**MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY**

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**INTEROFFICE COMMUNICATION**

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January 21, 2016

TO: File for Octamethylcyclotetrasiloxane (CAS #556-67-2)

FROM: Mike Depa, Toxics Unit, Air Quality Division

SUBJECT: Screening Level Derivation

The initial threshold screening level (ITSL) for octamethylcyclotetrasiloxane is 75 µg/m$^3$ based on an annual averaging time.

Previously, the averaging time (AT) assigned to octamethylcyclotetrasiloxane was 24 hours, as per the default methodology (see attached memo from Anne Kim dated April 9, 2007). The current file review concludes that the AT may appropriately be set at annual, based on the nature and duration of the key study and the ITSL value derivation, as allowed under Rule 229(2)(b). Therefore, the AT is set to annual.

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**MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY**

**INTEROFFICE COMMUNICATION**

TO: File for Octamethylcyclotetrasiloxane (CAS #556-67-2)

FROM: Anne Kim, Toxics Unit, Air Quality Division

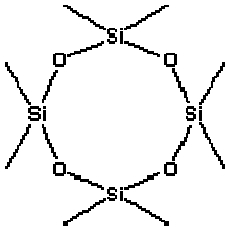
SUBJECT: Screening Level Derivation

DATE: April 9, 2007

**The initial threshold screening level (ITSL) for octamethylcyclotetrasiloxane is 75 µg/m³ 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 octamethylcyclotetrasiloxane. The molecular weight of octamethyl-cyclotetrasiloxane is 296.6 g. The molecular structure of octamethylcyclotetrasiloxane is shown in Figure 1.

**Figure 1**




An initial threshold screening level (ITSL) of 15 ug/$m^3$ with a 24-hour averaging time was established for octamethylcyclotetrasiloxane (D4) in 1992. This 1992 ITSL was based on a 3-month inhalation study investigating the effects of D4 exposure in Sprague-Dawley rats (Dow, 1989). Groups of 10 male and 10 female rats were exposed to concentrations of 0, 50, 300, or 700 ppm D4 vapors six hours per day, seven days per week for 13 weeks. An additional group of 10 male and 10 female rats were placed in both the control and high-dose group for a 28-day (4-week) recovery period. During the

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exposure period, the animals were observed for clinical signs of toxicity, growth changes, food consumption differences, and mortality. After the last day of exposure to D4, all animals were sacrificed excluding the rats designated for recovery. Organ weights were measured, blood and urine samples were tested, and clinical chemistry, gross pathology, and histopathology were evaluated. A slight decrease in body weight gain was observed in the 700 ppm females; this change did not persist in the recovery group animals. Mean absolute and relative liver weights were statistically significantly increased in all exposure groups except in the females of the lowest dose group. The increased liver weights were still evident in the females of the recovery group but not in the males. Because of the increased liver weights seen in the male rats at all doses, the LOAEL is 50 ppm. This LOAEL was used to establish the 1992 ITSL of 15 ug/$m^3$ with a 24-hour averaging time. The methodology that was used to develop this ITSL is from an outdated EPA RfC guideline (1989); EPA produced an updated RfC derivation guidance document in 1994. In addition to methodology improvements, more D4 toxicity studies have been conducted since the 1992 ITSL was derived. Thus, D4 was reassessed and the ITSL updated.

## Background

Octamethylcyclotetrasiloxane (D4) is insoluble with a boiling point of 175 degrees Celsius and a vapor pressure of 1 mmHg at room temperature (ChemFinder, 2006; HSDB, 2006). D4 is a liquid at room temperature that is used in a number of processes and products, such as “fermentation processes, instant coffee production, paper coatings and sizing, diet soft drinks, waste yeast tanks, food washing solutions, adhesives, textiles, de-asphalting, boiler treatments, detergents, cleaning solutions, surfactants, cosmetic products, and polishes” (HSDB, 2006).

## Animal Toxicity

A 3-month inhalation study reported the effects of D4 exposure in Fischer 344 rats (RCC, 1995). Groups of 20 or 30 rats per sex were exposed to target concentrations of 0, 0.3, 1.2, 5.0, or 12.0 mg/L (Group 1 – control, Group 2, Group 3, Group 4, and Group 5, respectively) six hours per day, five days per week for 13 weeks. Groups 1 and 5 consisted of 30 rats per sex and Groups 2, 3, and 4 consisted of 20 rats per sex. The additional 10 rats per sex from the control and highest dose groups were allowed a recovery period of four weeks after the last day of exposure. The actual exposure concentrations were reported to be 0.42, 1.48, 5.91, and 10.87 mg/L.

Only females from the highest dose group died due to D4 exposure; three died during the first week of exposure and two more died (one during the $7^{th}$ week and the other during the $12^{th}$ week of exposure).

Group 5 (highest dose) males and females showed statistically significant decreases in mean body weight and body weight gains. During recovery, the body weight gain was similar to that of control. During the first ten days of treatment, the males and females in Group 5 had statistically significant lower mean absolute and relative food intake compared to control.

Group 5 showed decreased mean body weight gains and reduced food consumption compared to the control rats in Group 1. Hematological and biochemical data showed changes mainly in the results from Groups 4 and 5. These changes in erythrocyte count, hemoglobin concentration, mean corpuscular volume, bilirubin and cholesterol

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concentrations, SGOT and SPGT activity, and/or protein concentration were found to be reversed after the recovery period (i.e., Group 5 rats showed similar results as Group 1 rats after four weeks of no exposure).

Statistically significant increases in absolute and relative liver weights, compared to control, were observed in Group 3 females and Group 4 and 5 male and female rats. The absolute and relative adrenal weights and thymus weights were increased and decreased, respectively, in the females of Groups 4 and 5. After recovery, only the liver weight changes persisted in Group 5 females.

Histological examination of the lungs showed minor alterations that are considered to be adaptive in nature, such as the increased number of alveolar macrophages in Groups 3, 4, and 5.

Group 5 females showed statistically significant decreases in absolute and relative ovarian weights, as well as vaginal mucification and mild ovarian atrophy. These changes were not found after the recovery period.

Other studies[a] showed toxic effects from much higher concentrations of D4 in rats (850 – 9000 mg/m$^3$). Results varied from decreased mean body weight and weight gains, decreased mean food consumption, changes in hematology and clinical biochemistry similar to the changes found in the RCC study (1995), increased absolute and relative liver weights, increased relative thyroid weights, decreased absolute and relative thymus weights, increased absolute and relative adrenal weights, and increased CYP450 activity (which is considered an adaptive and reversible response to D4 exposure).

Adverse effects reported by developmental or reproductive studies[b] occurred at doses significantly higher (800 – 8500 mg/m$^3$) than the NOAEL concentration from the critical study (420 mg/m$^3$). Results included reduced uterine and ovarian weights, decreased mating and fertility indices, reduced number of corpora lutea, decreased number of implantation sites and increased preimplantation loss, prolonged estrous cycles, delayed ovulation, extended parturition, reduced mean live litter size and mean number of pups born, and increased number of pups born dead. These reproductive and developmental toxic endpoints were observed at, again, relatively high exposure concentrations of D4.

## Human Toxicity

There are no studies assessing D4 toxicity in humans. Only one inhalation study (Dow, 1997) conducted in humans was found, for which only a summary was obtained. The study aimed to measure the pharmacokinetics of D4 exposure. The study subjects were exposed to 10 ppm of D4 via mouthpiece or by nasal exposure. Controls were exposed to air less D4. Parameters tested included clinical chemistry, immunological chemistry, serum chemistry, and pulmonary inflammatory indicators. The abstract does not provide any information on their findings and conclusion.

## Discussion

The RCC study is a robust study that is quite thorough in method details and study findings. Based on the exposure-induced increase in liver weights that was seen in Group 3 and higher, the NOAEL is set at 0.3 mg/L (actual concentration of 0.42 mg/L). The other studies reviewed support this finding of increased liver weights due to D4-exposure.

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While the same toxic endpoint of liver weight change was observed in the study – Dow, 1989 – originally used to calculate the 1992 ITSL, it did not provide a NOAEL, as did the RCC study; the 1989 Dow study results reported their lowest exposure level as an adverse effect level. Thus, the NOAEL from the 1995 RCC study will be used to derive the ITSL instead of the LOAEL from the 1989 Dow study.

Note: 0.42 mg/L was determined to be the NOAEL from RCC (1995)

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**Derivation of Screening Level**
**Conversion of concentration units from mg/L to mg/m$^3$:**
X mg/m$^3$ = mg/L x 1000
X mg/m$^3$ = 0.42 mg/L x 1000
X mg/m$^3$ = 420 mg/m$^3$

**Calculation of NOAEL$_{[ADJ]}$:**
NOAEL$_{[ADJ]}$ (mg/m$^3$) = E (mg/m$^3$) x D (hrs/24 hrs) x W (days/7 days)
>where 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
W = number of days of exposure/7 days

NOAEL$_{[ADJ]}$ = 420 mg/m$^3$ x (6 hrs/24 hrs) x (5 days/7 days)

NOAEL$_{[ADJ]}$ = 75 mg/m$^3$

**Calculation of NOAEL$_{[HEC]}$:**
NOAEL$_{[HEC]}$ (mg/m$^3$) = NOAEL$_{[ADJ]}$ (mg/m$^3$) x RGDR$_r$
>where 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$_{ER}$:**
$$RGDR_{ER} = \frac{(H_{b/g})_A}{(H_{b/g})_H}$$
>where $(H_{b/g})_A/(H_{b/g})_H$ = 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.

NOAEL$_{[HEC]}$ (mg/m$^3$) = 75 mg/m$^3$ x 1

NOAEL$_{[HEC]}$ (mg/m$^3$) = 75 mg/m$^3$

**Calculation of RfC:**
$$RfC = \frac{NOAEL_{[HEC]}}{UF}$$
>where RfC = reference concentration
NOAEL$_{[HEC]}$ = defined above
UF = uncertainty factor

>UFs that apply: 1) variation in sensitivity among members of the human population = 10
2) extrapolation from animal data to humans = 10
3) extrapolation from sub-chronic to chronic = 10

$$RfC = \frac{75\ mg/m^3}{10 \times 10 \times 10}.$$

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RfC = 0.075 mg/m$^3$ = **75 ug/m$^3$**

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Pursuant to Rule 232(1)(a), the ITSL is equal to the RfC; therefore, the ITSL for octamethylcyclotetrasiloxane is 75 ug/m$^3$ based on a 24-hour averaging time.

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