

**EPTC (S-Ethyl-Dipropylthiocarbamate)**  
**RISK CHARACTERIZATION DOCUMENT**

**Medical Toxicology and Worker Health and Safety Branches**  
**Department of Pesticide Regulation**  
**California Environmental Protection Agency**

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## EXECUTIVE SUMMARY

### Introduction

EPTC is the common name for S-Ethyl-dipropylthiocarbamate. A risk assessment of potential human health hazards from exposure to technical EPTC has been conducted because of the toxic effects reported in animal studies.

The current Risk Characterization Document addresses potential human exposures from the California use of EPTC as an active ingredient in thiocarbamate herbicide formulations to control annual grasses and broadleaf weeds and some perennials. The potential dietary risk from the consumption of foods containing the highest legal residues (tolerances) of EPTC is also assessed.

### The Risk Assessment Process

The risk assessment process consists of four aspects: hazard identification, dose response assessment, exposure evaluation, and risk characterization.

Hazard identification entails a review and evaluation of the toxicological properties of each pesticide. The dose response assessment then considers the chemicals toxicological properties and estimates the amount which could potentially cause an adverse effect. The basic principle of toxicology is that at a high enough dose, virtually all substances will cause some type of toxic manifestation. Although chemicals are often referred to as "dangerous" or "safe", as though these concepts were absolutes, in reality, these terms describe chemicals that require low or high doses, respectively, to cause toxic effects. Toxicological activity is determined in a battery of experimental animal studies which define the kinds of toxic effects that can be caused, and the exposure levels (doses) at which effects may be seen. State and federal testing requirements mandate that chemicals be tested in laboratory animals at doses high enough to produce toxic effects, even if such testing requires dose levels many times higher than those to which people might be exposed.

In addition to the intrinsic toxicological activity of the pesticide, the other parameters critical to determining risk are the level, frequency and duration of exposure. The purpose of the exposure evaluation is to determine the potential amount of the pesticide likely to be delivered through occupational, residential, or dietary routes on an acute or chronic basis.

The risk characterization then integrates the toxic effects observed in the laboratory studies, conducted with the high dosages of pesticides, to potential human exposures to low dosages of pesticides in the diet, home, or work place. The potential for non-cancer possible adverse health effects in human populations is generally expressed as the margin of safety (MOS), which is the ratio of the dosage which produces no effect in animal studies to the theoretical human dosage. For cancer effects, the probability of risk is determined by the cancer potency of the pesticide and the estimated potential dosage.

### Toxic Effects in Animal Studies

Various toxic effects including impaired blood clotting function, lowered body weight, damage to the heart, eye, muscles, brain, nerves, developing embryos, or nose were identified

in animal studies of EPTC. The brain effects were cell death (necrosis), or decreased brain weight in animals exposed to EPTC. The estimated dosage at which the brain damage would not be expected to occur, (i.e., the No-Observable-Effect-Level, or NOEL) was used to quantitate the potential risk from acute single-day human exposure. The potential risk to humans from repeated daily occupational exposures to EPTC was evaluated based upon damage to the lining of the nose and blood clotting problems in a rat inhalation toxicity study. The potential long-term (chronic) risk to humans from exposures to EPTC was evaluated based on the gradual onset of paralysis (nerve and muscle damage) in long-term rat studies.

### **Potential Human Exposure**

The potential combined occupational and dietary exposure associated with the use of technical EPTC in formulations used as herbicides was assessed for workers during mixing, loading, and/or application activities. EPTC exposure would not be significant during cultivation or harvesting. The lowest margin of safety (calculated as Animal NOEL/Estimated Human Exposure) for single-day exposure was 90. Margins of safety of 100 or greater are generally considered sufficient for protection of human health.

The potential occupational exposures of workers from repeated daily use during the growing season was also assessed. The margins of safety for potential repeated daily exposure were as low as 9 for chemigation center-pivot sprinkler mixer/loader/applicators.

A proposed exposure mitigation involved the use of an effective "closed-system" together with apron and chemical resistant gloves for mixing and loading emulsible EPTC concentrate. Full-body chemical-resistant protective clothing and a half-face respirator would be required during application of liquid mixes and loading and applying of granules. These mitigation measures would produce MOSs close to or greater than 100 for occupational exposures.

Exposure of the general public to EPTC via the dietary route is from potential EPTC residues in 208 raw or processed agricultural commodities. There is a margin of safety of greater than 100 for all population subgroups from potential dietary exposure to EPTC. The margins of safety were all greater than 7,000 for acute exposure, and greater than 500 for chronic exposure.

### **Tolerance Assessment**

Based on the 95th percentile of the potential consumption of foods at the highest legal residues (tolerances) of EPTC, the acute margins of safety were all greater than 2000. Based upon pesticide residue monitoring programs, the long-term consumption of foods containing residues at tolerance levels was considered highly improbable. Therefore, an assessment of the margins of safety from theoretical chronic exposure to foods with tolerance levels of EPTC was not undertaken.

## **Conclusions**

The margins of safety (MOSs) for the use of technical EPTC in herbicide formulations were as low as 90 for potential combined acute occupational and dietary exposure. The MOSs for potential seasonal combined occupational and dietary exposure were as low as 9. A proposed mitigation would produce MOSs close to or greater than 100 for occupational exposures. The MOSs from the theoretical consumption of foods with the highest legal residues (tolerances) of EPTC were all greater than 100.

## Contributors and Acknowledgments

Principal Author: Earl F. Meierhenry, D.V.M., Ph.D., A.C.V.P.  
Staff Toxicologist  
Health Assessment Section  
Medical Toxicology Branch

Toxicology Reviews: Thomas P. Kellner, Ph.D., D.A.B.T  
Staff Toxicologist  
SB 950 Data Review Section  
Medical Toxicology Branch

Gerald F. Chernoff\*, Ph.D.  
Staff Toxicologist  
SB950 Data Review Section  
Medical Toxicology Branch

Occupational Exposure: Robert K. Brodberg, \*\* Ph.D.  
Associate Pesticide Review Scientist  
Exposure Assessment Group  
Worker Health and Safety Branch

Tom Thongsinthusak, Ph.D.  
Staff Toxicologist  
Exposure Assessment Group  
Worker Health and Safety Branch

Dietary Exposure: Wesley C. Carr, Jr., MS.  
Associate Pesticide Review Scientist  
Health Assessment Section  
Medical Toxicology Branch

Peer Review: Carolyn Lewis, MS, DABT  
Associate Staff Toxicologist  
Health Assessment Section  
Medical Toxicology Branch

Keith Pfeifer, Ph.D., DABT  
Senior Toxicologist  
Health Assessment Section  
Medical Toxicology Branch

\* Currently with: Department of Toxic Substances Control, California Environmental Protection Agency. \*\* Currently with: Pesticide and Environmental Toxicology Section, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency.

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## I. SUMMARY

### Introduction

A health assessment for the active ingredient, S-Ethyl-dipropylthiocarbamate (EPTC) has been conducted. Toxic effects have been reported in experimental animal studies submitted to support EPTC registration in California. Liquid or granular formulations of EPTC are used to control preemergent annual grasses and broadleaf weeds, and some perennials. To be effective, EPTC formulations require immediate incorporation into the soil. The major crop uses of EPTC in California are for potatoes, beans, alfalfa and sugar beets. EPTC is soluble in water, has a relatively high vapor pressure for an agricultural chemical, and is unlikely to persist in the environment or in plants.

### Toxic Effects in Animal Studies

Neurotoxicity is a major concern in the risk assessment of EPTC. In an acute neurotoxicity study using rats, a single oral dose of EPTC at 200 mg/kg or greater produced brain damage (neuronal necrosis). As a NOEL was not established in the study, an estimated NOEL of 20 mg/kg was calculated from the LOEL of 200 mg/kg using a default uncertainty factor of 10. This estimated NOEL was selected for evaluating potential acute, single-day human exposures.

Various other toxic effects, including fatal impairment of blood clotting function, cardiac toxicity, skeletal muscle or nerve degeneration/atrophy, cataracts, embryotoxicity, nasal cavity degeneration/hyperplasia, changes in body or brain weights, brain cholinesterase inhibition, and cholinergic signs were identified in animal studies of EPTC. The potential seasonal risk to humans from repeated daily occupational exposures to EPTC was evaluated based upon a NOEL of 0.7 mg/kg/day for nasal cavity degeneration/hyperplasia and blood clotting abnormality (prolonged partial thromboplastin time) by exposure-day 17, in a rat inhalation toxicity study. The chronic risk to humans from potential dietary exposures to EPTC was evaluated based on a NOEL of 0.5 mg/kg/day for the gradual onset of paralysis (neuromuscular damage) in 2-year rat study.

### Potential Human Exposure

The potential combined occupational and dietary exposure associated with the use of technical EPTC in formulations used as herbicides was assessed for workers during the mixing, loading, and/or application activities. EPTC exposure is not significant during cultivation or harvesting. The lowest margin of safety (calculated as Animal NOEL/Estimated potential Human Exposure) for acute single-day exposure was 90. Margins of safety of 100 or greater are generally considered sufficient for protection of human health.

The potential occupational exposure of workers from repeated daily use during the growing season was also assessed. The margins of safety for repeated daily exposure were as low as 9 for chemigation center-pivot sprinkler mixer/loader/ applicators. A proposed exposure mitigation involved the use of an effective closed system together with apron and chemical resistant gloves for mixing and loading emulsible EPTC concentrate. Full-body

chemical-resistant protective clothing and a half-face respirator would be required during application of liquid mixes and loading and applying of granules. These mitigation measures would produce MOSs close to or greater than 100 for potential occupational exposures.

### **Tolerance Assessment**

Based on the 95th percentile of the potential consumption of foods at the highest legal residue levels (tolerances) for EPTC, the acute margins of safety were all greater than 2,000. Based upon pesticide residue monitoring programs, the chronic consumption of foods containing residues at tolerance levels was considered highly improbable. Therefore, an assessment of the margins of safety from theoretical chronic exposure to foods with tolerance levels of EPTC was not undertaken.

### **Conclusions**

The margins of safety (MOSs) for the use of technical EPTC in herbicide formulations were as low as 90 for potential combined acute occupational and dietary exposure. The MOSs for potential seasonal combined occupational and dietary exposure were as low as 9. A proposed mitigation would produce MOSs close to or greater than 100 for occupational exposures. The MOSs from the theoretical consumption of foods with the highest legal residues (tolerances) of EPTC were all greater than 100.

## II. INTRODUCTION

This document contains the occupational, home garden, and dietary health risk assessment for technical EPTC.

### **A. CHEMICAL IDENTIFICATION**

S-Ethyl dipropylthiocarbamate (technical EPTC) was the first thiocarbamate herbicide developed (Jordan and Cudney, 1987)). EPTC formulations are used for the control of preemergent weeds, especially grasses. EPTC inhibits photosynthesis, respiration, and the synthesis of lipids, proteins, and RNA in these seedlings. Resistant plants are less sensitive to the herbicidal action apparently due to their ability to rapidly metabolize EPTC.

### **B. REGULATORY HISTORY**

The United States Environmental Protection Agency (US EPA) has currently set the Reference Dose (Acceptable Daily Intake) for EPTC at 0.025 mg/kg/day based on a No-Observed-Adverse-Effect-Level (NOAEL) for degenerative cardiomyopathy in rats of 2.5 mg/kg/day, and an uncertainty factor of 100 (U.S. EPA, 1990b). The corresponding Maximum Permitted Intake (MPI) for a 60 kg human would be 1.5 mg/day. Previously, the MPI was 3.5 mg/day, based on a NOAEL of 5 mg/kg/day for prolonged clotting factor times in a rat oral toxicity study (US EPA, 1984b)

The US EPA has also established a reregistration guideline for pesticide products containing EPTC as the active ingredient (US EPA, 1983c). Additional details are presented in Section III (Toxicology Profile).

A registrant request to delete the use of EPTC 6-E, 7-E, 5-G, 10- G, and 20-G on flax, sweet potatoes, green peas, and table beets has been received by the US EPA (US EPA, 1993d). Additional information regarding the disposition of the request is not currently available.

There are no American Conference of Government Industrial Hygienists or Occupational Safety and Health Administration standards for EPTC. It has been reported that the registrant currently maintains its facilities such that employee exposure to active ingredient in the air is below 0.4 mg/m (CPP, 1993d).

### **C. TECHNICAL/PRODUCT FORMULATIONS**

EPTC is available as a technical material (98.5%) for formulating end-use products, and as liquid emulsifiable concentrates or granular formulations. The concentration of technical EPTC in the liquid emulsifiable concentrate formulations ranges from 72.4 to 87.8%. The N-nitroso content of formulated products has been reported to be within US EPA limits (US EPA, 1980,1987; Farina, 1984; Wigfield et al., 1990; ICI Americas, 1991). The technical EPTC concentration in the granular formulations is between 2.3 and 10%. Currently there are seven California registrants, for thirteen different formulations, with technical EPTC as the sole active ingredient.

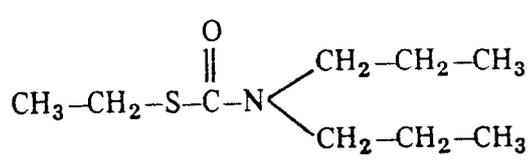
## D. USAGE

EPTC formulations are used as pre-emergent herbicides to control annual grasses and broadleaf weeds and some perennials. In several midwestern states, EPTC may also be tank-mixed with another thiocarbamate herbicide, cycloate, for additional control of weeds. To be effective, EPTC formulations require immediate incorporation into the soil by discing, metering into irrigation water, or injection by subsurface equipment. For 1990, the major crop uses of EPTC in California were for potatoes, beans, alfalfa, and sugar beets (DPR, 1991b). It is also used on corn, cotton, forage crops, for landscape and open land maintenance, and on ornamentals and flowers. In 1991, the last year for which data is available, 1,180,262 pounds of EPTC active ingredient were sold in California (DPR, 1992a)

## E. ILLNESS REPORTS

California worker illness associated with EPTC formulations is most often in the form of eye or skin irritation. Illness reports (DPR, 1987a, 1991a) document 6 cases of eye injuries between 1982 and 1988. During this period 4 cases of skin irritation and 5 cases of systemic illness were also recorded.

## F. PHYSICAL/CHEMICAL PROPERTIES (Stauffer Chemical Company, 1982 Lee, 1987)

Chemical Name:	S-ethyl dipropylthiocarbamate
Common Name:	EPTC technical
Trade Names:	Eptam, EPTC, Eradicane, Chacon Pre-Emergence Weed Control
CAS Registry Number:	759-94-4
Structural Formula:	
Empirical Formula:	C <sub>9</sub> H <sub>19</sub> NOS
Molecular Weight:	189.3
Physical State:	amber liquid
Boiling Point:	137- 138°C at 30 mm Hg
pH	7.9

Specific Gravity:	d = 0.9546
Stability:	EPTC is hydrolytically stable from pH 5 to pH 9 at 25°C and 40°C up to 30 days (Myers et al. 1983) It is thermally stable with a half-life greater than 483 days at 80°C and a half-life of 246 weeks at 120°C.
Flash Point:	229°C
Solubility:	EPTC is miscible in most organic solvents at 20°C including acetone, ethyl alcohol, kerosene, methylisobutylketone, and xylene. The solubility of EPTC in water is 344 ppm (25°C) (Meyers 1988).
Vapor Pressure:	2.4 X 10 <sup>-2</sup> mm Hg (25 C) (Myers, 1988)
Octanol/Water Partition Coefficient:	2200 (Lee, 1987b)

## **G. ENVIRONMENTAL FATE**

Technical EPTC is relatively non-persistent in the environment with a half-life of approximately 1 week in moist loam soil at 21-32° (Curry 1987a-c; Gray, 1971). The disappearance of EPTC from soil is primarily due to volatilization, with a smaller loss due to microbial degradation (Behki et al., 1991). The Henry's Law constant ( $K_H$ ) for EPTC is  $1.5 \times 10^{-5}$  atm m<sup>3</sup>/mol (Gray, 1971). The rate of volatilization increases with soil moisture content and temperature (Gray, 1965; Gary & Weierich, 1965).

### **Mobility**

The mobility of EPTC in soil varies significantly depending on the organic matter content of the soil (McBain, 1987). In a column leaching study, approximately 55-78% of the applied EPTC leached through loamy sand and sandy loam soil, whereas only 9% leached through loam or clay loam soil. A pesticide residue study which involved periodic collection of irrigation water from tailwater pits (basins up to three meters deep excavated to impound runoff from fields during irrigation), detected small amounts of EPTC in both pit water and pit bottom soil early in the growing season (Kadoum and Mock, 1978; U.S. EPA, 1983). Various rates and timing of pesticide application, soil pH and organic matter, amount of runoff water, and tillage and cultivation methods were not reported, however, and undoubtedly affected the amounts of residues in the pits. Since EPTC may leach in some soils, there exists at least a potential for contamination of ground water associated with irrigation systems utilizing tail water pits, although the product label indicates that tailwater should be recirculated. Based upon water solubility, soil adsorption coefficient and hydrolysis half-life, DPR determined that EPTC has a theoretical potential to leach to groundwater (DPR, 1993). However, EPTC was not detected in 557 California wells analyzed for EPTC during the years 1983 to 1992 (DPR, 1992b).

### **Photolysis**

In artificial UV light, EPTC underwent photodegradation in aqueous solutions at pH 7 (25°C) (Lee, 1987b). The major photodegradation products were dipropylamine, N,N-dipropylformamide, EPTC sulfoxide, EPTC sulfone, and ethanesulfonic acid.

### **Biodegradation or Microbial Degradation**

In soil metabolism studies, 25-30% of EPTC was volatilized by 7 days under both aerobic and anaerobic conditions (Miaullis, 1987). Approximately 20% of the parent compound was metabolized to carbon dioxide after 30 days. Virtually no metabolism occurred in sterilized soil, and the application of parathion to soil containing EPTC produced a 10-fold decrease in microbial degradation (Behki et al., 1991). The principal metabolites, sulfoxide and dipropylamine, were degraded faster than the parent compound. The formation of sulfoxide was proposed as the initial step in the metabolism of EPTC, followed by sulfur and carbon oxidation to their respective dioxides.

### **Plant Residues/Metabolism**

Studies with radiolabeled EPTC indicated that EPTC was readily absorbed by the roots of plants and translocated upward to the stems and leaves (Gray, 1971; Fang, 1969). In resistant plants, EPTC was rapidly metabolized to fructose, glucose, several amino acids, fatty acids, and carbon dioxide (U.S.EPA, 1983b).

### III. TOXICOLOGY PROFILE

The United States Environmental Protection Agency (US EPA) has established a reregistration guideline for pesticide products containing EPTC as the active ingredient (US EPA, 1983c). Further information was requested concerning the effect of EPTC on blood clotting in subchronic and chronic rat studies, as reviews of two subchronic studies in rats indicated impaired blood clotting function. The US EPA reviews of acute studies (oral, dermal, and inhalation) had also revealed effects suggestive of impaired blood clotting function, e.g. congested liver, kidneys, and adrenals; lung erythema, blood-like stains around the urogenital area, stained muzzle, red fluid in the urinary bladder, reddened intestinal mucosa, red discharge from the mouth, and reddened lungs. Laboratory studies of butylate, a close structural relative of EPTC, had also indicated effects of impaired blood clotting function. Information on EPTC was specifically requested by the US EPA for a one-year dog study, a rat oncogenicity study, teratology studies in two species, and a two-generation reproduction study. The required data were subsequently submitted by the registrants, and were included in this risk assessment.

#### **A. METABOLISM/PHARMACOKINETICS**

##### **Oral - Rat**

No Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Guideline metabolism studies were submitted to DPR by the registrants, however, several older studies were supplied. The US EPA indicated that, in view of negligible residues of EPTC found in raw agricultural commodities following recommended uses, residues of EPTC would not be expected to transfer to animals from the feed use of those commodities. Therefore, studies to delineate the animal metabolism of EPTC were not required (US EPA, 1983c). Based on submitted studies, and reviews of studies in the open literature, EPTC is rapidly metabolized in rats (Ong and Fang, 1970; Hubbell and Casida, 1977; Fay and Helmes, 1986; Hoffman et al., 1968; Miaullis, 1978; Miaullis, 1979a,b; Vispetto et al., 1979). When rats were given radiolabeled EPTC by gastric gavage, the first peak of  $^{14}\text{CO}_2$  appears 1-2 hours after administration. Approximately 88-97% of the administered dose was eliminated by 48 hours. The majority of the radiolabeled EPTC was expired as  $\text{CO}_2$  (38-85%), although as the dose increased from 0.6 to 100.6 mg, urinary excretion increased from 8 to 36%. The radioactivity in feces represented only 1 to 12% of the administered dosage. At 48 hours most of the radiolabel remaining in the tissues was in the blood, kidney, and liver. An oral absorption of 97% was estimated based on the amount of dose recovered by 48 hours.

##### **Oral/Intraperitoneal - Mice**

The metabolism in mice appears to be similar to rats, except only 62% of the administered dosage was recovered by 48 hours (Casida et al., 1975).

One major metabolic pathway for technical EPTC is sulfur oxidation. EPTC appears to be initially metabolized to EPTC sulfoxide via cytochrome P-450 (Ong and Fang, 1970; Hubbell and Casida, 1977). EPTC sulfoxide then readily reacts with glutathione-S-transferase. The

glutathione conjugates are further cleaved and acetylated before being excreted in the urine. The major urinary metabolites were identified as S-(N,N-dipropylcarbamoyl)-N-acetylcysteine, S-(N,N-dipropylcarbamoyl)cysteine, S-(N,N-dipropylcarbamoyl)mercaptoacetic acid, and urea. These urinary metabolites may be used for biological monitoring. Another major urinary metabolite in mice is ethyl methyl sulfone (Casida et al., 1975). The pathways for this metabolite and urea are unknown.

The LD<sub>50</sub> (ip) values in mice determined after one day of treatment with EPTC, EPTC-sulfoxide, or EPTC-sulfone were > 500, 325, and 135 mg/kg respectively. However, 7 days after a treatment, the LD<sub>50</sub> values were 58, 215, and 40 mg/kg, respectively, for EPTC, the sulfoxide, or the sulfone (Fay and Helmes, 1986; Hubbel and Casida, 1977). EPTC sulfoxide can undergo further microsomal oxidation to EPTC sulfone in vitro, but this is not likely to occur in vivo since the sulfoxide readily reacts with glutathione (Chen and Casida, 1978). EPTC sulfone has not been detected in the urine or livers of mice administered EPTC orally (Casida et al., 1975).

Carbon oxidation is another major metabolic pathway based on studies in mouse subcellular systems (Chen and Casida, 1978). The ester linkage of EPTC is cleaved with the release of carbonyl sulfide (COS) and acetaldehyde. The COS is further metabolized to CO<sub>2</sub>. Other stable products of carbon oxidation are beta-hydroxyethyl-EPTC, beta- and gamma-hydroxypropyl-EPTC, and N-dipropyl-EPTC. EPTC sulfoxide and EPTC sulfone do not undergo any significant carbon oxidation.

In an additional study, EPTC was metabolized by mouse liver post mitochondrial fractions fortified with NADPH with and without added glutathione (GSH) (Miaullis, 1979a). EPTC sulfoxide, dipropyl amine and glutathione conjugate were the observed products. The reactions were oxygen dependent. Metabolism of EPTC sulfoxide was limited to formation of the glutathione conjugate, a reaction which was shown to be independent of NADPH.

### **Dermal - Rat**

The percutaneous absorption of EPTC in rats was examined in a study using three dosage groups (573.7 ug/25 cm<sup>2</sup>, 91.8 ug/ 2.54 cm<sup>2</sup>, and 54.7 ug/2.54 cm<sup>2</sup>) (Knaak et al., 1986). Most of the applied dose was volatilised before it could be absorbed; however, a small percentage (14-22%) of the radioactivity was recovered in various tissues, urine, feces, and CO<sub>2</sub> 24 hours after application. By correcting for recovery and standard error, a conservative estimate of dermal absorption (18.25%) was derived (Appendix A). Only 1 to 3% of the dose remained on the skin after 24 hours. Due to the use of a different radiolabeling site compared to previous studies the results from this study indicate that the propyl groups are not readily metabolized to CO<sub>2</sub>.

## **B. ACUTE TOXICITY**

**Summary:** The LD<sub>50</sub> and LC<sub>50</sub> values for technical and formulated EPTC are summarized in Table 1. The most common clinical signs of acute toxicity were lethargy, salivation, ataxia, red facial stains, bloody nasal discharge, ano-genital stains, dyspnea, labored respiration, prostration, lachrymation, diarrhea, convulsions, tremors, vocalization, hyperactivity, and

hypersensitivity to stimuli. For EPTC technical, toxicity was reported at 2,600 mg/m (208 mg/kg), 215 mg/kg, and 10,000 mg/kg, the lowest doses tested for inhalation, oral and dermal exposures, respectively. Acute NOEL's were not established from those toxicity studies. For emulsifiable concentrates, toxicity was reported at 7,000 mg/m (571 mg/kg), 489 mg/kg, and 2000 mg/kg, the lowest doses tested for inhalation, oral, and dermal exposures. For granular formulations, toxicity was reported at 5,000 mg/kg for oral, and dermal exposures. Acute inhalation toxicity testing of a granular formulation was not undertaken because the investigators reported that a respirable aerosol could not be generated without destruction of the starting material (MacAskill et al., 1985).

Gross lesions most frequently observed at necropsy were reddened or hemorrhagic gastrointestinal mucosa, reddened or hemorrhagic lungs (irrespective of the route of administration), pale or dark organs (liver, kidney, spleen, thymus, lungs, testes), red fluid in the urinary bladder, lung and liver congestion, and blood on the nose or mouth.

### **Acute Effects in Other Studies**

Acute effects were also seen in developmental toxicity studies and in a neurotoxicity study (See Section G. Developmental Toxicity and Section H. Neurotoxicity for additional details). In a rat teratology study (Nemec et al., 1983) embryotoxicity (early death and resorption) was produced within a four day period after the beginning of exposure with a NOEL of 30 mg/kg/day. In a rabbit teratology study (Giles, 1987), maternal toxicity (cholinergic signs) were present by treatment-day 3 with a NOEL of 40 mg/kg/day. In a single- dose rat neurotoxicity study (Brammer, 1993), necrosis of brain cells was present at all dose levels, with a LOEL of 200 mg/kg. Using a default uncertainty factor of 10, for determination of a NOEL from a LOEL (Beck et al., 1989), the estimated NOEL was 20 mg/kg, and was the definitive NOEL used to assess the risk of potential human acute single-day exposure.

**Table 1. The Acute Toxicities of Technical EPTC and EPTC Formulations**

Species/Sex	Dose/Score	References <sup>a,b</sup>
<b>Technical Grade (98.5%)</b>		
<b>Inhalation LC<sub>50</sub></b>		
Rat (M/F)	3,800-4,300 mg/m <sup>3</sup> (304-351 mg/kg) (4-hour, whole body)	1
<b>Oral LD<sub>50</sub></b>		
Rat	1,620 mg/kg	2
Mice	3160	2
<b>Dermal LD<sub>50</sub></b>		
Rabbit	~ 10,000 mg/kg	2
<b>Intraperitoneal LD<sub>50</sub></b>		
Mice	> 500 mg/kg	3
<b>Ocular Irritation</b>		
Rabbit	Moderate Irritant	2
<b>Dermal Irritation</b>		
Rabbit	Mild Irritant	2
<b>Dermal Sensitization</b>		
Guinea Pig	Negative	4
<b>Emulsifiable Concentrate Formulation (72-87%)</b>		
<b>Inhalation LC<sub>50</sub></b>		
Rat	16,070 mg/m <sup>3</sup> (1311 mg/kg) (4-hr, whole-body)	5
Rat	> 7,000 mg/m <sup>3</sup> (571 mg/kg) (4-hr whole-body)	6
Rat	> 31,500 mg/m <sup>3</sup>	7
<b>continued...</b>		

<sup>a</sup> References: Miller, 1979; 2. PPG Industries, Inc., 1982; 3. Fay and Helmes, 1986. 4. Weir, et al., 1958. 5. Leong and Jessup, 1976; 6. Freeman and Salem, 1980; 7. US EPA, 1983c. <sup>b</sup> Values were from study data submitted by the registrants.

**Table 1. The Acute Toxicities of Technical EPTC and EPTC Formulations**  
(continued)

Species/Sex	Dose/Score	References <sup>a,b,c</sup>
<b>Emulsifiable Concentrate Formulation (72-87%)</b>		
<b>Oral LD<sub>50</sub></b>		
Rat	776-1,300 mg/kg; 1,325-1,500 mg/kg; 916-2,322 mg/kg; 1,025-1,326 mg/kg	8-11
<b>Dermal LD<sub>50</sub></b>		
Rabbit	> 2,000 mg/kg; 2,750	8-11
<b>Ocular Irritation</b>		
Rabbit	Severe Irritant	8-11
<b>Dermal Irritation</b>		
Rabbit	Mild Irritant	8-11
<b>Granular Formulation (2-10%)</b>		
<b>Oral LD<sub>50</sub></b>		
Rat	> 4,640- > 5,000	12-13
<b>continued...</b>		

<sup>a</sup> References: 8. Jamison et al., 1980; 9. Castles and Saunders, 1977; 10. Thompson, 1979; 11. Billow et al., 1982; 12. Castles, 1978; 13. Morgon & Bullock, 1974.

<sup>b</sup> Values were obtained from study data submitted by the registrants.

<sup>c</sup> The calculation for conversion of mg/m<sup>3</sup> to mg/kg for acute inhalation studies was:  
(exposure level mg/m<sup>3</sup>) x (rat respiration rate of 0.96 m<sup>3</sup>/kg/day) x (duration of exposure hours/24 hrs) x (50% respiratory retention).

continued...

**Table 1. The acute Toxicities of Technical EPTC and EPTC formulations**  
(continued)

<b>Granular Formulation (2-10%)</b>		
<b>Dermal LD<sub>50</sub></b>		
Rabbit	> 5,000 mg/kg > 4,460 mg/kg	12-13
<b>Ocular Irritation</b>		
Rabbit	Moderate Irritant Non-Irritant	12-13
<b>Dermal Irritation</b>		
Rabbit	Non-Irritant	12-13

<sup>a</sup> References: 12. Castles, 1978; 13. Morgon and Bullock, 1974.

### **C. SUBCHRONIC TOXICITY**

**Summary:** The subchronic toxicity of technical EPTC via dietary or inhalation exposure was studied in rats and dogs. Degenerative changes of the liver, heart, skeletal muscle, nasal cavity; decreased brain weight, body weight, and food consumption; cholinesterase inhibition; and/or impaired blood clotting functions were present to varying degrees. NOEL's determined from the studies are summarized in Table 2.

#### **Dietary-Rat**

In a 13-week feeding study, 15 albino rats/sex/group were administered technical EPTC at 0, 8, 16, or 32 mg/kg/day (Hollingsworth et al., 1967). Female rats at 32 mg/kg/day had decreased body weights and food consumption. Both sexes in this group had a slightly higher incidence of irregular hepatic cell size associated with some glycogen depletion. A 4% decrease in absolute brain weight was present at 16 and 32 mg/kg/day. The NOEL was 8 mg/kg/day based on these findings. This study had several major deficiencies including no verification of the EPTC concentration in feed and only a portion of the survivors from each group were submitted for necropsy and serum chemistry/hematology analyses.

**Table 2. No-Observed-Effect-Level (NOEL) /Lowest-Observed-Effect-Level (LOEL) for the Subchronic Toxicity of EPTC**

Species/Sex	Exposure Regimen	Effects at LOEL	NOEL	LOEL	(References)/ Comment <sup>a</sup>
			(mg/kg/day)		
Rats (M/F)	13-week diet	Decreased body weight & food consumption, hepatocyte glycogen depletion	16	32	(Hollingsworth, 1967) Incomplete histology & feed analysis.
Rats (M/F)	13-week diet	Myocarditis ---see text---	-	~ 10 <sup>b</sup>	(Tisdell, 1984) Dose levels changed.
Rats (M)	15-week diet	Impaired blood clotting function, mortality	5	80	(Scholler, 1977) No histology.
Dogs (M/F)	15-week diet	Brain cholinesterase inhibition (75-82% of control)	24	49	(Woodard, 1967) Feed analysis incomplete.
Dogs (M/F)	13-week diet	Weight loss and emaciation	-	6 <sup>b</sup>	(Daly, 1985)incomplete
Rats (M/F)	13-week inhalation	Nasal cavity degeneration/ hyperplasia, altered blood coagulation parameters, decreased food consumption. Note: nasal cavity & blood coagulation changes present by exposure day <b>17</b> . - --see text---	0.7 <sup>c,d</sup>	5	(Scott, 1985) Incomplete histology.

<sup>a</sup> Brain weight changes listed in Table 12.

<sup>b</sup> Lowest dose tested.

<sup>c</sup> The calculation used for conversion of mg/m<sup>3</sup> was: (exposure level of mg/m<sup>3</sup>) x (rat respiration rate of 0.96 m<sup>3</sup>/kg/day) x (duration of exposure hrs/24 hrs) x (number of days per week/7 days) x (50% pulmonary absorption/retention)

<sup>d</sup> NOEL of 0.7 mg/kg/day by exposure-day **17** was used to estimate potential repeated-day human health hazard.

### **Dietary-Rat**

In a 13-week feeding study of technical EPTC, 20 Crl:CD(SD)BR rats/sex/group initially received 0, 18, 36, 72, or 120 mg/kg/day (Tisdell et al., 1984). After the sixth week the 18 and 36 mg/kg/day groups were lowered to 3 and 15 mg/kg/day, respectively, since it appeared from the body weights that there might not be a NOEL. The body weights in all the dosage groups continued to be significantly lower than the controls until week 13. At that time the 18/3 mg/kg/day group no longer was statistically different than controls. The food consumption in all but the lowest dosage group was significantly lower. A dose-related chronic myocarditis was observed in both sexes receiving 36/15, 72, or 120 mg/kg/day. Only one male receiving 18/3 mg/kg/day had this cardiomyopathy which was minimal in severity. Aspartate aminotransferase (AST) levels and relative heart weights were elevated in the 72 and 120 mg/kg/day groups which was attributed to the cardiomyopathy. Animals in those higher dosage groups also had elevated liver weights, but no treatment-related liver histopathology. The females in the 120 mg/kg/day group had slightly reduced brain cholinesterase activity (86% of controls). A 5-9% decrease in absolute brain weight was present at the two highest dosages. Although the reduction in the lowest dose level confounded determination of the effect levels, the LOEL for cardiomyopathy appears to be approximately 10 mg/kg/day using a time-weighted average for the lowest dose level. No NOEL was established.

### **Dietary-Rat**

In a 15-week feeding study of technical EPTC, 40-80 male Sprague-Dawley derived rats/group received 0, 5, 80, or 160 mg/kg/day (Scholler, 1977). An additional group received 160 mg/kg/day of analytical grade EPTC. Changes in blood coagulation parameters, including prolongation of prothrombin (PT), activated partial thromboplastin (APTT or PTT), and in vivo clotting times, were present at 80 and 160 mg/kg/day. On study day 22, APTT and PT times were increased 53 and 61% at 80 mg/kg/day (control animals were not tested at that time point, day 22 values were compared to control values at termination). The values at 160 mg/kg/day were also stated to be increased at that time, but the actual numbers were not presented. In vivo clotting time was increased 32% at 80 mg/kg/day and >100% at 160 mg/kg/day. Five mortalities were recorded in the 160 mg/kg/day group between study days 18 and 25, and all were due to hemorrhaging. A single mortality at 80 mg/kg/day did not have evidence of hemorrhage when examined on day 46. The coagulation values at 80 mg/kg/day returned to the normal range by day 40. At 160 mg/kg/day, however, APTT and PT were still increased up to 46% and 26% at termination. Animals at 160 mg/kg/day had increased liver weights despite lower body weights. Body weights were reduced in all treatment groups, but remained within 10% of controls. Brain weights were not recorded. The food consumption in the 160 mg/kg/day group was reduced 11-15% with respect to the control group. Several clinical signs which occurred more frequently in one or more treated groups were blood-like material on the nose and cage, pale eyes/ears, unkempt appearance, and respiratory problems; however, no compound-related effects on clinical signs were reported at 5 mg/kg/day. This was not a standard subchronic study in that the main objective was to more fully investigate the toxic effects observed in ongoing chronic studies. As such, only a limited number of serum chemistry analyses were performed, and the results for histopathology and EPTC concentration in the feed were not reported. Based on prolonged prothrombin (PT), activated

partial thromboplastin (APTT), in vivo clotting times, and mortality, the NOEL was 5 mg/kg/day.

#### **Dietary-Dog**

When 3 beagle dogs/sex/group were administered 0, 450, 900, or 1800 ppm (males- 0, 10, 24, or 49 mg/kg/day; females- 0, 12, 26, or 50 mg/kg/day) technical EPTC in the feed for 15 weeks, only minimal toxicological effects were observed (Woodard et al., 1967). The most significant finding was slightly reduced brain cholinesterase activity (males 75% of control, females 82% of control) at the 1800 ppm level. One animal in that group had gastric mucosal changes which may have been compound-related and another animal had a progressive reduction in hemoglobin and a weight loss of 1.5 kg. Several dogs in the 900 and 1800 ppm groups had small areas of hair loss (cause unknown). A 9% decrease in absolute brain weight was present at 1800 ppm. The NOEL in this study was 900 ppm (24 mg/kg/day) based on the brain cholinesterase inhibition and decreased brain weight. This study had major deficiencies including no analysis of the feed for EPTC and only three animals per sex assigned to each dosage level.

#### **Dietary-Dog**

In a 13-week study, 6 beagle dogs/sex/group were fed diets containing 0, 200, 600, or 1800 ppm (males- 6, 18, 49 mg/kg/day; females- 6, 17, 54 mg/kg/day) technical EPTC (Daly et al., 1985). Plasma cholinesterase was slightly inhibited (71% of control) in 1800 ppm males. Two 1800 ppm males and one 200 ppm male had progressive weight losses of between 1.9 and 2.1 kg during the study, and were clinically described as emaciated. The weight loss in the two 1800 ppm males significantly reduced the group mean during most of the treatment period. These same animals had increased blood urea nitrogen levels which may have been related to the weight losses. Histological examination of the two revealed muscle atrophy (biceps femoris). Muscle tissue was histologically examined only in the control and 1800 ppm dose groups, and only liver, kidney, and stomach were histologically examined in the emaciated 200 ppm male. One of the 1800 ppm males frequently had excessive salivation during the exposure period. Food consumption at 1800 ppm was reduced during the first week in both sexes. The female food consumption returned to normal after the first week, but male food consumption continued to be slightly lower than the control group for the remainder of the study. A 4-8% decrease in absolute brain weight was present at the two higher dosages. A definitive NOEL for muscle atrophy could not be determined from this study since muscle tissue from 200 and 600 ppm males was not examined histologically. Based on weight loss and emaciation, the LOEL was 200 ppm (6 mg/kg/day).

#### **Inhalation-Rat**

In a 13-week study 24 Sprague-Dawley rats/sex/group were exposed to technical EPTC for 6 hrs/day for 5 days each week (Scott et al., 1985). Interim sacrifices occurred at weeks 3 and 9-10. The mean chamber concentrations for the four groups were 0, 8.3, 58, or 290 mg/m<sup>3</sup> (~0, 0.7, 5, or 25 mg/kg/day). Histologically, an increased incidence of myocardial degeneration was present in 25 mg/kg/day males and females starting at 3 weeks (exposure-day 15). Segmental degeneration of nasal olfactory epithelium was present in 5

mg/kg/day rats at 3 and 13 weeks. Necrotizing/suppurative rhinitis, or basal cell hyperplasia with squamous metaplasia of the nasal cavity epithelium were also present at 5 and 25 mg/kg/day at 3 and/or 13 weeks. Hepatocellular lipidosis was evident in 25 mg/kg/day females at 3, 9, and 13 weeks. The investigators suggested that the myocardial degeneration was due to a possible viral infection that may have been exacerbated by the treatment with EPTC. However, no evidence of a viral etiology was submitted. Elevated aspartate amino transferase (AST) levels in 25 mg/kg/day females were associated with the increased incidence and severity of myocardial degeneration. A 6-8% decrease in brain weight was present at 25 mg/kg/day. When compared to the control group, all the treatment groups except the 0.7 mg/kg/day females had slight reductions in brain cholinesterase activity (>80% of control). The investigators did not believe these reductions were all biologically significant, especially when the activity represented 85% or more of the controls.

Blood coagulation parameters evaluated included prothrombin time (PT), partial thromboplastin time (PTT or APTT), and Stypven time (Russell's Viper Venom Time). A dose-related 39-43% prolongation of PTT was present in 5 and 25 mg/kg/day females at 3 weeks. Values for males were increased 22-33%. Prolongation of PTT was variably present at later time points, including a 25-35% prolongation of Stypven and PTT times in 25 mg/kg/day males at termination. A 7% increase in prothrombin time was present in 5 and 25 mg/kg/day females at termination, but was not biologically meaningful (Dodds, 1989). Food consumption was occasionally lower at 5 and 25 mg/kg/day. Several clinical signs that occurred more frequently at 5 and 25 mg/kg/day were irritation around the eyes, chromodacryorrhea, and alopecia. The NOEL was 0.7 mg/kg/day based on decreased food consumption, clinical signs, prolonged PTT, and nasal cavity degeneration/hyperplasia. The 3-week (exposure-day 17) NOEL of 0.7 mg/kg/day for nasal cavity degeneration/hyperplasia and prolonged partial thromboplastin time was used to estimate the risk of potential human repeated daily occupational exposure. A deficiency of this study was an apparent lack of histological examination of peripheral nerve. However, this did not prevent the use of this study to evaluate potential human toxicity.

#### **D. CHRONIC TOXICITY/ONCOGENICITY**

**Summary:** The oncogenicity and/or chronic toxicity of technical EPTC was studied in rats, mice, and dogs. There was no evidence of oncogenicity in any study. Chronic toxicity included decreases in food consumption, brain weight, and body weight; cataracts; neuromuscular degeneration/atrophy; and/or cardiac toxicity. The LOEL's and NOEL's determined in the studies are listed in Table 3.

##### **Dietary Mouse**

In an oncogenicity study, groups of 60 CRL:CD-1 mice per sex were fed technical EPTC in the diet at 0, 200, 600, or 1800 ppm (males- 0, 27, 79, or 221 mg/kg/day; females- 0, 35, 96, or 252 mg/kg/day) for 78 weeks (Tisdell et al., 1986b). The incidence of neoplastic lesions was not significantly greater in any of the treatment groups with respect to the control group. The 600 and 1800 ppm groups had significantly lower body weights and food consumption (> 85% of control). No other treatment-related effects were apparent although brain weights were not reported, and muscle and nerve were not on the histopathology tissue list. Based

on these findings the NOEL was 200 ppm (27 mg/kg/day). DPR considered this study acceptable based on FIFRA guidelines.

#### **Dietary-Mouse**

In a two-year oncogenic study, 60 CD-1 mice/sex/group were fed technical EPTC at 0, 5, 20, or 80 mg/kg/day (Goldenthal et al., 1978). A 5-10% decrease in absolute brain weight was present at 5 mg/kg/day and above at the 12 month interim sacrifice, while a 3-9% decrease was evident at termination. The study was not acceptable to DPR due to the lack of achieving a Maximum Tolerated Dose (MTD).

#### **Dietary-Rat**

In a 54-week study, with a 47-week interim sacrifice, groups of 60 Sprague-Dawley rats/sex/group were fed diets containing 0, 5, 20, or 80 mg/kg/day technical EPTC (Trutter et al., 1978). The dosage level for a subgroup of 10 rats/sex from the 80 mg/kg/day group was increased to 160 mg/kg/day at the start of week 16. Two animals in the 80 mg/kg/day group and one in the 160 mg/kg/day group died from hemorrhaging between weeks 12 and 19. At the week 47 sacrifice, prolonged blood coagulation times were detected. A dose-related increase in Russell's Viper Venom Time (Stypven assay) was present in all male groups, reaching statistical significance at 80 and 160 mg/kg/day for 17 and 32% increases respectively. Generally, in the majority of male treated groups, mean values for coagulation time, PT, APTT, fibrinogen, and clotting factors II, VII, IX, and X tended to be greater than control, but not statistically different. All other deaths occurred in the control and lower dose groups after week 20, and did not appear to be treatment-related. A dose-related increase in the incidence and severity of chronic myocarditis was observed in the 20, 80, and 160 mg/kg/day groups and considered, by the investigators, to be an EPTC-related exacerbation of a spontaneous disease of aging rats. Hearts of 5 mg/kg/day animals were not histologically examined. The absolute and relative weights of the liver, kidneys, and testes were slightly higher in the 80 and 160 mg/kg/day groups. A 4-7% decrease in brain weight was also present in those groups. Reduced body weights and food consumption (>86% of control) were observed at 20 mg/kg/day and above. The study NOEL was 5 mg/kg/day based reduced body weights and reduced food consumption. A true NOEL for myocarditis at either the 47- or 54- week sacrifice periods could not be determined from the study due to the lack of cardiac histological examination in the 5 mg/kg/day animals. This study also had other major deficiencies in that the EPTC concentration in the feed was not reported and the hematology/serum chemistry analyses were not performed on all survivors.

**Table 3. No-Observed-Effect-Level (NOEL)/Lowest-Observed-Effect-Level (LOEL)/for the Chronic Toxicity of EPTC.**

<b>Species/Sex</b>	<b>Exposure Regimen</b>	<b>Effects at LOEL<sup>a</sup></b>	<b>NOEL mg/kg/day</b>	<b>LOEL</b>	<b>(Reference)/Comment</b>
Mouse (M/F)	78-week diet	Decreased body weight & food consumption.	27	79	(Tisdell, 1968b) Acceptable under FIFRA
Mouse (M/F)	2-year diet	No effects at highest dose.	≥80 <sup>b</sup>	-	(Goldenthal, 1978, Not acceptable under FIFRA
Rat (M/F)	54-week diet	Decreased body weight & food consumption ---see text---	5 <sup>c</sup>	20	(Trutter, 1978) Incomplete histology & feed analysis.
Rat (M/F)	2-year diet	Neuromuscular Degeneration ---see text---	0.5 <sup>d,e</sup>	5 <sup>f</sup>	(Warner, 1983) NOEL not established.
Rat (M/F)	2-year diet	Cardiomyopathy; neuro-muscular atrophy---see text---	-	9 <sup>f</sup>	(Dickie, 1987) Acceptable under FIFRA, incomplete interim histology.
Dog (M/F)	1-year diet	Only emesis at highest dose tested.	≥48 <sup>b</sup>	-	(Tisdell, 1986a) Acceptable under FIFRA
Dog (M/F)	1-year capsule	Neuromuscular & cardiac degeneration, mortality	8	60	(Sprague, 1987) Acceptable under FIFRA

<sup>a</sup> Brain weight changes listed in Table 12.

<sup>b</sup> Highest dose tested.

<sup>c</sup> NOEL for myocarditis not established due to lack of cardiac histological examination of 5 mg/kg/day animals.

<sup>d</sup> NOEL estimated from LOEL using an uncertainty factor of 10 as a default procedure.

<sup>e</sup> Used as the definitive NOEL to estimate potential chronic human health hazard.

<sup>f</sup> Lowest dose tested.

### Dietary-Rat

In a two year combined chronic/oncogenicity study, groups of 60 Charles River CD rats per sex were fed technical EPTC in the diet at 0, 5, 25, or 125 mg/kg/day (Warner et al., 1983; Goldenthal, 1985). Mortality was significantly higher in 125 mg/kg/day males (35/50 vs. 21/50 in control). The incidence of deaths in this group was highest during two periods (weeks 22 to 24 and weeks 98 to 104). At the 12-month interim sacrifice, chronic myocarditis was observed in 4/10 males and 5/10 females in the 125 mg/kg/day groups, but in none of the control animals. No other treatment-related effects were noted at that time. In addition, cardiac mononuclear cell inflammation or chronic myocarditis was present in 6/11 males at 125 mg/kg/day which died as early as week 24. Ophthalmoscopic examinations conducted at week 104 demonstrated an "unusually high" incidence of cataract changes in 125 mg/kg/day females. The actual incidence rate was not reported. At termination, there was a dose-related increase in neuromuscular atrophy and degeneration in both males and females (Table 4). Other treatment-related effects observed at the terminal sacrifice were chronic myocarditis and cataracts (females). There was no treatment-related neoplasia in any group. Dose-related reductions in body weights (15-40%) were noted at 25 and 125 mg/kg/day. Occasional statistically significant differences in the body weights occurred at 5 mg/kg/day, but they remained within 10% of the control mean. A 4-15% decrease in absolute brain weight was present at 25 and 125 mg/kg/day. Food consumption was reduced in a dose-related manner (8-16%) in all the treatment groups. Several clinical signs which occurred more frequently at 125 mg/kg/day were red or reddish-brown urine (males), impaired hindleg function, posterior testes, or cloudy/white cornea or whiteness internally in the eye. The true incidence of cataract formation in the female dose groups could not be determined due to the incomplete reporting of the ophthalmoscopic and histologic examinations.

The 2-year study LOEL was 5 mg/kg/day based on the neuromuscular degeneration in male rats. Muscular degeneration was also present in females at that dose, but the incidence (6%) did not reach statistical significance compared to the control incidence of zero. Using an uncertainty factor of 10 as a default procedure for determining a NOEL from a LOEL (Beck et al., 1989), the estimated-no-effect-level at 2-years, for neuromuscular degeneration, was 0.5 mg/kg/day. The NOEL of 0.5 mg/kg/day was one of the definitive NOEL's used to estimate the risk of potential chronic human exposure. This study was acceptable to DPR based on FIFRA testing guidelines.

**Table 4. Incidence of Treatment-Related Microscopic Lesions in CR-CD Rats Fed EPTC for 24 Months (Warner et al., 1983)**

Observation	Dosage (mg/kg/day)			
	0	5	25	125
<b>MALES</b>				
<b>Muscle, at sciatic</b>	(46) <sup>a</sup>	(49)	(47)	(39)
Atrophy	1 <sup>+++</sup>	0	22 <sup>***</sup>	36 <sup>***</sup>
Degeneration	0	5 <sup>*</sup>	9 <sup>**</sup>	1
<b>Nerve, sciatic</b>	(44)	(47)	(46)	(38)
Atrophy	0 <sup>+++</sup>	0	0	8 <sup>**</sup>
Degeneration	10 <sup>+++</sup>	9	37 <sup>***</sup>	25 <sup>***</sup>
<b>Heart</b>	(50)	(50)	(50)	(50)
Chronic Myocarditis	23	16	26	34 <sup>*</sup>
<b>Eye</b>	(46)	(21)	(10)	(39)
Cataracts	4 <sup>b</sup>	3	2	1
<b>FEMALES</b>				
<b>Muscle, at sciatic</b>	(47)	(46)	(50)	(43)
Atrophy	0 <sup>+++</sup>	0	3	34 <sup>***</sup>
Degeneration	0	3	10 <sup>***</sup>	0
<b>Nerve, sciatic</b>	(46)	(42)	(49)	(43)
Atrophy	0 <sup>+++</sup>	0	0	5 <sup>**</sup>
Degeneration	7 <sup>+++</sup>	4	32 <sup>***</sup>	33 <sup>***</sup>
<b>Heart</b>	(50)	(50)	(50)	(50)
Chronic Myocarditis	5	8	4	33 <sup>***</sup>
<b>Eye</b>	(47)	(7)	(11)	(48)
Cataract	0 <sup>b</sup>	3	2	18 <sup>***</sup>

<sup>a</sup>Number examined in parenthesis.

<sup>b</sup>Trend analysis could not be done due incomplete histological examination of 5 & 25 mg/kg/day animals.

<sup>+++</sup>Significant trend at  $p < 0.001$  based on a dose-weighted chi-square trend test (Peto et al., 1980)

<sup>\*</sup> $p < 0.05$  by the Fisher Exact Test

<sup>\*\*</sup> $p < 0.01$  by the Fisher Exact Test

<sup>\*\*\*</sup> $p < 0.001$  by the Fisher Exact Test

### Dietary-Rat

Groups of 90 Crl:CD(SD)BR rats were fed technical EPTC in the diet at 0, 9, 18, 36, or 72 mg/kg/day in another two year combined chronic/oncogenicity study (Dickie, 1987). There were no treatment-related differences in survival or tumor incidence. Dose-related degenerative changes in the peripheral nerve, skeletal muscle, and heart were observed at the 12 and 18-month interim sacrifices and at termination (Tables 5,6,7). These changes were not observed at the 6 month interim sacrifice with the exception of one female in the 36 mg/kg/day group that had cardiomyopathy. The hearts of other rats sacrificed at 6 months were not examined histologically. Steatosis was frequently associated with muscular atrophy in the males, but only occasionally in the females. The peripheral nerve degeneration was characterized by loss of myelin staining with an increase of space between axons, cholesterol clefts, and mineralization of the blood vessels for the nerve. The degenerative foci in the heart were frequently associated with fibrosis and mononuclear cell infiltration. There were dose-related elevations in AST (25-100%) in both sexes at 36 and 72 mg/kg/day, and in males only at 18 mg/kg/day. The elevations occurred at various points throughout the study, and at times reached statistical significance at all dose levels. The increases were thought to be related to the skeletal muscle or myocardial degeneration. Like the previous study (Werner et al., 1983), an increase in the occurrence of cataracts was observed in females. At 24 months, 8/21 (38%) of rats at 72 mg/kg/day had cataract vs 0/22 controls ( $p=0.001$ ). The incidence was 2/25, 0/27, and 2/20 for the 9, 18, and 36 mg/kg/day groups, respectively.

Body weights in all treatment groups were significantly reduced (>60% of control), although the 9 and 18 mg/kg groups were similar to the controls by week 104. The body weights in 9 mg/kg/day females were only significantly lower on a few occasions. Consistent treatment-related decreases in food consumption (>79% of control) occurred for both sexes at the 36 and 72 mg/kg/day levels. A 4-12% decrease in absolute brain weight was present at 9 mg/kg/day and above. A dose-related clinical sign present at all EPTC dose levels was a "hindquarter muscle syndrome" characterized by a gradual onset of paralysis, skeletal muscle atrophy in the rear legs, inability to support the hind quarters, rear legs hanging through the wire mesh cage floor, and a hypersensitivity to touch. The syndrome was first detected at about week 46 and eventually had a peak incidence of about 89% of the 72 mg/kg/day males. The condition was more prominent in rats which died during the study or were sacrificed in moribund condition.

Definitive six-month NOEL's for males and females could not be determined, as not all animals at that time point were histologically examined for the presence of cardiomyopathy. At the 12-month sacrifice, the LOEL for males and the NOEL for females was 9 mg/kg/day based on cardiomyopathy. At the 18-month sacrifice, the LOEL for males and females was 9 mg/kg/day based on cardiomyopathy. At 24-months, the male LOEL was 9 mg/kg/day, based on cardiomyopathy and necropsy evidence of skeletal muscle atrophy. The female LOEL was also 9 mg/kg/day, based on cardiomyopathy. The incidence of cardiomyopathy at 24 months was increased in all EPTC-treated groups as compared to controls. However, the incidence at the 9 mg/kg/day level did not reach statistical significance with the Fischer's Exact Test due to the incidence of age-related cardiomyopathy in controls, which hindered detection of chemical-related change (Burek, 1978; MacKenzie and Alison, 1990). A significant trend ( $p < 0.001$ ) was present in females when the occurrence of cardiomyopathy was analyzed using

the dose-weighted chi-square trend test. This study was acceptable to DPR as a combined chronic toxicity/oncogenicity study based on FIFRA testing guidelines.

**Table 5. Incidence of Degenerative Lesions in the Skeletal Muscle, Nerve, and Heart in Crl:CD(SD)BR Rats Fed EPTC for 12 months (Dickie, 1987).**

Observation	Dosage (mg/kg/day)				
	0	9	18	36	72
<b>MALES</b>					
<b>Skeletal Muscle</b>	(10) <sup>a</sup>	(10)	(10)	(10)	(10)
Degeneration	0	0	0	0	0
Monocyte Infiltration	0	0	0	0	0
<b>Sciatic Nerve</b>	(10)	(10)	(10)	(10)	(10)
Monocyte infiltration	0 <sup>+</sup>	0	0	1	1
<b>Heart</b>	(10)	(10)	(10)	(10)	(10)
Degenerative Cardiomyopathy	1 <sup>+++</sup>	7 <sup>**</sup>	10 <sup>***</sup>	10 <sup>**</sup>	10 <sup>***</sup>
Fibrosis	0 <sup>+</sup>	3	4 <sup>*</sup>	2	5 <sup>*</sup>
Monocyte Infiltration	2 <sup>+++</sup>	9 <sup>**</sup>	10 <sup>***</sup>	8 <sup>*</sup>	10 <sup>***</sup>
<b>FEMALES</b>					
<b>Skeletal Muscle</b>	(10)	(10)	(10)	(10)	(9)
Degeneration	0 <sup>+</sup>	0	0	0	1
Monocyte Infiltration	0 <sup>+</sup>	0	0	0	1
<b>Sciatic Nerve</b>	(10)	(10)	(10)	(10)	(10)
Monocyte Infiltration	0	0	0	0	0
<b>Heart</b>	(10)	(10)	(10)	(10)	(10)
Degenerative Cardiomyopathy	1 <sup>+++</sup>	2	6 <sup>*</sup>	9 <sup>***</sup>	10 <sup>***</sup>
Fibrosis	0 <sup>++</sup>	0	1	0	4 <sup>*</sup>
Monocyte Infiltration	3 <sup>+++</sup>	2	5	8 <sup>*</sup>	10 <sup>**</sup>

<sup>a</sup> Number examined in parenthesis  
<sup>+</sup> Significant trend at p<0.05 based on a dose-weighted chi-square trend test (Peto et al., 1980)  
<sup>++</sup> Significant trend at p<0.01 based on a dose-weighted chi-square trend test (Peto et al., 1980)  
<sup>+++</sup> Significant trend at p<0.001 based on a dose-weighted chi-square trend test (Peto et al., 1980)  
<sup>\*</sup> Significant different from the control group at p <0.05 by the Fisher Exact Test  
<sup>\*\*</sup> Significant different from the control group at p <0.01 by the Fisher Exact Test  
<sup>\*\*\*</sup> Significant different from the control group at p <0.001 by the Fisher Exact Test

**Table 6. Incidence of Degenerative Lesions in the Skeletal Muscle, Nerve, and Heart in Crl:CD(SD)BR Rats Fed EPTC for 18 Months (Dickie, 1987)**

Observation	Dosage (mg/kg/day)				
	0	9	18	36	72
<b>MALES</b>					
<b>Skeletal Muscle</b>	(10) <sup>a</sup>	(10)	(10)	(10)	(9)
Atrophy	0 <sup>+++</sup>	0	0	0	8 <sup>***</sup>
Degeneration	0 <sup>+</sup>	0	0	2	2
Steatosis	0 <sup>+++</sup>	0	0	0	5 <sup>*</sup>
<b>Sciatic Nerve</b>	(10)	(10)	(10)	(10)	(10)
Decreased Myelin	0 <sup>++</sup>	0	0	2	3
<b>Heart</b>	(10)	(10)	(10)	(10)	(10)
Degenerative Cardiomyopathy	3 <sup>+++</sup>	9 <sup>**</sup>	8 <sup>*</sup>	9 <sup>**</sup>	10 <sup>**</sup>
Fibrosis	1 <sup>+</sup>	2	1	3	5 <sup>*</sup>
Monocyte Infiltration	1 <sup>+</sup>	4	4	3	5 <sup>*</sup>
<b>FEMALES</b>					
<b>Skeletal Muscle</b>	(10)	(10)	(10)	(10)	(10)
Atrophy	0 <sup>+++</sup>	0	0	1	5 <sup>*</sup>
Degeneration	0	0	0	1	0
Steatosis	0	0	0	0	0
<b>Sciatic Nerve</b>	(10)	(10)	(10)	(10)	(10)
Decreased Myelin	1 <sup>+</sup>	1	1	3	4
<b>Heart</b>	(10)	(10)	(10)	(10)	(10)
Degenerative Cardiomyopathy	1 <sup>+++</sup>	7 <sup>**</sup>	10 <sup>***</sup>	10 <sup>***</sup>	10 <sup>***</sup>
Fibrosis	1	2	0	2	3
Monocyte Infiltration	1 <sup>+++</sup>	0	0	0	6

<sup>a</sup> Number examined in parenthesis  
<sup>+</sup> Significant trend at p<0.05 based on dose-weighted chi-square trend test (Peto et al., 1980)  
<sup>++</sup> Significant trend at p<0.01 based on dose-weighted chi-square trend test (Peto et al., 1980)  
<sup>+++</sup> Significant trend at p<0.001 based on dose-weighted chi-square trend test (Peto et al., 1980)  
<sup>\*</sup> Significantly different from the control group at p<0.05 by the Fisher Exact Test  
<sup>\*\*</sup> Significantly different from the control group at p<0.01 by the Fisher Exact Test  
<sup>\*\*\*</sup> Significantly different from the control group at p<0.001 by the Fisher Exact Test

**Table 7. Incidence of Degenerative Lesions in the Skeletal Muscle, Nerve, and Heart in CrI:CD(SD)BR Rats Fed EPTC for 24 Months (Dickie, 1987)**

Observation	Dosage (mg/kg/day)				
	0	9	18	36	72
<b>Males</b>					
<b>Skeletal Muscle</b>	(18) <sup>a</sup>	(30)	(28)	(24)	(25)
Atrophy	2 <sup>+++</sup>	4	18 <sup>***</sup>	20 <sup>***</sup>	25 <sup>***</sup>
Degeneration	0 <sup>+++</sup>	2	10 <sup>**</sup>	14 <sup>***</sup>	23 <sup>***</sup>
Steatosis	0 <sup>++</sup>	0	2	9 <sup>**</sup>	9 <sup>**</sup>
<b>Sciatic Nerve</b>	(18)	(30)	(28)	(24)	(24)
Cholesterol Clefts	0 <sup>+++</sup>	0	0	7 <sup>*</sup>	15 <sup>***</sup>
Decreased Myelin	0 <sup>+++</sup>	0	0	10 <sup>**</sup>	21 <sup>***</sup>
Mineralization	0 <sup>+++</sup>	0	0	8 <sup>*</sup>	18 <sup>***</sup>
<b>Heart</b>	(18)	(30)	(28)	(24)	(25)
Degenerative Cardiomyopathy	13 <sup>+</sup>	26	27 <sup>*</sup>	24 <sup>**</sup>	24 <sup>*</sup>
Fibrosis	5 <sup>+++</sup>	8	16 <sup>*</sup>	14 <sup>*</sup>	20 <sup>***</sup>
Monocyte Infiltration	0 <sup>++</sup>	3	13 <sup>***</sup>	8 <sup>**</sup>	10 <sup>**</sup>
<b>FEMALES</b>					
<b>Skeletal Muscle</b>	(22)	(25)	(27)	(20)	(21)
Atrophy	2 <sup>+++</sup>	3	3	12 <sup>***</sup>	21 <sup>***</sup>
Degeneration	1 <sup>+++</sup>	1	0	4	11 <sup>***</sup>
Steatosis	0 <sup>++</sup>	0	0	0	2
<b>Sciatic Nerve</b>	(22)	(25)	(27)	(20)	(20)
Cholesterol Clefts	0 <sup>++</sup>	0	0	0	3 <sup>**</sup>
Decreased Myelin	0 <sup>+++</sup>	1	0	4 <sup>*</sup>	13 <sup>***</sup>
Mineralization	0 <sup>+++</sup>	1	1	5 <sup>*</sup>	7 <sup>**</sup>
<b>Heart</b>	(22)	(25)	(27)	(20)	(21)
Degenerative Cardiomyopathy	11 <sup>+++</sup>	18	22 <sup>*</sup>	19 <sup>**</sup>	21 <sup>***</sup>
Fibrosis	8 <sup>+++</sup>	8	9	14 <sup>*</sup>	19 <sup>***</sup>
Monocyte Infiltration	2 <sup>+++</sup>	3	6	11 <sup>**</sup>	11 <sup>**</sup>

<sup>a</sup> Number examined in parenthesis

<sup>+</sup> Significant trend at  $p < 0.05$  based on dose-weighted chi-square trend test (Peto et al., 1980)

<sup>++</sup> Significant trend at  $p < 0.01$  based on dose-weighted chi-square trend test (Peto et al., 1980)

<sup>+++</sup> Significant trend at  $p < 0.001$  based on dose-weighted chi-square trend test (Peto et al., 1980)

<sup>\*</sup> Significantly different from the control group at  $p < 0.05$  by the Fisher Exact Test

<sup>\*\*</sup> Significantly different from the control group at  $p < 0.01$  by the Fisher Exact Test

<sup>\*\*\*</sup> Significantly different from the control group at  $p < 0.001$  by the Fisher Exact Test

### **Dietary-Dog**

Six beagle dogs/sex/group were fed diets containing 0, 200, 600, or 1800 ppm (males- 0, 5.6, 17.3, or 48 mg/kg/day; females- 0, 6.1, 17.4, or 54.7 mg/kg/day) technical EPTC for one year (Tisdell et al., 1986a). The severity of emesis was slightly increased at 1800 ppm. A 3-5% decrease in absolute brain weight was present at 200 ppm and above. The NOEL for emesis was greater than or equal to 1800 ppm (48 mg/kg/day).

### **Oral Capsule-Dog**

In a second one-year study, technical EPTC was administered in oral capsules at 0, 1, 8, or 60 mg/kg/day to 4-5 beagle dogs/sex/group (Sprague et al., 1987). One 60 mg/kg/day male was sacrificed on day 84 after developing severe signs of toxicity including weight loss and obvious incoordination and weakness in the hind legs. At 60 mg/kg/day, males gained 13% less weight than the controls and had slight reductions in hemoglobin and hematocrit values. Both sexes, at that dose level had a 3-fold elevation in alkaline phosphatase levels. A reduction in serum cholinesterase levels was also present, being more prominent in the males. The serum cholinesterase activity in males at 60 mg/kg/day was 57-68% of control, and in females was 74-77% of control. A 7-9% decrease in absolute brain weight was present in the two highest dose groups. Muscle degeneration was present in males, and degeneration of the spinal cord and peripheral nerves was present in both sexes, though more severe in males. The 60 mg/kg/day male dog sacrificed on day 84 had focally severe myocardial degeneration. In addition, bile stasis and thymus atrophy were noted in several animals at 60 mg/kg/day. The study was considered acceptable by DPR based on FIFRA testing guidelines. The variation in results between the two 1-year dog studies may have been related to the method of compound administration (diet vs. capsule).

## **E. GENOTOXICITY**

**Summary:** Results of the studies on genotoxicity of technical EPTC are summarized in Tables 8 and 9.

### **Gene Mutation**

The results from gene mutation assays using several different microorganisms (Salmonella typhimurium, Saccharomyces cerevisiae, and Escherichia coli) were all negative for technical EPTC. Two Ames assays conducted by independent laboratories were reviewed separately and were considered unacceptable by DPR due to the lack of replicates (Jagannath et al., 1977; and Shirasu et al., 1978). However, since both assays used similar concentrations (1 - 5000 ug/plate), one assay might be considered a replicate trial or confirmation of the other. An Ames assay reported in the open literature was negative, but no plate counts were included (Anderson et al., 1972). An additional assay employing both Salmonella typhimurium and Escherichia coli was also negative for induction of revertants (Callander, 1992). In mammalian cells, two independent mouse lymphoma forward mutation assays suggested that EPTC was mutagenic with activation (Majeska, 1984a; Rudd et al., 1986). However, one of these two assays was not acceptable to DPR since it did not include a second confirmatory trial (Rudd et al., 1986).

**Table 8. The Effects of EPTC on Gene Mutation**

Test Type/System	Strain	Dose	S9 <sup>a</sup>	Results	Comments/Reference
<u>S. typhimurium</u> <sup>b</sup>	TA98,TA100,TA1535 TA1537,TA1538	0.001,0.01,1.0, 5.0 ug/plate	±	Neg	Experiment not repeated, S9 activity not confirmed. (Jagannath et al., 1977)
<u>Saccharomyces</u>	D4	Not reported		Neg	
<u>S. typhimurium</u>	TA98,TA100,TA1535 ,TA1537,TA1538	10, 50, 100, 500, 1000 ug/plate	±	Neg	Experiment not repeated (Shirasu et al., 1978)
<u>E. coli</u> <sup>c</sup>	WP2P, WP2p, <u>uvra</u>	100-5000 ug/plate	±	Neg	
<u>Salmonella sp.</u>	Not reported	Not reported		Neg	Insufficient Information (Anderson et al., 1972)
Mouse Lymphoma	L5178Y	0.005,0.01,0.02,0.0 4,0.06 ul/m	+	Pos	3-5 fold increased mutation frequency at 0.06 ul/ml (Majeska, 1984a)
	L5178Y	0.0125,0.025, 0.05,0.1,0.15 ul/ml	-	Neg	
Mouse Lymphoma	L5178Y	42,60,86,175, 250 ug/ml	+	Pos	5-6 fold increased mutation frequency at 175 & 250 ug/ml, experiment not repeated (Rudd et al., 1986)
	L5178Y	118,132,145, 162,180,200 ug/ml	-	Neg	Experiment not repeated

<sup>a</sup>Rat S9 fraction used for activation. <sup>b</sup>Salmonella typhimurium. <sup>c</sup>Escherichia coli.

**Table 9. The Effects of EPTC on Structural Chromosomal Aberrations and Other Genotoxic Effects**

Test Type/System	Strain	Dose	S9 <sup>a</sup>	Results	Comments/reference
<b>STRUCTURAL CHROMOSOMAL ABERRATIONS</b>					
Cytogenic	L5178Y TK +/-	0.005,0.01,0.02,0.04,0.06 ul/ml	+	Neg	(Majeska, 1984b)
	L5178Y	0.0125,0.025,0.05,0.10,0.15 ul/ml	-	Pos	Increased aneuploidy at 0.0125, increased aberrations at 0.025 ul/ml. Not dose-related.
Cytogenic	CHO	15,30,75,150 ug/ml	+	Neg	(Ivett et al., 1985)
	CHO	30,60,90,120 ug/ml	-	Neg	
Micronucleus	CD-1 Mouse (M/F)	250,500,1000 mg/kg (single dose)		Pos	Insufficient data, not dose-related. (Majeska, 1984c)
	CD-1 Mouse (M/F)	1000,1200,1400 mg/kg (two doses)		Neg	Insufficient data, high mortality.
Micronucleus	C57BL/6JfB10/Alpk	0, 800 mg/kg		Pos	Only 2 sampling times. (Randal et al., 1992)
<b>OTHER GENOTOXIC EFFECTS</b>					
<u>B. subtilis</u> rec	M45, H17	1,5,10,25,50,100% V/V	-	Neg	Experiment not repeated, activation not included.(Shirasu et al., 1978)
Fibroblast DNA Nick Translation	Human Skin			Neg	Insufficient protocol (Synder, 1984)
Unscheduled DNA Synthesis (UDS)	Rat Hepatocyte	0.1 - 5000 ug/ml		Neg	(Bakke & Mirsalis)

<sup>a</sup> Rat S9 fraction used for activation

## **Structural Chromosome Aberrations**

In a mouse lymphoma cytogenetic assay, no concentration-dependent increases in structural or numerical aberrations were observed (Majeska, 1984b). No increase in chromosomal aberrations was detected in another cytogenetic assay in Chinese hamster ovary cells (Invett and Spicer, 1985). Both of these in vitro assays were considered acceptable by DPR.

The results from a bone marrow micronucleus assay in mice were equivocal (Majeska, 1984c). In the first trial there was an increase in micronuclei at 72 hours, although the increases were not dosage-related. In the second trial no increase was noted despite higher dosage levels and multiple doses. DPR considered this study unacceptable for several reasons including a high mortality rate in the second trial which made statistical analysis of the results for the mid and high-dose groups impractical. An additional bone marrow micronucleus assay in mice was also unacceptable (Randal et al., 1992). In that assay, a slight though statistically significant increase in micronucleated polychromatic erythrocytes was present at 24 hours. The study was deficient due to the lack of three sampling times.

## **Other Genotoxic Effects**

A microbial test for DNA damage using *Bacillus subtilis* rec (strains H17 and M45) was negative for EPTC (Shirasu et al., 1978). However, this test had several major deficiencies including no replicates and no activation included. In another test the ability of technical EPTC to produce DNA damage or elicit a repair response in human fibroblasts was evaluated by the nick translation assay and by alkaline sucrose velocity sedimentation (Snyder, 1984). The results were negative, but DPR considered this study unacceptable due to inadequate reporting of the protocol for this particular assay. In a third study, EPTC did not induce unscheduled DNA synthesis in rat primary hepatocytes (Bakke and Mirsalis, 1986). DPR considered this study acceptable.

## **F. REPRODUCTIVE TOXICITY**

**Summary:** Two FIFRA-guideline 2-generation studies in rats were available for evaluation of the reproductive toxicity of technical EPTC. In adult animals the NOEL was 4 mg/kg/day for cardiomyopathy, while a NOEL of 11.1 mg/kg/day was determined for decreased pup weight. In addition, one non-FIFRA-guideline rat reproductive study was conducted with technical EPTC and a formulation. The NOEL/LOEL information is included in Table 10.

### **Dietary-Rat**

In the first two-generation reproductive study, Sprague-Dawley rats were fed diets containing 0, 40, 200, or 1000 ppm (males- 0, 2.3, 11.1, or 53.4 mg/kg/day; females- 0, 3.0, 14.8, or 65.6 mg/kg/day) of EPTC (Minor et al., 1982). Fifteen males and 30 females were assigned to each dosage level with two matings per generation. Reduced body weights and food consumption (>80% of control) were noted in adults, and reduced body weight (93% of control) was observed in pups by 4 days of age at 1000 ppm. A decrease of up to 10% in absolute brain weight was present in both generations. The NOEL for decreased pup body weight was 200 ppm (11.1 mg/kg/day). DPR considered this study acceptable based on

**Table 10. No-Observed-Effect-Level (NOEL)/Lowest-Observed-Effect-Level (LOEL) for Reproductive and Developmental Toxicity of EPTC**

Species/Sex	Exposure Regimen	Effects at LOEL	NOEL (mg/kg/day)	LOEL	Reference <sup>a</sup>
Rat (M/F)	2-Generation Repro Diet	<u>Systemic</u> : ↓ maternal weights. <u>Reproductive</u> : ↓ pup weights by 4 days	11.1 11.1	53.4 53.4	(Minor et al., 1982)
Rat (M/F)	2-generation Repro Diet	<u>Systemic</u> : Adult F1a: cardiomyopathy (♂ & ♀) --- see text --- <u>Reproductive</u> : No effect at highest dose tested. ↓ pup weight at highest dose	4 ≥57 <sup>b</sup>	1 -	(Tisdell et al., 1986c)
Rat (M/F)	Repro Diet	↓ number fetuses & implantation sites.	-	32 <sup>c</sup>	(Woodard, 1975)
Rat (F)	Teratology Corn Oil Gavage	<u>Developmental</u> : ↑ early deaths and resorptions <u>Maternal</u> : Hemorrhage-induced mortality, ↓ body weight	30 100	100 300	(Nemec et al., 1983)
Rat (F)	Teratology Methylcellulose Gavage	<u>Developmental &amp; Maternal</u> No effect at highest dose tested.	≥300 <sup>b</sup>	-	(James et al., 1985a)
Rabbit (F)	Teratology Methylcellulose Gavage	<u>Developmental</u> : Malformations--- see text <u>Maternal</u> : No effect at highest dose tested.	- ≥300 <sup>b</sup>	30 <sup>d</sup> -	(James et al, 1985b)
Rabbit (F)	Teratology Corn Oil Gavage	<u>Developmental</u> : ↓ fetal weights <u>Maternal</u> : Hemorrhage-induced mortality, wt loss, ↓ food consumption, cholinergic signs	40	300	Gilles, 1987
Mouse (F)	Teratology Diet	No effects at highest dose tested	≥24 <sup>b</sup>	-	(Beliles et al., 1967)

<sup>a</sup>Brain weight changes listed in Table 12. <sup>b</sup>Highest dose tested. <sup>c</sup>Only dose tested. <sup>d</sup>Lowest dose tested.

FIFRA testing guidelines, with a notation that no histology data for the reproductive or target organs was reported.

**Dietary-Rat**

In another two-generation reproduction study, EPTC was administered in the diet at 0, 50, 200, and 800 ppm (males- 0, 4, 15, or 57 mg/kg/day; females- 0, 5, 18, or 92 mg/kg/day) to 30 CrI:CD(SD)BR rats/sex/group starting 10 weeks before mating (Tisdell et al., 1986c). A dose-related increase in cardiomyopathy was observed in the F1a adults at 200 and 800 ppm (Table 11). The hearts of FO animals were not examined histologically. The body weights of 880 ppm animals (parents) were significantly reduced (>80% of control). Pups at 800 ppm were about 10% lighter than controls at birth and 26% lighter by Day 4. The 200 ppm adult animals also occasionally had significantly lower body weights than the controls. Brain weights were not reported. A dose-related decrease in food consumption (>86% of control) was present at all treatment levels. The NOEL for systemic toxicity in the parents was 50 ppm (4 mg/kg/day) based on the cardiomyopathy. The reproductive NOEL was 800 ppm (57 mg/kg/day) based on no effects at the highest dose tested. The NOEL for decreased pup weight was 200 ppm (15 mg/kg/day). DPR considered this study acceptable based on FIFRA testing guidelines.

**Table 11. The Incidence of Cardiomyopathy in F1a Adult Rats Fed EPTC for 10 Weeks in a Two-Generation Reproductive Toxicity Study (Tisdell et al., 1986c)**

Observation	Dose (ppm)			
	0	50	200	800
<b>Cardiomyopathy</b>				
Males	(23) <sup>a</sup> 4 <sup>+++</sup>	(24) 3	(25) 15 <sup>**</sup>	(25) 25 <sup>***</sup>
Females	(25) 1 <sup>+++</sup>	(24) 0	(25) 5 <sup>*</sup>	(25) 25 <sup>***</sup>

<sup>a</sup> Number examined in parenthesis

<sup>+++</sup> Significant trend at p<0.001 based on dose-weighted chi-square trend test (Peto et al., 1980)

<sup>\*</sup> Significantly different from the control group at p<0.05 by the Fisher Exact Test

<sup>\*\*</sup> Significantly different from the control group at p<0.01 by the Fisher Exact Test

<sup>\*\*\*</sup> Significantly different from the control group at p<0.001 by the Fisher Exact Test

**Dietary-Rat**

In a non-FIFRA-guideline rat reproductive study of 7 thiocarbamate compounds, 10 female and 5 male Sprague-Dawley rats were fed 32 mg/kg/day technical or formulated (82.6%) EPTC (Woodard, 1975). No control group was included in the study design. Treatment was begun 3 days prior to mating. Females remained on the treatment until sacrifice on gestation-day 13 or post-partum day 21. Males were treated for 43 days, and

were then mated to an additional group of 5 untreated females. The additional group of females was sacrificed on gestation day 13. No evidence of reproductive toxicity was evident from the first mating. After the additional mating, there was a decrease in the number of viable fetuses and implantation sites in females mated to technical EPTC and EPTC-formulation treated males. Females mated to EPTC-formulation treated males also had a several fold increase in the number of resorption sites, as compared to the previous mating. Based on decreased numbers of viable fetuses and implantation sites, the LOEL was 32 mg/kg/day for technical EPTC. DPR considered the study unacceptable as a FIFRA guideline study due to non-standard protocol and insufficient data.

## **G. DEVELOPMENTAL TOXICITY**

**Summary:** The developmental toxicity of technical EPTC was studied in rats, mice, and rabbits. The NOEL for maternal toxicity was 40 mg/kg/day based on fatal uterine hemorrhage, decreased body weight, and cholinergic signs. The developmental NOEL was 30 mg/kg/day based on early deaths and resorptions. The signs of toxicity were more prominent when EPTC was administered via corn oil gavage. The NOEL/LOEL information is also included in Table 10.

### **Gavage-Rat**

EPTC was administered in a corn oil vehicle by oral gavage on gestation days 6-15 at dose levels of 0, 30, 100, or 300 mg/kg/day to 25 Charles River COBS CD rats/group (Nemec et al., 1983). Maternal toxicity, including mortalities (56%), reduced body weights (84% of control), and reduced food consumption (50% of control), was observed at 300 mg/kg/day. The mortalities were due to severe uterine or generalized bleeding, and first occurred on treatment-day 6. Fetal weights were also reduced in that group (82% of control). Embryotoxicity in the form of increased early death and resorption (< gestation day 10) was observed at 100 and 300 mg/kg/day. There was a 33% increase in fetal incidence rate of omphalocele at 300 mg/kg/day. The investigators considered the statistical significance of the finding to be due to the smaller number of fetuses examined at that dose level (6 litters vs 22 in control). Based on hemorrhage-induced mortalities, and reduced body weights, the maternal NOEL was 100 mg/kg/day. The developmental NOEL was 30 mg/kg/day based on the increased early death and resorption present within a four day period after the beginning of exposure. DPR considered this study acceptable based on FIFRA testing guidelines.

### **Gavage-Rat**

In another teratology study, technical EPTC was administered by gastric gavage in a 1% methylcellulose vehicle at 0, 30, 100, or 300 mg/kg/day on days 7-19 of gestation, to 25 Crl:COBS CD(SD)BR rats/group (James et al., 1985a). Since no maternal toxicity or embryotoxicity were observed, the maternal and developmental NOEL were both > 300 mg/kg/day. The difference in the results for these two studies may be due to the difference in the vehicles employed, as corn oil or its fatty acid constituents can alter nutritional status, hepatic microsomal drug metabolism, and gastrointestinal physiology (Condie et al., 1986; Kim et al., 1990; Mantel, 1986; Norred & Wade, 1972; Wallig et al., 1989). DPR considered the second study unacceptable since there was no maternal toxicity at the highest dosage tested.

### **Gavage-Rabbit**

Technical EPTC was administered in a 1% methylcellulose vehicle by gavage at 0, 30, 100, or 300 mg/kg/day, on days 6-18 of gestation to 16-18 New Zealand White rabbits/group (James et al., 1985b). The NOEL for maternal toxicity was >300 mg/kg/day based on highest dose tested. The LOEL for developmental toxicity was considered to be 30 mg/kg/day based on a higher incidence of all malformations combined in each treatment group. The evidence for a developmental effect was weakened, however, in that there was no clear increase in any specific type of malformation. The increase in combined malformations was also not statistically significant, and was not used to evaluate the risk of potential developmental effects of EPTC in humans. Although a maternal MTD was not reached in this study, DPR considered it acceptable since rabbits in a preliminary study had cholinergic signs at 350 mg/kg/day.

### **Gavage-Rabbit**

In a more recent teratology study, 16-18 New Zealand White rabbits/group received 0, 5, 40, or 300 mg/kg/day by gavage, in a corn oil vehicle on days 7-19 of gestation (Gilles, 1987). Maternal toxicity occurred at 300 mg/kg/day and included mortality (associated with systemic and reproductive tract hemorrhage), weight loss, reduced food consumption, cholinergic signs (loose stool, salivation, and wet stained fur near mouth), and reduced serum and RBC cholinesterase levels (30-44% of controls). The loose stool first occurred on treatment Day 3. Statistically significant reductions also were observed in the serum cholinesterase levels in both the 5 and 40 mg/kg/day groups and in RBC cholinesterase levels in the 40 mg/kg/day group. The reductions were not considered biologically significant since they were relatively small (> 80% of control). It was noted that animals from the 300 mg/kg/day group consistently bled longer after blood sampling for the cholinesterase determinations. Embryo/fetotoxicity was observed in the 300 mg/kg/day group in the form of decreased fetal weights. Based on bleeding-induced mortality, reduced food consumption, and cholinergic signs the maternal NOEL was 40 mg/kg/day. Based on decreased fetal weights (88% of control), the developmental NOEL was 40 mg/kg/day. DPR also considered this study acceptable based on FIFRA testing guidelines. The differences in results between the two rabbit studies also may have been influenced in some manner by the differences in vehicles mentioned previously for rat studies.

### **Dietary-Mice**

Twenty female mice were fed 0, 8, or 24 mg/kg/day EPTC from gestation day 6 through caesarian delivery on day 18, or natural delivery (Bililes et al., 1967). There were no signs of toxicity in the parent female mice, or teratological effects in the fetuses. DPR considered this study unacceptable due to major variances from FIFRA guidelines.

## **H. NEUROTOXICITY**

**Summary:** Neurotoxicity is the major concern in the risk assessment of EPTC. Neurotoxic effects have been detected in rats, mice, dogs, and hens, after dosing periods as short as a single dose, and by both oral and inhalation exposure routes. EPTC-induced brain cell necrosis and/or decreased brain weight, were present in shorter-term studies. Peripheral nerve damage with subsequent muscle degeneration also developed after chronic exposure .

A listing of the EPTC studies that detected neurotoxic effects is presented in Table 12. Specific neurotoxicity studies are discussed in this section. EPTC is not the only thiocarbamate herbicide with adverse neurotoxic effects. Animal studies submitted to DPR and the US EPA identified four other members of this class of chemicals as producing similar neurotoxicity (cycloate, pebulate, vernolate, and molinate), and one member lacking this activity (butylate).

### **Gavage - Rat**

Technical EPTC (98.4% purity) in corn oil vehicle was administered via single oral gavage to groups of 10 Alpk:APfSD (Wistar derived) rats/dose/sex at 0, 200, 1000, or 2000 mg/kg (Brammer, 1993). The animals were then observed for 14 days. At weekly intervals, quantitative assessment of landing foot splay, sensory perception and muscle weakness, and locomotor activity were performed. There were 3 mortalities at 2000 mg/kg, and one death at 1000 mg/kg. Clinically, cholinergic signs and reduced activity were present at 1000 and 2000 mg/kg. There was no evidence of any effect on the limited neurobehavior parameters examined. At the end of the study, 5 rats/sex/dose were sacrificed by perfusion tissue fixation prior to histologic examination of brain, spinal cord, spinal roots, dorsal root ganglia, sciatic nerve, sural nerve, tibial nerve, and gastrocnemius muscle. Tissues from the remaining 5 rat/dose/sex were fixed in formalin, but were not histologically examined. A 3-7% decrease in mean brain weight was present in 1000 and 2000 mg/kg animals. Histologically, dose-related neuronal cell necrosis in the pyriform/entorhinal cortex and/or dentate gyrus of the brain was present at all EPTC levels. Lesions at 200 mg/kg were detected in only 2/5 male animals, and were stated to be minimal. No evidence of spinal or peripheral nerve injury was reported. Based on neuronal necrosis of the brain, the study LOEL was 200 mg/kg. Using a default uncertainty factor of 10 for determination of a NOEL from a LOEL (Beck et al., 1989), the estimated no-effect level was 20 mg/kg. The study was not acceptable to DPR due to incomplete functional observational data and the lack of submission of concurrent or historical positive control data, as required by US EPA neurotoxicity testing guidelines (US EPA, 1991b). However, that did not prevent DPR use of the estimated NOEL of 20 mg/kg to calculate the margin of safety for potential acute single-day human exposure to EPTC.

**Table 12. Summary of EPTC Neurotoxicity**

Species/Sex	Exposure Regimen	Neurotoxicity	NOEL mg/kg/day	LOEL	Reference/Comment
Rats (M/F)	Single-dose gavage Neurotox	Brain necrosis, 3-7% ↓ brain wt	20 <sup>a,b</sup>	200 <sup>c</sup>	(Brammer, 1993) not acceptable---see text---
Rats (M/F)	13-week diet Neurotox	Brain necrosis, 4-11% ↓ brain wt	8	40	(Tinson, 1994) not acceptable --see text---
Rats (M/F)	13-week diet	4% ↓ brain weight	8	16	(Hollingsworth, 1967)
Rats (M/F)	13-week diet	5-9% ↓ brain weight	~25	72	(Tisdell et al., 1984)
Dogs (M/F)	15-week diet	9% ↓ brain weight	24	49	(Woodard et al., 1967)
Dogs (M/F)	13-week diet	4-8% ↓ brain weight	6	18	(Daly et al., 1985)
Rats (M/F)	13-week inhalation	3-6% ↓ brain weight	5	25	(Scott et al., 1985)
Rats (M/F)	54-week diet	4-7% ↓ brain weight	20	80	(Trutter et al., 1978)
Rats (M/F)	2-year diet	5-10% ↓ brain weight by 12 months	-	5 <sup>c</sup>	(Goldenthal et al., 1978)
Rats (M/F)	2-year diet	4-15% ↓ brain wt, neuromuscular degen.	0.5 <sup>a,d</sup>	5 <sup>c</sup>	(Warner et al., 1983)
Rats (M/F)	2-year diet	4-12% ↓ brain wt, neuromuscular degen.	-	9 <sup>c</sup>	(Dickie, 1987)
Dogs (M/F)	1-year diet	3-5% ↓ brain weight	-	~6 <sup>c</sup>	(Tisdell et al, 1986a)
Dogs (M/F)	1-year capsule	7-9% ↓ brain wt, neuromuscular degen	1	8	(Sprague et al., 1987)
Rats (M/F)	2-gen Repro diet	4-10% ↓ brain wt both gen.	-	2.3 <sup>c</sup>	(Minor et al., 1982)
Hen	Neurotox	Sciatic nerve degeneration	-	7200 <sup>e</sup>	(Sprague et al., 1981)

<sup>a</sup> NOEL estimated from LOEL using a default uncertainty factor of 10. <sup>b</sup>Used as the definitive NOEL to estimate potential acute single-day human health hazard. <sup>c</sup> Lowest dose tested, NOEL not established. <sup>d</sup> Used as the definitive NOEL to estimate potential chronic human health hazard. <sup>e</sup> Only dose tested.

### **Dietary - Rat**

Technical EPTC (98.4%) purity was administered in the feed to 12 Alpk:APfSD (Wistar-derived) rats/sex/dose at levels of 0, 100, 500, or 2500 ppm (~0, 8, 40, 200 mg/kg/day) for 13 weeks (Tinston, 1994). Dose-related clinical signs in the high-dose rats were limited to increased incidence of urinary incontinence in females. Body weights and food consumption were less than control in the 40 and 200 mg/kg/day dose groups. Brain damage, as evidenced by decreased brain weight and neuronal cell necrosis in the pyriform cortex and hippocampus, was also present in both sexes at 40 and 200 mg/kg/day. The study NOEL was 8 mg/kg/day. The study was unacceptable to DPR due to inadequate positive control data, dose level justification, and missing Functional Observational Battery results.

### **Gavage - Chickens**

In two separate studies using different dosage levels (4674 and 7200 mg/kg, respectively; Table 12) minimal to slight bilateral degeneration of the sciatic nerve was observed in several hens treated twice with technical EPTC with 21 days between treatments. No other evidence of neuropathy (motor impairment or similar lesions in the central nervous system, as in acute delayed neuropathy) was found. In both studies similar lesions were observed in the negative control animals and were attributed to the normal background incidence of Marek's disease or other field and vaccine viruses common to commercial chickens. The peripheral nerve degeneration was considered a possible adverse effect by DPR in the study in which chickens were dosed at 7200 mg/kg, since the incidence in the EPTC treated chickens was higher than the respective control animals (4/10 vs. 2/10)(Sprague et al., 1981). This study was considered unacceptable by DPR since no individual data was reported. The other study was considered acceptable by DPR, but with no adverse effect at 4674 mg/kg, the only dose tested (Roberts et al., 1984). The difference in the results from these two studies may be due to the different dosage levels.

### **Neurotoxicity of Structurally-Related Chemicals**

EPTC is not the only thiocarbamate herbicide with adverse neurotoxic effects. Animal studies submitted to DPR and the US EPA (DPR, 1993b; US EPA, 1993c) identified four other members of this class of chemicals as producing similar neurotoxicity (cycloate, pebulate, vernolate, and molinate), and one member lacking this activity (butylate).

## IV. RISK ASSESSMENT

### **A. HAZARD IDENTIFICATION**

A human health risk assessment of EPTC has been conducted to evaluate the significance of the toxicity demonstrated in various animal studies.

#### **Non-Oncogenic Effects**

##### **Acute Effects**

In the acute neurotoxicity study using rats, a single oral administration of EPTC at 200 mg/kg or greater produced brain damage (neuronal necrosis). As a NOEL was not established in the study, an estimated NOEL of 20 mg/kg was calculated from the LOEL of 200 mg/kg using a default uncertainty factor of 10 (presented in III. TOXICOLOGY PROFILE, H. NEUROTOXICITY). This estimated NOEL was selected for evaluating potential acute, single-day human exposures.

##### **Subchronic/Chronic Effects**

Various toxic effects including nasal cavity degeneration and hyperplasia, fatal abnormalities in blood coagulation, cardiac toxicity, skeletal muscle and nerve degeneration/atrophy, cataracts, embryotoxicity, changes in body or organ weights, reduced food consumption, brain cholinesterase inhibition, and cholinergic signs were identified in subchronic or chronic animal studies (Tables 2,3,10,11,12).

The potential subchronic human risk after occupational exposures (8, eight-hour work days in a 17 day "season") was assessed based on a NOEL of 0.7 mg/kg/day for nasal cavity degeneration/hyperplasia and blood coagulation abnormality (39% prolongation of partial thromboplastin time) after 17, six-hour exposure days in a rat inhalation toxicity study (Scott et al., 1985).

An estimated NOEL of 0.5 mg/kg/day, based on the gradual onset of paralysis (neuromuscular degeneration) during a two-year rat study (Warner et al., 1983), was used to assess the risk associated with potential long-term chronic human dietary exposure to EPTC. The estimated NOEL was calculated by dividing the LOEL by an uncertainty factor of 10 (Beck et al., 1989). This default procedure was justified since the study did not establish a NOEL.

#### **Oncogenic Effects**

No oncogenic effects were identified in animal studies.

## **B. EXPOSURE ASSESSMENT**

### **1. Occupational Exposure (Appendix A)**

A detailed discussion of the occupational exposures of workers is presented in Appendix A. Field applications of EPTC formulations are by pre- or post-emergent broadcast spray and immediate mechanical incorporation into the soil, by metering into irrigation water, or by aerial applications.

According to the label, persons using the various formulations are cautioned not to ingest EPTC-containing products or inhale mists or dusts produced by these products. They are also cautioned to avoid contact with eyes, skin, and clothing. Rubber gloves, clean clothing, and goggles are required for workers handling the liquid concentrates.

Because EPTC is a relatively volatile chemical, inhalation as well as dermal exposure could potentially occur during application. The assessment was based on dermal and inhalation routes of exposure, a body weight of 70 kg, an 8-hour work day, 47% clothing penetration, 18.25% percutaneous absorption, and 50% respiration uptake (Raabe, 1984,1986).

EPTC is mechanically incorporated into the soil during or immediately following spray or granular application, or is incorporated as it is metered into water during irrigation. The only potential exposure to EPTC on plant surfaces would be immediately after sprinkler irrigation (prior to evaporation of EPTC). The product label states that the area must be vacated by unprotected persons during sprinkler irrigation. Based on use patterns and available toxicity data, the U.S. EPA has not required EPTC specific reentry protection (U.S. EPA, 1983c).

Table 13 shows the potential dermal and inhalation Absorbed Daily Dosage (ADD) for the different workers potentially exposed to EPTC. The ADD was calculated based on the potential exposures derived from two studies of EPTC use (PPG Industries, 1986; Knaar and Iwata, 1986). Workers spraying liquid formulations are likely to be exposed for 8 hours per day. Simultaneous broadcast spraying and mechanical incorporation are slow procedures and would require about 8 hours to complete a 50 acre application. Table 13 also shows the potential Seasonal Average Daily Dosage (SADD) and Annual Average Daily Dosage (AADD).

Potential exposures and daily dosages during the agricultural and residential use of granular formulations are also listed in Appendix A. Granular formulations represent only about 4% of the EPTC used in California. Granular formulations may be used at a higher application rate but are not likely to lead to higher exposure. The granular formulation of pesticides reduces dust and aerosol inhalation, and pesticides adsorbed to granules are released more slowly in to the environment. Also, they can not penetrate clothing or be absorbed dermally as rapidly as liquids. Consequently, exposure to EPTC in granular formulations with the exception of aerial loaders should be less than to EPTC in emulsifiable concentrates.

Potential exposure to EPTC during chemigation is detailed in Appendix A. Exposure during water-run use of liquid formulations is quite small compared to field spray applications, as application essentially uses a "closed-system" to dispense EPTC. The potential

**Table 13. EPTC Exposure Estimates for Mixer/Loaders, Applicators, Mixer/Loader/ Applicators, Farmers' Employee, and Flaggers<sup>a</sup>**

		Exposure (ug/person/day)	(ug/kg/day)		
			ADD (MOS) <sup>b</sup>	SADD (MOS) <sup>b</sup>	AADD (MOS) <sup>b</sup>
<b>Liquid Formulation: ground application</b>					
<b>Mixer/loader<sup>c</sup></b>	Dermal <sup>c</sup>	14,644	38.23	18.0	0.84
	Inhalation	1,200	8.57	4.03	0.19
	Dietary <sup>d</sup>		1.20	1.20	0.50
	Total	15,964	48.00 (417)	23.2 (30)	1.53 (328)
<b>Applicator<sup>c</sup></b>	Dermal <sup>c</sup>	6,244	16.28	7.66	0.36
	Inhalation	532	3.80	1.79	0.08
	Dietary <sup>d</sup>		1.20	1.20	0.50
	Total	6,776	21.28 (940)	10.65 (66)	0.94 (532)
<b>Mixer/loader/ applicator<sup>c</sup> (commercial)</b>	Dermal <sup>d</sup>	27,628	72.03	33.90	3.16
	Inhalation	2,480	17.71	8.34	0.78
	Dietary <sup>e</sup>		1.20	1.20	0.50
	Total	30,108	90.24 (220)	43.40 (16)	4.43 (113)
<b>Farmers' employee<sup>c</sup> (M/L/A)</b>	Dermal <sup>d</sup>	27,628	72.03	33.90	1.58
	Inhalation	2,480	17.71	8.34	0.39
	Dietary <sup>e</sup>		1.20	1.20	0.50
	Total	30,108	90.94 (220)	43.40 (16)	2.47 (203)
<b>Granular Formulation: flowers/ornamentals</b>					
<b>Loader/<sup>c</sup> applicator</b>	Dermal <sup>f</sup>	4,840	12.62	5.94	0.28
	Inhalation	240	1.71	0.81	0.04
	Dietary <sup>e</sup>		1.20	1.20	0.50
	Total	5080	15.53 (1288)	7.94 (88)	0.82 (613)

<sup>a</sup> From Table 1 Appendix B. <sup>b</sup> MOS = NOEL (ug/kg/day)/absorbed dose (ug/kg/day).

<sup>c</sup> Mixer/loaders (M/L) and applicators (A) wore flannel shirts with sleeves rolled-up, jeans, boots, caps, sunglasses; long rubber were worn only during mixing/loading. A M/L/A wore a long-sleeved shirt, long pants, rubber boots; additionally mid-forearm length gloves and a hard hat with protective face shield were worn during mixing/loading. Assumed M/L, A and farmers' employee handled EPTC 8 days/17-day season and 8-days/year, except for a M/L/A (commercial) the exposure period was 16 days/year (For other work tasks, workdays/season was 8, and workdays/year was also 8, except for applicators who use center-pivot sprinkler where the exposure period per season or per year was 6 workdays). <sup>d</sup> Dermal exposure was the sum of exposures of hands, clothed and unclothed skin areas. <sup>e</sup> From Table 15 (male 13-19 years). <sup>f</sup> Body exposure not included.

**Table 13. EPTC Exposure Estimates for Mixer/Loaders, Applicators, Mixer/Loader/ (continued..) Applicators, Farmers' Employee, and Flaggers<sup>a</sup>**

		ug/kg/day			
		Exposure (ug/person/day)	ADD (MOS) <sup>b</sup>	SADD (MOS) <sup>b</sup>	AADD (MOS) <sup>b</sup>
<b>Granular Formulation: aerial application</b>					
<b>Pilots<sup>c</sup></b>	Dermal <sup>d</sup>	338	0.88	0.42	0.02
	Inhalation	110	0.79	0.37	0.02
	Dietary <sup>e</sup>		1.20	1.20	0.50
	Total	448	2.87 (6974)	1.98 (353)	0.54 (932)
<b>Flaggers<sup>c</sup></b>	Dermal <sup>d</sup>	2,866	7.53	3.54	0.16
	Inhalation	122	0.87	0.41	0.02
	Dietary <sup>e</sup>		1.20	1.20	0.50
	Total	3,008	9.60 (2084)	5.15 (136)	0.68 (731)
<b>Loaders<sup>c</sup></b>	Dermal <sup>d</sup>	21,202	55.30	26.00	1.21
	Inhalation	4,108	29.90	14.10	0.65
	Dietary <sup>e</sup>		1.20	1.20	0.50
	Total	25,382	86.30 (232)	41.30 (17)	2.37 (211)
<b>Chemigation: water-run</b>					
<b>Applicators<sup>c</sup></b>	Dermal <sup>d</sup>	2,354	4.91	2.31	0.11
	Inhalation	60	0.43	0.20	0.01
	Dietary <sup>e</sup>		1.20	1.20	0.50
	Total	2,414	6.54 (3059)	3.71 (189)	0.62 (810)
<b>Chemigation: center-pivot sprinkler</b>					
<b>Mixer/loader<sup>c</sup> /applicator</b>	Dermal <sup>d</sup>	84,000	220.00	77.7	3.62
	Inhalation	138	0.99	0.35	0.02
	Dietary <sup>e</sup>		1.20	1.20	0.50
	Total	84,538	222.00 (90)	79.20 (9)	4.13 (121)

<sup>a</sup> From Table 1 Appendix B. <sup>b</sup> MOS = NOEL (ug/kg/day)/absorbed dose (ug/kg/day).

<sup>c</sup> Exposure was estimated based on clothing protection provided by long-sleeved shirt, long pants, rubber gloves, shoes plus socks. <sup>d</sup> Dermal exposure was the sum of dermal exposure of hands, unclothed skin areas and clothed skin areas. <sup>e</sup> From Table 15.

ADD for applicators was 5.44 ug/kg/day and the SADD 2.51 ug/kg/day. Exposure to EPTC during center-pivot irrigation systems represents a more extreme exposure scenario due to potential contact of workers to EPTC during handling of containers, pouring, mixing, calibration and application. The use of center-pivot irrigation systems has not been well established in California. However, the potential ADD for mixer/loader/applicators was 221 ug/kg/day and the SADD 78 ug/kg/day.

## **2. Dietary Exposure**

### **a. Anticipated Residues**

Data for potential pesticide residues associated with US EPA and California label-approved direct food with tolerances, and any secondary residues in animal tissues are necessary for estimating potential human dietary exposures. The sources of residue data include surveillance programs conducted by the DPR, CDFA, and Federal agencies, field trials and survey studies by registrants. Residue data obtained from the monitoring programs are preferred for human dietary assessments since they are a more realistic estimate of potential exposure. When residues are at levels higher than established tolerances, they are not used since they are illegal and subject to other regulatory actions. In the absence of any measured residues, the DPR dietary exposure assessments utilize surrogate data from the same crop as defined by U.S. EPA or theoretical residues equal to U.S. EPA tolerances.

The DPR has four major sampling programs: 1) priority pesticide, 2) preharvest monitoring, 3) produce destined for processing, and 4) marketplace surveillance. The priority pesticide program focuses on pesticides of health concern as determined by DPR Enforcement and Medical Toxicology Branches. Samples are collected from fields known to have been treated with the specific pesticides. The preharvest monitoring program routinely examines the levels of pesticides on raw agricultural commodities in the field at any time during the growth cycle. Generally, these data are not used unless the application schedule is known and residue data are not available from the other monitoring programs. Samples destined for processing are collected in the field no more than 3 days prior to harvest, at harvest, or post-harvest before processing. For the market place surveillance program, samples are collected at the wholesale and retail outlets, and at the point of entry for imported foods.

The U.S. Food and Drug Administration (FDA) has two monitoring programs for determining residues in food: 1) regulatory monitoring and 2) total diet study. The former program, like the DPR and CDFA marketplace surveillance program, examines produce at the wholesale and retail levels of trade, as well as imported produce at the point of entry into the United States. The total diet study determines residues in food after they have been prepared for consumption.

The National Residue Program of the U.S. Department of Agriculture (USDA) provides data for potential secondary pesticide residues in meat and poultry. These residues in farm animals can occur from direct application, and from consumption of commodities or by-products in the feed.

Testing for secondary EPTC residues in meat, milk, poultry, or eggs has not been required and no tolerances have been established by the US EPA. Recommended uses of EPTC were believed to result in negligible residues in raw agricultural commodities used as animal feeds. Therefore, residues of EPTC would not be expected to transfer to animals from the feed use of the treated commodities (US EPA, 1983c). In addition, the established pre-harvest intervals of 14 to 60 days for various crops, which could potentially be fed to livestock, also reduces the potential for secondary EPTC residues (US EPA, 1983a). Therefore, potential human dietary exposure was estimated from potential EPTC residues in 208 raw or processed agricultural commodities following US EPA approved orchard, field, or garden applications (US EPA, 1983c; TAS, 1990a,b)

## **1 Acute Exposure**

Estimates of potential acute dietary exposure used the highest measured residue values at or below the tolerance for each commodity (Stauffer, 1963-81). The default procedure for acute dietary exposure assumed that "below detection limit" residues were equal to Minimal Detection Level (MDL) for each commodity. In the absence of any residue determinations for a particular commodity, the DPR acute dietary exposure assessments utilize surrogate data from the same crop group as defined by the US EPA, or theoretical residues equal to US EPA tolerances. The actual residue values reported are presented in Table 14.

The following assumptions are used to estimate potential acute dietary exposure from measured residues: 1) the residue does not change over time, 2) the concentration of residue does not decrease when the raw agricultural commodity (RAC) is washed, 3) processing of RAC's into various food forms does not reduce or increase the residue concentration, and 4) all foods that are consumed will contain the highest reported residue.

## **2 Chronic Exposure**

Estimates of potential chronic dietary exposure used the average of measured and "below detection limit" residues for each commodity. The default procedure assumed that "below detection limit" residues were equal to one-half (50%) of the MDL for each commodity. In the absence of any residue determination for a particular commodity, the DPR chronic dietary exposure assessments utilize surrogate data from the same crop group as defined by the US EPA. The actual residue values reported (Stauffer, 1963-81) are presented in Table 14.

The following assumptions were used to estimate potential chronic dietary exposures from measured residues: 1) the residue level does not change over time, 2) residues are not reduced by washing the RAC, 3) processing the RAC's into various food forms does not reduce or increase the residue levels, 4) individuals will consume foods that contain the average calculated residue, and 5) exposures to a commodity at all reported residue levels do occur, i.e. a commodity with the average calculated residue is consumed every day at an annual average level (dosage).

### **3. Dietary Assessment**

#### **a. Acute Exposure**

Acute dietary exposure analysis were conducted using the Exposure-4 software program developed by Technical Assessment Systems, Inc. (TAS). The Exposure-4 program estimates the distribution of user-day (consumer-day) exposure for the overall U.S. population and specific subgroups (TAS, 1990b). A user-day is any day in which at least one food from the commodity list of the residue file is consumed. The consumption analysis uses individual food consumption data as reported in the 1987-88 USDA Nationwide Food Consumption Survey (USDA, 1987-88).

Based on the 95th percentile of user-days exposures for all specific population subgroups, the potential acute dietary exposure of EPTC from all labeled uses ranged from 0.96 to 2.75 ug/kg/day (Table 15). Non-nursing infants less than 1 year old had the highest potential acute dietary exposure to EPTC residues. The complete dietary exposure analysis is available from DPR Medical Toxicology Branch.

#### **b. Chronic (Annual Average) Exposure**

The potential chronic dietary exposure was calculated using the Exposure-1 software program developed by TAS (TAS, 1990a). The food consumption data for chronic use analysis was also based on the 1987- 88 USDA Nationwide Food Consumption Survey (USDA, 1987-88). The program estimates the annual average exposure for all members of a designated population subgroup.

The mean potential chronic dietary exposure for all population subgroups ranged from 0.25 to 0.99 ug/kg/day (Table 15). The population subgroup of children (1-6 yrs) had the highest potential exposure. The complete chronic dietary exposure analysis is available from DPR Medical Toxicology Branch.

### **4. Combined Occupational and Dietary Exposure**

The potential combined exposure levels from the occupational and dietary sources are also listed in Table 13. Overall, potential occupational exposure accounted for most of the potential total EPTC exposure.

The acute and chronic potential dietary exposure levels used in combination with potential occupational exposure for adult agricultural workers was the level from males (13-19 yrs), as they had the highest potential dietary exposure of any age-defined employable (> 16 yrs) subgroup. Children were not considered to be occupationally exposed, as child labor laws do not permit them to be around the machinery used in EPTC field applications (CDFA, 1987; CDLSE, 1991; USDL, 1990).

**Table 14. EPTC Residue Database from Registrant Field Trials and CDFA Monitoring Programs**

Commodity <sup>b</sup>	Registrant Field Trials (Stauffer, 1963-81)				CDFA Data <sup>a</sup> 1987-88			
	n	highest (ppm)	mean <sup>c</sup> (ppm)	MDL (ppm)	n	highest (ppm)	mean <sup>c</sup> (ppm)	MDL <sup>d</sup> (ppm)
Almonds (meat only)	3	ND <sup>e</sup>	ND	0.02				
Asparagus (spears)	2	ND	ND	0.02				
Beans (all or unspecified)					11	ND	ND	.1-.2
Beans, hyacinth (dry)	1	ND	ND	0.02				
Beans, navy (dry pods)	2	ND	ND	0.02				
Beans, pinto (dry)	1	ND	ND	0.02				
Beans, snap (green pods)	5	ND	ND	0.02				
Carrot, root (root)	4	ND	ND	0.04				
Corn, sweet (ears only)	2	ND	ND	0.02				
Corn, pop (kernels only)	1	ND	ND	0.02				
Flax (seed)	3	0.07	0.03	0.02				
Grapefruit (peeled fruit)	2	ND	ND	0.02				
Lemons (peeled fruit)	2	ND	ND	0.02				
Oranges (peeled fruit)	1	ND	ND	0.02				
Peas, green (peas)	2	ND	ND	0.02				
Pineapple (fruit, no tops)	2	ND	ND	0.02				
Potatoes (tubers)	4	0.057	0.036	0.02	12	ND	ND	.1-.2
Sugar Beets (roots)	2	ND	ND	0.02				
Sunflower (seeds)	3	ND	ND	0.02				
Tangerines (peeled fruit)	4	ND	ND	0.02				
Tomatoes (cut fruit)	1	ND	ND	0.02				

<sup>a</sup> Priority Pesticide Sampling Program (Focused Monitoring). EPTC analyses were not conducted in 1989-90 (CDFA, 1987-90). <sup>b</sup> US EPA tolerance for all commodities is 0.01 ppm <sup>c</sup> Calculated as the mean of values below the detection limit and the actual values above the MDL <sup>d</sup> Minimal Detection Level <sup>e</sup> Not Detectable

**a. Acute Single-Day Exposure**

The highest potential combined total exposure to males 13-19 yrs with potential acute occupational exposure and acute dietary exposure to EPTC was 222.0 ug/kg/day for chemigation center-pivot sprinkler mixer/loader/applicators (Table 13). Over ninety-nine percent of the potential exposure was due to occupational activity.

**b. Seasonal Exposure**

The highest potential seasonal combined exposure of males 13-19 years old with seasonal occupational and acute dietary exposure was 79.2 ug/kg/day for chemigation center-pivot sprinkler mixer/loader/applicators (Table 13).

**Table 15. Potential Acute and Chronic (Annual Average) Dietary Exposure to EPTC Residues**

<b>Population Subgroups</b>	<b>Acute Exposure<sup>a</sup> (ug/kg/day)</b>	<b>Chronic Exposure (ug/kg/day)</b>
US Population	1.45	0.49
Western Region	1.48	0.50
Infants (nursing, < 1 yr)	1.77	0.25
Infants (non-nursing, < 1 yr)	2.75	0.94
Children (1-6 yrs)	2.57	0.99
Children (7-12)	1.70	0.71
Females (13-19 yrs) (not pregnant or nursing)	1.05	0.42
Females (13+ yrs) (pregnant, not nursing)	0.99	0.42
Females (13+ yrs) (nursing)	0.96	0.42
Females (20+ yrs) (Not pregnant or nursing)	0.97	0.38
Males (13-19 yrs)	1.17	0.51
Males (20+ yrs)	1.02	0.41
Seniors (55+ yrs) (male/female)	1.00	NA

<sup>a</sup> = 95th percentile. NA = Not Available

## **C. RISK CHARACTERIZATION**

The potential single-day acute, seasonal, and chronic human health risk associated with the use of EPTC is assessed in this section. The exposure scenarios are primarily based on occupational uses, but also include potential dietary sources. The health hazard effects are characterized in terms of a margin of safety (MOS). The MOS is calculated as the ratio of a NOEL from an animal study to the potential exposure dosage for humans.

### **1. Combined Occupational and Dietary Exposure**

The margins of safety (MOSs) for agricultural workers through potential combined occupational and dietary exposure to technical EPTC are presented in this section.

#### **a. Acute Single-Day Exposure Scenario**

The MOSs for acute single-day potential exposure ranged from 90 for chemigation center-pivot sprinkler mixer/loader/applicators to 6974 for aerial application pilots and are presented in Table 13.

#### **b. Seasonal Exposure Scenario**

EPTC is a pre-plant and post-cultivation herbicide not effective against established weeds. The worker exposure studies submitted to DPR indicated that workers may use EPTC on successive days during those times of the growing season. For this reason it was considered appropriate to use the assumption that potential "seasonal" exposure to liquid EPTC could be repeated daily exposures for 8 days of a 17-day season. The MOSs for potential seasonal exposure to liquid formulation EPTC are based upon exposure to the ADD for eight, 8-hour working days in a 17 day season, and ranged from 16 to 66 (Table 13). MOSs for potential exposure to granular formulation ranged from 17 to 353, while potential chemigation MOSs ranged from 9 to 189.

#### **c. Chronic Exposure Scenario (Annual Average Exposure)**

Margins of safety for potential annual exposures ranged from 113 to 532 for potential liquid exposure scenarios, from 211 to 932 for granular exposure scenarios, and from 121 to 810 for potential chemigation use. (Table 13).

### **2. Dietary Exposure**

#### **a. Acute Exposure**

The MOS's for potential acute dietary exposure ranged from greater than 7,000 for non-nursing infants to greater than 20,000 for females 13+ yrs (nursing). The MOS's are listed in Table 16.

**Table 16. Margins of Safety for Potential Acute and Annual Average Dietary Exposure to EPTC**

Population Subgroups	<u>Acute Exposure</u> (95th percentile exposure)		<u>Annual Average Exposure</u>	
	(ug/kg/day) <sup>a</sup>	MOS <sup>b</sup>	(ug/kg/day) <sup>a</sup>	MOS <sup>c</sup>
US Population	1.446	13,810	0.486	1,030
Western Region	1.471	13,590	0.497	1,030
Infants, < 1 yr, nursing	1.768	11,300	0.247	2,020
Infants, < 1 yr, non-nursing	2.745	7,280	0.938	530
Children, 1-6 yrs	2.571	7,770	0.993	500
Females, 13-19 yrs (not pregnant or nursing)	1.045	19,110	0.417	1200
Females, 13+ yrs (pregnant, not nursing)	0.998	20,220	0.363	1380
Females, 13+ yrs (nursing)	0.958	20,850	0.418	1200
Females 20+ yrs (not pregnant or nursing)	0.970	20,610	0.376	1330
Males (13-19 yrs)	1.167	17,130	0.508	980
Males (20+ yrs)	1.016	19,670	0.405	1240
Seniors, 55+ yrs (male/female)	0.998	20,050	_ <sup>d</sup>	_ <sup>d</sup>

<sup>a</sup> Exposure levels from Table 15.  
<sup>b</sup> MOS = NOEL (20,000 ug kg)/exposure level.  
<sup>c</sup> MOS = NOEL (500 ug/kg/day)/exposure level.  
<sup>d</sup> Not Available.

**b. Chronic (Annual Average) Exposure**

The MOSs for the subgroups analyzed ranged from 500 for children (1-6 yrs) to greater than 2,000 for nursing infants (< 1 yr). Data from seniors (55+ yrs) was not available from the TAS program. The MOSs are also listed in Table 16.

## V. RISK APPRAISAL

This risk assessment addressed the potential health risk of EPTC to agricultural workers through work activities, home garden users, and to the general population through the diet. An MOS of 100 is generally considered sufficient to protect humans against potential toxic effects, when the NOEL is based on results from animal studies with a comparable duration of exposure.

The risk assessment process is used to evaluate the potential for human exposure and the likelihood that the adverse effects of a substance will occur in humans under the specific exposure conditions. Every risk assessment has inherent limitations on the application of existing data to estimate the potential risk to human health. Therefore, certain assumptions and extrapolations are incorporated into the hazard identification, dose-response assessment, and exposure assessment processes. This, in turn, results in uncertainty in the risk characterization which integrates all the information from the previous three processes. Qualitatively, risk assessments for all chemicals have similar uncertainties. However, the degree or magnitude of the uncertainty can vary depending on the availability and quality of the data, and the types of exposure scenarios being assessed. Several specific areas of uncertainty associated with this risk assessment for EPTC are delineated in the following discussion.

### A. HAZARD IDENTIFICATION

#### Interspecies Extrapolation

In the absence of appropriate data from human observations, results from animal studies were extrapolated to humans in the hazard identification process. It was assumed that the absorption, distribution, metabolism, and excretion of EPTC in humans were similar to that in animals. Animals exposed to EPTC showed increases in the incidence of nasal cavity degeneration/ hyperplasia, fatal abnormalities in blood coagulation, cardiac toxicity, skeletal muscle or nerve degeneration/atrophy, cataracts, embryotoxicity, changes in body or organ weights, reduced food consumption, brain cholinesterase inhibition, and cholinergic signs. Similar effects of neuromuscular degeneration and cardiac toxicity, and nasal lesions, were observed in animals administered cycloate (S-ethyl-cyclohexylethyl-thiocarbamate), another thiocarbamate herbicide which may be used as a tank-mix with EPTC in several midwestern states (Fay and Helmes, 1986; Chin, 1984; Knapp and Thomassen, 1984; Knapp and Thomassen, 1986; Kundzins, 1979; Kurtz, et al., 1985; Kurtz, et al., 1987; and Sprague, 1984; ICI, 1992). The hazard identification and exposure assessment for cycloate have been prepared in a separate risk characterization document (DPR, 1993b).

Interspecies variability is another aspect that may affect the assessment of risk, most specially for the EPTC-induced nasal cavity degeneration/hyperplasia. The increased complexity of the nasal turbinates of the rats, as opposed to humans, the straighter nasopharyngeal region, and the regional lower flow rates might alter the toxicity at given exposure concentrations (Schreider, 1986). Additional information on the deposition, reactivity, solubility, absorption, metabolism, and clearance of EPTC in the nasal cavity epithelium of

animals and humans would permit additional consideration of interspecies dosimetric adjustment (Jarabeck, et al., 1990; EPA, 1990a). Such information would also help define the relative contributions of local versus systemically absorbed EPTC in production of nasal damage.

### **Significance of Effects Seen in Animal Studies**

Another area of uncertainty is the biological significance of the epithelial hyperplasia present in the nasal cavity. Hyperplasia is characterized by an absolute increase in the number of cells per unit of tissue due to an enhanced rate of cell proliferation. During hyperplasia the proliferating cells may appear less differentiated than their non-proliferating counterparts. This is believed to reflect the fact that the "cellular machinery" is dedicated to cell division rather than to production of gene products for normal function of the cell. In this manner, hyperplasia may alter the capabilities of the organ or tissue affected. Hyperplasia may regress when the stimulus causing it is removed, or the hyperplasia may persist as a cellular change, with organizational or cytological abnormalities, that is less subject to normal tissue regulatory mechanisms (Maronpot, 1991).

Published reports of inhalation toxicity studies of other chemicals have indicated that nasal cavity hyperplasia may be a preneoplastic change (Boorman et al., 1990; Feron et al., 1986; Haschek et al., 1991; and Sellakumar et al., 1983). It is not possible to predict, from the results of a subchronic study, whether hyperplasia will progress to neoplasia (Boorman et al., 1990). Current FIFRA guidelines state that carcinogenicity studies are required when hyperplasia is produced in a subchronic study (US EPA, 1994a).

Blood coagulation defects were also present in a number of animal studies. In the subchronic rat inhalation study, prolongation of prothrombin time, partial thromboplastin time (PTT), and/or Stypven (Russel's Viper Venom) times were present, but spontaneous hemorrhage was not recorded. The degree of increase (39% for PTT at the exposure-day 17 LOEL of 5 mg/kg/day) approaches the 50% increase in PTT which has been reported to significantly inhibit the coagulation process, without spontaneous bleeding, in humans following heparin administration (Creager and Dzau, 1991; MSD, 1982). In heparin experiments with dogs, PTT increases of greater than ~30-40% were reported to inhibit thrombus formation (Fedullo et al., 1982). The PTT may be abnormally long if any of the clotting factors it measures is below ~30% of the normal plasma concentration (Mosher, 1992). In four other rat and rabbit studies of EPTC, higher doses produced mortality secondary to hemorrhagic episodes (including two teratology studies with severe uterine bleeding). Appropriate laboratory tests were not always conducted or reported during the hemorrhagic episodes, hindering interpretation of the abnormal values present in the rat inhalation study. However, in the 15-week rat feeding study, PTT at study termination was increased 46% in the dose group that had previously incurred bleeding-induced mortality. This may indicate that in EPTC-exposed rats, PTT is a more sensitive indicator of coagulation function than has been reported for other anticoagulants, in other species.

The moderate prolongation of PTT with fatal hemorrhagic episodes was similar to the situation described by the National Toxicology Program in a chronic rat study of

hydrochlorothiazide (NTP, 1989). As was also the case with EPTC, not all animals at a given dose level were affected, but all hemorrhages were fatal.

The prolongation of clotting factor times was used by the US EPA to establish the Reference Dose for EPTC in 1984 (US EPA, 1984b). Since that time, a lower NOEL for heart damage in longer-term animal studies has been used for regulatory purposes. For subchronic effects, however, prolonged clotting factor times remain the most sensitive endpoint. An additional uncertainty regards the potential hazard to the fetus from any blood clotting abnormality. Uterine bleeding of the type seen in the rat and rabbit teratology studies could produce additional risk to the fetus, even if the hemorrhage did not produce mortality in the mother. Non-fatal maternal hemorrhagic episodes were not reported in teratology studies of EPTC, although the clinical observation of longer bleeding after blood sampling was reported in a rabbit study. If a non-fatal blood clotting abnormality would effect the fetus, the potential risk following repeated daily exposures to EPTC would be underestimated. The risk would also be underestimated if the exposed worker was being medicated with another anticoagulant, such as aspirin or coumarin, as anticoagulation effects may be additive (Mosher, 1992).

## **B. EXPOSURE ASSESSMENT**

### Dietary Exposure

Estimates of potential exposure to EPTC from dietary sources assumed that EPTC is applied to all commodities allowed for the registered use of this compound. It also assumes that the nature and concentration of EPTC in food does not change after harvesting, during the transportation/storage, or by cooking or food processing techniques. These conservative assumptions could result in an overestimate of the potential exposure. Assuming residue levels at half (50%) of the MDL for those samples having non-detectable residues could overestimate or underestimate the potential chronic exposure. Use of tolerance levels as the theoretical residues in some commodities, due to the lack of actual data, overestimated the potential exposure from those commodities. The use of acute dietary exposure estimates in combination with seasonal occupational exposure estimates slightly overestimated the potential combined seasonal risk.

### Occupational Exposure

The risk assessment for occupational exposure assumed that workers have a potential exposure to EPTC for up to 16 days/year depending on the job category. The potential risk calculated in this assessment could be an underestimate or overestimate for a worker having an exposure duration/frequency which deviates from this assumption.

The population subgroups potentially exposed to EPTC in the workplace are agricultural workers involved with the mixing/loading and/or application of pesticide formulations containing EPTC. The assessment of the potential health hazard associated with acute exposure was based on neurotoxicity (brain cell necrosis) observed in rats orally exposed to technical EPTC. As shown in Table 13, the MOSs for acute exposure ranged from 90 to 6974.

The assessment of the potential human health hazard associated with repeated daily occupational exposure during pre-plant and post-cultivation use of EPTC was based on nasal cavity degeneration/hyperplasia and a blood coagulation abnormality observed in rats after seventeen, 6-hour inhalation exposures to EPTC (102 total hours). That was longer than the estimate of eight, 8-hour working days exposure for liquid formulation mixer/loader/applicators (64 total hours). Thus, the assessment may represent an overestimation of risk for mixer/loader/applicators.

### **C. RISK CHARACTERIZATION**

In the risk characterization, data from dermal, dietary, or inhalation studies using animals were used to assess the potential effects derived from the exposure from dermal and inhalation routes for workers. A dermal absorption rate of 18.25%, as determined in experimental animal studies, was assumed to be the same for worker dermal exposure. A pulmonary retention/absorption rate of 50% was used to evaluate the potential effects to workers via the inhalation route of exposure (Raabe, 1986,1988; Appendix A). The use of such assumptions might lead to an overestimate or underestimate of the potential health effects.

The assessment of the potential health hazard associated with annual average (chronic) dietary exposure to technical EPTC was based on neuromuscular toxicity observed in rats during a chronic toxicity study. The NOEL was estimated using a default calculation from the LOEL, rather than an experimentally derived NOEL. This procedure was necessary because dose levels low enough to establish a no-effect level were not used. The use of default calculations and an estimated NOEL introduced additional uncertainty into determination of the MOS. The degree and direction of the uncertainty is difficult to quantify, but it does seem reasonable that the uncertainty may have incorporated some overestimation of risk into this assessment.

An MOS of 100 is generally considered sufficient for protection of human health when the NOEL is based on results from animal studies, with a comparable duration of exposure for humans. However, for serious, irreversible toxic effects, such as destruction of brain nerve cells, a higher MOS may be appropriate, and can be augmented by additional modifying factors based on scientific judgement (US EPA, 1988, 1993c). However, the conservative estimation factors used to determine the potential no-effect level from the acute study (p. 36, Hazard Identification) had already established an additional safety margin, making the use of modifying factors unnecessary.

Animal studies have also shown that EPTC causes brain damage at dose levels below that of its other acute effects. The brain areas affected have been reported to be involved with learning and memory formation in rats, monkeys, and humans (Tilson et al., 1990; Zola-Morgan et al., 1994; and Williams et al., 1975). Also, EPTC, unlike some other neurotoxicants (e.g organophosphate insecticides) does not produce clinical signs of exposure, such as tremors or diarrhea, that would give warning of contamination and subsequent neural effects.

An area of interest is the biological significance of the decreased absolute brain weight commonly seen in toxicity studies of EPTC (Table 12). Brain weight is relatively independent

of decreases in body weight (Hayes, 1989; Scharer, 1977), so that decreased brain weight may be considered a primary neurotoxic effect of EPTC. The weight of the whole brain would be an insensitive indicator of local damage to various brain regions (e.g. dentate gyrus) as was evident in the rat acute oral neurotoxicity study (Brammer, 1993). In that study, decreased total brain weight and neuronal necrosis were both observed at the two highest dose levels, while only neuronal necrosis was detected at the lowest dose.

Both the US EPA and the World Health Organization have indicated that brain weight is an important aspect of neurotoxicity testing (US EPA, 1991b,1993e,1994; WHO, 1986). The weight of various regions of the brain would provide the most useful information. However, these weights are seldom obtained in routine toxicity tests. The US EPA currently requires regional brain weight determinations only in developmental neurotoxicity testing (US EPA, 1991b).

## VI. RISK MITIGATION

The MOSs calculated for the Seasonal Average Daily Dosage (SADD) were lower than those calculated for acute exposure (ADD) (Table 13). Measures providing satisfactory mitigation for the SADD would also increase the level of protection for acute and repeated yearly exposures.

In order to reduce the Absorbed Daily Dosage (ADD), and resulting SADD, a proposed exposure mitigation involved the use of an effective closed-system together with apron and chemical resistant gloves for mixing and loading emulsible EPTC concentrate. Full-body chemical-resistant protective clothing and a half-face respirator would be required during application of liquid mixes and loading and applying of granules. These mitigation measures would produce MOSs close to or greater than 100 for potential combined occupational and dietary exposures. Appendix B provides more detailed discussion of the mitigation proposal.

Table 17 presents the potential dosage after the implementation of the proposed mitigation measures. For the dermal route, the acute exposure dosages following the proposed mitigation range from 1.91 ug/kg/day for liquid formulation mixer-loaders to 16.49 ug/kg/day for chemigation center-pivot sprinkler mixer/loader/applicators. For the inhalation route, the potential exposures range from 0.10 ug/kg/day for chemigation center-pivot sprinkler mixer/loader/applicators 2.99 ug/kg/day for granular formulation aerial application loaders.

For current potential acute single-day combined occupational and dietary exposure to EPTC, the MOSs range from 90 for chemigation center-pivot sprinkler mixer/loader/applicators liquid to 6974 for aerial applicators (Table 13). The proposed mitigation measures would increase the range of MOSs from 1,124 for chemigation center-pivot sprinkler mixer/loader/applicators to 5,650 liquid mixer/loaders (Table 17).

The MOSs for the SADD following the proposed mitigation are also shown in Table 17. The MOSs for potential combined exposures ranged from 99 for chemigation center-pivot sprinkler mixer/loader/applicators to 304 for liquid mixer/loaders.

The MOSs for the AADD (Annual Average Daily Dosage) for combined exposures following the proposed mitigation ranged from 647 for chemigation center-pivot sprinkler mixer/loader/applicators to 907 for liquid mixer/loaders.

**Table 17. Mitigated Exposure for Mixer/Loaders, Applicators, Mixer/Loader/Applicators, Farmers' Employee, and Flaggers<sup>a,b</sup>**

		Exposure/person (ug/8-h day)		ug/kg/day		
		Work Clothing	Mitigated	ADD (MOS) <sup>c</sup>	SADD (MOS)	AADD (MOS)
<b>Liquid Formulation: ground application</b>						
<b>Mixer/loader</b>	Dermal	14,664	733	1.91	0.90	0.04
	Inhalation	1,200	60	0.43	0.20	0.01
	Dietary			1.20	1.20	0.50
	Total	15,864	793	3.54 (5650)	2.30 (304)	0.55 (907)
<b>Applicator</b>	Dermal	6,244	2,376	6.19	2.91	0.14
	Inhalation	532	53	0.38	0.18	0.008
	Dietary			1.20	1.20	0.50
	Total	6,776	2429	7.77 (2573)	4.29 (163)	0.64 (776)
<b>Mixer/loader /applicator (commercial)</b>	Dermal	27,628	1,721	4.49	2.11	0.20
	Inhalation	2,480	239	1.70	0.80	0.07
	Dietary			1.20	1.20	0.50
	Total	30,108	1,960	7.39 (2707)	4.11 (170)	0.77 (648)
<b>Mixer/loader applicator (farmers' employee)</b>	Dermal	27,628	1,721	4.49	2.11	0.10
	inhalation	2,480	239	1.70	0.80	0.04
	Dietary			1.20	1.20	0.50
	Total	30,108	1,960	7.39 (2707)	4.11 (170)	0.64 (787)
<b>Granular Formulation: flowers/ornamentals</b>						
<b>Applicator</b>	Dermal	4,840	1,287	3.36	1.58	0.07
	Inhalation	240	240	1.71	0.81	0.04
	Dietary			1.20	1.20	0.50
	Total	5,080	1,527	6.27 (3190)	3.59 (195)	0.61 (818)

<sup>a</sup> From table 2, Appendix B. <sup>b</sup> Exposure mitigation is proposed according to Minimal Exposure Regulations with some exceptions (see text). A full-body chemical-resistant protective suit and approved half-face respirator are suggested during application of liquid mixes or loading and application of granular products. <sup>c</sup> MOS = NOEL (ug/kg/day)/absorbed dose (ug/kg/day).

**Table 17. Mitigated Exposure for Mixer/Loaders, Applicators, Mixer/Loader/Applicators, (continued.) Farmers' Employee, and Flaggers<sup>a,b</sup>**

		Exposure/ person (ug/kg/day)		ug/kg/day		
		Work Clothing	Mitigated	ADD (MOS) <sup>c</sup>	SADD (MOS)	AADD (MOS)
<b>Granular Formulation: aerial application</b>						
<b>Pilots</b>	Dermal	338		Mitigation not required		
	Inhalation	110		(Appendix B)		
	Dietary					
	Total	448				
<b>Flaggers</b>	Dermal	2,886		Mitigation not required		
	Inhalation	122		(Appendix B)		
	Dietary					
	Total	3,008				
<b>Loaders</b>	Dermal	21,202	2,167	5.65	2.66	0.12
	Inhalation	4,180	418	2.99	1.41	0.07
	Dietary			1.20	1.20	0.50
	Total	25,382	2,585	9.84 (2034)	5.26 (133)	0.69 (725)
<b>Chemigation: water-run</b>						
<b>Loaders</b>	Dermal	2,354		Mitigation not required		
	Inhalation	60		(Appendix B)		
	Dietary					
	Total	2,414				
<b>Chemigation: center-pivot sprinkler</b>						
<b>Mixer/ loader/ applicator</b>	Dermal	84,000	6,324	16.49	5.82	0.27
	Inhalation	138	13.8	0.10	0.03	0.002
	Dietary			1.20	1.20	0.50
	Total	84,538	6,338	17.79 (1124)	7.05 (99)	0.77 (647)

<sup>a</sup> From Table 2, Appendix B. <sup>b</sup> Exposure mitigation is proposed according to Minimal Exposure Regulations with some exceptions (see text). A full-body chemical-resistant protective suit and approved half-face respirator are suggested during application of liquid mixes or loading and application of granular products. <sup>c</sup> MOS = NOEL (ug/kg/day)/absorbed dose (ug/kg/day).

## VII. TOLERANCE ASSESSMENT

### **A. BACKGROUND**

A tolerance is the maximum amount of a pesticide residue that may remain in or on a food, or animal feed (US EPA, 1991a). The U.S. EPA tolerance program was developed as an enforcement mechanism to identify illegal residue concentrations resulting from potential non-compliance with the product label requirements (e.g. improper application rates or methods, inadequate pre-harvest intervals, direct or indirect application to unapproved commodities). Tolerances are enforced by Food and Drug Administration (FDA), the US Department of Agriculture (USDA), and state enforcement agencies (e.g. Pesticide Enforcement Branch of DPR).

The data requirement established by U.S. EPA for tolerances include: (1) residue chemistry which includes measured residue levels from field studies, (2) environmental fate studies, (3) toxicology studies which evaluate the potential hazards to humans, domestic animals, and non-target organisms, (4) product performance such as efficacy, and (5) product chemistry which includes physical-chemical characteristics and analytical method (CFR, 1992). The field studies must reflect the proposed use with respect to the rate and mode of application, number and timing of applications, and formulations proposed (US EPA, 1982a).

Currently, the tolerances set by the US EPA are at levels necessary for the maximum application rate and frequency, and are not expected to produce deleterious health effects in humans from chronic dietary exposure (US EPA, 1991a).

Assembly Bill 2161 (Bronzan and Jones, 1989) requires the DPR to "conduct an assessment of dietary risks associated with the consumption of produce and processed food treated with pesticides". In the situation where "any pesticide use represents a dietary risk that is deleterious to the health of humans, the DPR shall prohibit or take action to modify that use or modify the tolerance....." As part of the tolerance assessment, a theoretical dietary exposure for a specific commodity and specific population subgroups can be calculated from the product of the tolerance and the daily consumption rate.

### **B. ACUTE EXPOSURE**

An acute exposure assessment using the residue level equal to the tolerance was conducted for each individual label-approved commodity. The TAS Exposure-4 software program (TAS, 1990b) and the USDA consumption data base (USDA, 1987-88) were used in this assessment. The acute tolerance assessment does not routinely address multiple commodities at the tolerance levels since the probability of consuming multiple commodities at the tolerance decreases as the number of commodities included in the assessment increases. EPTC is a selective preemergent herbicide for use on certain field, vegetable, orchard, ornamental, and non-crop sites. Tolerances of 0.1 ppm have been established for the general crop groupings below (U.S. EPA, 1983c). Pre-harvest intervals of 14-60 days have been established for crops which could potentially be fed to livestock.

Almonds, hulls	Tree nuts
Root and tuber vegetables	Cotton, seeds
Leaves of root and tuber vegetables	Cotton, forage
Legume vegetables, succulent and dried	Castor beans
Foliage of legume vegetables	Flax, seed
Fruiting vegetables, except cucurbits	Flax, straw
Cereal grains, forage, fodder, and straw	Safflower, seed
Non-grass animal feeds	Sunflower, seed
Cereal grains	Sunflower, forage

### **Results**

Based on the 95th percentile of the theoretical consumption rate estimate, the acute MOSs were all greater than 2000. The range of MOSs for the most highly consumed commodities (US FDA, 1991), are presented in Table 18.

### **C. CHRONIC EXPOSURE**

A chronic exposure assessment using residues equal to the established tolerances for individual or combinations of commodities has not been conducted, because it is highly improbable that an individual would chronically consume single or multiple commodities with pesticide residues at the tolerance levels. Support for this conclusion comes from DPR (formerly CDFA) pesticide monitoring programs which indicate that less than one percent of all sampled commodities have residues at or above the established tolerances (CDFA, 1990; DPR, 1994).

**Table 18. Margins of Safety (MOS) for Potential Acute Dietary Exposure to Tolerance Levels of EPTC for the Most Highly Consumed Commodities.**

Agricultural Commodity <sup>a</sup>	Margin of Safety (Range) <sup>b,c</sup>		
Asparagus	25,000	-	315,000
Broccoli	21,000	-	73,000
Cabbage (green)	21,000	-	125,000
Carrots	13,000	-	212,000
Cauliflower	23,000	-	212,000
Celery	99,000	-	476,000
Corn (sweet)	2,000	-	22,000
Cucumbers	51,000	-	350,000
Grapefruit	13,000	-	54,000
Grapes	19,000	-	75,000
Lemons	121,000	-	11,524,000
Lettuce	65,000	-	140,000
Melons	5,000	-	48,000
Onions	95,000	-	531,000
Oranges	10,000	-	62,000
Peppers	136,000	-	806,000
Pineapple	10,000	-	95,000
Potatoes (sweet)	15,000	-	316,000
Potatoes (white)	19,000	-	65,000
Strawberry	71,000	-	1,582,000
Tomato	24,000	-	80,000

<sup>a</sup> US EPA established tolerance for all commodities is 0.1 ppm

<sup>b</sup> Margins of Safety listed are based on an acute animal NOEL of 20 mg/kg.

<sup>c</sup> Numbers rounded to the nearest thousand.

## VIII. CONCLUSIONS

The margins of safety for the use of technical EPTC in herbicide formulations were greater than 100 for potential acute occupational exposure, and acute or chronic dietary exposure. The MOS's for acute occupational exposures combined with dietary exposure were also greater than 100. EPTC exposure would not be significant during home garden use. The MOS's for potential seasonal, repeated daily pre-plant or post-cultivation agricultural use were less than 100 for most work tasks. A proposed mitigation would produce MOSs close to or greater than 100 for occupational exposures. The MOS's from the theoretical consumption of foods with the highest legal residues (tolerances) of EPTC were all greater than 100.

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## APPENDIX A: Agricultural Worker Exposure Assessment

ESTIMATION OF EXPOSURE OF PERSONS IN  
CALIFORNIA TO PESTICIDE PRODUCTS  
CONTAINING EPTC

By

Robert K. Brodberg, Staff Toxicologist\*  
Tom Thongsinthusak, Staff Toxicologist\*\*

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Worker Health and Safety Branch  
California Department of Pesticide Regulation  
1020 N Street, Sacramento, California 95814

ABSTRACT

EPTC is a broad spectrum herbicide that must be incorporated into soil to be effective. In California EPTC is applied primarily to alfalfa, corn, sugar beets, and potatoes. Possible adverse effects associated with EPTC exposure in animals include neurotoxicity, nasal cavity degeneration/hyperplasia, blood coagulation abnormality, and neuromuscular degeneration in experimental animals. Dermal absorption studies conducted in rats indicate that EPTC is rapidly absorbed and eliminated. Percutaneous absorption of a dose comparable to field worker exposure was estimated to be 18.25% of the administered dose in 24 hours. After the exposure dose is removed, EPTC in the skin is readily metabolized and eliminated. Elimination is primarily by urinary excretion of a number of metabolites. S-(dipropylcarbamoyl)-cysteine and S-(dipropylcarbamoyl)-N-acetylcysteine constitute more than 50% of elimination and can be used for biological monitoring. Some estimated absorbed daily dosages (ADD,  $\mu\text{g}/\text{kg}/\text{day}$ ) for occupational exposure are: mixer/loaders (liquid - ground application) - 46.8, mixer/loader/applicators (liquid - ground application) - 89.8, loaders (granule - aerial application) - 85.1, applicators (granule - flowers/ornamentals) - 14.3, mixer/loader/applicators (liquid - center-pivot) - 221, and applicators (water-run) - 5.34. Plant surface residues are not encountered by field workers since EPTC is immediately incorporated into the soil.

This report was prepared as an Appendix to the Department's risk assessment process for EPTC.

\* Present address: Pesticide and Environmental Toxicology Section, Office of Environmental Health Hazard Assessment, P.O. Box 942732, Sacramento, California 94234-7320

\*\* Revised this document

## APPENDIX A

### California Department of Pesticide Regulation Worker Health and Safety Branch

#### Human Exposure Assessment

#### EPTC

August 8, 1995

This Appendix A is being prepared as part of the ongoing California Department of Pesticide Regulation evaluation of pesticides pursuant to SB 950.

### INTRODUCTION

EPTC (S-ethyl-dipropylthiocarbamate) is an amber liquid with an amine odor. It is a storage stable compound with a half-life of 483 weeks at 80 °C. EPTC is non-corrosive and moderately water soluble (370 ppm). It has a high vapor pressure ( $3.4 \times 10^{-2}$  mm Hg at 25 °C) for an agricultural chemical. Its boiling point is 138 °C at 30 mm Hg and its molecular weight is 189.3 ( $C_9H_{19}NOS$ ).

### U.S. EPA STATUS

The U.S. Environmental Protection Agency (U.S. EPA) has published a reregistration guideline for EPTC (U.S. EPA, 1983). Additional information was requested in this guideline concerning the effect of EPTC on blood clotting in test animals. This request was based on impaired clotting in subchronic and chronic rat studies. Information on clotting was requested specifically for dog studies running a year or longer, rat oncogenicity studies, teratogenicity studies in two species, and from a two-generation reproduction study. U.S. EPA proposed a tolerance in all agricultural commodities of 0.1 ppm for EPTC.

### USAGE

EPTC is used as a pre- and postplant herbicide to control annual grasses, broadleaf weeds and some perennials. To be effective, EPTC requires immediate soil incorporation by discing, chemigation, or injection by subsurface equipment. Its mode of action involves inhibition of germination and seedling development. In 1992, the total amount of EPTC sold in California was 936,766 pounds (DPR, 1992a), whereas total reported use was 667,112 pounds equivalent to 71.2% of the total amount sold (DPR, 1992b). For 1992, the major crop uses of EPTC in

California were alfalfa (34.5% of total use), corn (15.2%), sugar beets (13.7%), and potatoes (11.1%). EPTC was also used on forage crops, for landscape and open land maintenance, and on ornamentals and flowers. Table 1 shows the maximum application rates for major crops.

Table 1. Label maximal application rates of EPTC on major crops.

Crop	Application	Formulation	lbs a.i./acre
alfalfa	chemigation	EC	3.0
corn	preplant soil incorporation	EC	4.0
sugar beets	pre- or postplant	EC	4.5
potato - Irish	lay-by, chemigation	EC	4.0

EC = Emulsifiable concentrate

Brodberg, WH&S, 1995

Most of the use of EPTC, an unrestricted compound, is by farmers and direct consumers, not by certified applicators. This has been confirmed by discussions with county agricultural personnel (Acosta, 1989; Perry, 1989; Gruenberg, 1989) who reported that field applications of EPTC on alfalfa and potatoes are primarily by chemigation. Spraying and incorporation are done simultaneously using boom sprayers mounted across the center of a tractor and rear mounted discing equipment. County agriculture personnel estimate that about 50 acres of beans can be treated per day (Acosta, 1989; Perry, 1989; Gruenberg, 1989).

## FORMULATIONS

There are 10 products registered for use in California in 1995. These products are either emulsifiable concentrates (82.6-87.8% a.i.) or granular formulations (2.3-20% a.i.). The liquid formulations are used for broadcast, chemigation, and lay-by weed control in crops. The granular formulations are used primarily for weed control on nursery, home flower, and ornamental plantings.

## LABEL PRECAUTIONS

The U.S. EPA registers EPTC products as Toxicity Category III pesticides bearing a signal word "CAUTION." Persons exposed to the various formulations are cautioned not to ingest EPTC-containing products or inhale mists or dusts produced by these products. They are also cautioned to avoid contact with eyes, skin, and clothing. The Worker Protection Standard (WPS) requires handlers of EPTC products to wear clean clothing (long-sleeved shirt, long pants), shoes plus socks, chemical-resistant gloves, and protective eyewear. However, some of the current product labels in the Department's library have not shown requirements under the WPS. Areas to which EPTC is applied by chemigation must be cleared of people during the application.

Clothing protection required for early entry to treated fields that involves contact with anything that has been treated is: coveralls, waterproof gloves, shoes plus socks, and protective eyewear.

## **WORKER ILLNESSES AND INJURIES**

The California Pesticide Illness Surveillance Program reported 12 cases of illness/injury (1985-1992) that were attributed to exposure to EPTC. Those that were attributed to exposure to EPTC in combination with other pesticides during the same time period numbered only 3 cases (Mehler, 1995). These illnesses/injuries associated with EPTC are in the form of eye irritation (5 cases), skin irritation (4 cases) or systemic illness (3 cases).

## **DERMAL TOXICITY**

EPTC is not highly toxic by any route. A dermal LD<sub>50</sub> of 2,750 mg/kg has been reported in New Zealand rabbits with a formulated product containing 87.8% a.i. (Sanders, 1979). Granular products are not skin or eye irritants in New Zealand rabbits. Liquid concentrates are moderate skin irritants and moderate to severe eye irritants (Sanders, 1979; Miller, 1981; Morgan, 1981-1982; Thompson, 1982; Billow, 1983; Jameison, 1982).

## **ANIMAL METABOLISM**

Metabolism studies have been conducted in both rats and mice. The rat studies are more relevant since they are comparable to dermal absorption studies that also used rats. The two available rat studies support similar conclusions with respect to absorption and elimination of EPTC and its metabolites.

Ong and Fang (1970) used ethyl-1-<sup>14</sup>C-EPTC to follow EPTC metabolism in adult female Wistar rats. Doses of 0.6, 1.0, 1.5, 3.0, 20.6, 50.6 and 100.6 mg/kg were administered in corn oil by stomach tube. Two to four animals were treated at each dose. Expired <sup>14</sup>CO<sub>2</sub> was measured directly in an ionization chamber calibrated against known standards. Urine and feces were collected daily for 3-4 days and stored frozen for analysis of <sup>14</sup>C-EPTC and metabolites. <sup>14</sup>CO<sub>2</sub> expiration was the primary route of elimination for all doses. The percent of dose recovered as CO<sub>2</sub> was inversely proportional to the dose administered (84.6% at the lowest dose vs. 38.2% at the highest dose). The production of <sup>14</sup>CO<sub>2</sub> was rapid and reached a peak 1-2 hours after administration. Elimination via this route was complete within 15 hours at low dosages (<20.6 mg/kg) and within 35 hours at high doses. Urinary excretion was also a major pathway of elimination and increased with dose. Elimination via urinary excretion increased from 8.4% at 0.6 mg/kg to 35.6% at 100.6 mg/kg. Fecal elimination ranges between 4.0% and 12.6% of the dose but does not show a consistent dose response. Some of this recovery may be due to urine contamination of feces. Dose remaining in the carcass is not reported, but recoveries for CO<sub>2</sub>, urine and feces account for 77.6-97.4% of the administered dose.

Hubbell and Casida (1977) examined the metabolism of EPTC using  $^{14}\text{C}$ -carbonyl-EPTC administered in methoxytriglycol via stomach tube to male Sprague-Dawley rats. Two animals were dosed with 13.5 mg/kg and one with 132.5 mg/kg and their metabolism of EPTC was followed for 48 hours. Expired  $^{14}\text{CO}_2$  was collected in a 2:1 mixture of monoethanolamine-methyl cellosolve. Recovery of expired  $^{14}\text{CO}_2$  was 46% and 52% of the low and high administered dose, respectively. Urine and feces were collected in glass metabolism cages. Urinary excretion accounted for 44.7% of the low dose and 33.9% of the high dose. Elimination via feces was minor, accounting for 1% or less of the administered high and low dose. After 48 hours, 3.3% of the low dose and 1.4% of the high dose remained in the carcass. About half of the recovered dose was expired or excreted in 6 hours, and 93-99% by 24 hours. Total recovery of the administered dose was 94.7% and 88.3% for the low and high doses, respectively.

These two rat studies are not directly comparable because the position of the radiolabel differs. However, both show a general trend toward rapid quantitative elimination of EPTC metabolites via  $\text{CO}_2$  expiration and urinary excretion after oral administration. Fecal elimination of EPTC metabolites represents a minor route that is greatly exceeded by urinary excretion. Body retention is also low. These same trends are noted in the mouse study of Casida *et al.* (1975).

The above studies also identified certain EPTC metabolites in the urine. Sulfur oxidation is a primary *in vivo* metabolic pathway in rats and carbon oxidation appears to be a secondary pathway elucidated with *in vitro* mouse studies (Casida *et al.*, 1975). Ong and Fang (1970) separated 9 urinary metabolites by paper chromatography or thin-layer chromatography. Metabolites were detected by autoradiography or color reactions. The relative amount of most of these metabolites varied with dose. Only urea was accurately characterized as a labeled metabolite by cochromatography (Ong and Fang, 1970). It represented 17% of urinary excretion at all dose levels. Some parent compound was detected (2-4%) by a nonspecific method (isooctane soluble products of steam volatilization). Hubbell and Casida (1977) characterized glutathione derivatives by cochromatography against synthetic standards in two two-dimensional solvent systems. Parent compound was absent in the urine in this study. S-oxidation and glutathione (GSH) conjugation produced primarily S-dipropylcarbamoyl (DPC) cysteine (with 1 or 2 impurities) and S-(DPC)-N-acetylcysteine. In a one solvent system, S-(DPT) cysteine represented 15% of urinary metabolites, and S-(DPC)-N-acetylcysteine represented 39%. In the second solvent system they accounted for 19% and 51%, respectively. The identity of both of these metabolites was confirmed by gas chromatography-mass spectrometry of methylated derivatives. These metabolites have been used for biological monitoring (Ross *et al.*, 1986). Ten unidentified minor metabolites were isolated and some S-(DPC) mercaptoacetic acid (3-6%) was characterized but not identified.

## DERMAL ABSORPTION AND INHALATION ABSORPTION

Two dermal absorption studies used male Sprague-Dawley rats dosed with propyl 1-<sup>14</sup>C-EPTC. Careful examination of the data from these investigations is important because 60-80% of the labeled dose may be lost to evaporation during dermal exposure. This volatility of EPTC makes high total recoveries difficult. Both studies maximized recovery by collecting volatiles in a filter or resin cartridge mounted over the site of application. Both studies also met many of the criteria set forth in the U.S. EPA Procedure for Studying Dermal Absorption (Zendzian, 1987) and are acceptable for estimating dermal absorption.

Knaak *et al.* (1986) did three experiments measuring percutaneous absorption of EPTC in male Sprague-Dawley rats. Each rat's back was shaved the day before dosing. Animals in all experiments were fitted with Queen Anne collars to restrict their access to the treatment site. Labeled formulated EPTC EC in an aqueous emulsion was used for each dose. Application was completed using a micropipette. The exposure time for each experiment was 24 hours. Urine, feces, <sup>14</sup>C-volatiles, and <sup>14</sup>CO<sub>2</sub> were collected through 24 hours. XAD-2 resin was used to collect <sup>14</sup>C-volatiles and <sup>14</sup>CO<sub>2</sub> was collected in 2N KOH. Animals were anesthetized at 24 hours by dosing with sodium pentothal and then sacrificed. The exposure site was not washed prior to sacrifice. Skin from the exposure site was excised prior to the collection of other samples. Skin was stretched and washed, and then frozen. A blood sample was collected by cardiac puncture using a heparinized needle and syringe. Tissue samples taken at sacrifice included heart, liver, kidney, gastrointestinal tract, fat, and remaining carcass. These samples were stored frozen at 0 °C.

In general, this study conformed closely to U.S. EPA guidelines for dermal absorption studies. Absorption was measured in male rats of a strain used in one of the metabolism studies. They were treated with an appropriate volume of an aqueous emulsion of the field product. A non-exchangeable carbon was radiolabeled at 1.67 μCi/μmole. The skin mounted resin cartridge used in experiments 2 and 3 of this study facilitated good recovery of the dose (85.9% and 95.3%, respectively) and protected the application site. Experiment 1 did not use this resin cartridge and showed a lower recovery (76.5%, Table 2). Because of this low recovery it has been excluded from further consideration in estimating percutaneous absorption. Although use of these cartridges increased recovery, the small size needed to reduce bulk and weight also had the effect of limiting exposure area in experiments 2 and 3 to 2.54 cm<sup>2</sup>. Other deviations from guidelines included the use of heavy animals (280-431 g), and only 3 subjects in experiments 1 and 3. Experiment 2 used four 280 g animals. Although a 24-hour exposure was used, no interim sample time points were taken. Sacrifices were handled well except that residual bladder urine was not collected and there was no pre-sacrifice skin wash. Overall experiment 2 was the most acceptable and Experiment 3 showed the same trends discussed below.

For propyl-labeled EPTC, CO<sub>2</sub> expiration is a negligible route of elimination. Evaporation accounts for the largest percentage of the dose (69.8% and 77.8% in experiments 2 and 3, respectively). Urine is the primary elimination route (about 5.8% of the total) and about 8% of the dose remained in the carcass and organs at 24 hours. Less than 2.8% of the dose remained at the application site at 24 hours, and fecal elimination accounted for 0.4% or less of the exposure

dose. Summing the percentage of dose in excreta, expired air, washed skin, body organs and carcass yields percutaneous absorption values of 13.7% and 14.7% for experiments 2 and 3, respectively (Table 2). These values are not corrected for recovery.

The study by Jeffcoat (1988) met more of the criteria of the U.S. EPA guidelines and produced similar results to Knaak *et al.* (1986). A higher specific activity (35 mCi/mmol) and larger exposure area (29.4 cm<sup>2</sup>) were used. Once again animals were fitted with a special filter cartridge to collect volatiles directly above the exposure site. Medical adhesive was used to attach a foam ring to the skin at the application site. Then a charcoal filter covered with gauze was attached to the ring. This resulted in 88-95% recovery of the exposure dose. Male Sprague-Dawley rats 228-260 g were exposed to one of four dilutions for 1-24 hours. The doses used were neat formulated EPTC EC, 1:10 dilution, 1:50 and 1:100 dilutions in water. These correspond to 8740, 890, 196, and 94 µg/cm<sup>2</sup> after correction for inaccurate dilution. The doses were applied using a Teflon<sup>®</sup> tipped glass syringe. The animals were housed in glass metabolism chambers that separated urine and feces. At 24 hours the dose was washed off and the filter cartridge extracted. A new charcoal filter was installed on some animals and they were followed for up to 96 hours. Data were collected for 4 animals at each dose sacrificed at the following time points: 1, 4, 10, 24, 48, 72, and 96 hours. Urine and feces were collected at sacrifice or every 24 hours. The skin at the exposure site was washed just before sacrifice. Prior to sacrifice animals were sedated and a blood sample withdrawn by cardiac puncture. Sacrifice was by injection of euthanasia solution (American Hoechst) directly into the heart. Residues on the second filter cartridge were also extracted. Bladder urine was aspirated and combined with the total cage urine. The remaining carcass was solubilized in ethanolic sodium hydroxide. It was possible to follow the absorption and elimination of EPTC and its metabolites through a 96 hour time course in this study. Both absorption and elimination were rapid and followed similar kinetics regardless of dose. Total percutaneous absorption was derived from the sum of the percentage of dose in the skin, excreta, and carcass versus the total exposure dose. Elimination was derived from the percentage of fecal and urinary excretion versus the total exposure dose.

The rate of absorption was most rapid in the first hour of exposure at all doses. EPTC levels increased in the body carcass and the skin to a maximum of 3.6% of the applied dose during the first 4 hours following application. Body values then declined to about 1% of the total exposure by 48 hours and fell to 0.6% by 96 hours. Maximal total absorption at all doses occurred at or before the 24 hour sacrifice point.

Elimination was also very rapid. Elimination at all time points was primarily by urinary excretion. During the first 24 hours there was a linear increase in the percentage of the exposure dose eliminated in the urine. Total urinary excretion, as a percent of dose, plateaued at 24 hours. This is the point at which the dermal dose was washed off. Fecal excretion reached a maximum between 24 and 72 hours and typically accounted for 0.2% of the applied dose.

These data show that EPTC was rapidly absorbed and initially accumulated in the body. By four hours after application it was being rapidly eliminated, primarily in the urine. By 10 hours after application the dose was being eliminated more rapidly than it was being absorbed. After the dose was washed off at 24 hours elimination of the absorbed dosage was nearly complete. Fecal

elimination was highest at and just after this time, and it accounted for at the most 5% of total elimination. This would seem to indicate that once the dose is removed from the skin surface there is no significant reservoir of bioavailability remaining in the skin or carcass and that elimination is essentially complete.

This absorption-elimination pattern validates the limited sample times used in the Knaak study (Knaak *et al.*, 1986). Sampling restricted to a 24 hour time point is adequate for the estimation of absorption because absorption was maximal and essentially complete at this time. Absorption at 24 hours for the doses used in this study was 9.3% (8740  $\mu\text{g}/\text{cm}^2$ ), 7.1% (890  $\mu\text{g}/\text{cm}^2$ ), 3.7% (190  $\mu\text{g}/\text{cm}^2$ ), and 6.4% (90  $\mu\text{g}/\text{cm}^2$ ) (see Table 2).

Table 2. Percutaneous absorption of EPTC in rats exposed for 24 hours<sup>a</sup>.

Dermal dose in $\mu\text{g}/\text{cm}^2$	% absorption <sup>b</sup>	% recovery
Knaak <i>et al.</i> (1986)		
36.1 (Experiment 2)	13.7	85.9
23.0 (Experiment 1)	20.9	76.6
21.5 (Experiment 3)	14.7	95.3
Jeffcoat (1988)		
8740	9.3	92.0
899	7.1	93.0
196	3.7	91.0
94	6.4	87.0

Brodberg, WH&S, 1989

<sup>a</sup> These data are for rats treated for 24 hours and then sacrificed.

<sup>b</sup> Total dermal absorption during a 24 hour time period. This includes residues bound to the skin.

When estimating percutaneous absorption in occupationally exposed workers it is most appropriate to use animal absorption from a similar exposure dose when human absorption is unknown. The dermal doses in both rat studies were greater than measured worker field exposures at the skin surface (see Table 3). The lowest dose used in the rat dermal absorption studies is about 16X the mixer/loader/applicator dermal dose. The rat absorption data were statistically analyzed to determine if they could be used to extrapolate to a dose and absorption corresponding to the field dose. The data cannot be combined because the absorption rates are significantly different ( $p < 0.01$ ,  $t = 4.215$ ,  $df = 5$ ). In addition a significant regression line cannot be fit to either data set (analysis by one-way ANOVA). This is true for the regression of absorption on dose (Knaak *et al.* (1986) data:  $F = 0.514$ ,  $df = 1, 1$ ; Jeffcoat (1988) data:  $F = 3.567$ ,  $df = 1, 1$ ), and absorption on the log of dose (Knaak *et al.* (1986) data:  $F = 0.495$ ,  $df = 1, 1$ ; Jeffcoat (1988)  $F = 3.479$ ,  $df = 1, 1$ ).

Table 3. Comparison of rat dermal absorption study doses and field study dermal exposure doses.

Study	Applied dermal dose	Estimated field dermal dose <sup>a</sup>
Knaak <i>et al.</i> (1986)	36.1 $\mu\text{g}/\text{cm}^2$	
	21.5 $\mu\text{g}/\text{cm}^2$	
Jeffcoat (1988)	8740 $\mu\text{g}/\text{cm}^2$	
	890 $\mu\text{g}/\text{cm}^2$	
	190 $\mu\text{g}/\text{cm}^2$	
	90 $\mu\text{g}/\text{cm}^2$	
Ross <i>et al.</i> (1986)		
	Mixer/loader	0.7 $\mu\text{g}/\text{cm}^2$
	Applicator	0.3 $\mu\text{g}/\text{cm}^2$
Knarr and Iwata (1986)		
	Mixer/loader/applicator	1.3 $\mu\text{g}/\text{cm}^2$

Brodberg, WH&S, 1989

<sup>a</sup> Field exposure doses are given as the dose that would accumulate at the skin during 8 working hours averaged over the whole body surface area (21,110  $\text{cm}^2$ ).

The Jeffcoat (1988) study essentially represents 4 high doses with a mean absorption of 6.6%, and the Knaak *et al.* (1986) study represents two low doses (Experiments 2 and 3) with a mean of 14.2%. (Experiment 1 was eliminated because of low recovery.) From this simplified viewpoint the data agree with the expectation that percent of dose absorbed at high doses is less than that at low doses (Wester and Maibach, 1976). Since it is not possible to extrapolate from these data to the field dose, the lowest dose used in the rat studies will be used to estimate potential human absorption. Absorption at this dose is  $14.7 \pm 2.7$  (S.E.). By adding in the standard error and correcting for recovery a conservative estimate of the upper limit of absorption can be derived. This value (18.25%) will be used as the best available estimate of worker absorption. No studies directly measuring the respiratory absorption of EPTC are available. A surrogate estimate of 50% of the inhalation exposure was proposed by one registrant (Ross *et al.*, 1986) based on studies of several chemicals in beagles (Raabe, 1986). A similar value from surrogate data has been reported in humans (Raabe, 1988). In general inhalation uptake of an organic vapor is less than 100% because not all of the vapor molecules reach the alveolar surfaces at which absorption occurs. The value of 50% uptake of the breathing zone exposure will be used as an estimate of potential human inhalation retention and absorption.

## WORKER EXPOSURE

### A. Exposure to EPTC from use of liquid formulations

Two worker exposure studies have been done on field crops. The exposure data from both studies have been recalculated by Worker Health and Safety Branch (WH&S) to reach standard exposure values based on the same surface area and as few additional assumptions as possible. From this starting point various factors estimating clothing penetration and dermal or inhalation absorption can be applied to each data set. After this standardization these studies yield similar exposure estimates as outlined below.

Ross *et al.* (1986) measured exposure during the broadcast spray application and mechanical incorporation of a liquid concentrate (87.8% a.i.) to red kidney beans. In this case a single person acted as the mixer/loader, applicator, and incorporator. Application and incorporation were done simultaneously using a tractor outfitted with both a boom sprayer and discing equipment. Monitoring of mixing and loading was separated from that of the application and incorporation phases by changing monitoring patches and collecting handwashes between these tasks. Fifteen replicates over 7 workdays were collected. Each replicate consisted of a mixer/loader sample and an applicator/incorporator sample. Applicator activity also included unplugging of spray nozzles and subsequent handwashes. These handwashes were monitored and included in the total handwash values. Application was performed at 3 lbs a.i./acre (3.5 pints/acre). This is the maximum recommended rate for beans. EPTC was used in a tank mix with ethalfluralin, another preemergent herbicide. Mixing was by open pouring. Protective clothing worn during the study were boots, jeans, a flannel shirt with the sleeves rolled up, and a cap. Long rubber gloves were worn only during mixing and loading. Sunglasses were worn at all times.

This study measured both potential dermal and inhalation exposure and used urine samples for biological monitoring. Potential exposure was monitored using 23.75 cm<sup>2</sup> gauze patches. These were attached on the surface of the worker's clothing at the back, shoulders, thighs, and shins. Forearm patches were on bare skin and chest patches were under the shirt. Hand exposure was monitored by collecting handwashes in surfactant. Each hand was washed two times in 200 mL of a 2% dioctyl sodium sulfosuccinate solution in a 0.5 gallon polyethylene bag. Each hand was shaken 50 times in the bagged solution. Inhalation monitoring was by air sampling in the breathing zone using a personal air sampling pump drawing air through a charcoal filter at 1 L/min. Charcoal filter and patch samples were extracted and analyzed on a gas chromatograph equipped with a sulfur specific detector. Handwash samples were analyzed using liquid chromatography. The cysteine and N-acetyl cysteine conjugates of S-(DPC) present in urine samples were acetylated and methylated to convert them to S-(N,N-DPC)-N-acetylmethylcysteine. This compound was quantified using gas chromatography with a flame photometric detector in the sulfur mode. S-(N,N-DPC)-N-acetylmethylcysteine values were converted to EPTC equivalents for use in biological estimates of exposure.

Field fortifications and quantification standards were run for all samples. The mean recovery for patches was 78 ± 20%, with 80 ± 10% for handrinse solutions, and 91 ± 5.3% for inhalation

samples. Recovery of the two EPTC metabolites from urine averaged 81%. These daily recoveries have been used by WH&S to normalize the data to 100% recovery and to recalculate the exposures derived from this study.

The surface areas used by the registrant to calculate exposure values are somewhat different than those in the U.S. EPA Pesticide Assessment Guidelines (U.S. EPA, 1987). The U.S. EPA surface area values were used by WH&S during recalculations. In this study chest exposures were from patches placed under the shirt. This is a direct measure of dermal exposure but all other patches were positioned externally to directly measure potential dermal exposure. To standardize exposure data to a uniform work and monitoring situation (potential dermal exposure on the shirt surface), the patch data for the chest was multiplied by a factor of 2.13 ( $1/0.47 = 2.13$ ). This factor is derived from the next study (Knarr and Iwata, 1986) in which it was demonstrated that 47% of the external dose penetrated a long-sleeved work shirt. The inhalation exposure values were also normalized using a respiration rate of 29 L/min. rather than the 25 L/min. originally used in the study. The resultant average dermal exposure estimates as recalculated by WH&S are presented in Table 4.

Knarr and Iwata (1986) also measured worker exposure to a liquid concentrate formulation of EPTC (87.8% a.i.). In this case a post-emergent application to Kennebec potatoes was monitored over 8 working days. The maximum recommended rate of 3.9 lbs a.i./acre (4.5 pints) was used. A single worker performed the mixer/loader/applicator functions, and samples were not collected in a manner so that mixer/loader exposure could be separated from applicator exposure. This same worker also did the mechanical incorporation at the same time as spray application. The worker wore a long-sleeved shirt, long-legged pants and rubber boots at all times. Mid-forearm length gloves and a hard hat with a protective face shield were worn during mixing/loading operations. An open pour system was used for mixing.

Both potential dermal and inhalation exposure were monitored in this study. Potential dermal exposure was monitored using Durham and Wolfe-type patches supplied by Western Paper Box Company. The collection medium was polyurethane foam rather than gauze. Foam was used because a fortified control study showed that it retained volatile EPTC better than gauze (about 10X as much over 8 hours). It was hoped that this modification would more closely represent the retentive qualities of skin. Patches were placed on the hat, shoulder, forearms, chest, back, thighs, and shins. Each patch had an exposed surface area of 23.75 cm<sup>2</sup>. (There is internal inconsistency concerning the exposure area in this study. To resolve this problem the surface area for cardboard holders supplied by Western Paper Box Company has been calculated as 23.75 cm<sup>2</sup> by WH&S.) Patches placed outside the shirt on the chest and under the shirt on a tee shirt were used to measure clothing penetration of EPTC. The detergent handrinse method was used to collect samples for estimation of hand exposure. A 0.1% sodium dodecyl sulfate solution (200 mL) in a one gallon bag was used for a single rinse of each hand. Each handrinse was done by shaking a single hand 50 times in a collection bag.

A personal air-sampling pump was used to collect samples to monitor inhalation exposure. Air was drawn through an XAD-2 resin cartridge in the worker's breathing zone at a rate of 200 mL/min. Sampling began before work commenced and ended after all cleanup was done.

Table 4. Normalized average dermal exposure to EPTC derived from field studies<sup>a</sup>.

Body region	Exposure in $\mu\text{g}/8\text{-hr day}$		
	mixer/loader <sup>b</sup>	applicator <sup>b</sup>	mixer/loader/applicator <sup>c</sup>
Hands	7176 <sup>d</sup>	4072	25
Unprotected skin <sup>e</sup>	130 <sup>d</sup>	134	1351
Protected skin <sup>f</sup>	7358 <sup>g</sup>	2038	26,252
Inhalation	1200	532	2480
Total	15,865	6,777	30,109

Brodberg, WH&S, 1989

<sup>a</sup> Dermal exposures were calculated by WH&S from raw patch and handwash data. U.S. EPA surface areas were used to extrapolate from the patch data to body regions. A clothing penetration factor of 47% was applied by WH&S to protected areas of the torso and trunk to estimate the exposure at the skin surface. Inhalation values from each study were normalized to a respiration rate of 29 L/min. from those originally assumed in each study. Calculated exposures have been corrected for recovery by WH&S.

<sup>b</sup> Recalculated from Ross *et al.* (1986) by WH&S.

<sup>c</sup> Recalculated from Knarr and Iwata (1986) by WH&S.

<sup>d</sup> Number of replicates is 14. One is excluded due to loss of a sample set.

<sup>e</sup> Includes the face and front and back of the neck.

<sup>f</sup> Includes the head, back, chest/stomach, upper arm, forearm, thigh, lower leg and feet. In Ross *et al.* (1986) the worker wore boots, jeans, a flannel shirt with the sleeves rolled up, a cap, and sunglasses. Long rubber gloves were worn during mixing and loading. In Knarr and Iwata (1986) the worker wore a long-sleeved shirt, long-legged pants, and rubber boots. Mid-forearm length gloves and a hard hat with a protective face shield were worn during mixing and loading.

<sup>g</sup> Number of replicates is 13 after rejection of a sample set that had a documented spill on a patch and due to loss of a sample set.

Sample analysis was by gas chromatography using either a N-P flame ionization (thermionic) detector or a flame photometric detector in the sulfur mode. Resin and patch samples were extracted with toluene, and aqueous wash samples were run over an XAD-2 resin column and then extracted prior to analysis by gas chromatography.

Untreated and fortified control samples were prepared in the field for patches, skin wash, and air samples to correct for recovery. Recoveries varied from 63-120%. Once again daily recoveries have been used by WH&S to normalize the data to 100% in the recalculated exposures derived

from this study. Fortified foam patches were set out in the field to follow the potential extent of EPTC loss during a sampling period. In a typical 5-hour work period 80-85% of the EPTC was observed to volatilize. This is similar to the volatilization of EPTC from the skin in dermal absorption studies.

The data for dermal exposure from this study were recalculated by WH&S so that the surface areas correspond to those used in U.S. EPA Subdivision U (U.S. EPA, 1987). Calculated dermal and inhalation exposure values are shown in Table 4. Inhalation exposure was also normalized by WH&S to a respiration rate of 29 L/min. from that assumed in this study (20 L/min.). A clothing penetration factor of 47% was derived by the registrant by comparison of patch residues inside and outside the shirt. This high penetration may be due to the volatility of EPTC. In this case exposure of protected skin may be from the vapor phase as well as liquid penetrating the clothing.

A comparison of the exposure data from these two studies is shown in Table 4. When mixing and loading is separated from application, the exposure to hands, protected skin, and via inhalation is greatest for the mixer/loader task. In the Ross *et al.* (1986) study, mixing and loading accounted for 10% of work time and application 90%. County agricultural personnel surveyed also estimated that time spent mixing and loading would be 10% and application 90% (Acosta, 1989; Perry, 1989; Gruenberg, 1989). The combined mixer/loader/applicator potential exposure calculated by WH&S for Ross *et al.* (1986) is 7686  $\mu\text{g}/8$  hr. This was less than observed in Knarr and Iwata (1986) (30,109  $\mu\text{g}/8$  hr). This difference may derive from the higher application rate in Knarr and Iwata (1986). Normalizing for the difference in pounds of a.i. applied, total mixer/loader/applicator exposure would be 24,633  $\mu\text{g}/8$  hr from Ross *et al.* (1986) versus 30,109  $\mu\text{g}/8$  hr from Knarr and Iwata (1986). (Normalizing factor = 1032 lbs Knarr and Iwata/322 lbs Ross *et al.* multiplied by the Ross *et al.* (1986) exposure.) This difference might be due to the use of the more retentive foam patches in Knarr and Iwata (1986).

Another difference between these studies is seen for hand exposure values. The values in Knarr and Iwata (1986) are lower than measured by Ross *et al.* (1986) (25 and 4072  $\mu\text{g}/8$  hrs., respectively). Since rubber gloves were used in both studies only during mixing and loading this should not be the source of the difference. Differences in handwash sampling between these studies may account for this difference. Ross *et al.* (1986) collected handwash samples by washing each hand twice in a fresh solution and then summing the values. They also used 20 times more surfactant in their handwash solution, and their protocol resulted in more frequent sampling. This is because they took samples each time the worker changed tasks between mixing/loading and application, and because they took handwash samples following maintenance cleaning of plugged nozzles. Some maintenance occurs in a typical work situation. Maintenance was done with bare hands which might increase hand exposure.

These estimates of potential dermal exposure can also be compared to an estimate of mixer/loader/applicator exposure derived from the biological monitoring reported by Ross *et al.* (1986). They reported EPTC-equivalents in urine samples normalized to a 1200 mL daily void volume and corrected for percent measured metabolites eliminated in the rat metabolism studies. Based on their measurement the total absorbed dose calculated by WH&S was 136  $\mu\text{g}/8$  hrs. This would be roughly equivalent to a dermal exposure of 1586  $\mu\text{g}/8$  hrs. (To arrive at this estimate of

dermal exposure the dosage above was corrected for the 47% clothing penetration and 18.25% dermal absorption used in calculating absorbed dosages in Table 5. This correction multiplies the inverse of these percentages by the internal dosage measured by biological monitoring. In this calculation, it was assumed that 100% of the absorbed dose was excreted in urine). This is about five times less than the dermal exposure derived from patches (7686  $\mu\text{g/hr}$ ) from Ross *et al.* (1986). This is a reasonable value since biological monitoring often yields an exposure estimate up to 50 times less than patch data (Maddy *et al.*, 1989).

#### Exposure Assessment Recommendations

The exposure values derived from these two studies describe a range of worker exposure to EPTC. For regulatory purposes the mixer/loader/applicator value is deemed to be the most appropriate for work conditions prevailing in California. When applying EPTC the mixer/loader and applicator tasks are typically done by the same individual. This will frequently be a farmer doing his own application. The mixer/loader/applicator values derived by WH&S from Knarr and Iwata (1986) are an acceptable estimate of EPTC exposure during work performed at the maximal label rate of EPTC application of liquid formulations. If separate values are desired for mixer/loader and applicator exposure, the values for these exposures from Ross *et al.* (1986) should be used as an acceptable estimate. The data from Knarr and Iwata (1986) cannot be used to estimate separate mixer/loader and applicator exposure.

Table 5 shows dermal and inhalation Absorbed Daily Dosage (ADD) for different workers occupationally exposed to EPTC. These values have been calculated by WH&S based on the potential dermal exposure values derived from the Ross *et al.* (1986) and Knarr and Iwata (1986) studies. The clothing penetration factor (47%) used in these calculations was derived from Knarr and Iwata (1986). The dermal absorption factor (18.25%) was derived from Knaak *et al.* (1986) as an upper-bound based on the dose closest to the measured field exposure dose. The factor for surrogate inhalation uptake (50%) is from Raabe (1988). Workers spraying EPTC are likely to be exposed for 8 hours per day. Simultaneous broadcast spraying and mechanical incorporation are slow procedures and would require about 8 hours to complete a 50 acre application.

There is no definitive period for a use season of EPTC in California. For the major use crops, use reporting indicates applications are made throughout the year with maximum use during approximately one month for each crop. Time to toxic effect is the most desirable time frame over which to amortize dosage to estimate seasonal exposure. Lacking this we utilize estimates of the season which are climatically determined for a particular crop. This is 17 days for EPTC in any given location. Supporting this estimate of the season is the length of the toxicology study. The default time to effect was 17 days (the first interim sacrifice time), and the first time the effects were observed after sequential daily dosing of laboratory animals.

The majority of EPTC applications are done by growers because major crops in which EPTC was used to control weeds are low value crops and EPTC products are Category III pesticides. This is supported by a report by Hunter (1995) on assessment of EPTC usage. For commercial application by PCOs, workdays per year are up to 15 days (Ross *et al.*, 1986). For the purpose of

exposure estimation, it was assumed that a PCO applied EPTC eight days per season and 16 days per years.

Table 5 also shows ADD, Seasonal Average Daily Dosage (SADD), and Annual Average Daily Dosage (AADD). Eight workdays per 17-day use season were employed to calculate SADD. This number of workdays was based upon information from two submitted exposure studies. The first study involved ground-spray application which was done prior to planting of red kidney beans at the Nichols Ranch of Chico, California (Ross *et al.*, 1986). The application of EPTC was done over a 7-day period. The second study was conducted using ground-spray application to potato fields in the Salinas Valley of California (Knarr and Iwata, 1986). The total application period was eight days. These two studies were conducted at two big ranches and the number of application days are considered the upper end. Selection of big fields for the studies was to ensure an adequate number of replicates. For the exposure estimation, eight workdays per season was used to calculate SADD for ground as well as application by other methods, except for chemigation employing the center-pivot irrigation system. Six workdays per season were used instead of eight because this irrigation system has not become well established in California.

Table 5. Normalized average daily dosages of EPTC for occupationally exposed workers<sup>a</sup>.

work task	exposure		normalized dosage		
	Dermal <sup>b</sup> ( $\mu\text{g}/\text{kg}/\text{day}$ )	Inhalation <sup>c</sup> ( $\mu\text{g}/\text{kg}/\text{day}$ )	ADD <sup>d</sup> ( $\mu\text{g}/\text{kg}/\text{day}$ )	SADD <sup>e</sup> ( $\mu\text{g}/\text{kg}/\text{day}$ )	AADD <sup>f</sup> ( $\mu\text{g}/\text{kg}/\text{day}$ )
Mixer/loader <sup>g</sup> (n=14)	209.5	17.1	46.8	22.0	1.03
Applicator <sup>g</sup> (n=14)	89.2	7.6	20.1	9.45	0.44
M/L/A <sup>h</sup> (PCO) (n=8)	394.7	35.4	89.8	42.2	3.94

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- <sup>a</sup> Daily dosages reported here includes both absorbed dermal and inhaled dosages. Dermal absorption = 18.25%. Inhalation uptake/absorption was 50% (Raabe, 1988).
- <sup>b</sup> Dermal exposure is given for a 70 kg worker at the skin surface for an 8 hour work day after a 47% penetration factor is applied to protected body regions.
- <sup>c</sup> Inhalation exposure is given at the worker's breathing zone.
- <sup>d</sup> ADD is calculated based on 18.25% percutaneous absorption and 50% respiration uptake.
- <sup>e</sup> SADD is calculated based on 8 working days of EPTC exposure per 17-day season.
- <sup>f</sup> AADD is calculated based on 8 working days of EPTC exposure per year, except for M/L/A which is 16 days.
- <sup>g</sup> Derived from Ross *et al.* (1986).
- <sup>h</sup> Derived from Knarr and Iwata (1986).

## B. Exposure to EPTC from use of granular formulations

Exposures of persons to EPTC were estimated during application of EPTC granular formulations for weed control in flowers and ornamentals, and aerial application of granular formulations in agriculture. There were no EPTC exposure studies available for these uses. Consequently, surrogate data obtained from exposure studies using chlorpyrifos, molinate and diazinon were utilized to estimate the exposure of persons to EPTC. These surrogate chemicals were selected because of their similarities in application methods and formulations. The surrogate exposure data were adjusted where appropriate to reflect factors associated with EPTC, including clothing penetration, application rate, application time, and dermal absorption value. The exposure estimates were reported as the arithmetic mean.

### B.1 Flowers and ornamentals: application of EPTC granules

There are several granular products of EPTC that are intended for use in flowers and ornamentals. Home gardeners can also use smaller bags of EPTC granular products in their home gardens and landscapes. The exposure for home gardeners to EPTC is expected to be lower than that for professional landscapers or workers who apply EPTC granules for weed control in flowers and ornamentals. Granular products for commercial uses are in larger size bags, e.g., 50 pounds.

A worker exposure study using an EPTC granular formulation was not available. A study using 14-G diazinon (Weisskopf *et al.*, 1988) was used as a surrogate for EPTC. Dermal and inhalation exposures were monitored for 6 workers by using patches, handwashes, and air sampling. These workers applied diazinon granules to eradicate Medfly larvae primarily in residential areas. The application rate was 40 pounds of product per acre (5.6 lbs a.i./acre). Types of application equipment were spreaders of three designs and a hand-held shaker. Only the exposure from the use of a belly grinder was used as a surrogate. The exposure from the use of a belly grinder was higher than that using other types of application equipment, namely coffee can applicator, Gandy spreader, and Lesco spreader. Also, a belly grinder is more appropriate for the application of Eptam<sup>®</sup> granules in the commercial production of flowers or ornamentals. After the application, diazinon was incorporated into the soil by a process called "watering in." This type of application is similar to that for EPTC granules which requires either soil or water incorporation.

Table 6 shows exposure estimates for workers to diazinon according to body regions. These exposure estimates were then adjusted to reflect an application rate of EPTC at 5.0 lbs a.i. per acre. The EPTC labels do not require applicators to wear coveralls during application. Therefore, adjustment of leg exposure was made as noted in the footnote (b) of Table 6. The estimated absorbed dosages ( $\mu\text{g}/\text{kg}/\text{day}$ ) for workers loading and applying EPTC granules to flowers/ornamentals are shown in Table 7. The maximum label rate of 15 lbs a.i. per acre, which is used for the control of mugwort (*chrysanthemumweed*), was not employed in the estimation of exposure. Although this kind of weed is widely distributed in California, growing along streams, irrigation ditches, railroads, highways, and in moist pasture lands (Robbins *et al.*, 1941), it does not appear to be a common pest in gardens. Use of EPTC to control mugwort should not constitute a significant amount in California.

Table 6. Exposure of workers during application of EPTC granules.

	Mean exposure (mg)					Total
	Anterior head & neck	Posterior head & neck	Legs	Hands	Air	
Diazinon at 5.6 lbs a.i./A	3.66	1.04	0.14	0.06	0.27	5.17
	<u>Dermal exposure = 4.90</u>			<u>Inhalation exposure = 0.27</u>		
EPTC at 5.0 lbs a.i./A <sup>a</sup>	3.27	0.93	0.13	0.05	0.24	4.62
EPTC at 5.0 lbs a.i./A	3.27	0.93	0.59 <sup>b</sup>	0.05	0.24	5.08
	<u>Dermal exposure = 4.84</u>			<u>Inhalation exposure = 0.24</u>		

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<sup>a</sup> Diazinon exposure was adjusted to reflect an application rate of EPTC at 5.0 lbs a.i./A.

<sup>b</sup> EPTC product labels do not require coveralls to be worn during application of EPTC granules. Therefore, exposure of legs to EPTC was adjusted as follows: 0.13 x clothing penetration of EPTC (47%)/clothing penetration of diazinon (10%)

## B.2 Agriculture: aerial application of EPTC granules

Exposures of pilots, flaggers, and loaders to EPTC during aerial application were estimated from two studies using molinate 10-G. Maddy *et al.* (1982) conducted the first study in Colusa County, California, using an application rate of 4 lbs a.i./acre. The second study was conducted by Knarr (1980) in Arkansas using an application rate of 3 to 5 lbs a.i./acre. The results of both exposure studies were reviewed and summarized by Formoli and Fong (1995); the geometric mean was employed in the estimation of exposure from a four-hour exposure per day for pilots, flaggers and loaders. In order to be consistent with exposure estimates for other work tasks, the authors of this exposure document recalculated the exposures in terms of the arithmetic mean. The dermal and inhalation exposures were adjusted to reflect an application rate of EPTC at 3 lbs a.i./acre which is the maximum application rate for alfalfa. The mean absorbed dosages ( $\mu\text{g}/\text{kg}/\text{day}$ ) observed for pilots, flaggers, and loaders are shown in Table 7. The ground application of EPTC granules by tractors was assumed insignificant in terms of the amount of a.i. usage. From the use report in 1992, Eptam<sup>®</sup> 10-G accounts for 21,355 lbs a.i. or 3.2% of the total EPTC usage (Hunter, 1995). Aerial applications would constitute a major use of granular formulation. Therefore, the exposure of workers to EPTC during the ground application of granules was not estimated.

Table 7. Exposure of workers to EPTC during aerial and ground applications of granules<sup>a</sup>.

	Unadjusted surrogate exposure (mg/person/day)		Adjusted EPTC exposure (mg/person/day)		ADD (µg/kg/day)	SADD (µg/kg/day)	AADD (µg/kg/day)
	Dermal	inhalation	Dermal	inhalation			
<b>B.1 Flowers and ornamentals: application of EPTC granules</b>							
Loader/Applicator <sup>b</sup> (n=6)	4.90	0.27	4.84	0.24	14.3	6.75	0.32
<b>B.2 Agriculture: Aerial application of EPTC granules<sup>c</sup></b>							
Pilots (n=5)	0.50	0.15	0.34 <sup>d</sup>	0.11	1.67	0.79	0.04
Flaggers (n=8)	5.62	0.09	2.89 <sup>e</sup>	0.12	8.40	3.95	0.18
Loaders (n=12)	32.0	5.57	21.2 <sup>f</sup>	4.18	85.1	40.1	1.86

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<sup>a</sup> Workers were assumed to be wearing long-sleeved shirts, long pants, shoes plus socks, and rubber gloves. These factors are applied: dermal absorption = 18.25%; inhalation uptake/absorption was 50% (Raabe, 1988); adult male body weight = 70 kg; clothing penetration of EPTC = 47%.

<sup>b</sup> The daily exposure was obtained from a study using diazinon 14-G at a rate of 5.6 lbs a.i./acre. The exposure was adjusted to reflect an application rate of 5 lbs a.i./acre for weed control in flowers and ornamentals. The number of workdays are 8 in a 17-day season. Percent of dermal exposure: Head and neck (86.8%), legs (12.2%), hands (1.0%)

<sup>c</sup> The surrogate data were from a study using molinate 10-G applied at an average rate of 4 lbs a.i./acre. Clothing penetration of molinate was 53%. The exposure data were adjusted to reflect an application rate of EPTC 10-G at 3 lbs a.i./acre. Eight workdays/17-day season.

<sup>d</sup> Pilots - Percent of dermal exposure: Body (83.9%), head and neck (11%), hands (5.1%). Clothing worn: long-sleeved shirts, long pants, shoes plus socks.

<sup>e</sup> Flaggers - Percent of dermal exposure: Body (94.7%), head and neck (4.4%), hands (0.9%). Same as pilots plus rubber gloves.

<sup>f</sup> Loaders - Percent of dermal exposure: Body (88.8%), head and neck (8.0%), hands (3.2%). Same as pilots plus rubber gloves.

### C. Exposure to EPTC During Chemigation

Liquid formulations of EPTC, Eptam<sup>®</sup> 7-E and Eptam<sup>®</sup> 6.7-E, may be applied and soil incorporated by using a chemigation system. A liquid formulation can be metered into the irrigation water at a constant flow rate. For flood, furrow, or sprinkler irrigation, liquid EPTC is metered into the water during the entire period. For sprinkler irrigation, liquid Eptam<sup>®</sup> may be metered into sufficient water to penetrate to a soil depth of 3 to 4 inches.

#### C.1 Water-run of liquid formulations

A worker exposure study for EPTC during a water-run irrigation (flood or furrow) was not available from the registrant. Therefore, exposure data generated for sodium tetrathiocarbonate (Haskell, 1994a, 1994b) was used as a surrogate. Sodium tetrathiocarbonate (Enzone<sup>®</sup>) was applied to grapes and citrus at three sites. The study design called for two applications per site at three sites utilizing three different irrigation systems: flood with furrows, drip and mini-sprinklers. The first application utilizing the nurse tank filled with water only and irrigation injection system was made with water from the nurse tank to generate background samples. The second application utilizing the same equipment, was made with Enzone<sup>®</sup> from the nurse tank. The long underwear dosimeters were worn underneath the worker's clothing and urine samples were collected before and after the application.

At each application site, one worker loaded the nurse tank with water for the pretreatment water application. The same worker also loaded Enzone<sup>®</sup> at the storage site into another nurse tank and transported it to the application site. These workers wore protective coveralls over normal work clothing, rubber boots, rubber gloves, and face shields or goggles. Two other workers, acting as applicators, attached the nurse tank to the irrigation system with hoses, pumps, and metering devices. They applied the Enzone<sup>®</sup> by injection into the irrigation system, then rinsed the nurse tank and injected the rinsate into the irrigation system. The workers then detached the pumps and hoses from the nurse tank. Injection of sodium tetrathiocarbonate into an irrigation system was done *using a closed system*. These applicators wore work clothing, rubber boots, and rubber gloves. The workers did not enter the treated area during the application at any of the sites. Under the work clothing, the workers wore long underwear which served as the dermal sampling matrix. The application time ranged from 5.75 to 11.33 hours averaging 8.31 hours per day. The average application rate for these sites was 136 lbs a.i. per acre.

Sodium tetrathiocarbonate is unstable in the environment after application. Collection of active ingredient residue samples for analysis was not practical, if not impossible. Therefore, a surrogate chemical, cesium ion in the form of cesium chloride, was added to the product before application at a rate of 0.0975% by weight. Estimation of dermal exposure per day was based on the amount of sodium tetrathiocarbonate that was proportional to the amount of detected cesium ion. Almost all samples collected for analysis showed that residues of cesium ion were either below the limit of detection (LOD) or the limit of quantitation (LOQ). When cesium was not detected in the underwear sample, the value observed was considered 1/2 LOD and values that were above the LOD but were too low to be quantified were expressed as 1/2(LOD+LOQ). All handwash sample results were estimated using the LOD. Dermal exposure was determined to be 2.27

mg/person/day, either for mixer/loaders or applicators. Standard deviation was not presented because of nondetection of residues by methods used in the estimation. Exposure of workers to EPTC was then estimated based on the label rates of 3 lbs a.i./acre for alfalfa (Tables 8 and 9). Inhalation exposure of mixer/loaders to Enzone<sup>®</sup> or its metabolite, CS<sub>2</sub>, was not directly monitored. Instead, exposure of workers to CS<sub>2</sub> was estimated from its urinary metabolite. This is not appropriate to be used as a surrogate for EPTC inhalation exposure. Therefore, EPTC inhalation exposure of 1,200 µg/person/day for M/L (Ross *et al.*, 1986) was employed. It was assumed that the application of liquid EPTC for a water-run used a closed system. Therefore, inhalation exposure would be 5% x 1,200 µg/person/day = 60 µg/person/day.

For weed control in alfalfa using a water-run application, the product label states "Meter 2 1/4 to 3 1/2 pints Eptam<sup>®</sup> 7-E (87.8%) per acre into the irrigation water applied to established stands prior to weed emergence." It was assumed that the system used to dispense this product is a *closed system*, similar to that used for sodium tetrathiocarbonate.

Table 8. Dermal exposure estimates for EPTC loaders during a water-run application<sup>a</sup>.

<u>Sodium tetrathiocarbonate</u>		<u>EPTC</u>			
Rate (lbs a.i./acre)	DE (mg/person/day)	Adjusted DE <sup>c</sup> (mg/person/day)	Adjusted DE <sup>d</sup> (mg/person/day)	Rate (lbs a.i./acre)	Adjusted DE <sup>e</sup> (mg/person/day)
136	2.27 <sup>b</sup>	22.7	107	3	2.35

DE = Dermal Exposure

Thongsinthusak, WH&S, 1995

- <sup>a</sup> Product label requires workers to wear long-sleeved shirt, long pants, chemical-resistant gloves, shoes plus socks, and protective eyewear.
- <sup>b</sup> From Haskell (1994a, 1994b).
- <sup>c</sup> Adjusted to reflect protection provided by one layer of clothing or (c) = (b) x 100%/10%.
- <sup>d</sup> Adjusted to reflect 47 percent clothing protection of EPTC or (d) = (c) x 47%/10% (default).
- <sup>e</sup> Adjusted to reflect the difference in the application rates or (e) = (d) x 3 lbs a.i./acre ÷ 136 lbs a.i./acre.

## C.2 Center-pivot irrigation system

For the potential worker exposure to EPTC during chemigation, it is anticipated that a center-pivot irrigation system would give a higher exposure than flood and furrow irrigation due to potential contacts of workers to EPTC during handling of containers, pouring, mixing, calibration and application of EPTC products. Therefore, the exposure to EPTC during chemigation using the center-pivot irrigation system should represent an extreme exposure scenario.

A chlorpyrifos exposure study in corn using the center-pivot irrigation system (Byers *et al.*, 1992) was used as a surrogate. This study monitored both dermal and inhalation exposures. Three-layer pads, each composed of a bottom layer of glassine, middle layer of tagboard, and top layer of 12-ply surgical gauze, were used for dermal exposure monitoring. The hand exposure was monitored using 100% cotton beauty gloves worn over protective polyvinyl chloride gloves. Inhalation exposure was measured by employing a portable air sampler which was calibrated at a flow rate of 2 L/min. Polyurethane foam plugs were used for trapping the insecticide residues in the ambient air near the worker's breathing zone. The application rate for chlorpyrifos was 1 lb a.i. per acre.

The dermal exposure estimate was calculated to reflect the clothing worn by the worker which consisted of long-sleeved shirt, long pants, and rubber gloves. The EPTC labels require this same clothing for handlers, with the addition of protective eyewear. The dermal exposure data were adjusted to reflect EPTC clothing penetration of 47% and protection provided by rubber gloves of 90% (Thongsinthusak *et al.*, 1993b). The exposure data were also adjusted to represent the application rate of EPTC for alfalfa at 3 lbs a.i. per acre. It was assumed that the exposure period for a worker was 2 hours per day. Eight workdays in a 17-day season was also assumed. These default values were based on a survey which indicated that use of the center-pivot irrigation systems has not been well established in California (Thongsinthusak *et al.*, 1993a). The estimated absorbed dosages ( $\mu\text{g}/\text{kg}/\text{day}$ ) are shown in Table 9.

Table 9. Exposure of workers to EPTC during chemigation, aerial and ground applications of granules.

	Unadjusted surrogate exposure (mg/person/day)		Adjusted EPTC exposure (mg/person/day)		ADD (µg/kg/day)	SADD (µg/kg/day)	AADD (µg/kg/day)
	Dermal	inhalation	Dermal	inhalation			
<u>C.1 Water-run (chemigation)</u>							
Applicator <sup>a</sup> (n=9)	2.27	1.20	2.35	0.06	5.34	2.51	0.12
<u>C.2 Center-pivot sprinkler irrigation</u>							
M/L/A <sup>b</sup> (n=9)	14.1	0.05	84.4	0.14	221	78.0	3.64

Thongsinthusak, WH&S, 1995

- <sup>a</sup> Based on a 70-kg adult male body weight, except for surrogate dermal exposure which was based on an average body weight of 87.5 kg (actual body weight). Dermal absorption = 18.25%. Inhalation uptake/absorption was 50% (Raabe, 1988). The number of workdays per 17-day use season is eight. The number of workdays per year is also eight.
- <sup>b</sup> Based on the chlorpyrifos application rate of 1 lb a.i./acre. Exposure time per workday = 2 hours; the exposures were adjusted based on the EPTC application rate of 3 lbs a.i./acre (for alfalfa); eight workdays per 17-day season. Adjusted dermal exposure (mg/2 hours): gloved hands 13.3, unclothed areas 8.9, clothed area 62.3.

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APPENDIX B  
MITIGATION OF EPTC EXPOSURE  
August 8, 1995

The Department of Pesticide Regulation evaluated health risks associated with exposure to EPTC from handling activities and dietary sources. EPTC was identified by the Department to cause, in experimental animals, neurotoxicity from acute exposure, nasal cavity degeneration/hyperplasia and blood coagulation abnormality from short-term exposure, and neuromuscular degeneration from moderate-term exposure. For the purpose of the risk assessment process, dietary and occupational exposure estimates were calculated as absorbed daily dosage (ADD) for acute exposure, seasonal average daily dosage (SADD) for short-term exposure, and annual average daily dosage (AADD) for moderate-term exposure.

The Medical Toxicology Branch determined the acute and chronic potential dietary exposure of the general population and population subgroups. The highest potential dietary exposure used in the risk assessment was obtained for males aged 13-19 years; the exposure levels ( $\mu\text{g}/\text{kg}/\text{day}$ ) are: 1.2 for ADD; 1.2 for SADD; and 0.5 for AADD (Meierhenry, 1995). The EPTC exposures for mixer/loaders (M/L), applicators (A), and mixer/loader/applicators (M/L/A) were estimated by the Worker Health and Safety Branch (Brodberg and Thongsinthusak, 1995). The ranges of occupational exposure estimates ( $\mu\text{g}/\text{kg}/\text{day}$ ) are: 1.67-221 for ADD; 0.79-78.0 for SADD; 0.04-3.94 for AADD. The combined dietary and occupational exposure data and resulting margin of safety (MOS) prior to mitigation are summarized in Table 1.

The exposure level to EPTC, either from dietary or occupational or a combination of both, is generally believed to be acceptable when an MOS is 100 or greater. The MOS is derived by dividing a no-observed-effect level (NOEL) by an appropriate exposure estimate. If an MOS is less than 100, mitigation of EPTC exposure is indicated. The target levels of exposure to achieve an MOS of 100 are: 200  $\mu\text{g}/\text{kg}/\text{day}$  for neurotoxicity (acute exposure); 7.0  $\mu\text{g}/\text{kg}/\text{day}$  for nasal cavity degeneration/hyperplasia or blood coagulation abnormality (short-term exposure); and 5.0  $\mu\text{g}/\text{kg}/\text{day}$  for neuromuscular degeneration (moderate-term exposure). The short-term exposure levels utilizing the values of SADD were one to 11 fold over target, except for exposures of applicators during chemigation by a water-run, or pilots and flaggers during application of granular formulation. Exposure mitigation appeared necessary for the majority of work tasks.

It is quite common that a pest control operator (PCO) or a farmer's employee performs all work activities mixing/loading and applying EPTC. The combined M/L/A exposure data were collected in a study conducted by Knarr and Iwata (1986); the results were reviewed and summarized by Brodberg and Thongsinthusak (1995). The occupational exposure of the combined M/L/A cannot be used to calculate the individual M/L and A work activities for the purpose of mitigation. Therefore, the exposure estimate for a M/L/A is subdivided into the exposure estimates for M/L and A for the purpose of mitigation. The exposure estimate of M/L/A and how the exposure data is subdivided for mixing/loading and applying activities are shown in Table 2. The EPTC exposure estimate for a M/L was obtained from a study conducted by Ross *et al.* (1986) which was subsequently reviewed by Brodberg and Thongsinthusak (1995). An exposure time period required for a mixing/loading activity is about one hour and that for application is

about seven hours in a typical 8-hour workday (Ross *et al.*, 1986). Dermal exposure for a M/L was adjusted to reflect a maximum label rate of 3.9 lbs a.i./acre for use in potatoes.

In order to attain an MOS of 100 or greater, the following personal protective equipment (PPE) and engineering controls are required to mitigate dermal and inhalation exposure for various work tasks.

1. A closed mixing/loading system together with apron and chemical-resistant gloves and boots is proposed while mixing/loading of liquid formulation or transferring of liquid mixes.
2. Full-body chemical-resistant protective clothing is proposed during application of liquid mixes and loading and application of granules. There is no exception even though: i) applicators using vehicle mounted or towed equipment to inject or incorporate EPTC into the soil; and ii) applicators using equipment with vehicle mounted spray nozzles directed downward and located below the level of the employee.
3. A half-face respirator approved by the National Institute for Occupational Safety and Health (NIOSH) and/or the Mine Safety and Health Administration (MSHA) is proposed during application of liquid mixes or granules or loading of granules. There is no exception even though: i) applicators using vehicle mounted or towed equipment to inject or incorporate EPTC into the soil; and ii) applicators using equipment with vehicle mounted spray nozzles directed downward and located below the level of the employee.

The mitigated values (Table 2) for a M/L, A, M/L/A, and a farmer's employee working as a M/L/A are all well below the target, except exposure of M/L/A during chemigation employing the center-pivot sprinkler system where mitigated exposure is very close to the target level. Exposure mitigation is not needed but might be required for uniformity for three work tasks: pilots and flaggers during aerial application of granular products and applicators during a water-run. Default protective values used in exposure mitigation are shown in Table 3. These protective values are used whenever actual values for EPTC are not available.

### **Conclusion:**

The PPE and engineering controls used to mitigate EPTC exposure below the target level are similar to those required for minimal exposure pesticides (MEP). It is, therefore, suggested that EPTC be identified as an MEP, but with certain exceptions as mentioned in numbers 2 and 3 above. Requirements for exposure reduction for MEPs are stated in the current California Code of Regulation, Title 3, Article 5, Section 6793 (CCR, 1992). Requirements on the labels of EPTC granular products for pilots and flaggers during application of granules are adequate to mitigate the exposure. The same is true for applicators of liquid EPTC during a water-run.

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Table 1. EPTC exposure estimates for mixer/loaders, applicators, mixer/loader/applicators, farmers' employee, and flaggers.

		Exposure ( $\mu\text{g}/\text{person}/\text{day}$ )	( $\mu\text{g}/\text{kg}/\text{day}$ )		
			ADD (MOS) <sup>b</sup>	SADD (MOS) <sup>b</sup>	AADD (MOS) <sup>b</sup>
<u>A. Liquid formulation: ground application</u>					
M/L <sup>a</sup>	Dermal <sup>c</sup>	14664	38.23	18.0	0.84
	Inhalation	1200	8.57	4.03	0.19
	Dietary <sup>d</sup>		1.20	1.20	0.50
	Total	15864	48.00 (417)	23.2 (30)	1.53 (328)
A <sup>a</sup>	Dermal <sup>c</sup>	6244	16.28	7.66	0.36
	Inhalation	532	3.80	1.79	0.08
	Dietary <sup>d</sup>		1.20	1.20	0.50
	Total	6776	21.28 (940)	10.65 (66)	0.94 (532)
M/L/A <sup>a</sup> (PCO)	Dermal <sup>c</sup>	27628	72.03	33.9	3.16
	Inhalation	2480	17.71	8.34	0.78
	Dietary <sup>d</sup>		1.20	1.20	0.50
	Total	30108	90.94 (220)	43.4 (16)	4.43 (113)
Farmers' employee <sup>a</sup> (M/L/A)	Dermal <sup>c</sup>	27628	72.03	33.9	1.58
	Inhalation	2480	17.71	8.34	0.39
	Dietary <sup>d</sup>		1.20	1.20	0.50
	Total	30108	90.94 (220)	43.4 (16)	2.47 (203)
<u>B. Granular formulation: B.1 flowers/ornamentals</u>					
L/A <sup>e</sup>	Dermal <sup>c</sup>	4840	12.62	5.94	0.28
	Inhalation	240	1.71	0.81	0.04
	Dietary <sup>d</sup>		1.20	1.20	0.50
	Total	5080	15.53 (1288)	7.94 (88)	0.82 (613)
<u>B. Granular formulation. B.2 aerial application</u>					
Pilots <sup>f</sup>	Dermal <sup>c</sup>	338	0.88	0.42	0.02
	Inhalation	110	0.79	0.37	0.02
	Dietary <sup>d</sup>		1.20	1.20	0.50
	Total	448	2.87 (6974)	1.98 (353)	0.54 (932)

Table 1 (cont.). EPTC exposure estimates for mixer/loaders, applicators, mixer/loader/  
applicators, farmers' employee, and flaggers<sup>a</sup>.

		Exposure ( $\mu\text{g}/\text{person}/\text{day}$ )	( $\mu\text{g}/\text{kg}/\text{day}$ )		
			ADD (MOS) <sup>b</sup>	SADD (MOS) <sup>b</sup>	AADD (MOS) <sup>b</sup>
<u>B. Granular formulation. B.2 aerial application (continued)</u>					
Flaggers <sup>f</sup>	Dermal <sup>c</sup>	2886	7.53	3.54	0.16
	Inhalation	122	0.87	0.41	0.02
	Dietary <sup>d</sup>		1.20	1.20	0.50
	Total	3008	9.60 (2084)	5.15 (136)	0.68 (731)
Loaders <sup>f</sup>	Dermal <sup>c</sup>	21202	55.3	26.0	1.21
	Inhalation	4180	29.9	14.1	0.65
	Dietary <sup>d</sup>		1.20	1.20	0.50
	Total	25382	86.3 (232)	41.3 (17)	2.37 (211)
<u>C. Chemigation. C.1 water-run</u>					
Applicators <sup>f</sup>	Dermal <sup>c</sup>	2354	4.91	2.31	0.11
	Inhalation	60	0.43	0.20	0.01
	Dietary <sup>d</sup>		1.20	1.20	0.50
	Total	2414	6.54 (3059)	3.71 (189)	0.62 (810)
<u>C. Chemigation. C.2 center-pivot sprinkler system</u>					
M/L/A <sup>f</sup>	Dermal <sup>c</sup>	84400	220	77.7	3.62
	Inhalation	138	0.99	0.35	0.02
	Dietary <sup>d</sup>		1.20	1.20	0.50
	Total	84538	222 (90)	79.2 (9)	4.13 (121)

<sup>a</sup> M/L and A wore flannel shirts with the sleeves rolled up, jeans, boots, caps, sunglasses; long rubber gloves were worn only during mixing/loading. A M/L/A wore a long-sleeved shirt, long pants, rubber boots; additionally mid-forearm length gloves and a hard hat with a protective face shield were worn during mixing/loading. Assumed M/L, A and farmers' employee handled EPTC 8 days/17-day season and 8 days/year, except for a M/L/A (PCO) the exposure period was 16 days/year (For other work tasks, workdays/season was 8 and workdays/year was also 8, except for applicators who use the center-pivot sprinkler system where the exposure period per season or per year was 6 workdays).

<sup>b</sup> MOS = NOEL ( $\mu\text{g}/\text{kg}/\text{day}$ )  $\div$  absorbed dose ( $\mu\text{g}/\text{kg}/\text{day}$ ).

<sup>c</sup> Dermal exposure was the sum of dermal exposures of hands, unclothed skin areas (face, back and front of the neck), and clothed skin areas (except for (°) where body exposure was not measured and was not included).

<sup>d</sup> Dietary exposure was estimated by the Medical Toxicology Branch, Department of Pesticide Regulation.

<sup>f</sup> Exposure was estimated based on clothing protection provided by long-sleeved shirt, long pants, rubber gloves, shoes plus socks.

Table 2. Mitigated EPTC exposure for mixer/loaders, applicators, mixer/loader/applicators, farmers' employee, and flaggers<sup>a</sup>.

		Exposure/person ( $\mu\text{g}/8\text{-h day}$ )		( $\mu\text{g}/\text{kg}/\text{day}$ )		
		Work cloth	Mitigated	ADD (MOS)	SADD (MOS)	AADD (MOS)
<b>A. Liquid formulation: ground application</b>						
M/L	Dermal	14664	733	1.91	0.90	0.04
	Inhalation	1200	60	0.43	0.20	0.01
	Dietary			1.20	1.20	0.50
	Total	15864	793	3.54 (5650)	2.30 (304)	0.55 (907)
A	Dermal	6244	2376	6.19	2.91	0.14
	Inhalation	532	53	0.38	0.18	0.008
	Dietary			1.20	1.20	0.50
	Total	6776	2429	7.77 (2573)	4.29 (163)	0.64 (776)
M/L/A <sup>b</sup> (PCO)	as M/L Dermal	1217	60.8	4.49	2.11	0.20
	Inhalation	195	9.8	1.70	0.80	0.07
	Dietary			1.20	1.20	0.50
	Total	1412	70.6 M/L/A	7.39 (2707)	4.11 (170)	0.77 (648)
	as A	Dermal	26411	1660		
		Inhalation	2285	229		
		Total	28696	1889		
Farmers' employee <sup>c</sup> (M/L/A)	as M/L Dermal	1217	60.8	4.49	2.11	0.10
	Inhalation	195	9.8	1.70	0.80	0.04
	Dietary			1.20	1.20	0.50
	Total	1412	70.6 M/L/A	7.39 (2707)	4.11 (170)	0.64 (787)
	as A	Dermal	26411	1660		
		Inhalation	2285	229		
		Total	28696	1889		
<b>B. Granular formulation: B.1 flowers/ornamentals</b>						
Applicator	Dermal	4840	1287	3.36	1.58	0.07
	Inhalation	240	240	1.71	0.81	0.04
	Dietary			1.20	1.20	0.50
	Total	5080	1527	6.27 (3190)	3.59 (195)	0.61 (818)

Table 2 (cont.). Mitigated EPTC exposure for mixer/loaders, applicators, mixer/loader/  
applicators, and farmers' employee.

		Exposure/person		(µg/kg/day)		
		(µg/8-h day)		ADD (MOS)	SADD (MOS)	AADD (MOS)
		Work cloth	Mitigated			
<u>B. Granular formulation. B.2 aerial application</u>						
Pilots	Dermal	338		Exposure mitigation is not needed.		
	Inhalation	110				
	Dietary					
	Total	448				
Flaggers	Dermal	2886		Exposure mitigation is not needed.		
	Inhalation	122				
	Dietary					
	Total	3008				
Loaders	Dermal	21202	2167	5.65	2.66	0.12
	Inhalation	4180	418	2.99	1.41	0.07
	Dietary			1.20	1.20	0.50
	Total	25382	2585	9.84 (2034)	5.26 (133)	0.69 (725)
<u>C. Chemigation. C.1 water-run</u>						
Loaders	Dermal	2354		Exposure mitigation is not needed.		
	Inhalation	60				
	Dietary					
	Total	2414				
<u>C. Chemigation. C.2 center-pivot sprinkler system</u>						
M/L/A	Dermal	84400	6324	16.49	5.82	0.27
	Inhalation	138	13.8	0.10	0.03	0.002
	Dietary			1.20	1.20	0.50
	Total	84538	6338	17.79 (1124)	7.05 (99)	0.77 (647)

<sup>a</sup> Exposure mitigation is proposed according to MEP regulation with some exceptions. A full-body chemical-resistant protective suit and an approved half-face respirator are suggested during application of liquid mixes or loading and application of granular products.

<sup>b</sup> The exposure estimate for M/L was obtained from a study conducted by Ross *et al.*, (1986); whereas, the applicator exposure was obtained from the exposure estimate of M/L/A (Knarr and Iwata, 1986) minus the above M/L exposure estimate. The exposure time is one hour per day for M/L and that for A is seven hours.

<sup>c</sup> Same PPE and engineering controls are required as in (<sup>b</sup>). Exposure estimates for M/L and A were derived as in (<sup>b</sup>).

Table 3. Default protective values (Thongsinthusak *et al.*, 1993) employed in exposure mitigation<sup>a</sup>.

Mitigation Option	Percent Protection	Exposure Route
Closed mixing/loading system with chemical-resistant apron	95%	dermal and inhalation exposure
Chemical-resistant gloves	90%	hand exposure
Full-body chemical-resistant protective suit	95%	dermal to clothed areas (assume to cover 75% of unclothed areas)
NIOSH/MSHA approved half-face respirator	90%	inhalation exposure

<sup>a</sup> Default protective values are not used when actual values for EPTC are available.

**Calculation of mitigated exposure:**

$$\begin{aligned} \text{ADD } (\mu\text{g}/\text{kg}/\text{day}) &= [(A + B) \div \text{body weight (70 kg)}] + C \\ \text{SADD } (\mu\text{g}/\text{kg}/\text{day}) &= \text{ADD} \times 6 \text{ or } 8 \text{ workdays/season} \div 17 \text{ days/season} \\ \text{AADD } (\mu\text{g}/\text{kg}/\text{day}) &= \text{ADD} \times 6, 8 \text{ or } 16 \text{ workdays/year} \div 365 \text{ days/year} \end{aligned}$$

Where:

A = Dermal exposure ( $\mu\text{g}/\text{person}/\text{day}$ )  $\times$  (100 - % default protective value)  $\times$  % dermal absorption (18.25%)  
 B = Inhalation exposure ( $\mu\text{g}/\text{person}/\text{day}$ )  $\times$  (100 - % default protective value)  $\times$  % inhalation uptake/absorption (50 %)  
 C = Dietary exposure ( $\mu\text{g}/\text{kg}/\text{day}$ )