May 17, 1993

To : Hexamethylenetetramine File (CAS # 100-97-0)

From : Gary Butterfield

Subject : ITSL for Hexamethylenetetramine

A CAS-on-line literature search conducted on December 21, 1992 found several articles describing short term mutagenicity assays, and a few long term animal bioassays with hexamethylenetetramine. Unfortunately none of these studies were conducted by the inhalation route of exposure. There were no studies identified that give an indication that oral route of administration is an appropriate substitute for inhalation. However, hexamethylene-tetramine is a crystalline material that is readily soluble in water. For purposes of ITSL calculation it will be assumed that oral data is a good substitute for the missing inhalation data.

Hexamethylenetetramine has a long history of being used as an antimicrobial food additive in Scandinavian countries. This antimicrobial action is believed to be due to hexamethylene-tetramine's ability to decompose to formaldehyde and ammonia at pH levels lower than 7.0.

Hexamethylenetetramine has also been used by humans as an oral treatment for urinary tract infections at doses of 4 to 6 grams/day. Higher rates of use, 8 g/day for periods greater than 3 to 4 weeks, is associated with urinary bladder irritation, painful and frequent micturition, albuminuria and hematuria, Goodman and Gilman (1975). Unfortunately, no further documentation of these adverse effects in humans was available. Because this information can't be substantiated it is of little value in development of the ITSL.

Repeated subcutaneous injection of a 35 to 40 % solution of hexamethylenetetramine, until a total dose of 25 to 30 g/rat was administered, produced sarcomas in 8/14 rats (Watanabe & Sugimoto 1955). However, hexamethylenetetramine has not been found to be carcinogenic in long term bioassays that have been conducted by the oral route of exposure (Natvig et al 1971, Lijinsky & Taylor 1977, Della Porta et al 1968, Hurini & Ohder 1973).

The study by Hurini & Ohder (1973), on first look, provides data that indicates dogs are more sensitive than rats or mice, for reproductive effects. Hurini & Ohder reported that at doses of 31 mg/kg (1250 ppm diet) there was an adverse effect on the reproduction of dogs. This adverse effect was evident as increased incidence of still born pups, a decrease in pup weight gain, and a reduction in the percentage of pups surviving until weaning. The next lower dose of 15 mg/kg (600 ppm diet) did not have these adverse effects. However, in this study, the pup's data was not analyzed by litter. Therefore the impact of one litter's condition was sufficient to influence the whole group. This has led to the

conclusion that the highest dose in this study as having an adverse effect on dogs reproductive ability, as being in question.

Lijinsky & Taylor (1977) administered hexamethylenetetramine to rats at a dose of 0.1 % in their drinking water for 50 weeks. There were no differences between control and dosed animals for survival, pathology, or incidence of tumors. Della Porta et al (1968) administered hexamethylenetetramine to mice and rats at a dose of 0.5, 1 or 5 % in their drinking water for 60 or 104 weeks. Treatment of mice at any dose or rats at 1 % was not associated with changes in survival, body weights, or increased tumor production. Rats, at 5 %, had reduced survival. Natvig et al (1971) fed diets with 0.16 % hexamethylenetetramine (or 100 mg/kg as reported by the authors) to rats over two generations. There was no treatment related changes on body weight, organ weights, or activity. There was a slight reduction in survival (by 6 to 9 %) in rats administered hexamethylenetetramine.

In general, the available animal studies can be described as having design flaws. Some of these flaws include: few animals per dose group, no statistical analysis of findings, and few details reported on pathological findings. These design flaws cause a reduction in the degree of confidence of the identified NOEALs. The study by Natvig et al (1971) identifies one of the lowest LOAELs in a multi-generation study. This study was able to evaluate toxicity from longterm dosing of hexamethylenetetramine, as well as, any reproductive impacts. Thus the ITSL will be calculated from the LOAEL of 100 mg/kg which caused reduced survival, and based on the equation from Rule 232 (1)(e).

ITSL = (100 mg/kg)/[100 x 0.9 x 10] = 100 mg/m3 annual average

where : - a 35 fold uncertainty factor from Rule 232 (1)(e) was dropped because this was a longterm study.
- 0.9 m3/kg is the inhalation rate for rats from EPA 1988.
- a 10 fold factor was used to adjust the LOAEL to an NOAEL.

References :

Della Porta et al. 1968. Non-carcinogenicity of hexamethylenetetramine in mice and rats. Fd Cosmet Toxicol 6:707-715.

EPA. 1988. Recommendations for and documentation of biological values for use in risk assessment. PB 88-179874.

Goodman and Gilman. 1975. The pharmacological basis of therapeutics. 5th Ed. Macmillian Co, NY.

Hurini & Ohder. 1973. Reproduction study with formaldehyde and hexamethylenetetramine in beagle dogs. Fd Cosmet Toxicol 11:459-462.

Lijinsky & Taylor. 1977. Feeding tests in rats on mixtures of nitrite with secondary and tertiary amines of environmental importance. Fd Cosmet Toxicol 15:269-274.

Natvig et al. 1971. A contribution to the toxicological evaluation of hexamethylenetetramine. Fd Cosmet Toxicol 9:491-500.

Watanabe & Sugimoto. 1955. Study on the carcinogenicity of aldehyde. 2nd report. Seven cases of transplantable sarcomas of rats appearing in the areas of repeated subcutaneous injections of urotropin. Gann 46:365.