

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for 1,3-Butadiene (CAS No. 106-99-0)

FROM: Robert Sills, Toxics Unit Supervisor, Air Quality Division

SUBJECT: ITSL Basis

DATE: August 14, 2017

The Initial Threshold Screening Level (ITSL) for 1,3-butadiene (BD) is 33 ug/m³ with annual averaging time (AT).

The previous ITSL for BD was 2 µg/m³, with 24-hr averaging time, established on November 6, 2002. The basis for that ITSL was an EPA (2002) RfC of the same value. This ITSL was posted by AQD for formal public comment on February 14, 2017. One comment was received by AQD on the ITSL for BD. They stated that the ITSL should be replaced by the more recent chronic health benchmark of the TCEQ (2008), which is a chronic Reference Value (ReV) of 33 ug/m³. The commenter suggested that AQD evaluate this TCEQ (2008) benchmark and base the ITSL on this more up-to-date and thorough assessment. The AQD has reviewed the basis for the ITSL for BD. As a result of that review, AQD agrees with the commenter that the ITSL basis was not the most appropriate in light of an assessment by TCEQ (2008). Therefore, the ITSL is changed from 2 ug/m³ (24 hr averaging time) to 33 ug/m³ (annual averaging time).

A review of TCEQ (2008) reveals that they initially based their evaluation on the EPA (2002) assessment, with the same key study and critical effect as EPA (2002), but with supplemental dose-response modeling to discern the appropriate point of departure. TCEQ (2008) utilized a 5% response level (BMCL₀₅) rather than the 10% response level (BMCL₁₀) as utilized by EPA (2002). They reasoned that the BMCL₀₅ has generally been considered a conservative NOAEL surrogate whereas the BMCL₁₀ may be analogous to a NOAEL or a LOAEL. As a result, TCEQ (2008) utilized a lower uncertainty factor for LOAEL-to-NOAEL conversion (UF_L) of 1, whereas EPA (2002) utilized a value of 10. Also, TCEQ (2008) accounted for the interspecies differences between the test species (mice) and humans, with regard to the ability to metabolize 1,3-butadiene to the presumptive toxic diepoxide metabolite (DEB). EPA (2002) also agreed with this concept, but defaulted to an interspecies toxicokinetic uncertainty factor (UF_{A-TK}) of 1: "There is strong evidence that the diepoxide metabolite (1,2:3,4-diepoxybutane, DEB) is required to elicit ovarian atrophy (U.S. EPA, 2002; Chapter 5),

and it is expected, based on pharmacokinetic data, that humans produce less DEB than mice (U.S. EPA, 2002, Chapter 3). However, DEB levels cannot be quantified without an adequate physiologically-based pharmacokinetic (PBPK) model. Thus, default dosimetry (i.e., 1,3-butadiene exposure concentration) was used for dose-response modeling, and the default value of 1 for the pharmacokinetic portion of the interspecies uncertainty factor for inhalation exposures was retained.” (EPA, 2002). TCEQ (2008) Toxicology Section (TS) found that, “However, there is empirical evidence to indicate that the toxicokinetic UF is considerably less than 1 because mice metabolize BD to the reactive metabolite DEB much more than humans as discussed in Section 4.1.2 MOA Analysis. Although the experimental data are not sufficient to develop a chemical-specific adjustment factor (CSAF) for BD, it would support a UF_A substantially less than 1. The toxicokinetic UF_A that will be used by the TS is 0.3, although it may be substantially less than 0.3, as discussed below. If a BD-specific toxicokinetic $UF = 0.3$ is used with the standard toxicodynamic $UF = 3$, the total $UF_A = 1$.”

These differences and other comparisons between EPA (2002) and TCEQ (2008) are shown below in Table 1.

Table 1. Comparison of the EPA (2002, IRIS) RfC and the TCEQ (2008) chronic ReV for 1,3-butadiene.

| Agency: | EPA (2002) | TCEQ (2008) |
|-----------------|---|--|
| Key study | NTP (1993) 2-yr mouse inhalation study | same |
| Critical Effect | Ovarian atrophy in B6C3F1 mice | same |
| NOAEL or LOAEL | LOAEL = 6.25 ppm, 6 hr/d, 5 d/wk | same |
| BMC | $BMC_{10} = 1.05 \text{ ppm (2320 } \mu\text{g/m}^3\text{)}^1$ | $BMC_{05} = 0.607 \text{ ppm (1341 } \mu\text{g/m}^3\text{)}$ |
| BMCL | $BMCL_{10} = 0.88 \text{ ppm (1945 } \mu\text{g/m}^3\text{)}^1$ | $BMCL_{05} = 0.462 \text{ ppm (1021 } \mu\text{g/m}^3\text{)}$ |
| Composite UF | 1000 | 30 |
| UF_H | 10 | 10 |
| UF_A | 3 ($UF_{A-TK} = 1$; $UF_{A-TD} = 3$) | 1 ($UF_{A-TK} = 0.3$; $UF_{A-TD} = 3$) |
| UF_L | 10^2 | 1^4 |
| UF_D | 3^3 | 3 (agreement with EPA (2002)) |
| Final benchmark | RfC = $2 \mu\text{g/m}^3$ | Chronic ReV = 15 ppb = $33 \mu\text{g/m}^3$ |

¹ $1 \text{ ppm} = 2.21 \text{ mg/m}^3 = 2210 \mu\text{g/m}^3$

² “An extrapolation factor for effect level is applied because the 10% response level used as a point of departure is an adverse effect level. Therefore, a factor analogous to

the LOAEL-to-NOAEL factor is needed to attempt to extrapolate to a level closer to a no effect level.” (EPA, 2002)

³ “Finally, a factor of 3 was used to reflect an incomplete database, in particular the absence of a multigeneration study and a developmental neurotoxicity study.” (EPA, 2002)

⁴ TCEQ utilized a $UF_L = 1$ because the BMC modeling was performed to determine a Point of Departure (POD) based on the $BMCL_{05}$, which is considered to be a conservative NOAEL surrogate (TCEQ, 2008).

It may be noted that TCEQ (2008) also derived a 24-hr ReV = 430 ppb (968 $\mu\text{g}/\text{m}^3$) based on a mouse developmental toxicity study. This value is 29 times higher than the chronic ReV of 33 $\mu\text{g}/\text{m}^3$.

Following this review of EPA (2002) and TCEQ (2008), AQD agrees with the commenter that TCEQ (2008) is a more appropriate basis for the ITSL. TCEQ (2008) performed more refined modeling of the low dose-response relationship to develop a surrogate no-effect level, and utilized the available data on interspecies differences to account for the relatively lower formation of the toxic metabolite in humans as compared to mice. AQD agrees with the TCEQ (2008) derivation of their ReV. AQD will be consistent with TCEQ (2008) by assigning an annual averaging time to this ITSL; the TCEQ (2008) 24-hr ReV is much higher and does not suggest and a shorter averaging time is appropriate or necessary for an ITSL of 33 $\mu\text{g}/\text{m}^3$.

References:

EPA. 2002. Integrated Risk Information System (IRIS database). 1,3-Butadiene. RfC last revised 11/5/2002.

Texas Commission on Environmental Quality (TCEQ). 2008. 1,3-Butadiene. Development Support Document. August 7, 2008.