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

9/17/1996

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Toxicology Review for the Reregistration Eligibility Document on Thiobencarb

TO: Paula Deschamp, Section Head
and
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Chemical: Thiobencarb
Case# 2665
Pesticide Chemical Code 108401
CAS Reg No. 28249-77-6

Attached is the Toxicology Chapter for the Thiobencarb RED.

1. Toxicology Data Base

The toxicological data base on Thiobencarb is adequate and will support reregistration eligibility.

a. Acute Toxicity

ACUTE TOXICITY DATA

TEST	RESULTS	TOX CAT	PURITY
Oral LD_{50} - rat	Males: LD_{50} = 1033 (924-1155) mg/kg Females: LD_{50} = 1130 (1033-1247) mg/kg	III	96.0%
Dermal LD_{50} - rabbit	LD_{50} > 2000 mg/kg (both sexes)	III	96.0%
Inhalation LC_{50} - rat	LC_{50} > 42.8 mg/L **(1 hour)**	IV	95.1%
Eye Irritation-rabbit	Slight irritation	III	95.1%
Dermal Irritation - rabbit	Slight irritation	IV	95.1%
Dermal Sensitization - guinea pig	Not a sensitizer	NA	84.0%

For acute oral toxicity in the rat (MRID# 42130701), the LD_{50} for males is 1033 (924-1155) mg/kg body weight and for females is 1130 (1033-1247) mg/kg, Toxicity Category III. For acute dermal toxicity in the rabbit (MRID# 42130701), the LD_{50} was greater than 2 grams/kg body weight, Toxicity Category III. For acute inhalation toxicity in the rat (MRID# 00040585, 00134976), the LC_{50} was greater than 42.8 mg/L **for 1 hour** (only data available with technical; usually 4 hour exposure is required), Toxicity Category IV. In a primary eye irritation study in the rabbit (MRID# 00040581), there was no corneal opacity and conjunctival irritation cleared by 48 hours, Toxicity Category III. In a primary dermal irritation study in the rabbit (MRID# 00040583, 00081900), slight irritation was observed (PIS 2.2/8.0) present for up to 72 hours, Toxicity Category IV. In a dermal sensitization study in guinea pigs (MRID# 00161699), no dermal sensitization was observed.

In an acute neurotoxicity study (MRID# 42987001, 43148202), male and female Sprague-Dawley rats (12-16 animals/ sex/group) were orally gavaged once with thiobencarb at doses of 0, 100, 500 or 1000 mg/kg. Neurobehavioral evaluations, consisting of Functional Observational Battery (FOB) and motor activity, were conducted at pre-study, Day 0, at time of peak effect (4 hrs post-dosing), Day

7 and Day 14. At Day 15, animals were euthanized and neuropathological examination performed on control and high-dose animals (5/dose/sex). With the exception of one high-dose female, which died on Day 3 of the study, all other animals survived until terminal sacrifice. An increased incidence of clinical signs, consisting of red deposits around the noses and mouths of high-dose animals, was noted. Gait abnormalities (rocking, lurching and swaying) were observed in some high-dose females. No significant differences were noted in either the mean body weight or body weight gain of any of the treated animals. Neurobehavioral evaluation revealed treatment-related FOB and motor activity findings at the mid- and high-dose levels. The effects were, in general, transient and observed only at the peak time of effect (4 hrs post-dosing). Although the incidences of FOB findings were not significantly different from control values, when taken together, a consistent, treatment-related pattern of neurobehavioral effects becomes clear. These findings included gait abnormalities (lurching, swaying and rocking), impaired mobility and decreased sensory responses (approach, touch, startle, tail pinch and pupil responses). In high-dose males, the startle response achieved statistical significance when measured at the time of peak effect. Hindlimb resistance was reduced in high-dose animals. Mean body temperature was significantly decreased in all treated males and mid- and high dose females. Total and ambulatory motor activity, measured at the peak time of effect on Day 0, showed significant treatment-related decreases in all mid- and high-dose animals. No treatment-related gross or neuropathological findings were present. Brain weights and measurements of the treated animals were comparable to control values. Based on the results of this study, for systemic toxicity, the NOEL was 100 mg/kg/day and the LOEL was 500 mg/kg. For neurobehavioral toxicity, the NOEL was 100 mg/kg/day and the LOEL was 500 mg/kg.

b. Subchronic Toxicity

The subchronic toxicity studies in rats or dogs conducted by the Industrial BioTest (IBT) Laboratories are classified as supplementary data, not adequate to satisfy Subdivision F guidelines. Therefore, the data requirements for the subchronic studies in rats and dogs are satisfied by the chronic feeding studies in the rat and dog (see chronic toxicity and carcinogenicity section).

In a 21 day dermal study (MRID# 42893001, revision of MRID# 42003401), Bolero 8EC (Lot# SX-1843; 85.2% a.i.) was applied dermally at doses of 0, 40, 160, or 500 mg/kg to young Sprague-Dawley® Crl:CD®BR rats from Charles River Laboratories, Inc. (Portage, MI), 5 days per week, over a 22-day period with animals

of the control and high dose used for a recovery period. Bolero 8EC produced a dose related increase in the incidence of skin irritation in treated versus control rats of both sexes. Six additional animals dosed with 0 and 500 mg/kg Bolero 8EC were held for 2 weeks following dosing as a recovery group. Reduced food intake with an associated reduction in body weight gain was observed in the mid- and high-dose groups. The reduction in body weight gain persisted in high-dose males in the recovery group. Statistically significant decreases in food efficiency were observed in mid-and high-dose males. For dermal toxicity the NOEL was less than or equal to 40 mg/kg/day and the LOEL was less than 40 mg/kg/day based on the skin irritation observed. For systemic toxicity, the NOEL was 40 mg/kg/day and the LOEL was 160 mg/kg/day based on decreases in body weight gain and food consumption in males and females, and statistically significant decreases in food efficiency in males.

In a subchronic neurotoxicity study (MRID# 43001001), male and female Sprague-Dawley rats (10/sex/group) were orally gavaged with test compound at 0, 2, 20 or 100 mg/kg/day for 13 weeks. All animals survived until terminal sacrifice. Clinical signs were evident only within the first 4-hours post-dosing. During this time there was an increased incidence of dried red material around the noses of all treated animals and dried tan or red material around the mouths of mid- and high-dose animals. Mean body weights and body weight gains of high-dose females were lower than controls. Food consumption was not affected by treatment. The absolute-and relative (to terminal body weight and brain weight) liver and kidney weights of high-dose males and females were significantly increased; the relative (to the terminal body weight) liver weights of mid-dose males and the kidney weights of mid-dose females were significantly increased. No treatment-related gross or neuropathological findings were present. Based on the results of this study, for systemic toxicity, the NOEL was 2 mg/kg/day and the LOEL was 20 mg/kg/day. For neurotoxicity, the NOEL was greater than 100 mg/kg/day (HDT) and a LOEL was not established.

c. Chronic Toxicity and Carcinogenicity

In a chronic feeding study (MRID# 00154506), Fischer 344 rats received either 0, 20, 100 or 500 ppm (approximately 0, 1, 5, and 25 mg/kg/day by standard conversion methods) Technical Bolero (95.3% a.i.; Lot# U0048) in the diet for 2 years. Systemic toxicity was noted at 100 ppm and above as decreased body weight gain, food consumption and food efficiency, also there was an increase in blood urea nitrogen. There was no evidence of carcinogenicity at the dose levels tested. For chronic toxicity, the NOEL was 1 mg/kg/day and the LOEL was 5 mg/kg/day based on decreased body weight gains, food consumption, food efficiency and increased blood urea nitrogen.

In a carcinogenicity study (MRID# 00086004), B6C3F1 hybrid mice (parents: C57 B1/6 male and C3H/He female) from Bantin and Kingman Limited received either 0, 25, 100, 400, or 1600 ppm (0, 3, 14, 56, and 235 mg/kg/day for males and 0, 5, 19, 75, and 302 mg/kg/day for females, respectively at week 13) Technical Bolero® (Lot# P7030; 93.7% a.i.). Systemic Toxicity was noted at 14 mg/kg/day for males and 19 mg/kg/day for females and above as histopathological changes in the liver. These observations included an increased incidence of hepatocytic (glycogen) pallor; the high dose animals also had increased incidence of fatty vacuolization (moderate or marked mid-zonar). High dose males had marked fine fatty periacinar, vacuolization and increased relative heart and liver weights; at 100 ppm and above males had decreased absolute and relative kidney weights, while high dose females had increased relative kidney weights. Upon gross examination there was an increased incidence of pale foci of the lungs of high dose animals and pale livers in the high dose males (external examination showed abdominal swelling). There was an increased incidence of focal epithelialization of the alveolar walls of the lungs with associated macrophages. High dose females had reduced body weight gains. There was no evidence of carcinogenicity in either sex at the dose levels tested. For systemic toxicity, the NOEL was 3 mg/kg/day for males and 5 mg/kg/day for females and the LOEL was 14 mg/kg/day for males and 19 mg/kg/day for females based on histopathological changes in the liver.

In a chronic oral toxicity study (MRID# 00144742), Beagles from Ridglan Farms, WI received either 0, 1, 8, or 64 mg/kg/day of Thiobencarb Technical (Lot# SX-1381; Purity 96.3% a.i.) by capsule. Systemic (non-cholinesterase) toxicity was noted in the high dose males as decreased body weight gains, also increased absolute and relative kidney and liver weights in high dose males and females. There were decreases in serum albumin and protein in high dose males and females (a slight effect was noted in mid dose males). Also there were decreased erythrocyte counts and

hemoglobin levels with a reduction in hematocrit in high dose males and females along with decreases in alanine aminotransferase and cholesterol levels in the high dose group. For systemic toxicity, the NOEL was 8 mg/kg/day and the LOEL was 64 mg/kg/day based on increased liver and kidney weights, and decreased hematological and clinical chemistry parameters. Based on biologically significant depression in cholinesterase levels, for Plasma Cholinesterase, the NOEL was 1 mg/kg/day and the LOEL was 8 mg/kg/day; for Erythrocyte Cholinesterase, the NOEL was 8 mg/kg/day and the LOEL was 64 mg/kg/day; for Brain Cholinesterase NOEL was equal to or greater than 64 mg/kg/day and the LOEL was greater than 64 mg/kg/day.

d. Developmental Toxicity

In a developmental toxicity (teratology) study (MRID# 00115248), albino rats of the Sim: (SD) FBR (Sprague Dawley Derived) strain from Simonsen Laboratories, Gilroy, CA received by oral gavage either 0, 5, 25, or 150 mg/kg/day Bolero® Technical (Purity: 97% a.i.; Lot No.: SX-1281) in Deionized Water/CMC/Tween 80. Maternal toxicity was observed as a treatment related decrease in body weight gains in the high dose group. There was no effect on food consumption; however, the high dose had lower food efficiency than the control group, an indicator of systemic toxicity. No other treatment related effects were noted. For Maternal Toxicity, the NOEL was 25 mg/kg/day and the LOEL was 150 mg/kg/day based on decreased body weight gains and decreased food efficiency. Developmental toxicity was noted as a slight increase in skeletal anomaly observations at the high dose mostly related to reduced ossification and an increase in runts in the high dose group. For Developmental Toxicity, the NOEL was 25 mg/kg/day and the LOEL was 150 mg/kg/day based on increased skeletal anomaly observations and an increase in the number of runts.

In a developmental toxicity (teratology) study (MRID# 00164313), New Zealand white rabbits from Ichikaways, Japan received either 0, 20, 100, or 200 mg/kg/day Technical Thiobencarb (96.0% a.i,) by oral gavage from days 6 through 18 of gestation. Maternal toxicity was observed at 200 mg/kg/day as statistically significant absolute and relative liver weights. For Maternal Toxicity, the NOEL was 100 mg/kg/day and the LOEL was 200 mg/kg/day based on increased liver weights. No Developmental toxicity was observed at dose levels tested. For Developmental Toxicity, the NOEL was equal to or greater than 200 mg/kg/day and the LOEL was greater than 200 mg/kg/day.

Based on the results of these studies, Thiobencarb is not considered to be a developmental toxicant in rat or rabbits.

e. Reproductive Toxicity

In a multigeneration reproduction study (MRID# 40446201), Charles River CD rats (Sprague Dawley derived) received either 0, 2, 20, or 100 mg/kg/day Technical Bolero (Lot# L 6006; 96.7% a.i.) by daily oral gavage in 0.5% CMC aqueous solution. Systemic toxicity was noted at 20 mg/kg/day and above based on enlargement of centrolobular hepatocytes (both generations) and hepatocyte single cell necrosis observed in both sexes of both generations including renal atrophic tubule consisting of regenerated epithelium. There were increased liver weights (absolute and relative) and increased kidney weights (absolute and relative) in the high dose group. There were also significant changes on body weights at 100 mg/kg/day and male kidney weights were increased in the high dose group. These observations are supported by a previously conducted reproduction study (MRID#) and by the chronic toxicity study in rats. There were no effects on reproductive parameters. For Parental/Systemic Toxicity, the NOEL was 2 mg/kg/day and the LOEL was 20 mg/kg/day based on histopathological changes of the liver and kidney. For Reproductive Toxicity, the NOEL was equal to or greater than 100 mg/kg/day and the LOEL was greater than 100 mg/kg/day.

f. Mutagenicity

In an Ames assay (MRID# 00041174, 00084131 and 00135285), Thiobencarb was negative in strains TA100, TA98 and TA1537 at levels up to 50 µg/plate both with and without metabolic activation.

In a clastogenicity test in human lymphocytes (MRID# 40352401), Benthiocarb (Thiobencarb; Lot# Z 5005; 96.0% a.i.) was tested a dose levels of 5, 10, and 20 µg/ml without S9 activation and a dose levels of 10, 20, and 40 µg/ml with S9 activation. No mutagenic activity was noted.

In a micronucleus test in mice (MRID# 40352402), Benthiocarb (Thiobencarb; Lot# Z 5005; 96.0% a.i.) was tested at dose levels of 270, 540, and 1080 mg/kg in males and at dose levels of 405, 810, and 1620 mg/kg in females, as a single oral dose. A dose related increase in micronuclei was noted, and was statistically significant in high dose males and in the 2 highest doses in females. Four consecutive daily doses of 540 mg/kg caused statistically significant increases in the incidence of micronuclei in both sexes. This was considered as a positive mutagenic response.

In a dominant lethal assay in mice (MRID# 00084133 and 00135282), Thiobencarb was negative at a single oral dose of 600 mg/kg and at an oral dose of 300 mg/kg for 5 days.

g. Metabolism

In a general metabolism study (MRID# 42340302), the disposition and metabolism of [Phenyl-U-^{14}C]-Thiobencarb (Lot # 2732-030; PTRL # 553-2; Radiochemical Purity: not stated, but data in report indicate acceptable purity of radiochemical; Specific Activity: 32.5 mCi/mmol prior to purification, specific activity following purification was not stated; Unlabeled Thiobencarb, Lot # Q516200; PTRL # 544-17; Purity: > 97.0%)) was investigated in male and female Sprague-Dawley rats at a low oral dose (30 mg/kg), repeated low oral doses (30 mg/kg x 14 days), and a high dose (300 mg/kg). Thiobencarb was rapidly absorbed after oral administration as judged by the rate of excretion. No significant sex-related or dose group differences in absorption were noted. Excretion was relatively rapid at all doses tested, with a majority of radioactivity eliminated in the urine and feces by 48 hours. The extent of excretion was not complete until 72 hours at the 300 mg/kg dose, but the mechanism responsible for this delay was not identified. No significant sex- or dose-related differences in urinary or fecal excretion of thiobencarb derived radioactivity were noted. Repeated low oral dosing did not affect elimination of Thiobencarb in either male or female rats.

Fecal elimination of [Phenyl-U-^{14}C]-Thiobencarb derived radioactivity was a minor route of excretion, and as for urine, no significant sex- or dose-related differences in amount of radioactivity excreted by this route were observed. Residual levels of Thiobencarb derived radioactivity were also minor (less than 0.5% of an administered dose).

Urinary and fecal metabolites of [Phenyl-U-^{14}C]-Thiobencarb were isolated and identified by HPLC, TLC, and mass spectral analysis. The major metabolite detected was the glycine conjugate 4-chlorohippuric acid, comprising between 74-81% of an administered dose in urine. Other metabolites detected included 4-chlorobenzyl methyl sulfoxide and -sulfone, des-ethyl thiobencarb, and 4-chlorobenzoic acid, each representing less than 10% of an administered dose of thiobencarb. A single high or repeated low oral doses did not significantly affect the urinary or fecal metabolite profile for Thiobencarb in male or female rats.

h. Dermal absorption

In a dermal absorption study (MRID# 41215311), Sprague-Dawley® Crl:CD® (SD)BR male rats received either 0.05, 0.5 or 5.0 mg/rat of ^{14}C-Thiobencarb (Radiochemical purity: 98.8%, Specific Activity: 359,092 dpm/µg) for exposure durations of 1, 2, 4, 10, or 24 hours (4 rats per dose per duration). The unlabeled compound used was Bolero 8EC (Thiobencarb, Lot# M20387; Purity: 89% a.i.). This study may represent a worst-case scenario since the skin was washed approximately 1 hour prior to dosing rather than the recommended 24 hours (which would allow normal replacement of skin oils), this might tend to over-estimate absorption. Based on the results of the study it was determined that Thiobencarb is rapidly and continuously absorbed at doses of 5.0, 46.8 and 498 µg/cm^2 for exposure times up to 24 hours. Absorption at 10 hours was 60.2, 52.6, and 17.1% for the 5.0, 46.8 and 498 µg/cm^2 dose groups, respectively. Maximum absorption at 24 hours, 71.5, 72.6, and 41.75 for the 5.0, 46.8 and 498 µg/cm^2 dose groups, respectively. It is rapidly excreted preferentially in the urine.

h. Reference Dose (RfD) for Chronic Oral Exposure

A Reference Dose (RfD) of 0.01 mg/kg/day was derived based on the NOEL of 1 mg/kg/day established in a two year dietary study in rats and an uncertainty factor (UF) of 100 to account for both inter-species extrapolation and intra-species variability. The LOEL of 5 mg/kg/day was based on decreased in body weight and increased BUN.

The HED/QA Peer Review Committee considered the carcinogenicity phases of the combined chronic toxicity/ carcinogenicity studies in rats (83-2a, MRID# 00154506) and the carcinogenicity study in mice (83-2b, MRID# 00086004).

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 was no treatment-related increase in tumors of any kind 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 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 determined 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 Thiobencarb should be classified as **"Group D Carcinogen"**, not classifiable as to human carcinogenicity.

i. Toxicity End-Point Selection

1. DERMAL ABSORPTION FACTOR

A dermal absorption factor of 60.2% (observed at 10 hours in a dermal absorption study, MRID# 41215311) will be used for risk assessment.

2. ACUTE DIETARY ASSESSMENT (ONE DAY)

The NOEL of 25 mg/kg/day established in a developmental toxicity study in rats (MRID# 00086873, 00093691, 00115248) will be used for this risk assessment. The LOEL of 150 mg/kg/day was based on increased in incidence of reduced ossification and an increase in fetal runts.

3. SHORT TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 TO 7 DAYS)

The NOEL of 25 mg/kg/day established in a developmental toxicity study in rats (MRID# 00086873, 00093691, 00115248) will be used for this risk assessment. The LOEL of 150 mg/kg/day was based on increased in incidence of reduced ossification and an increase in fetal runts. A MOE of 100 is adequate for this risk assessment.

4. INTERMEDIATE TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 WEEK TO SEVERAL MONTHS)

A NOEL of 2 mg/kg/day established in a subchronic neurotoxicity study in rats (MRID# 43001001) will be used for this risk assessment. The LOEL of 20 mg/kg/day was based on systemic toxicity. This NOEL of 2 mg/kg/day is supported by a similar NOEL

(2 mg/kg/day) established in the multigeneration reproduction study (MRID# 40446201, additional data: 40985701).

5. CHRONIC OCCUPATIONAL OR RESIDENTIAL EXPOSURE (SEVERAL MONTHS TO LIFETIME)

A NOEL of 1 mg/kg/day established in the chronic toxicity study in rats (MRID# 00154506) will be used for this risk assessment based on decreased body weight gains, food consumption, food efficiency and increased blood urea nitrogen. This study was also used to establish the RfD.

6. INHALATION EXPOSURE (for all above scenarios):

A risk assessment via this route is not required since the LC50 of > 42.8 mg/L/1 hour in an acute inhalation study, placed Thiobencarb in Toxicity Category IV.

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