11-5-76

Registration Human Safety Review PM: Lee #16 TOX Reviewer: G. Kreese

EPA #	Date	Product Name	Use Classification	Toxicity Category
239-EULE	11/5/76	Chevron Monitor Technical		I

RECOMMENDATION: JB objects to the registration until the following studies have been referenced or submitted:

1) eye irritation - 100mg/eye or appropriate dose which will not cause significant mortalities
2) skin irritation - dose amount which will not cause significant mortality
3) mutagenicity
4) oncogenicity in a 2nd species
5) teratology
6) [illegible]

E for OPP 11/8/76

		TECH/75%	TECH	FORMULATION	USE DILUTION	DATA ACCEPTABLE
Acute Oral (Rat)	LD50	21.0mg/Kg ♀	18.9mg/Kg ♀			yes

Toxic signs: severe tremors, salivation, chromodacryorrhea, dyspnea, rhinorrhea and rarely clonic convulsion signs evident 10minutes post-dosing; most deaths occurred between 3 and 24 hrs after dosing.

Comments:
95% confidence interval (16.3-27.1)mg/Kg ♀
95% confidence interval (17.2-20.8)mg/Kg ♀
no pathological conditions were seen at autopsy 2.8

Acute Dermal (Rabbit)	LD50	.118mg/Kg				yes

Tox. signs: miosis, salivation, rhinorrhea, ataxia, and CNS depression signs evident 1-3 hrs post-dosing; most deaths occurred between 6 and 48 hrs after dosing.

Comments:
95% confidence interval (97.5-143)mg/Kg.
no pathological conditions were seen at autopsy

Acute Inhalation (rats)	LC_{50}					yes

Toxic signs:

Comments: 95% tech used in the vapor inhalation study (4 hr exposure), material was heated to 40°C to enhance vaporization
Results no deaths although cholinesterase activity was 70 to 80% of the normal values
LC_{50} could not be determined

Primary Eye Irritation (Rabbit)		No data				

Comments:

Primary Skin Irritation (Rabbit)		No data				

Comments:

Other Studies: see attached sheets on all studies that were referenced for the registration of 239-EULE.

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MONITOR

Acute Rat Oral (95% Tech)	:	Male LD_{50} = 15.6 mg/KG Female LD_{50} = 13.0 mg/KG Typical cholinesterase inhibition signs were noted.
Acute Rat Oral (75% Tech)	:	Male LD_{50} = 21 mg/kg Female LD_{50} = 18.9 mg/kg
Acute Rat Oral (6 S)	:	Male LD_{50} =32.3 mg/KG Female LD_{50} = 24.1 mg/KG Tremors, salivation, dyspnea were noted.
Acute Mice Oral (95%)	:	Female LD_{50} = 16.2 mg/KG Tremors, salivation, dyspnea were noted
Acute Mice Oral (75%)	:	Female LD_{50} = 18.0 mg/KG Tremors, salivation, straub tail, dyspnea and rarely clonic convulsions were noted. No mortality occurred at 15 mg/KG or lower.
Acute Rabbit Dermal (Tech)	:	Male LD_{50} = 118 mg/KG. No gross pathological changes were noted. Toxic signs noted were miosis, salivation, rhinorrhea, ataxia, and CNS depression.

Acute Rabbit Dermal (Monitor 6 S)	:	Male LD_{50} = 125 mg/KG. No gross pathological changes were noted. Toxic signs noted were miosis, diarrhea, salivation, rhinorrhea and death.
Acute Rat Inhalation (95%)	:	An LC_{50} value was not established because of the vapor method used. A slight effect was shown by a depression of both the RBC and plasma Ch.E. activity. Exposure was four hours.
Acute Rat Inhalation (Monitor 6 S) (4 hours)	:	No LC_{50} value could be established because no measurement of vapors was made. No mortality or signs of intoxication was noted. A slight to moderate depression of the RBC level of Ch.E. activity was noted.
21 Day Subacute Rabbit Dermal (75% Tech)	:	Levels tested were 5.0 and 10 mg/KG. Two deaths were noted at high level and one at low level. Deaths were due to cholinergic reactions at the high level. Slight body weight loss was noted at the high level. No adverse findings were noted in hematologic and clinical blood chemistry studies. These findings are difficult to believe due to the dosage levels used.

90 Day Rat Feeding (75% Tech)	:	Levels tested were 0.3, 1.0, 3.0, and 10 ppm. Male showed plasma Ch.E. depression at 3.0 and 10 ppm; females at 10 ppm. RBC Ch.E. depression was noted at 10 ppm. Brain Ch.E. depression was noted at 3.0 and 10 ppm. The no-effect level is approx. 1.0 ppm. Recovery was noted several weeks post treatment.
90 Day Dog Feeding (75% Tech)	:	Levels tested were 0.025, 0.075, and 0.25 mg/KG. No clear-cut or consistent pattern of effects on cholinesterase activity was observed.
21 Day Rat Paired Feeding Study (97% Tech)	:	Tested at 30 ppm. No body weight loss was indicated.
Two Year Dog Oral (RE 9006-111, SX-116)	:	Levels tested were 0.075, 0.25 and 0.75 mg/KG seven days a week. No mortality was observed. No toxic effects were noted.
Two Year Rat Feeding (RE 9006-111, SX-116) (97%)	:	Levels tested were 3.0, 10, and 30 ppm. Body weight loss was observed at 30 ppm (see 21 day rat feeding). The no effect level is greater than 30 ppm.

Three Generation Rat Reproduction Study (75%)	:	The F1b litters of the 30 ppm level showed increased stillbirths a decrease in viable pups at day five and again at weaning. All test males showed a decreased heart weight. Histopathology on parent animals was negative. The F2a and F2b litters, both test and control showed a higher than normal number of stillbirths. The 5 day survival index for the F2a and F2b litters of the 30 ppm were higher than the control value. A greater than 20% decrease in Ch.E. activity was noted in both sex of the F1b parents. Histopathological examination revealed no adverse finding.
Microsomal Oxidation	:	Microsomes accelerate the hydrolysis of monitor to O,S-dimethyl phosphorothioate.
Metabolism in the Rat	:	

Approximately one-half of the dose was excreted within 24 hrs as CO_2 or in the urine.

Neurotoxicity in Chickens (75% Tech):		Neurotoxicity was not exhibited
Antidotal Study	:	Atropine and or 2-PAM are antidotal.

Thiono isomer impurity

Acute Rat Oral (RE 9169)	:	Male LD_{50} = 633 mg/KG Female LD_{50} - 549 mg/KG Death was proceeded by signs of intoxication associated with central nervous system depression.
Acute Rabbit Dermal (RE 9169) (SX 198)	:	LD_{50} = ~ 3.5 gm/KG on intact skin. LD_{50} = 1.57 gm/KG on abraded skin. Toxic signs were weakening hyporeflexia, loss of reflexes and salivation.
Human Exposure Reports	:	Sixty-six human contact reports with various concentrates did not show significant effects.