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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: **April 1, 1998**

MEMORANDUM

SUBJECT: ***DIAZINON*** - Report of the Hazard Identification Assessment Review Committee.

FROM: Jess Rowland 4/1/98
Executive Secretary,
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THROUGH: K. Clark Swentzel, Chairman, 4/1/98
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Mike Metzger, Co-Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C) 4/1/98

TO: Steve Dapson, Branch Senior Scientist
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PC Code: 057801

On March 17, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the existing Reference Dose (RfD) and the toxicological endpoints selected for acute dietary and occupational/ residential exposure risk assessments, and also determined the uncertainty Factors and/or Margins of Exposure for the various exposure scenarios. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to Diazinon as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented in this report.

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Committee Members in Attendance

Members present were Karl Baetcke, William Burnam, Robert Fricke, Karen Hamernik, Susan Makris, Mike Metzger, Melba Morrow, John Redden, Jess Rowland (Executive Secretary) and Clark Swentzel (Chairman). Data was presented by John Doherty of Toxicology Branch 2.

Data Presentation:

John Doherty
Toxicologist

Report Preparation:

Jess Rowland.
Executive Secretary

I. INTRODUCTION

On February 20, 1997 the Health Effects Division's RfD/Peer Review Committee established a Reference Dose (RfD) of 0.0007 mg/kg/day based on a NOEL of 0.02 mg/kg/day established in a human volunteers and an Uncertainty Factor of 30 which included 10 x for intra-species variability and 3 x to account for the close proximity of the NOEL (0.02 mg/kg/day) and LOEL (0.025 mg/kg/day) established as well as the use of only one sex (males) in the critical study. The NOEL established in the human study was supported by the results observed in animal studies (*Memorandum:* G. Ghali, HED to George LaRocca, RD, dated June 17, 1997).

On February 25, 1997, the Health Effects Division's Toxicology Endpoint Selection (TES) Committee selected the doses and endpoints for acute dietary as well as occupational and residential exposure risk assessments (TES Document dated 6/4/97).

On March 17, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) re-evaluated the existing Reference Dose (RfD) and the toxicological endpoints selected for acute dietary and occupational/ residential exposure risk assessments, and determined the Uncertainty Factors and/or Margins of Exposure for the various exposure scenarios. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to Diazinon as required by the Food Quality Protection Act (FQPA) of 1996. The application of the FQPA safety factor for the protection of infants and children as required by FQPA, will be determined during risk characterization.

The reader is referred to the RfD and TES Committee reports (cited above) for Executive Summaries of the studies as well as the rationale for doses and endpoints selected for the various exposure scenarios.

The conclusions of the March 17, 1998 HIARC meeting which included determination of the Uncertainty Factors and/or the Margins of Exposure for exposure scenarios (acute and chronic dietary as well as occupational/residential risk assessments), recommendations made for aggregate exposure risk assessments and the determination of the potential susceptibility to infants and children are presented in this report.

II. DETERMINATION OF UNCERTAINTY FACTORS AND/OR MARGINS OF EXPOSURES

1. Acute Dietary Risk Assessment (Acute RfD)

For acute dietary risk assessment, the Toxicology Endpoint Selection (TES) Committee selected the NOEL of 0.25 mg/kg based on inhibition of plasma cholinesterase activity in female rat observed at 2.5 mg/kg (LOEL). This NOEL was established based on the results of two single dose studies in male and female Sprague-Dawley rats. In the first study, rats received diazinon at 0, 2.5, 150, 300 or 600 mg/kg. In the second study at 0, 0.5, 0.5, 1, 10, 100 or 500 to malse and at 0, 0.05, 0.12, 0.25, 2.5, 25 or 250 mg/kg (MRID No.s 43132204 and 44219301).

Dose Selected for Establishing the Acute RfD = 0.25 mg/kg.

Uncertainty Factor (UF): 100 (10 x for inter-species extrapolation and 10 x for intra-species variability).

$$\textbf{Acute RfD} = \frac{0.25\ \text{mg/kg(NOEL)}}{100\ \text{(UF)}} = \textbf{0.0025 mg/kg}$$

Comments about Study/Endpoint/Uncertainty Factor: The human study was not used for acute dietary risk assessment because 1) it could not be determined when the depression in plasma cholinesterase activity started (the first assessment was on day 3 for the 0.025 mg/kg and on day 4 for the 0.02 mg/kg) and 2) reproducible animal studies were available following a single exposure as demonstrated in the two studies discussed above.

2. Chronic Dietary Risk Assessment (Chronic RfD)

For chronic dietary risk assessment, the RfD/Peer review Committee selected a NOEL of 0.02 mg/kg/day based on inhibition of plasma cholinesterase activity at 0.025 mg/kg/day (LOEL). This NOEL was established in a human study in which groups of 3 male volunteers were given diazinon in corn starch by capsules at 0.02 or 0.025 mg/kg/day for 38 or 43 days. A control group received corn starch only. Plasma and red blood cholinesterase activity was measured every 2-3 days. All three volunteers at 0.025 mg/kg/day exhibited plasma cholinesterase inhibition (8-38%); no effects were seen in red blood cell acetylcholinesterase. (MRID No. 00091536).

Dose Selected for establishing chronic RfD = NOEL=0.02 mg/kg/day

Uncertainty Factor (UF): 30 (10 x for intra-species variability and 3 x).

Chronic RfD = $\frac{\text{0.02 mg/kg/day (NOEL)}}{\text{30 (UF)}}$ **=0.0007 mg/kg/day**

Comments about Study/Endpoint/Uncertainty Factor: The NOEL established in the human study is supported by comparable NOELs established for the same endpoint (plasma ChEI) in rats (0.0037 mg/kg/day), dogs (0.0034 mg/kg/day) and monkeys (0.05 mg/kg/day). An additional factor of 3 x was applied to account for the close proximity of the NOEL (0.02 mg/kg/day) and LOEL (0.025 mg/kg/day) and the use of only one sex (males) in the critical study. The 10 x factor for inter-species extrapolation is not appropriate since a study with human volunteers was used.

3. Occupational/Residential Exposure Risk Assessments

(i). Dermal Exposure

For **Short-and Intermediate-Term and Chronic risk assessments**, the TESC selected the NOEL of 0.02 mg/kg/day established in the human volunteer study based on plasm cholinesterase inhibition at 0.025 mg/kg/day (LOEL). Since a dose from an oral study (i.e., oral NOEL) was selected, a dermal absorption rate of 100% should be used for these risk assessments. The TESC determined a 100% dermal absorption factor based on the similarity of results (mortality) observed at the same dose (100 mg/kg/day) via the oral (in the developmental toxicity study) and dermal (21-day dermal) routes in the same species (rabbits) thus indicating that an assumption of 100% absorption to be appropriate.

For dermal risk assessments, the HIARC determined that a MOE of 30 is required which includes a 10 x for intra-species variation and an additional factor of 3 x to account for the closeness of the NOEL/LOEL and the use of only one sex (males) in the critical study. The 10 x factor for inter-species extrapolation is not appropriate since a study with human volunteers was used.

(ii) Inhalation Exposure

For Short-and Intermediate-Term and Chronic risk assessments, the TESC selected the LOEL of 0.1 µg/L for plasma ChEI in both sexes and RBC ChEI in males established in a 21-day inhalation toxicity study. In that study groups of male and female Sprague-Dawley rats were exposed to aerosol concentrations of diazinon at 0, 0.1, 10 or 100 µg/L, 6 hours/day 7 days/week for 3 weeks (MRID No. 40815002).

For inhalation risk assessments, the HIARC determined that a MOE of 300 is required which includes 10 x for inter-species extrapolation, 10 x for intra-species variation and an additional 3 x (under FIFRA) for the use of a LOEL (lack of a NOEL in the critical study).

4. Recommendation for Aggregate Exposure Risk Assessments

The **acute** aggregate exposure risk assessment should be made by combining the high end exposure values from food plus water and comparing it to the oral NOEL to calculate the MOE.

The **Short, Intermediate and Chronic** aggregate exposure risk assessments should be made by combining the average exposure values from food plus water together with the aggregate exposures from **dermal** sources and comparing it to the oral NOEL (selected for dermal risk assessments) to calculate the MOE.

The MOE obtained for **Short and Intermediate Term and Chronic inhalation** risk assessment can also be combined with the dermal MOE's since a common toxicological endpoint (i.e., cholinesterase inhibition) was identified via the oral and inhalation routes.

$$\text{Total MOE} = \frac{1}{\frac{1}{MOE_{Dermal}} + \frac{1}{MOE_{Inhalation}}}$$

III. FQPA CONSIDERATIONS

1. Adequacy of Data Base

The data base to assess the *in utero* and postnatal exposures of diazinon included prenatal developmental toxicity studies in rats and rabbits as well as a two-generation reproduction study in rats. In addition, adequate neurotoxicity studies, following single and repeated exposures in rats as well as subchronic and chronic toxicity studies in rats, dogs and monkeys were available to characterize the neurotoxic potential of diazinon.

2. Determination of Susceptibility

Prenatal developmental toxicity studies in rats and rabbits provided no indication of increased susceptibility of rat or rabbit fetuses to *in utero* exposure to diazinon. There was no indication of increased susceptibility in the fetuses as compared to parental animals in the two generation reproduction study. In these studies, effects in the offspring were observed only at or above treatment levels which resulted in evidence of parental toxicity.

3. Developmental Neurotoxicity

The RfD Committee, based on a weight-of-the-evidence basis determined that a developmental neurotoxicity study is **not required** (RfD Report date 6/17/97).

4. Determination of the FQPA Factor:

The application of an FQPA factor for the protection of infants and children from exposure to diazinonn as required by FQPA, will be determined during risk characterization by the FQPA Safety Committee. However, the HIARC, based on hazard assessment, recommends to the FQPA Safety Factor Committee that the additional 10 x factor should be removed because:

(i) The data provided no indication of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to diazinon.:

(ii) No evidence of developmental anomalies, including abnormalities in the development of fetal nervous system was observed in the pre-and/or post natal studies.

(iii) The toxicology data base is complete and there are no critical data gaps.

VI. DATA GAPS

There is one data gaps for the standard Subdivision F Guideline requirements for a food-use chemical by 40 CFR Part 158.

§81-3 Acute Inhalation Toxicity Study

V SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

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

EXPOSURE SCENARIO	DOSE	ENDPOINT	STUDY
Acute Dietary	NOEL=0.25 mg/kg	Plasma cholinesterase inhibition	Acute Neurotoxicity - Rat
	UF =100	**Acute RfD = 0.0025 mg/kg/day**	
Chronic Dietary	NOEL= 0.025 mg/kg/day	Plasma cholinesterase inhibition	Human Study
	UF=30	**Chronic RfD = 0.0007 mg/kg/day**	
Short-Term (Dermal) [a]	Oral NOEL= 0.025 mg/kg/day	Plasma cholinesterase inhibition	Human Study
Intermediate-Term (Dermal) [a]	Oral NOEL= 0.025 mg/kg/day	Plasma cholinesterase inhibition	Human Study
Long-Term (Dermal) [a]	Oral NOEL= 0.025 mg/kg/day	Plasma cholinesterase inhibition	Human study
Inhalation (Any Time Period)[b]	LOEL=0.1 µg/L	Plasma cholinesterase inhibition	21-Day Inhalation - Rat

a = Appropriate route-to-route extrapolation should be performed for these risk assessments (i.e., the dermal exposure components using the appropriate dermal absorption rate (100%) should be converted to equivalent oral doses and compared to the oral NOEL. HIARC recommends a MOE of 30 for dermal risk assessments.

b = The HIARC recommends a MOE of 300 for inhalation risk assessments.