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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: February 12, 1998

MEMORANDUM

SUBJECT: **NALED - *ADDENDUM -FQPA REQUIREMENT* -** Report of the Hazard Identification Assessment Review Committee.

FROM: Jess Rowland 2/11/98
Executive Secretary,
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THROUGH: Melba Morrow,
Acting Chairman, Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Karen Whitby
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PC Code: 034401

BACKGROUND: On February 3, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee met to re-assess the FQPA requirement for Naled. The Committee's decisions are summarized below.

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I. INTRODUCTION

On September 2, 1997, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) determined that the **10 x factor** to account for enhanced sensitivity of infants and children (as required by FQPA) **should be retained** to ensure protection from exposure to Naled for the following reasons:

(i) In an acute delayed neurotoxicity study in hens, a single oral dose (42 mg/kg/day) caused deaths, clinical signs indicative of neurotoxicity, inhibition of brain cholinesterase activity (50%) and axonal degeneration of the spinal cord. There was concern for potential to induce adverse effects in the functional neurologic development of the fetus based on the severity of the effects seen in the brain and the spinal cord after a single dose.;

(ii) Cholinesterase activity was not determined in either the acute or the subchronic neurotoxicity studies in rats or in the developmental and reproduction studies. For Naled, inhibition of cholinesterase activity is considered to be the primary effect or the critical endpoint. Since this endpoint is not measured in the developmental and reproduction studies (although not required by the Subdivision F Guidelines), it was not possible with the available data to determined any possible increased susceptibility between adults and offspring.

(iii) A subchronic neurotoxicity study (28/90-day) in hens was considered to be a data gap because of the effects seen in the acute delayed neurotoxicity study and data from this study will assist in determining the need for a developmental neurotoxicity study in rats.

Since the September 2, 1997 meeting, HED located the review of a 28-day study in hens. Also, the Agency has received a rebuttal from the Registrant on the HIARC review of Naled.

On February 3, 1998, the HIARC met to evaluate the 28-day study in hens, re-assess the FQPA factor in light of that study and address the concerns raised by the Registrant in their rebuttal. The Committee's conclusions are presented below:

II. Evaluation of the 28-Day Study: (MRID No. 43223902)

Groups of laying hens (14/dose) received oral administrations of Naled (91.7%) at dose levels of 0, 0.4, 2.0 or 4.0 mg/kg/day for 28 days. Minimal transient body weight decrease was seen in hens at 4.0 mg/kg/day. Brain cholinesterase activity was significantly decreased at 2 mg/kg/day (29% of control) and at 4 mg/kg/day (49% of control). No treatment-related clinical evidence of neurotoxicity or delayed neuropathy was observed. The NOEL was 0.4 mg/kg/day and the LOEL, based on brain cholinesterase inhibition, was 2.0 mg/kg/day.

III. Determination of Developmental Neurotoxicity Study

The Committee determined that, based on a weight-of-the-evidence review of the available data, a developmental neurotoxicity study with Naled in rats is not required at this time. The following information was considered in arriving at this decision.

- No evidence of abnormalities in the development of the fetal nervous system, were observed in the prenatal developmental toxicity studies in either rats or rabbits, at maternally toxic oral doses up to 40 or 8 mg/kg/day, respectively. No clinical evidence of behavioral alterations was observed in pups from the two-generation reproduction study in rats.

- Neither brain weight nor histopathology (nonperfused) of the nervous system were affected by treatment in the subchronic and chronic toxicity studies examined.

- Although Naled is a neurotoxic chemical with occurrence of inhibition of plasma, erythrocyte and brain cholinesterase in various species (mouse, rat, rabbit, dog) , acute and subchronic neurotoxicity studies in rats did not identify brain weight changes or neuropathological lesions.

IV. Re-assessment of FQPA Factor

The Committee determined that the **10 x factor** factor to account for enhanced sensitivity of infants and children (as required by FQPA) **should be removed.** The FQPA factor is removed based on the following factors:.

(i) Developmental toxicity studies showed no increased sensitivity in fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits.

(ii) A two generation reproduction toxicity study in rats showed no increased sensitivity in pups when compared to adults.

(iii) The toxicology data base is complete and there are no data gaps for the assessment of hazard to infants and children.

V. Determination of Uncertainty Factors (UFs)and Margins of Exposures (MOEs)

1. Acute Dietary Risk Assessment: The Committee determined that a **MOE of 100 is adequate** for the protection of the U.S. General Population including infants and children from acute exposure to Naled.

2. Chronic Dietary Risk Assessment: The Committee determined that an **UF of 100 is adequate** for the protection of the U.S. General Population including infants and children from chronic exposure to Naled. Based on the UF of 100 (10 x for inter-species and 10 x for intra-species variations), the Reference Dose (RfD) is revised as follows:

Revised RfD = $\frac{0.2 \text{ mg/kg/day (NOEL)}}{100 \text{ (UF)}}$ = **0.002 mg/kg/day**

3. Occupational/Residential Risk Assessments. The Committee determined that a **MOE of 100 is adequate** for the protection of the U.S. General Population including infants and children from occupational/residential exposures to Naled.

VI. Toxicology Endpoints Selected for Risk Assessments

The doses and endpoints for acute and chronic dietary as well as occupational/residential exposure risk assessments are tabulated below. The reader is refered to the RfD/Peer Review report and the Toxicology Endpoint Selection Documents for Executive Summaries and rationales employed in selecting the doses and endpoints for the various risk assessments.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY	MOE REQUIRED
Acute Dietary	NOEL=1.0	cholinergic signs and plasma and brain cholinesterase inhibition	28-Day Oral Toxicity	100
Chronic Dietary	NOEL=0.2	Inhibition of brain cholinesterase activity	2-year Chronic toxicity - Rat	100
	Revised RfD = 0.002 mg/kg/day			
Short-Term (Dermal)	NOEL=1.0	Plasma, RBC and brain cholinesterase inhibition	28-Day Dermal - Rat	100
Intermediate-Term (Dermal)	NOEL=1.0	Plasma, RBC and brain cholinesterase inhibition	28-Day Dermal - Rat	100
Long-Term (Dermal)[a]	Oral NOEL=0.2	Inhibition of brain cholinesterase activity	2-Year Chronic -Rat	100
Inhalation (Any time period)	NOEL=0.50[b]	Plasma and RBC cholinesterase inhibition	90-Day Inhalation-Rat	100

a =Since an oral NOEL is selected, appropriate route-to-route extrapolation should be done. The dermal exposure component (mg/kg/day), using a 100% dermal absorption factor, should be converted to an equivalent oral dose, and this dose should then be compared with the oral NOEL.

b= The dose presented is a converted dose (i.e., the NOEL in mg/L is converted to mg/kg/day). So the inhalation exposure should be compared to the NOEL presented.