OEL Methods Harmonization – Perspectives from the WEEL Committee

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History

- Committee setting health-based OELs since 1978
- Formerly AIHA and transition to the Occupational Alliance for Risk Science (OARS) in 2012

Members

- Approximately 35 active members – many from Pharma practices (n=9)
- Occupational toxicologists, industrial hygienists, adjuncts in specialties

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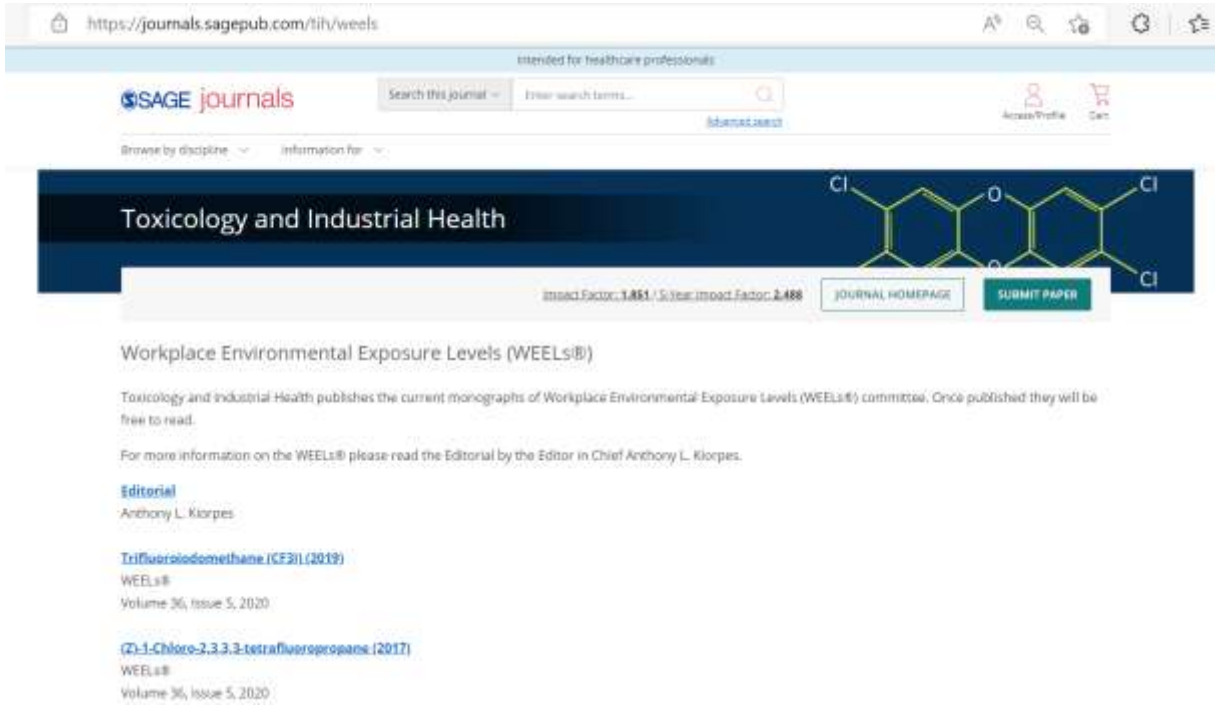
Workplace Environmental Exposure levels

Impact Assessment

- Cited in U.S. EPA (TSCA) and U.S. FDA (PMTA) guidance
- Cited in OSHA guidance on chemicals with no PELs
- WEELs used in emergency response applications (PACs)
- WEELs used as part of NIOSH banding validation effort
- Accepted as peer reviewed values in ASHRAE/ISO-817
- Accepted as authoritative OELs by SafeWork Australia
- U.S. NASA Standard 1800.1D Chapter 4
- Cited on many SDSs

WEEL Values

- Currently 190 health-based OELs
  - https://tera.org/OARS/
- Types of substances
  - Specialty Chemicals
  - **Pharmaceuticals**
  - Fluorocarbon refrigerants
- Open access publication of new dossiers



https://journals.sagepub.com/tih/weels

Maximizing our Impact

- Focus on chemicals with limited available guidance
- Chemical nomination and selection process
  - New
    - High priority based on exposure and hazard
    - External nominations
    - External sponsorships
  - Revisions
    - New data or 10 years

Filling an Important Gap

Approach to verify current OEL Landscape: Will our efforts add to the community of practice?

- Step 1 - Work-flow to identify current assessments
  - Challenge to identify source of all expert group OELs
- Step 2 - Identify if assessment rationale is available for critical review
- Step 3 – Review for potential added value of a WEEL
  - No current published OEL for the chemical?
  - Existing assessment not active in review cycles?
  - Health-based vs policy-based only?

Why Do OELs Differ - Policy

- Consideration of Feasibility
  - Economic and technical achievability (e.g. OSHA PEL)
  - Analytical detection feasibility (e.g. NIOSH REL)
- Policy differences in residual risk (e.g., PEL vs REL vs WEEL)
  - Depends on endpoint
  - Definitions can be quantitative or qualitative
- Periodicity of reviews and updates

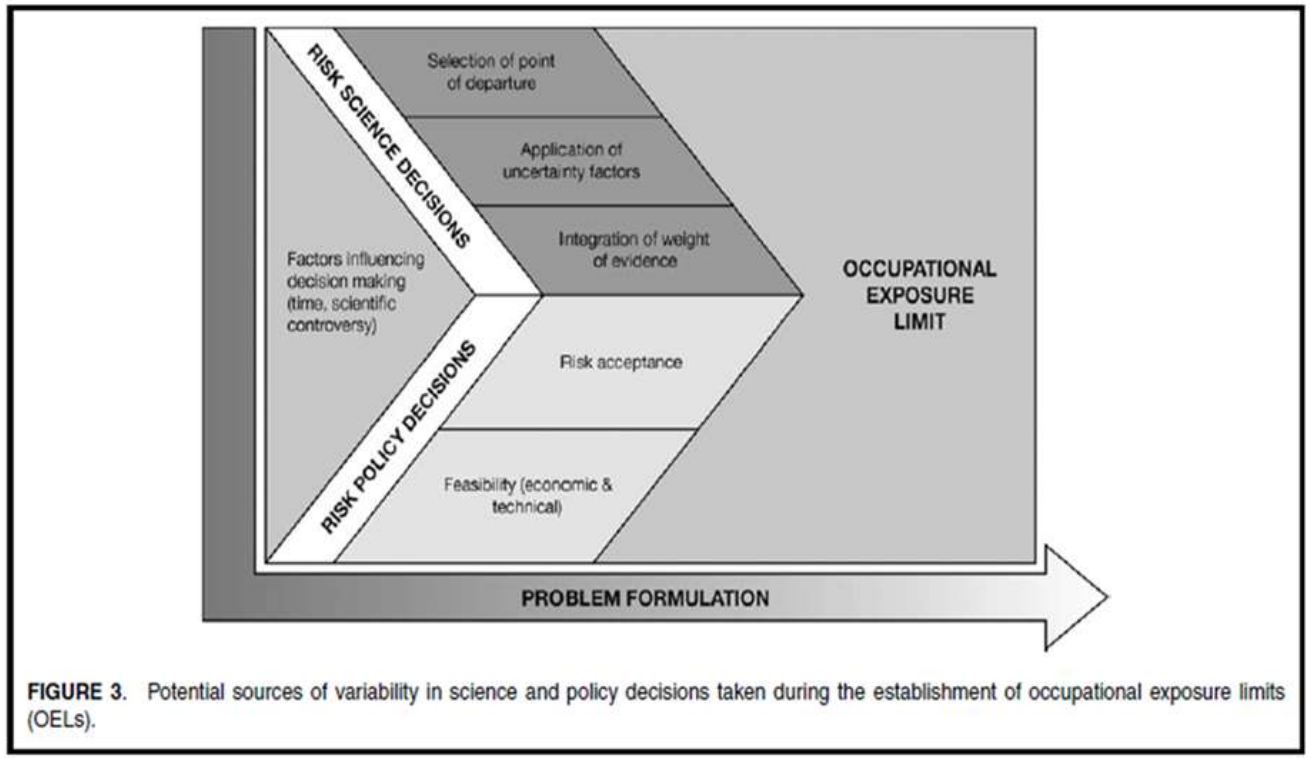


FIGURE 3. Potential sources of variability in science and policy decisions taken during the establishment of occupational exposure limits (OELs).

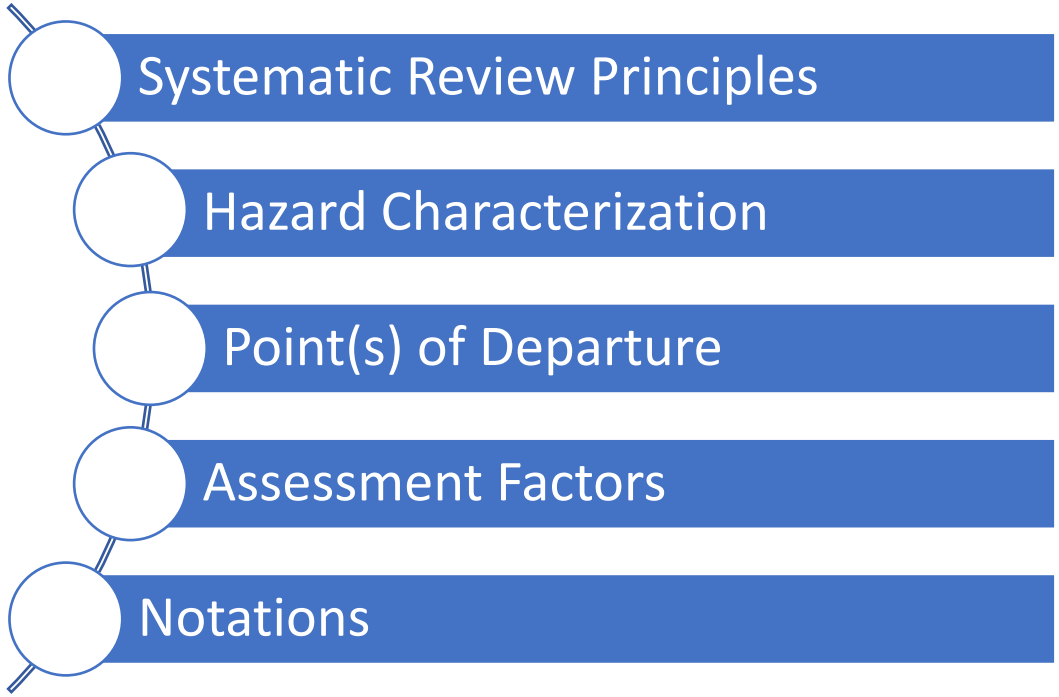
Deveau, M., C-P. Chen, G. Johanson, D. Krewski, A. Maier, K. Niven, S. Ripple, P. Schulte, J. Silk, J.H. Urbanus, D.M. Zalk, R. Niemeier. 2015. The Global Landscape of Occupational Exposure Limits—Implementation of Harmonization Principles to Guide Limit Selection. J Occup Environ Hygiene.12(Suppl 1): S127-S144.

Why Do OELs Differ - Methods

- Methods evolve over time (occupational and environmental convergence); transparency increasing
- BMD Modeling
  - Moving to default status for most government-based organizations
  - Some expert groups use on case-by-case: does it always add value beyond the NOAEL?
- Inhalation dosimetry adjustments
  - Moving to default status for many government-based organizations
  - Highly variable application among organizations – most do not have a default methodology
- Most organizations try to maximize use of available toxicokinetic data for route extrapolation, but default approaches exist
- Linear Dose Extrapolation
  - Most organizations consider Mode of Action (MOA) as an initial step
  - Some use as default for direct genotoxicants; others use to inform weight of evidence in 10-3 and 10-4 range

WEEL Similarity in Methods

- Harmonisation
  - Current OECD effort
  - Shared understanding, but not standardization
  - OTR and Pharma Forum great for benchmarking!
- Methods can differ
  - Recognize value in transparency of methods
- Key consideration
  - Balance science judgement vs prescriptive guidelines



Science Operating Procedures

- Methods continue to evolve – so critical to stay fluent in these methods among organizations
- Developing practice guidance to increase consistency and transparency
- Various endpoints
  - Cancer approach - mode of action-based dose response
  - Point of departure - effect level supported by modeling
  - Assessment factors - standard five areas but present composite
  - Sensitization notations - DSEN and RSEN with new methods tracking
  - Read across – use as line evidence in gap filling

Cancer Endpoint Approach

- Consider directly in WEEL
  - to ensure IH professionals have numeric guidance
- Process includes:
  - MOA review
  - Genotoxicity and carcinogenicity data assessment
  - BMDL of tumor or Key Event
    - AF approach
    - linear extrapolation (1:1000 to 1:10,000)
  - Final assessment based on WOE

Picolines WEEL

- Lung tumors in female rats
- $BMDL_{10}$ 20.1 mg/kg/day
- Dosimetry and linear extrapolation
- Protective of noncancer effects
- Proposed WEEL of 0.3 ppm TWA

POD Selection and Modeling

- Assess traditional NOAEL and LOAEL
- Favor BMD modeling
  - Poor dose spacing
  - LOAEL only
  - Tumor endpoints
- POD adjustment with Dosimetry
  - Inhalation dosimetry
    - Vapor – gas phase (default of 1)
    - Aerosols (MPPD)
    - Consider inhalation bioavailability
  - PBPK models

N-methyl pyrrolidone WEEL

- Developmental toxicity in rats
- WoE from three PBPK models
- STEL to address potential irritation
- WEEL:
  - 20 ppm TWA
  - 30 ppm STEL

Assessment Factors

Consider similar considerations as most frameworks

No defaults formally assigned but author team considers range of defaults

Composite factor and key uncertainties clear from WEEL rationale

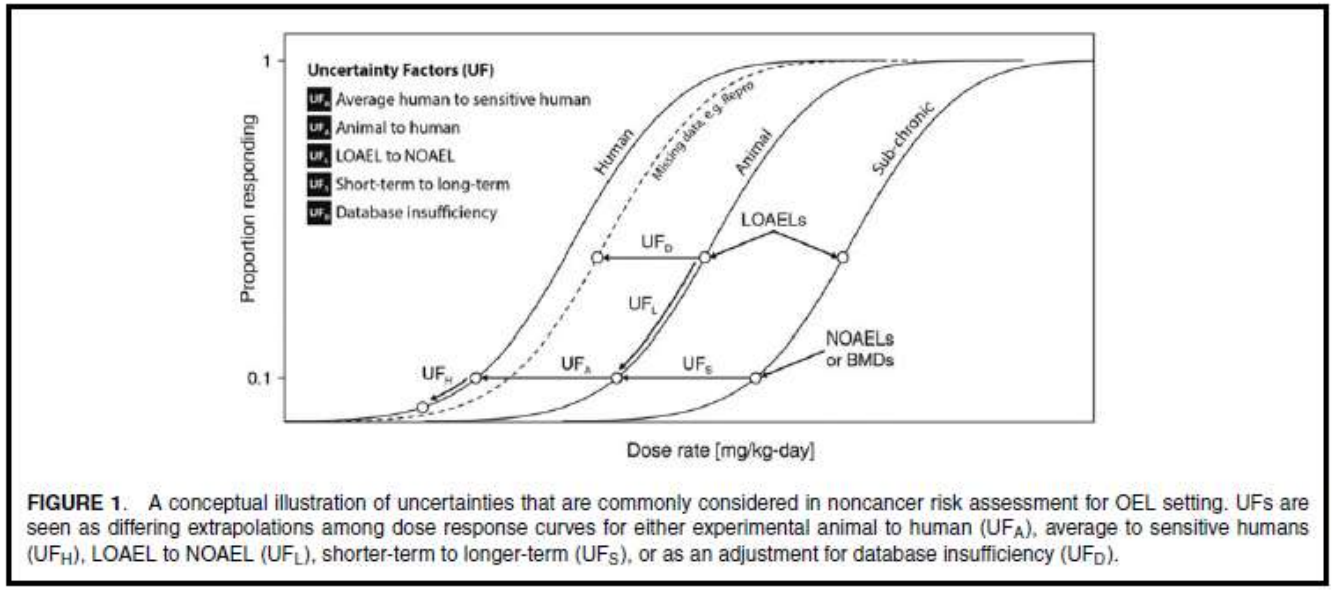


FIGURE 1. A conceptual illustration of uncertainties that are commonly considered in noncancer risk assessment for OEL setting. UFs are seen as differing extrapolations among dose response curves for either experimental animal to human (UF_A), average to sensitive humans (UF_H), LOAEL to NOAEL (UF_L), shorter-term to longer-term (UF_S), or as an adjustment for database insufficiency (UF_D).

Dankovic, D.A., B.D. Naumann, M.L. Dourson, A. Maier, L. Levy. 2015. The Scientific Basis for Uncertainty, Safety and Modifying Factors in OEL setting. J Occup Environ Hygiene. 12(Sup 1): S55-S68.

Read Across Approaches

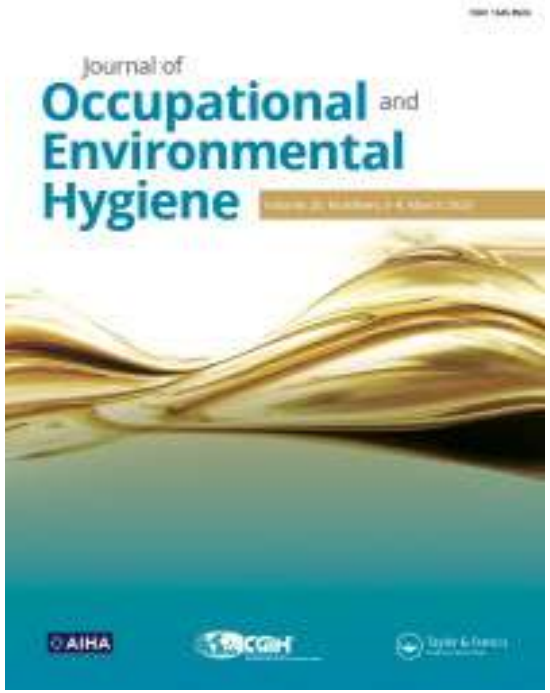
- Procedure similar to OECD and ECHA frameworks
- Consider evidence integration from numerous tools
  - OECD ToolBox
  - U.S. EPA Generalized Read Across Tool
  - NICEATM Integrated Chemical Environment
- Example applications in finalized WEELs:
  - Siloxane reproductive organ effects interpretation (D4 and D5)
  - Picolines – gap filling for inconsistent skin sensitization testing results
  - Chlorosilanes – relative potency evaluation based on HCl content

WEELs for Pharmaceuticals

- Many OELs relevant to excipients and impurity assessments
  - Sometimes commercial chemical WEELs are useful for Pharma sector
- Several examples of requests for pharmaceutical
  - Antibiotics
  - Waste anesthetic gases
  - Drugs of abuse
  - ***Any other general types of interest?***

Antibiotics

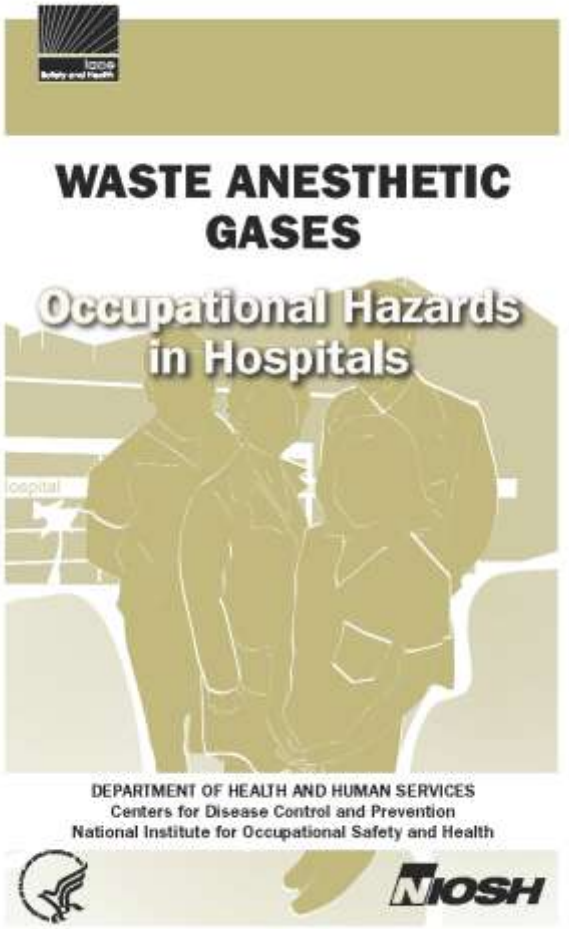
- Initial request from municipal POTWs related to presence in biosolids for EPA occupational risk assessments
- Ciprofloxacin and Azithromycin WEELs in preparation for external comment
- Considerations:
  - Clinical effects (side effects) and Nonclinical toxicology yield similar OELs
  - Is microbial efficacy and effect on human microbiome an adverse effect?
  - Many classes of antibiotics and need to consider when these approaches may not apply



Niang et al., (2023) Ciprofloxacin and azithromycin resistant bacteria in a wastewater treatment plant., Journal of Occupational and Environmental Hygiene, DOI: 10.1080/15459624.2023.2205485

Anesthetic Gases

- Original request from Department of Defense for healthcare applications
- Concern for waste anesthetic gases - isoflurane, desflurane, sevoflurane
- Modern anesthetic gases have much lower liver toxicity profile and have been tested for DART effects
- Recent OELs have not been published for many of these newer molecules
- WEEL for Desflurane in preparation for external comment



Controlled Substances Occupational Hazards

- Pharmaceutical workers
- Pharmacy and health care workers
- Emergency responders
- Contaminated site clean up workers
- Custodial staff at public facilities
- *Gathering case studies*

Requests for Engagement

Original Initiative arose from AIHA Clandestine Lab Work Group

Recently AIHA initiated an Opioids work group

NIOSH Forensic Laboratory Safety Study

From the Synergist

- NIOSH: Forensic Laboratory Chemists Exposed to Controlled Substances

- NIOSH recently investigated possible exposures of laboratory workers to several illicit substances, including cocaine, fentanyl, heroin, and methamphetamine. Following a request from the management of a police forensic sciences division, NIOSH conducted site visits at three of the division's laboratories to observe work practices, assess conditions, interview employees, review records, and collect samples. NIOSH personnel reported finding detectable levels of the controlled substances in employees' air and handwipe samples, and on laboratory surfaces. **Since no occupational exposure limits for these substances have been set by the federal government or consensus organizations,** NIOSH compared the workers' exposures with other types of guidelines available from the pharmaceutical industry and at the state level.

Requested WEELs by Fall 2023

- Methamphetamine (drafted)
- Heroin
- Cocaine
- Fentanyl (possibly with ACGIH)

- NIOSH Collecting exposure data Summer 2023
  - Air
  - Surface
  - Skin
  - Urine

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Outreach and Education

- Recognition of the importance of OELs for worker protection – increase the number of chemicals covered
- Increase awareness of OELs – teaching professional development courses (e.g. AIHce events, etc.)
- Mentor initiative to reach graduate students having an interest in occupational toxicology
- Keeping pace with science – interaction with New Approach Methodology developers

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Summary and Thank you

- WEEL Committee provides health-based OELs for many chemicals lacking other published values
- Well recognized by many authoritative bodies
- Methods harmonization assists in leveraging OEL coverage among organizations
- Risk science methods continue to evolve and requires ongoing tracking
- These methods impact the pharmaceutical sector

- Questions? maier@oarsweel.org