Health-Effects Equivalent Temporal Extrapolation for Short-Term Inhalation Exposures to Hazardous Chemicals

Thesis Proposal




Thesis Proposal: November 7th 2014

Jedidiah Snyder - GEH

Thesis Advisors:

Field Advisor

Eugene Demchuk, Ph.D.

DTHHS/ATSDR/CDC

edemchuk@cdc.gov

RSPH Faculty Advisor

P. Barry Ryan, Ph.D.

Professor, Department of Environmental Health

bryan@sph.emory.edu

Field Mentor

Andrew Prussia, Ph.D.

CDC ORISE Research Fellow

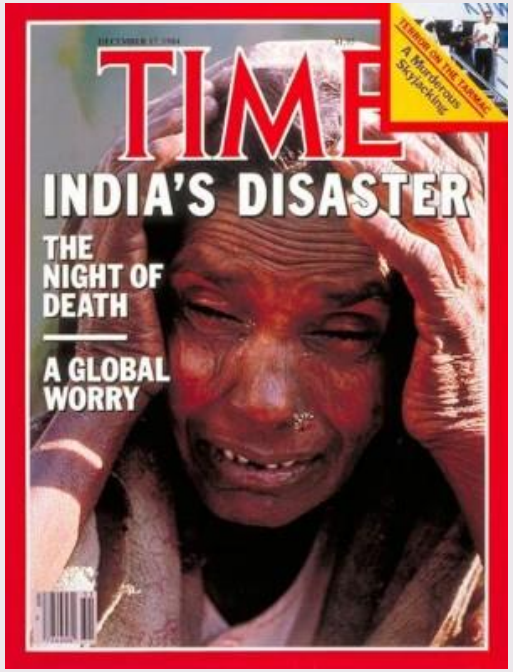
xby2@cdc.gov

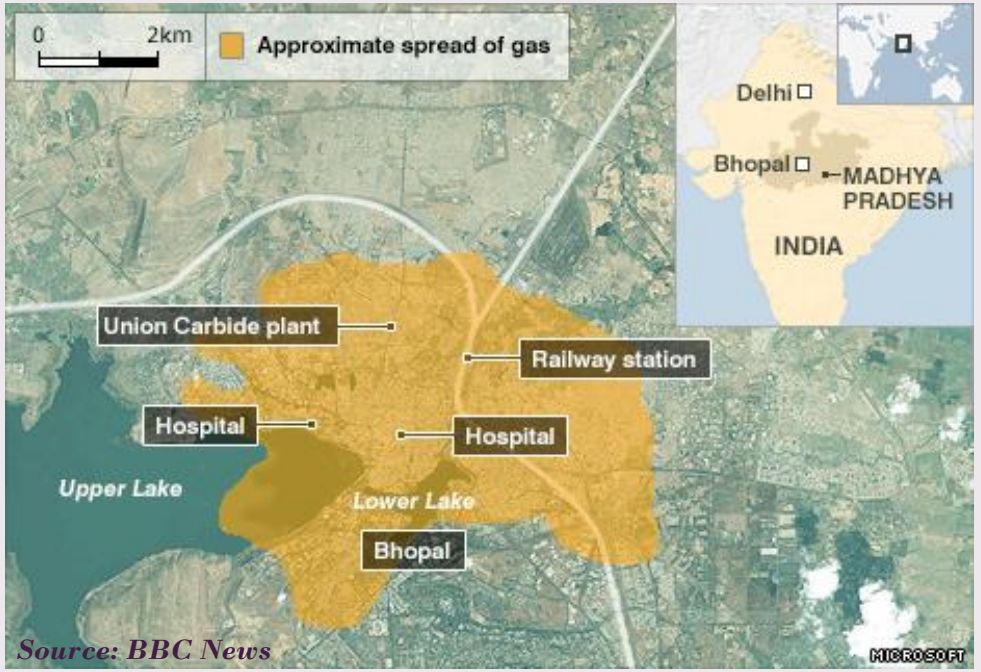
Background:

Chemical emergencies: risk in the acute exposure of chemical substances to first responders and unprotected civilian populations

Bhopal Disaster - 1987

- Methyl isocyanate gas leak
- Immediate mortality of thousands
- Morbidity and premature deaths of thousands more





EPA's Response:

Develop Acute Exposure Guideline *L*evels (AEGLs) for hazardous substances

AEGL-1 (Discomfort/Reversible)
Notable discomfort, irritation, or certain asymptomatic non-sensory effects

---

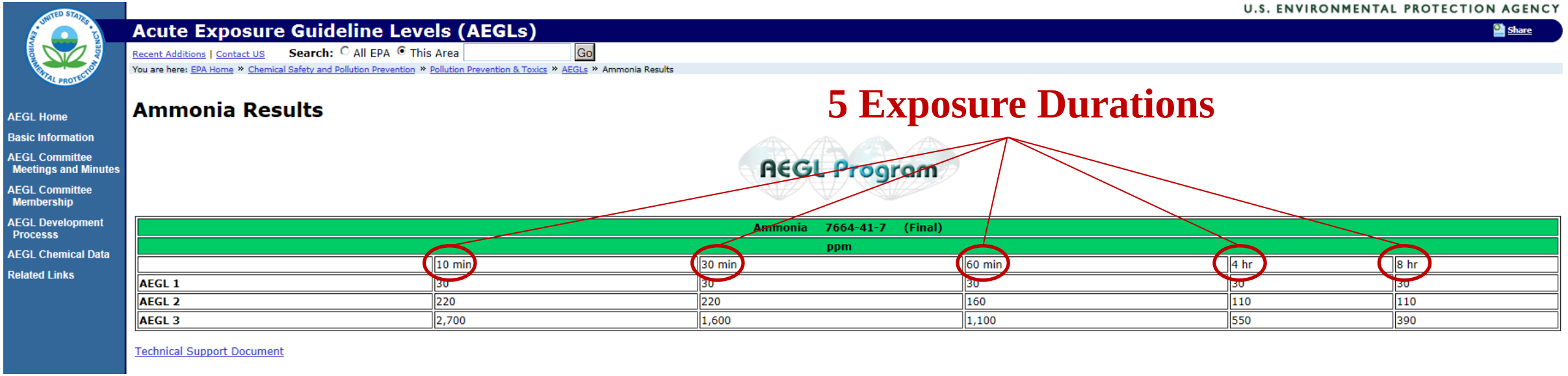
AEGL-2 (Disabling/Irreversible)
Irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape

---

AEGL-3 (Life Threatening)
Experience life-threatening health effects or death

The Problem: Extrapolation

AEGL-committee must often **extrapolate** values from empirical information



U.S. ENVIRONMENTAL PROTECTION AGENCY

Acute Exposure Guideline Levels (AEGLs)

Share

Recent Additions | Contact US Search: All EPA This Area Go

You are here: EPA Home » Chemical Safety and Pollution Prevention » Pollution Prevention & Toxics » AEGLs » Ammonia Results

- AEGL Home
- Basic Information
- AEGL Committee Meetings and Minutes
- AEGL Committee Membership
- AEGL Development Processs
- AEGL Chemical Data
- Related Links

Ammonia Results

5 Exposure Durations

AEGL Program

Ammonia 7664-41-7 (Final)					
ppm					
	10 min	30 min	60 min	4 hr	8 hr
AEGL 1	30	30	30	30	30
AEGL 2	220	220	160	110	110
AEGL 3	2,700	1,600	1,100	550	390

Technical Support Document

Time scaling-ten Berge (1986)

$$C^n \times t = k$$

C = exposure concentration
n = an empiric chemical-specific time-scaling factor (TSF)
t = exposure duration
k = toxic load

The Problem: Limited Data

In absence of supporting data to develop chemical-specific TSFs, AEGL committee uses **default TSFs**

AEGL: Standard Operating Procedure

tration vs time yields a progressive decrease in the slope of the curve.

In cases in which adequate data are available, the NAC/AEGL Committee conducts an analysis of chemical-specific toxicity and exposure data to derive a chemical-specific and health-effect-specific exponent (n) for use in extrapolating available exposure data to AEGL-specified exposure durations. If data are not available for empirically deriving the exponent n, the NAC/AEGL Committee identifies the most appropriate value for n by comparing the resultant AEGL values derived using n = 1 and n = 3. The value of n = 1 has been used historically by others and results in rapid reductions in concentrations

Default TSFs

TSF = 1 *short-to-long term extrapolation*
TSF = 3 *long-to-short term extrapolation*

Default Support

ten Berge (1986) *90% of TSFs of the chemicals analyzed range from 1-3 (only 20 chemicals…)*

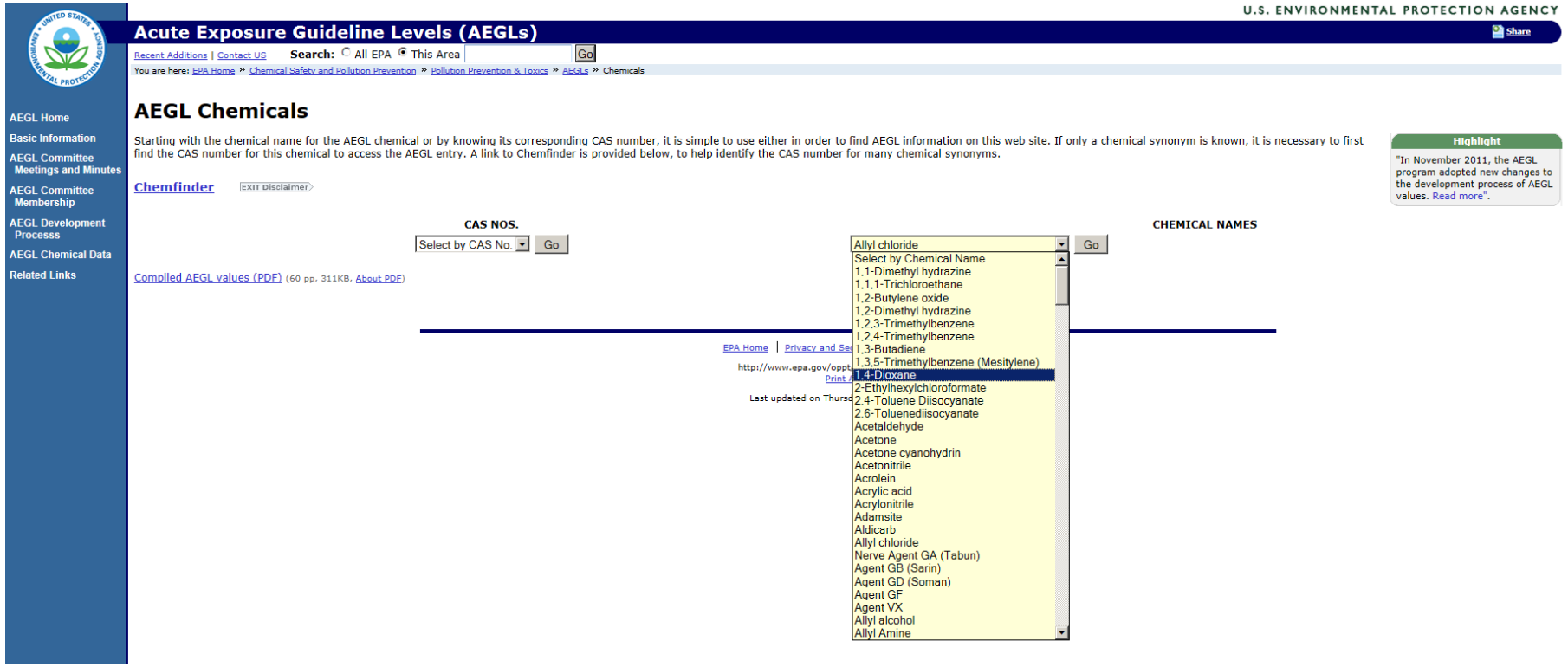
Research Questions:

I. Are default TSFs adopted in the AEGL standard operating procedures statistically appropriate?

II. Can predictive modeling techniques be used for temporal extrapolation of inhalation compounds?

Database:

200 chemicals have published AEGL concentrations derived from **expert panel literature reviews** of either human observations and/or animal studies



Specific Aim I:

Specific Aim I: To extract empirically supported evidence on concentration-exposure relationships for airborne extremely hazardous substances from relevant literature

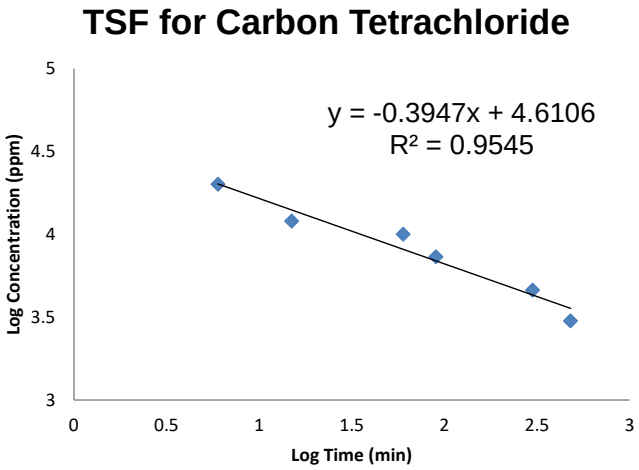
Hypothesis: AEGLs contains large source of rich expert-validated chemical-specific information about temporal extrapolation

Method: Simple linear regression (SLR) fit of endpoint concentrations (i.e. LC_{50}) and corresponding exposure durations on the log-log scale

TSF = -1/Slope

Evaluate SLR: R^2 and F-statistics

Example: Slope = -0.3947, TSF = -1/-0.3947 = 2.53 (R^2 = 0.9545)



Time (min)	LC_{50} (ppm)
6	20000
15	12000
60	10000
90	7300
300	4600
480	3000

Specific Aim II:

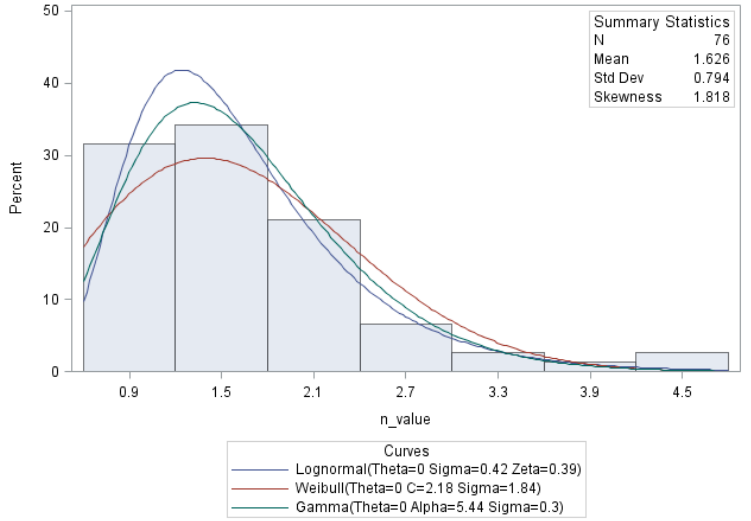
Specific Aim II: To assess the statistical power of default TSFs adopted by the AEGL committee

Hypothesis: Adopted defaults have poor statistical power (only 20 chemicals). Defaults, derived from parametric estimates in the present study, will more accurately represent the true TSF distribution of inhalation compounds

Method: Parametric estimates by fitting TSF statistics to normal distribution (log-normal expected)

Bootstrap distribution: (10,000 samples) to determine confidence intervals on complex estimator parameters such as percentile points (5 and 95%)

Preliminary Distribution Analysis

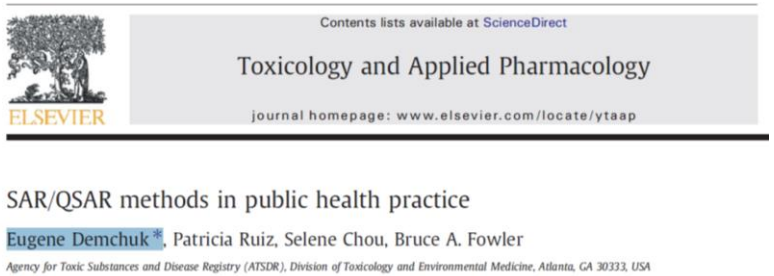


Specific Aim III:

Specific Aim III: To evaluate the ability of chemical-specific TSFs to be predicted using quantitative structure-activity relationships (QSAR) modeling

Hypothesis: Modeling ability is dependent on the size and diversity of the data used to train the model. These models may assist in providing supplementary risk assessment via cross-chemical extrapolation

Method: Partial Least Squares regression of relevant molecular descriptors using organic chemical and their TSFs


Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/ytaap

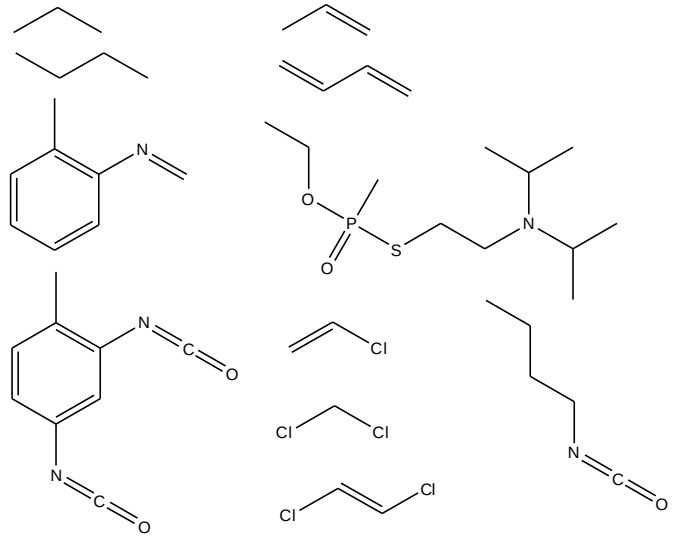
SAR/QSAR methods in public health practice

Eugene Demchuk*, Patricia Ruiz, Selene Chou, Bruce A. Fowler

Agency for Toxic Substances and Disease Registry (ATSDR), Division of Toxicology and Environmental Medicine, Atlanta, GA 30333, USA

400 Molecular Descriptors:

Molecular Weight
Rotatable Bonds
H-Bond Acceptors
H-Bond Donors
Lipinski Score
ALogP
Polar Surface Area
Atom Count



Study Significance:

Novel: Surprisingly, no such statistical analysis has been performed on the entire AEGL database

Decrease Risk Uncertainty: Develop upper and lower boundaries for default TSFs that are more statistically supported

Improve Risk Guidelines: No attempts have been reported on the strengths of predictive modeling techniques for temporal extrapolation of inhalation compounds

References:

National Research Council, Subcommittee on Acute Exposure Guideline Levels. 2001. **Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals**. National Academies Press. Washington, DC: National Academy Press.

Krewski D, Bakshi K, Garrett R, Falke E, Rusch R, and Gaylor D. 2004. **Development of acute exposure guideline levels for airborne exposures to hazardous substances.** Regulatory Toxicology and Pharmacology 39(2): 184-201.

Fortun K: **Advocacy after Bhopal.** Chicago, University of Chicago Press; 2001:259.

MacKenzie D: **Fresh evidence on Bhopal disaster.** *New Scientist* 2002, 19(1).

Sharma DC: **Bhopal: 20 Years On.** *Lancet* 2005, 365(9454):111-112.

Rusch, G.M. **The History and Development of Emergency Response Planning Guidelines.** Hazard Materials 1993, 33, 193–202.

Rusch, George M., Roger Garrett, Paul Tobin, Ernest Falke, and Po-Yung Lu. **The Development of Acute Exposure Guideline Levels for Hazardous Substances.** Drug and Chemical Toxicology 25.4 (2002): 339-348.

Haber, F., 1924. **Zur Geschichte des Gaskrieges. In: Fünf Vorträge aus den Jahren 1920–1923**. Verlag von Julius Springer, Berlin, pp. 77–92.

William E. Rinehart Sc.D. & Theodore Hatch S.M. (1964) **Concentration-Time Product (CT) as an Expression of Dose in Sublethal Exposures to Phosgene**, American Industrial Hygiene Association Journal, 25:6, 545-553.

Witschi, H. **Some Notes on the History of Haber's Law.** Toxicological Sciences 50.2 (1999): 164-68.

Berge, W.f. Ten, A. Zwart, and L.m. Appelman. **Concentration—time Mortality Response Relationship of Irritant and Systemically Acting Vapours and Gases.** Journal of Hazardous Materials 13.3 (1986): 301-09.

Gardner, D. E., F. J. Miller, E. J. Blommer, and D. L. Coffin. **Influence of Exposure Mode on the Toxicity of NO_2.** Environmental Health Perspectives 30 (1979): 23-29.

Gaylor, David W. **The Use of Haber's Law in Standard Setting and Risk Assessment.** Toxicology 149.1 (2000): 17-19.

Miller, Frederick J., Paul M. Schlosser, and Derek B. Janszen. **Haber's Rule: A Special Case in a Family of Curves Relating Concentration and Duration of Exposure to a Fixed Level of Response for a given Endpoint.** Toxicology 149.1 (2000): 21-34.

Mioduszewski, R., J. Manthei, R. Way, D. Burnett, B. Gaviola, W. Muse, S. Thomson, D. Sommerville, and R. Crosier. **Interaction of Exposure Concentration and Duration in Determining Acute Toxic Effects of Sarin Vapor in Rats.** Toxicological Sciences 66.2 (2002): 176-84.

Hulet, S., D. Sommerville, D. Miller, J. Scotto, W. Muse, and D. Burnett. **Comparison of Sarin and Cyclosarin Toxicity by Subcutaneous, Intravenous and Inhalation Exposure in Gottingen Minipigs.** Inhalation Toxicology 26.3 (2014): 175-84.

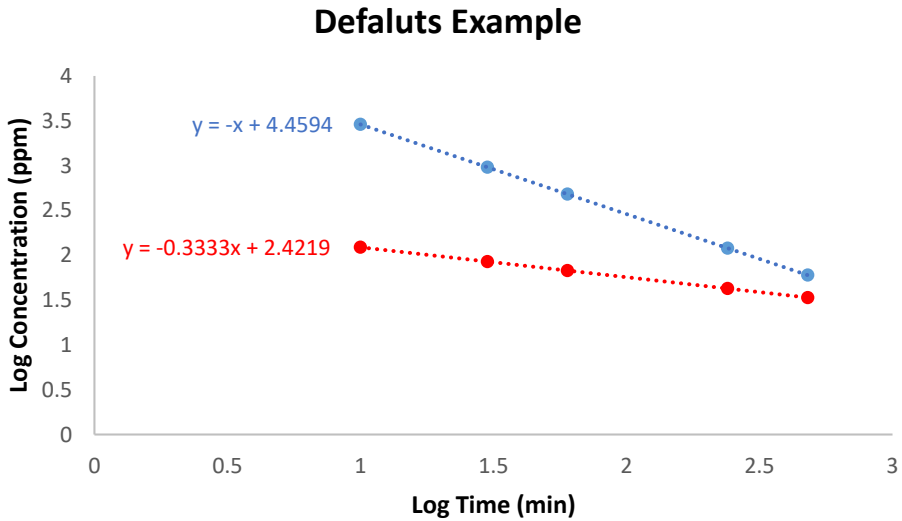
Bide, R. W., and D. J. **Risk. Inhalation Toxicity in Mice Exposed to Sarin (GB) for 20-720 Min.** Journal of Applied Toxicology 24.6 (2004): 459-67.

Questions?

Discussion Slides:

Long-to-short ← → Short-to-long

	10min	30min	1hr	4hr	8hr
AEGL-3 (TSF = 3)	123	85	67	43	34
AEGL-3 (TSF = 1)	2880	960	480	120	60



Discussion Slides:

TABLE 4

Value of the exponent n for several gases and vapours, of which the probit Y of the mortality response in relation to exposure concentration c and exposure period t can be predicted by eqn. (3).

Gas or vapour	Exponent n	95% confidence limits
Local irritants		
NH_3	2.0	(1.6, 2.4)
HCl	1.0	(0.7, 1.3)
ClF_5	2.0	(1.4, 2.6)
NO_2	3.5	(2.7, 4.3)
Cl_2	3.5	(2.5, 4.4)
Perfluoroisobutylene	1.2	(1.1, 1.4)
Crotonaldehyde	1.2	(1.1, 1.3)
HF	2.0	(1.2, 2.8)
Ethylene imine	1.1	(0.8, 1.3)
Br_2	2.2	(2.0, 2.4)
Dibutylhexamethylenediamine	1.0	(0.6, 1.4)
Systemic action		
HCN	2.7	(1.8, 3.7)
H_2S	2.2	(1.6, 2.7)
Methyl t-butyl ether	2.0	(1.0, 2.9)
CH_2ClBr	1.6	(1.4, 1.8)
$C_2H_4Br_2$	1.2	(1.1, 1.2)
C_2Cl_4	2.0	(1.4, 2.6)
C_2HCl_3	0.8	(0.3, 1.4)
CCl_4	2.8	(1.9, 3.7)
Acrylonitrile	1.1	(1.0, 1.2)

Source: Berge et al (1986)

Discussion Slides:

TABLE G1. VALUE OF THE HABER'S LAW EXPONENT (*n*) FOR VARIOUS GASES AND VAPORS FOR ACUTE RELS[1]

Chemical	*n*	Species/Effect (site of action)	References, Comments
Acrolein	1.2	rat/lethality (local irritant)	U.S. EPA (1992a; U.S.EPA, 1992b)[2]
Acrylonitrile	1.1	rat/lethality (systemic)	(Dudley and Neal, 1942; Appel et al., 1981)[3]
Allyl chloride	0.5	rat/lethality (local irritant)	Adams *et al.* (1940)[2]
Ammonia	4.6	Human/irritation	Rosenbaum *et al.*(1993)
	2.02	rat/lethality (local irritant)	Appelman *et al.*(1982)
Arsine	2.2	rat/lethality (systemic)	IRDC (1985)[2] for 0.5 to 1 hr (n dependent on exposure duration)
	1.0	rat/lethality (systemic)	IRDC (1985)[2] for 4 hr to 1 hr (n dependent on exposure duration)
	2	mice/lethality (systemic)	Levvy (1947)
Benzene	2	not given	AICE (1989)
Bromine	2.2	mice/lethality (local irritant)	Bitron & Aharoson (1978)[3]
Carbon monoxide	1	not given	AICE (1989)
Carbon tetrachloride	2.8	rat/lethality (systemic)	Adams *et al.*(1952)[3]
Chlorine	2.8	rat/lethality (local irritant)	Zwart & Woutersen (1988)[2] for 0.5 hr to 1 hr (n dependent on exposure duration)
	1.0	rat/lethality (local irritant)	Zwart & Woutersen (1988)[2] for 4 hr to 1 hr (n dependent on exposure duration)
	1.3	mouse/lethality (local irritant)	Zwart & Woutersen (1988)[2]
	3.5	mouse/lethality (local irritant)	Bitron & Aharoson (1978)[3]
Chlorine pentafluoride	2	rat, mouse, dog, monkey/lethality (local irritant)	Darmer *et al.* (1972)[3]
Crotonaldehyde	1.2	rat/lethality (local irritant)	Rinehart (1967)[3]
Dibutyl hexamethylene-diamine	1	rat/lethality (local irritant)	Kennedy & Chen (1984)[3]
1,2-dichloro-ethylene	2	(not applicable)/lethality (systemic)	U.S.EPA (1996), based on the mid-point range of n values from lethality data of[3]
Dimethyldichloro-silane	2	(not applicable)/lethality (local irritant)	U.S.EPA (1996), based on the mid-point range of n values from lethality data of[3]
Ethylene dibromide	1.2	rat/lethality (systemic)	(Rowe *et al.*, 1952b)[3]
Ethylene imine	1.1	rat, guinea pig/lethality (local irritant)	(Carpenter *et al.*, 1948)[3]
Fluorine	1.9	rat/lethality (local irritant)	U.S.EPA (1996), derived from LC_{50} data of Keplinger & Suissa (1968)
	1.8	mouse/lethality (local irritant)	U.S. EPA (1996), derived from LC_{50} data of Keplinger & Suissa (1968)
	1.6	guinea pig/lethality (local irritant)	U.S.EPA (1996), derived from LC_{50} data of Keplinger & Suissa 1968)
Formaldehyde	2	not given	AICE (1989)
Hydrazine	2	(not applicable)/lethality (systemic)	U.S.EPA (1996), based on the mid-point range of n values from lethality data of[3]
Hydrogen chloride	1	rat, mouse/lethality (local irritant)	Darmer (1972)[3]
	1.5	rat/lethality (local irritant)	Hartzell & Johnson (1985)[2]
Hydrogen cyanide	2.7	numerous species/lethality (systemic)	Barcroft (1931)[3]
Hydrogen fluoride	2	rabbits, guinea pigs/ lethality (local irritant)	Machle (1934)[3]
Hydrogen fluoride (low humidity)	1	rat/lethality (local irritant)	Haskell Lab. (1988)[2]
Hydrogen sulfide	2.2	cat, rabbit/lethality (systemic/local irritant)	Lehmann (1892)[3]
	8.2	lethality (systemic/local irritant)	Arts (1989)
Methyl bromide	4.0	severe morbidity (systemic/local irritant)	Pharmaco: LSR, (1994) as cited in DPR (2004)[2], DPR (1996)
	1	not given	AICE (1989)
Methylene chloro-bromide	1.6	rat/lethality (systemic)	Torkelson (1960)[3]
Methyl hydrazine	1.0	squirrel monkey/lethality (systemic and local irritant)	Haun (1970)[2]
	1.0	dog/lethality (systemic and local irritant)	Haun (1970)[2]
Methyl isocyanate	1.1	human/eye irritation	Mellon Institute (1963)[2]
	0.5	rat/lethality (local irritant)	Kimmerle & Eben (1964)[2]
	0.7	rat/lethality (local irritant)	DOW Chemical (1990)[2]
Methyl mercaptan	2	(Not applicable)/lethality (systemic and local irritant)	U.S.EPA (1996), based on the mid-point range of n values from lethality data of[3]
Methyl t-butyl ether	2.0	lethality (systemic)	Snam Progretti (1980) as cited in ten Berge et al., (1986)[3]
Nitrogen dioxide	3.5	guinea pig, mouse, dog, rat, rabbit/lethality (local irritant)	Hine *et al.*, (1970)[3]
Nitric acid	3.5	not applicable (local irritant)	U.S.EPA (1996), based on NO_2 from Hine *et al.* (1970)
Perfluoroisobutylene	1.2	rat/lethality (local irritant)	Smith *et al.* (1982)[3]
Phosgene	1	lethality (local irritant)	Rinehart & Hatch (1964)
Propylene oxide	2.2	rat/lethality (local irritant)	Rowe *et al.* (1956)[2]
	1.5	guinea pig/lethality (local irritant)	Rowe *et al.* (1956)[2]
Sulfur dioxide	1	not given	AICE (1989)
Tetrachloroethylene	2.0	rat/lethality (systemic)	Rowe *et al* (1952a)[3]
Toluene	2.5	not given	AICE (1989)
Trichloroethylene	0.8	rat/lethality (systemic)	Adams *et al.* (1951)[3]

[1] developed using procedures specified in OEHHA (1999a). [2]derived by OEHHA.
[3]derived by ten Berge (1986).

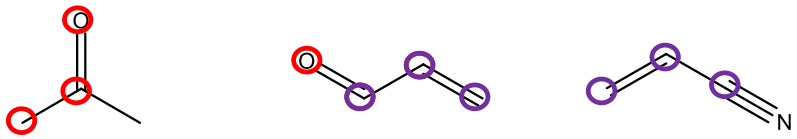
Source: (OEHHA)

Discussion Slides:

Identify a Training Dataset

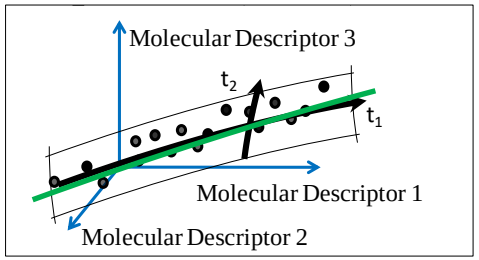
ID	Name	MRL
MRL_1	ACETONE	26 ppm
MRL_2	ACROLEIN	0.003 ppm
MRL_3	ACRYLONITRILE	0.1 ppm

Knowledge Development

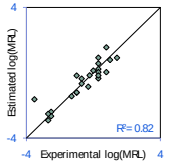


MRL_1 MRL_2 MRL_3

Select Training Features and Descriptors



Partial Least Squares (PLS) Regression



Build Model

Source: Catharine J. Collar