MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for 1,2,4,5-tetrachlorobenzene [CAS# 95-94-3]

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: January 13, 2017

SUBJECT: 1,2,4,5-tetrachlorobenzene [CAS# 95-94-3] ITSL change in the averaging time from 24 hours to annual

The current initial threshold screening level (ITSL) for 1,2,4,5-tetrachlorobenzene is 1 µg/m^3 based on an annual averaging time. The ITSL established on 6/12/2007 is based on the EPA's oral reference dose (RfD) of 0.0003 mg/kg. The EPAs RfD was based on a 13 week rat feeding study by Chu et al., (1984), which found increased frequency and severity of kidney lesions in male rats. When the screening level was derived in 2007 the averaging time was set at 24 hours. The ITSL may be appropriately set to an annual averaging time to reflect the duration of the 13 week study. Therefore, the averaging time is being changed from 24 hours to annual at this time.

References:

APCR. 2016. Air Pollution Control Rules, Promulgated pursuant to Part 55, Air Pollution Control, of the Natural Resources and Environmental Protection Act, Michigan Department of Environmental Quality. 1994. Act 451, as amended (NREPA).

Chu I, Villeneuve DC, Valli VE, and Secours VE. 1984. Toxicity of 1,2,3,4-, 1,2,3,5- and 1,2,4,5-tetrachlorobenzene in the rat: Results of a 90-day feeding study. Drug Chem. Toxicol. 7:113-127.

EPA. 1991. Integrated Risk Information System. 1,2,4,5-Tetrachlorobenzene (CASRN 95-94-3). Available online at: https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=107

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for 1,2,4,5-tetrachlorobenzene CAS# 95-94-3

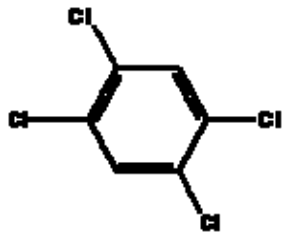
FROM: Margaret M. Sadoff, AQD, Toxics Unit

DATE: June 12, 2007

SUBJECT: Request for Screening Level for DOW Permit 156-07

The final ITSL for 1,2,4,5-tetrachlorobenzene is 1 ug/m3 (24-hour average).

A search of the literature and the following databases was performed for information regarding 1,2,4,5-tetrachlorobenzene (1,2,4,5-TCB): American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values, National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, EPA Integrated Risk Information System (IRIS), EPA High Production Volume Information System, 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, National Library of Medicine ToxSeek, Health Effects Assessment Summary Tables (HEAST), National Toxicology Program (NTP) Study Database, Entrez PubMed, Scirus, IPCS Intox Databank and CalEPA's Toxicity Values Database



1,2,4,5-tetrachlorobenzene [95-94-3]

USE, ENVIRONMENTAL FATE & EXPOSURE SUMMARY

(Source: NLM Toxline Hazardous Substances Databank)
(Source: NTP (Oral) Toxicity Studies of 1,2,4,5-TCB in F344 Rats and B6C3F1 Mice, January 1991)

1,2,4,5-Tetrachlorobenzene exists as colorless-white flakes or needle-like solids with a strong unpleasant odor. It is soluble in ether, benzene, chloroform and carbon disulfide, slightly soluble in ethanol, and insoluble in water. 1,2,4,5-TCB has been produced in the past as an insecticide and intermediate in the production of herbicides and defoliants. Commercial production of this compound in the U.S. ceased in 1983 but it is still used as an intermediate in

the manufacture of various industrial and commercial chemicals including antifungal agents, herbicides, and mordant dyes.

As a degradation byproduct of pentachlorobenzene, hexachlorobenzene and lindane, 1,2,4,5-TCB may enter the environment as a result of the microbial degradation of these compounds. Based on a boiling point of 245ºC and a vapor pressure of 0.005 mmHg at 25ºC, 1,2,4,5-tetrachlorobenzene has very low volatility but, if present, would be expected to exist as a vapor in ambient air. Very low concentrations of tetrachlorobenzenes have been found in the environment (0.14 to 0.2 ng/m3 detected in rural and urban areas in Canada in 1988-89).

Vapor-phase 1,2,4,5-tetrachlorobenzene is degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals with an estimated atmospheric half-life of 200 days, which makes it a relatively persistent pollutant. The general population may be exposed to 1,2,4,5-tetrachlorobenzene via inhalation of ambient air, ingestion of food and drinking water. Occupational exposure to 1,2,4,5-tetrachlorobenzene may be through inhalation and dermal contact with this compound at workplaces where it is produced or used.

Persistence and Bioaccumulation

Studies in several species indicate that the 1,2,4,5 isomer is easily absorbed and more slowly metabolized than the 1,2,3,4 and 1,2,3,5 isomers. This is likely due to its molecular configuration which renders it is less conducive to metabolic transformation because of steric and electronic hindrance. 1,2,4,5-TCB readily accumulates and persists in adipose tissue and organs with high fat content. It has been found in breast milk at low concentrations (~ 200 ug/kg) and human adipose tissue samples (0.02-200 ug/kg). Administration of 1,2,4,5-TCB to beagle dogs at 5 mg/kg/day in the diet for 2 years resulted in achieving 98% and 97% of the calculated steady-state concentrations in fat and plasma, respectively. (Braun et al 1978 as reported by NTP). 28-day and 13 week oral toxicity studies in Sprague-Dawley rats found dose-dependent accumulation of 1,2,4,5-TCB in the fat and liver (Chu et al, 1984).

HUMAN TOXICITY/EXPOSURE DATA

(Source: NLM Toxline Hazardous Substances Databank)

Only one occupational epidemiological study was found in the literature for human exposure to 1,2,4,5-TCB (see Genotoxicity section). There were no case studies reported in the literature. However, all isomers of TCB have been found in human tissue, with the 1,2,4,5-isomer being predominant for reasons discussed in the previous section.

Unidentified tetrachlorobenzene isomer(s) were found in human blood samples taken from a resident in the area of the Love Canal at a concentration of 2.6 ug/L(1). Concentrations of 0.008 to 0.039 mg/kg 1,2,4,5-tetrachlorobenzene were detected in human adipose tissue in Japan(2). Mean concentrations of 0.016 ug/g were detected in Yugoslavian human adipose tissue and 2 ug/kg in human milk, respectively(3).
[(1) Barkely J et al; Biomed Mass Spect 7: 143 (1980) (2) Morita M et al; Environ Pollut 9: 175 (1975) (3) Jan J; Bull Environ Contam Toxicol 30: 595 (1983)]**PEER REVIEWED**

Combined trichlorobenzene and tetrachlorobenzene isomers were detected in human adipose tissue in Slovenia at a concn of 60 ng/g and in human hair samples at 40 ng/g(1).
1,2,4,5-Tetrachlorobenzene was identified, not quantified, in the adipose tissue of non-occupationally exposed individuals in Germany(2).

[(1) Zupancic-Kralj L, Jan J; Acta Chim Slov 41: 447-56 (1994) (2) Geyer H et al; Reg Toxicol Pharmacol 6: 313-47 (1986)]**PEER REVIEWED**

The World Health Organization (WHO) estimates the average daily intake of all tetrachlorobenzene isomers for humans is less than 0.1 ng/kg body weight(1).
[(1) Gunderson EL; J Assoc Off Anal Chem 71: 1200-1209 (1988)]**PEER REVIEWED**

ANIMAL TOXICITY DATA

INHALATION
There are no inhalation data available for this chemical.

Acute Oral Toxicity

Some reported LD50s are:

Species	Oral LD50 (in mg/kg)	Citation
Albino rats and rabbits	1,500	Fomenko (1965)
Mice	1,035-2,650	Fomenko (1965)
Male Sprague–Dawley rats	3,105 (2498-3915)	Chu Et al (1983, 1984)*
Female Sprague-Dawley rats	> 2,700	Chu Et al (1983, 1984)*

*The 14-day study ranked the 1,2,4,5- isomer as the least acutely toxic of the three TCB isomers, but a subsequent 28 day study by the same group found 1,2,4,5 to be the most toxic. The authors attributed this greater toxicity to greater tissue accumulation of 1,2,4,5 over the longer exposure period.

Source: NTP (Oral) Toxicity Studies of 1,2,4,5-TCB in F344 Rats and B6C3F1 Mice, January 1991

Subchronic & Chronic Oral Toxicity
Source: NTP (Oral) Toxicity Studies of 1,2,4,5-TCB in F344 Rats and B6C3F1 Mice, January 1991)

NTP Protocol: 1,2,4,5-TCB was nominated for study as a high priority compound owing to its high potential to bioaccumulate in human tissues, and it structural similarity to other chlorinated benzenes that are carcinogenic. Target dietary exposure concentrations were achieved by dissolving > 99% pure compound in corn oil. Groups of 5 M/F F344/N rats and B6C3F1 mice received diets containing 0, 30, 100, 300, 1,000 or 3,000 ppm 1,2,4,5-TCB in 1% corn oil for 14 days. In a separate protocol, groups of 20 M/F rats and 10 M/F mice were fed diets containing 0, 30, 100, 300, 1,000 or 2,000 ppm 1,2,4,5-TCB in 1% corn oil for 13 weeks (equates to ~ 0, 2, 7, 22, 75, and 150 mg/kg/day in rats and 0, 5, 17, 50, 145, 290 mg/kg/day in mice).

Results of the 14-day Studies

There was no mortality observed in rats. Food consumption by rats receiving 3,000 ppm was about 20% lower than controls, resulting in 15% and 18% lower final mean body weights in this group for females and males, respectively. Clinical signs were reported in the 3,000 ppm group

that included tremors, lethargy, thin appearance, rough hair coats, ataxia, and chromodacryorrhea ("blood tears" from the harderian gland) in both sexes and rapid breathing in females. Increases were reported for absolute and relative liver weights in both sexes and absolute and relative kidney weights in males receiving 300 ppm or more TCB. Liver congestion was noted in males receiving 1,000 ppm or more and females receiving 3,000 ppm TCB. Males rats exhibited histological markers of "hyaline droplet nephropathy" or alpha-2-mu globulin syndrome which is not relevant to humans.

All mice in the 3,000 ppm group died during the study (females by Day 6 and males by Day 9). Compound-related clinical signs occurred in the 3,000 ppm group and were similar to that of rats with the addition of hunched posture, dyspnea, and prostration. Absolute and relative weights were significantly increased for males receiving 1,000 ppm and females receiving 300 or 1,000 ppm. Histopathology revealed depletion and necrosis of lymphoid tissue of the spleen, thymus, and lymph nodes in both sexes receiving 3,000 ppm which is an indicator of moribund condition.

13 Week Results

There was no mortality in rats throughout the study. Final mean body weights for rats in the 1,000 and 2,000 ppm groups were 10% and 20% lower for males and 8% and 16% lower for females. Although a number of clinical chemistry and histopathology changes were noted, a **NOEL of 30 ppm (2 mg/kg/day)** was identified based primarily on histologic lesions in the kidney (various) and thyroid (follicular cell hypertrophy). Induction of thyroid proliferative lesions in animals and humans is a well-documented effect of many chlorinated benzene compounds including hexachlorobenzene, pentachlorobenzene, 1,4-dichlorobenzene, dioxins and PCBs. There were also increased absolute and relative liver weights and decreases in thyroid hormones observed at higher doses.

Two of the ten female mice receiving 2,000 ppm were killed in a moribund condition during the study (at weeks 2 and 13). Final mean body weights of exposed mice were significantly different from that of controls. As in rats, a number of clinical chemistry and histopathology changes were noted, but ultimately a **NOEL of 300 ppm (50 mg/kg/day)** was selected based on liver lesions.

Overall, the major target organs of 1,2,4,5-TCB toxicity were kidney (from the 14-day study) and liver in rats and liver in mice. Minimal thyroid lesions also occurred in rats. In general, effects were more extensive in rats than mice.

Reproductive/Developmental

(Source: NTP (Oral) Toxicity Studies of 1,2,4,5-TCB in F344 Rats and B6C3F1 Mice, January 1991)

Studies in rats have demonstrated that the 1,2,4,5-isomer crosses the placenta and accumulates in fetal tissue to a greater extent than the other two isomers. Reproductive toxicity studies report either no compound-related effects on fetuses or effects secondary to high maternal toxicity.

The three TCB isomers were administered individually in corn oil by gavage on days 6 to 15 of gestation to pregnant Sprague-Dawley rats at levels of 50, 100 or 200 mg/kg. The highest dose level of 1,2,4,5-TCB caused maternal deaths in 9/10 animals by circulatory collapse. A

decrease in the number of fetuses was also noted at the lowest dose of 1,2,4,5-TCB but not at the mid-dose and thus, no dose-response relationship could be established. None of the congeners produced any visceral or skeletal anomalies in pups. Residues of all three congeners were found in maternal and fetal tissues with levels of 1,2,4,5-TCB generally an order of magnitude higher than the other two isomers. Accumulation of this isomer occurred in a dose-dependent manner with whole body having the highest concentration followed by liver and brain. No significant reproductive or developmental toxicity was found from this study. *(Source: TSCA Submission by Dow Chem Co. (1/04/92) Initial Submission: Placental Transfer and Teratological Evaluation of Tetrachlorobenzene Isomers in the Rat with cover letter dated 1/20/92, Kacew et al.)*

M/F CD-1 Swiss mice were exposed to 1,2,4,5-TCB at levels of 0.028, 0.072 and 0.18% w/w in the diet using a continuous breeding protocol. 19/20 females in the highest dose group died or had to be sacrificed at parturition. Tissues from 8 of these females were taken to determine the cause of death; two had hepatocellular degeneration, one showed signs of lymphoma, and the other causes could not be determined histologically. There were no deaths in males but males showed transient inactivity and rough hair coat. In the mid-dose group, a significant decrease (9%) was noted in the number of live pups. No other fertility or reproductive effects were noted. At terminal sacrifice, the average and relative liver weights in F0 generation males exposed to 0.18% TCB was almost twice that of controls. In the F1 generation, liver and kidneys were enlarged in both sexes exposed to 0.072% TCB. Sperm abnormalities and seminal vesicle weight were greater in the high dose males as compared to controls. The F2 generation was reared consuming either control diet or 0.072% TCB. At sexual maturity, no effects on fertility or reproductivity were noted. At F2 necropsy, there were increases in absolute and relative weights of liver and kidney in both sexes in the exposed group and increases in relative and absolute testis weight in males. Microscopically, middle dose treated males and females showed greater incidences and severity of hepatic cytomegaly and karyomegaly, and renal tubular regeneration, compared to controls. Under these experimental conditions, 1,2,4,5-TCB was reported to exert mild reproductive toxicity secondary to considerable systemic toxicity. The data show that the hepatic and renal effects of TCB were significantly greater than the modest reproductive effects observed (reduced pup number, F_0 generation). The authors concluded that 1,2,4,5-tetrachloro-benzene is not a selective reproductive toxicant, and had no greater effect on the second generation than upon the first in this study design.
(*Source: NTP (Oral) Reproductive toxicity of 1,2,4,5-TCB in CD-1 Swiss Mice)*

Summary: Studies on reproductive/developmental toxicity with exposure to tetrachlorobenzenes have not shown consistent dose-response relationships and have generally been associated with doses resulting in high maternal toxicity. In addition, since liver, kidney and thyroid effects have been demonstrated at even lower concentrations than those employed in reproductive studies, protection of maternal toxicity (i.e. liver, kidney or thyroid effects) should be protective of potential effects to offspring.

Cancer and Genotoxicity
(Source: Toxline ITER International Toxicity Estimates for Risk)

Neither IARC nor IRIS has evaluated 1,2,4,5-TCB (or any of the other TCB isomers) for carcinogenicity. Health Canada has done an evaluation but deemed 1,2,4,5-TCB to be unclassifiable as a human carcinogen. “Adequate epidemiological studies of exposed populations and investigations of the chronic toxicity or carcinogenicity of the tetrachloro-benzene isomers in experimental animals have not been identified. None of the

tetrachlorobenzene isomers has been genotoxic in *in vitro* studies with a limited range of endpoints. On the basis of these observations, each of the three isomers of tetrachlorobenzene are "unclassifiable with respect to carcinogenicity in humans " (Group VI)."

There is no data linking 1,2,4,5-TCB (or any of the TCB isomers) to carcinogenicity although a few studies have noted its potential promoter capability as a P450 type enzyme inducer. (Herren-Freund & Pereira, 1986; Chu et al, 1984). TCBs are a metabolic product of hexachlorobenzene which is a know animal carcinogen and a possible human carcinogen (IARC Group 2B).

One occupational epidemiological study showed an increase in chromosomal aberrations in peripheral lymphocytes of workers employed in a pesticide manufacturing complex producing 1,2,4,5-TCB when compared to 14 workers who were minimally exposed and 49 individuals from the local community. Exposure concentrations were not quantified. *(Kiraly J, Szentesi I, Ruzicska M & Czeize A. (1979). Chromosome studies in workers producing organophosphate insecticides. Arch Environ Contam Toxicol 8(3): 309-19.*

By-products of disinfection were tested for cancer initiating and/or promoting activity in rat liver using the rat liver foci bioassay. This bioassay uses increased incidence of GGT foci (gamma glutamyltranspeptidase positive foci) as an indicator for carcinogenicity. In this assay, 1,2,4,5-tetrachlorobenzene (but not 1,2,3,4- or 1,2,3,5-tetracholorbenzene) acted as a promoter in male (but not female) Sprague-Dawley rats when administered IP at 0.25 mmole/kg at 1 and 5 weeks after gavage administration of 0.5 mmol/kg diethylnitrosamine. The authors note that validation of the tumor-promoting activity of 1,2,4,5-TCB still requires a demonstration of enhancement of tumor incidence initiated by diethylnitrosamine. *(Source: Herren-Freund SL & Pereira MA (1986). Carcinogenicity of By-Products of Disinfection in Mouse and Rat Liver. EHP 69: 59-65.)*

1,2,4,5-TCB was tested in numerous Ames Salmonella assays at concentrations ranging from 0.3 to 1,333 ug/plate (CCRIS database reports 15 negative assays). Results were negative in either the presence or absence of S9 metabolic activation. Other tests report negative results for sex-linked recessive mutation (in Drosiphila), induction of sister chromatic exchanges, or chromosal aberrations. One Hungarian occupational study concluded that 1,2,4,5-TCB was mutagenic as evidenced by chromosomal abnormalities in peripheral lymphocytes, but this study is not reliable due to “marked methodologic deficiencies.” (*Source: NTP (Oral) Toxicity Studies of 1,2,4,5-TCB in F344 Rats and B6C3F1 Mice, January 1991)*

Overall, evidence of genotoxicity for 1,2,4,5-TCB is lacking.

HUMAN HEALTH RISK VALUES

Acute emergency inhalation values for 1,2,4,5-TeCB are as follows:

TEEL 0 = 10 mg/m3; TEEL 1 = 30 mg/m3; TEEL 2 = 50 mg/m3; TEEL 3 = 500 mg/m3

Health Canada and U.S. EPA have evaluated the noncancer oral toxicity data for 1,2,4,5-tetrachlorobenzene. Health Canada derived a tolerable daily intake (TDI) of 0.00021 mg/kg-day based on a NOAEL of 2.1 mg/kg bw/day (NTP, 1991) and a very conservative uncertainty factor of 10,000 (10 each for intraspecies variation, interspecies variation, less than chronic study, and lack of adequate data on carcinogenicity and reproductive toxicity). EPA derived a reference dose (RfD) of 0.0003 mg/kg-day based on a NOAEL of 0.34 mg/kg-day (dose conversions

provided by study authors) for kidney lesions in a subchronic oral study in rats (Chu et al., 1984). EPA applied an uncertainty factor of 1000 (10 each for intraspecies and interspecies variability and 10 for extrapolation of a subchronic effect level to its chronic equivalent. There is low confidence in the database and, therefore, low confidence in the RfD for this chemical. *(Source: Toxline ITER International Toxicity Estimates for Risk)*

EPA IRIS Evaluation (based on Chu et al., 1984)
(*Source: EPA IRIS online RfD last revised 3/1/91)*

The principal study is a 13 week feeding study with groups of 15/sex Sprague-Dawley rats fed diets containing 0, 0.5, 5.0, 50, and 500 ppm 1,2,4,5-TeCB (equates to 0, 0.034, 0.34, 3.4 and 34 mg/kg/day for males and 0, 0.041, 0.41, 4.1 and 41 mg/kg/day for females). Increased frequency and severity of kidney lesions were observed in male rats at 5.0 ppm dose level and greater. However, the severity of effects was considered to be significant only at the 50 and 500 ppm levels due to the high incidence of mild kidney lesions observed in controls. Liver lesions were observed in female rats at 500 ppm.

The principal supporting study was a 28-day feeding study in rats (10/sex/group) with dose related effects for liver and kidney pathology were observed at 3.4 and 32 mg/kg/day, respectively. Liver lesions were mild to moderate while kidney lesions were mild. Relative liver weights were increased significantly (by 20-30%) and hepatic microsomal enzymes were induced 2 to 12-fold at the 32 mg/kg/day dose level. Males were more susceptible than females for all criteria. No adverse effects were noted at the lower doses (0.04 and 0.4 mg/kg/day).

ITSL Derivation

Collectively, the existing data for chlorinated benzenes indicate the liver and kidneys are the principal target organs. Thyroid changes have also been noted for some of these chemicals, including the tetrachlorobenzenes.

IRIS identified a LOAEL of 50 ppm in the diet (3.4 mg/kg/day) and a **NOAEL of 5.0 ppm (0.34 mg/kg/day)** from these studies based on the critical effect of kidney lesions A total UF of 1,000 was applied resulting in an RfD of 3x10-4 mg/kg/day. An ITSL could be derived from this value using the (70kg/20m3) conversion factor for inhalation

on exposure pursuant to R232(1)(b):

ITSL = Oral RfD x 70 kg/20m3 = 0.0003 mg/kg x (70kg/20m3)

= 0.00105 mg/m3 or ≈ 1 ug/m3, 24 hour average

Given that there is no inhalation toxicity data in humans or animals and no occupational exposure values, use of the oral RfD is appropriate in this case. The effect (kidney) is remote (systemic) and therefore plausible via the inhalation route. Since this chemical is not very water soluble (< 1 mg/L at 25C), there is low potential for portal of entry effects (e.g. respiratory irritation).

The final RfD-based ITSL for 1,2,4,5-tetrachlorobenzene is 1 ug/m3 (24-hour average).

ADDITIONAL RATIONALE & SUPPORT FOR DEVELOPMENT OF THE ITSL FOR 1,2,4,5-TECB

For chlorinated benzenes, in general, liver and kidney are the principal target organs. Decreases in thyroid hormone levels have also been noted after oral and ip administration of 1,2,4,5-TeCB and other chlorinated benzenes. Changes in thyroid hormone have been considered adverse or pre-cursor events in some studies and treated as LOAELs. Other studies have characterized these types of changes as biomarkers of exposure only and used them as NOAELs.

The NTP and Chu et al. studies are both well designed, well controlled feeding studies. The Chu study used Sprague-Dawley rats at lower exposure concentrations than the NTP study which used F344/N rats and B6C3F1 mice. The Chu study (on which the RfD is based) did have a high incidence in kidney lesions in control animals, as well as experimental animals, which introduces additional uncertainty in interpretation of those effects. EPA rated the study confidence as medium, the database confidence as low, and the RfD as low confidence. The NTP report came out in January of 1991 and the EPA RfD was last revised on 3/01/1991. EPA updated their literature review in 2002 and found "one or more studies" that were relevant to the RfD but have not updated the value.

Rats were reported to be more sensitive than mice and male rats more sensitive than female rats. It also appears that the Sprague-Dawley rats utilized by Chu were more sensitive than the Fischer rats utilized by NTP. So if rat data only is considered, the most sensitive endpoint in the most sensitive species would be kidney lesions in rats from the Chu study and the RfD-based ITSL would be 1 ug/m3 (24-hr avg). It is not clear if the kidney lesions from this study are consistent with hyaline droplet nephropathy but they were observed in both males and females which makes that particular male rat-specific phenomenon less likely. Lesions were described as moderate to severe in nature and were dose-dependent.

The NTP study observed less severe toxic endpoints above a higher NOEL than the Chu study which could be attributed to the different species of rat utilized. The NTP NOEL of 2 mg/kg/day is very close to the Chu LOAEL of 3.4 mg/kg/day (albeit for different endpoints). The Chu study did not include thyroid hormone levels in their serum chemistry protocol, but did conduct histopathology on the thyroid itself and reported no lesions. NTP reported decreases in thyroid hormone levels and follicular cell hypertrophy above their NOEL of 2 mg/kg/day (about 6 times higher than the Chu NOEL for the more severe kidney lesion).

<u>IIf TSL based on NTP values:</u>

Rat NOEL = 30 ppm or **2 mg/kg/day**
endpoint = histologic lesions in the kidney and thyroid
Total UF = 1,000
RfD = 0.002 mg/kg/day
ITSL = 7 ug/m3 (24 hr avg)

If considering the NOEL as a LOEL for thyroid hormone changes….

Rat LOEL = 30 ppm or **2 mg/kg/day**
endpoint = thyroid hormone changes as low as 30 ppm in females
Total UF = 3,000 (additional factor of 3 for LOEL to NOEL given the mild nature of the effect)
RfD = 0.0007 mg/kg/day

ITSL = 2 ug/m3 (24 hr avg)

These values are supportive of the ITSL of 1 ug/m3 based on Chu et al.

By all available evidence, the 1,2,4,5-TCB isomer is the most toxic of the three owing to its longer residence time in the body. One might expect that if a true chronic study were available, toxicity would be more severe over a longer duration. Therefore, the more protective ITSL should stand.

MS:lh