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

DEC 11 1991

MEMORANDUM

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

Subject: Prodiamine
ID Number 55947
Tox Chem No. 727A
Project No. 1-2283; 1-1427

From: John H.S. Chen, D.V.M. John H S Chen 11/6/91
Review Section I
Toxicology Branch II
Health Effects Division (H7509C)

To: Joanne I. Miller, PM 23
Herbicide-Fungicide Branch
Registration Division (H7505C)

Thru: Yiannakis M. Ioannou, Ph.D., Section Head J M Ioannou 12/10/91
Review Section I
Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia Van Gemert, Ph.D., Branch Chief Marcia Gemert 12/10/91
Toxicology Branch II
Health Effects Division (H7509C)

Sponsor: Sandoz Crop Protection Corporation
Des Plaines, Illinois 60018

Action Requested:

1. Review of the proposed 6-week feeding study in rats to investigate thyroid effects (with recovery); and

2. Review of the proposed neurotoxicity testing and the protocol submitted to determine the nature of the neurotoxicity effect(s) of prodiamine to rats.

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Recommendation:

1. The proposed 6-week feeding study (protocol) in rats to investigate thyroid effects (with recovery):

Reviewer's Comments: This proposed study was based on the HED Peer Review Committee's recommendation (Peer Review Document on Prodiamine 6/10/91 G.J. Burin) to measure alterations in TSH, T3 and T4 in prodiamine-treated rats from a subchronic toxicity study in rats.

In the experimental design for investigating the effect of prodiamine on the thyroid of rats in a 6-week rat feeding study, the documentation of test substances, dose material preparation and administration, analysis of diets, animal acclimation, animal husbandry, and clinical observations are considered to be adequate in accordance with the Pesticide Assessment Guidelines (Subdivision F 82-1) for conducting the subchronic oral toxicity study. The parameters specifically designed to measure alterations in serum enzyme activities, and thyroid hormone and TSH levels in prodiamine-treated rats, bile duct cannulation, study termination (including recovery period), macroscopic examination, organ weights, liver biochemistry, histopthology and statistical analysis are considered to be appropriate. However, the petitioner should be apprised of the following inadequacies noted in this protocol:

A. Single Sex of Wistar Rats Used

Reviewer's Comments: Since there was only a statistically significant increase in follicular cell adenoma of thyroid in female rats receiving 3200 ppm from a 2-year rat feeding study with prodiamine previously submitted, the use of female rats in this study may be justified. Wistar rats have been known for their sensitivity in the development of thyroid neoplasms induced by propylthiouracil (PTU) (Van Dyke, J.H. Arch Pathol. 56: 613-628, 1953; Willis, J. J. Pathol. Bacteriol. 82: 23-27, 1961), this animal selection may also be justified for this study although both the sprague-Dawley male and female rats used in the original 2-yeat rat feeding study are preferred.

B. Three Dosage Levels Used (200, 800, & 8000 ppm)

Reviewer's Comments: In order to have a dose response relationship, the intermediate dose level should produce minimal observable response. It is, therefore, questionable whether the 800 ppm dose level was appropriately chosen for the intermediate dose level in this study.

C. Parameters Used in Blood Chemistry

Reviewer's Comments: The parameters recommended to detect hepatocellular disease by measuring the liver function enzymes in serum (ASLT, AIAT, GGT, & LDH) are believed to be appropriate because these enzymes originate in hepatocyte cytoplasm and during disease leak to extracellular fluid. However, the detection and evaluation of cholestasis (hepatocellular swelling) are generally accomplished by measuring both the serum alkaline phosphatase and the total serum bilirubin concentrations. We believe the radioimmunoassay used to determine the serum T3 and T4 concentrations is generally more sensitive than the results obtained from the competitive protein binding assay. But the radioimmunoassay should be validated for precision and accuracy of the serum samples. The detailed description of Amersham kit used to determine the TSH concentration was not provided in this protocol.

D. Criteria for Evaluation of Test Results

Reviewer's Comments: The evaluation criteria of test results are not provided in this protocol. We believe that the positive control substance (PTU) is used to demonstrate the sensitivity of this study design to detect an increase in TSH. In the 6-week recovery period in which rats were fed only control diet, if all prodiamine fed rats had T3 and T4 values similar to concurrent control values, these results can indicate that the cytochemnical effects of prodiamine are reversible if exposure is discontinued. The indictment of thyroid/pituitary hormonal imbalance as an oncogenic mechanism can be supported by the results of this study.

2. The proposed neurotoxicity testing and the protocol submitted to determine the nature of neurotoxicity effect(s) of prodiamine to rats

Reviewer's Comments: See Dr. William Sette's Review Comments (attached)

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

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PESTICIDES AND TOXIC
SUBSTANCES

December 10, 1991

MEMORANDUM

SUBJECT: Prodiamine: Request for Comment on Protocols and Content of Proposed Neurotoxicity Testing.

TO: John H.S. Chen, D.V.M.
Review Section I
Toxicology Branch II

FROM: William F. Sette, Ph.D. William F. Sette
Science Support and Special Review Section (H7509c)

THRU: Kerry Dearfield, Ph.D. Section Head (Acting) Kerry Dearfield
Science Support and Special Review Section
Science Analysis and Coordination Branch

I recommend that the registrant conduct the acute and subchronic neurotoxicity studies as recommended by the Peer Review Committee and as described in the submitted protocols, with a few minor comments, namely consideration of using mice or doing a pilot study in rats to demonstrate some sensitivity; measurement of rectal body temperature; and consideration of more cerebral sections.

1. Background

The Carcinogenicity Peer Review Committee (6/10/91) recommended acute and subchronic neurotoxicity testing in mice based on results reported in the mouse oncogenicity study (MRID 405897-02), namely skin lesions attributed to the consequences of increased fighting in mice gang caged at 5000 ppm. A statistically significant increase in fibrosarcomas (1,3,2, and 8, all of 52 mice/group, respectively) at the high dose was not considered toxicologically significant because of increased dermal collagen (1,0,3, and 5 mice, respectively), and some increase in skin scabs (15, 16, 25, and 29 mice, respectively), both considered as a consequence of increased fighting. The absolute incidence of the skin scabs and ulcerations in male mice at all levels was about ten times as high as for females . There was also increased mortality at the high dose level of 5000 ppm. The NOEL for all systemic

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effects was reported as 500 ppm (60-65 mg/kg).

In the subchronic rat feeding study DER of Prodiamine, rats given 4000 ppm showed increased yellow discoloration of the fur and tail, considered a consequence of the color of the chemical; the NOEL was 1200 ppm (80-97 mg/kg). No signs related to the nervous system or other target organs were noted in this study.

2. Studies Considered.

In a letter of response, Sandoz note the submission of an acute oral mouse study (MRID 418930-01) and a reproduction study in rats (MRID 405934-21, 22), and briefly noted their effects.

In the acute mouse study, groups of four male mice were given doses of 0, 500, 1,000, 2,000, or 5,000 mg/kg. They showed a number of signs referable to nervous system function. There was systematic observation at 30, 90, 150, and 300 minutes after dosing. Increased touch response was the most frequent effect in all dose groups; then increased response to pain, piloerection, and some increased aggressiveness; time of peak effect was 150-300 minutes. Other changes noted in some mice included straub tail, vocalisation, and abnormal gait. A consistent and dose dependent reduction in body temperature was also seen. No NOEL for the behavioral effects or body temperature decrease was apparent.

In the rat reproduction study, diets of 50, 200, or 2000 ppm were given. No clinical signs were reported in the parents. No consistently significant effects on the development of behavior were seen in this study, as reflected in the DER.

In summary, we have an acute study and a chronic study, both in mice, where neurobehavioral effects related to increased aggressiveness or dermal lesions believed secondary to increased fighting, as well as increased response to touch or pain were noted. There is insufficient detail and report, probably as a result of limited study conduct, of the clinical signs in rats to ascertain whether these effects are specific to mice for some reason.

3. Review of Protocols submitted.

While the available data, in particular the acute study, provides a fair amount of useful information, but the absence of more than 4 animals/dose and no neuropathology, among other things, are not sufficient to satisfy the need for the conduct of the neurotoxicity studies as described in the new neurotoxicity test guidelines.

The registrant also included protocols from Huntingdon Laboratories for an acute and subchronic neurotoxicity study in rats.

While in general I would expect neurobehavioral effects to be

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produced in both rats and mice, it would probably be more prudent in this case to pursue these effects in mice. Alternatively, if a pilot study in rats indicates similar effects to those seen in mice, then the rat would be acceptable. Since reduced rectal temperature was noted in the mice, this measure should be included in the rat study.

The submitted protocols look generally adequate as protocols based on the new guidelines. A carefully conducted observational battery in individually caged animals should pick up these effects of increased aggressiveness in terms of ease of handling of the animals, as well as the other signs seen. Last, the number of CNS sections above the pons/cerebellum, at two, seems a bit limited, although this comment is intended as a suggestion .