

Scientific Review Panel

November 1, 2013

Noncancer Effects of Benzene

Office of Environmental Health Hazard Assessment



Air Toxics Hot Spots Overview

- Air Toxics Hot Spots program provides for:
 - reporting of emissions to the air from stationary sources in California
 - assessment of the health risks to the general public
 - emissions reductions when appropriate
- OEHHA is responsible for developing and updating risk assessment guidelines



Air Toxics Hot Spots Program Risk Assessment Guidelines

- OEHHA adopted Risk Assessment Guidelines for emissions from stationary sources subject to AB 2588 (H&SC section 44360(b)(2))
- Included were Technical Support Documents for Derivation of Noncancer Reference Exposure Levels, Cancer Potency Factors, Exposure Assessment
- Guidance Manual for conducting site-specific risk assessment (2003)



Role of SRP in Reviewing Risk Assessment Guidelines

- **“The scientific review panel established pursuant to Section 39670 shall evaluate the guidelines adopted under this paragraph and shall recommend changes and additional criteria to reflect new scientific data or empirical studies.”** H&SC section 44360(b)(2)
- This requirement applies to:
 - the Technical Support Documents
 - the Risk Assessment Guidance Manual
 - the derivation of Reference Exposure Levels and Cancer Potency Factors for use in the risk assessments



Children's Environmental Health Protection Program (SB25)

OEHHA's major roles:

- **Consider infants and children in quantitative risk assessment (H&SC section 39660(c)(1)(A))**
- **Identify toxic air contaminants which may disproportionately impact children's health (H&SC section 39669.5(a))**



Consideration of Infants and Children in Assessing Risk

- SB 25 triggered OEHHA to re-evaluate Air Toxics Hot Spots risk assessment methodologies to ensure methods are child-protective.
- OEHHA completed updates of TSDs for Noncancer REL Derivation(2008), Cancer Potency Factor derivation and application in risk assesment (2009), and Exposure Assessment (2012)
- New REL methods were applied to benzene RELs undergoing SRP review (today's item)



TACS that Impact children

Under SB 25, OEHHA establishes a list of existing TACs that disproportionately impact children (“that may cause infants and children to be especially susceptible to illness”)

- Initial list of 5 required by statute (2001)
- SRP reviewed initial list
- SRP reviews additions to the list



Today's SRP Meeting - Benzene

- Review Acute Reference Exposure Level
- Review 8-hour and chronic Reference Exposure Levels
- Review OEHHA's proposal to add benzene to the list of TACs that may disproportionately impact infants and children



Benzene RELs

Benzene Reference Exposure Levels

Technical Support Document for the Derivation of Noncancer Reference Exposure Levels

Appendix D I

SRP Draft

October 2013



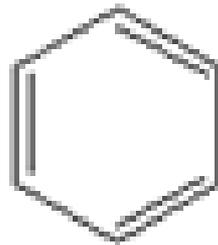
Benzene

- Multipurpose organic solvent
- Newspaper printing
- Oil industry
 - formerly high levels in gasoline
 - leaking underground storage tanks
- Tire industry
- Shoe manufacturing
- Cigarette smoking

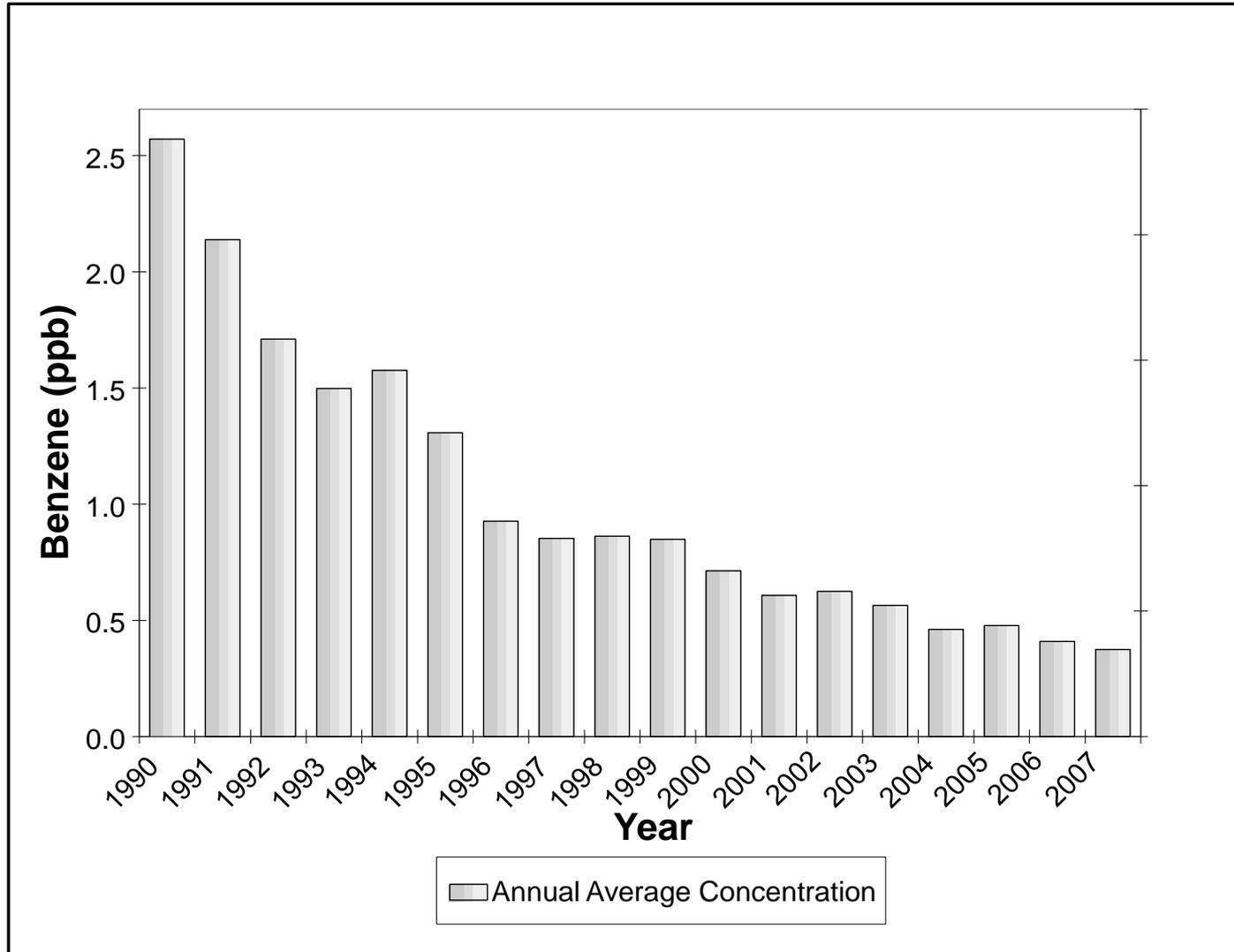


Benzene

- First Toxic Air Contaminant in CA -1985
- Listed under Proposition 65 for cancer, developmental toxicity, and male reproductive toxicity
- Ambient levels have fallen greatly in CA



Statewide Benzene Levels Have Dropped



Benzene

- US production in 2010 = 13.3 billion lbs
- CA emissions in 2008 = 21.7 million lbs
- Top CA stationary source = 49,000 lbs



Acute RELs

- RELs are based on the most sensitive, relevant health effect reported in the literature.
- Acute RELs are levels at which infrequent one-hour exposures are not expected to result in adverse health effects.



Key Study:

Keller and Snyder 1988

Exposure of mice in utero to 5, 10 and 20 ppm benzene on days 6-15 of gestation resulted in:

- suppression of erythropoietic precursor cells;
- persistent, enhanced granulopoiesis in peripheral blood cells of 2-day neonates;
- increased granulocytes in the livers of 2-day neonates and the spleens of adults at 6 weeks.



Critical Effects from the Keller and Snyder 1988 Data

Benzene Exposure	Dividing granulocytes	Nondividing granulocytes	Early nucleated red cells	Late nucleated red cells	Lymphocytes
2-day neonates					
Air	3.80±0.66	67.60±2.44	7.30±1.36	6.20±1.79	14.0±3.1
5 ppm	3.10±0.57	72.30±3.09	1.70±0.62*	3.60±0.88	17.9±2.4
10 ppm	5.90±1.04	67.90±2.88	0.50±0.22*	7.30±0.83	16.9±2.0
20 ppm	2.10±0.62	80.40±2.67*	0.00±0.00*	1.60±0.45*	14.2±2.5
*p < 0.05 vs corresponding control by Dunnett's test. Values are mean±SE.					



Benzene MADL

- OEHHA staff previously used this study to develop a Maximum Allowable Dose Level (MADL) for Proposition 65 ([OEHHA, 2001](#)).



Results of BMD Analysis of Early Nucleated Red Cells

Variance	Deviation	BMC (ppm)	BMCL (ppm)	p for fit*	AIC (fitted)
Constant	1 SD	4.14	3.01	0.0364	98.0831
Constant	0.5 SD	2.07	1.51	0.0364	98.0831
Constant	0.05 Relative	0.48	0.40	0.0364	98.0831
Not	1 SD	8.11	5.18	0.015	76.4167
Not	0.5 SD	4.06	2.59	0.015	76.4167
Not	0.05 Relative	0.548	0.512	0.015	76.4167

Dropped 20 ppm dose.

All results are for the linear model.

***In BMD the p for curve fit must be > 0.1.**

Proposed acute REL - I

- *Key study* Keller and Snyder, 1988
- *Study population* pregnant female rats
- *Exposure method* inhalation of 0, 5, 10, or 20 ppm benzene
- *Exposure continuity* 6 hours per day
- *Exposure duration* 10 days (days 6-15 of gestation)
- *Critical effects* altered cell counts in fetuses and offspring
- *LOAEL* 5 ppm (16 mg/m³)
- *NOAEL* not found
- *BMCL_{0.5SD}* not used due to poor fit

Proposed acute REL - 2

<i>Human equivalent conc.</i>	5 ppm (RGDR = 1) (systemic effect)
<i>Time adjustment factor</i>	Not done
<i>LOAEL uncertainty factor (UF_L)</i>	$\sqrt{10}$
<i>Interspecies uncertainty factor</i>	
<i>Toxicokinetic (UF_{A-k})</i>	2 (default) (OEHHA, 2008)
<i>Toxicodynamic (UF_{A-d})</i>	$\sqrt{10}$ (default)
<i>Intraspecies uncertainty factor</i>	
<i>Toxicokinetic (UF_{H-k})</i>	10 (default)
<i>Toxicodynamic (UF_{H-d})</i>	$\sqrt{10}$ (default)
<i>Database uncertainty factor</i>	1 (developmental studies are available)
<i>Cumulative uncertainty factor</i>	600
<i>Acute Reference Exposure Level</i>	8 ppb (27 $\mu\text{g}/\text{m}^3$)



Chronic REL

- A chronic Reference Exposure Level is an airborne concentration at or below which no adverse noncancer health effects are anticipated to individuals, even in sensitive subpopulations, indefinitely exposed to that concentration.



Benzene Exposure in China

- A collaboration among the National Cancer Institute, the Shanghai Hygiene and Anti-Epidemic Center, UC Berkeley, and other institutions has produced an impressive amount of data on levels of benzene exposure and its effects on nearly 75,000 Chinese workers in 672 factories in 12 cities.



Key Study: Lan et al. 2004

- A cross-sectional survey studied 250 (86 male and 164 female) Chinese workers exposed in two shoe manufacturing facilities to glues containing 0.6 to 34% benzene for 6.1 ± 2.1 years.

Critical Effects from the Lan et al. 2004 Data

	Controls (n = 140)	Low 0.57 ppm (n = 109)	Medium 2.85 ppm (n = 110)	High 28.73 ppm (n = 31)	p for 0.57 ppm vs. controls
WBC	6480	5540	5660	4770	< 0.0001
Granulocytes	4110	3360	3480	2790	< 0.0001
Lymphocytes	2130	1960	1960	1800	0.018
CD4⁺T cells	742	635	623	576	0.003
B cells	218	186	170	140	0.003
Monocytes	241	217	224	179	0.018
Platelets	230 × 10 ³	214 × 10 ³	200 × 10 ³	172 × 10 ³	0.023



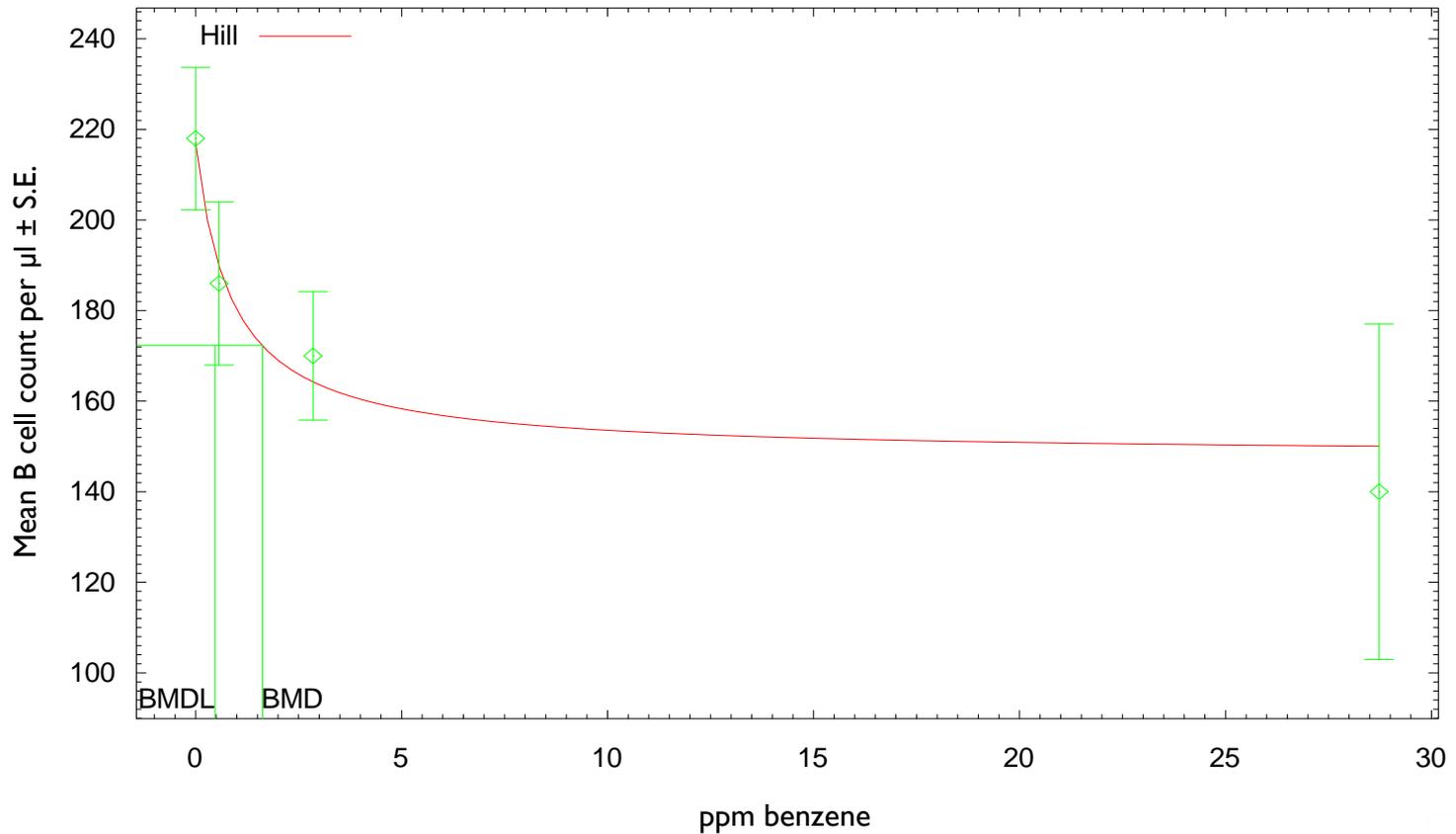
Results of BMD Analysis of B Cells

Model	Deviation	BMC (ppm)	BMCL (ppm)	BMC/ BMCL	p (test 4)	AIC (fitted)
Polynomial	0.5 SD	3.04	2.05	1.5	0.04099	3907.44
Exponential (Models 4 &5)	0.5 SD	1.22	0.44	2.8	0.1105	3905.811
Power	0.5 SD	20.35	14.03	1.7	0.0006241	3916.02
Linear	0.5 SD	20.35	14.03	1.7	0.0006241	3916.02
Hill	0.1 SD	0.131	0.0299	4.4	0.303	3904.325
Hill	0.25 SD	0.422	0.1039	4.1	0.303	3904.325
Hill	0.5 SD	1.624	0.4764	3.4	0.303	3904.325
Hill	0.05 Rel. Dev.	0.164	0.038	4.3	0.303	3904.325
Hill	1.0 SD	Failed (BMR not in range of mean function)				



Hill Model Fit to B Cell Data

Hill Model with 0.95 Confidence Level



11:57 10/04 2011



Proposed Chronic REL - I

- *Study* Lan et al. (2004)
- *Study population* 250 male and female Chinese shoe workers (vs. 140 controls)
- *Exposure method* Discontinuous occupational exposure
- *Exposure continuity* 8 h/d (10 m³/20 m³ day), 6 d/wk
- *Exposure duration* 6.1 ± 2.1 years
- *Critical effects* Decreased B cells
- *LOAEL* 0.57 ± 0.24 ppm (1.9 ± 0.8 mg/m³)
- *NOAEL* Not found
- *BMCL_{0.5SD}* 0.476 ppm (Hill Model v 2.15)

Proposed chronic REL - 2

- *Average occupational exposure* 0.204 ppm (0.476 ppm × 10/20 × 6/7)
- *Human equivalent concentration* 0.204 ppm (0.67 mg/m³)
- *LOAEL uncertainty factor (UF_L)* Not applicable with BMC
- *Subchronic UF (UF_S)* √10 (8-≤12% expected lifetime)
- *Interspecies UF* 1 (default, human study)
- *Intraspecies UF* 30
- *Database UF* 1 (developmental studies are available)
- *Cumulative UF* 100
- *Chronic REL* **0.002 ppm (2 ppb; 7 µg/m³)**

Eight-hour RELs

Eight-hour RELs are:

concentrations at or below which noncancer adverse health effects are not anticipated in the general human population with daily exposures of eight hours.



Proposed 8-hour REL

- For a health protective approach the 8-hour REL is the same as the chronic REL.
- It is unclear whether the adverse effects of repeated benzene exposure are reversed by periods of non-exposure overnight or over the weekend.
- The effects are likely to continue to worsen with additional exposure.



TAC Impacting Children (SB 25)

In view of:

- wide-spread exposure to benzene,
- documented toxicokinetic variability in benzene metabolism
- dynamic hematopoiesis during development

Benzene exposure may disproportionately impact infants and children.

OEHHA proposes that benzene be identified as a toxic air contaminant which may disproportionately impact children pursuant to H&SC, Sec. 39669.5(c).



Issues from Public Comments on the Acute REL

- An inappropriate choice of endpoints used.
 - No alterations in the maturation or development of circulating erythrocytes were observed.
 - The biological significance of the endpoints is unknown



Issues from Public Comments on the 8-hour and Chronic REL

Comments revolved around:

- Choice of study (Lan et al., 2004)
 - commenter wanted Schnatter (2010)
- Choice of endpoint (B cells)
- Models of dose-response
- Lack of effects at low levels of exposure (<1 ppm) in literature

Charge Questions on the Acute REL

- Study and endpoint selection:
 - Is the study of Keller and Snyder (1988) the most appropriate study for establishing the acute REL for benzene?
 - Is the effect on the developing hematologic system the appropriate endpoint for development of the acute REL?
- Modeling:
 - Was the approach to characterizing the dose response relationship appropriate?
 - Was the choice of the LOAEL as the point of departure appropriate?
- Uncertainty factors:
 - Was the selection of uncertainty factors appropriate and adequately justified given the noncancer risk assessment guidelines?
 - Were potential sensitive populations adequately captured?



Charge Questions on the Chronic REL

- Study and endpoint selection:
 - Is the study of Lan et al. (2004) the most appropriate one for establishing the chronic REL for benzene? For example, one commenter proposed the study of Schnatter et al. (2010).
 - Is the effect on the B cell population the appropriate endpoint for development of the chronic REL?
- Modeling:
 - Was the approach to characterizing the dose response relationship appropriate?
 - Was the choice of the benchmark response level $BMCL_{0.5SD}$ for continuous data appropriate?
- Uncertainty factors
 - Was the selection of uncertainty factors appropriate and adequately justified given the noncancer risk assessment guidelines?
 - Were potential sensitive populations adequately captured?





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Schnatter Figure 3

