recorded pretest, weekly through 13 weeks, biweekly 14 through 26 weeks, monthly thereafter and terminally.

Clinical studies consisting of the following parameters were determined on day 45 and 3, 6 and 12 months on 10 animals/sex in the control and high dose groups; the tests were to be done on low and mid-dose groups if significant changes were noted in high-dose animals.

Hematology:

- hemoglobin
- hematocrit
- erythrocytes
- total and differential leukocytes
- erythrocyte morphology
- clotting time

Clinical Chemistry:

- serum glutamic pyruvic transaminase
- alkaline phosphatase
- blood urea nitrogen
- fasting glucose

Urinalysis:

- gross appearance
- pH
- protein
- glucose
- ketones
- bilirubin
- occult blood
- specific gravity

All animals were given a complete gross necropsy examination; weights of brain, pituitary, adrenals, ovaries, testes, spleen; kidneys and liver were recorded and ratios to brain and body weight were calculated. Histopathologic evaluation was performed on the following organs and tissues from 10 animals/sex in the control and high dose-groups sacrificed at the 6 and 12 month intervals and suspect masses from all animals were examined microscopically.

adrenal (2)*
bone marrow, sternal
brain (2 sections)
eye (2-with optic nerve)
gall bladder
gonad (2)
mammary gland
pancreas
pituitary
prostate
salivary gland
skeletal muscle
heart (with coronary vessels)
intestine
  colon
  duodenum
  ileum
kidney (2)
liver (2 sections)
lung
lymph node (mesenteric)
skin
spinal cord (cervical)
spleen
stomach
thyroid
urinary bladder
uterus
gross lesions (including a section of normal-appearing portion of same tissue)
  tissue masses

*Figures in parentheses give the number of sections.

Statistical analysis were performed on body weight, food consumption, hematology and clinical chemistry parameters, organ weights, and organ/body and organ/brain weight ratios. Mean values of all dose groups were compared to control.

Results:

Since the only data in this abbreviated report were those for mortality, all statements regarding results are taken directly from the Bio/dyanmics Inc. report summary.

Clinical chemistry, hematology and urinalysis parameters of treated animals were comparable to control, except that there was a slight reduction in mean fasting glucose for high-dose females at 12 months and slight elevations in BUN for both sexes. Body weights were generally comparable to controls, but high-dose females weighed less during the last 2-3 months of the study. Food consumption, ophthalmology, and the incidence of animals with one or more palpable tissues masses of treated animals were comparable to control animals.

Absolute and relative (to body and brain weights) adrenal weights of high-dose females were slightly elevated while those of males in this group were less than control values and relative (to body weight) weights of the kidneys were generally elevated for high-dose animals throughout the study. Relative (to body weight) weights for the liver were elevated for all treated females, but not in a dose-related pattern.

Gross and histopathological evaluation of the animals did not reveal any effects attributable to CP76100 administration. Gross findings included abnormalities of the kidneys, liver, lungs and lymph nodes. Microscopic examination showed hyalization of the liver (particular in females at 12 months), kidney, spleen, and adrenal cortical tissue. The hyaline material was similar to that found in amyloidosis, commonly encountered in aging hamsters. Degenerative aging changes were seen in the kidneys; pneumonia in the lungs; and lymphoid element proliferation, secondary to inflammation, in the mesenteric lymph nodes.

One confusing aspect of this "abbreviated" report was that in his summary, Dr. Dirks made statements that laboratory studies (clinical chemistry, hematology and urinalysis) and histopathologic findings did not reveal any dose-related effects. The Bio/dynamics Inc. summary mentioned findings only for high-dose and control animals for clinical chemistry and hematology and stated that histopathologic evaluation was performed on all animals from control and high-dose groups from the 6 and 12-month necropsies, as well as on suspect masses noted in all animals through terminal sacrifice. How could Dr. Dirks speak of dose-related effects when results from only the high dose were available.

Winnie Teeters 1/6/82

Winnie Teeters, Ph.D.
Toxicology Branch
Hazard Evaluation Division (TS-769)

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