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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Metiram® - Amendment to 52-Week Dog Study Report

TO: Terri Stowe
Product Manager (71)
Reregistration Branch, SRRD (H7508C)

FROM: Linda L. Taylor, Ph.D. Linda Lee Taylor 11/16/92
Toxicology Branch II, Section II,
Health Effects Division (H7509C)

THRU: K. Clark Swentzel K. Clark Swentzel 11/16/92
Section II Head, Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D. Marcia van Gemert 11/17/92
Chief, Toxicology Branch II/HFAS/HED (H7509C)

Registrant: BASF
Chemical: mixture of ammoniates of [ethylenebis (dithiocarbamate)]zinc with ethylenebis [dithiocarbamic acid], bimolecular and trimolecular cyclic anhydrosulfides and disulfides
Synonyms: Metiram®, Polyram®, Polram-Comi®, Carbatene® Zinc Metiram®
Submission No.: 427363
Case: 818620
Caswell No.: 041A
DP Barcode: D183539
Schnaughnessy No.: 014601
MRID No.: 424914-01 (amendment to MRID # 421331-01)
Action Requested: Please review additional metiram data for GLN 83-1B Dog Chronic Feeding Study (MRID 42491401). In addition, please give a comprehensive status report on the metiram toxicological requirements, especially the following GLNS for the METIRAM/ETU Data Call-In Notice that is currently being prepared by RB. The GLNs that I do not have a status on and need copies of the reviews if the studies were reviewed are MRIDs 42440601 (90-d--- ---- chronic rat, carc. mouse; 40497001 (21-day dermal); 407114 tox. rat & rabbit); 40931001 (dev. tox. rabbit); and 2-ge (no MRID #).

D183539

Comment: In response to a letter from the Agency (dated 5/22/92) regarding the chronic dog study, the Registrant has submitted a report of the results of the neuropathological examination of the sciatic nerve. The chronic dog study was classified supplementary, pending submission of the neuropathological examination.

According to Protocol Amendment # 5 of the dog study, the right hindlimb of each dog had been perfused with 2.5% glutaraldehyde and then immersed in the same fixative. The sciatic nerve, including its extensions, sural, tibial, and peroneal nerves as well as parts of the interosseous muscle were taken and embedded in resin blocks for possible future histopathologic examination. Only the routine (hematoxylin and eosin) histological examination of the sciatic nerve was reported in the final report. Although none of the neurological examinations performed to assess gait, postural reactions, spinal reflexes, and cranial nerves was affected by treatment with Metiram, microscopic lesions can occur in the absence of any clinical signs, and TB II requested that the neuropathological examination of the sciatic nerve be performed and the results submitted.

Longitudinal and transverse one micrometer sections of sciatic nerve were cut from all dogs and stained with toluidine blue, and the sections were examined by light microscope.

There were no microscopic abnormalities identified in any section, which confirmed the findings of the H&E-stained 5 µm sections of sciatic nerve.

CONCLUSION

The chronic dog study can be upgraded to Core Minimum, based on the submission of the histopathological examination of the sciatic nerve. The NOEL can be set at 80 ppm (2.49 ♂/2.69 ♀ mg/kg) and the LEL at 1000 ppm (29.8 ♂/29.9 ♀ mg/kg), based on decreased body-weight gain/food consumption, changes in hematology/clinical chemistry parameters indicative of thyroid toxicity/anemia, increased thyroid weight, and follicular (thyroid) hyperplasia. This study satisfies the guideline requirement [83-1(b)] for a chronic toxicity study in a non-rodent.

Comprehensive Status Report - With regard to the MRID #'s you cited, MRID # 42440601 (you have listed this for the 90-day rat feeding study, the chronic toxicity rat study, and the mouse carcinogenicity study) was the MRID # associated with the supplementary information submitted by the Registrant for six acute studies (TB II memo dated 9/30/92). The "bean" transmitting the supplemental acute data cited interim reports (MRID #'s 419298-01 & 419298-02, previously reviewed by TB II, memo dated 5/18/92) of 90-day bridging studies (rat, mouse) that are to be provided by the Registrant to upgrade guideline requirements 83-1A and 83-2B. date, the final reports of the 90-day bridging studies have

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been submitted to TB II for review, and therefore, the rat chronic toxicity and mouse carcinogenicity studies remain classified supplementary. Appended are MRID #'s 404970-01 (21-day dermal study DER) and 4-7114-01/409310-01 (rabbit developmental toxicity study DER). The MRID # you listed for the rat developmental toxicity study is a rabbit study (listed above); the rat study is the one listed in the Registration Standard (1988), which is classified supplementary pending submission of stability data. TB II is not aware of any such data being submitted to upgrade this study. A 2-generation reproduction study was a data requirement listed in the 1988 Registration Standard, and 7/90 was listed as the due date. TB II has not received this study for review, to date.

DATA AVAILABLE

A. Acute oral LD_{50} - rat	LD_{50} > 10000 ♂/8000 ♀ mg/kg Tox.Cat. IV
B. Acute dermal LD_{50} -rabbit	LD_{50} > 2000 mg/kg Tox.Cat.III
C. Acute inhalation LD_{50} - rat	LC_{50} > 5.7 mg/L Tox.Cat. IV
D. Primary eye irritation - rabbit	nonirritating; Tox.Cat. III
E. Primary dermal irritation - rabbit	nonirritating; Tox.Cat. IV
F. Dermal sensitization - guinea pig	strong-to-severe sensitizer
G. 21-Day dermal - rabbit	Supplementary
H. 90-day feeding - rat	bridging study needed
90-day inhalation - rat	minimum
I. 13-week subchronic - dog	not required
J. Developmental toxicity - rat	Minimum
K. Developmental toxicity - rabbit	Supplementary
L. Chronic toxicity - dog	Minimum
M. 2-Generation reproduction - rat	Minimum
N. Chronic tox/carcinogenicity - rat	minimum for carcinogenicity supplementary for chronic toxicity
O. Carcinogenicity - mouse	Supplementary
P. Mutagenicity - Category I	Acceptable
Category II	Acceptable
Category III	Acceptable
Q. Metabolism - rat	Minimum