RECOMMENDATIONS OF THE SCIENTIFIC ADVISORY PANEL

TETRACAINE HYDROCHLORIDE

CAS # 136-47-0
DECEMBER 8, 1994

Basis for ITSL:

A CAS- and NLM-online literature search was conducted for tetracaine hydrochloride in February 1993, but it did not produce any relevant information to calculate an ITSL. In a MSDS provided by The Upjohn Company, an unpublished, internal rat LD_{50} study was identified. However, there was no specific data provided to substantiate the conditions and quality of this study. A search of studies listed in RTECS found many LD_{50}s by an injection route of exposure and a LD_{50} from a foreign journal - not available for review. Due to the lack of available toxicity data meeting the criteria of Rule 232(1), the ITSL for tetracaine hydrochloride was determined to be 0.04 $\mu g/m^3$ based on annual averaging (Rule 232(1)(i)).

Summary of Public Comment:

The only public comment received for this compound was from The Upjohn Company. They commented that other toxicological information was available to derive a screening level, rather than use the default value of 0.04 ug/m^3. This data consisted of a LD_{50} of 160 mg/kg which was published in the company MSDS.

Response to Public Comment:

A complete reference check was conducted for tetracaine hydrochloride, but only limited information was available. Upjohn stated that the MSDS sheet that they provided was not theirs, but their supplier's - Hoechst-Roussel. This supplier could not provide additional information about the rat LD_{50} study.

The only available information to derive an ITSL was a Japanese study entitled, Acute Toxicity in Mice, Rats, and Rabbits and its Concentration and Hydrolysis in the Rabbit's Plasma of p-Butylaminobenzoyldiethylaminoethanol Hydrochloride (Oyo-yakuri 9(3):413-420, 1975). The Upjohn Company provided a review of this document through their translation services. In this study, tetracaine hydrochloride was orally administered to 5 mice/sex/group using the "up and down" dosing methodology of Brownlee (1953). Clinical signs included loss of balance after 3 to 5 minutes, and deep, slow breathing. Stiffened limbs, twitching, apnea, and cyanosis occurred at 3 minutes which lead to animal death. Surviving animals showed recovery within 40 to 60 minutes, and lasted for the remainder of the 3-day study. The LD_{50} was determined using Litchfield-Wilcoxon methodology. Male mice had an LD_{50} of 170 mg/kg, while female mice had an LD_{50} of 160 mg/kg.

In this same study, tetracaine hydrochloride was also administered intravenously to rabbits. Plasma levels reached 0.38 $\mu g/ml$ after 5 minutes, but was unmeasurable at 15 minutes. The *in vitro* hydrolysis of tetracaine hydrochloride in rabbit plasma showed that this compound is rapidly cleaved, with a hydrolysis rate of almost 100% at 60 minutes. Information regarding excretion rates was not mentioned.

The currently recommended observation period for an LD_{50} study is 14-days. The study duration was only 3-days, however, the compound appeared to be readily metabolized due to rapid hydrolysis and test animals recovered quickly after dosing. Because of this, death would not be expected to occur a latter time. Therefore, it seems appropriate to use the derived LD_{50} from this study.

The ITSL was derived as follows using Rule 232(1)(h):

The LD_{50} for female mice = 160 mg/kg
W_A = Body weight of experimental animal in kilograms (kg).
I_A = Daily inhalation rate of experimental animal in cubic meters/day.
Since body weights and daily inhalation rates were not available, assume a default value of 1.677 m^3/kg.

$$ITSL = \frac{1}{500} \times \frac{1}{40} \times \frac{1}{100} \times \frac{LD_{50}\ mg/kg \times W_A}{0.167 \times I_A}$$

$$ITSL = \frac{1}{500} \times \frac{1}{40} \times \frac{1}{100} \times \frac{160\ mg/kg}{0.167 \times 1.677\ m^3/kg} = 0.000286\ mg/m^3$$

0.286 mg/m^3 x 1000 = 0.3 $\mu g/m^3$ based on annual averaging.

Because of the many uncertanties in using an oral rat LD_{50} to derive an ITSL, the ITSL derived in this manner was compared to the therapeuptic dose level for tetracaine hydrochloride. A therapeutic dose doesn't imply that the dose is safe from adverse effects. Tetracaine hydrochloride is a topical anesthetic causing local anesthesia of accessible mucous membranes at therapeutic doses. However, since the therapeutic dose is based upon human experience, such a comparison can help provide confidence as to whether or not the ITSL will be protective of public health. To make the comparison between the ITSL and the therapeutic dose, the ITSL was converted to a delivered dose as shown below. A comparison was made by determining the ratio of the therapeutic dose to the delivered dose. Therapeutic doses are not necessarily no effect doses. However, the ratio of calculated ITSLs and therapeutic doses were so large as to preclude, in the judgement of the committee, the existence of even a therapeutic effect at the ITSL.

COMPARISON OF DELIVERED DOSE[A] TO THERAPEUTIC DOSE

Compound Name	Proposed ITSL (ug/m3)	Therapeutic Dose[B] Range (mg/kg/day)	Delivered Dose (mg/kg)	Ratio of Doses[D] (Range)
tetracaine hydrochloride	0.3	0.07 - 0.286[C]	0.00009	778 - 3178

A. Based on the formula: Delivered dose = {ITSL (mg/m3) x 20 m3}/70 kg

B. No implications are made that a therapeutic dose is a safe dose.

C. Tetracaine hydrochloride injectable: 5-20 mg/treatment (acute). Based on a 70 kg person = 5 mg/70 kg (or 20 mg/70 kg).

D. Therapeutic Dose/Delivered Dose = Ratio of Doses.

The ITSL for tetracaine hydrochloride = 0.3 $\mu g/m^3$ based on annual averaging.