4-10-97

114501, TE2

TOXICOLOGY ENDPOINT SELECTION DOCUMENT

REVISED APRIL 10, 1997

Chemical Name: **THIODICARB**

PC Code: 114501

Structure

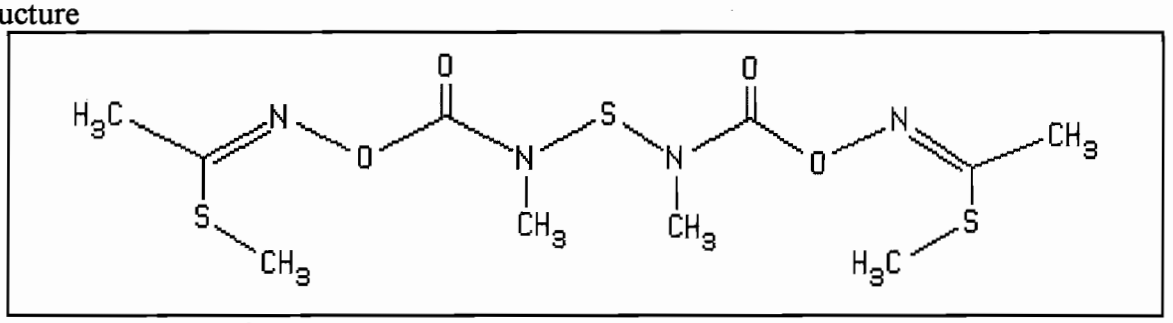

Figure 1 Thiodicarb

The Health Effects Division Toxicology Endpoint Selection Committee considered the available toxicology data for THIODICARB at a meeting held on April 23, 1996. Based upon a review of the toxicology database for the chemical listed above, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below. A brief capsule of the study is presented for use in preparation of risk assessments.

Where no appropriate data have been identified or a risk assessment is not warranted, this is noted. Data required to describe the uncertainties in the risk assessment due to the toxicology database are presented. These include but are not limited to extrapolation from different time frames or conversions due to route differences. If route to route extrapolation is necessary, the data to perform this extrapolation are provided.

TOXICOLOGIST: Linda L. Taylor, Ph.D._____ Date: _____

SECTION HEAD: K. Clark Swentzel _____ Date: _____

BRANCH CHIEF: Yiannakis M. Ioannou, Ph.D. _____ Date: _____

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DERMAL ABSORPTION DATA

MRID: There are no dermal absorption data available; no study was located.

The NOEL of the developmental toxicity [oral] study in rabbits [20 mg/kg/day] was compared to the 21-day dermal toxicity study in the same species [1000 mg/kg/day], which indicates a dermal absorption of approximately 2%. This estimation of low dermal absorption is supported by the lack of systemic toxicity in the 21-day dermal study. .

% absorbed: 2% [estimated]

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ACUTE DIETARY ENDPOINT (ONE DAY) - Females 13+ years

Study Selected - Guideline No.: §83-3(a); OPPTS 870.3700

MRID No.: Accession No.099377 and 099223

EXECUTIVE SUMMARY - Study 1: In a developmental toxicity study, Pregnant Fisher 344 rats were dosed via the diet either on (1) gestation days 6 to 15 or (2) gestation days 0-20 at dose levels of 0.5, 1.0, 3.0, and 100 mg Thiodicarb.

Maternal toxicity was observed at 100 mg/kg/day in the form of decreased body-weight gains [25-27% of control at day 12]. Pregnancy rate was decreased at the 3.0 [60%] and 100 [60 %] mg/kg/day, compared to the negative control [88%]. There were slightly fewer live fetuses per dam at 100 mg/kg/day following the 6-15 day exposure period compared to control. Resorptions were increased at the 100 mg/kg/day dose level following both exposure periods.

Developmental toxicity was observed at 100 mg/kg/day, as evidenced by the a slight, but statistically significant, decrease in both fetal body weight and body length relative to the control following the 0-20 day exposure period. Additionally, skeletal variations [bilobed thoracic vertebral centra] were increased at the 100 mg/kg/day dose level compared to the negative control following both exposure periods.

EXECUTIVE SUMMARY - Study 2: In a developmental toxicity study, Pregnant Charles River CD COBS rats were dosed via gavage once a day on gestation days 6 through 19 at dose levels of 0 [vehicle 0.5% methocel], 10, 20, and 30 mg technical grade UC 51762/kg/day.

Maternal toxicity was observed at the 20 and 30 mg/kg/day dose levels, as evidenced by inactivity, tremors, and a clear oral discharge observed for 1-4 hours post dose.

Developmental toxicity was observed at all dose levels. There was a dose-related decrease in fetal body weight [89%, 75%, and 69% of control at 10, 20, and 30 mg/kg/day, respectively] that was statistically significant at all dose levels. There was a dose-related
increase in the number of litters and fetuses with developmental variations [unossification of the

hyoid, sternebrae #5 and/or #6 and other sternebrae], and increases in reduced ossification of the skull and vertebrae and unossification of the pubis and entire sternum were observed at the 20 and 30 mg/kg/day dose levels.

The maternal NOEL is 10 mg/kg/day, the LOEL is 20 mg/kg/day, based on clinical signs [tremors, inactivity]. A developmental toxicity NOEL is 3 mg/kg/day, and the LOEL is 10 mg/kg/day, based on skeletal variations and decreases in pup body weights.

Dose and endpoint for use in risk assessment: Developmental NOEL = 3 mg/kg/day based on skeletal variations and decreases in pup body weights at 10 mg/kg/day.

Comments about study and/or endpoint: Although there were deficiencies in both studies, if the data from both exposure periods in the first study are combined with the data from the second study, the NOEL is supported by these two developmental toxicity studies in rats, when considered together. Also considered subsequent to the original TES document and RfD was the issue of additional sensitivity to offspring following pre- and/or postnatal exposure to Thiodicarb. It was determined that since there is no unequivocal evidence of additional sensitivity, the use of an additional uncertainty factor is not recommended.

This risk assessment is required.

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ACUTE DIETARY ENDPOINT (ONE DAY) - General Population [including infants and kids]

Study Selected - Guideline No.: §83-3(a); OPPTS 870.3700

MRID No.: Accession No.099377 and 099223

EXECUTIVE SUMMARY - Study 1: In a developmental toxicity study, Pregnant Fisher 344 rats were dosed via the diet either on (1) gestation days 6 to 15 or (2) gestation days 0-20 at dose levels of 0.5, 1.0, 3.0, and 100 mg Thiodicarb.

Maternal toxicity was observed at 100 mg/kg/day in the form of decreased body-weight gains [25-27% of control at day 12]. Pregnancy rate was decreased at the 3.0 [60%] and 100 [60 %] mg/kg/day, compared to the negative control [88%]. There were slightly fewer live fetuses per dam at 100 mg/kg/day following the 6-15 day exposure period compared to control. Resorptions were increased at the 100 mg/kg/day dose level following both exposure periods.

Developmental toxicity was observed at 100 mg/kg/day, as evidenced by the a slight, but statistically significant, decrease in both fetal body weight and body length relative to the control following the 0-20 day exposure period. Additionally, skeletal variations [bilobed thoracic vertebral centra] were increased at the 100 mg/kg/day dose level compared to the negative control following both exposure periods.

EXECUTIVE SUMMARY - Study 2: In a developmental toxicity study, Pregnant Charles River CD COBS rats were dosed via gavage once a day on gestation days 6 through 19 at dose levels of 0 [vehicle 0.5% methocel], 10, 20, and 30 mg technical grade UC 51762/kg/day.

Maternal toxicity was observed at the 20 and 30 mg/kg/day dose levels, as evidenced by inactivity, tremors, and a clear oral discharge observed for 1-4 hours post dose.

Developmental toxicity was observed at all dose levels. There was a dose-related decrease in fetal body weight [89%, 75%, and 69% of control at 10, 20, and 30 mg/kg/day, respectively] that was statistically significant at all dose levels. There was a dose-related increase in the number of litters and fetuses with developmental variations [unossification of the hyoid, sternebrae #5 and/or #6 and other sternebrae], and increases in reduced ossification of the skull and vertebrae and unossification of the pubis and entire sternum were observed at the 20 and 30 mg/kg/day dose levels.

The maternal NOEL is 10 mg/kg/day, the LOEL is 20 mg/kg/day, based on clinical signs [tremors, inactivity]. A developmental toxicity NOEL is 3 mg/kg/day, and the LOEL is 10 mg/kg/day, based on skeletal variations and decreases in pup body weights.

Dose and endpoint for use in risk assessment: Maternal NOEL =10 mg/kg/day based on clinical signs [tremors, inactivity] at 20 mg/kg/day (LOEL).

Comments about study and/or endpoint: Although there were deficiencies in both studies, if the data from both exposure periods in the first study are combined with the data from the second study, the NOEL is supported by these two developmental toxicity studies in rats, when considered together.

This risk assessment is required.

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

Study Selected - Guideline No.: None

MRID No.:N/A

Summary:None

Endpoint and dose for use in risk assessment: Not applicable

Comments about study and/or endpoint: No appropriate endpoint was identified. No treatment-related effects were observed at 1000 mg/kg/day in a 16-day repeated dose dermal toxicity study in rabbits or at 1000 mg/kg/day in a 21-day dermal toxicity study in rats (Accession Nos. 071181 and 044967).

This risk assessment is NOT required

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

Study Selected - Guideline No.: None

MRID No.: None

Summary: None.

Dose and endpoint for use in risk assessment : Not applicable

Comments about study and/or endpoint: See Short-Term

This risk assessment is Not required.

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CHRONIC OCCUPATIONAL OR RESIDENTIAL EXPOSURE (SEVERAL MONTHS TO LIFETIME)

Study Selected - Guideline No.: §83-1/§83-2

MRID No.: 43308201 and 43000501

EXECUTIVE SUMMARY: Sprague-Dawley rats were fed Thiodicarb for 105 weeks at dose levels of 0, 60 ppm [♂♂ 3.3/♀♀ 4.5 mg/kg/day], 200 ppm [♂♂ 12/♀♀ 15 mg/kg/day], and 900 ppm [♂♂ 60/♀♀ 80 mg/kg/day]. The systemic NOEL is 60 ppm [♂♂ 3.3/♀♀ 4.5 mg/kg/day], and the LOEL is 200 ppm ♂♂ 12/♀♀ 15 mg/kg/day], based on the increased incidence of extramedullary hemopoiesis in males and decreased RBC cholinesterase in females.

Charles River CD®-1 mice of both sexes were administered Thiodicarb in the diet at dose levels of 5, 70, and 1000 mg/kg/day for 97 weeks . The NOEL is 70 mg/kg/day, the LOEL is 1000 mg/kg/day, based on increased mortality, decreased body-weight gain [males], decreased hemoglobin, hematocrit, and RBCs, increased liver and spleen size, and increased incidence of non-neoplastic lesions in the kidney, liver, and spleen. However, as per the HED Carcinogenicity Peer Review Committee recommendation, the MOE should be based on the NOEL of 5 mg/kg/day as the point of departure for liver tumors.

Dose and endpoint for use in risk assessment: NOEL = 3 mg/kg/day, based on the increased incidence of extramedullary hemopoiesis in males and decreased RBC cholinesterase in females.

Comments about study and/or endpoint: This dose was used to establish the RfD. Since a NOEL from an oral study was used, a dermal absorption factor of 2% should be used in the calculations. The dose [3 mg/kg/day] identified here should be used for non-carcinogenic effects. A dose of 5 mg/kg/day should be used for carcinogenic effects [see Cancer Classification on page 8].

This risk assessment is required.

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INHALATION EXPOSURE [any time period]:

Study Selected - Guideline No.: none; 9-day inhalation study; not a guideline study

MRID No.: None; HED Document # 003706

Executive Summary: In a 9 day dust inhalation study, Hilltop Sprague-Dawley rats were exposed to Thiodicarb via repeated inhalation [6 hours/day for 9 days at mean measured atmospheric concentrations of ♂♂ 0.00595/♀♀ 0.0054, ♂♂ 0.00177/♀♀ 0.00196, and ♂♂ & ♀♀ 0.0048 mg/L. A NOEL was not determined. Clinical signs associated with cholinesterase effects [pinpoint pupils and tremors] were observed in both sexes. No significant differences from control were observed in plasma, RBC, and brain cholinesterase at the low- and mid-dose levels.

Dose and endpoint for use in risk assessment: LOEL = 0.0048 mg/L, based on pinpoint pupils and tremors.

Comments about study and/or endpoint: This is a [**non-guideline**] 9-day study in which a NOEL was not determined. Use 100% inhalation for risk assessment.

This risk assessment is required.

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CANCER CLASSIFICATION AND BASIS: Thiodicarb was classified as a Group B2 - probable human carcinogen, based on increases in liver tumors in both sexes of the CD-1 mouse, statistically significant by both pair-wise and trend analysis and statistically- significant increases in testicular interstitial cell tumors in the male Sprague-Dawley rat. While there was low concern for mutagenicity, data from related structural analogs provided additional support.

The CPRC noted that while the highest dose in mice may have been excessive, the overall dose selection was improper with the highest dose [1000 mg/kg/day] more than 10-fold that of the mid-dose [70 mg/kg/day]. The CPRC also noticed that there was a suggestive tumor response in the male mouse liver even at the mid-dose, and the incidence exceeded that of historical controls. Additionally, the tumor incidences were unusually high [hepatocellular combined adenoma/carcinoma at the highest dose was 76% vs 18% in the controls for males and 62% vs 2% in the controls for females].

Q_1* = none. The CPRC felt it was inappropriate to apply a linear low-dose extrapolation to the animal data because the increased incidences of tumors were statistically significant only at the highest dose in both species; in the case of the mice, the highest dose may even have been excessive. In addition, there was no evidence of genotoxicity. Therefore, for the purposes of risk characterization, the CPRC recommended that a non-linear methodology [MOE] be applied for the estimation of human risk, based on the hepatocellular combined adenoma/carcinoma in male mice, with the point of departure set at the 5 mg/kg/day dose [NOEL].

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RfD AND BASIS: The RfD was calculated to be 0.03 mg/kg/day, based on the NOEL of the 1994 rat chronic study. The LOEL was 12 ♂♂/15 ♀♀ mg/kg/day, based on increased incidence of extramedullary hemopoiesis in males and decreased red blood cell cholinesterase activity in females.

NOEL for critical study: 3.3 mg/kg/day [rat] and 5 mg/kg/day [mouse]

Study Type - Guideline No.: Chronic rat §83-1 and Carcinogenicity mouse §83-2

MRID: 43308201 and 43000501

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ACUTE TOXICITY ENDPOINTS:

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral - rat	071181	LD_{50} = ♂♂ 46.5/♀♀ 39.1 to ♂♂ 398/♀♀ 248 mg/kg	I II
81-2	Acute Dermal - rabbit	44025501	LD_{50} > 2000 mg/kg	III
81-3	Acute Inhalation - rat	099581/099224	LC_{50} = ♂♂ 0.126/ ♀♀ 0.115 mg/L > 0.32 mg/L [dust]	II II
81-4	Primary Eye Irritation rabbit	44025502	Slight irritant	III
81-5	Primary Skin Irritation rabbit	44025503	Non-irritant	IV
81-6	Dermal Sensitization guinea pig human	071181 41891004 43373201	negative in guinea pig; positive in human volunteers [10 occlusive applications over 3 weeks irritation 2+ (erythema & mild edema) during induction phase] weak dermal sensitivity reaction	- -
81-8	Acute Neurotoxicity	044962	negative	-