

**Michigan Department of Environmental Quality**

**Interoffice Communication**

TO: File for 2,3,7,8-Tetrachlorodibenzo-p-dioxin (CAS #1746-01-6)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

SUBJECT: Screening Levels for 2,3,7,8-Tetrachlorodibenzo-p-dioxin  
(CAS #1745-01-6)

DATE: April 5, 2012

The initial threshold screening level (ITSL) for 2,3,7,8-tetrachlorodibenzo-p-dioxin is  $2 \times 10^{-6} \mu\text{g}/\text{m}^3$  based on an annual averaging time.

A review of the Environmental Protection Agency Integrated Risk Information System (EPA IRIS) reference dose (RfD) of  $7 \times 10^{-10}$  mg/kg-day for chronic oral exposure was performed to evaluate whether this value should be adopted as an ITSL. EPA IRIS determined a chronic RfD based on two epidemiologic cohort studies: Mocarelli et al., (2008) showed decreased sperm count and motility in men exposed to TCDD as boys; and Baccarelli et al., (2008) showed increased thyroid stimulating hormone (TSH) in neonates exposed before birth to TCDD. Both of these studies are of a human population that was exposed to TCDD through an industrial accident in Seveso, Italy in 1976.

Mocarelli et al., (2008) reported decreased sperm concentration and motility in men who were exposed when they were 1 – 9 years old (at the time of the Seveso accident in 1976). “These results identify the first 10 years of life as the critical window of susceptibility for TCDD-induced sperm effects. Serum TCDD levels (as LASC [lipid adjusted serum concentration]) were measured in samples collected within one year of the initial exposure. Serum TCDD levels and corresponding responses were reported by quartile, with a reference group of individuals assigned a TCDD LASC value of 15 ppt (the mean of the TCDD LASC reported in individuals outside the contaminated area). In the reference group, mean sperm concentrations and motile sperm counts of approximately 73 million sperm/mL and 41%, respectively. The lowest exposed group (1<sup>st</sup> quartile) TCDD LASC median was 68 ppt. In the 1<sup>st</sup> quartile, mean sperm concentrations of approximately 55 million sperm/mL and motile sperm counts of approximately 35% were reduced about 25 and 12%, respectively, from the reference group. Further decreases in these measures in the groups exposed to more than 68 ppt was minimal, with maximum reductions of 33% for sperm concentration and 25% for progressive sperm motility in the 4<sup>th</sup> and 3<sup>rd</sup> quartiles, respectively. The lowest exposure group (TCDD LASC = 68 ppt) in Mocarelli et

al. (2008) is designated as a LOAEL. Using the Emond PBPK model (Emond et al., 2005), EPA estimated both the peak initial exposure and the average exposure over the critical window. Because of the uncertainty in the influence of the peak exposure relative to the average exposure over the entire 10 year window, the LOAEL of 0.020 ng/kg day was calculated as the average of the peak exposure (0.032 ng/kg day) and the average exposure across the critical exposure window (0.008 ng/kg day).” (EPA, 2012).

“Baccarelli et al., (2008) reported increased levels of thyroid stimulating hormone (TSH) in newborns exposed to TCDD in utero, indicating a possible dysregulation of thyroid hormone metabolism. The study authors related TCDD concentrations in maternal plasma to neonatal TSH levels using a multivariate linear regression model adjusting for a number of covariates including gender, birth weight, birth order, maternal age, hospital, and type of delivery. Based on this regression modeling, EPA defined the LOAEL for Baccarelli et al (2008) to be the maternal TCDD LASC of 235 ppt (parts per trillion) at delivery, corresponding to a neonatal TSH level of 5 µU/mL. Using the Emond human PBPK model (Emond et al, 2005), the corresponding daily oral intake at the LOAEL is estimated to be 0.020 ng/kg day. The World Health Organization (WHO, 1994) established the 5 µU/mL standard as an indicator of potential iodine deficiency and potential thyroid problems in neonates. The 5 µU/mL limit for TSH measurements in neonates was recommended by WHO (1994) for use in population surveillance programs as an indicator of iodine deficiency disease (IDD). For TCDD, the toxicological concern is not likely to be iodine uptake inhibition, but rather increased metabolism and clearance of the thyroid hormone, thyroxine (T4).” (EPA, 2012).

The EPA used an uncertainty factor (UF) of 30: an UF of 10 for LOAEL to NOAEL extrapolation; and an UF of 3 to account for variability in susceptible individuals. The confidence in the chronic oral RfD is high as the two principle studies were well conducted and the effects were reported in human populations. The EPA chronic oral RfD of  $7 \times 10^{-10}$  mg/kg-day will be used to derive an ITSL for TCDD.

Rule 232(1) (b) uses an oral RfD to determine an ITSL using the following equation:

$$ITSL = Oral \dots RfD \times \frac{adult \dots body \dots weight}{adult \dots breathing \dots volume \dots per \dots day}$$

$$ITSL = 7 \times 10^{-10} \frac{mg}{kgday} \times \frac{70kg}{20m^3} = 2 \times 10^{-9} \frac{mg}{m^3} = 2 \times 10^{-6} \frac{\mu g}{m^3}$$

According to Rule 232(2)(b), a 24-hour averaging time would generally be used, but after discussion with Bob Sills and with the epidemiological studies based on long term low level exposures, it was decided that an annual averaging time would be more appropriate based on the scientific data under Rule 229.

Therefore, the initial threshold screening level (ITSL) for 2,3,7,8-tetrachloro-dibenzo-p-dioxin is  $2 \times 10^{-6} \mu\text{g}/\text{m}^3$  based on an annual averaging time.

### References:

AQD. 1994. Act 451, Natural Resources and Environmental Protection Act Pollution Control Rules, Michigan Department of Environmental Quality.

Baccarelli, A; Giacomini, SM; Corbetta, C; Landi, MT; Bonzini, M; Consonni, D; Grillo, P; Patterson, DG; Pesatori, AC; Bertazzi, PA. 2008. Neonatal thyroid function in Seveso 25 years after maternal exposure to dioxin. PLoS Med 5: e161.

Emond, C; Michalek, JE; Birnbaum, LS; DeVito, MJ. 2005. Comparison of the use of a physiologically based pharmacokinetic model and a classical pharmacokinetic model for dioxin exposure assessments. Environ Health Perspect 113:1666-1668.

EPA. 2012. Integrated Risk Information System. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) CASRN 1746-01-6. Available online at <http://www.epa.gov/iris/subst/1024.htm>

Mocarelli, P; Gerthoux, PM; Patterson, DG, Jr; Milani, S; Limonata, G; Bertona, M; Signorini, S; Tramacere, P; Colombo, L; Crespi, C; Brambilla, P; Sarto, C; Carreri, V; Sampson, EJ; Turner, WE; Needham, LL. 2008. Dioxin exposure, from infancy through puberty, produces endocrine disruption and affects human semen quality. Environ Health Perspect 116:70-77. <http://dx.doi.org/10.1289/ehp.10399>.

WHO/UNICEF/ICCIDD (World Health Organization/United Nations Children's Fund/International Council for the Control of Iodine Deficiency Disorders). 1994. Indicators for assessing iodine deficiency disorders and their control through salt iodization (WHO/NUT/94.6). Geneva: World Health Organization.

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