**Michigan Department of Environmental Quality**

**Interoffice Communication**

TO: File for Benzene (CAS # 71-43-2)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

SUBJECT: Initial Threshold Screening Levels for Benzene (CAS # 71-43-2)

DATE: February 6, 2012

The acute initial threshold screening level (ITSL) for benzene (CAS # 71-43-2) is 30 µg/$m^3$ based on a 24-hour averaging time. This memo describes the basis and derivation of that acute ITSL. This acute ITSL is derived as a short-term exposure and will be used in conjunction with the chronic ITSL derived for benzene in 2003. The U.S. Environmental Protection Agency (EPA) has a chronic RfC of 30 µg/$m^3$ (EPA, 2003) and the chronic ITSL is identical to the RfC. EPA's RfC is based on the Rothman et al. (1996) human occupational exposure study, where decreased lymphocyte counts were observed. [BMCL (adj) = 8.2 mg/$m^3$. A $UF_T$ = 300 was applied by EPA (2003) to derive the RfC of 30 µg/$m^3$]. Further details of the derivation of that chronic RfC are provided in EPA (2003). The averaging time for the ITSL derived in 2003 for benzene will be changed from 24-hours to annual to ensure protection from long-term exposure and health risks in conjunction with the acute ITSL's protection from short-term peak exposures. Although it is unusual for AQD to adopt an acute and a chronic ITSL with the same value (30 ug/$m^3$) as in this case, doing so will provide better clarity of the protective levels on both an acute and a chronic basis, which will be helpful in various applications of the screening levels by AQD.

A review of other regulatory agencies' acute guidelines was conducted to help determine the acute (second) ITSL for benzene. These included: the California Environmental Protection Agency (Cal EPA) Reference Exposure Level (RELs); Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Level (MRLs); EPA's Acute Exposure Guideline Levels (AEGLs); American Industrial Hygiene Association (AIHA) Emergency Response Planning Guidelines (ERPGs); the Department of Energy (DOE) Temporary Emergency Exposure Limits (TEELs) now called Protective Action Criteria (PACs); the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values-Time-Weighted Average (TLV-TWAs), TLV-Short-Term Exposure Limit (TLV-STEL), and Biological Exposure Indices (BEIs); the National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Limits (RELs) and Immediately Dangerous to Life and Health Limits (IDLHs); and the Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PELs).

Cal EPA set an acute inhalation REL at 1,300 µg/$m^3$ for a 6-hour exposure based on reproductive and developmental toxicity. In the key study, Coate et al. (1984) exposed groups of 40 female Sprague-Dawley rats to 0, 1, 10, 40, and 100 ppm benzene for 6 hours/day during days 6-15 of gestation. Teratologic evaluations and fetotoxic

measurements were performed on the fetuses. A significant decrease was detected in the body weights of fetuses from dams exposed to 100 ppm benzene. No changes were observed in dams exposed to 100 ppm benzene. No effects were observed at the 40 ppm concentration. The 40 ppm concentration is considered a NOAEL for reduced fetal weight. An uncertainty factor of 100 was applied (10 for intraspecies and 10 for interspecies variation). The level protective against adverse developmental effects for benzene is therefore 0.4 ppm or 1.3 $mg/m^3$ (1,300 $\mu g/m^3$). Cal EPA also commented on two other studies: Kuna and Kapp (1981) on pregnant rats exposed 6 hours/day during gestation days 6-15 to concentrations of benzene up to 500 ppm, which reported a NOAEL of 10 ppm for developmental hematopoietic effects in rats; and, Svirbely et al., (1943) exposed mice 18/group for 7 hours to various benzene concentrations, where a NOAEL was determined at 4,980 ppm.

In other developmental studies, persistently altered fetal hematopoiesis occurred in mice at 20 ppm (Keller and Snyder 1986, 1988) (ATSDR, 2007). According to ATSDR, additional information is needed to assess the hematopoietic system of the developing fetus following low-level *in utero* exposures to benzene. "There are numerous studies in which animals have been exposed to benzene during pregnancy. None of these studies demonstrated that benzene was teratogenic even at levels that induced maternal and fetal toxicity." (ATSDR, 2007).

US EPA set an interim AEGL-1 value for benzene at 52 ppm ($2.0 \times 10^5$ $ug/m^3$) for a 1-hour exposure duration based on Srbova et al. (1950), which studied human volunteers reporting no subjective symptoms during exposure to benzene at 110 ppm for 2 hours. However no skin or eye exposure was involved in this study and clinical symptoms were not systematically investigated. Although the Srbova et al. (1950) study has some weaknesses (no details on all individual exposures and time durations, the lack of symptoms was reported by a single remark, no active investigation of health effects), the 110 ppm level for 2 hours was taken as a NOEL for CNS effects (NAS/COT, 2009). An uncertainty factor of 3 was used for intraspecies variability between groups in the population; for shorter durations, the equation $C^2 \times t = k$ was used. $(110 \text{ ppm})^2 \times 120 \text{ min} = 1{,}452{,}000 \text{ ppm}^2 = k$. For a 1-hour AEGL = $(k \times \text{min}/60 \text{ min})^{½}/3$. Inputting the number for above for k gives $(1{,}452{,}000 \text{ ppm} \times \text{min}/60 \text{ min})^{½}/3 = 52$ ppm. The Srbova et al. (1950) study level of exposure is indirectly supported by metabolism studies with humans in which substantial numbers of volunteers or workers were exposed. This level is also supported by historic knowledge on occupational exposure (NAS/COT, 2009). "An AEGL-1 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure." (NAS/COT, 2009). "AEGLs are intended to describe the risk to humans resulting from once-in-a lifetime, or rare, exposure to airborne chemicals. The National Advisory Committee for AEGLs is developing these guidelines to help both national and local authorities, as well as private companies, deal with emergencies involving spills, or other catastrophic exposures." (Hellwig, 2007). As such, these values are not meant to be used in evaluations to fully protect public health from potentially repeated exposures and are only used with caution to derive an acute ITSL on a case-by-case basis.

AIHA set an ERPG-1 value for benzene at 50 ppm ($2.0 \times 10^5$ $\mu g/m^3$). The odor threshold for benzene is 61 ppm, therefore odor should be detected near ERPG-1. An ERPG "is the maximum concentration in the air below which it is believed nearly all individuals

could be exposed for up to one hour without experiencing other than mild transient adverse health effects or perceiving a clearly defined objectionable odor." (http://www.atlintl.com/DOE/teels/teel/teeldef.html) As with the AEGL, ERPG values are not meant to be used in evaluations to fully protect public health from potentially repeated exposures and are only used with caution to derive an acute ITSL on a case-by-case basis.

The DOE set a TEEL-0 for benzene at 3 mg/m$^3$. "TEEL-0 is the threshold concentration below which most people will experience no appreciable risk of health effects." (http://www.hss.doe.gov/nuclearsafety/techstds/docs/handbook/DOE-HDBK-1046-2008.pdf). TEELs are recommended for a peak 15-minute time weighted average concentration. "TEELs are temporary limits for chemicals until AEGLs or ERPGs are developed, at which time the TEELs should no longer be used and the AEGLs or ERPGs should be used exclusively." (http://www.hss.doe.gov/nuclearsafety/techstds/docs/handbook/DOE-HDBK-1046-2008.pdf). Since there are developed AEGLs and ERPGs for benzene, TEELs will not be used to derive an acute ITSL for benzene.

ACGIH set a TLV-TWA of 1.6 mg/m$^3$ and a TLV-STEL at 8 mg/m$^3$ for benzene to minimize the potential for leukemongenesis caused by environmental exposures. "The TLV-TWA concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect." (ACGIH, 2010). A TLV-STEL is "a 15-minute TWA exposure that should not be exceeded at any time during a workday, even if the 8-hour TWA is within the TLV-TWA." (ACGIH, 2010). In the case of benzene, the TLV-STEL should not be exceeded "to protect against excess risk of leukemia due to the dose rate-dependent hematopoietic toxicity of benzene." (ACGIH, 2010). The TLVs are derived for workers who are typically healthy adults that are exposed during work hours and do not consider long-term exposures or their effects on susceptible subpopulations such as infants, children, the elderly, sensitive individuals, or those with illnesses. Therefore, TLVs may generally be divided by 100 to derive an acute ITSL that may be presumed to be protective of the general population including sensitive subgroups.

NIOSH set a REL of 0.319 mg/m$^3$ for benzene and a short-term (ST) REL of 3.19 mg/m$^3$. NIOSH RELs are time-weighted average concentrations for up to a 10-hour workday during a 40-hour workweek. An ST REL is a 15-minute time-weighted average exposure that should not be exceeded at any time during the workday. Benzene has been marked with a "Ca," which is used to designate a potential occupational carcinogen (http://www.brown.edu/Administration/EHS/resources/NPG/pgintrod.htm). As with the ACGIH TLVs above, these values are derived for workers and may be divided by 100 to be presumed to be protective for the general population including sensitive subgroups.

OSHA set a PEL of 1 ppm (3,190 ug/m$^3$) for benzene and a short-term (ST) PEL of 5 ppm (15,950 ug/m$^3$). The 8-hour PEL is the highest level of exposure an employee may be exposed to without incurring the risk of adverse health effects, while the ST PEL is averaged over any 15-minute period. As with the NIOSH RELs and ACGIH TLVs above, these values are for workers and may be divided by 100 to be presumed to be protective for the general population including sensitive subgroups.

ATSDR's acute-duration inhalation MRL is 0.009 ppm (approximately 30 ug/m$^3$, with one significant figure). It is based on Rozen et al. (1984): "male C57BL/6J mouse study (7-

8/group) were exposed to benzene (0, 10.2, 31, 100, or 301 ppm) in whole body inhalation chambers for 6 hours/day for 6 consecutive days. Control mice were exposed to filtered, conditioned air only. Erythrocyte counts were depressed in mice exposed at 100 and 301 ppm. The 10.2 ppm exposure level resulted in significant depression of femoral lipopolysaccharide-induced B-colony-forming ability in the absence of a significant depression of total numbers of B cells. At 31 ppm, splenic phytohemag-glutinin-induced blastogenesis was significantly depressed without a concomitant significant depression in numbers of T-lymphocytes. Peripheral lymphocyte counts were depressed at all exposure levels. These results demonstrate that short-term inhaled benzene exposure even at low exposure concentrations can alter certain immune associated processes." (ATSDR, 2007) ATSDR used the lowest observed adverse effect level (LOAEL) of 10.2 ppm for reduced lymphocyte proliferation following mitogen stimulation in mice and adjusted from intermittent to continuous exposure by multiplying the LOAEL by 6 hours/24 hours to correct for less than a full day of exposure. The adjusted LOAEL = 2.55 ppm. Benzene is a category 3 gas and after dosimetrically adjusting the LOAEL to a human equivalent concentration according to the EPA (1994) methodology, the resulting LOAEL remained at 2.55 ppm. ATSDR used an uncertainty factor of 300 (consisting of 10 for use of a LOAEL instead of a NOAEL, 3 for animal to human extrapolation using dosimetric conversion, and 10 for human variability). The resulting acute inhalation minimal risk level = 0.009 ppm (30 ug/$m^3$). ATSDR states that acute MRLs are applicable to exposure of 14 days or less. The most appropriate and practical averaging time for AQD to assign to an acute MRL value is 24 hours.

The acute inhalation MRL from ATSDR was adopted as the acute ITSL (30 ug/$m^3$, 24-hr AT) because it is recently derived, it is well documented and justified, and it provides an appropriate level of protection. Table 1 provides a useful comparison of this and other acute benchmarks discussed above, and the associated candidate acute ITSLs.

Table 1. Benzene acute toxicity benchmarks and candidate acute ITSLs.

| Available benchmark type | Value (ug/$m^3$) | Candidate acute ITSL (in descending order) | Candidate ITSL AT |
|---|---|---|---|
| AEGL-1 | 200,000 | 200,000 | 1 hour |
| CalEPA acute REL | 1,300 | 1,300 | 6 hour |
| OSHA ST PEL | 15,950 | PEL/100= 160 | 1 hour |
| ACGIH TLV-STEL | 8,000 | TLV/100= 80 | 1 hour |
| OSHA PEL and NIOSH ST-REL | 3,190 | PEL and REL/100= 32 | 8 hour |
| ATSDR acute MRL | 30 | 30 | 24 hour |
| ACGIH TLV-TWA | 1,600 | TLV/100= 16 | 8 hour |
| NIOSH REL | 319 | REL/100= 3.2 | 8 hour |

Benzene concentrations in ppm were converted to µg/$m^3$ using equation 4-1b on page 4-20 in EPA (1994) with the assumptions that the testing was performed at 25°C and 760 mmHg, and that 1 g-mole of a perfect gas occupies 24.45 L.

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

The molecular weight of benzene is 78.1 g/mol. Using the equation above:

$$mg/m^3 = \frac{0.009\,ppm \times 78.1\,{}^{g}/_{mol}}{24.45} = 0.028748466\,{}^{mg}/_{m^3} = 28.75\,{}^{\mu g}/_{m^3}$$

After rounding to one significant figure, the acute (second) ITSL is 30 µg/m$^3$ with a 24-hour averaging time.

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