Scientific Review Panel
February 13, 2014

Reference Exposure Levels for Benzene

Revisions based on SRP Comments

Office of Environmental Health Hazard Assessment

Timeline of the Benzene RELs

- The Proposed Reference Exposure Levels (RELs) for benzene document was first released on June 21, 2013 for public review and comment.
- Two public workshops were held on July 17, 2013 in Sacramento and July 26, 2013 in Diamond Bar.
- The public comment period ended August 20, 2013
- OEHHA reviewed the comments received, prepared responses, and revised the REL document where appropriate.

Timeline of the Benzene REL

- The benzene REL document, the public comments and OEHHA's responses to these comments, were sent to the SRP October 9, 2013 for peer review.
- The SRP met on November 1, 2013 and provided comments to OEHHA.
- OEHHA revised version of the document discussed reflecting changes based on comments of the SRP and sent it to the SRP on January 17, 2014.
- The SRP will consider the revised document on February 13, 2014.

Key Change in Revised REL

- Primary change was increasing the intraspecies Uncertainty Factor (UF_H) to account for interindividual variability in humans for the chronic REL (and thus the 8 hr REL)
- Added text to describe data underlying the change and our rationale.

Chronic REL Intraspecies UF

- OEHHA initially used a total UF_H of 30 (equivalent to default), but which was not apportioned into toxicokinetic and toxicodynamic subfactors
- SRP asked OEHHA to reconsider value of UF_H of 30 or strengthen the rationale for 30.

Chronic REL Intraspecies UF

- After much deliberation, OEHHA decided to use a UF_H of 60 based on:
  - Chen et al. (2007) 20 fold variability in chronic benzene toxicity in workers based on a three-gene interaction related to benzene metabolism
  - Other studies of variability in the production of benzene metabolites and liver enzyme content or activity consistent with about a 10 fold kinetic variability for the enzymes or metabolites studied
  - Uncertainties remain in toxicokinetics and toxicodynamics of benzene in infants and children
- Thus, we used a UF_H of 60 to account for both toxicokinetic and toxicodynamic uncertainties among humans.

Revised chronic REL - 1

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 m^3/20 m^3 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/m^3)
NOAEL	Not found
$BMCL_{0.5SD}$	0.476 ppm (Hill Model v 2.15)

Revised chronic REL - 2

Average occupational exposure	0.204 ppm (0.476 ppm x 10/20 x 6/7)
Human equivalent concentration	0.204 ppm (0.67 mg/m^3)
LOAEL uncertainty factor (UF_L)	Not applicable with BMC
Subchronic UF (UF_S)	√10 (8-≤12% expected lifetime)
Interspecies UF	
Toxicokinetic (UF_{A-k})	1 (default, human study)
Toxicodynamic (UF_{A-d})	1 (default, human study)
Intraspecies UF	**60**
Toxicokinetic (UF_{H-k})	
Toxicodynamic (UF_{H-d})	
Database UF	1 (developmental studies are available)
Cumulative UF	200
Chronic REL	**0.001 ppm (1 ppb; 3 µg/m**

Changes related to UF_H

- Expanded discussion of toxicokinetic studies in humans (pp 12-14)
- Expanded discussion of genetic polymorphisms in enzymes involved in metabolism of benzene (pp 24-25)
- Expanded discussion regarding variability in humans in metabolism of benzene and impact on chronic benzene poisoning (pp 51-55)

Changes related to UF_H

- pp 52: added Table 8.5 which lists some results of studies quantifying variability in human toxicokinetics of benzene metabolism
  - Largest OR from studies on association of OR for chronic benzene poisoning and metabolic enzymes (referring to tables in section 6)
  - Variability in liver enzyme activity or content by age or ethnicity
  - Highest ratio of 90th percentile to median for metabolite from Rappaport et al 2013 (referring to Table 8.5)

Changes related to UF_H

- pp 53: added text and table describing results of Rappaport et al. on benzene metabolism in Chinese subjects at low benzene levels (Table 8.5)
- pp 54, 55: Additional text clarifying
  - limitations of Bois modeling study which theorized a 20-fold range in benzene metabolism
  - limitations of metabolism studies and difficulty translating into a value for UF_H.
- pp 55-56 rationale for UF_H of 60, and not dividing into toxicokinetic and toxicodynamic subfactors.

Changes related to UF_H

pp 55-56 summary statement on rationale for UF_H of 60:

"In view of the remaining uncertainties with regard to toxicokinetics in infants and children, and the larger variation in response observed by Chen et al. (2007) based on specified metabolic enzyme gene polymorphism interactions, it is considered prudent to assign an overall uncertainty factor for human inter-individual variability of 60, which is twice the default. This UF_H is not further subdivided into $UF_{H\text{-}k}$ and $UF_{H\text{-}d}$ since this assignment is uncertain."

Acute REL

- pp 43: did not change acute REL value of 8 ppb (27 μg/m³)
- pp 44-45: elaborated on use of default UF_H of 30 for acute REL:
- The results of the Chen et al. (2007) study on the association between OR for chronic benzene poisoning and gene polymorphisms in metabolizing enzymes do not seem relevant to the UF_H for the acute REL, which is used to evaluate infrequent one hour exposures.

Acute REL UF_H

- For the acute REL, the critical effect is developmental with pre-natal exposure
- Therefore, it is reasonable to assume that concern regarding systematic interindividual differences associated with early life-stage (including effects *in utero*) are accommodated in the toxicity data.

Other Changes in Response to SRP

- Clarifications on ambient measurements of benzene
- Re-organization and additions to metabolism section
- Additions to chronic benzene toxicity section (some described earlier)
- Addition to Acute Toxicity to children
- Benzene as a Toxic Air Contaminant that disproportionately impacts infants and children

Benzene in Ambient Air - BAAQMD and SCAQMD measurements

- pp 5 and 6
  - Added footnote to Table 3.1 – values are 24-h integrated samples
  - Added information on MATES III
  - Included maximum values in Table 3.2
  - Highlighted paired stations in Table 3.3
  - Mentioned MATES IV

Metabolism

- pp 8: used more recent diagram of metabolism by Rappaport
- pp 9&10: added clarifying statements on possible metabolites responsible for toxicity
- pp 10: mentioned obesity as possible risk factor
- pp 11-14: subdivided animal and human information; added study by Kim on polymorphisms; summarized studies

Metabolic Interaction

- New Section 4.3
- Discusses interaction of benzene and ethanol, including induction of CYP2E1 by ethanol

Acute Toxicity to Infants and Children

- pp 17: added recent (2013) report
- D'Andrea and Reddy. Health Effects of Benzene Exposure among Children Following a Flaring Incident at the British Petroleum Refinery in Texas City.
  - Benzene one of several chemicals
  - Adverse effects on nervous system & liver
  - No exposure concentrations

Chronic Toxicity of Benzene

- pp 20: added paragraph on myeloproliferative disorders and myelodysplastic syndrome and how they are considered to be cancer
- pp 24 and 25 added:
  - Table 6.3 on NQO1*2/*2,
  - Table 6.4 on GST genotypes
  - Table 6.5 on interaction of three genes from Chen et al, 2007
- pp 27: mentioned HIV and $CD4^{+}$-T cells

Developmental and Reproductive Toxicity

- pp 39: added footnote about difference between early and late nucleated red cells
- pp 41: added 2013 study by Zhu et al. on increased sensitivity to hydroquinone in immature hematopoietic cells in mice

TAC Impacting Children

- pp 57-58: added information to strengthen the argument that benzene should be added to the list of TACs that may disproportionately impact infants and children

- Questions?
- Comments?
- Suggestions?

Staff Update on Items Likely Coming to the Panel in 2014

- Guidance Manual for Preparation of Health Risk Assessments
- Reference Exposure Levels
  - Carbonyl Sulfide
  - Toluene Diisocyanate
  - Methylene Diphenyl Diisocyanate
- Potency Values
  - Arsenic
  - Isoprene