Supplemental Material

Development of a data visualization platform that uses evidence-based recommendations of short-term guidelines for ambient air levels of benzene during disaster response

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Development of Short-Term Reference Values for Benzene

Benzene health effects through inhalation

Benzene is a well-studied, aromatic hydrocarbon and known human carcinogen [1]. Aplastic anemia and pancytopenia in humans from inhalation exposure to benzene has been studied since the 19th century [2]. The primary route of exposure to benzene by humans in the workplace and the environment is through inhalation. Once inhaled, approximately half of the benzene is absorbed and metabolized primarily in the liver and the lung, with secondary metabolism in the bone marrow [3, 4]. Benzene toxicity occurs through its metabolites with hematopoietic progenitor cells and bone marrow stromal cells as the primary targets of these metabolites [5]. Changes in hematopoiesis and hematotoxic effects, including altered blood cell counts and lymphocyte counts and immunotoxicity, are consistent indicators of benzene effect following exposures [2-4]. Cumulative exposure to benzene can lead to myelodysplastic syndrome and the hematotoxicity associated with benzene exposure carries a future risk of hematological cancers [1].

A review of the existing health-based guidance values [6-8] shows that the literature evaluated to support benzene acute toxicity guidelines are dominated by several studies in mouse models that report hematotoxic and immunotoxic effects in response to subacute exposures to benzene. These are summarized in Table S1. Even though not all these studies were used as key or supporting studies, they are briefly summarized here. The lowest observed adverse effect levels (LOAELs) catalogued by regulatory agencies range from 10.2 ppm to 103 ppm. The highest LOAELs for benzene reported reduced lymphocytes in response to exposures of 100 and 200 ppm of benzene in B6C3F$_1$ mice [9]. Similarly, reduced granulocytes, lymphocytes, and marrow cellularity were reported in response to inhalation exposure of 103 ppm of benzene for 6 hours/day for 7 days in male CD-1 mice [10]. Mid-range LOAELS were associated with reductions in both T- and B-lymphocytes and reduced resistance to Listeria monocytogenes following exposure to 30 ppm of benzene for 6 hours/day for 6 days in C57BL/6 mice [11], reductions in leukocytes in mice after exposure to 50 ppm of benzene for 14 days [12], or reduction in lymphocytes after exposure to 25 ppm of benzene for 2 weeks [13]. Exposure to 21 ppm of benzene for 2 weeks resulted in increased micronucleated polychromatic erythrocytes and decreased granulopoietic stem cells [14]. Rozen reported reduced peripheral lymphocytes and B-lymphocyte proliferation in mice when exposed to 10 ppm of benzene for 6 hours/day for 1 to 12 days [15]. Researchers found decreased erythroid progenitor cell colony forming units in response to 10ppm of benzene for 6 hours/day for 5 days in adult mice [16] as well in response to 10 ppm of benzene for 6 hours/day for 6-15 days [17].

Table S1. Summary of literature that were used to derive or support existing health-based guidance values by TCEQ, OEHHA and ATSDR

Author	Year	Mouse Strain	Duration	NOAEL	LOAEL	Response at LOAEL
Green et al. [10]	1981	CD-1 (male)	6h/d x 5d	9.9	103	granulocytopenia, lymphocytopenia, and decreased marrow cellularity and polymorphonucleucytes
Toft et al. [14]	1982	NMRI (male)	8h/d x 5d/wk x 2wk	10.5	21	increased micronucleated polychromatic erythrocytes and decreased granulopoietic stem cells
Rozen et al. [15]	1984	C57BL/6J (male)	6h/d x 6d	-	10.2	depressed blood lymphocytes, depressed mitogen-induced blastogenesis of femoral B-lymphocytes
Rosenthal & Snyder [11]	1985	C57BL/6 (male)	6h/dx 1-12d	10	30	T- and B-lymphocyte depression and increased *Listeria monocytogenes* infection bacterial counts
Cronkite et al. [13]	1985	C57B1/6B NL	6h/d x 5d/wk x 2wk	10	25	lymphopenia
Aoyama [12]	1986	BALB/c	14d	-	50	reduced blood leukocyte count
Dempster & Snyder [16]	1991	DBA/2J (male)	6h/d*5d	-	10.3	decreased erythroid progenitor cell colony forming units
Corti & Snyder [17]	1996	Swiss Webster (male)	6h/d*6-15gd	-	10.2	decreased erythroid progenitor cell colony forming units
Farris et al. [9]	1997	B6C3F1/ CrlBR	6h/d x 5d/wk x 1-8wk	10	100	lymphopenia and other blood effects

Studies conducted by Kim et al. [18, 19] and Rappaport et al. [20] indicate there are potentially two metabolic pathways with the higher affinity pathway demonstrating supralinear metabolic production at low concentrations of benzene. The exposure-response curve has been debated [3, 21]; however, as noted by Smith [21], EPA cited studies showing supralinear benzene-related protein adducts at concentrations less than 1 ppm to lower benzene content in gasoline. Higher-affinity metabolic pathways at low benzene exposure suggests that previous risk assessments may have underestimated risk at low benzene concentrations [21, 22].

Review of protocols and literature update

To understand how existing benzene guidance values have been established, Texas Commission on Environmental Quality [TCEQ] and the California Office of Environmental Health Hazard Assessment [OEHHA], guidelines to develop risk assessments and the risk assessment support documents for benzene exposure guidelines were reviewed [2, 3, 6-8, 23]. Key and supporting

studies used by each agency to develop exiting exposure guidelines were also reviewed. These supporting studies are all more than 20 years old, thus new literature was reviewed to determine if changes in regulatory limits are justified. A literature review was conducted using systematic methodologies to identify new studies that may play a role in improving our current understanding of benzene toxicity and exposure-response relationships.

Review of recent toxicological literature on short-term effects of benzene exposure

A comprehensive literature search was performed to identify studies that measured short-term effects of benzene exposure through inhalation. Search logic was developed from key terms that were used in combination to identify potentially relevant studies (Table S2).

A list of seed studies was developed to test how well the search terms identified seminal research. The seed studies were compiled using key studies, supporting studies and seminal background studies used by the regulatory agencies to derive current benzene guidance documents for acute and chronic noncancer adverse effects. The full list of 17 studies is provided in Table S3.

The search logic described in Table S2 identified 16 of the 17 seed studies. The one missing study, Toft et al. 1982, was one of the oldest citations to be considered for a seed-study. It is possible that this citation was mis-indexed when converted to electronic format because search terms included in the logic are found in the abstract. Despite this missing citation, it was determined that the search logic was appropriate to query the literature for relevant studies on acute exposure effects for benzene. Searches were conducted electronically using Web of Science and PubMed for publications dated January 1, 2010 to February 13, 2020.

Table S2. Search logic for identifying new studies that measured short-term effects of benzene exposure through inhalation

Database	**Search Logic**
PubMed	((benzene OR "71-43-2")) AND (immuno* OR hemat* OR CBC OR RBC OR WBC OR platelets OR lymphocytes OR monocytes OR granulo* OR neutrophils OR eosinophils OR basophils OR "peripheral blood" OR "polychromatic erythrocytes")
Web of Science	TS = ((benzene OR "71-43-2")) AND TS = (immuno* OR hemat* OR CBC OR RBC OR WBC OR platelets OR lymphocytes OR monocytes OR granulo* OR neutrophils OR eosinophils OR basophils OR "peripheral blood" OR "polychromatic erythrocytes")

The titles and abstracts were screened for relevance using EndNote [24] by two independent reviewers. EndNote is a reference management software that can also be used by reviewers to efficiently screen titles and abstracts and manage research manuscripts, as described by Bramer

et al. [25-27]. The following PECO statement was generated to identify appropriate research: studies conducted on (P) populations of humans and/or *in vivo* studies on standard mammal organisms; (E) exposed to benzene through inhalation, based on administered dose or concentration, biomonitoring data, or environmental measures. These populations were (C) compared to populations with no exposure or exposure below detection; with (O) outcomes that include hematological or immunological responses. Studies that did not meet these conditions were excluded from consideration. Discrepancies regarding inclusion were discussed and resolved by at least two reviewers and when needed a third reviewer was brought in to clear unresolved discrepancies. At full-text review, articles included at the screening level were read for final inclusion. The search identified 1111 studies; 857 studies were excluded based on title-abstract screening. In addition, 45 environmental epidemiology studies, 94 mechanistic studies, and 21 reviews were excluded. A total of 55 studies were carefully read and examined using the PECO statement given above and 20 of these studies were considered for inclusion (Table S4).

Table S3. Seed studies used to test the search logic; these studies were derived from the key or supporting studies for noncancer effects of benzene used by TCEQ, OEHHA and ATSDR

Seed study	Key or supporting	Found in search
Aoyama K. Effects of benzene inhalation on lymphocyte subpopulations and immune response in mice. Toxicol Appl Pharmacol 1986. 85(1): 92-101.	ATSDR, OEHHA	Y
Baarson KA, Snyder CA, Albert RE. Repeated exposure of C57Bl mice to inhaled benzene at 10 ppm markedly depressed erythropoietic colony formation. Toxicol Lett. 1984. 20(3):337-42.	ATSDR, OEHHA	Y
Corti M, Snyder CA. Influences of gender, development, pregnancy and ethanol consumption on the hematotoxicity of inhaled 10 ppm benzene. Arch Toxicol. 1996. 70(3-4):209-17.	TCEQ	Y
Cronkite EP, Drew RT, Inoue T, Bullis JE. Benzene hematotoxicity and leukemogenesis. Am J Ind Med. 1985. 7(5-6):447-56.	TCEQ, ATSDR, OEHHA	Y
Cronkite EP, Drew RT, Inoue T, Hirabayashi Y, Bullis JE. Hematotoxicity and carcinogenicity of inhaled benzene. Environ Health Perspect. 1989. 82:97-108.	TCEQ, OEHHA	Y
Dempster AM, Snyder CA. Kinetics of granulocytic and erythroid progenitor cells are affected differently by short-term, low-level benzene exposure. Arch Toxicol. 1991. 65(7):556-61.	TCEQ, ATSDR	Y
Farris GM, Robinson SN, Gaido KW, Wong BA, Wong VA, Hahn WP, Shah RS. Benzene-induced hematotoxicity and bone marrow compensation in B6C3F1 mice. Fundam Appl Toxicol. 1997. 36(2):119-29.	TCEQ, OEHHA	Y
Green JD, Snyder CA, LoBue J, Goldstein BD, Albert RE. Acute and chronic dose/response effects of inhaled benzene on multipotential hematopoietic stem (CFU-S) and granulocyte/macrophage progenitor (GM-CFU-C) cells in CD-1 mice. Toxicol Appl Pharmacol. 1981. 58(3):492-503.	TCEQ, ATSDR	Y
Keller KA, Snyder CA. Mice exposed in utero to 20 ppm benzene exhibit altered numbers of recognizable hematopoietic cells up to seven weeks after exposure. Fundam Appl Toxicol. 1988. 10(2):224-32.	OEHHA	Y
Lan Q, Zhang L, Li G, Vermeulen R, Weinberg RS, Dosemeci M, Rappaport SM, Shen M, Alter BP, Wu Y, Kopp W, Waidyanatha S, Rabkin C, Guo W, Chanock S, Hayes RB, Linet M, Kim S, Yin S, Rothman N, Smith MT. Hematotoxicity in workers exposed to low levels of benzene. Science. 2004.. 306(5702):1774-6.	TCEQ, ATSDR, OEHHA	Y
Qu Q, Shore R, Li G, Jin X, Chen LC, Cohen B, Melikian AA, Eastmond D, Rappaport SM, Yin S, Li H, Waidyanatha S, Li Y, Mu R, Zhang X, Li K. Hematological changes among Chinese workers with a broad range of benzene exposures. Am J Ind Med. 2002. 42(4):275-85.	ATSDR, OEHHA	Y
Rosenthal GJ, Snyder CA. Modulation of the immune response to Listeria monocytogenes by benzene inhalation. Toxicol Appl Pharmacol. 1985. 80(3):502-10.	TCEQ, ATSDR	Y
Rothman N, Li GL, Dosemeci M, Bechtold WE, Marti GE, Wang YZ, Linet M, Xi LQ, Lu W, Smith MT, Titenko-Holland N, Zhang LP, Blot W, Yin SN, Hayes RB. Hematotoxicity among Chinese workers heavily exposed to benzene. Am J Ind Med. 1996. 29(3):236-46.	ATSDR	Y
Rozen MG, Snyder CA, Albert RE. Depressions in B- and T-lymphocyte mitogen-induced blastogenesis in mice exposed to low concentrations of benzene. Toxicol Lett. 1984. 20(3):343-9.	TCEQ, ATSDR	Y
Toft K, Olofsson T, Tunek A, et al. Toxic effects on mouse bone marrow caused by inhalation of benzene. Arch Toxicol 1982. 51:295-302	TCEQ, ATSDR	N
Ward E, Hornung R, Morris J, Rinsky R, Wild D, Halperin W, Guthrie W. Risk of low red or white blood cell count related to estimated benzene exposure in a rubber worker cohort (1940-1975). Am J Ind Med. 1996. 29(3):247-57.	ATSDR, OEHHA	Y
Wells MS, Nerland DE. Hematotoxicity and concentration-dependent conjugation of phenol in mice following inhalation exposure to benzene. Toxicol Lett. 1991. 56(1-2):159-66.	ATSDR	Y

Table S4. Summary of the 20 studies that satisfied PECO constraints and were considered for inclusion in developing benzene acute toxicity RELs

Study	Study Type	Duration	Concentration	Response
Bassig, BA., L Zhang, R Vermeulen, X Tang, G Li, W Hu, W Guo, MP Purdue, S Yin, SM Rappaport, M Shen, Z Ji, C Qiu, Y Ge, HD Hosgood, B Reiss, B Wu, Y Xie, L Li, F Yue, LE Freeman, A Blair, RB Hayes, H Huang, MT Smith, N Rothman, Q Lan. Comparison of hematological alterations and markers of B-cell activation in workers exposed to benzene, formaldehyde and trichloroethylene. Carcinogenesis. 2016. **37**(7): 692-700.	Occupational	Subchronic to chronic	1.2 ppm	Declines in cell types derived from myeloid progenitor cells, including granulocytes and platelets. Alterations in lymphoid cell types, including B cells and CD4+ T cells, and B-cell activation markers
Casale, T, C Sacco, S Ricci, B Loreti, A Pacchiarotti, V Cupelli, G Arcangeli, N Mucci, V Antuono, F De Marco, G Tomei, F Tomei, MV Rosati. Workers exposed to low levels of benzene present in urban air: Assessment of peripheral blood count variations. Chemosphere. 2016. **152**: 392-398.	Occupational	subchronic to chronic	<0.5 ppm	Changes in white blood cells, lymphocytes, and neutrophils
Chen, LP, P Guo, HY Zhang, WX Li, C Gao, ZL Huang, JL Fan, YL Zhang, X Li, XL Liu, FP Wang, S Wang, QY Li, ZN He, HY Li, S Chen, XN Wu, LZ Ye, Q Li, HW Tang, Q Wang, GH Dong, YM Xiao, W Chen, DC Li. Benzene-induced mouse hematotoxicity is regulated by a protein phosphatase 2A complex that stimulates transcription of cytochrome P4502E1. Journal of Biological Chemistry. 2019 **294**(7): 2486-2499.	Mouse	subacute (6h/d x 6d/wk x 4wk)	0, 1, 10, 100 ppm	Changes in peripheral blood cell counts, altered gene expression
Chen, Y, P Sun, X Guo, A Gao. MiR-34a, a promising novel biomarker for benzene toxicity, is involved in cell apoptosis triggered by 1,4-benzoquinone through targeting Bcl-2. Environ Pollut. 2017 **221**: 256-265.	Occupational	subchronic to chronic	0.83 ppm	Elevated miR-34a expression, lowered white blood cell counts

Study	Study Type	Duration	Concentration	Response
Guo, XL, W Zhong, YJ Chen, W Zhang, J Ren, A Gao. Benzene metabolites trigger pyroptosis and contribute to haematotoxicity via TET2 directly regulating the Aim2/Casp1 pathway. Ebiomedicine. 2019 **47**: 578-589.	Occupational	subchronic to chronic	0.6 ppm	Decreased peripheral blood cells counts, increased IL8, decreased IL-10, elevated Casp1 and IL1β expressions
Hosgood, HD, L Zhang, M Shen, SI Berndt, R Vermeulen, G Li, S Yin, M Yeager, J Yuenger, N Rothman, S Chanock, M Smith, Q Lan. Association between genetic variants in VEGF, ERCC3 and occupational benzene haematotoxicity. Occupational and Environmental Medicine. 2009 **66**(12): 848-853.	Occupational	subchronic to chronic	5.4 ppm	Genetic polymorphisms correlated with WBC/subtypes (WBC, granulocylte, lymphocyte, CD4+, BCell, monocyte)
Huang, JS, MD Zhao, P Wang, XJ Li, L Ma, JH Zhang, YL Zhou. Effects of Low Concentrations of Benzene Exposure on Levels of Platelet-Associated Antibodies and Platelet Parameters. Journal of Occupational and Environmental Medicine. 2014. **56**(10): E92-E97.	Occupational	subchronic to chronic	0.5 ppm	Increased large-platelet cell ratios, platelet distribution width, mean platelet volume, platelet-associated immunoglobulin levels
Jorgensen, KM, E Faergestad Mosleth, K Hovde Liland, NB Hopf, R Holdhus, AK Stavrum, BT Gjertsen, J Kirkeleit. Global Gene Expression Response in Peripheral Blood Cells of Petroleum Workers Exposed to Sub-Ppm Benzene Levels. Int J Environ Res Public Health. 2018. **15**(11).	Occupational	subacute (3 x 12-hr shifts)	0.15 ppm	Altered gene expression (elevated expression of IL6 and reduced expression of IL19)
Li, J, X Xing, X Zhang, B Liang, Z He, C Gao, S Wang, F Wang, H Zhang, S Zeng, J Fan, L Chen, Z Zhang, B Zhang, C Liu, Q Wang, W Lin, G Dong, H Tang, W Chen, Y Xiao, D Li. Enhanced H3K4me3 modifications are involved in the transactivation of DNA damage responsive genes in workers exposed to low-level benzene. Environ Pollut. 2018. **234**: 127-135.	Occupational	subchronic to chronic	0.1 ppm	Decrease in the counts of white blood cells, neutrophils, lymphocytes, and monocytes

Study	Study Type	Duration	Concentration	Response
Liang, BX, YC Chen, WX Yuan, F Qin, Q Zhang, N Deng, XX Liu, XJ Ma, X Zhang, B Zhang, QF Deng, M Huang, HW Tang, LH Liu, W Chen, YM Xiao. Down-regulation of miRNA-451a and miRNA-486-5p involved in benzene-induced inhibition on erythroid cell differentiation in vitro and in vivo. Archives of Toxicology. 2018. **92**(1): 259-272.	Occupational	subchronic to chronic	0.035 ppm	Increased red blood cells, increased serum plasminogen
Liang, BX, YZ Zhong, KK Chen, LH Zeng, GL Li, JW Zheng, L. Jiang, ZW Xie, BL Que, GC Lai, BH Wu, XF Yang, JL Wu, YM Xiao, W Chen, ZL Huang. Serum plasminogen as a potential biomarker for the effects of low-dose benzene exposure. Toxicology. 2018. **410**: 59-64.	Mouse	subacute (6h/d x 6d/wk x 2-4wk)	0, 1, 5, 25 ppm	Changes in peripheral blood cell counts, altered gene expression
Liu, D, YJ Chen, PL Sun, WL Bai, A Gao. STAT3 methylation in white blood cells as a novel sensitive biomarker for the toxic effect of low-dose benzene exposure. Toxicology Research. 2016. **5**(3): 800-807.	Occupational	subchronic to chronic	0.6 ppm	Decreased STAT3 methylation of white blood cells, decreased platelets and 8-isoprostane-PGFs; increased ALT and 8-hydroxy-2 deoxyguanosine (8-OHdG)
Moro, AM, N Brucker, MF Charao, M Baierle, E Sauer, G Goethel, A Barth, SN Nascimento, B Gauer, J Durgante, BS Amaral, FRA Neto, A Gioda, SC Garcia. Biomonitoring of gasoline station attendants exposed to benzene: Effect of gender. Mutation Research-Genetic Toxicology and Environmental Mutagenesis. 2017. **813**: 1-9.	Occupational	subchronic to chronic	0.04 ppm	changes in peripheral blood cell counts
Moro, AM, N Brucker, MF Charao, E Sauer, F Freitas, J Durgante, G Bubols, S Campanharo, R Linden, AP Souza, C Bonorino, R Moresco, D Pilger, A Gioda, S Farsky, A Duschl, SC Garcia. Early hematological and immunological alterations in gasoline station attendants exposed to benzene. Environmental Research. 2015. **137**: 349-356.	Occupational	subchronic to chronic	0.05 ppm	changes in δ-aminolevulinate dehydratase (ALA-D) activity, CD80 and CD86 expression in lymphocytes and monocytes, and serum interleukin-8 (IL-8)

Study	Study Type	Duration	Concentration	Response
Mukherjee, AK, BP Chattopadhyay, SK Roy, S Das, D Mazumdar, M Roy, R Chakraborty, A Yadav. Work-exposure to PM10 and aromatic volatile organic compounds, excretion of urinary biomarkers and effect on the pulmonary function and heme-metabolism: A study of petrol pump workers and traffic police personnel in Kolkata City, India. Journal of Environmental Science and Health Part a-Toxic/Hazardous Substances & Environmental Engineering. 2016. **51**(2): 135-149.	Occupational	subchronic to chronic	17.8 ppm	Changes in blood cell counts
Neghab, M, K Hosseinzadeh, J Hassanzadeah. Hematological study of petrol station workers exposed to unleaded petrol. Toxicological and Environmental Chemistry. 2014. **96**(6): 951-961.	Occupational	subchronic to chronic	0.25 ppm	Changes in red blood cell distribution width
R Schnatter, PJ Kerzic, Y Zhou, M Chen, MJ Nicolich, K Lavelle, TW Armstrong, MG Bird, L Lin, H Fu, RD Irons. Peripheral blood effects in benzene-exposed workers. Chem Biol Interact. 2010. **184**(1-2): 174-181.	Occupational	subchronic to chronic	7.8 ppm	neutrophils and the mean platelet volume (MPV)
Spatari, G, S Saitta, C Giorgianni, MT Cristani, P Quattrocchi, A Abbate, M Carrieri, G Ferraro, A Saija, S Gangemi. Interleukin-10 involvement in exposure to low dose of benzene. Toxicol Ind Health. 2015. **31**(4): 351-354.	Occupational	subchronic to chronic	0.02 ppm	serum concentration of IL-10 over time
Sun, PL, XL Guo, YJ Chen, W Zhang, HW Duan, A Gao. VNN3, a potential novel biomarker for benzene toxicity, is involved in 1, 4-benzoquinone induced cell proliferation. Environmental Pollution. 2018. **233**: 323-330.	Occupational	subchronic to chronic	1.1 ppm	increased expression in VNN3, decreased red blood cells and hemoglobin
Zhang, L, Q Lan, Z Ji, G Li, M Shen, R Vermeulen, W Guo, AE Hubbard, CM McHale, SM Rappaport, RB Hayes, MS Linet, S Yin, MT Smith, N Rothman. Leukemia-related chromosomal loss detected in hematopoietic progenitor cells of benzene-exposed workers. Leukemia. 2012. **26**(12): 2494-2498.	Occupational	subchronic to chronic	< 10 ppm	monosomies 7 and 8 produced in a dose-dependent fashion in the blood progenitor cells

The majority of these 20 studies are studies of occupational cohorts. The bioindicators and observed adverse effects of benzene exposure observed in these populations can be short-lived and hence qualify as acute exposures, but these studies were conducted on workers who had likely been exposed to benzene over much longer timeframes and may also reflect the impacts from longer-term exposures.

Two studies identified adverse hematological effects in mice exposed to 1 ppm of benzene under subacute conditions; these results indicate adverse effects at benzene concentrations that are an order of magnitude lower than studies cited previously by regulatory agencies. These studies seemed the most appropriate studies for a possible change in regulatory limits and are discussed below.

Key and supporting studies

Liang et al. sought to elucidate the underlying mechanism of benzene effects on erythroid differentiation [28]. They examined the relationship between microRNA expression and perturbation of erythroid cell differentiation through in vitro studies, demonstrating a negative correlation with hydroquinone (benzene metabolite) and miRNA-451a and miRNA-486-5p expression in hematopoietic progenitor cells. In a subacute study of mice treated with benzene as low as 1 ppm, the researchers found benzene exposure over 28 days led to a decrease in red blood cells, which was correlated to the downregulation of the identified microRNAs. They also measured an increase in platelets with benzene exposure over 14 days, which was not correlated to the microRNA expression. The researchers were able to show that a decline in microRNAs found in male chronic benzene poisoned workers was correlated with a decrease in red blood cell counts These workers had been exposed to benzene at less than 1 ppb and were diagnosed with chronic benzene poisoning through peripheral blood cell counts.

Chen et al., using a mouse model, identified a protein phosphatase complex that is involved in the transcription of cytochrome P4502E1, a key enzyme in benzene metabolism [5]. Through a series of studies, the researchers demonstrated that suppressing this gene reduces the metabolism of benzene and its toxicity. Wild-type and knock-out mice (with a hepatocyte-specific homozygous deletion of the Ppp2r1a gene) were exposed to 0, 1, 10, 100 ppm of benzene for 28 days. The researchers found that suppression of protein phosphatase 2A reduced benzene metabolism, probably through its regulation of p4502E1. They also demonstrated that wild-type mice showed significant reduction of reticulocytes, lymphocytes, and white blood cell counts at benzene exposures of 1 ppm compared to the mice with the deletion of the Ppp2r1a gene.

This review found only a few studies on acute benzene exposure on humans that also study effects to the hematological systems. This was also noted by ATSDR in their addendum to the benzene report [29]. However, one study, summarized by ATSDR, was considered important.

Kirkeleit et al. [29, 30] studied ten benzene exposed workers on a crude oil vessel. The researchers measured peripheral blood lymphocyte levels in workers, as well as serum levels of immunoglobulins, after three 12-hour shifts with an average benzene exposure of 0.15 ppm. They found that the benzene exposed workers had reduced levels of immunoglobulins (IgM and IgA) and decreased blood CD4 T cells compared to non-benzene exposed workers. They found no significant changes in IgG or lymphocyte counts.

POD Calculations for key and supporting studies

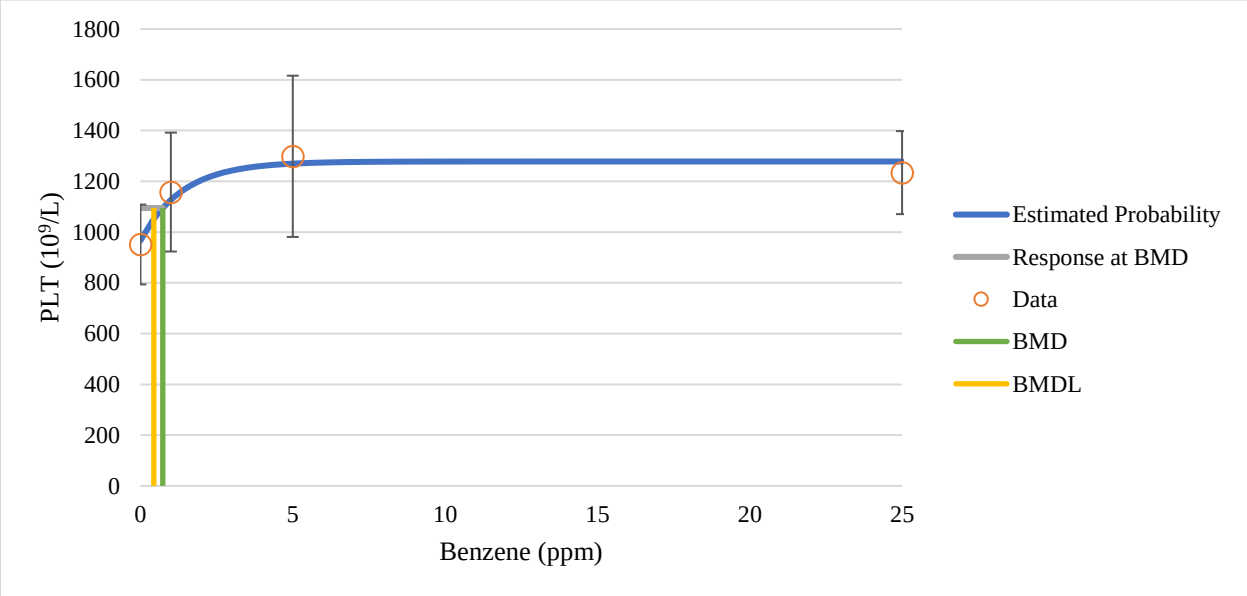
TCEQ guidelines were used to develop points of departure (POD) for the three key studies mentioned above [5, 28, 30]. These PODs were then compared to existing guidelines to determine if a new regulatory guideline was needed. Point of departure is defined as the dose or concentration on a dose-response curve that corresponds to the lowest observable effect, as determined through experimental data.

In Liang et al., male mice had statistically measurable responses in platelet counts after 14 days of exposure and in red blood cells after 28 days of exposure ($p < 0.001$; 6 hr/d, 6 d/wk). There were a total of 64 animals in 8 groups, 4 male and 4 female in each of four treatment groups (0, 1, 5, 25 ppm), for two exposure durations (14 days and 28 days). The POD for each endpoint was derived as a function of benzene concentration and the continuous models in the USEPA BMDS (v 3.2, 2020) software [31]. One standard deviation from the control mean was used as a benchmark response value, as suggested by 2012 USEPA Benchmark Dose Technical Guidance [32]. This guidance describes benchmark dose (BMD) as the "dose levels corresponding to specific response levels, or benchmark responses, near the low end of the observable range of the data"[32], where BMD refers to the central estimate of this value and BMDL is the lower 95% confidence limit of this value.

Platelet count and red blood cell count were modeled using exponential, Hill, linear, polynomial, and power models (restricted and unrestricted frequentist) assuming a normal distribution with constant and non-constant variance. Models can be considered "questionable" due to poor goodness-of-fit p-values, BMD/BMDL ratios greater than 20, or BMDL values that are three times lower than the lowest non-zero dose, among other considerations. Models can be considered "unusable" if BMD or Akaike's Information Criterion (AIC) cannot be estimated. The BMDS software recommendations are consistent with the US EPA BMD Technical Guidance [32]. Models that were considered "viable" are summarized in Table S5 and Table S6 and the models are shown in Supplemental Figure 1 and Supplemental Figure 2.

Table S5. Results of modeling the platelet count responses in mice from benzene exposure over 14 days [28] using BMDS (v 3.2, 2020)

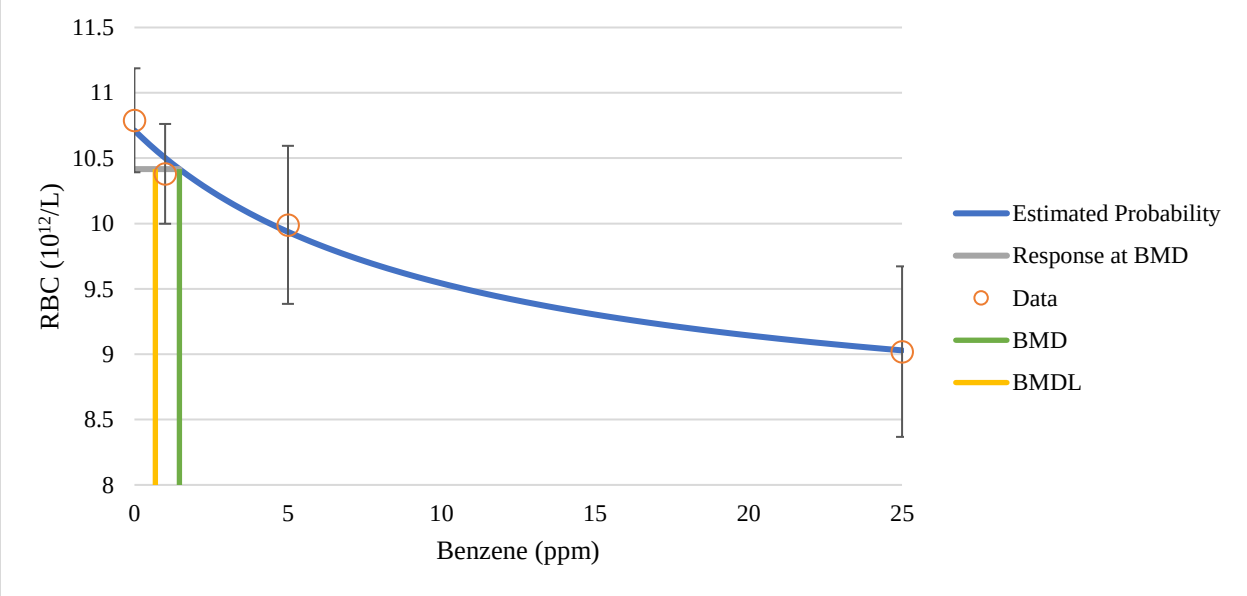
Restriction	Model	BMD (ppm)	BMDL (ppm)	P (test 4)	AIC	BMDS	Notes
Constant Variance (rho = 0)							
Restricted	Exponential (model 4)	0.735	0.441	0.317	208.624699	Viable - Recommended	Lowest AIC
Unrestricted	Polynomial	1.915	1.186	0.129	209.9318783	Viable	
Non-Constant Variance (rho ≠ 0)							
Restricted	Exponential (models 4 & 5)	0.460	0.232	0.227	209.6177997	Viable - Recommended	Lowest AIC; BMDL 3x lower than lowest non-zero dose



Supplemental Figure 1. Fit of the Frequentist Exponential Degree 4 Model to the platelet count responses in mice from benzene exposure over 14 days [28] showing the benchmark response value of 1 Std. Dev. for the BMD and the 95% Lower Confidence Limit for the BMDL.

Table S6. Results of modeling the red blood cell count responses in mice for benzene exposure over 28 days [28] using BMDS (v 3.2, 2020)

Restriction	Model	BMD (ppm)	BMDL (ppm)	P (test 4)	AIC	BMDS	Notes
Constant Variance (rho = 0)							
Restricted	Exponential (models 4 & 5)	1.669	0.929	0.248	14.54707	Viable	
Restricted	Hill	1.465	0.682	0.286	14.35516	Viable - Recommended	Lowest AIC
Unrestricted	Polynomial	1.899	1.187	0.215	14.75242	Viable	
Non-Constant Variance (rho ≠ 0)							
Restricted	Exponential (models 4 & 5)	1.261	0.510	0.185	15.67948	Viable	
Restricted	Exponential (model 5)	1.253	0.510	0.185	15.67974	Viable	
Restricted	Hill	1.010	0.323	0.231	15.3544	Viable - Recommended	Lowest AIC; BMD/BMDL ratio > 3; BMDL 3x lower than lowest non-zero dose
Unrestricted	Polynomial	1.521	0.803	0.150	15.99849	Viable	



Supplemental Figure 2. Fit of the Frequentist Exponential Degree 4 Model to the red blood cell count in mice from benzene exposure over 28 days [28] showing the BMD and the 95% Lower Confidence Limit for the BMDL.

With a specified POD of one standard deviation, which corresponds to an extra risk of 10% for individuals below the 1.4th percentile or above the 98.6th percentile of controls for normally distributed effects [32], a BMD of 0.74 ppm and a BMDL of 0.44 ppm was identified for platelet counts and a BMD of 1.47 ppm and BMDL of 0.68 ppm was identified for red blood cell counts.

A similar methodology was employed to develop a BMDL for data presented in the Chen et al. study [5]. The point of departure for each endpoint (reduced white blood cell count and reduced lymphocyte count) was derived as a function of benzene concentration and the continuous models in the BMDS software [31]. Here, the best fit for the data with a specified POD of one standard deviation used Frequentist Power model, which calculated a BMD of 2.72 ppm and a BMDL of 0.48 ppm for white blood cell counts. A viable BMDL model for lymphocyte counts could not be obtained. This POD is comparable to that calculated using the Liang et al. data [28]. However, while this calculation is considered viable, the ratio of BMD to BMDL is greater than 3, which reflects greater model uncertainty. Furthermore, numerical summary data were only given for two of the three endpoints found to be significant in the study.

Due to a lack summary data and the potential uncertainty in the BMDL model for the Chen et al. data, and because the study conducted by Kirkeleit et al. was limited in scope, Liang et al. was chosen as the key study to calculate reference exposure values.

Dosimetry adjustments

Dosimetry adjustments are used to convert animal-based doses into human exposures and to adjust timescales from longer experimental durations to those appropriate for regulatory guidance values. Again, using TCEQ guidelines, the following dosimetric adjustments were applied to the BMDL derived from the key study [28].

POD_{HEC}: Dosimetry Adjustments from Animal-to-Human Exposure.

Benzene is defined as a category 3 gas [23], which are generally absorbed in the deeper pulmonary region [33]. Category 3 gases produce non-respiratory effects at lower concentrations.

For category 3 gases:

$$POD_{HEC} = POD \times ((H_{b/g})_A/(H_{b/g})_H)$$

Where: POD_{HEC} = the POD Human Equivalent Concentration, or POD adjusted for animal-to-human dosimetry; $H_{b/g}$ = ratio of the blood:gas partition coefficient, A = animal, and H = human

If the animal blood:gas partition coefficient is greater than the human blood:gas partition coefficient, a default value of 1 is used for the regional gas dose ratio). For benzene, the blood:gas partition coefficients for mice and humans are 17.44 and 8.12, respectively [34]. Therefore, no animal-to-human dosimetry adjustments were made.

$POD_{ADJ,\ 1\text{-}hr}$: Adjustment from Longer to Shorter Exposure Duration

Default procedures discussed in TCEQ Guidelines [8], with n = 3, were used to adjust exposure duration from the subacute study to 1-hr exposure:

$$C_2 = [(C_1)^3 \times (T_1 / T_2)]^{1/3} = [(0.44\ ppm)^3 \times (6\ hrs/1\ hr)]^{1/3} = 0.799\ ppm = POD_{ADJ,\ 1\text{-}hr}$$

Where: C_2 is the theoretical equivalent POD concentration for a shorter exposure, based on the POD found experimentally at a longer time-scale; T_1 is the original time-scale in hours, and T_2 is the shortened time-scale in hours.

$POD_{ADJ,\ 24\text{-}hr}$: Duration Adjustments for Subchronic Studies.

Default procedures discussed in TCEQ [34], where the toxicokinetic or toxicodynamic half-life of the chemical is long, were used to adjust exposure duration from the intermittent subacute study to 24-hr continuous exposure:

$$POD_{ADJ,\ 24\text{–}h} = POD \times (N\ hrs/24\ hrs) \times (D\ days/week) = 0.44\ ppm \times (6\ hrs/24\ hrs) \times (6\ days/7days) = 0.094\ ppm = POD_{ADJ,\ 24\text{–}h}$$

Where: N is the daily exposure duration in hours, and D is the number of days per week used during the experiment.

Uncertainty Factors (UF)

Uncertainty factors are used to take into account vulnerable sub-populations of humans and uncertainty in our understanding of how the toxic effects of benzene on animals converts to humans. The following is a summary of the justification for uncertainty factors as described by TCEQ and ATSDR [6, 23].

An interspecies UF of 3 was used because, while metabolic pathways between humans and mice are similar, there are sufficient differences to not be able to predict human metabolism accurately [6, 23]. An intraspecies UF of 10 was used because of the wealth of experimental data that suggest a wide variation in benzene-sensitive human subpopulations [6, 23]. A LOAEL UF of 1

was used because this factor is not applicable with BMDL as the POD. Finally, the Database UF was 1 because of the high quality and quantity of benzene studies [6, 23].

Health-Based 1-hr and 24-hr Acute ReVs

To derive the health-based acute reference values, the UFs described above were applied to the POD_{ADJ} derived from the key study [28], as well as the supporting studies[5, 22] (Table S7).

Liang et al. 2018 (key study), (see Table 1 in the main text):

> Acute 1-hr ReV = POD_{ADJ} / (UFA x UFH x UFL x UFD) = 0.80 ppm / (3 x 10 x 1 x 1) = 0.0267 ppm

Chen et al. 2019 (supporting) (see Table S7):

> Acute 1-hr ReV = POD_{ADJ} / (UFA x UFH x UFL x UFD) = 0.87 ppm / (3 x 10 x 1 x 1) = 0.0291 ppm

Kirkeleit et al. 2006 (supporting) (see Table S7):

> Acute 1-hr ReV = POD_{ADJ} / (UFA x UFH x UFL x UFD) = 0.34 ppm / (1 x 10 x 3 x 1) = 0.011 ppm

The acute ReV value was rounded to two significant figures at the end of all calculations. Rounding to two significant figures, the 1-h acute ReV is 27 ppb (85 $\mu g/m^3$) and is supported by similar calculations based on Chen et al. and Kirkeleit et al.

Table S7. Summary Acute 1-hr ReV and 24-hr ReV based on the supporting studies (A) Chen et al. 2018 [5] and (B) Kirkeleit et al. 2006 [30].

Parameter	**Summary (1hr)**	**Summary (24-hr)**
Study	Chen et al. (2019) [5]	
Study population	C57BL/6J mice (male), 10 animals per group, 2 groups	
Exposure Methods	6 h per day for 6 days/wk for 4 wks via inhalation from 0 to 100 ppm	
Critical Effects	Reduced white blood cell count	
LOAEL	1 ppm (average analytical concentration)	
NOAEL	Not Found	
$BMDL_{1SD}$	0.48 ppm (Frequentist Power model, v.3.2)	
Exposure Duration	6 h	
Extrapolation to 1-h/24-hr	TCEQ (2015) default procedures (n=3) 0.87 ppm = $((0.48\ ppm)^3 \times (6/1))^{1/3}$	TCEQ (2015) default procedures 0.094 ppm = (0.48 ppm x 6/24 x 6/7)
POD_{ADJ}	0.87 ppm	0.10 ppm
POD_{HEC}	0.87 ppm (RGDR = 1)	0.10 ppm (RGDR = 1)
Total Uncertainty Factors (UFs)	**30**	
Interspecies UFA	*3*	
Intraspecies UFH	*10*	
LOAEL UFL	*1 (BMDL)*	
Incomplete Database UFD	*1 (database quality = high)*	
Acute ReV	**29.1 ppb (93 ug/m^3)**	**3.4 ppb (11 ug/m^3)**

Parameter	**Summary (1hr)**	**Summary (24-hr)**
Study	Kirkeleit et al. 2006 [30]	
Study population	13 Tank Workers, 9 unexposed referents	
Exposure Methods	Individual geometric mean benzene exposure in the breathing zone of tank workers over 3 consecutive shifts	
Critical Effects	Reduced concentrations of serum IgM, IgA and CD4 T-cells	
LOAEL	0.15 ppm (average analytical concentration)	
NOAEL	Not Found	
$BMDL_{1SD}$	Not found	
Exposure Duration	12 h	
Extrapolation to 1-h/24-hr	TCEQ (2015) default procedures (n=3) 0.34 ppm = $((0.15\ ppm)^3 \times (12/1))^{1/3}$	TCEQ (2015) default procedures 0.032 ppm = (0.15 ppm x 12/24 x 3/7)
POD_{ADJ}	0.34 ppm	0.032 ppm
Total Uncertainty	**30**	
Interspecies UFA	*1*	
Intraspecies UFH	*10*	
LOAEL UFL	*3*	
Incomplete Database	*1 (database quality = high)*	
Acute ReV	**11 ppb (36.5 ug/m^3)**	**1.0 ppb (3.4 ug/m^3)**

Comparison of existing guidance documents

Different agencies have different reference guidance values based on differing assumptions of exposure. TCEQ has two acute exposure durations, each of which assume a single, independent exposure event: 1-hr and 24-hr [8]. The longer exposure duration is based on averaging times calculated in air permitting. These are defined as an estimate of an inhalation exposure that is likely to be without an appreciable risk of adverse effects to the human population for a single 24-h exposure. California OEHHA defines an acute reference exposure limitation (REL) as an infrequent 1-hr exposure, as well as an 8-hr REL [7]. The 8-hr REL is defined as shorter, daily exposure (eight-hour exposures), and is differentiated from the chronic REL, which is designed to be protective against long-term 24-hour a day exposure. Finally, ATSDR defines its Minimal Risk Levels (MRLs) as an estimate of the daily human exposure to a hazardous substance without an appreciable risk of adverse noncancer health effects over a specified duration of exposure [6]. The shortest duration of exposure is between 1 to 14 days.

Given the differences in assumed exposure duration across agencies, in order to compare current guidance values to the proposed guidance values, dosimetry calculations were performed for OEHAA (1-hr to 24-hr) and ATSDR (1 day to 1-hr). The uncertainty factors presented in each guidance document was then applied to the adjusted POD to calculate reference values. The comparison of these values is summarized in Table S8 and Table S9.

Adjustment from Longer to Shorter Exposure Duration: ATSDR

Default procedures discussed in TCEQ Guidelines, where n = 3, were used to adjust exposure duration from the subacute study to 1-hr exposure:

C2 = [(C1)3 x (T1 / T2)]1/3 = [(10.2 ppm)3 x (6 hrs/1 hr)]1/3 = 19 ppm= PODADJ, 1-hr

UF = 300 (ATSDR 2007)

MCL1-hr = 19 ppm/300 = 0.062 ppm = 62 ppb

Adjustment from Shorter to Longer Exposure Duration: OEHHA

Default procedures discussed in TCEQ, with n = 1, were used to adjust exposure duration from the 1-hr study to 24-hr exposure:

$C_2 = [(C_1) \times (T_1 / T_2)] = [(5\ ppm) \times (6\ hrs/24\ hr)] = 1.25\ ppm = POD_{ADJ,\ 24\text{-}hr}$

UF = 600 (OEHHA 2014)

REL24-hr = 1.25 ppm/600 = 0.0021 ppm = **2.1 ppb**

Table S8. Comparison of existing Acute 1-hr ReVs to the proposed value of 27 ppb

	TCEQ (1-hr)	**ATSDR (1-hr, calculated)**	**CA (1-hr)**	**PROPOSED (1-hr)**
Citation	Rozen et al. (1984) [15]		Keller and Snyder, 1988 [35]	Liang et al. (2018) [28]
Endpoint	depressed femoral B-lymphocytes following mitogen stim.		Decreased nucleated RBC (2-d neonates)	Increased PLT
POD (POD_{ADJ}) in ppm	10.2 (18.5)	10.2 (18.5)	5 (not adjusted)*	0.44 (0.80)
Intraspecies (H)	10	10	30	10
Interspecies (A)	3	3	6	3
LOAEL to NOAEL (L)	3	10	3	1
Database (D)	1	1	1	1
UF	**100**	**300**	**600**	**30**
Final	**180 ppb**	**62 ppb**	**9 ppb**	**27 ppb**

Table S9. Comparison of existing Acute 24-hr ReVs to the proposed value of 3 ppb

	TCEQ* (24-hr)	**ATSDR (24-hr)**	**CA (24-hr, calculated)**	**PROPOSED (24-hr)**
Citation	Rozen et al. (1984) [15]		Keller and Snyder, 1988 [35]	Liang et al. (2018) [28]
Endpoint	depressed femoral B-lymphocytes following mitogen stim.		Decreased nucleated RBC (2-d neonates)	Increased PLT
POD (POD_{ADJ}) in ppm	10.2 (10.2)*	10.2 (2.55)	5 (1.3)	0.44 (0.09)
Intraspecies (H)	10	10	30	10
Interspecies (A)	3	3	6	3
LOAEL to NOAEL (L)	3	10	3	1
Database (D)	1	1	1	1
UF	**100**	**300**	**600**	**30**
Final	**100 ppb**	**9 ppb**	**2.2 ppb**	**3 ppb**

* Toxicokinetic considerations: assume inadequate elimination means not independent acute exposure (TCEQ 2015)

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