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

MAY 5 1982

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Jay Ellenberger (12)
Registration Division (TS-767)

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

SUBJECT: Review of Validated Thidiazuron Mouse Oncogenicity Study conducted at IBT (No. 8580-10725)
Tox. Chem. 659A

NOTE: The review of this study was also included in my memo of April 30, 1982.

Recommendation:

This study is classified as Core Minimum Data.

Although an MTD was not demonstrated it is likely that the high dose (1000 ppm) approaches the MTD based on slightly decreased body weight gains in both males and females. In addition, administration of thidiazuron at levels of 600 ppm and greater for periods of more than 90 days has shown an effect (decreased weight gain) in rats and dogs. The differences in termination dates of the female test groups (22, 22, 22 and 18 months for the control, 250, and 1000 ppm groups, respectively) makes comparison of tumor incidence in control and high dose females difficult. However, based on the very low incidence of tumors observed in high dose females after 18 months and the comparable incidences of tumors in control, low and mid dose females after 22 months at each tissue site, this reviewer considers it unlikely that the shorter duration of the T-III female exposure period has concealed an oncogenic effect. It is also noted that a thorough validation of the gross and histopathologic examination has determined that gross lesions and clinical observations of possible tumor masses were adequately followed up histologically.

Review:

Oncogenicity, Mouse. Conducted at IBT (IBT No. 8580-10725) and submitted by Nor-Am Agricultural Products, Inc. on December 12, 1980.

("This study was validated for the Agency by Experimental Pathology Laboratories on April 29, 1982 and classified as "Valid". The following three minor deficiencies were noted during the validation.

1. High dose females were terminated at 18 months on test. All other females were sacrificed after 22 months on test.

2. Mammary gland and parathyroid were not routinely collected for histological examination, although their collection was specified in the protocol.

3. Several deficiencies related to the thoroughness of clinical observations.")

Swiss White mice of unknown age (body weights ranging from 22.5 to 27.6 grams) were assigned to test groups as follows:

	Males	Female	Level (ppm)
Vehicle Control	50	50	0
T-I	50	50	50
T-II	50	50	250
T-III	50	50	1000

Treated groups received thidiazuron technical, Batch Number 261103B0000, 100% purity for periods ranging from 18 months (T-III females) to 22 months (control, T-I and T-II females). Test material was mixed with acetone and added to stock feed to achieve the desired dietary concentration. Body weights were recorded on a monthly basis. Food consumption was measured one week of each month. Observations were recorded 5 days a week (not including weekends or holidays). The following hematologic studies were conducted on 11 female mice from the T-III group on test day 560: total leukocyte count, erythrocyte count, hemoglobin, MCV, MCH, MCHC and differential leukocyte count.

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A gross pathologic examination was conducted on all animals on test. Microscopic examination was conducted on tissues of all animals (when not precluded by autolysis) and in addition, to those tissues appearing grossly abnormal, the following tissues were examined:

Heart
Liver
Lung
Pancreas
Stomach (cardia, fundus, pylorus)
Small intestine (duodenum, jejunum and ileum)
Caecum
Colon
Spleen
Kidneys
Urinary bladder
Testes
Ovaries
Prostate gland
Uterus
Epididymides
Gall bladder
Seminal vesicles
Pituitary gland
Adrenal glands
Salivary glands (sublingual, parotid, submandilunar)
Lymph nodes (cervical and mesenteric)
Thyroid gland
Parathyroid glands
Skeletal muscle
Sternum with marrow
Peripheral nerve (sciatic)
Trachea
Spinal cord
Eyes with optic nerve
Brain (cerebrum, cerebellum and pons)
Aorta
Esophagus

Results:

No histological lesions or tumors were observed which could be associated with compound exposure. The most common histological findings were either artifactual i.e., congested livers resulting from not being bled prior to examination or were common to aging mice i.e., amyloidosis. The most frequently occurring tumor type was adenoma of the lung (4, 8, 2, and 5 animals in the control, 50, 250 and 1000 ppm groups, respectively); the incidences of all other tumor types were low (three or less per group) and similar in control and treated groups. Body weight gains were similar in all test groups, although slightly less in high dose males and females compared to controls. Mortality was slightly higher among treated males (29, 36, 40 and 39 deaths through final sacrifice for the control, 50, 250 and 1000 ppm groups) but the increase was not dose related and could not be associated with compound exposure. Skin lesions were somewhat increased in treated females, (6, 12, 15 and 15 females with lesions

in the control, 50, 250 and 1000 ppm group) but histological examination of the lesions found them to be changes considered to be spontaneous and common in mice (such as ulcerative dermatitis, acanthosis, parakeratosis and hyperkeratosis). Hematology conducted on the T-III females on day 560 revealed no remarkable findings (based on a comparison with historical control values for Charles River CD-1 females, personal conversation with Dr. Lee of Charles River Breeding Laboratories, Wilmington, MA, April 27, 1982).

Conclusion:

Although an MTD was not demonstrated it is likely that the high dose (1000 ppm) approaches the MTD based on slightly decreased body weight gains in both males and females. In addition, administration of thidiazuron at levels of 600 ppm and greater for periods of more than 90 days has shown an effect (decreased weight gain) in rats and dogs. The differences in termination dates of the female test groups (22, 22, 22 and 18 months for the control, 250, and 1000 ppm groups, respectively) makes comparison of tumor incidence in control and high dose females difficult. However, based on the very low incidence of tumors observed in high dose females after 18 months and the comparable incidences of tumors in control, low and mid dose females after 22 months at each tissue site, this reviewer considers it unlikely that the shorter duration of the T-III female exposure period has concealed an oncogenic effect. It is also noted that a thorough validation of the gross and histopathologic examination has determined that gross lesions and clinical observations of possible tumor masses were adequately followed up histologically.

Core Classification: Core-Minimum

Gary J. Burin 5/5/82

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