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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PREVENTION, PESTICIDES, AND TOXIC SUBSTANCES
WASHINGTON, D.C. 20460

December 6, 1999

MEMORANDUM

SUBJECT: ***DIMETHOATE:*** **Addendum: Reevaluation of 5-Day Dermal Toxicity Study in Rats and the Short Term Dermal Endpoint Selection**

FROM: Paul Chin, Ph.D.
Reregistration Branch I
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Pauline Wagner, Co-Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Diana Locke, Risk Assessor
Reregistration Branch II
Health Effects Division (7509C)

PC Code: 035001

On July 8, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the 5-day dermal toxicity study in rats (MRID No. 44818902) and the NOAEL of 10 mg/kg/day was selected as the dose for short term dermal exposure risk assessment. The LOAEL of 20 mg/kg/day was based on a statistically significant reduction in plasma, RBC, and brain (cortex) ChE activity on days 3 or 5.

On Sep 28, 1999, the HIARC reevaluated the acceptability of the 5-day dermal toxicity study with dimethoate and its impact on the dose and endpoint selected for short-term dermal risk assessment. **HIARC made no changes to the conclusions reached at the July 8, 1999 meeting.** The issues discussed at this meeting is presented in this Addendum report.

ISSUE 1.

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Should the 5-day dermal toxicity study be used to select short term dermal exposure endpoint since this study used formulation (Dimethoate 4E (43.5% a.i.) instead of technical dimethoate? The current guideline states that the technical should be used.

HIARC DECISION

Dimethoate 4E is formulated in [redacted] and therefore, [redacted] Dimethoate 4E is also the highest formulation (43.5% a.i.) available in the U.S. Based on the particular solvent used in this dimethoate formulation and the relative high % a.i., the HIARC believes that use of the study for short-term dermal endpoint selection would not underestimate the potential risks to workers exposed to either a formulated product or the technical.

ISSUE 2.

Should the 5-day dermal toxicity study be used to select short term dermal exposure endpoint since this study used small and inconsistent volumes of dosing solution (ranging from 2 to 42 ul)?

HIARC DECISION

In the study with dimethoate, although test material was applied in a small volume (2-42 ul), it would have minimum effects on skin absorption because the report indicated that the small volume was distributed evenly on the prescribed application site. In addition, the RBC ChE inhibition data indicated a good dose response which indicated that absorption was not a factor.

A great deal of variability in the RBC ChE inhibition may be attributed to the small volume of test chemical applied onto the test site. **HIARC** discussed a similar dermal toxicity study conducted by the same registrant with a small volume of methyl parathion. The committee concluded that although the volume of carrier for dermal application was much higher than the dimethoate study, ChE data were much more variable in methyl parathion study compared to the dimethoate study. In addition, the committee also noted that variable ChE inhibition in the methyl parathion study might indicate variable absorption.

ISSUE 3.

Should the LOAEL for cholinesterase inhibition be lowered to 10 mg/kg/day from the previously selected LOAEL of 20 mg/kg/day? This study showed that in female rats treated at 20 mg/kg/day, there was a statistically significant reduction in plasma (**33%, $p<0.05$**, day 5), RBC (**35%, $p<0.05$**, day 3 and 5), and cortex (**21%, $p<0.01$**, day 5) ChE activity. At the next lower dose of 10 mg/kg/day there was a 30% inhibition of RBC and 8-10% inhibition of brain ChE. At 5 mg/kg/day there was a 20-25% inhibition of RBC and 3-9% inhibition of brain ChE. Although there were no statistical significance, there might be a biological significance because a dose-response relationship was shown in RBC ChE inhibition.

HIARC DECISION

Although there appears to be a dose-response relationship in RBC ChE inhibition, this relationship was not found in plasma and brain ChE inhibition (two other compartments). **Based on this observation, the previously selected LOAEL of 20 mg/kg/day remains unchanged. Therefore, HIARC made no changes on** doses and endpoints selected for dermal exposure risk assessments as presented in the HIARC Document (HED Doc. No. 013580) and summarized in the following table.

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Table 1. Toxicological endpoints for risk assessments with dimethoate

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL= 2.0 UF = 100	Absence of pupil response and lack of cholinesterase inhibition at 1-week and 3-week measurements	Acute Oral Neurotoxicity in Rats & 90-day studies
	Acute RfD = 0.02 mg/kg/day		
Chronic Dietary	NOAEL=0.05 UF = 100	RBC and brain cholinesterase inhibition	Chronic Toxicity/Carcinogenicity -Rat
	Chronic RfD = 0.0005 mg/kg/day		
Short-Term (Dermal) 1	Dermal NOAEL= 10.0	Plasma, RBC and Brain cholinesterase inhibition in female rats	5-Day Dermal Study in Female Rats
Intermediate-Term (Dermal) 2	Oral LOAEL=3.2	Plasma, RBC and Brain cholinesterase inhibition at 3 and 4 week intervals	90-Day Studies in Rats
Long-Term (Dermal)	None	The use pattern and exposure scenario do not indicate a need for long term risk assessment	
Short-Term (Inhalation) 3	Oral NOAEL= 2.0	Absence of pupil response and lack of cholinesterase inhibition at 1-week and 3-week measurements	Acute Oral Neurotoxicity in Rats & 90-day studies
Intermediate-Term (Inhalation) 4	Oral LOAEL =3.2	Plasma, RBC and Brain cholinesterase inhibition at 3 and 4 week intervals	90-Day Studies in Rats
Long Term (Inhalation)[1]	None	The use pattern and exposure scenario do not indicate a need for long term risk assessment.	

1. A MOE of 100 is adequate.
2. Oral value was selected therefore 11% dermal absorption factor should be used for route-to-route extrapolation. Also, a MOE of 300 is required for use of a LOAEL.
3. Oral value was selected therefore 100% inhalation absorption factor should be used for route-to-route extrapolation. A MOE of 100 is adequate.
4. Oral value was selected therefore 100% inhalation absorption factor should be used for route-to-route extrapolation must be used. Also, a MOE of 300 is required for use of a LOAEL.