An Updated Inhalation Unit Risk Factor for Arsenic and Inorganic Arsenic Compounds

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What's in a name?

Background

- **Goal:** To protect the general population including children and pregnant women from **Lung Cancer/Respiratory Cancer** from chronic exposure to inorganic arsenic in **ambient air.**

- **Problem Formulation** focused on **Inhalation Pathway & Human Epidemiology Studies**

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Background

- The Toxicology Division (TD) of TCEQ has developed Inhalation Screening values called Air Monitoring Comparison Values (AMCVs) for ambient air monitoring
- These values are similar to EPA's Reference Concentrations (RfC) and California's Reference Exposure Levels (RELs)

TCEQ's Process

- Using the Toxicity Factor Guidelines TCEQ developed a Unit Risk Factor (URF) based on Updated and New Epidemiological data with Statistical Support provided by Sielken & Associates
- Toxicology Excellence For Risk Assessment (TERA) organized a Peer-Review.
  - Dr. David Gaylor, Dr. Kyle Steenland, & Dr. Kirk Kitchin were the peer-reviewers.
  - 2 Rounds of Public Comment period
  - URFs are available on the Toxnet website
  - http://toxnet.nlm.nih.gov/

TCEQ Arsenic Unit Risk Factor (URF)

- Erraguntla NK, Sielken RL Jr, Valdez-Flores C, Grant RL. (2012)An updated inhalation unit risk factor for arsenic and inorganic arsenic compounds based on a combined analysis of epidemiology studies. Regul Toxicol Pharmacol 64(2):329-41.

- Development Support Document (DSD) is available
  - http://www.tceq.state.tx.us/toxicology/dsd/final.html

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Table 1. Summary of the 4 epidemiological studies of arsenic with adequate dose-response data for cancer risk assessment

Study location and exposure period	Most recent dose-response data	Last year of cohort follow-up	Number of workers Person-years (PY)	Cancer site SMR[a] (p-value) (Standard Mortality Ratios)	Range of cumulative arsenic exposure (mg/m^3- yr)[b]
Tacoma, WA Asarco copper smelter (1940-64)	Enterline *et al.* (1995)	1986	2,802 84,916	Respiratory 209.7 (p<0.01)	<0.750 to 45+
Montana copper smelter (1938-1958)	Lubin *et al.* 2000; Lubin *et al.* 2008	1989	8,014 144,851[c] (restricted cohort) 256,850 (full cohort)	Respiratory 187 (P<0.001) (restricted cohort) 156 (p<0.001) (full cohort)	1 to 26.2+
Ronnskar, copper smelter (1928-1967)	Järup *et al.* (1989); Viren and Silvers (1994)	1981	3,916 127,189	Lung 372 (p<0.001)	<0.25 to 100+
United Kingdom tin smelter (1937-1991)	Jones *et al.* 2007	2001	1,462 35,942	Lung 161 (p<0.001)	<0.002 to 4.5+

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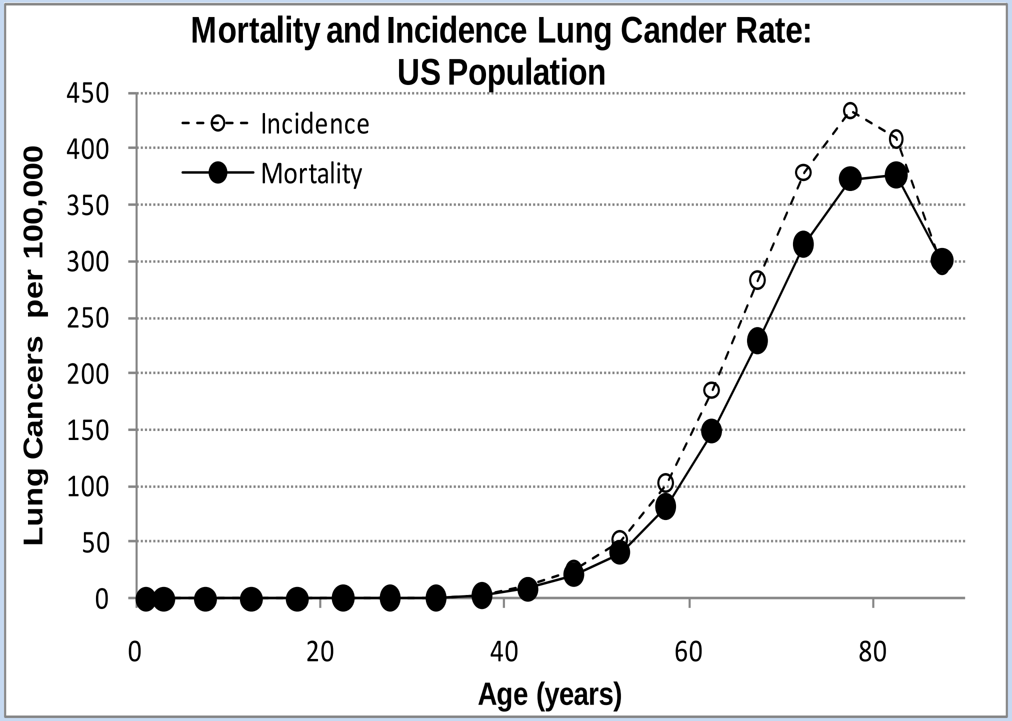
Figure 1. Lung Cancer Mortality Rates versus Incidence Rates[a]



Lung cancer mortality is reasonably predictive of lung cancer incidence (i.e., five-year survival is only about 15% according to the American Cancer Society 2005)

Dose Metric & Dose-Response Assessment

- Occupational concentrations were converted to environmental concentrations for the general population using standard procedures.

- The dose metric used for the dose-response assessments is cumulative arsenic exposure (µg/m^3-yr)

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URFs Contd…

- The models used here are based on human epidemiological studies and have been fit to a linear equation (linear multiplicative relative risk model) for use with the BEIR IV methodology (NRC 1988).
- Air concentrations are solved iteratively with life-table analyses using the BEIR IV approach (NRC 1988). Air concentrations based on extra risk are calculated as opposed to added risk.
- Mortality and survival rates are used to calculate air concentrations based on a lifetime exposure of 70 years, the default used by TCEQ for exposure analysis (TCEQ 2006).

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Texas and US Specific Mortality Rates

- Texas-specific mortality rates for 2001-2005 for lung cancer and Texas-specific survival rates for 2005 are used in the calculation of PODs and URFs.
- Didn't make much difference in final URF what mortality rates were used.

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Peer Reviewer's Suggestions resulted in 3 types of Analysis

1) Combined- Analysis using Inverse Variance
2) Meta-Analysis Using Dose-Response Models to Fit the Combined Data
3) Sensitivity analysis with the UK study and using US Mortality and Survival rates (See Appendix of the Arsenic DSD)

Combined- Analysis using Inverse Variance

- The individual URF's were weighted based on inverse variance
- The individual weighted URFs were then combined together to calculate a final URF.

Preferred URFs and 10^{-5} Risk Air Concentrations Tacoma, Montana & Swedish Cohorts

Study and Inverse Variance 1. (Person Years -PY)	β (Maximum Likelihood Estimate-MLE) URF 10^{-5} Risk Air Concentration	β (95% Lower Confidence Limit - LCL) URF 10^{-5} Risk Air Concentration	β (95% Upper Confidence Limit- UCL) URF 10^{-5} Risk Air Concentration	Ratio: URF (95% UCL) to URF (MLE)
Tacoma cohort (Enterline et al. 1995) All workers adjusting for year of hire 3.13E+08 (84,916 PY)	1.19E-04/ $\mu g/m^3$ 0.0837 $\mu g/m^3$	2.72E-05/ $\mu g/m^3$ 0.367 $\mu g/m^3$	2.12E-04/ $\mu g/m^3$ 0.0471 $\mu g/m^3$	1.8
Montana cohort (Lubin et al. 2008) Full cohort 2.65E+08 (256,850 PY)	2.18E-04/ $\mu g/m^3$ 0.046 $\mu g/m^3$	1.18E-04/ $\mu g/m^3$ 0.0850 $\mu g/m^3$	3.19E-04/ $\mu g/m^3$ 0.0313 $\mu g/m^3$	1.5
Sweden cohort (Järup et al. 1989) All workers adjusting for year of hire 2.60E +08 (127,189 PY)	1.11E-04/ $\mu g/m^3$ 0.0902 $\mu g/m^3$	8.76E-04/ $\mu g/m^3$ 1.14 $\mu g/m^3$	2.13E-04/ $\mu g/m^3$ 0.0470 $\mu g/m^3$	1.9
Ratio: high to low URFs (MLE)	2.0			

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Final URF

- Final URF (Risk per µg/m^3) =

= [(URF$_1$ x Weight$_1$) + (URF$_2$ x Weight$_2$) + (URF$_3$ x Weight$_3$)]/[Weight$_1$ + Weight$_2$ + Weight$_3$]

- Where, Weight$_i$ = [1/SE(URFi)]^2 for i=1, 2, and 3.

= 1.5 E-04 per µg/m^3 (Rounding to 2 significant figures)

- The resulting air concentration at a 1 in 100,000 excess lung cancer risk is 0.067 µg/m^3 (rounded to two significant figures).

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Meta-Analysis

- Meta-Analysis on the combined data from the three studies with similar dose metric was conducted.
  - The linear multiplicative rate ratio model was fit to the combined data using Poisson regression and maximum likelihood estimation (MLE).

- **URF (MLE) = 1.60E-04 per μg/m^3 (95% UCL: 2.19E-4 per μg/m^3) based on meta-analysis with different alpha intercepts for different cohorts and common slope**

Summary

- Combined- Analysis Using Inverse Variance of the URFs to Weight Individual URFs:
- **URF (MLE) =1.5E-04 per µg/m^3 (95 % UCL: 2.05 ×10-4 per µg/m^3)**

- Meta-analysis
  - **URF (MLE) = 1.60E-04 per µg/m^3 (95% UCL: 2.19E-4 per µg/m^3)**

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Uncertainty Analysis

- Uncertainty in Dose-Response modeling due to use of cumulative dose as the dose-metric
- Estimating risks for the general population from occupational workers
- Co-exposures to other compounds

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Questions

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