Independent Toxicology Assessment for Diacetyl

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Presentation Outline

- Who is *TERA*?

- What is *TERA*'s role?

- Applying a systematic approach to health-based occupational limit development.

- Some initial thoughts on diacetyl risk assessment.

Toxicology Excellence for Risk Assessment (*TERA*)

Toxicology Excellence for Risk Assessment (*TERA*) is a non-profit, 501(c)(3) corporation organized for scientific and educational purposes.

The mission of *TERA* is to inform the protection of public health by developing and communicating risk assessment values, improving risk assessment methods through research, and to educate on risk assessment issues.

- Independent non-profit – funding from individual mission-related projects sponsored by government and industry
- Objective approach with a focus on science
- Scientific opinions are released to the public

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Recent *TERA* Sponsors

- Approximately 70% of *TERA* funding is from government.
- U.S. EPA:
  - Support of IRIS Assessments
  - Science Support Document for NO_2 NAAQS.
  - Exposure and effect progression for phosgene-induced fibrosis.
- U.S. NIOSH:
  - Development of IDLH values.
  - Implementation of new skin notation methodology.
- State of Texas:
  - Peer Review of ESL values (e.g., 1,3-butadiene).
- Industry Consortia:
  - Chloropicrin acute inhalation values presented to U.S. and CA agencies.
- Volunteer Groups:
  - Approximately 7% of *TERA* budget, including service on AIHA WEEL Committee.

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TERA's Role for Diacetyl Issue

- *TERA* is being funded for this work by a consortium of food producers.

- Provide an independent toxicology review document for diacetyl.

- Ensure the document is made available to interested OEL-setting organizations and agencies as an aid to their deliberations.
  - Sponsor group requesting the AIHA WEEL committee to evaluate data and set an OEL.

- Evaluate key issues related to potential OEL development and provide independent opinions and outreach as requested by interested groups.

Occupational Risk Assessment Methods

Occupational Risk Assessment

- The normal progression in risk assessment is *from* reliance on qualitative hazard-based approaches *to* quantitative risk-based assessments as the available data increases.

- Hazard approach
  - Advantage: rapid assessment allows for action to be taken quickly to address most likely health concerns.
  - Disadvantage: absence of an objective measure of likelihood for health concern can lead to: 1) inadequate protection, 2) less confidence in the assessment, 3) difficulty in communicating risks.

- The preferred practice is to use hazard-based approaches as an interim procedure until an OEL can be developed.

- Periodic evaluations of each chemical-specific database are used to determine if new data are adequate to move to a quantitative approach.

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Is there a minimum data set for OEL development?

- Most groups that establish OELs do not have a specific minimum data set requirement for OEL development.

- Rather, an overall weight of evidence approach using multiple lines of evidence is used, including (in order of greatest weight):
  - Analytical epidemiology studies.
  - Longer-term (90-days or greater) inhalation toxicity studies.
  - Short-term repeat-exposure inhalation studies (28-days or greater).
  - Longer-term studies for other routes of exposure.
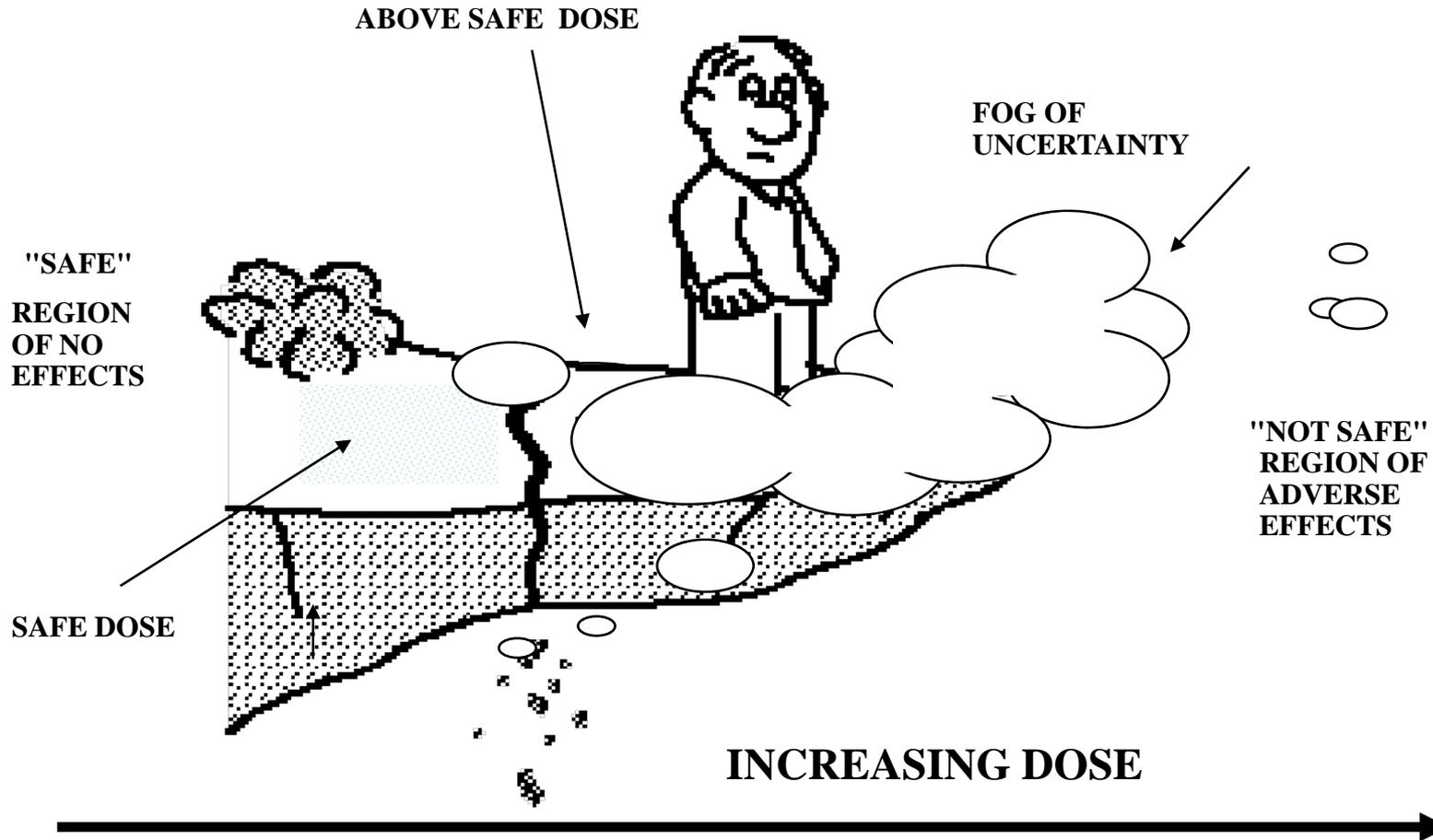 - studies for functionally- or structurally-related chemicals.

Is there a minimum data set for OEL development?

- Typically all relevant data are summarized in making an overall judgment on the value of the OEL.

- It would be unusual to develop an OEL in the absence of at least one of the types of studies described above.

- Preliminary or screening OEL approaches use lesser data sets. Such screening OEL approaches are not dissimilar to current control-banding concepts.

- U.S. EPA defines the availability of a single subchronic inhalation study that has evaluated potential target organs – including the respiratory tract as the minimum data set for developing an RfC.

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The Risk Value Process

This process incorporates the fundamental concepts of toxicology – that for non-cancer effects, there is an exposure threshold below which exposure is safe and the onset of toxicity is a function of the exposure concentration.

Risk Value Derivation for Dose-Response Assessment

$$\text{Risk Value} = \frac{\text{Measure of Dose-Response}}{\text{Factors to Address Uncertainty in Extrapolation}}$$

Nearly all groups - whether evaluating food, product, environmental, or occupational risk - use this basic concept for non-cancer dose-response assessments. However, the specific terminology differs among these groups.

Risk Value Derivation for Dose-Response Assessment

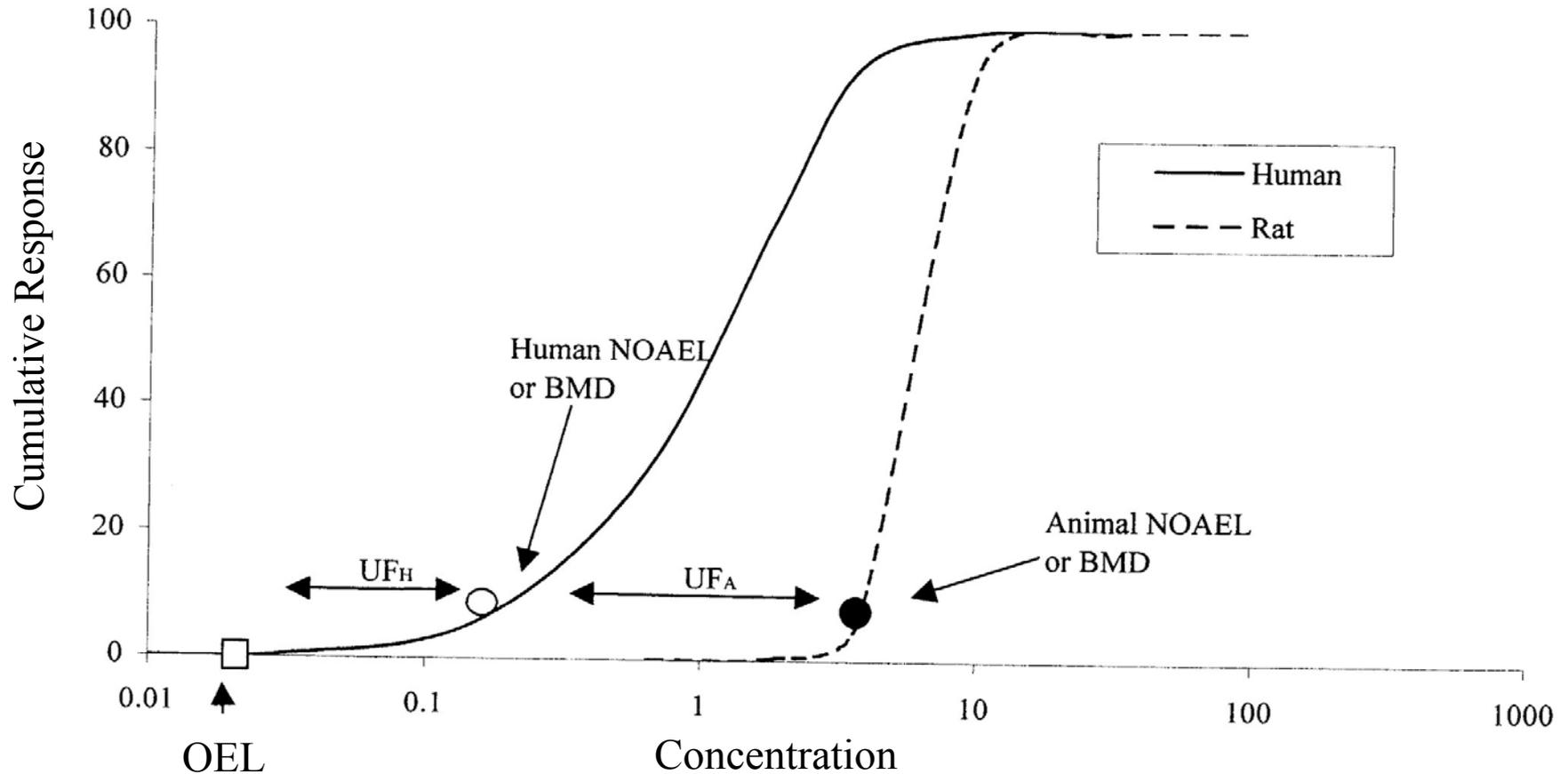$$\text{OEL} = \frac{\text{NOAEL, LOAEL or BMC}}{\text{UF}}$$

NOAEL – No observed adverse effect level

LOAEL – Lowest observed adverse effect level

BMC – Benchmark concentration

UF = Uncertainty Factor

Cumulative Response as a Function of Dose – Animal and Human Data

Selecting the Point of Departure

- Basic Principle:
  - Select the effect level (from the data set or modeled data) that provides the best estimate of the concentration *boundary* for the onset of the effect from the *most sensitive* species and effect that *is most relevant* (or assumed to be relevant) to humans.

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Uncertainty Factors Used for Risk Values

UFs	Health Canada	IPCS	RIVM	ATSDR	EPA
Interindividual (H)	10 (3.16 x 3.16)	10 (3.16 x 3.16)	10	10	10 (3.16 x 3.16)
Interspecies (A)	10 (2.5 x 4.0)	10 (2.5 x 4.0)	10	10	≤10 (3.16 x 3.16)
Subchronic to chronic (S)			10	NA	≤ 10
LOAEL to NOAEL (L)	1-100	1-100	10	10	≤ 10
Incomplete Database (D)			NA	NA	≤ 10
Modifying Factor (MF)	1-10	1-10	NA	NA	0 to ≤ 10 discontinued

Note: Occupational risk assessment groups consider the same areas of uncertainty, but most do not have a specific approach for use of default UF values.

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Diacetyl Epidemiology and Toxicology

Diacetyl Epidemiology

- 16 different microwave popcorn or flavoring facilities or companies were assessed by NIOSH or other investigators.

- An increased prevalence of pulmonary function test (PFT) deficits was identified in all of these facilities. Weight of evidence supports the conclusion that exposure to diacetyl causes adverse respiratory tract effects (e.g., PFT deficits).

- 9 possible cases of bronchiolitis obliterans were identified in one of these facilities (Akipnar-Elci et al. 2004). Other case reports without full diagnosis in some studies. The causal link between diacetyl and the onset of bronchiolitis obliterans is not certain (Galbraith and Weill 2008).

Diacetyl Epidemiology

- Case Series and cross-sectional designs limit ability to determine causality.

- Most of the studies had limited sample sizes or limited exposure measurement – precluding dose-response analysis.

- Exposure estimates are inaccurate or not specific:

    - There could be other contaminants causing the same or similar symptoms (i.e., capsaicin in jalapeno flavorings)

    - Air concentrations are highly dependent on the type of flavoring used (powder, paste or liquid) and can change daily.

    - Confounding factors such as smoking may impact the risk of obstruction in workers (Kanwal et al. 2006; Parmet 2002).

Diacetyl Epidemiology

- Exposure estimates are inaccurate or not specific continued:
  - Relative humidity (RH) can cause underestimation of exposure based on current NIOSH and OSHA air sampling methods. This consideration of RH may yield over estimates of dose-response potency.
  - This RH issue would not affect the robustness of medical surveillance data.
  - The animal studies - which measured air concentrations directly - would not be impacted by RH.

Diacetyl Epidemiology

- Lockey et al. (2008) included robust exposure measurement, analysis of effects against multiple exposure metrics, and a prospective design.

- Mixers were exposed to higher levels of diacetyl than other employees.

- Mixers exposed prior to use of PAPRs show evidence of a statistically-significant decrease in FEV1, and significantly increased risk of airway obstruction.

- Cumulative exposures greater than or equal to 0.8 ppm-yrs were associated with FEV1 changes.

Diacetyl Epidemiology
Lockey et al. 2008

Table 3--Cross-Sectional Logistic Regression Analysis of Exposure Groups and Obstructive PFT Pattern in Non-Asian Males

Variable	Non-Asian Males[‡] (n = 400)		Non-Asian Males w/o pre-employment asthma** (n = 384)	
	Odds Ratio	95 % CI	Odds Ratio	95 % CI
Pack-Yrs[1]	1.6	1.3 - 2.0	1.6	1.3 - 2.0
Current Smoker[2]	1.1	0.4 - 3.2	1.4	0.5 - 4.0
BMI	1.0	0.9 - 1.1	1.0	0.9 - 1.1
Pre-PAPR Mixer[3]	8.1	2.3 - 29.2	8.2	2.3 - 30.0
PAPR Mixer[4]	5.7	1.2 - 26.2	3.2	0.6 - 18.7
Intermittent Pre-PAPR Mixing[5]	1.0	0.3 - 3.2	1.0	0.3 - 3.3

[‡] Employees reporting pre-employment asthma and currently on asthma medication removed (n = 21)

** Employees reporting any history of pre-employment asthma removed (n = 37)

[1] Odds ratio given for 10-year increase in pack-yrs

[2] Current smokers compared to never and former smokers

[3] Mixing room employees prior to April 2003 compared to employees with no mixing room employment

[4] Mixing room employees after April 2003 with no pre-PAPR experience compared to employees with no mixing room employment

[5] Employees with >30 minutes/month estimated time in mixing room pre-PAPR compared to employees with no mixing room employment
Note: No employees in the quality assurance group had an obstructive PFT pattern. Therefore, for this analysis these employees were included in the non-mixing room employment group

Summary Diacetyl Epidemiology

- Epidemiology Findings:
    - Hazard Characterization - numerous cross-sectional studies and case series provide qualitative evidence for respiratory tract effects in humans and support the toxicology findings.
    - Concentration-Response - The recent analytical epidemiology study (Lockey et al., 2008) provides quantitative concentration-response information to inform OEL development.
    - Together the epidemiology data support the conclusion that mid-respiratory effects (e.g., as evidenced by symptoms or PFT changes) are the critical sensitive effect for risk assessment and provide information for developing effect threshold estimates.

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Diacetyl Toxicology

- Hazard Characterization Toxicology Data:
  - Acute inhalation studies of butter flavoring vapors and diacetyl in rats (Hubbs et al. 2008) show that average daily exposure explains tracheobronchial (TB) effects more than peak exposures.
  - Morris and Hubbs (2008) developed information on lung dosimetry of diacetyl in the rat to inform rodent-human concentration extrapolation.
  - A well-conducted mouse subchronic inhalation study (Morgan et al. 2008) provides concentration-response data for respiratory tract effects.
  - Older oral dosing systemic toxicity study in rats (Colley et al., 1969) and developmental toxicity studies in rats and hamsters (FDA 1973) verify that the body's local site of exposure is the target for diacetyl.

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Diacetyl Toxicology

- Key End Point from Morgan et al. (2008)

Lesion	HEC* 0 mg/m^3 (0 ppm)[†]	HEC* 112 mg/m^3 (25 ppm)[†]	HEC* 223 mg/m^3 (50 ppm)[†]	HEC* 447 mg/m^3 (100 ppm)[†]
Table 3. Lung Lesion Incidence Following Subchronic Exposure				
6-Week Exposures				
Peribronchial lymphocytic inflammation	0/5	3/5	5/5	5/5
Bronchial epithelial atrophy and denudation	0/5	0/5	1/5	5/5
Bronchial epithelial regeneration	0/5	0/5	0/5	5/5
Peribronchiolar lymphocytic inflammation	2/5	0/5	1/5	3/5
12-Week Exposures				
Peribronchial lymphocytic inflammation	0/5	2/5	4/5	5/5
Bronchial epithelial atrophy and denudation	0/5	0/5	0/5	5/5
Bronchial epithelial regeneration	0/5	0/5	0/5	5/5
Peribronchiolar lymphocytic inflammation	0/5	0/5	0/5	3/5

Table adapted from Morgan et al. 2008
*HEC – Human Equivalent Concentration
[†]Concentration used in the animal study

Diacetyl Toxicology

- Concentration-Response for Morgan et al. (2008) using U.S. EPA models. BMCL10 is 8.9 mg/m^3.

Multistage Model with 0.95 Confidence Level
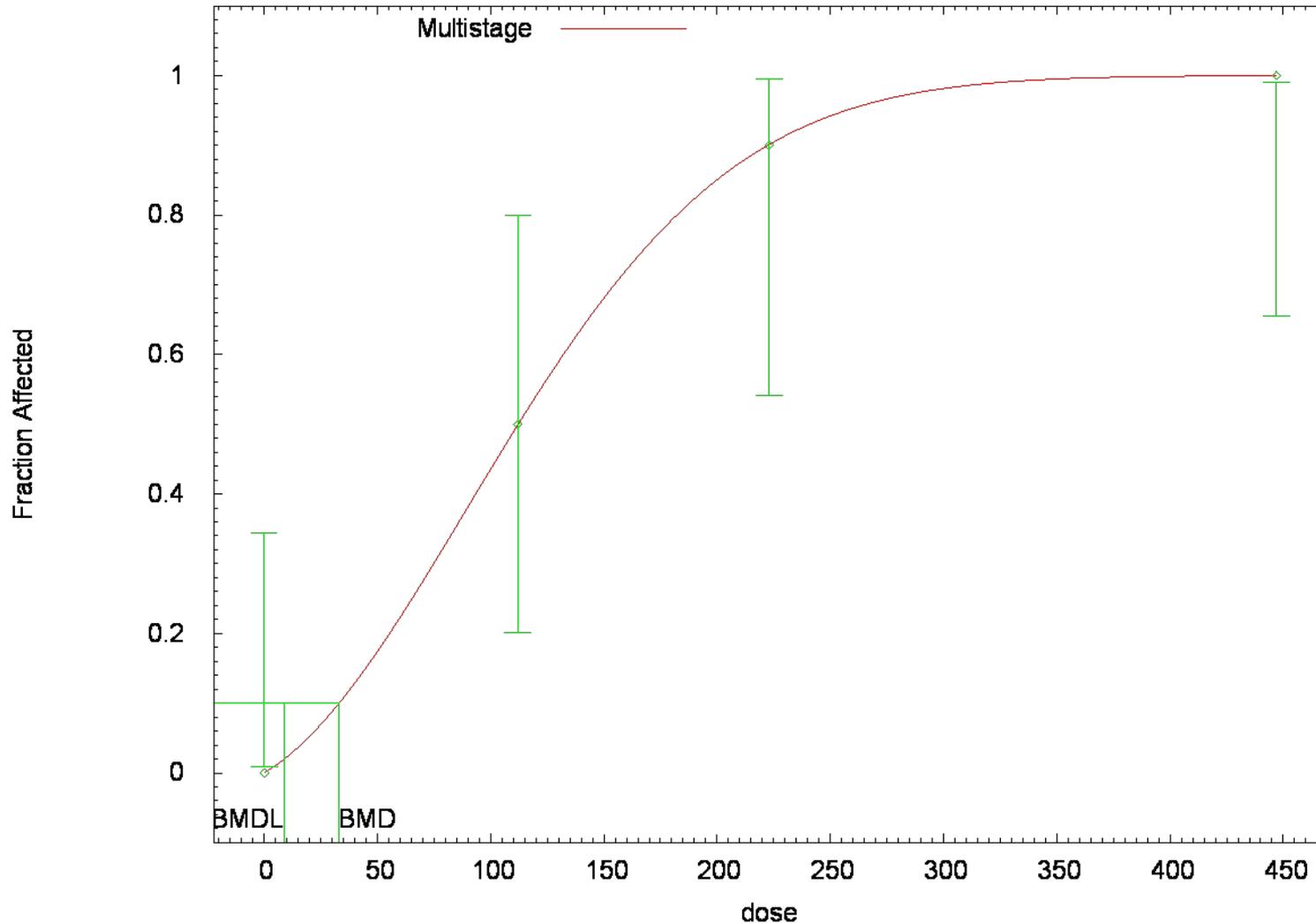
Diacetyl Toxicology

- Other Important Toxicology Findings:
  - The evaluation from the findings in rodents demonstrate that over the course of a single exposure day cumulative exposure is better than peak concentration as a predictor of adverse TB inflammation effects (Hubbs et al. 2008).
  - Whether peak or cumulative exposure is the better predictor of fibrotic effects is uncertain, although the results of Morgan et al. (2008) suggest high concentration peak exposures may be involved. In practice, development of an OEL on a TWA basis includes a guideline for short-term exposures, and thus, would be expected to be protective of fibrotic effects (such as bronchiolitis obliterans).
  - Overall the data suggest that an OEL based on an 8-hr TWA approach is most appropriate.

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Diacetyl Toxicology

- Other Important Toxicology Findings:
  - The overall weight of evidence supports inflammation as the primary mode of action. No data for potential respiratory sensitization from inhalation were identified.
  - Existing human data (Lockey et al., 2008) are sufficiently robust to identify thresholds for respiratory effects, regardless if whether they are secondary to sensitization or inflammation.
  - The results from a recent mouse local lymph node assay (Anderson et al., 2007) suggest that diacetyl is a potential skin sensitizer following dermal application.
  - This finding is consistent with the biochemical properties (ability to bind to amino acid residues) of diacetyl.
  - Although the data are limited to a single assay, such information informs the assignment of hazard notations and suggests a DSEN notation may be appropriate to be prudent.
  - Data are inadequate to develop cancer classification. 28

Summary Diacetyl Toxicology

- Toxicology Findings:
  - A well-conducted mouse subchronic inhalation study has been completed that included thorough examination of the respiratory tract.
  - The toxicology database as a whole supports the conclusion that the respiratory tract is the critical target for diacetyl.
  - The critical study provides adequate concentration-response data for an effect that is relevant to humans (evidence of tracheobronchial inflammation).
  - Other high-quality studies provide information that addresses additional key considerations for OEL setting, such as respiratory tract dosimetry, the appropriate approach for time averaging, and the need for hazard notations.

Summary Diacetyl OEL Issues

- Overall Findings:
  - The analytical epidemiology and recent animal toxicology studies provide a robust data set for diacetyl.
  - The database is more robust than for many chemicals with published OELs.
  - Confidence in the database is medium to high since the data from multiple lines of evidence identify the same critical effect and converge on a likely OEL range.
  - OEL estimates can be derived using standard approaches from both the epidemiology and toxicology data.
  - There are remaining uncertainties in toxicology understanding that are typically addressed through the application of uncertainty factors.
  - Thus, a level of airborne diacetyl that will not produce respiratory tract changes in nearly all workers can be established.
  - An OEL developed from the existing database can be refined as new studies are completed – this is the standard evolution process in occupational risk assessment.

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Questions?