CASWELL FILE
10-28-86

REFERENCE DOSES (RFDs) FOR ORAL EXPOSURE

Chemical: EPTC (Eptam)

CAS #: 759-94-4
Caswell #: 435

Carcinogenicity: No evidence of carcinogenicity in two animal species (mouse, rat).

Systemic Toxicity: See below.

Preparation Date: 8/06/86

Endpoint	Experimental Doses	UF	MF	RfD
IRDC (1983)	5 mg/kg/day Systemic NOEL	1000	—	0.005 mg/kg/day
2-Year Rat Feeding/ Oncogenic Study	25 mg/kg/day Systmeic LEL			
neuromuscular atrophy/degeneration; weight loss				

Endpoint and Experimental Doses:

IRDC (for Stauffer)
Two-Year Rat Feeding/Oncogenic Study
Study No. T-10001; September 30, 1983

Charles River CD (Sprague-Dawley) rats (60/sex/group) were fed diets providing 0, 5, 25 and 125 mg/kg/day EPTC for 24 months. At 25 and 125 mg/kg/day, hindquaters neuropathy was observed, and confirmed histologically by a dose-related increased axonal degeneration of the sciatic nerve and associated muscle atrophy. Additionally, at the HDT (125 mg/kg/day), the following compound-related effects were noted: chronic myocarditis in both sexes (combined with organized atrial thrombosis in high-dose females-dying-on-study); increased SGOT enzyme activity in both sexes; decreased AChE activity in both sexes; decreased body weight and food consumption in both sexes; increased cataracts in females. No EPTC-induced neoplasia were recorded.

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Uncertainty Factors (UFs):

Based on a chronic exposure study, an uncertainty factor of 100 was used to account for inter- and intraspecies differences. An additional UF of 10 was used to account for the fact that the data base on chronic toxicity is incomplete and therefore, the most sensitive toxicological endpoint can not be established.

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Modifying Factors (MFs):

None

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Additional Comments:

Data Considered for Establishing the RfD

1) 2-Year Feeding/Oncogenic - Rat Systemic NOEL = 5 mg/kg/day, Systemic LEL = 25 mg/kg/day (neuropathy; body weight loss; Not oncogenic at the HDT (125 mg/kg/day); core grade minimum

2) Teratology - Rat Maternal/Fetal NOEL = 100 mg/kg/day, Maternal/Fetal LEL = 300 mg/kg/day (based on: maternal mortality and reduceded body weight gain; increased resorptions and fetal growth retardation; decreased fetal weight); Teratogenic NOEL > 300 mg/kg/day; No effects at the LDT (30 mg/kg/day); core grade minimum

3) 2-Generation Reproduction - Rat Reported NOEL = 200 ppm (10 mg/kg/day); Provisionally reported LEL = 1000 ppm (50 mg/kg/day)(including decreased parental and F1 body and brain weight; decreased pup weight) No histopathology reported; core grade supplementary

*4) Subchronic Feeding - Dog (PPG) AChE NOEL = 600 ppm (15 mg/kg/day); AChE (plasma only) LEL = 1800 ppm (45 mg/kg/day)(HDT)

*5) Subchronic Feeding - Rat (PPG) NOEL = 3 mg/kg/day (LDT); LEL = 15 mg/kg/day (decreased body weight gains and food consumption); In addition, at 72 and 120 mg/kg/day (HDT) dose-related increase in AST correlated with chronic myocarditis (NOEL = 15 mg/kg/day); In HDT females only, depressed brain cholinesterase activity

* PPG studies still in progress

Data Gap(s)

1) Chronic Dog Study
2) Rat Reproduction Study
3) Rabbit Tereatology Study

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Other Data Considered

1) Oncogenicity - Mouse NOEL = 20 mg/kg/day (actually calculated at 16 mg/kg/day), LEL = 80 mg/kg/day (actually calculated at 66 mg/kg/day) based on decreased food consumption and transient (mid-study) body weight gains. No evidence oncogenicity at the HDT.

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Confidence in the RfD:

Study: Medium Data Base: Low RfD: Low

The critical study is of fair quality and is given a medium confidence rating. Since a second chronic rat study is to be submitted as well as a chronic dog study and a rat reproduction study, the RfD is given a low confidence rating.

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Documentation of RfD and Review:

Registration Standard, September 1983
Registration Files

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Agency RfD Review:

First Review: 10/28/86
Second Review:
Verification Date: 10/28/86

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