Understanding risks for non-constant exposure patterns: experimentation and defining dose metrics

Presented by Lisa M. Sweeney, Ph.D., DABT
Henry M. Jackson Foundation for the Advancement of Military Medicine, on detail to Naval Medical Research Unit Dayton, Wright-Patterson Air Force Base, Ohio

January 27, 2016

US EPA Workshop on Temporal Exposure Issues for Environmental Pollutants: Health Effects and Methodologies for Estimating Risk, Research Triangle Park, NC

Disclaimers/Acknowledgments

- The views expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government.
- The study protocol was reviewed and approved by the Wright-Patterson Air Force Base Institute of Research Institutional Animal Care and Use Committee (IACUC) in compliance with all applicable Federal regulations governing the protection of animals in research.
- This work was supported by the Defense Threat Reduction Agency, Work Unit Numbers H1107 and H1502.

Copyright

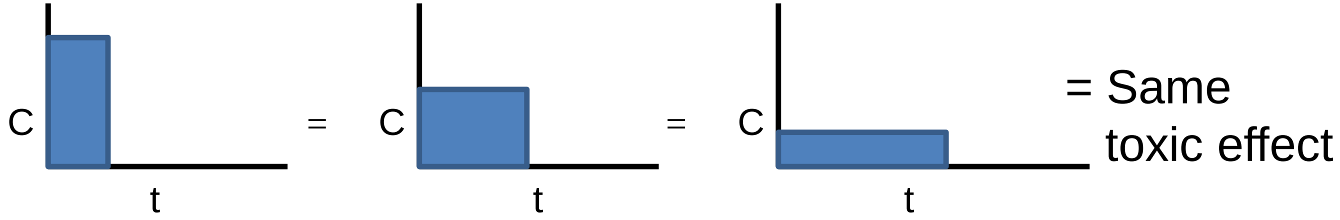
- I am a military service member (or employee of the U.S. Government). This work was prepared as part of my official duties. Title 17 U.S.C. §105 provides that 'Copyright protection under this title is not available for any work of the United States Government.' Title 17 U.S.C. §101 defines a U.S. Government work as a work prepared by a military service member or employee of the U.S. Government as part of that person's official duties.

Outline

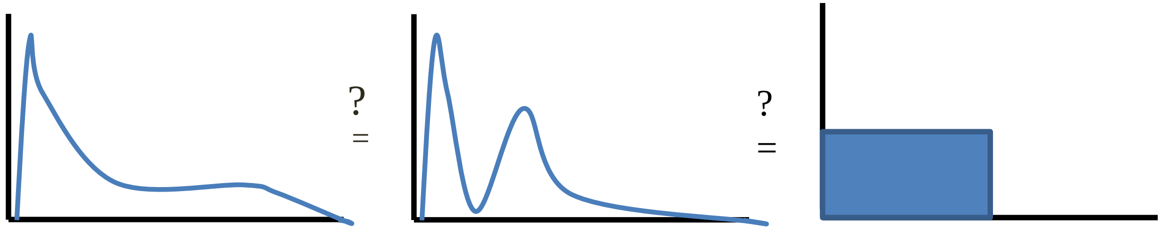
- Department of Defense perspective
- Experimental approach
- Hydrogen cyanide studies
- Carbon monoxide studies
- HCN and human modeling
- Conclusions

DOD Perspective

- The Toxic Load Model (ten Berge's law) has been used to develop 79 human C × t toxicity estimates for DOD compounds of concern
- DOD uses these toxicity estimates for consequence (casualty) assessments and planning (e.g., National Strategic Stockpile)
- Primary interest is in predictivity, rather than conservatism or precautionary assumptions (UFs)
- Concentration vs. time profiles for releases of interest are likely to deviate from traditional laboratory exposure profiles



$C \times t = k$ or $C^n \times t = k$



DOD Perspective

- Questions centered around how to integrate/degree of resolution needed for C vs. t profile (i.e., continuous integration of C^n x dt, or computation as $(Cavg)^n \times t$, peaks vs. time weighted average)
- No suitable experimental data to answer the questions were identified
- Experimental work and data analysis was funded by the Defense Threat Reduction Agency, conducted by NAMRU-Dayton and U.S. Army Edgewood Chemical Biological Center (Aberdeen Proving Ground, MD)

Experimental Investigations

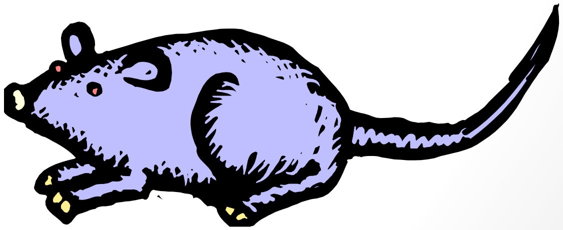
- **Hypothesis**: The toxic load model will not always be valid when C varies during the exposure event
- **Goal 1**: Develop data sets to address the hypothesis
- **Goal 2**: Identify the domain of applicability for the toxic load model, based on analysis of data
- **Selection of chemicals and endpoints**
  - Toxic load exponent (n) $\neq 1$
    - Previous data
  - Unambiguous endpoint
  - Operational relevance desirable, but not a requirement
  - Ease of handling/atmosphere generation
  - Quick-acting

Experimental Investigations

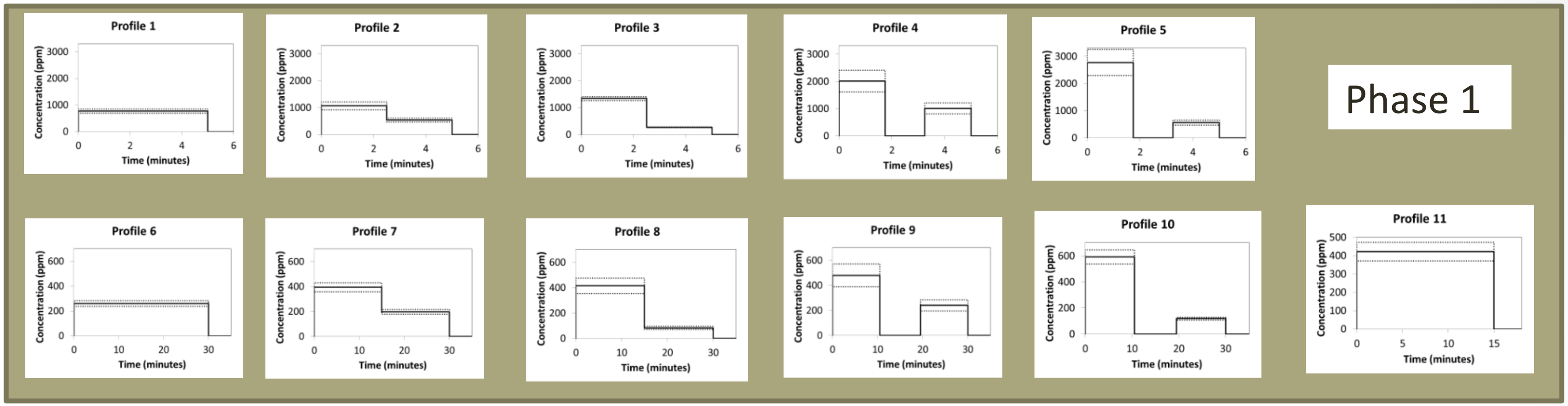
- **Study design**
  - Single concentration (baseline exposures)
    - To determine toxic load model parameters
  - Within each of 3 studies, a limited number of descriptors for C vs. t profile were considered
  - Exposures with two concentrations, with or without a recovery period (gap)
  - Concentrations were selected to provide coverage of full dose-response range, with emphasis on EC_{50} confidence

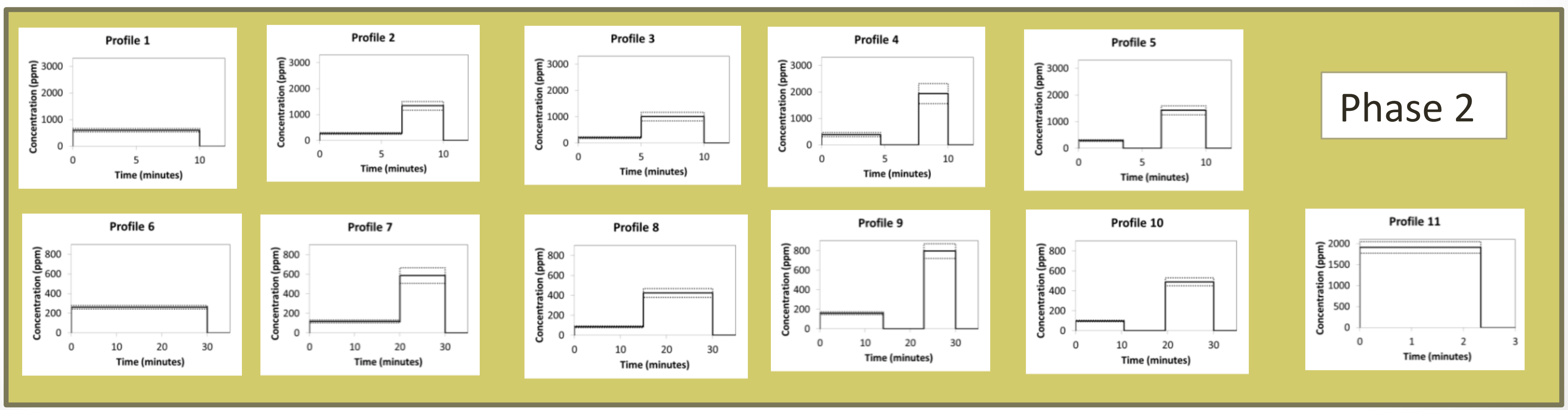
HCN Studies (Sweeney et al., 2014, 2015)

- Endpoint: lethality of HCN during inhalation exposures of adult male Sprague Dawley rats (2.33-30 min.)
- Duration of non-constant exposures: 5, 10, or 30 minutes
- Gap: 0 or 30% of total duration
- Pulse duration ratio: 1:1 or 2:1
- Pulse height ratio: 5:1 or 2:1
- Pulse height ordering: High/low or low/high



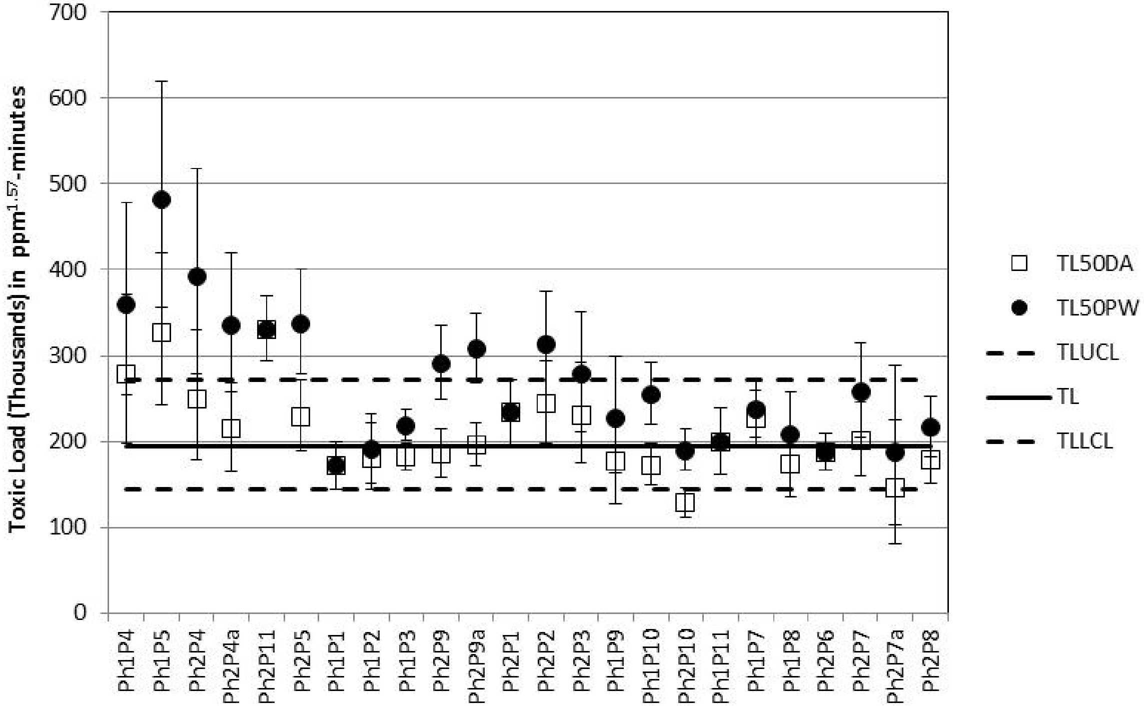
HCN Results (Sweeney et al., 2014, 2015)





Concentrations for median lethality in rats for different profiles determined by BMDS (4-9 trials per profile, 10 rats/trial)

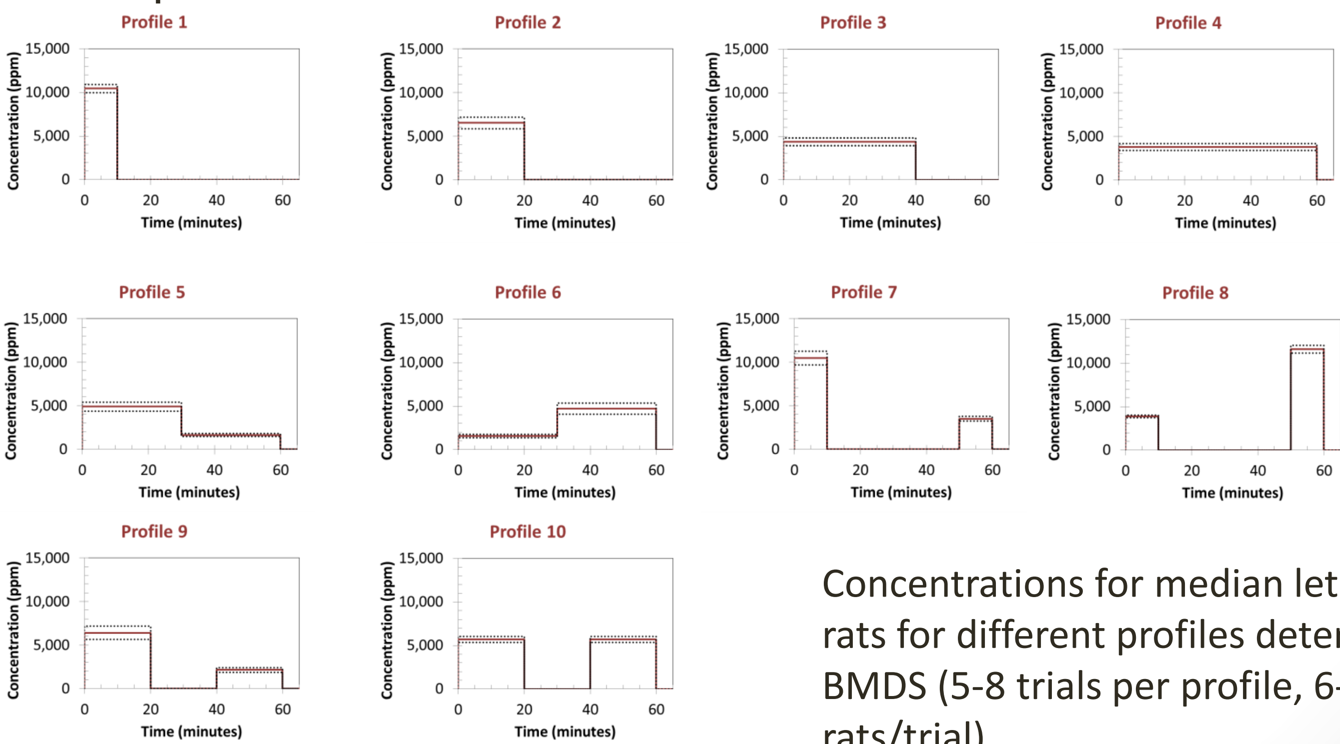
HCN Results (Sweeney et al., 2014, 2015)



Toxic loads computed by the duration averaging approach (TL50DA = unfilled squares) or piecewise method (TL50PW = filled circles); symbols overlap for constant-concentration exposures and appear as squares surrounding a filled circle. Solid line = toxic load (computed from 5-, 10-, 15-, and 30-minute constant concentration exposures); dashed line = maximum upper and lower confidence limits on the toxic load from the same exposure profiles. X-axis labels indicate Phase 1 (Ph1) (Sweeney et al., 2014) or Phase 2 (Ph2) (Sweeney et al., 2015) and the Profile number and are arranged according to increasing duration of continuous exposure (shortest pulses with a gap, vs. longer pulses with no gap, or 30-minutes continuous exposure).

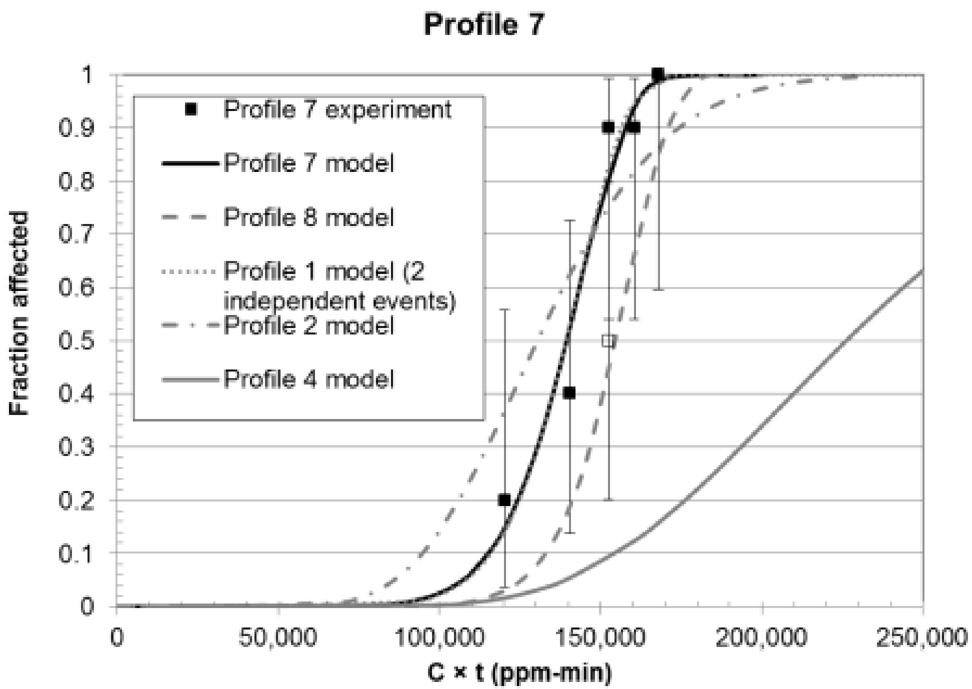
Carbon Monoxide (CO) Study

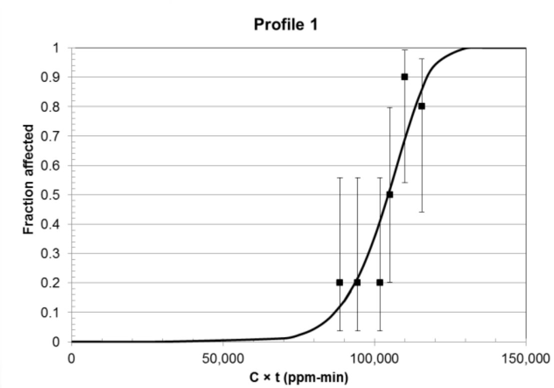
- Key differences from HCN studies:
  - Larger gap tested (67% of event duration)
  - A profile with equal pulse heights was tested
  - Analysis considered full response range, not just discrete response levels

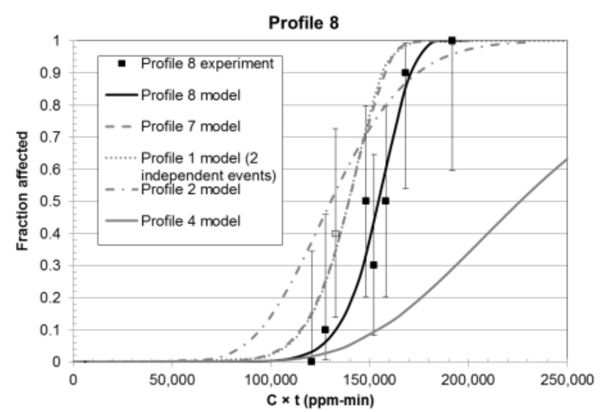


Concentrations for median lethality in rats for different profiles determined by BMDS (5-8 trials per profile, 6-10 rats/trial)

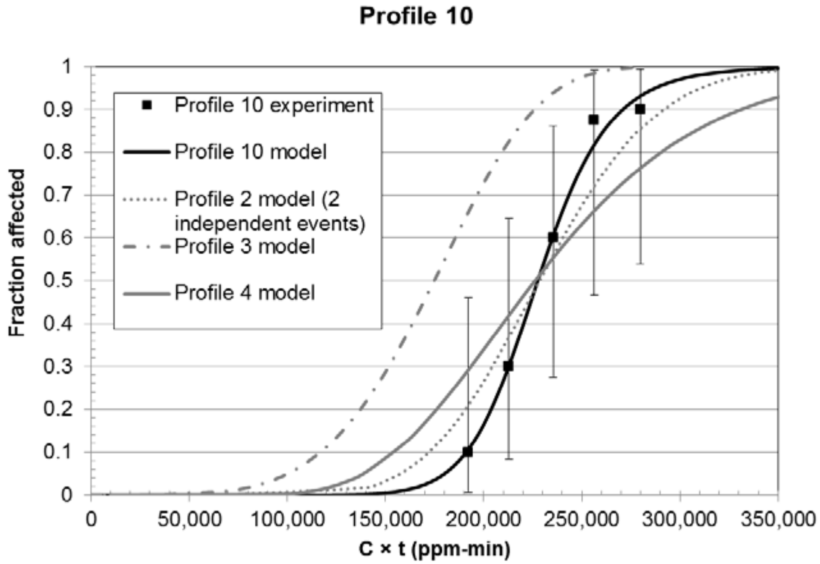
Carbon Monoxide (CO) Study

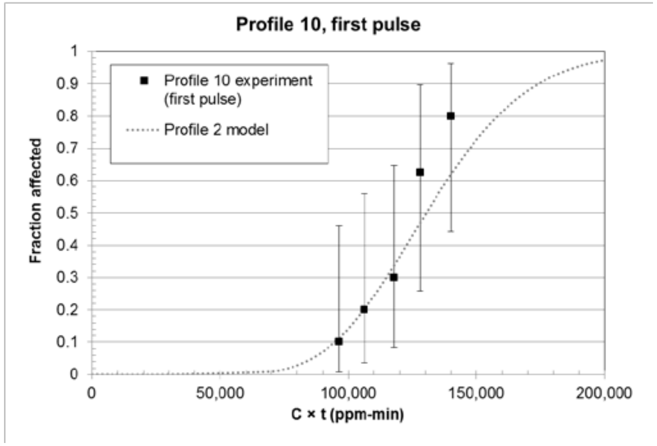


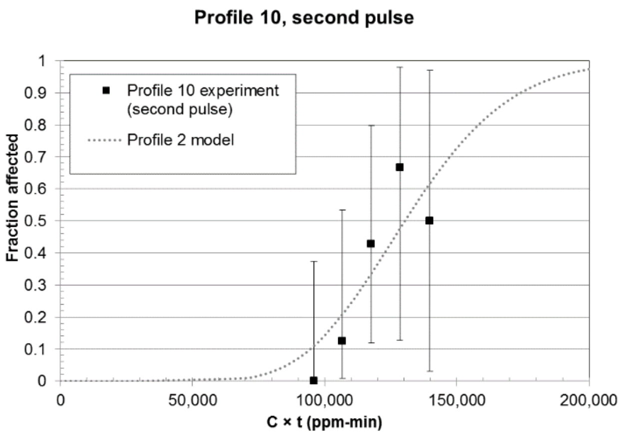




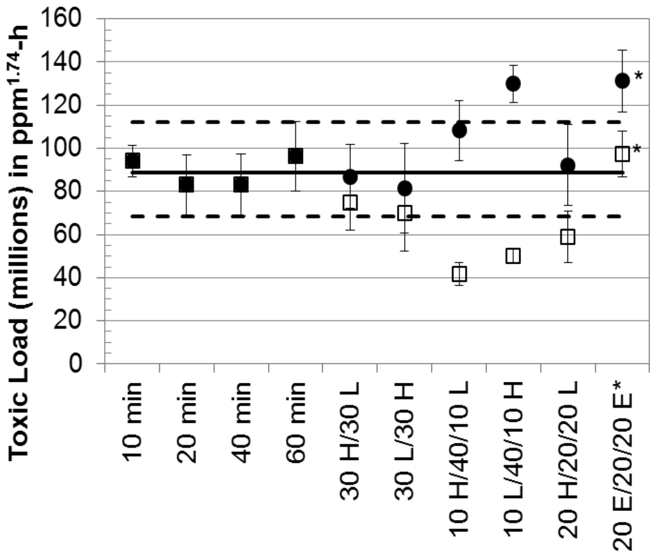
Carbon Monoxide (CO) Study



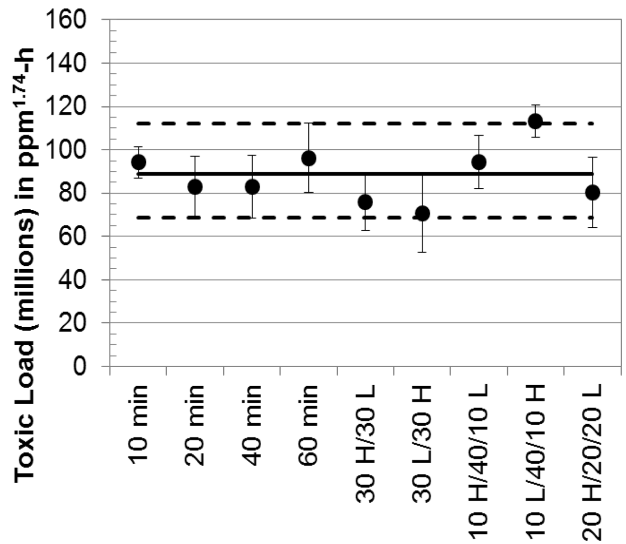




Carbon Monoxide (CO) Study



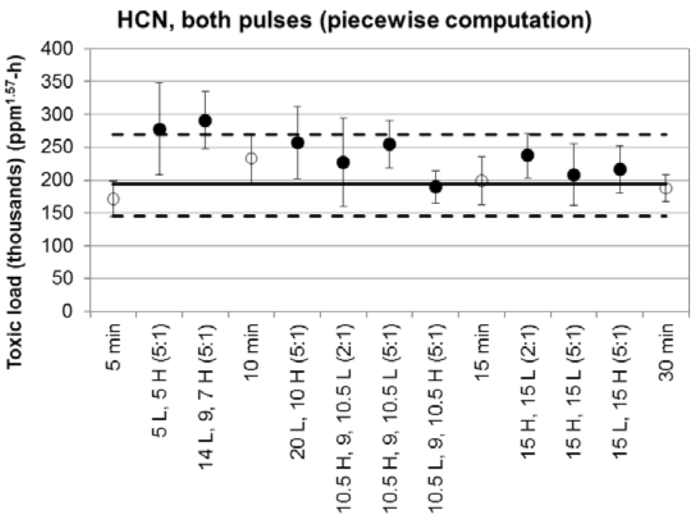
(a)

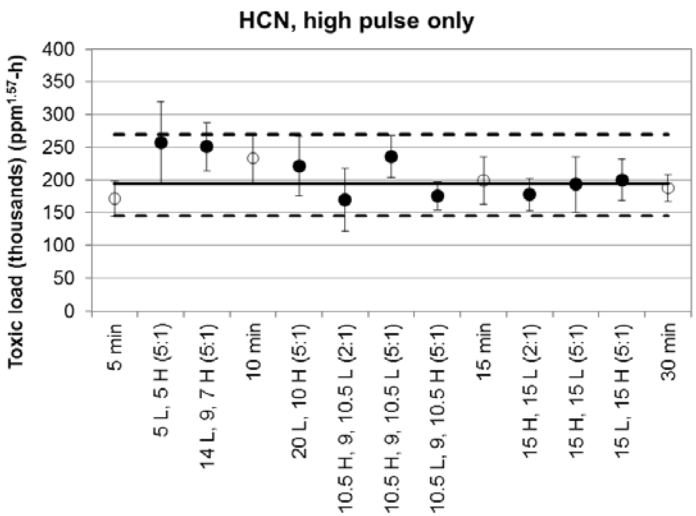


(b)

TLs for median lethality of inhaled CO in male Sprague-Dawley rats. The horizontal lines represents the TL estimated from the single pulse LC_{50} values. The squares represent TLDA, while the circles represent TLPW. (a) TLs computed for the full duration of the profile. (b) TLs computed for only the higher concentration pulse.

HCN Study Revisited





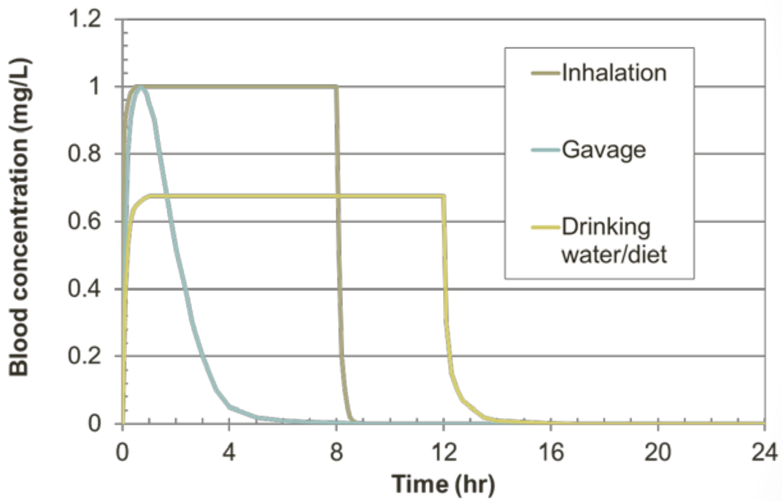
Toxic loads for median lethality of inhaled HCN in male Sprague Dawley rats. The horizontal line represents the toxic load estimated from 4 single pulse LC_{50} values. Toxic loads were computed piecewise for both pulses (left) or for only the high concentration pulse (right) from previously reported data (Sweeney et al., 2014, 2015; minimum pulse duration of 5 min, to exclude possible effects of breath holding). Unfilled circles indicate single-pulse profiles, while filled circles indicate two-pulse profiles.

Observations in Light of HCN and CO Experiments

- Specific:
  - Due to rapid clearance, response, and recovery, peak concentrations determined the outcome
  - Steepness of dose-response relationship was important
  - Relatively simple non-constant profiles demonstrated the impact of concentration changes (fluctuation) and non-exposure periods
- General:
  - The extent to which the exposure profile deviates from constant exposure should be considered; similarity to equal “peak” or equal “TWA” exposures may apply
  - Extrapolation to more complicated C vs. t profiles would be facilitated by PK modeling
  - Data sets against which modeling approaches (e.g., key dose metric identification) can be tested are lacking, preventing model validation

What is the “Right” Dose Metric?

- Candidate dose metrics
  - Peak vs. AUC
  - Parent compound vs. metabolite
    - Amount metabolized as a surrogate for concentration of metabolite
- May be a source of significant uncertainty for extrapolation across exposure scenarios
- When studies are conducted via different exposure scenarios, discrimination among dose metrics may be facilitated



Modeling HCN Lethality in Humans (Stamyr et al., 2015)

- Does *not* follow Haber's Law

Exposure level (ppm)	Time to effect	Reference
270	6-8 minutes	Flury and Zernik (1931)
181	10 minutes	Hall and Rumack (1986)
135	30 minutes	Hall and Rumack (1986)
110-135	30-60 minutes	Flury and Zernik (1931)

- Lethal concentration of HCN in whole blood determined (Alarie, 2002)
- PBPK model for HCN developed; two pathways for HCN clearance, one limited by availability of sulfur donors
- Times to lethal HCN blood concentration determined by the PBPK model compare favorably with observed time to effect

Summary

- A disconnect exists between C vs. t profiles of interest for many risk assessment scenarios and the available experimental data on effects
- Appropriately designed studies and modeling can help bridge the gap
- The available effect data for CO and HCN in rats illustrate the importance of PK and PD half-lives and dose-response characteristics for toxicants under non-constant exposure conditions
- Development of additional case studies would provide anchoring data to aid in the development of frameworks for risk assessment of exposures with temporal variability

Acknowledgements

- Doug Sommerville (ECBC)
- Steve Channel (Leidos)
- Nathan Gargas, Michelle Goodwin, Brian Sharits, Chet Gut, Kathy Frondorf, Elizabeth Phillips, Brian Wong (NAMRU-Dayton)
- Defense Threat Reduction Agency

Back up slide(s)

Experimental Investigations

- **Exposure system design**
  - Two separate gas generation systems
  - Mass flow controllers to meter gas and dilution air
  - Solenoid valves to start and stop flows
  - Nose-only exposure system (low volume)