MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Triethyl Citrate, CAS# 77-93-0

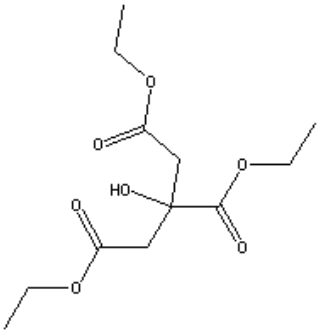
FROM: Margaret M. Sadoff, AQD, Toxics Unit

DATE: October 18, 2006

SUBJECT: Request for Screening Level for PTI 243-06

The final ITSL for triethyl citrate is 290 ug/m3 (annual average).

A search of the literature and the following databases was performed for information regarding triethyl citrate: American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values, National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Integrated Risk Information System (IRIS), Registry of Toxic Effects of Chemical Substances (RTECS), Environmental Protection Bureau Library, International Agency for Research on Cancer (IARC) Monographs, CAS Registry Online, Hazardous Substance Data Bank (HSDB), National Library of Medicine/Toxline, Health Effects Assessment Summary Tables (HEAST), National Toxicology Program (NTP) Study Database, Entrez PubMed, and CalEPA's Toxicity Values Database.



MW = 276

General Toxicity & Usage

Triethyl citrate is an odorless, colorless, oily liquid. Extremely low concentrations of this chemical are found naturally in sour cherries and red currants. Triethyl citrate is used industrially as a plasticizer in various applications, including medical devices, enteric coatings for pharmaceutical products, and in certain hair care spray products. It is generally recognized as safe by FDA as a food and cosmetic additive. FAO and WHO working groups estimate an acceptable daily intake in humans to be 0-20 mg/kg (WHO Food Additive Series, Vol. 19: 115-16, 1984). Triethyl citrate metabolizes to citric acid and ethanol.

There is very little toxicity data on triethyl citrate via the inhalation route. Most of the available studies are oral studies which is not surprising given this chemical's prevalent use in food, drug and cosmetic products. Triethyl citrate has not been shown to be a skin irritant or sensitizer in animals or humans. No information is available with regard to carcinogenicity.

A very low vapor pressure of 0.00225 mmHg at 25C limits the potential for triethyl citrate to exist as a vapor in ambient air. There is some potential for exposure to the aerosol, especially in occupational settings, but there is no TLV for this chemical.

Acute and Chronic Oral Data in Experimental Animals

A rat LD50 of 8 g/kg and a cat LD50 of 4 g/kg were reported by Finkelstein and Gold (1959). Lethal doses in cats produced nausea, vomiting, ataxia, weakness, muscle twitching, tremors, reflex hyperexcitability, decreased body temperature and breathing rate, convulsions, respiratory failure and death. Rats fed triethyl citrate in the diet at 1, 2, and 4 g/kg for 8 weeks revealed no toxics effects in any organ. Cats receiving daily doses at 7% of the LD50 for an 8-week period did not differ from controls with respect to weight or blood parameters but displayed weakness, ataxia and depression after the fourth or fifth dose which progressed over the duration of the exposure. The animals appeared to return to normal 1-4 days after treatment was discontinued. Dogs dosed at 0.05 and 0.25 ml/kg for 6 months revealed no adverse effects but increasing the daily dose to 2.5 to 3.5 ml/kg for 7-12 weeks resulted in characteristic liver pathology. Three groups of15 Sprague-Dawley rats/sex/group were fed 0.33, 1.0 and 3.0% triethyl citrate in the diet for 2 years. Weight gain and food intake were reduced when the level in the diet was increased. Blood, urine, gross and histopathology examination revealed no adverse effects. Triethyl citrate was not mutagenic in standard Salmonella and yeast tests nor was it teratogenic in developing chick embryos.

Source: Evaluation of the Health Aspects of Citric Acid, Sodium Citrate, Potassium Citrate, Calcium Citrate, Ammonium Citrate, Triethyl Citrate, Isopropyl Citrate, and Stearly Citrate as Food Ingredients, Prepared for FDA, 1977.

An ITSL based on oral data would not be appropriate because there is insufficient data on systemic toxicity to justify route extrapolation. In addition, toxicity via the oral route appears to be quite low except perhaps in cats in which CNS symptoms were obvious. Further, oral toxicity does not address the concern for respiratory or eye irritation by exposure to triethyl citrate vapor or aerosol.

HSDB reports one rat LC50 of 3,500 ppm. RTECS lists one LC50 from a 6 hour rat study as 1300 ppm (14,675 mg/m3). An ITSL pursuant to rule 232(1)(f) based on the lower of the two lethal doses is as follows:

$$\frac{14{,}675 \text{ mg/m3}}{(500 \times 100)} = 293 \text{ ug/m3, annual (290 rounded)}$$

The final ITSL for triethyl citrate is 290 ug/m3 (annual average).

MS:LH