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

011956
6-10-96

JUN 10 1996

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Thiobencarb (Bolero); S-[(4-Chlorophenyl) methyl] diethylcarbamothioate.

CASRN: 28249-77-6
EPA Chem. Code: 108401
Caswell No.: 207DA

FROM: George Z. Ghali, Ph.D.
Manager, RfD/QA Peer Review Committee
Health Effects Division (7509C)

THRU: William Burnam
Chairman, RfD/QA Peer Review Committee
Health Effects Division (7509C)

TO: Joanne Miller, PM 23
Fungicide-Herbicide Branch
Registration Division (7505C)

Chief, Reregistration Branch
Special Review and Reregistration Division (7508W)

The Health Effects Division-RfD/Peer Review Committee met on February 8, 1996 to discuss and evaluate the toxicology data submitted in support of Thiobencarb reregistration and to reassess the Reference Dose (RfD) for this chemical.

Material available for review consisted of data evaluation records (DERs) for a chronic toxicity/carcinogenicity study in rats **(83-5 or 83-1a and -2a)**, a chronic (one-year) feeding study in dogs (83-1b), a carcinogenicity study in mice **(83-2b)**, two multi-generation reproductive toxicity studies in rats **(83-4)**, developmental toxicity studies in rats **(83-1a)** and rabbits **(83-1b)**, acute and subacute neurotoxicity studies in rats **(81-7 and 82-6)**, delayed neurotoxicity study in hens **(81-5)** and a battery of mutagenicity studies **(84-2)**.

A. Chronic and Subchronic Toxicity:

The Committee considered the chronic toxicity phase of the rat study (83-1a, MRID No. 00154506) to be acceptable, and the data evaluation record (HED Doc. No. 001272, 004291, 0004735) to be adequate. The NOEL/LOEL were considered to be 20 ppm (1 mg/kg/day) and 100 ppm (5 mg/kg/day), respectively based on decreased food consumption, decreased body weight gain, and increased blood urea nitrogen.

The Committee considered the chronic toxicity study in dogs (83-1b, MRID No. 00144742) to be acceptable and the data evaluation record (HED Doc. No. 004737) to be adequate. Biologically significant depression in plasma cholinesterase activity was reported for both males and females of the 8 and 64 mg/kg/day groups for the duration of the study. Decreases in red blood cell cholinesterase activity were noted in both males and females of the 64 mg/kg/day dose group. No changes in brain cholinesterase activity were observed throughout the study. The NOEL/LOEL for plasma cholinesterase inhibition were considered to be 1 and 8 mg/kg/day, respectively. The NOEL/LOEL for red blood cell cholinesterase inhibition were considered to be 8 and 64 mg/kg/day, respectively. The NOEL for brain cholinesterase inhibition was considered to be 64 mg/kg/day, the highest dose level tested. The NOEL/LOEL for systemic toxicity were considered to be 8 and 64 mg/kg/day, based on decreases in serum albumin and protein in both males and females observed at 64 mg/kg/day, the highest dose level tested.

There were no subchronic toxicity studies in rats (82-1a) or dogs (82-1b) available for review by the Committee.

B. Carcinogenicity:

The Committee considered the carcinogenicity phases of the combined chronic toxicity/carcinogenicity studies in rats (83-2a, MRID No. 00154506) and the carcinogenicity study in mice (83-2b, MRID No. 00086004) to be acceptable and the data evaluation records (HED Doc. No. 001336) to be adequate.

The highest dose level tested in the rat (500 ppm, or 25 mg/kg/day) was considered to be adequate for carcinogenicity testing based on depression of cholinesterase activity and reduced body weight gain. The highest dose level tested in the mouse (1600 ppm, or 235 mg/kg/day in males and 302 mg/kg/day in females) was considered to be adequate based on body weight gain depression.

In rats, there were no treatment-related increase in tumors of any kind observed at any dose level. The Committee, therefore, concluded that the treatment did not alter the spontaneous tumor profile in this strain of rat.

In mice, adenomas and carcinomas of the harderian glands appeared to be increased in females (1, 2, 6, 5 and 7 for the 0, 25, 100 and 1600 ppm groups, respectively). However, the concurrent control incidence was said to be lower than expected for females of this strain and the possibility that the incidence is due to chance could not be precluded. The Committee noted also that mortality was increased in the treatment groups, which, if factored into the overall picture, the response could have been, probably, more pronounced. It was also noted that the study was carried out for 121 weeks, a significantly longer period than the Guideline calls for. This also could have complicated the situation even further. There were no historical control data available for review by the committee. The Committee also speculated that historical control incidence from studies conducted for shorter duration may not be accurately compared to the incidences observed in the study in question.

On this basis, the Committee concluded that the chemical should be classified as **"Group D"**, not classifiable as to human carcinogenicity, based on possible potential of carcinogenic response which could not be ascertained or dismissed using the existing mouse data.

C. Reproductive and Developmental Toxicity:

The Committee considered the reproductive toxicity study in rats (83-4, 1987, MRID No. 40446201) to be acceptable and the data evaluation record (HED Doc. No. 006645) to be adequate. The LOEL for systemic toxicity was considered by the scientific reviewer to be 2 mg/kg/day, the lowest dose level tested. The Committee considered the lowest dose level to be a NOEL for systemic toxicity. Liver weight changes, enlargement of centrolobular hepatocytes, and atrophy of renal tubules were noted at higher dose levels, but were considered to be marginal at the lowest dose level tested. The reproductive toxicity NOEL was considered to be 100 mg/kg/day, the highest dose level tested. There were no significant developmental toxicity. The Committee recommended revising the data evaluation record for this study and the addition of an executive summary to reflect the Committee's recommendations.

The Committee examined the older reproductive toxicity study in rats (83-4, 1984, MRID No. 00125372, 00149780, 00154507). The data evaluation record (HED Doc. No. 004556, 004941) for this study was considered to be inadequate. Because of inadequacy of the data evaluation record and discrepancies observed in this data record, the Committee was unable to adequately evaluate the findings and determine the acceptability of the study. The Committee also noted that the current data evaluation record made unnecessary emphasis on minor problems normally observed in reproductive toxicity studies.

The Committee considered the developmental toxicity study in

rats (83-3a, MRID No. 00086873, 00093691, 00115248) to be acceptable and the data evaluation record (HED Doc. No. 002291) to be adequate. NOEL/LOEL for both maternal and developmental toxicity were considered to be 25 and 150 mg/kg/day. Maternal toxicity was observed as a treatment- related body weight decrease accompanied by some decrease in food efficiency. Developmental toxicity was manifested as a slight increase in skeletal anomalies mostly related to reduced ossification and an increase in runts.

The Committee considered the oral developmental toxicity study in rabbits (83-3b, MRID No. 00164313) to be acceptable and the data evaluation record (HED Doc. No. 005883) to be adequate. The maternal toxicity NOEL/LOEL were considered to be 100 and 200 mg/kg/day, respectively, based on abortion and decreased body weight gains and food consumption. The developmental toxicity NOEL was considered to be 200 mg/kg/day, the highest dose level tested.

D. Acute and Subchronic Neurotoxicity:

The Committee considered the acute neurotoxicity study (81-7, MRID No. 42987001, 43148202) and subchronic neurotoxicity study (82-6, MRID No. 43001001) to be acceptable and the data evaluation records (HED Doc. No. 0011219; 011109) to be adequate. The Committee considered the delayed neurotoxicity study in hens (MRID No. 00084135) to be acceptable and the data evaluation record (HED Doc. No. 000143) to be adequate.

E. Mutagenicity:

The Committee considered the following mutagenicity studies to be acceptable:

1) In vitro chromosome aberrations in human lymphocytes (MRID No. 40352401, HED Doc. No. 006530): The test is negative up to cytotoxic levels (20 µg/ml -S9; 40 µg/ml +S9).

2) Mouse micronucleus assay (MRID No. 40352402, HED Doc. No. 006530): The test is positive for the induction of micronucleated polychromatic erythrocytes (MPCE) in male and female BDF1 mice with dose-related increases following the single oral administration of 270, 540 or 1080 mg/kg (males) or 405, 810 or 1620 mg/kg (females). Effects were significant ($p<0.01$) at the HDT in both sexes and at the mid-dose in females. Significant ($p<0.01$) increases in MPCEs were also seen in both sexes following 4 consecutive daily administrations of 540 mg/kg/day.

The Committee considered the following studies to be unacceptable:

1) Salmonella typhimurium reverse gene mutation assay (MRID No. 097568; Doc. Nos. 000143/000144). The test was negative;

however, the highest doses assayed varied for different tester strains without justification and did not adequately demonstrate cytotoxicity in any of the strains used. Additionally, the complete battery of strains (TA1535 not included) was not evaluated.

This study was initially classified by the scientific reviewer as acceptable; the DER and one-liner should be revised to reflect conclusion of the Committee as stated above.

2) Two mouse dominant lethal assays were available for review; both were considered to be unacceptable. IBT study No. 8533-10026 (MRID No.097658, HED Doc. No. 000143, 001142, 001556) contained no data. LSR Study No. 7/KC138/294 (MRID No 097658, HED Do. Nos. 000143, 000144) showed no evidence of a mutagenic effect at 600 mg/kg (once by oral gavage) or at 33, 100 or 300 mg/kg/day for 5 days. However, the maximum tolerated dose was not achieved and an insufficient number of pregnant females were used.

Although these dominant lethal studies were unacceptable, it is doubtful that repeating the test would alter the negative outcome since neither the reproductive toxicity studies nor the developmental studies indicated a concern for germinal cells at this time.

The Committee concluded that the following studies are required to satisfy the current mutagenicity initial testing battery guidelines.

1. Salmonella typhimurium reverse gene mutation assay

2. Mouse lymphoma L5178Y forward gene mutation assay, TK locus (with colony sizing).

No other genetic toxicology data requirements have been identified at this time.

F. Structural-Activity Relationship:

Thiobencarb is a thiocarbamate herbicide and structurally related to molinate, eptam, butylate, ethiolate, vernolate, pebulate and cycloate. Among all analogues that have been tested in the micronucleus assay, only molinate, which is classified as a Group C carcinogen, is positive. Molinate is also genotoxic in vitro in mammalian cell gene mutation and chromosomal assays. Until the genetic toxicology profile for thiobencarb is complete, however, a comparative analysis with the molinate data is not possible. Although we note that a reasonably strong correlation exists between micronuclei induction and carcinogenesis, the

findings from the 2-year feeding/carcinogenicity studies in rats or mice do not support an oncogenic effect for thiobencarb. Therefore, the relevance of the positive micronucleus assay is unclear.

G. Reference Dose (RfD):

The Committee recommended that the existing RfD for this chemical remain unchanged. The RfD for this chemical was based on the two year rat feeding study with a NOEL of 20 ppm dietary concentration (1 mg/kg/day). Decreased body weights and increased blood urea nitrogen levels were observed at the next higher dose level of 100 ppm dietary concentration (5 mg/kg/day).

An uncertainty factor (UF) of 100 was applied to account for both inter-species extrapolation and intra-species variability. On this basis, the RfD was estimated to be 0.01 mg/kg/day.

It should be noted that this chemical has not been reviewed by the FAO/WHO joint committee meeting on pesticide residue (JMPR) and that an acceptable daily intake (ADI) has not been established by that Committee.

H. Individuals in Attendance:

Peer Review Committee members and associates present were William Burnam (Chief, SAB; Chairman, RfD/Peer Review Committee), George Ghali (Manager, RfD/Peer Review Committee), Karl Baetcke (Chief, TB I), Mike Ioannou (Acting Chief, TB II), Stephen Dapson, Roger Gardner, Nancy McCarroll, Guruva Reddy, Ester Rinde, Henry Spencer and Rick Whiting. In attendance also was Kit Farwell of HED as an observer.

Scientific reviewers (Committee or non-committee member(s) responsible for data presentation; signature(s) indicate technical accuracy of panel report)

Stephen Dapson _____

Mike Ioannou _____

Respective Branch Chief (Committee member; signature indicates concurrence with the peer review unless otherwise stated)

Mike Ioannou _____

CC: Stephanie Irene
Debra Edwards
Albin Kocialski
Mike Ioannou
Stephen Dapson
Beth Doyle
Paula Deschamp
Amal Mahfouz (OW)
RfD File
Caswell File

I. Material Reviewed:

1. Cummins, H. (1984). Technical Bolero: Combined Oncogenicity and Toxicity Study in Dietary Administration to the Rat: MRID No. 00154506. HED Doc. No. 001272, 004291, 0004735. Classification: Core minimum data as upgraded by the RfD Committee. This study satisfies data requirement 83-5 (or 83-1a and 83-2a) of Subpart F of the Pesticide Assessment Guideline for chronic toxicity and carcinogenicity testing in rats.

2. Macrae, S. M. et al. (1981). Technical Bolero (R): Potential Oncogenicity in Dietary Administration to Mice. MRID No. 00086004. HED Doc. No. 001336. Classification: Core minimum data. This study satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity and carcinogenicity testing in mice.

3. Johnson, D. (1985). One Year Subchronic Oral Toxicity Study with Thiobencarb Technical in Dogs. MRID No. 00144742, 92182036. HED Doc. No. 004737, 005207. Classification: Core minimum data. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

4. Hatakeyama, Y. (1987). Reproduction Study by Oral Forced Administration of Thiobencarb in Rats--Main Experiment. MRID No. 404446201. HED Doc. No. 006645, 007823. Classification: Core Minimum data. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

5. Schroeder, R. (1984). A Two Generation Reproduction Study in Rats with Bolero Technical: Project No. 82-2615. MRID No. 00125372. 00149780, 00154507. HED Doc. No. 004556, 004941. Classification: Core Supplementary data. This study does not satisfy data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

6. Harris, Stephen B. (1982). Teratology Study in Rats with Bolero Technical. MRID No. 00086873, 00093691, 00115248, 92182039. HED Doc. No. 002291. Classification: Acceptable data. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

7. Tauchi, K. (1979). Teratology Study of Thiobencarb in the Rabbit. MRID No. 00164313, 92182040. HED Doc. No. 005883.

Classification: Core Minimum data. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

8. Lamb, I. C. (1993). A Subchronic 13-Week) Neurotoxicity Study of BOLERO Technical in Rats. MRID No. 43001001. HED Doc. No. 011109. Classification: Core guideline data. This study satisfies data requirement 82-6 of Subpart F of the Pesticide Assessment Guideline for subchronic neurotoxicity testing in rats.

9. Lamb, I. C. (1993 & 1994). Acute Neurotoxicity Study of BOLERO Technical in Rats. MRID No. 42987001, 43148202. HED Doc. No. 011219. Classification: Core guideline data. This study satisfies data requirement 81-7 of Subpart F of the Pesticide Assessment Guideline for acute neurotoxicity testing in rats.

10. Ben-Dyke, R. and Cavanagh, J. B. (1978). Bolero: Examination for Potential to Cause Delayed Neurotoxicity in Hens. MRID No. 00084135, HED Doc. No. 000143. Classification: Core minimum data. This study satisfies data requirement 81-7 of Subpart F of the Pesticide Assessment Guideline for delayed neurotoxicity testing in hens.

11. Bootman, J. et al. (1985). In Vitro Assessment of the Clastogenic Activity of Benthiocarb in Cultured Human Periphral Lymphocytes. MRID No. 40352401, 40352402. HED Doc. No. 006530. Classification: Acceptable data. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

12. Inoue, H. (1986). Micronucleus test in mice treated with Benthiocarb. MRID No. 40352402, HED Doc. No. 006530. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

13. Boatman, J. and Whalley, H. E. (1978). Bolero (Thiobencarb): Dominant lethal study in mice after acute and subacute oral administration. MRID No. 00084133, HED Doc. No. 000143, 001142, 001556. Classification: Unacceptable. This study does not satisfy data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

14. Bullock, C. H. (1977). The potential of Benthiocarb technical and Benthiocarb standard to mutate histidine-deficient strains of Salmonella typhimurium. MRID No. 00084131, HED Doc. No. 000143, 000144. Classification: Unacceptable. This study

does not satisfy data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.