MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Tetramethylurea (CAS #632-22-4)

FROM: Anne Kim, Air Quality Division, Toxics Unit

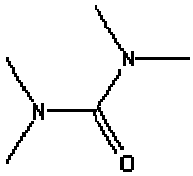
SUBJECT: Screening Level Derivation

DATE: October 5, 2006

The initial threshold screening level (ITSL) for tetramethylurea is 0.8 µg/m³ based on an annual averaging time and 230 ug/m^3 based on a 24-hour averaging time.

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System, Registry for Toxic Effects of Chemical Substances, American Conference of Governmental and Industrial Hygienists Threshold Limit Values, National Institute for Occupational Safety and Health Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer Monographs, Chemical Abstract Service (CAS) - Online (1967 – 2006), National Library of Medicine, Health Effects Assessment Summary Tables, and National Toxicology Program Status Report. The EPA has not established a reference concentration or reference dose for tetramethylurea. The molecular weight of tetramethylurea is 116.16 g. The molecular structure of tetramethylurea is shown in Figure 1.

Figure 1



Background

TMU is a colorless liquid that is used as a solvent and as a reagent in industrial applications. (ChemFinder.com, 2006; HSDB, 2006)

Animal Toxicity

A study conducted by Munley et al. (2001) found developmental effects in rats exposed to TMU but at a concentration that also caused maternal toxicity. Twenty-five female Crl:CD BR rats were exposed by inhalation to target concentrations of 0, 2, 20, or 100 ppm TMU six hours per day from day 6 to day 20 of gestation. The actual exposure concentrations were 0, 2.3, 19, and 110 ppm TMU. On gestation day 21, all animals were euthanized and examined. The number of live and dead fetuses and resorptions were recorded, the number of corpora lutea were

recorded, all offspring were weighed and examined for external alterations, and half were further examined for visceral alterations. Evidence of maternal toxicity in animals exposed to 20 ppm included significant decreased body weight changes and a slight decrease in food consumption. Significant decrease in body weight, weight change, and food consumption were found in the dams exposed to 100 ppm TMU. A reduction in mean fetal weight was seen at the 100 ppm dose level, and no other developmental effects (external or visceral alterations) were observed in all fetuses from exposed dams. Thus, the investigators determined the NOAEL to be 2 ppm due to maternal body weight gain reductions at 20 ppm.

Groups of 10 male rats were exposed via inhalation to 0, 2, 20, or 100 ppm TMU six hours per day for a total of 9 exposures (O'Neill et al., 2001). At study termination, clinical examination (blood chemistry and urinalysis) was conducted. Five rats from each group were sacrificed for pathologic examination and the remaining rats were allowed an 18-day recovery period, after which clinical and pathological examinations were performed. Rats exposed to 100 ppm TMU showed significantly decreased mean body weight throughout the entire study period and significantly decreased overall mean body weight gains. No other changes from control were observed except degeneration, necrosis, and ulceration of olfactory mucosa in the 100 ppm treated rats. These respiratory effects were still evident after the recovery period of 18 days, but they were described to be less severe and undergoing the healing process. The investigators established 20 ppm as the NOAEL based on body weight depression and respiratory effects at the 100 ppm dose level.

An older study conducted by Teramoto et al. (1981) reported developmental effects in rats and mice exposed in utero to TMU. A single oral dose of 250 mg/kg and 500 mg/kg was administered to 6 and 4 rats, respectively, on gestation day 12, 250 mg/kg and 500 mg/kg TMU to 5 rats each on gestation day 14, and 1000 mg/kg TMU to 12 mice on gestation day 10 (Table 1).

Table 1. Exposure Regimen (Teramoto et al., 1981)

Species	Number of animals	Concentration of TMU (mg/kg)	Gestation day of exposure
Rat	6	250	12
	4	500	12
Rat	5	250	14
	5	500	14
Mouse	12	1000	10

The rats and mice were sacrificed on gestation day 20 and 18, respectively. The number of live and dead fetuses was recorded. All live fetuses were weighed and examined for gross abnormalities. Half of each litter was examined for skeletal defects and the other half were examined for visceral anomalies. Nine of 11 rat fetuses of dams treated with 500 mg/kg on gestation day 12 had short and kinky tails. Fetuses of dams exposed to 500 mg/kg on gestation day 14 showed decreased fetal survival and decreased body weight. Mouse fetuses showed multiple developmental effects: cleft palate, short tail, oligodactyly and syndactyly of the forelimb, and fusion of caudal vertebrae.

Human Toxicity

There are no human studies on TMU toxicity available.

Discussion
The developmental effects seen as a result of TMU exposure in the study conducted by Teramoto et al. (1981) were produced following a single dose of TMU by oral intubation. This single dose of TMU was at a concentration much higher than those tested in the other studies detailed above (greater than a factor of 10). Thus, this study was not chosen to be used as the critical study to develop the initial threshold screening level (ITSL).

Munley et al. (2001) reported both maternal effects and developmental effects. The developmental effects were seen at a TMU dose level of 100 ppm whereas maternal effects were seen starting at an exposure level of 20 ppm TMU. In conjunction with this study, the results of O'Neill et al.'s (2001) inhalation study conducted in male adult rats show that pregnant females are more susceptible to TMU-induced inhalation toxicity. The NOAEL established as a result of decreased body weight gains and upper respiratory effects (20 ppm) in O'Neill's study is higher than the 2-ppm NOAEL determined as a result of the maternal toxic effects reported in Munley et al.'s (2001) study.

The EPA states in their Guidelines for Developmental Toxicity Risk Assessment (1991) that "[i]f the maternal effect level is lower than that in other evaluations of adult toxicity, this implies that the pregnant female is likely to be more sensitive than the nonpregnant female." Thus, the NOAEL of 2 ppm was used to develop an ITSL.

Note: 2.3 ppm was determined to be the NOAEL from Munley et al. (2001)
Derivation of Screening Level

Conversion of concentration units from ppm to mg/m^3:

$$X\ mg/m^3 = \frac{ppm \times MWT}{24.45}$$

$$X\ mg/m^3 = \frac{2.3\ ppm \times 116.16\ g}{24.45}$$

$$X\ mg/m^3 = 10.9\ mg/m^3$$

Calculation of ITSL:

$$ITSL = \frac{NOAEL}{35 \times 100} \times \frac{\text{hours exposed per day}}{24\ \text{hours per day}}$$

>where NOAEL = no-observed-adverse-effect level

Note NOAEL & hours exposed per day:
NOAEL = 10.9 mg/m^3
Hours exposed per day = 6 hours

$$ITSL = \frac{10.9\ mg/m^3}{35 \times 100} \times \frac{6\ \text{hours per day}}{24\ \text{hours per day}}$$

$$ITSL = 0.000779\ mg/m^3$$

ITSL = 0.779 ug/m^3 = **0.8 ug/m^3** - based on an annual averaging time

Discussion
An ITSL based on the developmental effects from Munley et al. (2001) was also developed because, while the maternal effects occurred at a lower dose than the dose at which fetal effects were seen, developmental toxic effects "may result from short-term exposure (including single exposure situations). …[F]or developmental toxic effects, a primary assumption is that a single exposure at a critical time in development may produce an adverse developmental effect, i.e., repeated exposure is not a necessary prerequisite for developmental toxicity to be manifested" (EPA, 1991).

Therefore, in addition to deriving an ITSL from the maternal-toxicity-derived NOAEL of 2 ppm to predict against chronic exposures, an ITSL was derived using the developmental-toxicity-derived NOAEL of 20 ppm to protect against short-term exposures, especially for the developing fetus.

The water solubility for TMU is $1x10^6$ mg/L, and it has a low octanol/water partition coefficient (log K_{ow} = 0.19) (HSDB, 2006). Category 1 gases are highly water-soluble and rapidly reactive, and Category 2 gases are water-soluble and able to accumulate in the blood. Although it is a water-soluble chemical, TMU is not highly reactive in the upper respiratory tract, and, therefore, is not a Category 1 gas. The properties of TMU are most consistent with a Category 2 gas. The equations for deriving a RfC for a Category 2 gas, however, have been established as faulty, and EPA has advised that calculations for Category 2 gases be completed by defaulting to Category 3 gas equations. The calculations for deriving a RfC value for TMU are shown below.

Note: 19 ppm was determined to be the NOAEL from Munley et al. (2001)
Derivation of Screening Level

Conversion of concentration units from ppm to mg/m^3:

$$X\ mg/m^3 = \frac{ppm \times MWT}{24.45}$$

$$X\ mg/m^3 = \frac{19\ ppm \times 116.16\ g}{24.45}$$

$$X\ mg/m^3 = 90\ mg/m^3$$

Calculation of $NOAEL_{[ADJ]}$:

$NOAEL_{[ADJ]}$ (mg/m^3) = E (mg/m^3) x D (hrs/24hrs)

- $NOAEL_{[ADJ]}$ = the effect level obtained with an alternate approach, adjusted for duration of experimental regimen
- E = experimental concentration level
- D = number of hours exposed/24 hours

$NOAEL_{[ADJ]} = 90\ mg/m^3 \times 6\ hrs/24\ hrs$

$NOAEL_{[ADJ]} = 22.5\ mg/m^3$

Calculation of $NOAEL_{[HEC]}$:

$NOAEL_{[HEC]}$ (mg/m^3) = $NOAEL_{[ADJ]}$ (mg/m^3) x $RGDR_r$

$NOAEL_{[HEC]}$ = the effect level obtained with an alternate approach, dosimetrically adjusted to an HEC

$NOAEL_{[ADJ]}$ = defined above

$RGDR_r$ = the regional gas dose ratio; a dosimetric adjustment factor for respiratory tract region, r (in this case extrarespiratory – ER)

Calculation of $RGDR_{ER}$:

$$RGDR_{ER} = \frac{(H_{b/g})_A}{(H_{b/g})_H}$$

$(H_{b/g})_A/(H_{b/g})_H$ = the ratio of the blood:gas (air) partition coefficient of the chemical for the laboratory animal species to the human value.

*In the absence of data on the ratio of the blood:gas (air) partition coefficients, it is assumed that $(H_{b/g})_A/(H_{b/g})_H$ equals 1.

Using substitution into the $NOAEL_{[HEC]}$ equation:

$NOAEL_{[HEC]} = 22.5\ mg/m^3 \times 1$

$NOAEL_{[HEC]} = 22.5\ mg/m^3$

Calculation of RfC:

$$RfC_{DT} = \frac{NOAEL_{[HEC]}}{UF}$$

RfC_{DT} = developmental reference concentration

$NOAEL_{[HEC]}$ = defined above

UF = uncertainty factor

> UFs that apply: 1) lab animal data to human extrapolation = 10
> 2) data on effects of average healthy humans to sensitive = 10

$$RfC_{DT} = \frac{22.5\ mg/m^3}{10 \times 10}$$

$RfC_{DT} = 0.225\ mg/m^3$

$RfC_{DT} = 225\ ug/m^3$ = **$230\ ug/m^3$** - based on a 24-hour averaging time

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The ITSLs for tetramethylurea is 0.8 ug/m^3 based on an annual averaging time and, pursuant to Rule 232(1)(a), also 230 ug/m^3 based on a 24-hour averaging time.

References

ChemFinder.com – Internet World Wide Web. 2006. Chemical and physical properties for tetramethylurea. http://chemfinder.cambridgesoft.com/.

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