The Impact of Workplace Environmental Exposure Levels™ (WEELs)

Jessica C. Graham, PhD, DABT[1,2], Ann Parker[2,3], Chijioke Onyema, MS, MPH[2], Patricia M. McGinnis, PhD, DABT[2] and Andrew Maier, PhD, DABT CIH[2,4]

[1] Genentech, Inc., South San Francisco, CA; [2]Toxicology Excellence for Risk Assessment (TERA), Cincinnati, OH; [3]Shepherd Chemical, Cincinnati, OH; [4]Cardno ChemRisk, Cincinnati, OH

Introduction

Workplace Environmental Exposure Levels™ (WEELs) are health-based guideline values for chemical stressors. WEELs are limits that represent "safe" [or "relatively safe"] air concentrations that will protect most workers from adverse health effects related to occupational chemical exposures over a working lifetime. They can be used across industries as a central tool for worker health protection. Over the past 45 years, 182 WEELs have been established. WEELs are cited in numerous publications and are looked to as reliable and scientifically sound, occupational exposure limits (OELs). They are established by the Occupational Alliance for Risk Science (OARS) - WEEL Committee, which is a volunteer group consisting of toxicologists and industrial hygienists from academic, governmental, corporate, and consulting sectors. Since their beginning, WEELs have had a positive impact in the field of occupational health and safety, being publicly available and filling gaps for high priority chemicals lacking published OELs.

Workplace Environmental Exposure Levels (WEELs®) are health-based guideline values for chemical stressors.

- Air concentrations intended to protect most workers from adverse health effects related to occupational airborne chemical exposures
- Derived as 8-hour time weighted average (TWA) concentrations, short-term exposure limits (STEL), or ceiling limits
- Developed by a volunteer technical expert committee
- Published for approximately 182 chemicals (see: https://tera.org/OARS/)

WEELs Are Unique

Excellence in Evidence Integration

Accessible – Open Access Publication in the Journal of Toxicology and Industrial Health

Save Industry Time and Resources

Encourage Stakeholder Engagement

WEELs are Established by a Committee of Experts

Opportunities for Sponsorship

Increased Coverage of OEL Gaps Without Duplication

- **Established for chemicals without OELs (e.g., ASHRAE refrigerants)**
  - Enable increased coverage of WEELs without OEL duplication
- **WEELs are Established by a Committee of Experts**
  - The WEEL Committee has extensive experience with the development, use and application of OELs across industries.
  - The WEEL committee considers all relevant available data (public and private). Original data publications / sources are reviewed and data quality is evaluated (e.g., Klimisch scores assigned).
  - The WEEL Committee considers the practical application and implementation of WEELs.
- **WEELs are Harmonized**
  - OELs continue to be a central tool for worker health protection.
  - Collaboration through an alliance of interested parties to enhance occupational risk assessments, ensure education and proper use of different sources of information, and ensure best use of the current science.
- **Coverage of non-traditional environments**
  - Methamphetamine for use by law enforcement officers
  - Waste anesthetic gases for use in hospitals
  - Refrigerants for use in chemical manufacturing companies

WEEL Development → Systematic Review → Formal Evidence Integration → Expert Elicitation Process

The WEEL Committee

The WEEL Committee at a Glance:

- A volunteer technical expert committee that works to develop occupational exposure limits (OELs) called Workplace Environmental Exposure Levels (WEELs)
  - Full Members: 30
  - Associate Members: 6
- Subject Matter Experts (SMEs) in Occupational health professions such as Industrial Hygiene and Toxicology as well as other fields such as Epidemiology & Medicine (**Figure 1**).
- WEEL members span several sectors including Government, Industry, Consulting and Academia (**Figure 2**).

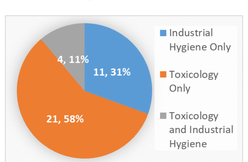


Figure 1. WEEL Committee Member Expertise

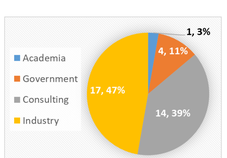


Figure 2. WEEL Committee Member Primary Affiliations

WEELs Incorporate the Science

Use of Benchmark Dose (BMD) Models

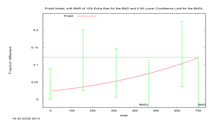
Picolines (methylpyridines; MPs) WEEL Derivation (currently in draft)

- MPs are used in a variety of industrial activities including adhesives, elastomers, and pharmaceuticals. They are also found in cigarette smoke, coal tar, and coal conversion oils, and have been measured in the working zone near coke ovens.
- 2-, 3-, and 4-MP are considered volatile organic compounds and, if released to air, the vapor pressures of these MPs indicate that they will exist solely as vapors.

Chemical Name	2-methylpyridine	3-methylpyridine	4-methylpyridine
CAS Number	109-06-8	108-99-6	108-89-4
Structural Formula (shown without methane group attached)			

MPs have similar toxicity profiles

- **General Toxicity:** Low acute toxicity; Effects observed in repeat-dose inhalation studies consisted mainly of liver effects, which were reversible and generally not adverse.
- **Local Effects:** Undiluted 2-, 3- and 4-MP are eye and skin irritants and not expected to be dermal sensitizers.
- **Genetic Toxicity:** A weight of evidence approach suggests that MPs are not mutagenic.
- **Reproductive and Developmental Toxicity:** A weight of evidence approach suggests MPs are not expected to be reproductive or developmental toxicants.
- **Carcinogenicity:** 2-year carcinogenicity studies were conducted in rats and mice exposed to 3-methylpyridine via drinking water.
- These studies were selected as the basis for the WEEL for 2-, 3- and 4-methylpyridines.
- Systemic toxicity was observed as well as some evidence of carcinogenicity in female rats and clear evidence of carcinogenicity in male and female mice after oral exposure.
  - Tumors observed in rats (in females only):
    - Lung tumors: alveolar bronchiolar adenoma and/or carcinoma
  - Tumors observed in mice (males and females):
    - Lung tumors: alveolar bronchiolar adenoma and/or carcinoma
    - Liver tumors: hepatoblastoma, hepatocellular carcinoma



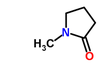
Benchmark Dose software was utilized to model the $BMDL_{10}$ (benchmark dose lower confidence limit) for the adverse effects noted in these studies.

- **Other Considerations:** Note the potential for respiratory irritation given the observed irritation in skin and eye irritation studies.
- **WEEL Derivation:** The lowest $BMDL_{10}$ (for lung tumors) was calculated as 20.1 mg/kg/day. Further adjustments to account for a 1 in 1,000 excess risk of cancer and potential interspecies differences were applied.
- **Evaluation for Assignment of Notations:**
  - Methylpyridines can be absorbed by inhalation, ingestion, and skin contact. Because the skin serves as a direct pathway which can result in systemic effects equal to other routes, the dermal route was considered in determining the potential body burden and in protecting the worker. Therefore, a Skin Notation is assigned.

Picolines WEEL: TWA 1 mg/m³ (0.3 ppm), Skin

Use of Physiologically Based Pharmacokinetic (PBPK) Models

n-Methyl-2-Pyrrolidone (NMP; CAS No. 872-50-4) WEEL Derivation



- NMP is a widely used solvent with a large variety of applications including paint stripping; coating systems; spinning, molding, and extruding synthetic fibers; manufacture of wire insulation enamels; fuel and lube oil additive; and pharmaceutical solvent.
- NMP can exist as a vapor and aerosol depending on air temperature and humidity.

- **General Toxicity:** Low acute and chronic toxicity:
  - Chronic studies in the rat provided a NOAEL of 10 ppm (40 mg/m³) with a minimal LOAEL of 100 ppm (400 mg/m³) causing only minor effects in males (slightly reduced mean body weight).
- **Genetic Toxicity:** Neither genotoxic nor carcinogenic
- **Developmental Toxicity:** Effects in offspring observed in developmental toxicity studies. The NOAEL for developmental toxicity was associated with a BMDL internal dose ranging from 350 – 470 mg*hr/L AUC among several PBPK models.
  - PBPK models are scientifically defensible and allow for the use of specific understanding of the toxicokinetics of NMP and the physiology of both rats and humans to obtain a more accurate human equivalent concentration (HEC) exposure.

Table 1. The human equivalent external concentration derived from the rat internal dose models

Assessment	Endpoint	Data Set(s)	Dose Measure	BMR	PBPK Model	Rat POD: Internal Dose (mg*h/L)	Rat Route of Exposure	PBPK Model	Human POD: HEC (ppm occupational)	Human Route of Exposure
Poet et al. (2010)	Fetal/pup body weight changes	Geometric mean of Saillenfait et al., 2003 and Solomon et al., 1995	Average daily AUC: NMP in maternal blood during gestation period	1SD	Original model	350	Inhalation (nose-only)	Original model	480	Inhalation and dermal absorption of vapors
USEPA (2015)	Fetal body weight changes	Saillenfait et al., 2003	Average daily AUC NMP in maternal blood during gestation period	5%	Minor corrections and reoptimization of original model parameters[a]	411	Inhalation (nose-only)	US EPA refined model[a]	NA (MOE was assessed in terms of internal dose)	Inhalation and dermal absorption of vapors, plus dermal absorption of liquid (under paint shredder scenario; dermal absorption)
Poet et al. (2016)	Fetal/pup body weight changes	Geometric mean of Saillenfait et al., 2003 and Solomon et al., 1995	Average daily AUC: NMP in maternal blood during late gestation period (GD13-20), based upon a window-of-susceptibility analysis	1SD	Minor corrections and reoptimization of original model parameters[a]	470	Inhalation (nose-only)	Poet et al. refined model[a]	Poet Model: 630 USEPA Model: 460	Inhalation of vapors, only
									Poet Model: 400 USEPA Model: 350	Inhalation and dermal absorption of vapors

[a]Revised rat models used by US EPA and Poet et al. (2016) are effectively the same.
[b]The primary difference between the revised human models pertain to the use of Bader et al. (2007, 2008) data for optimizing metabolism parameters: (1) US EPA used data only collected at the lowest concentration (i.e., 2.5 ppm; below the POD HEC); and (2) Poet et al. (2016) utilized data from all concentrations (i.e., 2.5, 10 and 20 ppm;- nearer to the POD HEC).

The PBPK modeled exposure concentration is preferred for the POD in the development of the WEEL.

- Three PBPK models for NMP were developed to determine the internal NMP dose [i.e., as the area under the plasma concentration versus time curve; (AUC)] associated with the inhaled exposures that resulted in developmental toxicity in rats following oral, dermal or inhalation exposures.
- For each exposure route, decreased fetal / pup body weights in rats, were identified as the critical effect.
  - The AUC values were analyzed utilizing BMD software to identify the POD for developmental toxicity. The AUC corresponding to the benchmark dose lower confidence limit (BMDL) is considered equivalent to the use of a NOAEL for this response for WEEL derivation.
  - The internal rat BMDL (as an AUC) approximates the human equivalent internal exposure NOAEL (as an AUC). It is then extrapolated to a human equivalent concentration (HEC), the external worker inhalation exposure of NMP in air that would generate this internal dose based on a human PBPK model (Poet et al., 2010; US EPA, 2015; Poet et al., 2016). The three available PBPK models are compared in Table 1.

- **Local Effects:** In human volunteers exposed under controlled conditions, 20 ppm NMP (80 mg/m³) was considered a NOEL for irritation for an 8-hour exposure period. Weak and transient eye irritation was reported following shorter-term peak exposures of 40 ppm (160 mg/m³; the highest concentration tested). In workplace investigations, irritation and headache were reported among workers at these and higher air concentrations of NMP with potential exposure to other chemicals.
- **Other Considerations:** The air concentration of NMP contributes to the degree of dermal absorption under the conditions of the test system and this needs to be considered when interpreting study results.

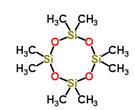
- **WEEL Derivation:** While there is uncertainty in the PBPK model, adjustment factors for animal toxicodynamics and human intraspecies variability are applied to address these uncertainties. The calculation of a WEEL from either PBPK model results in similar values that differ by less than 20%, considering a conservative approach and to address any residual variability of the model, the WEEL derived from the POD range was rounded to 15 ppm.
- **Short Term Exposure Limit (STEL):** The irritation concentration-response information for NMP indicated that a 15-minute STEL is appropriate. A STEL of 30 ppm (120 mg/m³) is recommended to prevent eye and upper respiratory irritation.
- **Conclusion:** The following WEEL is expected to be protective of irritation and chronic target organ effects, including developmental effects.
- **Notations:** Because of the ability of NMP to be absorbed through the skin, and because developmental and reproductive effects have been shown in dermal studies, a skin notation is assigned to NMP.

NMP WEEL: TWA: 15 ppm (60 mg/m³), Skin
STEL: 30 ppm (120 mg/m³)

Use of Mode of Action Considerations

Octamethylcyclotetrasiloxane (D4; CAS No. 556-67-2) WEEL Derivation

- D4 is used as a monomer in the manufacture of polymeric materials, which are widely used in various industrial and/or medical applications, such as breast implants.



- **Toxicity Data:**
  - **General Toxicity**: Low acute toxicity; repeat dose toxicity - 24 month inhalation exposure in rats
    - 150 ppm: Mild to minimal inflammatory responses; this level was determined to be the no-observed-adverse-effect level (NOAEL)
    - 700 ppm D4: Effects in the liver, kidney, and uterus (weight changes, hepatocellular hypertrophy, endometrial hyperplasia, and nephropathy).
  - **Local Effects:** Not considered to be a dermal or eye irritant or to be a dermal sensitizer
  - **Genetic Toxicity:** D4 has not been shown to be genotoxic/mutagenic when tested in short-term *in vitro* and *in vivo* assays.
  - **Reproductive Toxicity**: Adverse effects on specific female reproductive endpoints at high exposure concentrations.
  - **Developmental Toxicity**: No D4 exposure-specific effects were noted with respect to developmental endpoints.
  - **Other Relevant Information:** No appreciable dermal absorption of D4 based on results from *in vivo* and *in vitro* studies.
- **Critical effect:** Adverse changes in the respiratory tract, kidney, and female reproductive tract in the chronic inhalation study.
- **POD (point of departure)** = 150 ppm (NOAEL in 24 month rat inhalation study)
- **WEEL Derivation:** The inhalation NOAEL was adjusted to account for interindividual variability and residual uncertainty regarding upper respiratory tract changes still occurring at 150 ppm.
- **Conclusion:** An 8-h time-weighted average WEEL value of 10 ppm is expected to provide a significant margin of safety against any potential adverse health effects in workers exposed to airborne D4.

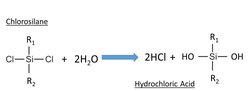
D4 WEEL
TWA: 10 ppm

Use of Read-Across

Chlorosilanes: WEEL Derivation

- **The critical effect** caused by inhalation of chlorosilanes is due to toxicity caused by the release of hydrochloric acid. Therefore, a **hydrochloride-based read-across technique was utilized for chlorosilane WEELs** based on the release of hydrochloric acid.

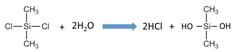
Chlorosilane → Hydrochloric Acid



Chlorosilane WEELs include trimethylchlorosilane and dimethyl-dichlorosilane presented below:

Trimethyl-chlorosilane (CAS No. 75-77-4)

- **General Toxicity:** Comparative studies between chlorosilanes and hydrogen chloride (HCl) conclude a relationship between chlorine content and acute toxicity and suggest chlorosilanes are less toxic than HCl.
  - Rat 1-hr LC_{50} = of 4257 ppm for trimethylchlorosilane; Rat 1-hr LC_{50} = 2910-3327 ppm for HCl
  - LC_{50} values for trichlorosilanes ranged from 1257-1611 ppm
    - Conclude correlated well with a calculated structure-activity relationship (r^2 = .97) between chlorine content and LC_{50} value.
    - The acute inhalation toxicity of these chlorosilanes was concluded to be similar to, or less than, that for hydrogen chloride.
    - A whole body inhalation reproductive screening study for trimethylsilanol in rats concluded that the NOAEL was 600 ppm (the maximum exposure).
      - Adverse effects were limited to changes in hematology and serum chemistry but occurred in the absence of correlating histologic changes and, therefore were not considered adverse. There are no long-term exposure data available.



- **WEEL Derivation:** There is a 1:1 conversion of trimethylchlorosilane to hydrogen chloride when the former reacts with water vapor. Moderate to severe corrosivity has been demonstrated by all routes of exposure. Based on acute dermal and inhalation data, the toxic effects of trimethylchlorosilane are expected to be qualitatively similar to hydrogen chloride. It is recommended that existing occupational exposure data for hydrochloric acid (HCl) be referenced in order to develop best industrial hygiene practices.

Dimethyl-dichlorosilane (CAS No. 75-78-5)

- **General Toxicity:** The toxic effects of dimethyl-dichlorosilane are qualitatively similar, and directly related, to those produced by HCl.
  - It has moderate acute toxicity and is corrosive to the eye and skin. There are no data on reproductive toxicity and no definitive evidence of genotoxicity.
- **Local Effects:** Testing demonstrates that when 1 mole of dimethyl-dichlorosilane reacts with water, 2 moles of hydrogen chloride are released. Inhalation is one of the primary occupational routes of exposure. While the acute inhalation LC_{50} for dimethyl-dichlorosilane (based on hydrogen chloride equivalents) is estimated to be somewhat less than HCl, the primary toxic endpoints are related to the high degree of corrosivity in liquid and vapor states.
- **WEEL Derivation:** In the absence of relevant chemical-specific data, no specific WEEL value is recommended for dimethyl-chlorosilane. It is recommended that existing occupational exposure data for hydrochloric acid (HCl) be referenced in order to develop best industrial hygiene practices.

Impact Analysis Recognition

182 WEELs are available
https://tera.org/OARS/

WEELs are Recognized and Cited by: ASHRAE, OSHA, FDA, CDC, EPA (TSCA and SNAP), ACGIH, US HHS, Chemical and pharmaceutical companies, Scientific organizations (NIOSH, AIHA, ERPG) and others.

Table 2. WEELs Recently Published in the Journal of Toxicology and Industrial Health

WEEL Monograph*	WEEL Year	Toxicology and Industrial Health (TIH) Publication Details**	Downloads (as of Feb2023)
Dimethyl ether (DME)	2022	Volume 38, Issue 11, 2022	167
(E)-1,2-Difluoroethylene (HFO-1132E)	2022	Volume 38, Issue 8, 2022	120
n-Methyl-2-pyrrolidone	2022	Volume 38, Issue 6, 2022	141
1,1,1,2,3,4,4,5,5,5-Decafluoropentane (HFC-4310mee)	2020	Volume 37, Issue 8, 2021	123
Methoxytridecafluoroheptene isomers (MPHE)	2020	Volume 37, Issue 8, 2021	245
Trifluoroiodomethane (CF3I)	2019	Volume 36, Issue 5, 2020	1650
(Z)-1-Chloro-2,3,3,3-tetrafluoropropene	2017	Volume 36, Issue 5, 2020	687
Cis-1,1,1,4,4,4-hexafluoro-2-butene (HFO-1336mzz-Z)	2018	Volume 35, Issue 3, 2019	122
1,1,1,3,3,3-Hexamethyldisilazane (2018)	2018	Volume 35, Issue 3, 2019	116
1,1,2,2-Tetrafluoroethane (HFC-134)	2018	Volume 35, Issue 3, 2019	158
Trans-1,1,1,4,4,4-hexafluoro-2-butene (HFO-1336mzz-E)	2018	Volume 35, Issue 3, 2019	150
2,4-Dinitroanisole (DNAN)	2014	Volume 34, Issue 1, 2018	767
3-Nitro-1,2,4-triazol-5-one	2014	Volume 34, Issue 1, 2018	368
Nitroguanidine (NQ)	2016	Volume 34, Issue 1, 2018	428
Octamethylcyclotetrasiloxane (D4)	2014	Volume 33, Issue 1, 2017	5529
Decamethylcyclopentasiloxane (D5)	2015	Volume 33, Issue 1, 2017	4861
Editorial (Author: Anthony L. Kiorpes)	N/A	Volume 33, Issue 1, 2017	556

* WEEL monographs are authored by the WEEL Committee
** Since 2018, WEEL monographs have been published in the journal, Toxicology and Industrial Health (TIH).

The 17 WEELs published within the past 5 years in Toxicology and Industrial Health (TIH) have seen >15,000 downloads.

Need an OEL? Sponsorship?

When a Sponsor supports the Committee for WEEL derivation or peer review, they can expect:

- **An Open and Transparent Process**
  - Invitation of stakeholders to attend science deliberations and provide data
- **Active communication**
- **A Quality, Unbiased Evaluation of the Chemical of Interest**
- **A Science-backed, appropriate WEEL and Supporting Monograph**

Email Dr. Patricia McGinnis at: mcginnis@tera.org

Acknowledgements

Toxicology Excellence for Risk Assessment (TERA)

TERA is a non-profit and tax-exempt organization for scientific research, and educational purposes and has provided sponsors with independent, transparent science since 1995. TERA solves human health risk challenges for diverse government and private sponsors through research and collaboration that emphasizes partnership building across scientific expertise and multiple perspectives to ensure the use of the best science. These strengths are the basis for TERA's research and development of independent and science-driven analyses for risk assessment.

The Occupational Alliance for Risk Science (OARS)

OARS encourages stakeholder engagement through:

- Open and transparent processes – Invitation of stakeholders to attend science deliberations and provide data
- Active outreach and communication – Information sharing via web posting, free WEEL® documentation, and active outreach to affiliates
- Opportunities for direct involvement – Sponsorship of OEL development for chemicals of interest to external parties

The WEEL Committee would also like to thank Dr. Anthony Kiorpes and Toxicology and Industrial Health.

References:

- Dimethyl-dichlorosilane WEEL Monograph.
- n-Methyl-2-Pyrrolidone (NMP; CAS No. 872-50-4) WEEL Monograph. Toxicology and Industrial Health. In Press.
- Octamethylcyclotetrasiloxane (D4; CAS No. 556-67-2) WEEL Monograph. 2017. Toxicology and Industrial Health. 33(1): 2-15.
- Picolines (Methylpyridines) WEEL Monograph. Draft. In queue for public comment.
- Trimethyl-chlorosilane WEEL Monograph.
- Poet TS, Kirman CR, Bader M, van Thriel C, Gargas ML, Hinderliter PM (2010) Quantitative Risk Analysis for N-Methyl Pyrrolidone Using Physiologically Based Pharmacokinetic and Benchmark Dose Modeling. Toxicol Sci 113: 468–482.
- Poet TS, Schlosser PM, Rodriguez CE, Parod RJ, Rodwell DE, Kirman CR (2016) Using Physiologically Based Pharmacokinetic Modeling and Benchmark Dose Methods to Derive an Occupational Exposure Limit for N-Methylpyrrolidone. Regul Toxicol Pharmacol 76: 102–112.
- Saillenfait AM, Gallissot F, Morel G (2003) Developmental Toxicity of N-Methyl-2-Pyrrolidone in Rats Following Inhalation Exposure. Food Chem Toxicol 41: 583–588.
- Solomon HM, Burgess BA, Kennedy GL, Staples RE (1995) 1-Methyl-2-Pyrrolidone (Nmp): Reproductive and Developmental Toxicity Study by Inhalation in the Rat. Drug Chem Toxicol 18: 271–293.
- U.S. Environmental Protection Agency (EPA) (2015) TSCA Workplan Chemical Risk Assessment N-Methylpyrrolidone: Paint Stripping Use CASRN: 872-50-4. EPA Document# 740-R1-5002; Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency (EPA): Washington, DC.