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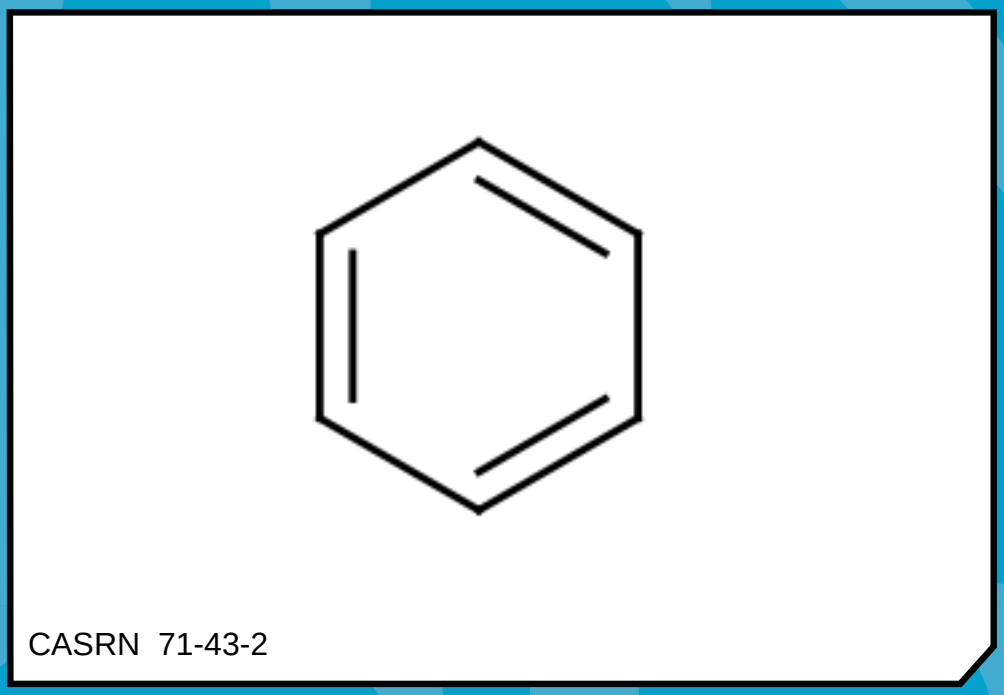
# Chemical-Specific Reference Values for Benzene (CASRN 71-43-2)



CASRN 71-43-2

National Center for Environmental Assessment
Office of Research and Development

U.S. Environmental Protection Agency
Research Triangle Park, NC

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## Overview

The reader is strongly encouraged to read Section 1 of the following report for critical background information regarding the health effect reference values discussed in this summary: *Graphical Arrays of Chemical-Specific Health Effect Reference Values for Inhalation Exposures [Final Report]* (U.S. EPA, 2009). This report is available on-line at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=211003.

In general, inhalation health effect reference values have been included which have been developed and formally reviewed by an authoritative governing body (government agency or professional association) for use in assessments of risk to support regulatory decision-making. This is a review of existing reference values, including the basis for each of the reference values as provided in the available technical support documents for those values, along with some basic contextual references; this is not a comprehensive review of the health effects literature for benzene.

*General Properties*

Benzene ($C_6H_6$; MW = 78.11) is a clear colorless liquid with a characteristic sweet odor at low concentrations, and is disagreeable and irritating at high levels (Cavender, 1994). Benzene is known by a large number of synonyms (annulene, coal naphtha, cyclohexatriene, fenzen [Czech], mineral naphtha, motor benzol, NCI-C55276, phene, phenyl hydride, pyrobenzol, pyrobenzole) and by the registered trade name Polystream. Benzene readily becomes a vapor (Vapor Pressure = 94.8 mm Hg at 25 degrees Celsius), and the vapor is denser than air (Vapor Density = 2.8; air = 1). Benzene is moderately soluble in water but tends to partition into organic solvents [Octanol/Water Partition Coefficient (log Kow) = 2.13] and fatty tissues once absorbed by the body (NLM, 1998).

*Production and Uses*

Benzene is industrially the most important of the so-called BTEX aromatics (benzene, toluene, ethylbenzene, and xylene). In industrial chemistry, benzene forms the basis for a great variety of aromatic intermediates and for the group of cycloaliphatic compounds. Benzene is used as the basis for the manufacture of plastics, synthetic rubber, dyestuffs, resins, raw materials for detergents, and plant protection agents, and is used extensively as a solvent. Global benzene consumption in 2010 was 40,000 tons (i.e., 80 billion pounds) (http://www.chemsystems.com/about/cs/news/items/PPE%20PCMD%20Aromatics%202011.cfm, accessed 28 June 2012).

*Exposure Potential*

Benzene has historically been a major component in gasoline, but the percent benzene content in gasoline has been declining due to regulatory pressure. In 2007, the average benzene content in gasoline was 1.06% (by volume) and it is expected to be reduced to 0.62 vol% by 2015 (U.S. EPA, 2010a). The Toxics Release Inventory for 2010 (U.S. EPA, 2010b) reported 3,909,186 pounds of benzene were emitted to air from all industrial sources in the United States, with 2,362,313 pounds emitted from point sources (stacks, vents, ducts, or pipes) and 1,546,872

pounds coming from fugitive sources (equipment leaks, evaporative losses from surface impoundments and spills, and releases from building ventilation systems). Ambient air concentrations in the United States have been reported to range from 1.4 ppb (4.5 µg/m$^3$) in remote rural areas, with concentrations up to 34 ppb (109 µg/m$^3$) near industrial facilities and roadways, and up to 32 ppm (102 mg/m$^3$) near service stations (NLM, 1998). Benzene is also present in tobacco smoke and has been detected in the expired air of smokers (Cavender, 1994).

*Potential Health Effects*

Benzene is responsible for various toxicity effects including central nervous system (CNS) depression, eye and airway irritation, general developmental toxicity, genotoxicity, and bone marrow toxicity which may result in carcinogenesis (leukemia).

*Cancer Potential*

*Benzene is classified as a "known" human carcinogen (Category A) under the Risk Assessment Guidelines of 1986* (U.S. EPA, 2000). Under the revised Carcinogen Risk Assessment Guidelines (U.S. EPA, 2005), benzene is characterized as a known human carcinogen for all routes of exposure based upon convincing epidemiologic evidence of a causal association between human exposure and cancer, as well as supporting evidence from animal studies. The International Agency for Research on Carcinogens (IARC, 1998) found that "*There is sufficient evidence that benzene is carcinogenic to man.*"

*Consideration of Peak versus Continuous Exposure*

It is important to note that rather than cumulative exposures to low concentrations, it is repeated peak benzene exposures which have been deemed determinative of bone marrow toxicity with a greater potential for leukemia. This was noted in the documentation for the Threshold Limit Value Short-term Exposure Limit (TLV-STEL) developed by the American Conference of Governmental Industrial Hygienists (ACGIH, 2007), where it states: "*A TLV–STEL of 2.5 ppm is recommended to protect against excess risk of leukemia due to the dose-rate-dependent hematopoietic toxicity of benzene"* (Schnatter et al., 1996). The dose-rate dependent toxicity of benzene indicates that peak exposures may be of greatest concern; however, ACGIH also states that cumulative exposures over time must still be considered and also lowered the TLV-TWA from 1.0 ppm to 0.5 ppm.

The consideration of peak exposures is important when attempting to compare the emergency response reference values to the short-term occupational exposure limits (OELs), and to the acute, non-emergency reference values for the general public. Acute Exposure Guideline Level (AEGL) and Emergency Response Planning Guideline (ERPG) values are developed under an assumption of once-in-a-lifetime exposure potential[1]. OELs are developed for protection of an assumed healthy population of working-age adults, with a higher workplace exposure level assumed during the work day, along with intermittent peak exposure events. Both the short-term OELs and the acute general public reference values include consideration of the

[1] *"… [occupational exposure] limits are not easily or directly translated into emergency exposure limits for exposures at high levels but of short duration, usually less than 1 hr, and only once in a lifetime for the general population, which includes infants, children, the elderly, and persons with diseases, such as asthma, heart disease, or lung disease."* (From NRC (2001, 192042), Standing Operating Procedures for Developing Acute Exposure Guideline Levels, Page 2.)

potential for events to occur more frequently than once-in-a-lifetime in their derivation, and in the case of OELs, include provision for occurrence on a more regular basis.[2]

**Emergency Response Values**

The emergency response values for toluene include interim Acute Exposure Guideline Level (AEGL) values and final Emergency Response Planning Guideline (ERPG) values for all three severity levels (1 = mild, transient effects; 2 = irreversible effects or impeding ability to escape; and 3 = threshold for life threatening effects).

The Technical Support Document for the benzene AEGL (NAC/AEGL, 2009) cites effects on the CNS for both the AEGL-1 and AEGL-2. Developmental effects for the AEGL-2 were not considered because: *"The developmental toxicity effects of benzene are considered to be induced by repeated exposure and it is not likely that the same extent of effects will be induced by a single exposure. Therefore, developmental toxicity will not be used for AEGL-2."* This underscores the "once-in-a-lifetime" nature of the AEGLs and how effects appropriate for the derivation of the AEGL values for benzene included that consideration.

The AEGL-3 for benzene was based on the *"Highest reliable level without mortality observed in rats (5940 ppm for 4h)"* from the study of Molnar (1986). The final AEGL-3 values were derived with application of a total uncertainty factor of 3 (no interspecies differences were anticipated[3] and a factor of 3 was applied because *"experience with anesthetic gases have shown that the variability between groups in the population does not vary by more than a factor 2-3"*); duration extrapolation was accomplished using the $C^n \times t$ equation with n=2 for shorter and n=1 for longer durations. The ERPG-3 for benzene was established based on 10% of the rodent LC50, with no other adjustments as noted in the ERPG documentation (AIHA, 2002), where it states: *"Exposure to benzene concentrations greater than 1000 ppm have been tolerated."*

**Occupational Exposure Limits (OELs)**

Although ACGIH makes the point that peak exposures are critical for benzene toxicity in setting the TLV-STEL (as stated earlier), it also notes that cumulative exposure over time must still be considered and notes: *"…that exposure for a working lifetime at the current OSHA PEL of 1 ppm, equivalent by this metric to 45 ppm-years, results in an unacceptable risk of leukemia"* and lowered the TLV-TWA from 1.0 ppm to 0.5 ppm.

The NIOSH Occupational Safety and Health Guideline for Benzene *"recommends that benzene be controlled and handled as a potential human carcinogen in the workplace and that exposure be reduced to the lowest feasible limit"* and further states that the "*NIOSH REL [of 0.1 ppm] is the lowest concentration detectable by current NIOSH-validated sampling and analytical methods"* (NIOSH, 1988). More recently developed analytical methods have

[2] The ACGIH (2006) definition of a TLV-STEL states that *"Exposures above the TLV-TWA up to the TLV-STEL should be less than 15 minutes, should occur no more than four times per day, and there should be at least 60 minutes between successive exposures in this range."*

[3] From the Benzene AEGL TSD (NAC/AEGL, 2009): *"Because the mortality of benzene is caused by severe CNS depression (paralysis of the respiratory center), this effect is correlated to the benzene level in the brain lipid fraction ... This concentration will be related directly to a build-up of benzene in the tissue, which is directly related to the inhalation rate ... Therefore, it is expected that humans require higher external concentrations compared to rodents, to obtain a similar level of benzene in the blood or brain as is observed also for other VOC's (trichloroethylene, toluene)… For this reason, an interspecies uncertainty factor of 1 is used."*

significantly greater sensitivity (NIOSH, 2003). In 1986 NIOSH used a cancer risk assessment to derive a health-based NIOSH-REL (TWA) of 0.1 ppm. This corresponded to a cancer risk of 1:1000 for workers exposed to 0.1 ppm for a working lifetime (NIOSH, 1990, 1986). Nonetheless, the NIOSH REL is less than an order of magnitude lower than the more recently adopted TLV-TWA of 0.5 ppm (ACGIH, 2007).

A subset of OELs applicable only to workers in specific industries are mentioned here but are not included in the following graphical array of reference values for benzene, nor in the table showing details on value derivation. Appendix F of the NIOSH Pocket Guide (NIOSH, 2007) states:
*"The final OSHA Benzene standard in 1910.1028 applies to all occupational exposures to benzene except some subsegments of industry where exposures are consistently under the action level (i.e., distribution and sales of fuels, sealed containers and pipelines, coke production, oil and gas drilling and production, natural gas processing, and the percentage exclusion for liquid mixtures); for the excepted subsegments, the benzene limits in Table Z-2 apply (i.e., an 8-hour TWA of 10 ppm, an acceptable ceiling of 25 ppm, and 50 ppm for a maximum duration of 10 minutes as an acceptable maximum peak above the acceptable ceiling)."*
The related OSHA statute (Table Z-2) is cited in 29 CFR 1910.1028 and is available online at http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_id=10042&p_table=STANDARDS.

*Special Use Occupational Values*

In addition to the standard occupational values, a set of special use occupational values are also available for benzene which were developed by and/or reviewed by the National Research Council (NRC): Spacecraft Maximum Acceptable Concentrations (SMACs) for durations of 1 and 24 hours, and 7, 30, 180, and 1000 days; and values derived for submarine crews – the Emergency Exposure Guideline Levels (EEGLs) for 1 and 24 hours, and the Continuous Exposure Guideline Levels (CEGL) for 90 days. The EEGL values [40 ppm (12.8 $mg/m^3$) for 1-hour and 3 ppm (9.6 $mg/m^3$) for 24-hours] and the CEGL values [0.2 ppm (0.64 $mg/m^3$) for 90 days) are fairly consistent with the AEGL-1 and traditional occupational TWA values. Largely due to the confined working environment with no opportunity to be removed from exposure, the 180 and 1000 day SMACs are lower than other occupational reference values for similar durations. The SMACs for durations of 7-days or longer were based on concerns for potential narcosis and neurotoxic effects, including hearing loss (ototoxicity) for the values.

## General Public Values (Routine Non-emergency Exposures)

Values for the general public include California Reference Exposure Levels (CA-RELs, developed by the Office of Environmental and Hazard Assessment – OEHHA) for both acute (6 hours and shorter) and chronic (lifetime) durations; Minimal Risk Levels (MRLs) developed by the Agency for Toxic Substances and Disease Registry (ATSDR) for chronic exposures (periods longer than 1 year), intermediate durations of 15-364 days, and for durations of 1-14 days; and a chronic Reference Concentration (RfC) developed by the U.S. Environmental Protection Agency (EPA) for the Integrated Risk Information System (IRIS) database.

The Acute CA-REL for benzene used developmental effects as the basis for derivation, in contrast to the derivation of the AEGL-2 values noted earlier. The Acute CA-REL did not, however, apply any duration extrapolation, and therefore is stated as a 6-hour value instead of

the more commonly reported 1-hour value for acute CA-RELs. The California Office of Environmental Health Hazard Assessment does not consider duration extrapolation for developmental toxicants but instead considers the derived values as "not to exceed" at any time, as noted in Section 4.4.6.3 (page 55 et seq.) of their Technical Support Document for the Derivation of Noncancer Reference Exposure Levels (OEHHA, 2008b). Therefore, although the Acute CA-REL for benzene is a 6-hour value, it is also applicable to shorter durations (e.g., 1-hour). It is also important to note that the Acute CA-REL for benzene was derived for "severe effects" because there were no good data upon which to derive a value for mild effects.

Most of the other general public health values (EPA Reference Concentration [RfC], Chronic ATSDR MRLs, and Chronic CA-REL) were based on effects on the blood forming capabilities of bone marrow, as shown in Table 1. The Acute and Intermediate ATSDR MRLs, were based on decreases in immunological function related to white blood cell formation, and hence also related to bone marrow toxicity.

An Inhalation Unit Risk (IUR) estimate was developed for cancer potential over the range of $2.2 \times 10^{-6}$ to $7.8 \times 10^{-6}$ for an increase in the risk for an individual who is exposed for a lifetime to 1 µg/m$^3$ benzene in air (U.S. EPA, 2000). From those IUR risk values, the exposure levels resulting in a 1:1,000,000 (one in a million) risk of cancer range from 0.13 to 0.45 µg/m$^3$ (0.00013 to 0.00045 mg/m$^3$), and exposure levels of 13 to 45 µg/m$^3$ (0.013 to 0.045 mg/m$^3$) result in a 1:10,000 risk range for cancer. In comparison, the exposure levels predictive of potential increases in cancer incidence at the one in one million risk range are well below the range of reference values for noncancer effects; however, exposures near the chronic RfC (0.03 mg/m$^3$) are within the range of exposures predictive for an increased risk potential of one in 10,000 for leukemia. The exposure levels associated with those cancer risk levels are shown in Figure 1 as ranges but are not covered in more detail in Table 1. This information is provided for the reader to consider the balance of risks between both cancer and noncancer effects.

**Summary**

As noted earlier, effects on the blood forming capacity of bone marrow have been identified as precursor events for leukemia. Therefore the majority of chronic reference values for the general public and for workers are based on those effects. The organizations developing the occupational also considered the potential for leukemia in their derivation of short-term and ceiling values for workers. This concern is founded on the previous discussion on *Consideration of Peak versus Continuous Exposure* presented earlier in this document. The effects on the CNS are the key driver for the emergency response reference values; the application of a once-in-a-lifetime exposure scenario in the development of those values diminishes the concern for the potential development of cancer.

*Comparisons among Acute Reference Values in Risk Screening*

Risks from acute exposures which may occur on a intermittent basis (i.e., more commonly than the once-in-a-lifetime scenario used with the emergency response values) are most appropriately addressed by values designed for that purpose – namely, the acute California RELs and the acute ATSDR MRLs. Emergency response values (such as the AEGLs and ERPGs) are designed for rare, once-in-a-lifetime accidental releases; however, the one-hour AEGL-1 and/or ERPG-1 is often used in screening assessments when no other value is available, or as a "back-stop" value when a preferred screening reference value is exceeded to help identify

a level where effects may be "expected" in the exposed population. Occupational exposure levels (OELs) are not typically used in characterizing public health risks. Occupational ceiling values (typically 15 minutes or less) are commonly set at levels higher than a one-hour AEGL-1 or ERPG-1 for most chemicals, and are not considered protective for the general public.

In the case of benzene, however, the emergency response reference values (AEGLs and ERPGs) have been established at concentrations that are much higher than the short-term occupational exposure levels (OELs), with the one-hour ERPG-1 (50 ppm; 156 mg/m$^3$) and AEGL-1 (52 ppm; 170 mg/m$^3$) values ten times higher than the highest short-term OEL – the 15-minute OSHA Ceiling value (5 ppm; 15.6 mg/m$^3$). The ACGIH TLV® ceiling value of 2.5 ppm (8.0 mg/m$^3$) is designed as "*not to be exceeded at any time*" (ACGIH, 2006). The NIOSH REL-Short-term Exposure Limit of 1.0 ppm (3.2 mg/m$^3$) is applicable "*for any 15 minute period in a work day*" (NIOSH, 2007). This information calls into question the appropriateness of the one-hour AEGL-1 or ERPG-1 values for benzene in screening risks for the general population beyond the once-in-a-lifetime exposure scenarios for which they were designed.

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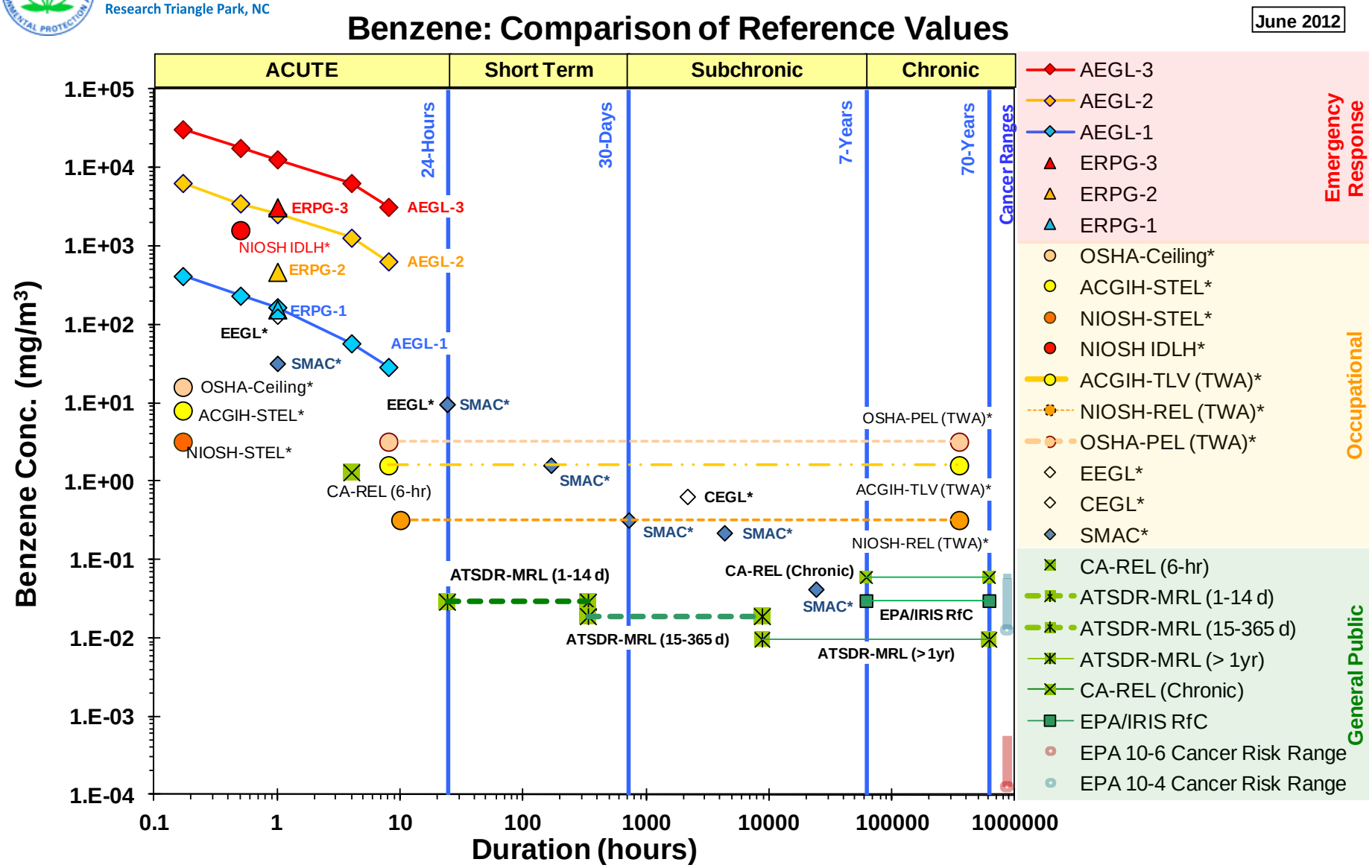


* Indicates an occupational value; expert judgment necessary prior to applying these values to the general public.

**Figure 1. Available health effect reference values for inhalation exposure to benzene**

**Table 1. Details on derivation of the available health effect reference values for inhalation exposure to benzene**

| | Reference Value Name | Duration | Reference Value ($mg/m^3$) | Reference Value (ppm) | Health Effect | Point of Departure | Qualifier | Principal Study | Uncertainty Factors[4] | Notes on Derivation | Review Status |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Emergency Response | **AEGL-3** | 10 minutes<br>30 minutes<br>1 hour<br>4 hours<br>8 hours | 31,000<br>18,000<br>13,000<br>6500<br>3300 | 9700<br>5600<br>4000<br>2000<br>990 | Highest dose without mortality within the AEGL time frame – rats, 4-h exposure. | 5940 ppm | NOAEL | (Molnar et al., 1986) | Total UF = 3<br>$UF_A$ = 1<br>$UF_H$ = 3 | Duration adjustments: $C^n$ x t = k, where n = 2 for shorter and n = 1 for longer durations | Interim (NAC/AEGL, 2009) |
| | **AEGL-2** | 10 minutes<br>30 minutes<br>1 hour<br>4 hours<br>8 hours | 6500<br>3600<br>2600<br>1300<br>650 | 2000<br>1100<br>800<br>400<br>200 | Increase in locomotor activity with some incoordination and tremor – rats, 4-h exposure. | 4000 ppm | LOAEL | (Molnar et al., 1986) | Total UF = 10<br>$UF_A$ = 3<br>$UF_H$ = 3 | | |
| | **AEGL-1** | 10 minutes<br>30 minutes<br>1 hour<br>4 hours<br>8 hours | 420<br>240<br>170<br>58<br>29 | 130<br>73<br>52<br>18<br>9.0 | No report of symptoms in humans exposed up to 2 hours via inhalation only | 110 ppm | NOAEL | (Srbova et al., 1950) | Total UF = 3<br>$UF_A$ = 1<br>$UF_H$ = 3 | | |
| | **ERPG-3** | 1 hour | 3190 | 1000 | Lethality in mice<br><br>Observed occupational levels | 10,000 ppm<br><br>1000 ppm | $LC_{50}$<br><br>Estimated NOAEL for Level 3 effects | (Drew and Fouts, 1974) | NR | Note: ~10x reduction from $LC_{50}$ to derived value | Final (AIHA, 2002) |
| | **ERPG-2** | 1 hour | 470 | 150 | 5 hr exposure; headaches, lassitude, and general weakness | 150 ppm | Estimated NOAEL for Level 2 effects | (Greenburg, 1926) | NR | | |
| | **ERPG-1** | 1 hour | 156 | 50 | Transient neurological effects expected.<br>Mean threshold for odor detection | 50 ppm<br><br>61 ppm | Estimated LOAEL<br><br>Odor threshold | (Gerarde, 1960)<br>(Greenburg, 1926) | NR | | |

[4] $UF_H$ – inter-human variability; $UF_A$ – animal to human variability; $UF_L$ – LOAEL to NOAEL adjustment; $UF_S$ – subchronic to chronic adjustment; $UF_{DB}$ – database uncertainty

| | Reference Value Name | Duration | Reference Value ($mg/m^3$) | Reference Value (ppm) | Health Effect | Point of Departure | Qualifier | Principal Study | Uncertainty Factors[4] | Notes on Derivation | Review Status |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Occupational** | **ACGIH TLV-STEL** | Any | 8.0 | 2.5 | Peak exposures causing hematopoietic toxicity | 20 - 25 ppm | LOAEL | (Schnatter et al., 1996) | NR | Note: ~10x reduction from LOAEL | Final (ACGIH, 2007) |
| | **OSHA-Ceiling** | < 15 minutes | 16 | 5.0 | NR | NR | NR | | NR | | Final (NIOSH, 2007) |
| | **NIOSH STEL** | < 15 minutes | 3.2 | 1.0 | NR | NR | NR | | NR | | |
| | **NIOSH IDLH** | 30 minutes | 1600 | 500 | Acute inhalation toxicity data in humans; Potential carcinogen | 500 ppm | LOAEL | (Gerarde, 1960) (NIOSH, 1996) | NR | | |
| | **ACGIH TLV-TWA** | 8 hour TWA | 1.6 | 0.5 | Committee interpretation of 3 papers analyzing cumulative exposure (ppm-year) – Pliofilm cohort | 45 ppm-years (1 ppm for 45 years) | Judged to be an unaccept-able risk | (Schnatter et al., 1996) | NR | Assumed WOE approach. | Final (ACGIH, 2007) |
| | **NIOSH REL (TWA)** | 10 hour TWA | 0.32 | 0.1 | Potential carcinogen; lowest current detectable level | NR | NR | (NIOSH, 1988) | NR | | Final (NIOSH, 2007) |
| | **OSHA PEL (TWA)** | 8 hour TWA | 3.2 | 1.0 | NR | NR | NR | | NR | | |
| | **EEGLs** | 1 hour | 128 | 40 | CNS Depression in humans | 110 ppm | NOAEL | Srbova et al. (1950) | Total UF = 3 $UF_H$ = 3 | Rounded from 37 to 40 ppm | Final (NRC, 2008a) |
| | | 24 hour | 96 | 3.0 | Immunosuppression and hematologic effects in mice | 100 ppm | LOAEL | Gill et al. (1980) | Total UF = 30 $UF_L$ = 3 $UF_A$ = 3 $UF_H$ = 3 | Rounded from 3.3 to 3 ppm | |
| | **CEGL** | 90 day | 0.64 | 0.2 | | | | | | | |
| | **SMACs** | 1 hour | 32 | 10 | | | | | | | Final (NRC, 2008b) |
| | | 24 hour | 96 | 3.0 | | | | | | | |
| | | 7 day | 1.6 | 0.5 | | | | | | | |
| | | 30 day | 0.32 | 0.1 | | | | | | | |
| | | 180 day | 0.22 | 0.07 | | | | | | | |
| | | 1000 day | 0.042 | 0.013 | | | | | | | |

| | Reference Value Name | Duration | Reference Value ($mg/m^3$) | Reference Value (ppm) | Health Effect | Point of Departure | Qualifier | Principal Study | Uncertainty Factors[4] | Notes on Derivation | Review Status |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **General Public** | **Acute CA-REL (Severe Effects)** | 6 hour | 1.3 | 0.4 | Decreased fetal body weights of pregnant female rats exposed 6-h/d, GD 6-15 | 40 ppm | NOAEL | (Coate et al., 1984) | Total UF = 100<br>$UF_A$ = 10<br>$UF_H$ = 10 | No time extrapolation | Final (OEHHA, 2008a) |
| | **Acute ATSDR MRL** | 1 -14 days | 0.029 | 0.009 | Immunological effects in exposed mice (6-h/d, 6 days) | 10.2 ppm<br>2.55 ppm | LOAEL<br>$LOAEL_{HEC}$ | (Rozen et al., 1984) | Total UF = 300<br>$UF_L$ = 10<br>$UF_A$ = 3<br>$UF_H$ = 10 | Adjustment: (6-h/24-h) | Final (ATSDR, 2007) |
| | **Intermediate ATSDR MRL** | 15 – 364 days | 0.019 | 0.006 | Immunological suppression effects in rats | 10 ppm<br>1.8 ppm | LOAEL<br>$LOAEL_{HEC}$ | (Rosenthal and Snyder, 1987) | Total UF = 300<br>$UF_L$ = 10<br>$UF_A$ = 3<br>$UF_H$ = 10 | Duration adjusted: (6-h/24-h) × (5-d/7-d) | |
| | **Chronic CA-REL** | Chronic | 0.06 | 0.02 | Hematological effects for workers with an average exposure of 7.4 years (32% exposed for more than 10 years) | 0.53 ppm<br>0.19 ppm | NOAEL<br>$NOAEL_{HEC}$ | (Tsai et al., 1983) | Total UF = 10<br>$UF_H$ = 10 | Adjustments: occupational breathing rate ($10m^3$ vs. $20m^3$) and 5 days per week. | Final (OEHHA, 2008a) |
| | **Chronic ATSDR MRL** | Chronic (> 1 year) | 0.0096 | 0.003 | B cell counts in workers of shoe manufacturing industries in Tianjin, China | 0.10 ppm<br>0.03 ppm | $BMCL_{0.25sd}$<br>$BMCL_{ADJ}$ | (Lan et al., 2004) | Total UF = 10<br>$UF_H$ = 10 | Duration adjusted: (8-h/24-h) × (6-d/7-d) | Final (ATSDR, 2007) |
| | **Chronic RfC (IRIS)** | Chronic | 0.03 | 0.0094 | Decreased lymphocyte count (Human occupational inhalation study, 8-hr TWA) | 23 $mg/m^3$<br>8.2 $mg/m^3$ | BMCL<br>$BMCL_{HEC}$ | (Rothman et al., 1996) | Total UF = 300<br>$UF_L$ = 3<br>$UF_S$ = 3<br>$UF_H$ = 10<br>$UF_{DB}$ = 3 | Adjustments: occupational breathing rate ($10m^3$ vs. $20m^3$) and 5 days per week. | (U.S. EPA, 2002) |

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