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

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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 Chronic Rat Study
Conducted at IBT (No. 8560-09631)
CASWELL#659A

NOTE: The review of this study was also included in my memo of April 30, 1982. As noted below, it has been validated and classified as Supplementary Data. It has also been core classified as Supplementary Data. In addition to the deficiencies regarding histopathology (discussed in detail in the study validation addendum prepared by EPL), the following items compromise the utility of this study:

1. Poor animal survival (less than 50% for all male groups at 18 months). Therefore, an excessive number of animals did not survive long enough to demonstrate a potential oncogenic response.

2. High dose males were sacrificed approximately two months prior to sacrifice of their control counterparts, making comparison of tumor incidences extremely difficult.

3. Although compound related effects are suggested at 500 ppm, a Maximum Tolerated Dose is not firmly established. High mortality in control animals, a reflection of animal husbandary problems and ubiquitous respiratory disease, make the identification of compound related effects difficult.

Recommendation:

This study is classified as Core Supplementary Data.

Available data suggested a compound related effect on mortality (in both males and females) and body weight (females only) in T-III animals. Although no effects were observed at dose levels less than 500 ppm, this study does not permit the establishment of a NOEL due to the deficiencies noted in the validation regarding histopathology.

Review:

Chronic Oral, Rat. Conducted at IBT (IBT No. 8560-09631) and submitted by Nor-Am Agicultural Products, Inc. on December 12, 1980.

[On September 10, 1980 a validation of this study was conducted by Experimental Pathology Laboratories and a classification of "Invalid" was assigned. Based on additional information submitted by the registrant on May 5, 1981, EPL prepared an addendum to the original validation. The addendum upgraded the classification to "Supplementary Data" and noted that "... there is additional toxicologic information such as effects on body weight, survival, clinical signs, hematology and clinical chemistry which do provide useful information about the the chronic toxicity of SN 49537."

Deficiencies that were noted in the addendum related primarily to histopathology. The validation notes that "... there was an excessive number of tissues not examined microscopically" and that "Failure to report the severity of microscopic alterations made it impossible to determine if administration of the compound was responsible for exacerbation of naturally occurring lesions which frequently is a manifestation of toxicity." Other deficiencies were noted in the presentation of neoplastic pathology data and the excessive mortality which necessitated the early termination of the study (greater than 50% at 18 months for all groups of males).]

Thidiazuron technical (Batch No. 251201 B00000 and 261103 B00000) was fed to Charles River Albino rats at dose levels of 0, 40, 120 and 500 ppm in the diet. Fifty animals per sex per dose level were used. Animals were observed monthly after week 20 until month 8, twice monthly until test day 514, and then daily until day 730. Food consumption was measured individually for 10 animals, or all surviving if less than 10, for each sex and group for the first 13 weeks, and one week per month for months 4 through 24. Animals were weighed weekly

for the first 13 weeks and monthly for the remainder of the study. Blood samples were collected by suborbital sinus puncture and were collected from 10 rats/sex of the control and T-III group at 3, 6, 12 and 18 months, all surviving males of the T-III group (unfasted) after 21 months of testing, and 10 T-I, 10 T-II males (unfasted), 10 control and 10 T-III females prior to sacrifice after 102 weeks. Samples were analyzed for leukocyte count, RBC count, Hb, hematocrit, MCV, MCH, MCHC, platelet count, differential leukocyte count, blood glucose, BUN, SAP, SGPT, SGOT, cholesterol, protein and albumin/globulin ratio.

Urine samples were collected from the same animals at the same intervals with the exception of males after 18 months, for whom data was not collected. Urine was analyzed for glucose, albumin, bilirubin, ketones, pH, specific gravity and microscopic elements present.

Gross necropsies were conducted on all animals, excluding those severely autolyzed. Animals were sacrificed at the following times:

a. T-III males on day 637
b. Control, T-I and T-II males on days 705 and 706
c. All females on day 731 and 732

Animals were sacrificed by CO_2 asphyxiation and immediately exsanguinated. Weights of adrenals, brain, gonads, heart, kidney, liver, spleen and thyroid were recorded. "Sections of all available tissues and organs of all rats in the control and high dose groups were made into slides and examined histologically. Selected organs and tissues from rats in the low (40 ppm) and middle (120 ppm) dose groups were made into slides and examined histologically. The organs and tissues selected were those which showed tissue masses or lesions suggestive of possible neoplasms by gross examination."

Results:

(Diet analysis data indicates that animals received the following average amounts of test compound in the diet; control 1.7 ppm, T-I 40.3 ppm, T-II 120.9 ppm, T-III 477.7 ppm.)

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Body weights of T-III females were consistently lower than control females, male body weights did not appear to be affected by test compound exposure. Mortality of both T-III males and females was somewhat greater than control animals over the course of the study (through 21 months, 39 (78%) control males had died vs. 45 (90%) T-III males, through 24 months, 37 (74%) control females had died vs. 44 (88%) T-III females.

No effects considered to be compound related were observed on food consumption, hematology, clinical chemistry, urinalysis, or organ weights.

Available observation data and histopathology data did not suggest compound related effects but further confirmed the presence of respiratory disease.

Core-Classification: Supplementary Data.

Available data suggested a compound related effect on mortality (in both males and females) and body weight (females only) in T-III animals. Although no effects were observed at dose levels less than 500 ppm, this study does not permit the establishment of a NOEL due to the deficiencies noted in the validation regarding histopathology.

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5/6/82

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