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

Author: Jedidiah Samuel Snyder[1,2]
Field Advisor: Eugene Demchuk[2], RSPH Advisor: P. Barry Ryan[1]
Date of submission: October 30th, 2014

[1]Department of Global-Environmental Health, Rollins School of Public Health, Emory University, Atlanta GA,
[2]Agency for Toxic Substances and Disease Registry, Atlanta, GA

Specific Aims and Hypothesis:

Specific Aim 1: To extract empirically supported evidence on concentration-exposure relationships for airborne extremely hazardous substances from relevant literature.
Hypothesis: The Acute Exposure Guideline Levels (AEGLs) developed by the Environmental Protection Agency (USEPA) contains large source of rich expert-validated chemical-specific information about temporal extrapolation.

Specific Aim 2: To assess the statistical power of default time scaling factors (TSFs) adopted by The National Advisory Committee for Acute Exposure Guideline Levels (NAC/AEGL).
Hypothesis: The adopted defaults have poor statistical power because they have been derived using a small sample of only 20 chemicals. Defaults, derived from parametric estimates in the present study, will more accurately represent the true TSF distribution of inhalation compounds. Therefore, AEGLs and other inhalation health guidance values that have been derived using former default TSFs may be insufficiently protective and may need reexamination.

Specific Aim 3: To evaluate TSF relationships with relevant chemical and health-effects properties (i.e. volatility, boiling point, molecular weight, organic nature, systemic/local health effects, tested species, etc.).
Hypothesis: Stratification of TSFs by chemical properties and health effects may reveal relationships that prove to be valuable in better understanding TSF distribution and therefore help in developing new guidelines for assigning defaults to chemicals in absence of supporting data.

Specific Aim 4: To evaluate the ability of chemical-specific TSFs to be predicted using quantitative structure-activity relationships (QSAR) modeling.
Hypothesis: The quality of TSF predictive models is dependent on the size and diversity of the data used to train the model. However, these models may assist in providing supplementary risk assessment via cross-chemical extrapolation when chemical-specific empirical data for temporal extrapolation is lacking.

Background and Significance:

Background: Airborne extremely hazardous substances can be released into the environment accidentally as a result of chemical spills, explosions, natural disasters, or industrial accidents as well as intentionally in the form of chemical warfare and terrorist attacks. These chemical emergencies may post great risks in the acute exposure of chemical substances to first responders and unprotected civilian populations[1,2].

Acute Exposure Guideline Levels (AEGLs) are exposure limits for the general public that are designed for assessing the risk of rare exposure to hazardous airborne chemicals. AEGLs permit broad application because, for each inhalation compound, up to fifteen AEGL values may be developed that address three health severity tiers (discomfort, disabling, and life threatening) at five exposure durations (1/6, 1/2, 1, 4, and 8 hrs). It is rare to find supporting data that describe concentration thresholds for all five AEGL-specific exposure periods, and concentration-exposure duration extrapolation is often applied, by which $C^n \times t = k$, where C is exposure concentration, n is an empiric chemical-specific time-scaling factor (TSF), t is exposure duration, and k is toxic load[3].

In absence of supporting data to evaluate estimated chemical-specific TSFs, the AEGL committee selects a default TSF of 1 for short-to-long term extrapolation and a default TSF of 3 for long-to-short term extrapolation and considers thus derived AEGL values to be protective and scientifically credible[1]. These upper and lower boundaries for default TSFs are associated with the work of ten Berge et al. (1986), as 90% of TSFs of the chemicals analyzed range from 1 to 3.

Significance: We argue that the statistical power of Berge's study is low and implementing NAC/AEGL default values based on percentiles of only 20 chemicals is risky. AEGL values are derived by an international panel of public and private stakeholders that execute a comprehensive peer-review process of primary toxicological information used to identify "key" toxicity studies. The AEGL database contains valuable information on chemical-specific temporal extrapolation, along with derived TSFs for some chemicals. Surprisingly, no such statistical analysis has been performed on the entire AEGL database of empirically-derived TSFs or TSFs that could be derived from the key studies. Additionally, no attempts have been reported on the strengths of predictive modeling techniques for temporal extrapolation of inhalation compounds.

Research methods:

Data: The AEGL database contains 273 chemicals for which AEGLs have been derived at the "Final," "Interim," and "Proposed" development stages. Chemical-specific concentration-exposure duration relationships identified in "key" studies will be extracted using the USEPA AEGL Chemical Data portal (*http://www.epa.gov/oppt/aegl/pubs/humanhealth.htm*). 200 of the 273 chemicals are known to have AEGL concentrations derived from either human observations and/or animal studies. In addition to the AEGL database, concentration-exposure duration relationships will be synthesized from ten Berge et al. (1986) and the Office of Environment Health Hazard Assessment (OEHHA).

Analysis plan: (*Aim 1*) TSF statistics for each chemical will be derived using simple linear regression (SLR) fit of AEGL concentrations and corresponding exposure durations on the log scale[3]. Logarithmic transformation of concentration and exposure duration allow the non-linear equation to be converted into a linear equation, where chemical-specific TSFs can be determined by solving for -1/slope. Linear fit will be assessed by r-squared values and F-statistics. TSFs will be evaluated based on the strength of the empirical data used to derive them. This will include: experimental end point, species, length of duration exposures and number of exposures used to derive TSFs.

(*Aim 2*) Parametric estimates will be performed by fitting the TSF statistics to a normal distribution (log-normal is expected). In addition, a bootstrap distribution (10000 samples) will be used to determine confidence intervals for complex estimator parameters such as percentile points[4]. This procedure has demonstrated the ability to increase confidence in parametric estimates of a log-normal distribution[5]. The sample size is expected to be small, less than 200 chemical-specific TSFs; therefore, bootstrapping will allow us to account for distortions in our sample that may not fully represent the true population[6]. However, this method will be dependent on how well the sample represents an underlying distribution.

(*Aim 3*) USEPA software, *EPIsuite*, will be used to determine physical and chemical properties (molecular weight, melting point, boiling point, vapor pressure and organic and ionic nature) of each chemical in the AEGL database. TSFs will be stratified based on physical and chemical properties in attempt to reveal any underlying distributions or correlations between TSF magnitude and physical or chemical properties.

(*Aim 4*) QSARs are predictive mathematic models that utilize physical characteristics based on chemical structure, known as molecular descriptors. These simple QSAR models can then be used for predictive purposes using Partial Least Squares regression of relevant molecular descriptors. Model training, in collaboration with Andrew Prussia, Ph.D., will be performed on organic-chemical TSFs against 400 molecular descriptors. The quality of model fitting will be assessed using the r-squared values of the model regression as well as residual analysis between the experimentally derived TSFs and the model predicted value using a validation dataset.

References:

1. 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.

2. 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.

3. 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.

4. Efron, Bradley. **Second Thoughts on the Bootstrap.** Statistical Science 18.2 (2003): 135-40.

5. Angus, John E. **Bootstrap One-Sided Confidence Intervals for the Log-Normal Mea**n. Journal of the Royal Statistical Society. Series D (The Statistician) 43.3 (1994): 395-401. JSTOR.

6. Adèr, Herman J., G. J. Mellenbergh, and D. J. Hand. **Advising on Research Methods: A Consultant's Companion.** Huizen, Netherlands: Johannes Van Kessel Pub., 2008.

Detailed timeline for completion of the thesis:

Weeks working on thesis	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**
Month	**Nov.**		**Dec.**			**Jan.**		**Feb.**		**Mar.**		**Apr.**	
Day of week (Monday)	**3**	**17**	**1**	**15**	**29**	**13**	**27**	**10**	**24**	**10**	**24**	**7**	**21**
Data													
Review AEGL technical support documents to extract empirically derived TSFs	**X**												
Review studies referenced by ten Berge and OEHHA on TSFs	**X**												
Introduction and methods													
Literature review for introduction				**X**	**X**								
Write methods section				**X**	**X**								
Submit thesis progress form						**X**							
Results and Discussion													
Perform parametric statistic on database		**X**	**X**										
Evaluate relationships between chemical characteristic and TSFs							**X**	**X**					
QSAR model training (collaboration with Andrew Prussia Ph.D.)				**X**	**X**	**X**	**X**	**X**					
Write results section									**X**	**X**			
Write discussion section									**X**	**X**			
Final Reporting													
Thesis rough draft submitted to advisors										**X**			
Final revisions											**X**	**X**	
Sign and submit thesis													**X**