# Proposition 65 Maximum Allowable Dose Level (MADL) for Reproductive Toxicity for Ethyl Dipropylthiocarbamate (EPTC)

## June, 2004


## Office of Environmental Health Hazard Assessment (OEHHA)
## Reproductive and Cancer Hazard Assessment Section


## Summary


The maximum allowable dose level (MADL) for ethyl dipropylthiocarbamate (EPTC) exposure is **700 micrograms/day (µg/day)** for the oral and inhalation routes of exposure and **6700 µg/day** for the dermal route of exposure. These values were derived as described below, based on developmental effects in a 2-generation reproductive toxicity study in rats (Hazelton 1986).


## Background

This report describes the derivation of a MADL for EPTC (CAS No. 759-94-4).

EPTC is a thiocarbamate pesticide. In 2001, it was the 59$^{th}$ most used pesticide in California at 276,782 pounds (CDPR, 2002). EPTC is a pre and post-emergent herbicide most highly used on alfalfa, feed corn and potatoes.

EPTC is listed under Proposition 65 (the Safe Drinking Water and Toxic Enforcement Act of 1986) as known to the State to cause reproductive toxicity (developmental toxicity endpoint), effective April 27, 1999. The Proposition 65 listing of EPTC was based on a formal identification by the U.S. Environmental Protection Agency (U.S. EPA) of EPTC as causing developmental toxicity (U.S. EPA 1994a,b). U.S. EPA is an authoritative body under Proposition 65 for identification of chemicals as causing reproductive toxicity (Title 22, California Code of Regulations § 12306(*l*)). In December, 1999, U.S. EPA published a Reregistration Eligibility Decision (RED) for EPTC (U.S. EPA, 1999). That document reviewed the developmental toxicity of EPTC under the requirements of the Food Quality Protection Act, stating that EPTC did not produce any significant developmental or reproductive toxicity and that there does not appear to be any concern about the reproductive or developmental toxicity of EPTC. OEHHA reviewed the RED and determined that these statements specific to the requirements of FQPA did not constitute a repudiation of the prior formal identification under TRI of EPTC as causing developmental toxicity.

Procedures for the development of Proposition 65 MADLs are provided in regulation (Title 22, Cal. Code of Regs. § 12801 and 12803). Exposure at a level 1,000 times greater than the MADL is expected to have no observable effect. As defined in regulations, a MADL is derived from a No Observable Effect Level (NOEL) based on the

most sensitive study deemed to be of sufficient quality (Title 22, Cal. Code of Regs. § 12803(a)(4)).

## Study Selection

Relevant studies on the reproductive toxicity of EPTC have been identified through literature searches. These studies have been reviewed and considered for the establishment of the MADL.

Four developmental toxicology studies were conducted in the mid-1980's for pesticide registration purposes, two in rats and two in rabbits (Table 1). A similar dose range was used in all studies, with a high dose of 300 mg/kg-day. The two studies within each species used different vehicles, corn oil or water suspension (with methyl cellulose emulsifier), for the gavage treatment, and were conducted in different laboratories. The purity of the EPTC ranged from 97.6 to 98.6%. In addition, two multigeneration studies conducted for pesticide registration are available (Table 1).

**Table 1. Developmental and multigeneration toxicity studies with EPTC**

| | | | | | Maternal Effects at the LOEL |
|---|---|---|---|---|---|
| Developmental toxicity studies | | | | | |
| WIL 1983 | Rat, **S-D**[1] | Gavage/ Corn oil | 0, **30**, 100, 300 Developmental toxicity | Resorptions | Maternal mortality; ↓ weight gain |
| Huntingdon 1985a | Rat, S-D | Gavage/ Methyl cellulose | 0, 30, 100, **300** | No effects | No maternal toxicity |
| Stauffer 1987 | Rabbit NZW[2] | Gavage/ Corn oil | 0, 5, **40**, 300 Developmental toxicity | Rudimentary ribs | ↓ weight gain gd 13-19 |
| Huntingdon 1985b | Rabbit NZW | Gavage/ Methyl Cellulose | 0, 30, 100, 300 Developmental toxicity | Malformation | No maternal toxicity |
| Two-generation studies | | | | | |
| Stauffer 1982 | Rat, S-D | Feed | 0, 3, 15, **60**[3] 2-generation | No effects | ↓ parental body weight (10-17%) at high dose |
| Hazleton 1986 | Rat, S-D | Feed | 0, 3, **12**, 50[3] 2-generation | ↓ birthweight F1 litter | ↓ parental body weight (5-10%) |

[1]Sprague-Dawley
[2]New Zealand White
[3] calculated by RCHAS from gestational food intake data in the original report

Across the four developmental toxicity studies, EPTC maternal toxicity was limited, with the exception of the rat corn oil study (WIL 1983). In that study, sixty percent maternal

mortality was seen in rats gavaged with 300 mg/kg-day EPTC in corn oil (WIL 1983). In contrast, rabbit dams gavaged with 300 mg/kg-day EPTC in corn oil vehicle demonstrated only reduced weight gain on gd 13-19 (Stauffer 1987). When EPTC was administered as an emulsion, no maternal toxicity was reported in rats or rabbits at doses up to 300 mg/kg-day (Huntingdon 1985a,b).

As regards fetal toxicity, no fetal effects were seen in rats with water emulsion (Huntingdon 1985a), whereas increased resorptions and lower fetal weights were reported with 300 mg/kg-day EPTC in corn oil (WIL 1983). Higher resorption rates were also seen at 100 mg/kg-day. It was not clear whether this represented maternal or fetal toxicity.

The rabbit studies demonstrated increased malformation rates in association with EPTC treatment as an emulsion (Huntingdon 1985b). The numbers of malformed fetuses were 1, 4, 4, and 5 in the 0, 30, 100 and 300 mg/kg-day groups, respectively. Malformations included gastroschisis, cleft palate, extra vertebrae, hydrocephalus and encephalocele. Seven of the 13 affected EPTC-treated fetuses had multiple malformations. Malformations seen in more than one fetus were missing intermediate lung lobe, and absent or unossified parietal bones. The only malformation seen in the control group was a retro-esophageal subclavian artery.

With the corn oil vehicle, resorptions and reduced fetal weights were reported at the highest dose in rabbits (Stauffer 1987). The NOEL for the study was 40 mg/kg-day.

In addition to the above developmental toxicity studies, two multigeneration studies in rats were conducted for pesticide registration (Stauffer 1982, Hazelton 1986) (Table 1). They used similar dose ranges and both administered the compound in feed. The Stauffer (1982) study produced two litters per generation, while the Hazleton (1986) study produced one litter per generation. Lower birthweight was indicated in both studies in EPTC-treated groups. In the Hazleton (1986) study, reduced birthweights were statistically significant in the F1 generation at the highest dose. A similar trend was seen in the F2 generation, but was not statistically significant. In the other study (Stauffer 1982) birthweights were also lower in the high dose group in all four litters (F1a, F1b, F2a, F2b), but the effects were not statistically significant. In both studies, statistically significant pup growth retardation in terms of body weight was seen later in lactation. The NOEL for the two studies was 12 mg/kg-d from the Hazleton (1986) study. This is also the highest NOEL that is lower than the lowest LOEL across the six studies reviewed. The Hazleton (1986) study is considered the most sensitive study of sufficient quality for MADL development, using the NOEL of 12 mg/kg-d.

**MADL Calculation**

The NOEL is the highest dose level which results in no observable reproductive effect, expressed in milligrams of chemical per kilogram of bodyweight per day (Title 22, Cal. Code of Regs. § 12803(a)(1)). The NOEL is converted to a milligram per day dose level by multiplying the assumed human body weight by the NOEL (Title 22, Cal. Code of

Regs. § 12803(b)). The results obtained from the most sensitive study deemed to be of sufficient quality have been used. Since the data do not allow the determination of a NOEL from the most sensitive study of sufficient quality, the lowest observable effect level (LOEL) divided by 10, is used to establish a NOEL for purposes of assessment (Title 22, Cal. Code of Regs. § 12803(a)(7)):

NOEL = 12 mg/kg-day

For oral and inhalation routes of exposure, the following calculations were performed to derive the MADL for EPTC, based on a NOEL of 12 mg/kg-day derived from the Hazelton (1986) study.

The NOEL is converted to a milligram per day dose level by multiplying the assumed human body weight by the NOEL (Title 22, Cal. Code of Regs. § 12803(b). For developmental toxicity, the assumed body weight of a pregnant woman is 58 kg.

12 mg/kg-day × 58 kg = 696 mg/day

The MADL is derived by dividing the NOEL by one thousand (1,000) to arrive at the maximum allowable dose level (Title 22, Cal. Code of Regs. § 12801(b)(1)). Thus, the adjusted NOEL is divided by 1,000 to obtain the MADL:

**$MADL_{oral}$** = 696 mg/day ÷ 1000 = 696 µg/day = **700 µg/day** after rounding.

This value is applicable to oral and inhalation routes of exposure, in the absence of sufficient data for developing a separate MADL for inhalation exposure.

**$MADL_{inhalation}$** = 700 mg/day ÷ 1000 = **700 µg/day**.

For the dermal route of exposure, absorption values of 9.3 % by the dermal route (Jeffcoat 1988) and 90% by the oral route (Davies 1996a,b) were used to derive a MADL. These values were based on studies with labeled EPTC in the rat.

**$MADL_{dermal}$** = (696 µg/day × 0.90) ÷ 0.093 = 6735 µg/day = **6700 µg/day** after rounding**.**

If exposures occur by multiple routes, the total exposure to the chemical from a single source or product must be considered. If the total absorbed dose resulting from any one or multiple routes is less than or equal to 630 µg/day (696 µg/day x 90%), the MADL has not been exceeded.

## References

California Department of Pesticide Regulation (CDPR 2002) Summary of Pesticide Use Report Data 2001 by Commodity. Available at http://cdpr.ca.gov.docs/pur

California Department of Pesticide Regulation (CDPR 1999) Summary of Toxicology Data: EPTC.

Davies DJ (1996a) EPTC: Excretion and tissue retention of a single oral dose (300 mg/kg) in the rat. Project ID #CTL/P/4917, Zeneca Central Toxicology Laboratory, Alderley Park, UK.

Davies DJ (1996b) EPTC: Excretion and tissue retention of a single oral dose (3 mg/kg) in the rat. Project ID #CTL/P/4916, Zeneca Central Toxicology Laboratory, Alderley Park, UK.

Hazleton (1986) Two-generation reproduction study with EPTC in rats. Hazleton Study No. 6100-108. Hazleton Laboratories America, Madison, WI.

Huntingdon (1985a) Effect of EPTC on pregnancy of the rat. Huntingdon Research Centre, Huntingdon, UK.

Huntingdon (1985b) Effect of EPTC on pregnancy of the rabbit. Huntingdon Research Centre, Huntingdon, UK.

Jeffcoat AR (1988) Dermal absorption of EPTAM in rats. Study ID# 3586-40. Research Triangle Institute, Research Triangle Park, NC.

Narotsky MG, Pegram RA, Kavlock RJ (1997) Effect of dosing vehicle on the developmental toxicity of bromodichloromethane and carbon tetrachloride in rats. Fundam Appl Toxicol 40: 30-6.

Stauffer (1982) A two-generation rat reproduction study with Eptam technical. Study T-10123. Stauffer Chemical Company, Farmington, CT. .

Stauffer (1987) A teratology study in rabbits with Eptam technical. Stauffer Chemical Company, Farmington, CT.

U.S. Environmental Protection Agency (U.S. EPA) (1994a) Addition of Certain Chemicals; Toxic Chemical Release Reporting: Community Right to Know. Proposed Rule. Federal Register Vol. 59, p. 1788.

U.S. Environmental Protection Agency (U.S. EPA) (1994b) Chemicals: Toxic Chemical Rules: Reporting: Community Right to Know; Chemicals. Final Rule. Federal Register Vol. 59, p. 61432.

U.S. Environmental Protection Agency (U.S. EPA) (1999) Reregistration Eligibility Decision (RED) EPTC. EPA-738-F-99-011. (http://www.epa.gov/oppsrrd1/REDs/0064red.pdf)

WIL (1983) A teratology study in rats with Eptam. Study No. WIL –27013. WIL Research Laboratories, Ashland, OH.

Withey JR, Collins BT, Collins PG (1983) Effect of vehicle on the pharmacokinetics and uptake of four halogenated hydrocarbons from the gastrointestinal tract of the rat. J Appl Toxicol 3: 249-53.