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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Metiram: Response to the Evaluations of a 13-Week Inhalation Study in Rats, a Chronic Toxicity/Oncogenicity Study in Rats and an Oncogenicity Study in Mice.

TO: Rossi/Grable PM 21
Registration Division (H7505C)

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EPA ID No.: 7969-70,71
Project No.: 9-0934
Caswell No.: 41A
Registrant: BASF Corp.

Action Requested

Comment on registrant's response to TB's evaluation of the subject studies.

I. Thirteen-week Inhalation Study in Rats

This study consisted of 2 phases: 1) an exposure period in which rats were exposed to airborne Metiram dust (head only) 6 hrs/day, 5 days/week for 13 weeks at concentrations of 2.1, 20.0 or 101.0 mg/m^3 and 2) a 13-week recovery period. Each study was initially evaluated by Dynamac Corp. (April 1, 1987 and January 13, 1989, respectively) and further evaluated by TB (EPA memoranda, Ghali, HED, to Rossi, RD April 2, 1987 and Ghali to Werdig, RD, February 28, 1989, respectively). The main study was originally classified Core-supplementary because the purity of the test material was not provided; the recovery phase was classified Core-minimum. The main study was upgraded to Core-minimum when the purity of the test material was subsequently submitted.

A. Deficiencies

1. Food consumption was not measured.

2. There is no indication in the report that the possible effect of circadian rhythm on TSH levels was considered.

3. Alveolitis observed in the mid- and high-dose rats is a toxic effect, therefore the NOEL in this study was 2.1 mg/m^3 and the LEL was 20.0 mg/m^3.

B. Registrant's Response

1. Food Consumption

"The interpretation of food consumption data in inhalation studies is difficult and does not provide essential information" (referred to statement from investigator, IRDC, which indicated that "For inhalation studies food consumption is not a very useful parameter to monitor, therefore, it is not usually measured and diet is provided in block form"). Also, "BASF Toxicology Department is not performing food consumption in its own inhalation studies due to misleading information of this parameter experienced when pelleted food was supplied. Data on an inhalation study with a coded BASF test substance show that even if there is no effect on body weight in an inhalation study the amount of food intake varies to high degree." The registrant also stated that "the question should be taken into consideration, if data on food consumption, even if they are accurate, will be of help in the evaluation of an inhalation study in general and in the Metiram study in particlular. As the animals do not receive the test substance via the feed but by inhalation, the food consumption is irrelevant for determination of test substance intake." The registrant contended that the decrease in body weight (observed in high-dose males) "has to be assessed as a toxic effect of the test substance and measurement of food consumption would not have offered any further information."

2. Circadian Rhythm

The registrant asked the test laboratory when measurements of TSH were performed; IRDC responded that the blood was withdrawn for hormonal analysis at essentially the same time each day.

3. Alveolitis

BASF did not agree that alveolitis, observed at 20.0 and 101.0 mg/m^3, was a toxicologically significant effect; they contend that the NOEL should be 20.0 mg/m^3, not 2.1 mg/m^3. They contend that the following criteria for an inert dust apply to Metiram in this study: 1) collagenation was absent or insignificant in the reacting lung tissue, 2) there was continued anatomical integrity of the air spaces in spite of the presence of dust and 3) the lesions were potentially reversible. It was stated that reversibility was supported by the 13-week recovery data.

C. TB Comments

1. Food Consumption

TB agrees with the registrant's opinion that food consumption data generated in inhalation studies can be variable and not always useful, however, it is not an impossible task and in some studies, these data can provide useful information. For example, in studies in which there is marked treatment-related inhibition of body weight gain, measurement of food consumption can provide useful information regarding efficiency of food utilization. It is TB's opinion that these data are not critical for the subject study, however, since body weight gain was inhibited only in males at the high-dose level, which was above the LEL (mid-dose).

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2. Circadian Rhythm

The investigator's procedure of withdrawing blood at approximately the same time each day for hormone analysis essentially eliminates circadian rhythm as an experimental variable for the measurement of TSH.

3. Alveolitis

The incidence of alveolitis was high in both mid- and high-dose males and females (80 - 100%) while it was not observed in any low-dose or concurrent control rats. The investigator contended that this effect was reversible based on observations at the end of a 13-week recovery period, however, 13 weeks is a lengthy period of time in which to demonstrate reversibility. Furthermore, chemically-induced irritation responses are often reversible; this does not mean that induced irritation is not a toxic effect, particularly when recovery requires an significant period of time. Therefore, it is still TB's opinion that the LEL in the subject study was the mid-dose level (20.0 mg/m^3), based on induced alveolitis, and the NOEL was 2.1 mg/m^3.

D. Additional Comments

The registrant misquoted a statement made by the original reviewer (Dynamac): the reviewer stated that the study design (not the study) was adequate and the conduct of the study was acceptable.

The reviewer's concerns regarding levels of Metiram in the urine and liver of concurrent controls, which were evaluated during the recovery phase, were not addressed by the registrant in this submission.

II. Chronic Toxicity/Oncogenicity Study in Rats

Metiram was administered in the diet of male and female Charles River CD rats at levels of 5, 20, 80 or 320 ppm for 111 weeks (females) to 119 weeks (males). This study was originally reviewed by Dynamac Corp. (DER dated August 14, 1986) and further reviewed by TB (EPA memorandum, Ghali, HED, to Rossi, RD, December 12, 1986).

A. Deficiencies

1. The summary tables should be corrected to indicate the actual number of tissues examined (these tables showed only the number of animals examined).

2. The rats could possibly have tolerated a slightly higher dose since the only toxic effect noted was an increased incidence of minimal to moderate muscular atrophy of the thighs in male and female rats receiving 320 ppm.

B. Registrant's Response

1. Histopathology Tables

Revised histopathology tables will be available within 3 months.

2. Adequacy of Administered Dosages

The registrant contends that the noted muscular atrophy in the thighs of males and females receiving 320 ppm was a toxic effect. They indicated that hindlimb paralysis (females) and muscular atrophy with concomitant histopathologic changes (males and females) were seen in a subchronic (90-day) study (originally reviewed by Dynamac Corp., December 11, 1985 and further reviewed by TB, EPA memorandum, Ghali, HED, to Jacoby, RD, July 11, 1986) in the same strain of rats at a dietary level of 900 ppm (high dose) while histopathologic changes were also observed in females at 300 ppm. Evidently this effect was more severe in a 4-week range-finding study among rats receiving 3000 ppm dietary Metiram.

Changes seen in treated rats in the subchronic study included: significant decreases in weight gain during the first 3 weeks of the study in 900 ppm males and females, serum thyroxine (T_4) levels were decreased after 11-12 weeks in males and females receiving 300 or 900 ppm, ^{131}I uptake by the thyroid (measured at week 13) was decreased in all treated male groups and in females receiving 100 ppm or higher levels of Metiram, liver to body weight ratios were increased in males and females receiving 300 ppm or higher, a minimal degree of thyroid hyperplasia was seen in 2/15 high-dose males.

Kinetic and metabolism data in rats show that the rate of absorption from the GI tract decreases as the oral dosage of Metiram is increased (ie. 37 to 47% of administered radioactivity was excreted in the urine after the administration of a single 5 mg/kg dose whereas 21 to 25% was excreted in urine after the administration of 50 mg/kg). Therefore, higher doses of Metiram in this study would have resulted in lower absorption rates.

Justification for selected dosages:
- the dose section of the 24-month study is justified by subacute/subchronic studies,
- the 24-month study was performed in accordance with EPA'S guidelines, valid at the time when the study was peformed,
- kinetic studies show that a further increase in doses would mainly result in an increase of unresorbed compound in the gastrointestinal tract,
- the study was performed with an additional 2% ETU (more than four times the maximum content of the technical compound) which is of major toxicological concern.

C. TB Comments

1. Histopathology Tables

No comment

2. Adequacy of Administered Dosages

TB agrees that the noted thigh muscle paralysis and atrophy, with histopathologic change, in rats administered Metiram is a toxic effect, however, the effect was transient at the dosages administered in the 24-month study. Therefore, this effect alone would not likely indicate that an MTD was achieved in the study. However, the dosages selected for the 24-month study appear to be justified on the basis of noted treatment- and dosage-related effects observed in the subchronic and range-finding studies. Based on a consensus opinion, TB previously reached the same conclusion (EPA memorandum, Jones, HED, to Werdig, RD, August 15, 1988). However, it is somewhat perplexing that some of the effects seen in the subchronic and range-finding studies (other than muscular atrophy) were not observed in the 24-month study.

INERT INGREDIENT INFORMATION IS NOT INCLUDED

The registrant did not discuss the examination of the sciatic nerve relative to the noted effects in skeletal muscle; any associated information should be submitted.

It is TB's opinion that the registrant's statements regarding absorption rates from the gastrointestinal tract are not relevant to the consideration of dosage adequacy. Although absorption rates decrease at higher dosage levels, absolute quantities absorbed increase at higher dosages, based on urine excretion data.

D. Additional Comments

The test material analysis, which was not included in the report, is included in this submission; analysis showed [redacted] and 2.02% ETU. As previously noted, the test material was fortified with 2.0 % ETU.

III. Oncogenicity Study in Mice

Metiram (fortified with 2% ETU) was administered in the diet to male and female CFLP mice for 96 weeks at levels of 100, 300 or 1000 ppm. This study was reviewed by TB (EPA memorandum, Ghali, HED, to Jacoby, RD, February 16, 1981).

A. Deficiencies

1. The extent of histopathological examinations was not described.

2. Summarized histopathologic findings should show the number of respective tissues examined.

3. Historical control data for hepatic lesions in this strain of mice should be provided.

4. The mice could have tolerated a higher dosage level since no treatment-related effects were observed.

B. Registrant's Response

1. The registrant indicated that data will be available within 3 months to address Deficiencies 1 - 3 above.

2. Adequacy of Administered Dosages

The registrant reiterated the consideration presented for the rat study that increased dosage levels of Metiram would result in decreased absorption rates from the gastrointestinal tract; they also speculated that higher dosages might result in palatability problems since 1000 and 3000 ppm in a range-finding study (4 weeks) caused decreases of food consumption of 7 and 9%, respectively. Increased liver weight in males and females at 1000 ppm was also observed in the range-finding study.

C. TB Comments

1. Response to deficiencies 1 - 3

No comment

2. Adequacy of Dosage Selection

It is TB's opinion that the dosages administered in this study were not adequate for the following reasons:

a) a treatment-related effect was not observed at any dosage level,
b) decreased body weight gain, seen at 1000 ppm in the range-finding study, was a transient effect in males only,
c) the only noteworthy effect observed in the range-finding study was increased liver weights in males and females receiving 1000 ppm, however, correlation with histopathologic changes was not noted.