103801.TE2 10-15-96

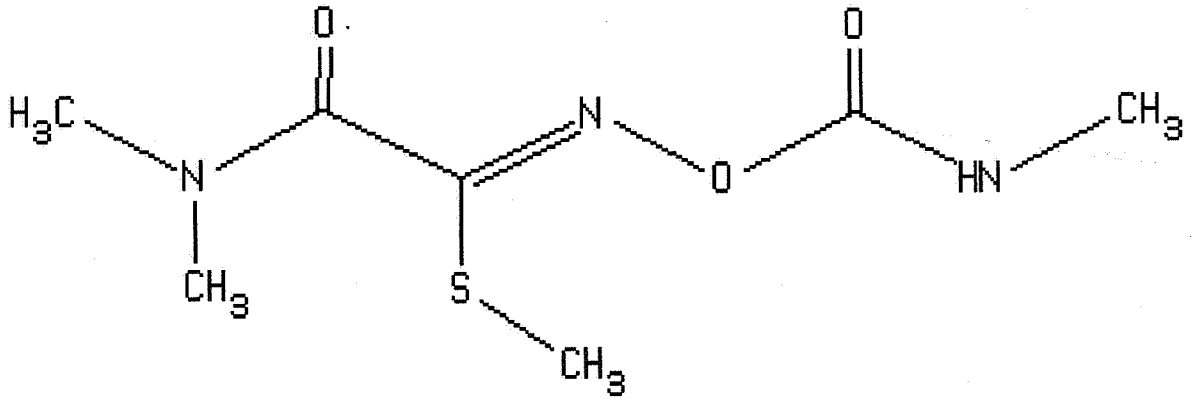
TOXICOLOGY ENDPOINT SELECTION DOCUMENT

REVISED 10/15/96

Chemical Name: Oxamyl

PC Code: 103801

Structure



The Health Effects Division Toxicology Endpoint Selection Committee considered the available toxicology data for oxamyl at a meeting held on 8/27/96. 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. **This revision reflects the use of extra Uncertainty Factors for both the acute and chronic dietary exposure 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: _____ Date: _____
Whang Phang

SECTION HEAD: _____ Date: _____
James Rowe

BRANCH CHIEF: _____ Date: _____
Mike Ioannou

DERMAL ABSORPTION DATA: Not applicable for short- and intermediate-term dermal exposure risk assessments since a NOEL from a 21-day dermal toxicity study was selected. However, for chronic dermal exposure risk assessment, a dermal absorption factor of 100% should be used since the NOEL was selected from a developmental toxicity study in which the route of administration was oral. Dermal absorption of 100% was selected due to lack of dermal absorption studies as well as scaling of the skin seen in the 21-day dermal toxicity study (i.e., following repeated application), a condition likely to occur during repeated application/exposure.

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ACUTE DIETARY ENDPOINT (ONE DAY)

Study Selected - Developmental Toxicity - rat (Guideline No.: 83-3a)

MRID No.: 40859201

Summary: In a rat developmental toxicity study, groups of pregnant Crl:CD BR rats (25/dose group) received oxamyl by gavage at doses of 0, 0.2, 0.5, 0.8, and 1.5 mg/kg/day from gestation day 7 to 16. On gestation day 22, the fetuses were delivered with cesarean section, and the dams were sacrificed. Under the conditions of the study, maternal toxicity was seen at 0.8 mg/kg/day and above as indicated by a decrease in maternal body weight and food consumption. An increase in the clinical signs (tremors), which were associated with cholinesterase inhibition. A decrease in fetal body weight was seen at 0.5 mg/kg/day and above. No increase in the incidence of structural malformations or variations was seen in the treated groups relative to the controls. The LEL for maternal toxicity was 0.8 mg/kg/day; maternal NOEL, 0.5 mg/kg/day. The LEL for developmental toxicity was 0.5 mg/kg/day based on the decrease in fetal body weights. The developmental NOEL was 0.2 mg/kg/day.

Dose and Endpoint for use in risk assessment: Maternal NOEL of 0.5 mg/kg/day based on cholinergic signs (tremors) observed in dams at 0.8 mg/kg/day (LOEL).

Comments about dose/study: For calculating the MOE, an extra safety factor of 10 will be used in addition to the 100 (i.e., MOE = 1000) due to the lack of acute and subchronic neurotoxicity data (data gaps) as well as the severity of effects (tremors and ChE inhibition) seen in dams at the 0.8 mg/kg/day dose.

This risk assessment is required.

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

Study Selected - 21- Day Dermal Toxicity Study (Guideline No.: 82-2)

MRID No.:40827601

Summary: In a 21-day dermal toxicity study, groups of New Zealand white rabbits (5/sex/dose for 2.5 and 50 mg/kg/day; 10 sex/dose for controls and 250 mg/kg/day) received oxamyl by dermal application at dose levels of 0, 2.5, 50, and 250 mg/kg/day. The test material was mixed with water and applied as a paste onto the shaved skin for 6 hours/day for 22 consecutive days. At 50 and 250 mg/kg/day, both males and females showed significant decreases in plasma, red blood cell and brain cholinesterase activity. In addition, there was an increase in serum glucose level in 250 mg/kg/day males and females. Based on the decrease in cholinesterase activity, the LEL was 50 mg/kg/day; NOEL, 2.5 mg/kg/day.

Dose and endpoint for use in risk assessment: NOEL of 2.5 mg/kg/day based on inhibition of red blood cell, plasma and brain ChE activity at 50 mg/kg/day (LOEL).

Comments about dose/study: None.

This risk assessment is required.

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

Study Selected - 21-Day Dermal Toxicity (Guideline No.: 82-2)

MRID No.: 40827601

Summary: See Short-term

Dose and Endpoint for use in risk assessment: NOEL of 2.5 mg/kg/day based on inhibition of red blood cell, plasma and brain ChE activity at 50 mg/kg/day (LOEL).

Comments about dose/study: None.

This risk assessment is required.

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CHRONIC OCCUPATIONAL OR RESIDENTIAL EXPOSURE (SEVERAL MONTHS TO LIFETIME)

Study Selected - Guideline No.: Developmental Toxicity - Rats (Guideline No. 82-3a)

MRID No.: 40859201

Summary: Same as the summary in "Acute Dietary"

Dose and Endpoint for use in risk assessment: NOEL of 0.2 mg/kg/day based on decreased fetal body weights in 0.5 mg/kg/day group.

Comments about dose/study: This study was used to establish the RfD. For calculating the MOE, an extra safety factor of 10 will be used in addition to the 100 (i.e., MOE = 1000) due to the lack of acute and subchronic neurotoxicity data (data gaps) as well as the severity of the effects seen in the developmental toxicity study (tremors and ChE inhibition) at a dose of 0.8 mg/kg/day. Since the dose selected was from an oral study, the dermal absorption rate of 100% should be used for this risk assessment.

This risk assessment is required.

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INHALATION EXPOSURE (ANY TIME PERIOD):

Based on the LC_{50} values of 0.12 mg/L and 0.064 mg/L after 1-hour and 4-hour exposures, oxamyl is placed in Toxicity Category I and II, respectively. Therefore, this risk assessment for inhalation exposure is required.

Study Selected - 21-Day Dermal Toxicity - Rat (Guideline No. 82-2)

MRID No.: 40827601

Summary: See Short-term

Dose and Endpoint for use in risk assessment: NOEL of 2.5 mg/kg/day based on inhibition of red blood cell, plasma and brain ChE activity at 50 mg/kg/day (LOEL).

Comments about dose/study: The combined risk resulting from dermal and inhalation exposure to oxamyl may be calculated by combining MOEs for these routes. The following equation should be used to calculate a total MOE (**MOE_T**):

$$MOE_T = \frac{1}{\frac{1}{MOE_{dermal}} + \frac{1}{MOE_{inhalation}}}$$

This risk assessment is required.

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CANCER CLASSIFICATION AND BASIS: The cancer classification for oxamyl is E. The data on both rat and mouse carcinogenicity studies did not indicate a compound-related increase in tumor incidence.

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RfD AND BASIS:

NOEL for critical study: 0.2 mg/kg/day based on a decrease in fetal body weights in 0.5 mg/kg/day dose group.

Study Type - Guideline No.: 83-3a

MRID: 40859201

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ACUTE TOXICITY ENDPOINTS:

Acute Toxicity of Oxamyl

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	00063011	LD_{50} = 3.1 mg/kg (M); 2.5 mg/kg (f)	I
81-2	Acute Dermal	40606501	LD_{50} >5000 mg/kg (M) >2000 mg/kg (F) For abraded skin 90 mg/kg produced death with 50% a.i. in water.	IV
81-3	Acute Inhalation	00066902 00066902	LC_{50} =0.064 mg/L (4 hr) 0.17 mg/L (M) 0.12 mg/L (F) (1 hr)	II I
81-4	Primary Eye Irritation	00066984	Marked pupillary constriction, conjuctival irritation, reversible by 7 days.	III
81-5	Primary Skin Irritation	00066900	Minor irritation was found at the application site. Severe systemic toxicity was seen after application on the abraded skin	IV
81-6	Dermal Sensitization	00006690	4/7 animals died (25% test material) 1/5 animals died (intraderrmal injection). Effects seen on the test site were slight.	
81-8	Acute Neurotoxicity-hens 20 and 40 mg/kg as a 1% suspension; the hens were protected with 0.5 mg/kg atropine.	00066893	Clinical signs included: depression, lethargy, ruffled feathers, ataxia, incoordination, and slight respiratory difficulty. 12 hr. later all symptoms disappeared. No compound-related histological changes were found. No deaths occurred.	