Occupational Concerns for Inter-Individual Variability

Terry Gordon, PhD
TLV Committee, ACGIH
Core Principles for Setting a TLV

- Focus on airborne exposures in occupational settings
- Utilize the “threshold” concept
- Primary users are industrial hygienists
- Goal is toward protection of “nearly all” workers
General Approach to Setting an OEL

- Identify a reference point, e.g. a no observed adverse effect level (NOAEL)
  - Human studies are best but often rely on animal studies
- Set the exposure level below the reference point (threshold)
  - Often called a POD such as a NOAEL or LOAEL
- Apply uncertainty factor
- Sometimes use a modifying factor for “infusion of professional judgment”
- However – there is not a lot of guidance for selecting or using uncertainty factors in developing occupational exposure limits
  - Also called a safety factor, extrapolation factor, assessment factor
Who Uses This General Health-Based Approach to Setting OELs?

- TLV Committee
- WEEL/OARS
- OSHA
- NIOSH
- MAK Commission
- EU’s SCOEL
- Nordic Expert Group
- DECOS
Who Uses This General Health-Based Approach to Setting OELs?

- TLV Committee
- WEEL/OARS
- OSHA
- NIOSH
- MAK Commission
- EU’s SCOEL
- Nordic Expert Group
- DECOS
TLV Committee

• 1941 - TLV Committee Created
  – Subcommittee on Threshold Limits

• 1946 - First published list of 150 “MACs”
  – renamed TLVs in 1948

• 1955 – Added written documentations
Process from Under Study to Adopted takes a minimum of 3 years
Assuming Inter-Individual Variability, How Does an OEL Setting Body Apply Uncertainty Factors

- Who to protect?
TLV

• “protect nearly all workers”

• A bit vague, but over the decades, it has been very useful
  – protect gender/reproductive concerns
  – pre-existing disease (e.g., flour dust-induced asthma; heightened response to NO2 by asthmatics)
MAK

• No wording to protect sensitive individuals

EPA

• protect “particularly sensitive citizens”

SCOEL

• “the variability of response between individuals at the same level of exposure, and the existence of special risk groups, may mean that the recommended OEL may not provide adequate protection for every individual.”
What Leads to Uncertainty?

• Nature of data
  – Amount of data
  – Human vs. animal
  – Animal species
  – Route of exposure
  – Quality of data
  – Availability of a “no effect level”

• Nature of exposed population & exposure situation
  – Age and gender effects
  – Underlying health status effects may increase sensitivity
How to Consider Inter-individual Variability in Setting OELs
Gender Uncertainty Factor?

• Are there differences in response between males and females?
  – Yes

• Do gender differences get considered in setting OELs?
  – Reproductive effects – Yes
  – Male vs. female effects (e.g., dose, metabolism) - No
Age Uncertainty Factor?

• Are there differences in response between young and old?
  – Yes

• Do age differences get considered in setting OELs?
  – No: children are not present in the (U.S.) work force
Extrapolation of Animal Data

• Can inter-animal variability affect the extrapolation of animal data to humans?
  – Consider host genetic factors in susceptibility
Intra-Strain Contributions to Uncertainty?
F2 mice are ‘roughly’ equivalent to heterogeneous human population
Inbred mice are quite varied despite being 99.99% genetically identical.
Inter-Strain Contributions to Uncertainty?
Inbred Strain Responses to 3 Inhaled Pollutants

A

Survival Time (hours)

NiSO₄

B

Survival Time (hours)

PTFE

C

Survival Time (hours)

O₃

Strain Responses to Silver NPs and CNTs

PMN Response to Inhaled Ag NPs

PMN Response to CNTs

Saunders, NYU
Are Mouse Genetic Data (e.g., B6 mice, the most widely used inbred strain, are generally non-responsive) Considered in Extrapolation to OELs?

- No
Are Human Genetic Data Considered in Extrapolation to OELs?

• No, but they probably should be (e.g., chronic beryllium disease)
Individual Susceptibility and Biases in Occupational Cohort Studies

- In examining dose-response effects in an occupational study population, are the most sensitive individuals really the most sensitive?
Healthy Worker Effect

- The term “healthy worker effect” was first used by McMichael, 1974

- “Workers usually exhibit lower overall death rates than the general population, because the severely ill and chronically disabled are ordinarily excluded from employment” - Last, 1995
Healthy Worker Effect

• “HWE is the most common selection bias in occupational studies and occurs because relatively healthy individuals are likely to gain employment and to remain employed” - McMichael 1987; Checkoway, 1989
Is the Healthy Worker Effect Considered in Setting OELs?

• Yes
In General, Is Inter-Individual Susceptibility Considered in Setting OELs?

• Yes
Sulfur Dioxide

• Old TLV (1980) – 2 ppm TWA with 5 ppm STEL

• New TLV (2009) – 0.25 ppm STEL
Sulfur Dioxide

What drove the Committee decision to change the TLV?

Key Issues

• What is the critical effect?
• Should the TLV protect a subpopulation of workers?
Sulfur Dioxide

• What is the critical effect?

Pre-1980 Data

- Respiratory symptoms in pulp mill workers at 10 to 20 ppm (1964)
- Accelerated loss of lung function and increased cough at 1 to 2.5 ppm (1977) but not corroborated in a follow-up study (1986)
Sulfur Dioxide

• What is the critical effect?

Post 1980 - Controlled clinical exposure studies – healthy subjects

- Reduced lung function at 5 to 25 ppm in nose-breathing subjects
- Increased nasal airflow resistance at 1 ppm
- Reduced lung function at 0.75 to 3 ppm in mouth-breathing subjects
Sulfur Dioxide

• What is the critical effect?

Post 1980 Controlled clinical exposure studies – asthmatic subjects

- Reduced lung function at 0.4 and 0.5 ppm, but not at 0.25 ppm, in nose-breathing and mouth-breathing subjects
- Transient decrease in heart rate variability in healthy and asthmatic subjects at 0.2 ppm
Sulfur Dioxide

• What is the critical effect?
  ✓ Decreased lung function (bronchoconstriction) and symptoms in asthmatic individuals

• Should the TLV protect a subpopulation of workers?
  ✓ Yes, asthmatics are part of “nearly all workers”
Uncertainty Factors for Inter-Individual Variability

• TLV committee does not use a fixed set of uncertainty factors (e.g., 10X for extrapolation from animal data)

• TLV committee uses 'common sense' based upon:
  - severity of the critical effect
  - extrapolation issues
Uncertainty Factors for Inter-Individual Variability

• What about other OEL setting bodies?
  - Some do and some don’t use uncertainty factors
  - REACH – use of DNELs
    - Apply a formula with prescribed uncertainty factors to extrapolate subchronic or chronic animal data to OELs
ACGIH Statement of Position adopted by the ACGIH® Board of Directors on March 1, 2002

ACGIH is not a standards setting body

TLVs

- Are an expression of scientific opinion
- Are not consensus standards
- Are based solely on health factors; it may not be economically or technically feasible to meet established TLVs
TLV Subcommittees

- D&I, MISCO, and HOC
- Up to 10 members on each
- Membership from academia, government, labor, industry within 4 key disciplines:
  - Industrial hygiene
  - Toxicology
  - Occupational Medicine
  - Occupational Epidemiology

✓ Committee expenses (travel and literature searches) are supported by ACGIH
✓ Time is donated by the members