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

013834

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: November 8, 1999

MEMORANDUM

SUBJECT: **Methidathion** - REVISED Report of the Hazard Identification Assessment Review Committee

FROM: Susan L. Makris *Susan L Makris*
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THROUGH: Jess Rowland, Chairman, *Jess Rowland 11/8/99*
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Robert Travaglini
Reregistration Branch 3
Health Effects Division (7509C)

PC Code: 100301

On October 28, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee reevaluated the 1986 21-day dermal toxicity study in rabbits with **Methidathion**, reassessed the toxicological endpoints selected for occupational/residential exposure risk assessments, and reevaluated the dermal absorption factor. The Committee's conclusions are presented in this report.

Committee Members in Attendance

Members present were: Jess Rowland (chair), Bill Burnam, Pamela Hurley, Mike Ioannou, Tina Levine, Susan Makris, Nicole Paquette, and PV Shah. Member(s) in absentia: Brenda Tarplee (Executive Secretary), Virginia Dobozy, Kathleen Raffaele, and Pauline Wagner. Data were presented by Susan Makris (RRB4).

Also in attendance were: Gary Banks (RRB3), Michael Goodis, chemical review manager (SRRD).

Data Presentation:
and
Report Presentation

Susan L. Makris

Susan L. Makris
Toxicologist

I. INTRODUCTION

Methidathion, an organophosphate pesticide, has been previously evaluated for the selection of toxicology endpoints for dietary and occupational/residential risk assessment. The most recent HED peer review reports available at the time of the 10/28/99 HIARC meeting included a Toxicity Endpoint Selection document (6/4/96), a HIARC report on methidathion (10/8/97), the HIARC report titled *Hazard Assessment of the Organophosphates* (7/7/98), and a HIARC reevaluation report (3/9/99).

The Registrant, Gowan, submitted a response, dated July 1, 1999, addressing the critical studies and endpoints that HED had selected for use in the short- and intermediate-term dermal risk assessment for methidathion. In brief, Gowan disagreed with the default to a 90-day feeding study in rats, with a dermal absorption factor, for the intermediate-term dermal risk assessment. Additionally, Gowan stated that the NOAEL for the 1986 21-day dermal study in rabbits should be 20 mg/kg/day, not 5 mg/kg/day as indicated by the March 9, 1999 HIARC report. These issues are addressed more fully in the applicable segments of the following HIARC report.

II. HAZARD IDENTIFICATION

A. Acute RfD

An acute dietary endpoint was not reevaluated by the HIARC at this meeting.

The acute RfD was derived from the NOAEL of 0.2 mg/kg/day established in a 90-day study in rats based on inhibition of plasma and red blood cell and brain cholinesterase activity at 0.6 mg/day (LOAEL). The acute neurotoxicity study was not selected for acute dietary risk assessment, since a NOAEL was not identified. However, the 1996 TES document states that the NOAEL (0.2 mg/kg/day) and endpoint (cholinesterase inhibition), which were derived from the subchronic neurotoxicity study, are supported by the results of the acute neurotoxicity study. In this study, the LOAEL was 1.0 mg/kg, based upon a 41% decreased in brain (cerebral cortex) cholinesterase activity at 1.0 mg/kg after two weeks and cholinergic signs at 4 mg/kg/day. An uncertainty factor (UF) of 100 (for inter- and intraspecies variability) was applied to the NOAEL.

$$\text{Acute RfD} = \frac{0.2 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = 0.002 \text{ mg/kg}$$

B. Chronic RfD

The chronic dietary endpoint was not reevaluated by the HIARC at this meeting.

The Chronic RfD was derived from the NOAEL of 0.15 mg/kg/day established in a chronic toxicity study in dogs based on red blood cholinesterase inhibition and hepatic toxicity observed at 1.33 mg/kg/day (LOAEL). An UF of 100 was applied to the

NOAEL.

$$\text{Chronic RfD} = \frac{0.15 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = 0.0015 \text{ mg/kg/day}$$

C. Occupational/Residential Exposure

1. Dermal Absorption

Dermal Absorption Factor: 30%

A dermal absorption factor is required since oral values were selected for Intermediate- and Long-term dermal risk assessments. The history of the discussions regarding the appropriate dermal absorption factor follows.

On December 3, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology database of 16 organophosphates, including methidathion, to determine if the 100% dermal absorption factor for use in occupational and/or residential dermal exposure risk assessments is appropriate.

The comparison of the results from the oral and dermal studies yielded conflicting data. In the oral developmental toxicity study in rabbits, the LOAEL was 12 mg/kg/day, the highest dose tested, based on cholinergic signs. Dermal studies in rabbits produced conflicting results: in one study, in which the exposure was to the occluded skin, the LOAEL was 1 mg/kg/day based on mortality and cholinesterase inhibition; whereas, in another study in which exposure was to non-occlusive skin, the LOAEL was 20 mg/kg/day based on decreases in body weight gain and hypoactivity in one male. Comparison of the Acute Oral LD₅₀ (46 mg/kg) and Dermal LD₅₀ (1663 mg/kg) values in rats indicates dermal absorption to be approximately 3%. Comparison of the Acute Oral LD₅₀ (80 mg/kg) and Dermal LD₅₀ (640 mg/kg) values in rabbits indicates dermal absorption to be approximately 13%. Therefore, the Committee decided to retain the 100% dermal absorption factor pending re-evaluation of the dermal toxicity studies.

On February 23, 1999 the HIARC evaluated the results of the two 21-day dermal toxicity studies and discounted the 1987 study because the exposure was to the occluded skin which resulted in mortality and severe cholinesterase inhibition at the lowest dose tested. The Committee determined that the 1986 study (non-occluded) was appropriate for use in estimating a dermal absorption factor. The Committee concluded that a 60% dermal absorption value was appropriate for methidathion. This decision was based upon the reevaluation of the oral and dermal data associated with the rabbit developmental study and the 21-day dermal

toxicity study in rabbits. Comparisons of LOAELs in the oral developmental toxicity (12 mg/kg/day, based on cholinergic signs) and 21-day dermal toxicity studies (20 mg/kg/day, based on decreased BW/BWG and hypoactivity in one male) in rabbits resulted in a 60% dermal absorption value. Cholinesterase activity was measured only in the 21-day dermal study (not in the developmental study), and inhibition was not observed.

It was recognized that 60% may be somewhat of an overestimate of dermal absorption for the technical grade product, since the physical/chemical properties of the technical (i.e., low melting point and good water solubility) would argue for moderate dermal absorption. It was also noted that the emulsifiable concentrate (EC) formulation is severely irritating to the skin, which would greatly enhance absorption.

At the HIARC meeting of October 28, 1999, the Committee determined that the NOAEL for the 1986 21-day dermal toxicity study in rabbits (MRID 40079804) was 20 mg/kg/day (the HDT), rather than 5 mg/kg/day as previously assessed. Discussion of this decision is presented in more detail below, in the section on short-term dermal risk assessment. Since this 21-day dermal study had been used in the calculation of the 60% dermal absorption factor, as described above, this issue was readdressed by the HIARC. After reviewing all information presented above, the HIARC determined that the most appropriate calculation of the dermal absorption factor would be based upon a comparison of the NOAELs from the oral developmental toxicity study in rabbits (6 mg/kg/day) and the 1986 21-day dermal toxicity study in rabbits (20 mg/kg/day), to yield a dermal absorption factor of 30%. It is recognized that there are some limitations in the accuracy achieved when comparing the no-adverse-effect levels in these particular studies, since comparable endpoints were not identified at the LOAELs (the NOAEL in the dermal study was based upon the absence of cholinesterase inhibition, while this endpoint was not measured in the oral developmental study and the LOAEL was based on cholinergic clinical signs of toxicity). Nevertheless, this calculation was believed to result in a conservative, yet reasonable, estimate of dermal absorption.

2. Short-Term Dermal - (1-7 days)

Study Selected: 21-Day Dermal in Rabbits - §82-2

MRID No.: MRID 40079804

Executive Summary: In a 21-day dermal toxicity study in New Zealand White rabbits (MRID 40079804), methidathion technical was administered at doses of 1, 5, or 20 mg/kg/day (in PEG 300) by dermal application for 6 hours/day under a non-occlusive dressing. The rabbits were examined daily for signs of toxicity, dermal irritation, and mortality. Body weight and food consumption data were

recorded weekly. Blood was collected pretest and at day 19 for the evaluation of hematology and clinical chemistry parameters, including plasma and erythrocyte cholinesterase levels; brain cholinesterase levels were measured at termination (day 22 or 23). Postmortem examination consisted of a gross necropsy, selected organ weights, and histopathological examination of numerous tissues.

There were no treatment-related mortalities. No evidence of cholinesterase inhibition was noted at any dose level. No treatment-related findings were observed at postmortem examination. At 20 mg/kg/day, clinical signs were limited to hypoactivity on treatment days 6-19 in one male, and a non-statistical decrease in body weight (5%) and body weight gain (18%) was noted in the males at 20 mg/kg/day throughout the study. In the absence of cholinesterase inhibition, these findings were not considered to be related to treatment. The NOAEL was 20 mg/kg/day; no LOAEL was identified.

Dose and Endpoint for Risk Assessment: NOAEL of 20 mg/kg/day, the highest dose tested (HDT).

Comments about Study/Endpoint: The HIARC determined that the NOAEL of 20 mg/kg/day from the 1986 21-day dermal toxicity study in rabbits is appropriate for assessing risks for handlers (mixers, loaders, applicators, and flaggers), since the route (dermal) and the duration (21-days) of exposure is appropriate for the handler exposure period of concern (up to 30 days).

The history of previous considerations follows:

In the past, the 1986 21-day dermal toxicity study was not selected by the HIARC because of the apparent discrepancy between the results of this study and another 21-day dermal study in rabbits conducted in 1987. In the 1987 study, the systemic LOAEL was established at the LDT of 1 mg/kg/day, based upon mortality and clinical signs consistent with ChEI (anorexia, ataxia, bloated, hunched, languid, altered respiration, and soft feces) in males. The ChEI NOEL was 1 mg/kg/day, based upon inhibition of plasma, RBC, and brain ChE at 10 mg/kg/day. However, the use of occlusive wraps in the 1987 study compromised the results of that study, and it was graded Supplementary. The rubber dams likely increased dermal permeability, and may have additionally induced stress-related reactions in the animals. For that reason, and since an occluded dermal exposure scenario is not applicable to potential human exposure to methidathion, the HIARC determined that the 1987 study should not be used to support the use of an oral NOAEL for dermal risk assessment (02/23/99).

It was believed that the 90-day dietary rat study, with a NOAEL of 0.2 mg/kg/day, which had been previously selected by the Toxicology Endpoint Selection Committee for short-term dermal risk assessment,

appears to provide an overly conservative estimate of hazard response following dermal exposure to methidathion.

There were some concerns expressed by Committee members that the rat may be more sensitive to methidathion exposure than the rabbit, and that the assessment of rabbit dermal toxicity may be somewhat compromised by the need for metabolic activation. However, these concerns were not considered to be quantifiable, and were thought to be adequately addressed by the use of a 100-fold margin of exposure.

The HIARC had previously rejected the Registrant's contention that a ChEI NOEL of 20 mg/kg/day from the 1986 21-day dermal study should be used in dermal risk assessment because cholinesterase inhibition has been determined to be the common endpoint for risk assessment of cumulative effects. However, at the 10/28/99 meeting, the HIARC reevaluated the scientific validity of the designated study NOAEL (5 mg/kg/day) and LOAEL (20 mg/kg/day). Consideration of the individual animal data for this study suggested that the findings at 20 mg/kg/day were not adequate to support the study LOAEL, as previously determined. Clinical observations were minimal and occurred only in one male rabbit; decreased body weight values were not statistically significant in high-dose males, as compared to controls, and a high degree of variability was observed in the body weight gain data. In addition, there was no cholinesterase inhibition observed in either male or female rabbits at any treatment level. The Committee decided that the NOAEL should be established at the HDT of 20 mg/kg/day.

This risk assessment is required.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: 90-day neurotoxicity study in rats - §82-7

MRID No.: 43582501

Executive Summary: When methidathion was administered for 90 days in the diet to male and female Sprague Dawley rats at dose levels of 0, 3, 10, 30, or 100 ppm (equal to 0.2, 0.6, 1.9, or 6.3 mg/kg/day for males and 0.2, 0.7, 2.0, or 7.2 mg/kg/day for females), the compound was associated with effects on the FOB in females, only at levels which exceeded the LOAEL for systemic toxicity. The NOAEL was 3 ppm (0.2 mg/kg/day) and the LOAEL was 10 ppm (0.6 mg/kg/day) based on statistically and biologically significant decreases in red blood cell, serum, and central nervous system cholinesterase inhibition.

Dose/Endpoint for Risk Assessment: NOAEL of 0.2 mg/kg/day, based on statistically and biologically significant decreases in plasma, RBC, and brain cholinesterase at 0.6 mg/kg/day.

Comments about Study/Endpoint: At the 3/9/99 HIARC meeting, it was determined that the most current available information indicated that occupational exposure of up to 180 days might be anticipated. For that reason, the 21-day dermal study in rabbits (selected for short-term risk assessment) was not considered to be of adequate duration for this exposure scenario (i.e., intermediate-term). On the other hand, the 90-day dietary study is considered to be adequate to assess effects of longer term exposure since a comparison of the cholinesterase inhibition observed in the 90-day study and the 2-year chronic study in rats indicate that a steady state in this parameter has been attained by 90 days.

At the 10/28/99 meeting, the HIARC considered a registrant response indicating that applicator exposure intervals could not attain 180 days; postapplication activities were not specifically addressed in this response document. The HIARC determined that the NOAEL from the 21-day dermal study in rabbits is not appropriate for assessing the potential post-application exposure risk. The HIARC selected the oral NOAEL of 0.2 mg/kg/day established in the subchronic rat study as appropriate because: 1) the principal toxicological endpoint (cholinesterase inhibition, ChEI) was observed following a longer exposure (90 days) in this study (no ChEI was seen in the dermal study); 2) the NOAELs in the 2-year chronic toxicity (0.2 mg/kg/day) and the two generation reproduction studies in rats (0.25 mg/kg/day) are comparable to the NOAEL of 0.2 mg/kg/day in the subchronic study; 3) exposures of 30 days or more are considered highly likely for post-application activities; and 4) in the absence of a long-term dermal toxicity study, a lower NOAEL is used for the protection of worker health.

Since an oral value was selected, a dermal absorption factor of 30% should be used for this risk assessment.

This risk assessment is required.

4. Long-Term Dermal (Several Months to Life-Time)

The long-term dermal endpoint was not reevaluated by the HIARC at this meeting.

The current use pattern does not indicate a concern for long-term dermal exposure. However, should a concern arise, the HIARC (3/0/99) had reaffirmed the TES Committee's selection of an oral value for this exposure risk assessment.

The long-term dermal risk assessment would be based upon the NOAEL of 0.15 mg/kg/day established in a chronic toxicity study in dogs, based on red blood cell cholinesterase inhibition and hepatic toxicity observed at 1.33 mg/kg/day (LOAEL).

This risk assessment is not required for the current use pattern..

5. Inhalation Exposure (any time period)

The inhalation exposure endpoints were not reevaluated by the HIARC at this meeting.

The database for methidathion contains only acute inhalation toxicity studies with two formulated products, (22.6% methidathion, LC50 (F) = 0.167 mg/L and 25% methidathion, LC50 (F) = 0.11 mg/L). Therefore, the HIARC selected the oral NOAEL of 0.2 mg/kg/day established in the 90-day neurotoxicity study in rats. Since an oral value was selected, the following route-to-route extrapolation should be used.

Step I. Convert the inhalation exposure component ($\mu\text{g a.i./day}$) using 100% absorption rate (default value) and application rate should be converted to an **equivalent oral dose** (mg/kg/day) and compared to the oral NOAEL of 0.2 mg/kg/day.

NOTE: Dermal and Inhalation exposures should not be combined since there is not a common toxicological endpoint of concern.

This risk assessment is required.

D. Margin of Exposure for Occupational/Residential Risk Assessments

A MOE of 100 is adequate for occupational and residential dermal and inhalation exposure risk assessments. The FQPA safety factor was removed for methidathion by the FQPA Safety Factor Committee on June 15, 1998.

E. Recommendation for Aggregate (Food, Water and Dermal) Exposure Risk Assessments

There are no residential uses, therefore, aggregate risk assessment is limited to food and water.

III. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL = 0.2	Plasma, RBC and brain cholinesterase inhibition	90-Day Neurotoxicity-Rat
	UF= 100	Acute RfD = 0.002 mg/kg	
Chronic Dietary	NOAEL= 0.15	Erythrocyte cholinesterase inhibition and liver lesions	1-Year Toxicity-Dog
	UF=100	Chronic RfD = 0.0015 mg/kg/day	
Short-Term (Dermal)	Dermal NOAEL = 20	No toxicity observed at HDT	21- Day Dermal Toxicity- Rabbit
Intermediate-Term (Dermal) ^a	Oral NOAEL=0.2	Plasma, RBC and brain cholinesterase inhibition	90-Day Neurotoxicity-Rat
Long-Term (Dermal)	Oral NOAEL= 0.15	Erythrocyte cholinesterase inhibition and liver lesions	1-Year Toxicity-Dog
Inhalation (Any Time Period) ^b	Oral NOAEL= 0.2	Plasma, RBC and brain cholinesterase inhibition	90-Day Neurotoxicity-Rat

^a A 30% dermal absorption factor should be used for these risk assessments.

^b Since an oral value was selected, route-to-route extrapolation should be followed.