# Methods for Deriving Inhalation Effect Levels for Comparison to Health-Protective Values

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**Science and Decisions Workshop 4**

**May 24, 2012 Austin, TX**

# Overview

- Method Purpose: To derive air concentration effect levels based on available dose-response data at which health effects have been observed in toxicity studies. This is to put the corresponding health-protective level (e.g., RfC) into context for risk managers, the public, etc.
- The method for *identification of inhalation effect level* fits into the quantitative dose-response evaluation case study portion of the workshop framework as the natural corollary to the "screening level safe dose" component.

# Overview

- Problem formulation
- Definition of effect levels
- Method to derive effect levels
- Effect levels developed for example chemicals based on Mode of Action (MOA)

# Overview

- Effect Levels developed for example chemicals
  - Non Threshold MOA, Cancer:
    - Methylene Chloride (animal data);
    - Chronic 1,3-Butadiene (occupational epidemiology studies)
    - Chronic Benzene (occupational epidemiology studies)
  - Threshold MOA:
    - Acute 1,3-Butadiene (BMC modeling)
    - Subacute Benzene (subacute animal studies)
    - Acute Acrolein (human studies)
    - Chronic Acrolein (subchronic animal studies)

# Problem Formulation

- The general public typically believes that if an exceedance of a health-protective level occurs, then adverse health effects will occur
- A comparison of health-protective levels (e.g., RfCs) and the levels where adverse effects have been observed in the critical study provide useful information and important perspective for risk managers and the general population.
- This information is an important part of the risk communication process.

# Problem Formulation

- Perspective
- Information

# Effect Level

- Definition may vary depending on the available point of departures (PODs) in the critical study
  - Lowest observed adverse effect level (LOAEL)
  - Benchmark concentration (BMC) modeling
    - Central Estimate
    - Continuous data versus dichotomous data
  - For cancer, the maximum likelihood estimate at the concentration where effects were statistically significant or a range of $10^{-4}$ to $10^{-3}$ risk level

# Definition of an Effect Level

- Effect level based on human dose-response data is an estimate of the lowest point of departure ($POD_{HEC}$) that has been observed to cause an adverse response in some humans exposed over a similar or longer duration.
- Potential human effect levels based on animal dose-response data are estimated by the range of $POD_{HEC}$ values where adverse effects were observed in animal studies. It is possible some humans exposed over a similar or longer duration may have an adverse response (assuming no sufficient data on interspecies variability are available).

# Definition of an Effect Level

- The probability of response associated with the POD(s) used to estimate an effect level may be informative as to the probability of response in similarly-exposed individuals (e.g., $BMC_{10}$ or % response at the $LOAEL_{HEC}$)

# Methods

- Effect levels are based on the lowest concentrations demonstrated to cause adverse health effects for the critical effect (i.e., LOAELs or central estimate)

- PODs associated with effects should generally not be divided by uncertainty factors (UFs) or duration adjusted since these procedures often have an unknown effect on the probability of a response actually occurring

# Methods

- Predictive adjustments - such as PBPK, CSAF, or animal-to-human dosimetry adjustments are performed to derive a $POD_{HEC}$

- Duration adjustments believed to be toxicologically predictive for the chemical and endpoint are performed. Otherwise, the estimated effect level is tied to the exposure scenario under which adverse effects were observed

# Narrative

- An actual “bright line” cannot be accurately predicted
- Effect levels have appropriate and often unavoidable caveats. The caveats associated with an effect level will vary based on the data available
- When effect levels are developed, the values should be accompanied by a narrative that discusses the associated uncertainties of the effect levels

# Methylene Chloride Carcinogenic Effect Level

- Based on dose-response data and mouse-to-human PBPK modeling ($TD_{HEC\ 0.05}$ values), it would be reasonable to expect a carcinogenic response in some individuals exposed chronically to around 650 to 4,100 ppm.

- This range is 6,500 to 41,000 times higher than TCEQ's long-term health-based comparison value for ambient air of 0.1 ppm (TCEQ 2011)

# Methylene Chloride Carcinogenic Effect Level

- The carcinogenic effect levels may fit well with relevant human data for the chemical.

- For example, concentrations in excess of 500 ppm may be needed to saturate the high-affinity MFO metabolic pathway, and MC is not known to cause cancer even in workers exposed to high MC concentrations (e.g., no excess risk of death from malignant neoplasms has been detected in workers exposed to MC at levels up to 475 ppm) (ATSDR 2000).

# 1,3-Butadiene Carcinogenic Effect Level

- **9.1 ppb:** $10^{-5}$ Excess Cancer Risk for leukemia mortality based on a URF of 1.05E-03/ppm (95% UCL) calculated for the general population and including a Age-Dependent Adjustment Factor

- **130 ppb to 1300 ppb: :** $10^{-4}$ to $10^{-3}$ Excess Cancer Risk Range for leukemia mortality based on a URF of 7.471E-04/ppm (maximum likelihood estimate (MLE))

- **800 ppb:** A free standing NOAEL for biomarkers of effect (HPRT mutations and chromosome aberrations) at mean BD exposure concentrations of 800 ppb was observed in a small initial study of workers in the Czech Republic (Albertini et al. 2001).

# 1,3-Butadiene Carcinogenic Effect Level

- **2700 ppb (general population):** ≤ 300-ppm-years was the lowest cumulative ppm-years interval (occupational exposure) where the likelihood ratio test that slope = 0 was *not* statistically significant ($p < 0.0591$) for leukemia deaths (Sielken et al. 2011)

- **3600 ppb (general population):** ≤ 400-ppm-years was the lowest cumulative ppm-years interval (occupational exposure) where the likelihood ratio test that slope = 0 *was* statistically significant ($p < 0.0156$) for leukemia deaths (Sielken et al. 2011)

# Benzene Carcinogenic Effect Levels

- **Carcinogenic Effect Levels ≈120-230 ppb mean lifetime exposure**: Based on USEPA's (1998) confidence that the risk of leukemia increases at 40 ppm-years of occupational benzene exposure based on epidemiological study dose-response data, which equates to a lifetime environmental exposure level of approximately 120 ppb (assumes no dose rate effect), as well as a 1E-03 excess risk level (lower bound rule-of-thumb detectable excess risk for a well-conducted study) of 230 ppb.
- TCEQ's long-term health-based comparison value for ambient air is 1.4 ppb (86-164 times lower) (TCEQ 2007)

# 1,3-Butadiene: Acute adverse effect level using BMC modeling (threshold MOA)

- **1.7 ppm:** The acute 1-hr reference value (ReV) is based the $BMCL_{1\,SD}$ (HEC) of 51.3 ppm for reduction in maternal extragestational weight gain divided by total UFs of 30 (developmental study in mice).

- **66 ppm:** This effect level is based on the $BMC_{05}$ (HEC) of 65.8 ppm for decreased fetal body weight (developmental study in mice). The NOAEL was 40 ppm and the LOAEL was 200 ppm.

- **1,500 ppm:** This effect level is based on the LOAEL for persistent reductions in body weight parameters in F0 and F1 males and females rats, an animal species known to be more similar to humans (two generation study).

- **2,000 ppm:** This value is the lowest known effect level in humans for slight smarting of the eyes and difficulty in focusing on instrument scales after two humans were exposed for seven hours to BD

# Benzene

## Subacute adverse effect level

- **Subacute Effect Levels ≈10-100 ppm over multiple consecutive days**: Based on dose-response data for hematotoxicity (e.g., decreased lymphocytes)from subacute mouse studies in various strains, the range for human effect levels may be around 10-100 ppm for subacute exposure (e.g., 6 h per day, 5-6 day). For comparison, TCEQ's 1-hour health-based comparison value for ambient air is 0.18 ppm (56-556 times lower) (TCEQ 2007).

- This effect level range may be viewed as reasonable given long-term worker exposure levels that result in blood cell decrements. For example, 7.2-13.6 ppm resulted in lymphocyte depression in the Rothman et al. (1996) study.

# Acute Effect Level for Acrolein

- **4.8 ppb:** The health-protective 1-hr reference value (ReV) is based on the critical effects of eye, nose and throat irritation and decreased respiratory rate in a study with both male and female human volunteers. There was no NOAEL. At the LOAEL of 0.3 ppm, a significant number of volunteers ($p<0.01$) experienced a 10 percent decrease in respiratory rate after 40 min of exposure to 0.3 ppm acrolein. The ReV is based on that LOAEL divided by total UFs of 63 (TCEQ 2010)

- **300 ppb:** The effect level is the LOAEL of 0.3 ppm from the same key human study as above.

# Acrolein Subchronic/Chronic Effect Levels

- **0.22 ppb:** The health-protective chronic reference value (ReV) is based on the critical effect of mild hyperplasia of the respiratory epithelium of male F344 rats, without recovery, in a subchronic study. The ReV is based on the NOAEL of 0.2 ppm converted to a duration-adjusted HEC concentration of 0.006678 ppm and divided by total UFs of 30 (TCEQ 2010)
- **110 ppb:** This subchronic effect level is based on the same critical effect as above. The LOAEL in the study was 0.6 ppm and the HEC concentration was 0.11 ppm
- **260 ppb:** This subchronic effect level is based on the critical effect of bronchiolar epithelial necrosis in male and female F344 rats in a subchronic study (62 d). The LOAEL was 1.4 ppm and the HEC concentration was 0.26 ppm
- **(100 ppb:** This chronic effect level is based on the critical effects of inflammation, hyper- and metaplastic changes in the nasal cavity of male and female Syrian hamsters in a chronic (1-yr) study. The LOAEL was 4 ppm and the HEC concentration was 1.14 ppm

# Conclusions

- **The goal is to use available D-R data to calculate the HEC for the lowest level at which adverse effects were observed in the critical study** such that there is as high a confidence as possible that effects could occur in an similarly-exposed human population.

- Only adjustments believed to be toxicity-predictive for the specific chemical and effect are performed (maintain the probability of response), as opposed to nonchemical-specific adjustments amounting to speculation about how low an effect level might be.

- For comparison to health-protective level.

# Conclusions

- Chemical-specific effect levels are determined considering MOA (threshold versus nonthreshold).
- Threshold:
  - LOAEL- or BMC-based HECs or range based on animal data when interspecies sensitivity unknown.
- Nonthreshold: $POD_{HEC}$ associated with the lowest excess risk detected and/or 1E-03 MLE risk (e.g., interspecies sensitivity or worker exposure duration/dose rate considerations).

# Conclusions

- The definition and caveats for an effect level will vary based on the available data (e.g., effect, interspecies, intrahuman, response level).
- Presenting information on **observed** effect levels provides perspective and information to risk managers and the general public.
- It may be difficult to calculate a "bright line."

# Charge Questions

- Please comment on the usefulness of providing information on effect levels or effect level intervals to understand potential health effects when health-protective levels are exceeded.

# Charge Questions

- When both concentration and duration play a role in toxicity, and only a subacute or subchronic animal study is used for developing an effect level, how should the corresponding human exposure duration be determined (e.g., 90-day mouse exposure = x-day human exposure, the proportion of lifespan, etc.).

# Charge Questions

- Comment on the "meaning" or definition of an effect level if central tendency values of the distribution of $UF_H$ and $UF_A$ are applied to effect levels

# Charge Questions

- The main purpose of determining effect levels is to provide perspective on the health-protective levels (e.g., RfC, ReV) and useful information to risk managers and risk assessors conducting health effects reviews of data when an exceedance of a health-protective value is observed.

- Instead of providing a single effect level value, please comment on the utility of providing "effect level intervals"

# Questions


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