Understanding the Derivation and Impact of Occupational Exposure Levels: CrVI Example

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ASSETS Defense Workshop 2018
Denver, CO

August 21, 2018

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Purpose and Outline

Purpose: To provide an overview of occupational exposure levels (OEL) and data supporting Cr VI. Address Army impact.

Outline:

- Background OELs
- Derivation
  - ACGIH update: CrVI
- Impact
  - Issues/sampling
  - Importance of alternatives
  - Forecast

Toxicology

- “Solely the dose determines that a thing is not a poison.”

Paracelsus, born Philippus Aureolus Theophrastus Bombastus von Hohenheim, was a Swiss German philosopher, physician, botanist, astrologer, and general occultist. He is credited as the founder of toxicology.

Risk Assessment

Hazard

inherent capacity of the substance to cause an adverse response

Exposure

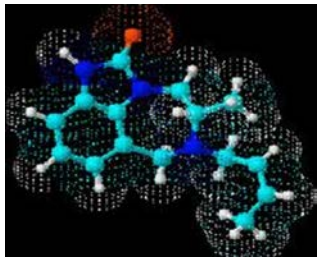
frequency, timing, and levels of contact of environmental receptors with the substance

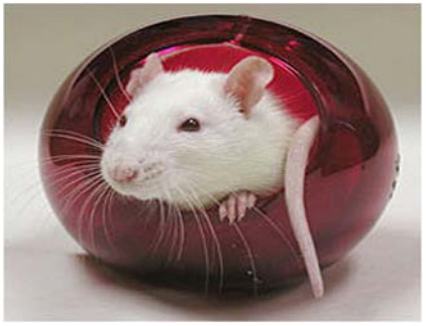
Risk

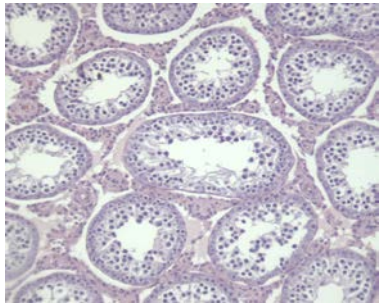
scientific judgment regarding the probability that a chemical could harm environmental receptors

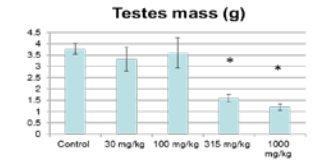
Occupational Exposure Level Derivation

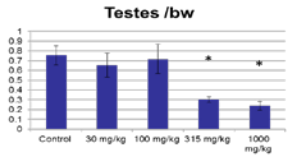
HQ = Exposure (mg/m^3) / OEL (mg/m^3)

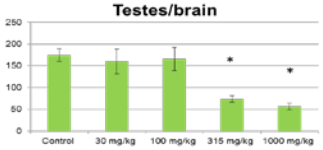


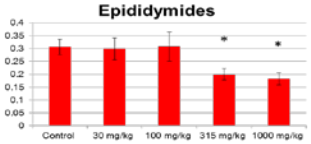


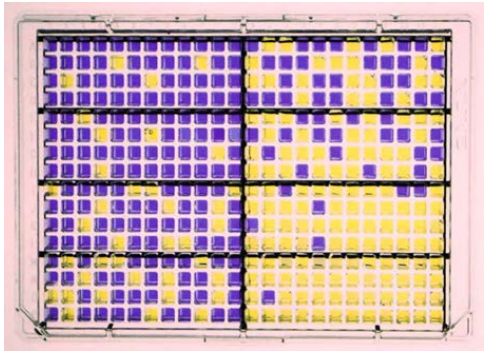












Considerations

- Must know predictive capabilities
- Type I and Type II Error rates
- Interlaboratory variation
- Weight-of-Evidence approach
- Understand physiology
  - Dynamics
  - Kinetics
- One-size does not fit all
- Mixtures
- PBPK models
- Need to know how much is safe

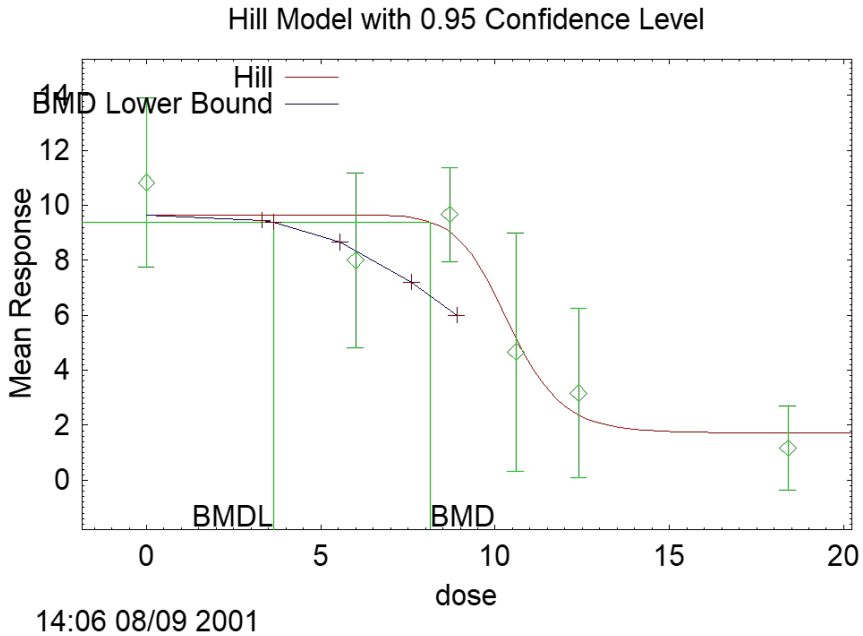
Toxicity Benchmarks

- Based on toxicity threshold
- Always derived or extrapolated
- Examples:
  - Immediately Dangerous to Life and Health (IDLH)
  - OELs
    - OSHA Permissible Exposure Levels (PELs)
    - NIOSH Recommended Exposure Limits (RELs)
    - AIHA Workplace Environmental Exposure Levels (WEELs)
    - ACGIH Threshold Limit Values (TLVs)
  - Environmental Exposure Levels
    - NAAQCs
    - Lifetime Drinking Water Health Criteria
    - Maximum Contaminant Levels (MCLs)
    - Reference Doses (RfDs, RfCs)
    - Acute Exposure Guideline Levels (AEGLs)
    - Temporary Environmental Exposure Levels (TEELs)

Derivation of a Toxicity Benchmark

- Literature review (systematic review)
- Identify toxicity targets/thresholds
- Corroborate study findings
- Determine point of departure (POD)
- Apply weight of evidence*
- Extrapolate value
  - e.g., Uncertainty factors
    - Interspecies differences (10x)
    - Intraspecies differences (10x)
    - Duration (e.g., subchronic-chronic; 10x)
    - Effect level – no adverse effect level (LOAELs-NOAELs; 10x)

Toxicity Benchmark Derivation



- Divide UF_{IA}
- Multiply UF_{IS}
- X UF_{DU}
- 5/10x10x10 = 0.005 mg/m3

OELs vs Environmental Criteria

OELs

- Based on literature review
- Professional judgement
- UFs use implied
- Healthy workers
- Group consensus
- Stakeholder Input (PEL)

ADDs

- Based on systematic review
- Weight of evidence
- UF use explicit
- Sensitive subpopulations
- Peer review

Tri-Service Toxicology Consortium Review of the draft ACGIH Chromium OELs

- Army has policy – OSHA PELs or ACGIH TLVs, whichever are lower
- Half the OEL initiates action; Action level (AL)
- ACGIH Threshold Limit Values (usually 8 hr Time Weighted Averages; TWAs)
  - Short Term Exposure Limits (STELs) – 15 minutes values, often for irritants.
  - Ceiling Values – Not to be exceeded
- TSTC was asked to review the derivation of the TLVs/TWAs for Cr0, CrIII, CrVI and CrVI STEL
- Four phased approach
  - Phase I – Review keystone primary literature
  - Phase II – Conduct systematic review since 2015/review
  - Phase III – Conduct systematic review since USEPA Cr (1998)
  - Phase IV - Conduct stand-alone systematic review

ACGIH Chromium TLVs

- 2005
  - TWA 0.5 mg/m^3 as Cr0 and/or CrIII
  - TWA 0.05 mg/m^3 as CrVI (water soluble)
  - TWA 0.01 mg/m^3 as CrVI insoluble
  - No STEL
  - “Total” particulate
  - Missed earlier critical studies cited in 2017 draft (42 refs, pp. 6).
- 2018
  - TWA 0.5 mg/m^3 as Cr0 (inhalable)
  - TWA 0.003 mg/m^3 as CrIII (inhalable): sensitizer; A4 not classifiable as carcinogen
  - TWA 0.0002 mg/m^3 as CrVI (inhalable); A1 Confirmed human carcinogen
  - STEL 0.0005 mg/m^3 as CrVI (inhalable)
  - Used three lines of evidence to support CrVI TWA (animal, occupational, cancer risk 1:1000; 162 refs, pp. 34)

Table 1. Relationship of exposure to Cr(VI) and upper respiratory tract symptoms among chrome platers exposed exclusively to chromium(VI) oxide (from Lindberg and Hedenstierna 1983)*

	Mean 8-hour TWA Exposure		Highest Exposure Level		
Exposure (mg Cr/m^3)	<0.002	0.002-0.020	0.0002-0.0012	0.0025-0.011	0.020-0.046
No.	19	24	10	12	14
Symptoms of nasal irritation	4 (21%)	11 (46%)	0	8 (75%)	4 (29%)
Nasal mucosal atrophy	4 (21%)	8 (33%)	1 (10%)	8 (75%)	4 (29%)
Nasal mucosal ulceration	0	8 (33%)*	0	0	7 (50%)‡
Septal perforation	0	3. (13%)	0	0	3 (21%)

*Two of 8 also had a perforated septum
‡ Two of 7 also had a perforated septum

*Johnson MS, Bannon DI, Putzrath R., Marcel B. 2018. Review of the Primary Literature Used to Support the ACGIH Threshold Limit Values for Chromium. Tri-Service Toxicology Consortium. Information Paper.

Controlled animal studies (Glaser et al. 1985, 1990)

HEC = POD*3.85 = 0.050 x 3.85 mg/m^3 = 0.193 mg/m^3 (page 9 of NIC).

The TLV was calculated as the HEC (0.193 mg/m^3) divided by the total composite UFs of 1000.

TLV = HEC ÷ UFs
TLV = 0.193 mg/m^3 ÷ 1000
TLV = 0.000193 mg/m^3 or 0.0002 mg/m^3

Uncertainty Factor	***Value***	***Rationale***
Intraspecies (UF_H)	3	Default value of 10 was reduced to 3 based on the worker population being comprised of healthy adults.
Interspecies (UF_A)	3	Default value of 10 was reduced to 3 based on use of allometric scaling to adjust for pharmacokinetic differences between animals and humans. Factor of 3 was retained to account for remaining pharmacodynamics differences.
Subchronic to chronic (UF_S)	10	A default value of 10 was used to account for effects that could occur from longer-term chronic exposures..
Database (UF_D)	1	Default value of 10 was reduced to 1 because an extensive database in several species is available including human data are available.
LOAEL to NOAEL (UF_L)	10	Default value of 10 was used to convert from a LOAEL to a NOAEL.

*The point of departure (POD) was either 0.025 or 0.050 mg/m^3 to estimate and support the TLV. For the sake of this exercise, we assumed the following: That the subchronic oral LOAEL was converted to a human-equivalent inhalation concentration and adjusted to account for inter-species (UF_A) and intra-species (UF_H) variability, duration of exposure (UF_S) to adjust from a LOAEL to a NOAEL (UF_L), and insufficiencies in the toxicity database (UF_D).

Short-term Exposure Limit (STEL)

- STEL = 15 minutes
- Used for irritants
- Irritant effects for CrVI between 0.0002 and 0.002 (Lindberg and Hedenstierna 1983).
- Specific criteria for 0.0005 mg/m^3 not identified

- Issue: Gathering sufficient air volume in 15 minutes

STEL Analysis Limitations

- APHC LAB follows OSHA ID-215; Quantitation limit = 0.03 ug

- $V = QL \div OEL$
  - V = Volume of air required (L)
  - QL = Quantitation limit (ug)
  - OEL = Occupational Exposure Limit (mg/m^3)

- STEL - Require 60 L of air for quantitation, 120 L for 2X buffer
  - **CANNOT** be accomplished at 2 lpm

- TLV - Require 150 L of air for quantitation, 300 L for 2X buffer
  - Must sample for at least 150 minutes at 2 lpm

Particulate Matter

- ACGIH particulate TLVs are not size specific and are expressed in terms of “total” particulate matter unless otherwise specified

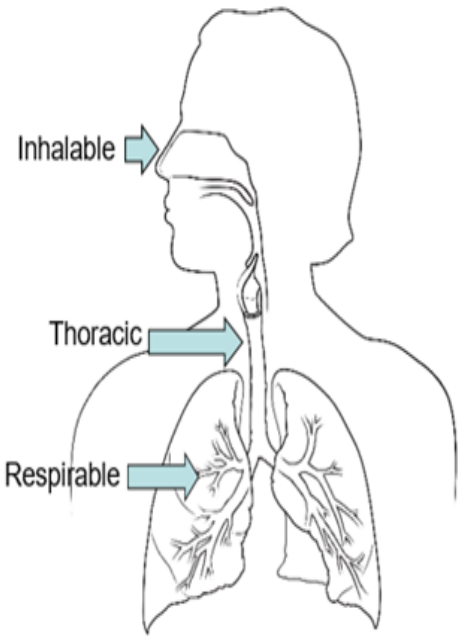
- Hazards of particulates however, may depend upon particle size
  - Size impacts where the particle is deposited in the respiratory tract
  - Occupational diseases are often associated with substances finding their way to specific locations within the body

- ACGIH is re-examining existing “total” particulate TLVs to:
  - Define the size-fraction associated with health effect of concern
  - Determine the TLVs within the given size fraction

Particulate Matter

"The intent of ACGIH is to replace all "total" particulate TLVs with inhalable, thoracic, or respirable particulate mass TLVs." *

- Inhalable (I)- fraction that enters the nose and/or mouth during breathing; hazardous when deposited anywhere in respiratory tract (50% cut point of sampler = 100 um)
- Thoracic (T)- sub-fraction of inhalable that reaches the respiratory tract below the larynx; hazardous when deposited within the lung airways and gas-exchange region (50% cut point of sampler = 10 um)
- Respirable (R)- sub-fraction of inhalable that reaches the gas-exchange region of the lung; hazardous when deposited here (50% cut point of sampler = 4 um)



In 2018, Cr(VI) changed from a total TLV to an inhalable TLV [TLV(I)]

*American Conference of Governmental Industrial Hygienists (ACGIH): 2018 TLVs and BEIs

Total vs Inhalable Particulate Matter

	Total	Inhalable
Media	37mm Closed Face Cassette (CFC)	Institute of Medicine Sampler (IOM)
Flow Rate	2.0 lpm	2.0 lpm
Efficiency (<0.2 m/s wind speed)	100% @ 1 um 0% @ 30 um	100% @ 1 um 50% @ 100 um

Total vs Inhalable Particulate Matter

- Existing Army Cr (VI) sampling data is expressed as "total" particulate
- Werner et al., 1996 suggested conversion factors (total to inhalable) based upon collection efficiencies for different processes/sizes*

Particle/Process	Factor	2018 "total" TLV (mg/m^3)	2018 "total" AL (mg/m^3)
Dust	2.5	0.00008	0.00004
Mist	2.0	0.0001	0.00005
Hot Process	1.5	0.00013	0.000067
Welding/Smoke	1	0.0002	0.0001
Unknown**	2.5	0.00008	0.00004

** Low Confidence in Process Characterization

- Factors were used to convert the 2018 TLV(I) to a theoretical "total" TLV for processes to predict impact of new OELs

*Werner, MA, Spear TM, and Vincent JH (1996). Investigation into the impact of introducing workplace aerosol standards based on the inhalable fraction, The Analyst, 121, pp. 1207-1214.

Projected Impact to the Army

- If concentrations remain the same, we expect a 413% increase in TLV(I) exceedances and 283% increase in AL(I) exceedances

- Increase due to sampling methodology and lowering of the TLV, NOT an actual increase in concentration

Particle/ Process	# ≥ 2017 "total" TLV	# ≥ 2017 "total" AL	Projected # ≥ 2018 TLV(I)	Projected # ≥ 2018 AL(I)	Projected % Increase # ≥ TLV	Projected % Increase # ≥ AL
Dust	189	100	1707	464	903	464
Mist	435	108	907	108	209	0
Hot Process	11	1	26	1	236	0
Welding/ Smoke	29	6	88	34	303	567
Unknown	0	0	12	2	>100	>100

Data retrieved from the Defense Occupational Environmental Health Readiness System 30 July 2018

Projected Impact to the Army

- Monetary
  - CFC vs IOM cost
  - Increased personal protective equipment
  - Increased sampling equipment requirements
  - Increased laboratory analyses

- Manpower
  - Increased medical surveillance
  - Increased laboratory support
  - Increased sampling support

Research Needs

- Growing demand for inhalable fraction sampling
  - Beryllium – 0.00005 mg/m^3 (I) TLV
  - Chromium – 0.0002 mg/m^3 (I) TLV
  - Nickel – 0.1 mg/m^3 (I) TLV
  - Thallium – 0.02 mg/m^3 (I) TLV
  - Tin - Notice of intended changes – 2.0 mg/m^3 (I) TLV

- The IOM is considered the Gold Standard for inhalable fraction sampling

- IOM operates at 2 lpm, which often times does not collect enough particulate for quantitative analysis

Research Needs

- Develop new inhalable sampler that is capable of higher flow rates to meet the STEL and shorten sampling time for the TLV
  - Button sampler (4 lpm) – Poor agreement with IOM, Vol issues
  - Disposable sampler* (10 lpm) – Laboratory digestion issues

- Test the IOM sampler at higher flow rates
  - Zhou and Cheng, 2010 tested IOM at 10.6 lpm – no sig diff
  - Anthony et al, 2016 tested modified IOM at 8.2 lpm – no sig diff
  - Steward et al., 2017 tested modified IOM at 10 lpm – no sig diff

- SKC, Technical Note 2018 "SKC concludes that the original IOM Sampler or a similar design employing the IOM inlet can be used not only at 2 lpm, but also at flow rates between 8.2 and 10.6 lpm to provide good agreement with the inhalable convention"

*L'Orange et al., A Simple and Disposable Sampler for Inhalable Aerosol. Ann Occup Hyg, 2016 Mar;60(2):150-60

Research Needs

- Purpose: Determine if the IOM sampler can be used at higher flow rates to meet Cr(VI) STEL(I) sampling requirements

- Method 1 (Ideal):
  - Conduct testing of IOM in controlled environment
  - Flow rates 2-10 lpm
  - Wind speeds representing different occupational settings
  - Particle sizes from 1 – 100 um

- Method 2 (Expedient):
  - Conduct limited testing in operational, non-controlled environment
  - Side by side testing of IOM @ 2 lpm vs IOM @ 9 lpm on worker
  - Multiple Cr operations representing different particle sizes
  - Statistical comparison using IOM @ 2 lpm as the Gold Standard

Questions and Discussion