Factors Contributing to Variability; Conundrums in Occupational Risk Assessment

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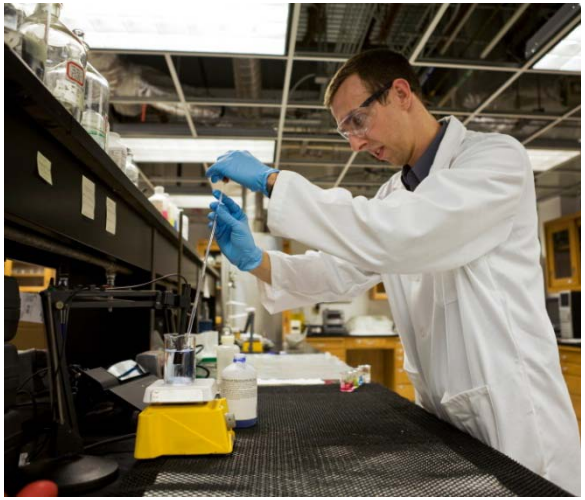
Variability in Occupational Risk

- Reminder: Variability reflects the innate characteristics of the factors involved in the assessment – our goal is to better understand and estimate the variability
- Question: Why have a session on variability in occupational risk assessment? Answer: The nature of the occupational environment and its risk assessment is changing – with new sources of variability increasing impact:
- Two important areas becoming more divergent:
  - Exposure scenarios and scope of industrial hygiene
  - Consideration of populations of concern

Evolving Domain of Occupational Risk Assessment



Assessing Chemical Safety

- Evaluate Toxicology data to derive an occupational exposure limit (OEL)

$$\text{OEL} = \frac{\text{Point of Departure (POD)}}{\text{Uncertainty Factors (Ua x Uh x Ud)}}$$

- Characterize Risk

$$\text{Hazard Quotient (HQ)} = \frac{\text{Exposure}}{\text{OEL}}$$

Risk Characterization

HQ is << 1

HQ >> 1

Presentation Topics

- Temporal Patterns and Task Based Approaches
  - Andrew Maier - TERA
- Human Variability
  - John Lipscomb – U.S. EPA
- Military Exposure Guidelines
  - Kevin Ulmes – U.S. APHC
- Cumulative Risk for Occupational Settings
  - T.J. Lentz – NIOSH
- Risk to Male Reproductive Health: It is More than Sperm Count!
  - Steve Schrader – NIOSH

Variable Temporal Patterns of Exposure and Tasked Based Risk

Andrew Maier, PhD, CIH, DABT

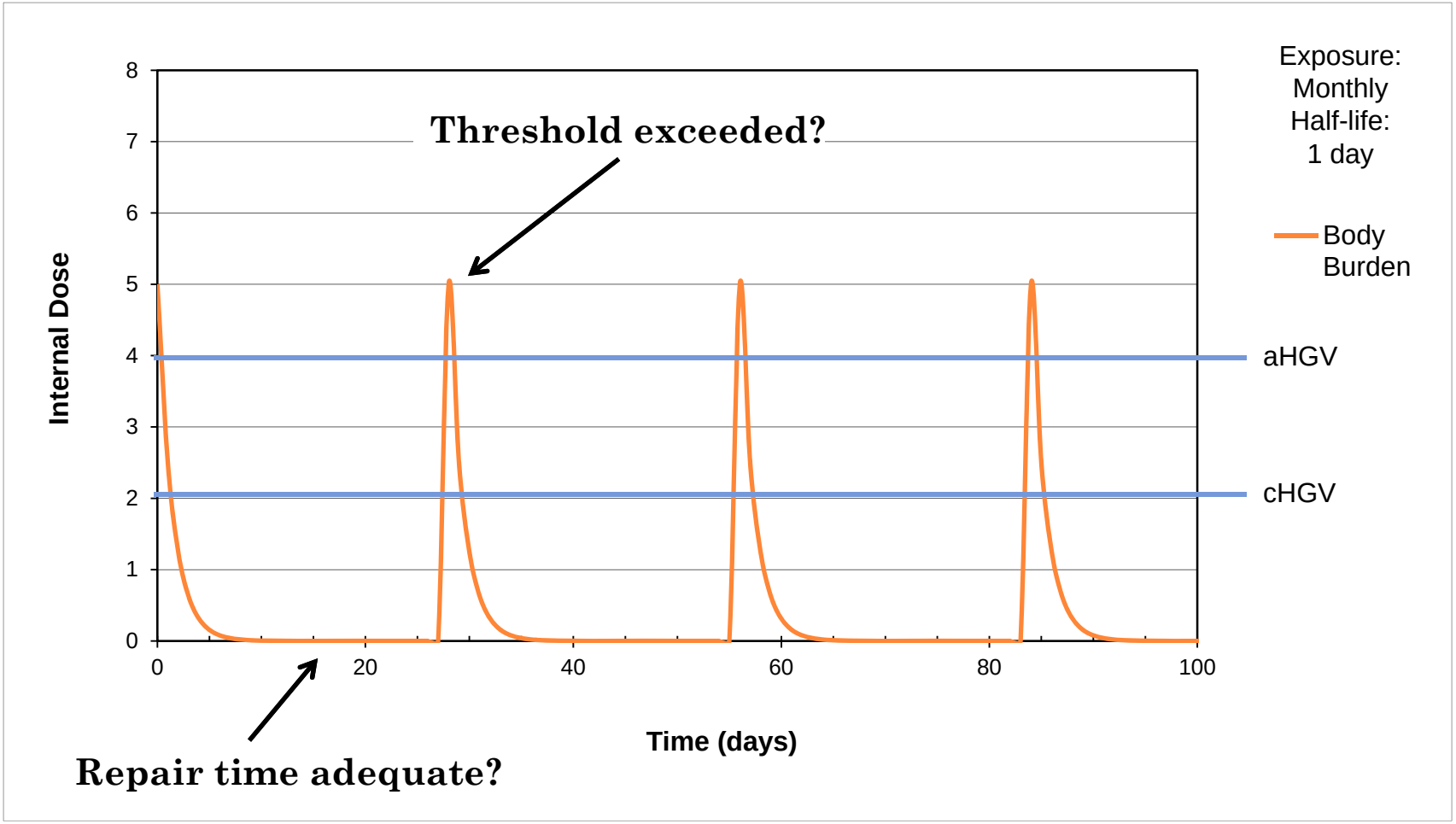
Overview

- The Nature of Real-life Exposures
- Approaches for Addressing Variable Temporal Exposure Patterns

Toxicology Insights Help!

- Mode of Action (MOA): Description of how a chemical causes its toxic effect
  - Toxicokinetics - characterization of the amount/concentration of a chemical in the body over time
    - i.e., absorption, distribution, metabolism and elimination
  - Toxicodynamic - characterization of the body's response to a chemical
    - sequence of events at the cellular and molecular levels leading to a toxic response

Body Burden



aHGV – acute health guidance value; cHGV – chronic health guidance value

What can we do?

- Exposure averaging
  - Change exposure to better match the OEL duration
- Exposure limit adjustment
  - Adjust the OEL to match the exposure duration
- Exposure limit development
  - Develop an OEL that is specific to the scenario

Exposure Averaging

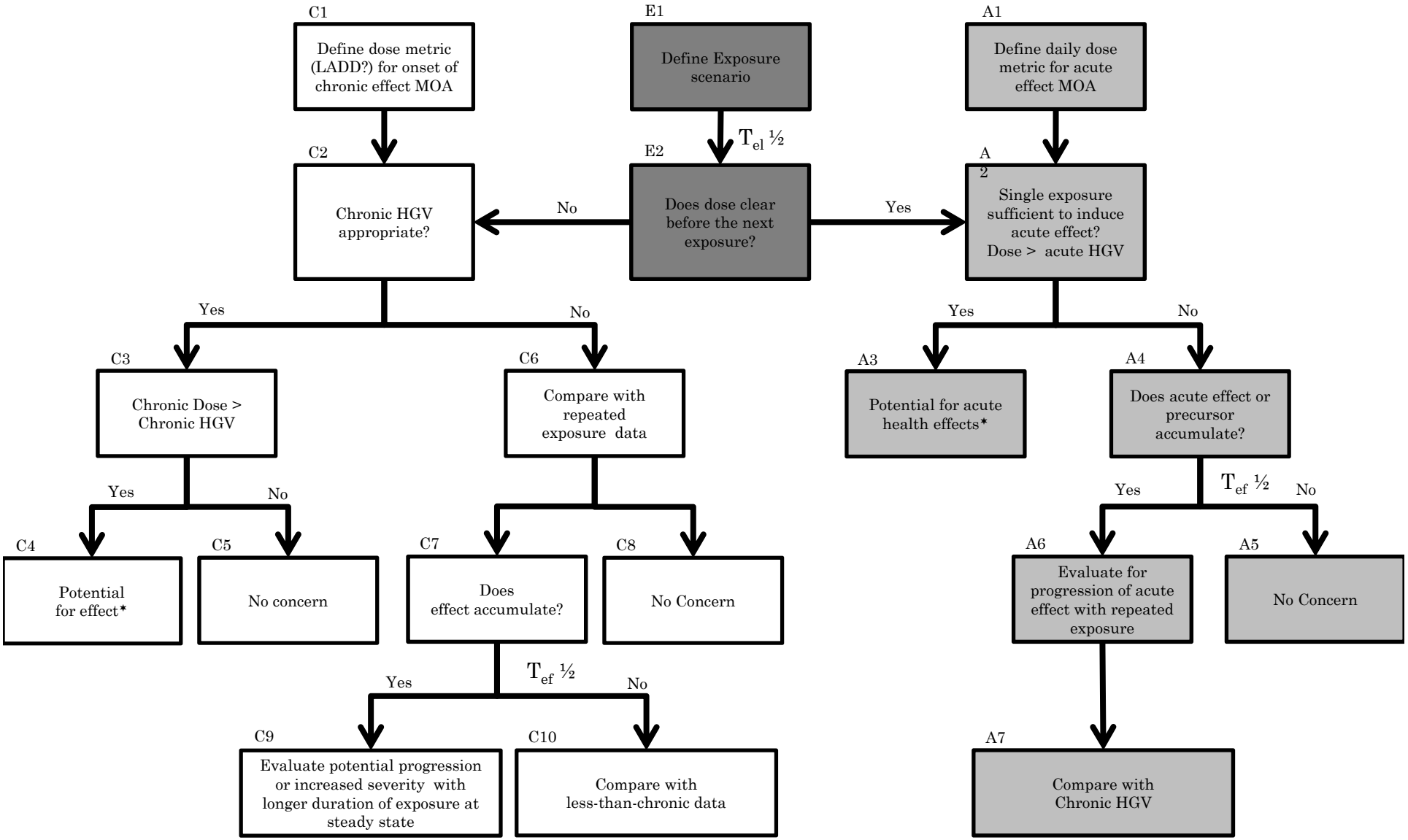
- Typical approach in occupational risk assessment is to develop OELs for 2 broad categories of exposure duration:
- Acute (for quick on-set effects)
  - Short term exposure limit (STEL)
  - Ceiling
- Chronic (for effects with onset from longer periods of accumulated exposure)
  - Full-shift Time Weighted Average (TWA)

Exposure Averaging

- Integrate exposure over time
  - Determine a suitable averaging time for exposure to compare with a standard guideline value (TWA, STEL, etc.)
- Haber's Law
  - C x T = constant dose
  - Toxicity is equivalent with constant dose
  - Robustness of assumption depends on the chemical's MOA

Exposure Averaging Time based on Biologic Residence (half-life) - (inhalation example)

- Experiencing the exposure as a steady 24 hour average could give very different biological results than if the person got the same dose delivered in a 1 hour's exposure during that 24 hour period
- Example:
  - CO (with a half life of a few hours)
  - 10 ppm over 400 hr (4000 ppm-hr) no effect
  - versus a dramatic effect of 4000 ppm over 1 hr


C1
Define dose metric (LADD?) for onset of chronic effect MOA
E1
Define Exposure scenario
A1
Define daily dose metric for acute effect MOA
T_{el} ½
C2
Chronic HGV appropriate?
E2
Does dose clear before the next exposure?
A 2
Single exposure sufficient to induce acute effect? Dose > acute HGV
No
Yes
Yes
No
Yes
No
C3
Chronic Dose > Chronic HGV
C6
Compare with repeated exposure data
A3
Potential for acute health effects*
A4
Does acute effect or precursor accumulate?
Yes
No
Yes
T_{ef} ½
No
C4
Potential for effect*
C5
No concern
C7
Does effect accumulate?
C8
No Concern
A6
Evaluate for progression of acute effect with repeated exposure
A5
No Concern
T_{ef} ½
Yes
No
C9
Evaluate potential progression or increased severity with longer duration of exposure at steady state
C10
Compare with less-than-chronic data
A7
Compare with Chronic HGV

Exposure Limit Adjustment

- Brief and Scala Model
  - Scales values to match longer "shift" work durations
  - Reduces OEL proportionately for increased exposure and reduced recovery
  - Approach incorporates adjustments related to the Biological half-life
- Several other variations are available
- AIHA WEEL Committee is also developing a category approach to address this issue

Exposure Limit Development (1)

- A variety of Approaches are available to develop new OELs that match the scenario:
  - Use a precautionary OEL
  - Select alternative toxicity studies that match the exposure duration
  - Derive new OELs with duration adjusted toxicology study data to match the duration of interest

Exposure Limit Development (2)

- Precautionary Approach
  - Use lower OEL with longer averaging time than the exposure duration.
- Margin of Exposure (MOE)
  - Compare effect levels from studies of different durations of interest to various exposure scenarios – commonly used by EPA for pesticide use scenarios.

$$\text{MOE} = \frac{\text{Measure of Dose-Response}}{\text{Exposure Concentration}}$$

Exposure Limit Development (3)

- Basic Approach for deriving a unique OEL:
  - Selected point of departure (POD) for sensitive toxicity endpoint: e.g., No Observed Adverse Effect Level (NOAEL) for relevant study type
    - Acute; subacute, subchronic, chronic
  - Divide by safety or uncertainty factors (human variability, animal to human variability, and database uncertainties)

$$\text{OEL} = \frac{\text{POD (NOAEL, LOAEL, or BMD)}}{\text{UF}}$$

Exposure Limit Development (4)

- Apply duration adjustment to the critical toxicology study POD before developing the OEL
  - This basic approach assumes Haber's Law
  - There are refinements to this that account for higher impact of concentration than duration for short-term scenarios (the ten Berge approach)
  - There are also advanced approaches using kinetic modeling to adjust the POD average in terms of actual tissue dose (the PBPK approach)

Exposure Limit Development (5)

- Many examples:
  - Agency for Toxic Substances and Disease Registry derives acute; intermediate; and chronic exposure guidelines – using studies of different durations
  - Acute Emergency Exposure Guidelines derived for non-routine exposures – AEGLs for three different severities of effect set for:
    - 10 min; 30 min; 1 hour; 4 hours, or 8 hours using different studies and study duration extrapolation techniques

Conclusions

- Occupational risk assessment relies on a comparison of exposure and a health guideline that is relevant to that exposure scenario
- For task-based exposures there are a variety of approaches to align the exposure with an exposure guideline
- Selecting the best approach requires:
  - an evaluation of the exposure scenario
  - understanding of the mode of toxic action (kinetics and dynamics) of the chemical