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Statistical analysis of concentration-time extrapolation factors for acute inhalation exposures to hazardous substances

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By

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2010

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2015

Abstract

Statistical analysis of concentration-time extrapolation factors for acute inhalation exposures to hazardous substances

By Jedidiah S. Snyder

Background: Acute Exposure Guideline Levels (AEGLs) are exposure limits for the general public that are designed for assessing the risk of rare exposures to hazardous airborne substances. For each chemical substance, AEGLs may be developed for up to five exposure durations (10 min, 30 min, 1 hr, 4 hr, and 8 hr). 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 x $t = k$, where C is exposure concentration, n is an empirical chemical-specific "toxic load exponent," t is exposure duration, and k is toxic load.

Rational: In absence of empirical data, the AEGL Committee selects a default toxic load exponent (TLE) of 1 for short-to-long term extrapolation and 3 for long-to-short extrapolation. These upper and lower boundaries for default TLEs are associated with the work of ten Berge *et al.* 1986, as approximately 90% of the values of n for chemicals (N = 20) analyzed in their study ranged from 1 to 3. Because of the small sample size these defaults have poor statistical power.

Methods: In the present work, we reevaluate the numbers using more representative statistics. A thorough review of data from ten Berge *et al.* 1986, AEGL technical support documents and literature identified 127 unique chemical substances with empirically supported TLEs.

Results: Non-parametric estimates revealed that 90% of the chemical substances (N = 127) had designated values of n that were confined between 0.77 (95%CI: 0.66 – 0.88) and 3.62 (95%CI: 3.03 – 4.32). Notably, our interval estimation failed to include the AEGL Committee's default n value of 1 for short-to-long term extrapolation and 3 for long-to-short term extrapolation at the 95% confidence level.

Conclusion: Thus, our estimation suggests 0.75 and 3.5 as appropriate defaults for concentration-exposure duration extrapolation. Therefore, AEGLs and other inhalation health guidance values that have been derived using defaults of 1 and 3 for concentration-exposure duration extrapolation may be insufficiently protective and may need reexamination.

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Chapter 1

Background and Literature Review

I. BACKGROUND

Extremely hazardous airborne 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 (NRC, 2001; Krewski, 2004). Although durations of exposures to such chemicals may be short, it is imperative to understand how dangerous they might be and what steps to take to mitigate threats to public health associated with these chemical releases. This oversight was sadly recognized in the Bhopal disaster of 1984, where a methyl isocyanate gas leak from a pesticide plant led to immediate mortality of thousands of civilians as well as causing significant morbidity and premature deaths in thousands more (Fortun, 2001; MacKenzie, 2002; Sharma, 2005). This incident sparked national and international attention concerning local preparedness for chemical emergencies and the availability of information on hazardous substances (Rusch, 1993).

Exposures to hazardous substances during a chemical emergency can be at life/health-threatening levels. Therefore, even though of a short duration, these exposures should be treated differently from other health guidance values established by organizations such as the Agency for Toxic Substances and Disease Registry's (ATSDR)

minimal risk levels (MRLs), the U.S. Environmental Protection Agency's (U.S. EPA) reference concentrations (RfCs), and the National Institute for Occupational Health's (NIOSH) recommended exposure limits (RELs) (NRC, 2001; Krewski, 2004). The National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (AEGL Committee) was established in 1995 by the U.S. EPA to develop Acute Exposure Guideline Levels (AEGLs) for hazardous substances. The primary goal of the AEGL Committee is to develop the most scientifically credible exposure levels possible; given the constraints of comprehensive data, funding, and time (Rusch, 2002). These published values are then used to aid state and local government agencies in a variety of applications including the development of emergency preparedness and prevention plans, hazard assessment, and safety analysis.

II. ACUTE EXPOSURE GUIDELINE LEVELS

Acute Exposure Guideline Levels, or "AEGLs," are exposure limits for the general public, including sensitive subpopulations, that are designed for assessing the risk of acute once-in-a-lifetime or rare exposure to hazardous airborne chemicals. Developed by an international panel of public and private stakeholders, AEGLs permit broad application because, for each inhalation compound, up to fifteen AEGL values may be developed that address three health severity tiers (AEGL-1: discomfort/reversible, AEGL-2: disabling/irreversible, AEGL-3: life threatening) at five exposure durations (10 min, 30 min, 1 hr, 4 hr, and 8 hr) (*See example for ammonia below).* U.S. EPA AEGL definitions for the characteristics associated to each health severity tier demonstrate by what means AEGL values are established for unique endpoint classifications:

Official U.S EPA AEGL Definitions:

AEGL-1 "is the airborne concentration, expressed as parts per million or milligrams per cubic meter (ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure."

AEGL-2 "is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape."

AEGL-3 "is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death."

Finalized AEGLs in parts per million (ppm): Ammonia (CAS: 7664-41-7)

Severity Tier	10 minutes	20 minutes	60 minutes	4 hours	8 hours
AEGL-1	30	30	30	30	30
AEGL-2	220	220	160	110	110
AEGL-3	2,700	1,600	1,100	550	390

III. DEVELOPMENT OF ACUTE EXPOSURE GUIDELINE LEVELS

For full description of AEGL methodology, refer to "*Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals*" (NRC, 2001). To summarize, a comprehensive peer-review process of primary toxicological information is used to identify "key" toxicity studies from which AEGL values are derived, many of which come from controlled animal-based studies (NRC, 2001). Within this review process, the AEGL Committee centers its attention on results from short-term or acute exposure studies, as these best represent the rare, accidental exposures associated with AEGL value development (Rusch, 2002). Studies involving multiple exposures are reviewed, however, they predominantly function to provide understanding of the mechanism of toxicity as oppose to assigning chemical-specific AEGL values (Rusch, 2002). When available, multiple studies (including those from different animal models) are reviewed to evaluate relative agreement between studies.

The AEGL Committee has published AEGL values for 271 chemicals identified on their priority list. 167 chemicals have "*Finalized*" AEGLs, while 92 and 12 chemicals have AEGLs at the "*Interim*" and "*Proposed*" stages, respectively (*Appendix B-D*). An additional 46 chemicals have AEGLs that are on hold due to insufficient data (*Appendix E*). For each chemical, the Committee develops a technical support document (TSD) that contains a thorough analysis of referenced data, methods, scientific rationale, and other aspects used in the derivation of AEGL values. Key toxicity studies and supporting data used for AEGL derivations may be from government databases, peer-reviewed journals, and published documents from the public and private sector in the U.S. and internationally, as well as data from private industries or organizations (NRC, 2001). As stated, AEGL values are developed for five target exposure durations ranging from 10 min to 8 hr. However, to date, not a single chemical is associated with empirical data that describe

concentration thresholds for all fifteen combinations of AEGL-specific tiers and exposure periods. Therefore, the AEGL Committee has to extrapolate AEGL values from empirical information expressing critical exposure durations and concentrations.

IV. CONCENTRATION – EXPOSURE DURATION RELATIONSHIPS

There are several models that allow extrapolation of AEGL values from one time period to another. Knowledge of the chemical's mechanism of toxic action can aid in deciding which extrapolation method is most appropriate. For instance, if the response is viewed as a concentration threshold and independent of time, AEGL values may be held constant across all exposure durations (NRC, 2001). This approach may be associated with the AEGL-1 response to an irritant (Rusch, 2002; Belkebir, 2011). Historically, duration adjustments have been performed using "Haber's rule" proposed in the early 1900s (Flury, 1921; Haber, 1924):

$$C \times t = k \qquad \text{Eq. (1)}$$

Eq. (1) states that exposure concentration (C) of a chemical and exposure duration (t) can be reciprocally adjusted to obtain a cumulative exposure-response constant (k). The cumulative exposure-response constant is an estimate of the total amount of toxic material (toxic load) delivered to the lungs over the exposure duration, assuming the respiratory rate remains constant. The concept of this estimate was established by Haber's "death product" which proposed that the cumulative exposure to produce death is a constant (Haber, 1924). Supplementary investigation of concentration-exposure duration relationships also found Haber's postulate adequate (Rinehart & Hatch, 1964).

Although valuable and commonly considered a fundamental principle in inhalation toxicology, many toxicologist are guilty of apply this rule for extrapolation purposes regardless of whether individual chemicals, biological endpoints or exposure scenarios are appropriate candidates for the rule (Salem & Katz, 2014). As stated, Haber's rule has many limitations. Suggested in Rinehart & Hatch *et al.* (1964), Haber's rule can not apply to chronic exposures, as this would contradict the concept of safe exposure limits for prolonged or repeated exposures. Additionally, Haber's rule assumes that the exposure is entirely cumulative and damage is irreversible. However, this is generally not the case for short-term exposures (NRC, 2001) and Haber's rule is only applicable if damage from the chemical substance has reversibility kinetics that are slower than its elimination kinetics (Belkebir, 2011). Finally, it is acknowledged that the success of the relationship proposed by Haber is dependent of factors such as respiratory rate, retention of the dose delivered to the lungs and physical activity, all of which can change the effective dose rate (Rinehart & Hatch, 1964).

Haber's rule only applies when the chemical response is equally dependent on concentration and exposure duration. The relationship suggest that a chemical exposure of short-term, high concentration produces equivalent biological effects as that of long-term, low concentration exposures. However, very crude exposure scenarios can help disprove this. For example, exposure to 400 ppm of carbon dioxide over the course of a day would yield far less health risks compared to that of 57,600 ppm within a ten minute period. As classically illustrated by Paracelsus' "the dose makes the poison," the concentration of a chemical is commonly considered the most important factor of determining toxicity (Witschi, 1999). This notion of Haber's rule was first systematically evaluated in ten Berge *et al.* (1986). ten Berge's study showed that for large classes of hazardous airborne

chemicals, Haber's rule was not always the best predictor of lethality, as it was only appropriate to a limited number of chemicals (ten Berge, 1986). Alternatively, he found that the concentration and exposure duration was reasonably approximated by an exponential function of concentration, and thus for steady-state conditions:

$$C^n \times t = k \qquad \text{Eq. (2)}$$

where, similar to Haber's rule, the toxic load, k, is a determinant of the adverse health effects in a specified percentage of the population (e.g. LC_{50}). ten Berge's analysis of mortality data for 20 structurally different chemicals revealed that chemical-specific relationships between exposure concentration and exposure duration are often exponential, where n is a chemical-specific "toxic load exponent" (TLE) greater than zero. These TLEs, empirically derived in ten Berge's study, ranged from 0.8 to 3.5. As illustrated in Eq. (2), when $n = 1$, the toxicity of a substance is equally dependent on exposure concentration and exposure duration and follows Haber's rule; when $n < 1$, the toxicity is more dependent on the duration of exposure than on the concentration, and conversely when $n > 1$.

V. DERIVATION OF TOXIC LOAD EXPONENTS

Toxic load exponents were derived by ten Berge and co-authors using a probit model with two independent variables (Finney, 1947). This method assumes that the mortality response, plotted against log-transformed chemical concentration or exposure duration, follows a cumulative normal distribution. As such, the probit model is a type of regression where regression coefficients are derived from raw data using the method of maximum likelihood (Finney, 1947). The ratio between the regression coefficient of the

concentration and exposure duration can then be used to derive the chemical-specific *n* value, which expresses the chemical's concentration-exposure duration relationship (ten Berge, 1986). This statistical method is the preferred approach for deriving values of *n* because it allows for maximum likelihood estimates with 95% confidence limits to be determined (NRC, 2001).

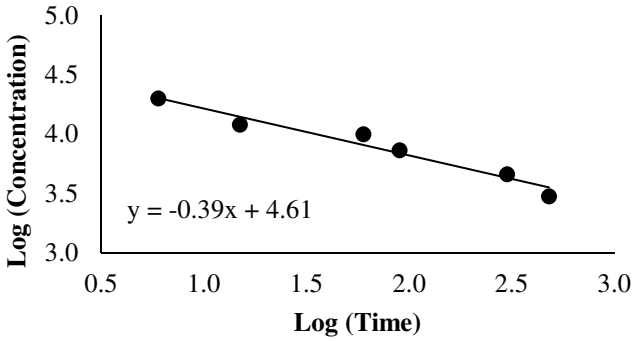
However, probit analysis requires individual animal data to derive an *n* value. These data expressing concentration-exposure duration relationships are typically unavailable and often only LC_{50} values are reported (NRC, 2001). When this is the case, TLEs can be derived similarly using a simple linear regression model of log-log transformed concentration-exposure duration data. Logarithmic transformation of concentration and exposure duration linearizes the non-linear Eq. (2) (NRC, 2001)

$$\log C = (-1/n) \log t + (\log(k))/n \qquad \text{Eq. (3)}$$

where, *C* is a regressed concentration that causes a health effect (usually LC_{50} or EC_{50}) at exposure duration of *t*; *k* is a determinant of the adverse health effect. Chemical-specific TLEs can then be determined by solving -1/*n* (the slope of the regressed line) for *n*. This method is illustrated using rat concentration-exposure duration relationships expressed as LC_{50} data at six different time points (Adams *et al*. 1952; Dow Chemical Company, 1960; Mellon Institute, 1947) for carbon tetrachloride:

(1) *Plot of logarithmic transformed concentration and exposure duration*:

Time (min)	LC_{50} (ppm)
6	20,000
15	12,000
60	10,000
90	7,300
300	4,600
480	3,000



(2) *Simple linear regression fit to determine slope*:

$Slope = -0.39$

(3) *Solve for toxic load exponent (n)*:

$Toxic\ load\ exponent\ (n) = -1/-0.39 = 2.56$ and thus, the toxicity of carbon tetrachloride is more dependent on the duration of exposure than on the concentration.

Strength of derived TLEs are dependent on how well the log-transformed data fit the regression line. Typically, this strength can be evaluated using a coefficient of determination (r^2). However, this statistic becomes less useful when the number of data points are few; "the chance of obtaining a particular correlation coefficient is equal to that of obtaining any other" (Alder & Roessler, 1968). The number of endpoint specific data points available to the AEGL Committee for deriving TLEs are usually less than four (NRC, 2001), so r^2 statistics become far less informative. However, this approach is "generally the best when empirical data are used to derive *n* values for developing AEGL values for specified exposure durations" (NRC, 2001). Additionally, professional judgment

is always exercised by the AEGL Committee when deriving or selecting values of *n* by evaluating the subsequent AEGL values to other supporting data (NRC, 2001).

VI. EXTRAPOLATION WITHOUT EMPIRICAL DATA

In absence of supporting data to evaluate chemical-specific TLEs, the AEGL Committee selects a default *n* of 1 for short-to-long term extrapolation and a default *n* of 3 for long-to-short extrapolation and considers thus derived AEGL values to be protective and scientifically credible (NRC, 2001). These upper and lower boundaries for default TLEs are associated with the work of ten Berge *et al.* (1986), as 90% of values of *n* for the chemicals analyzed range from 1 to 3. As stated, an *n* of 1 assumes that chemical response is equally dependent on concentration and exposure duration and has been used historically in risk assessment (Haber's rule). Extrapolating concentration estimates from shorter to longer durations with an *n* of 1 results in rapid decrease in extrapolated concentration estimates. Whereas, extrapolating concentration estimates from longer to shorter durations with an *n* of 3 results in less rapid rates of increase in concentration estimates. Therefore, by applying default TLEs in such a manner, the AEGL Committee applies conservative extrapolation procedures when developing AEGL estimates. Again, derived AEGL estimates are then compared to supporting data to examine if they are scientifically reasonable (NRC, 2001).

VII. AEGL PROGRAM'S FUTURE

The AEGL program has been highly successful in its development of scientifically credible exposure levels for a majority of the chemicals listed on its priority list (U.S. EPA, "*AEGL Process*"). Coupled with decreased demand for operation and budget constraints,

the AEGL Committee was eliminated for future work in November 2011. Given the limited resource available, the primary focus of the AEGL program has shifted to finalizing AEGL chemicals in the "*Interim*" development stage with the National Academy of Sciences (NAS) (U.S. EPA, "*AEGL Process*"). Moving forward, contractors alone respond to the NAS comments, as the AEGL Committee is no longer available for deliberation and approval (U.S. EPA, "*AEGL Process*").

VIII. MOVING FORWARD

ten Berge's systematic investigation of the concentration-exposure duration response relationships of extremely hazardous airborne substances provided insight on chemical characteristics that have demonstrated great utility in the development of hazard assessments and safety analysis plans for emergency responses. However, the statistical power of ten Berge's study is low and implementing AEGL default values based on percentiles of only 20 chemicals may be risky. The international growth of newly synthesized and isolated chemicals is high. In fact, data from the *CAS Statistical Summary from 1907-2007* indicates an exponential increase in registered chemicals over that time period (ACS, 2008; Binetti, 2008). Furthermore, the U.S. EPA's Toxic Substances Control Act (TSCA) *Chemical Substance Inventory* currently contains more than 84,000 chemical substances and the agency receives between 500 and 1,000 new "Notices of Commencement of Manufacture or Import" (NOCs) each year (U.S. EPA, "*TSCA Chemical Substance Inventory*").

It is without question that within this growth of new chemicals contains substances that could cause toxic effects after acute inhalation exposure, and therefore call for chemical-specific AEGL value development. The discontinuation of the AEGL

Committee's involvement in the AEGL program may limit the validity of these newly derived AEGL values. Moreover, substantial uncertainty may be present in future AEGL values as a result of limited relevant empirical studies to identify chemical-specific concentration-exposure duration relationships. Therefore, default values adopted by U.S. EPA's AEGL program may be of significant importance in the future.

It has been nearly 30 years since ten Berge's 1986 publication in which the distribution of TLEs was first explored. The AEGL database contains large source of rich expert-validated chemical-specific information about temporal extrapolation. Surprisingly, no statistical assessments have been performed on AEGL Committee approved TLEs in the AEGL database. Additionally, open access journals and journal archives provide a wealth of information on empirical studies that can be compiled in a similar fashion to ten Berge's study to complement temporal extrapolation characteristics found in the AEGL database. These untouched resources could be used to build on ten Berge's contribution to inhalation risk assessment by providing additional information on concentration-exposure duration relationships that may reduce statistical uncertainty associated with default TLEs adopted by the AEGL Committee.

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Chapter 2

Manuscript (Peer Reviewed Style)

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ABSTRACT

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Statistical analysis of concentration-time extrapolation factors for acute inhalation exposures to hazardous substances

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ABSTRACT

Background: Acute Exposure Guideline Levels (AEGLs) are exposure limits for the general public that are designed for assessing the risk of rare exposures to hazardous airborne substances. For each chemical substance, AEGLs may be developed for up to five exposure durations (10 min, 30 min, 1 hr, 4 hr, and 8 hr). 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 empirical chemical-specific "toxic load exponent," t is exposure duration, and k is toxic load.

Rational: In absence of empirical data, the AEGL Committee selects a default toxic load exponent (TLE) of 1 for short-to-long term extrapolation and 3 for long-to-short extrapolation. These upper and lower boundaries for default TLEs are associated with the work of ten Berge *et al.* 1986, as approximately 90% of the values of n for chemicals (N = 20) analyzed in their study ranged from 1 to 3. Because of the small sample size these defaults have poor statistical power.

Methods: In the present work, we reevaluate the numbers using more representative statistics. A thorough review of data from ten Berge *et al.* 1986, AEGL technical support documents and literature identified 127 unique chemical substances with empirically supported TLEs.

Results: Non-parametric estimates revealed that 90% of the chemical substances (N = 127) had designated values of n that were confined between 0.77 (95%CI: 0.66 – 0.88) and 3.62 (95%CI: 3.03 – 4.32). Notably, our interval estimation failed to include the AEGL Committee's default n value of 1 for short-to-long term extrapolation and 3 for long-to-short term extrapolation at the 95% confidence level.

Conclusion: Thus, our estimation suggests 0.75 and 3.5 as appropriate defaults for concentration-exposure duration extrapolation. Therefore, AEGLs and other inhalation health guidance values that have been derived using defaults of 1 and 3 for concentration-exposure duration extrapolation may be insufficiently protective and may need reexamination.

1. INTRODUCTION

Risk assessment is an art of balancing extrapolation with uncertainties. The National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (AEGL Committee) routinely performs such tasks when developing exposure limits for the general public for once-in-a-lifetime or rare exposures to hazardous airborne substances. These Acute Exposure Guideline Levels, or "AEGLs," permit broad application because, for each inhalation compound, up to fifteen AEGL values may be developed that address three health-effects severity tiers (AEGL-1: discomfort/reversible, AEGL-2: disabling/irreversible, AEGL-3: life threatening) at five exposure durations (10 min, 30 min, 1 hr, 4 hr, and 8 hr) (NRC, 2001). The primary goal of the AEGL Committee is to develop the most scientifically credible protective short-term inhalation exposure levels possible; given the constraints on data, funding, and time (Rusch, 2002). Adding further challenges, to date, not a single chemical is associated with empirical data that describe concentration thresholds for all fifteen combinations of AEGL-specific tiers and exposure periods. Therefore, the AEGL Committee has to extrapolate AEGL values from limited empirical information expressing critical exposure durations and concentrations.

Extrapolation of a threshold concentration from one exposure duration to another can be attained using the concept popularized in the 1920's (Flury, 1921; Haber, 1924), by which the product of concentration (C) of inhaled noxious gas and exposure duration (t) produce a constant effect outcome (k). While historically Haber's rule has been documented as $C \times t = k$, it is only applicable when the response effect to the chemical is equally dependent on concentration and exposure duration. Deviations from Haber's rule have been noticed early, and a number of fixes has been considered (Haggard & Haggard, 1924; Flury & Zernik, 1931). A comprehensive and nowadays commonly accepted revision stems from experience with pest control fumigation (Busvine, 1938; Bliss, 1940), by which

Haber's hyperbolic relationship is replaced with exponential function. Several forms of the revised relationship are known (Miller, 2000; Belkebir, 2011) but the original Busvine's expression remains most popular. It is frequently referred as the toxic load model. By introducing the toxic load exponent (n or TLE), Busvine has argued that that the concentration and exposure duration can be reasonably approximated by an exponential function of concentration, $C^n \times t = k$. As such, the presence of the TLE in the relationship better represents the relative contribution of C and t (Miller, 2000). In the late 1980's ten Berge *et al*. (1986, 1989) and Zwart *et al*. (1988, 1990) applied the toxic load model to diverse classes of inhalation compounds with different modes of action and argued that it reasonably explains observed survival rates.

In their study, ten Berge and co-authors evaluated relationships between exposure concentrations and exposure durations for 20 structurally different chemicals by means of mortality data. For these 20 inhalation compounds, they derived meta-analysis averaged chemical-specific TLEs that ranged from 0.8 to 3.5 (ten Berge, 1986). As illustrated by ten Berge and co-authors, when $n = 1$, the toxicity of a substance is equally dependent on exposure concentration and exposure duration and follows Haber's rule; when $n < 1$, the toxicity is more dependent on the duration of exposure than on the concentration, and conversely when $n > 1$.

The TLE is considered to express a chemical- and toxic endpoint-specific relationship and therefore, derivation and utility of such a value is limited by the availability of appropriate experimental data (Salem & Katz, 2014). In absence of supporting data to derive chemical-specific n values, the AEGL Committee selects a default n of 1 for short-to-long term extrapolation (i.e. extrapolating an AEGL value at 30 minutes from a 20 minute study endpoint) and a default n of 3 for long-to-short

extrapolation (i.e. extrapolating an AEGL value at 60 minutes from a 120 minute study endpoint) (NRC, 2001). These upper and lower boundaries for default TLEs are associated with the work of ten Berge *et al*. (1986), "as these two values encompassed over 90% of the *n* values calculated by ten Berge *et al*., they represent conservative approaches" (Rusch, 2002).

The systematic investigation of concentration-exposure duration response relationships of hazardous airborne substances led by ten Berge provided a novel insight in chemical characteristics and over years has been proven of indispensable utility to public health practitioners. However, we argue that the statistical power of ten Berge's study is low and implementing AEGL default values based on the distribution of only 20 chemicals is risky. We aim to further investigate concentration-exposure duration relationships in hopes to reduce statistical uncertainty associated with default TLEs adopted by the AEGL Committee. The AEGL database represents a large source of rich expert-validated chemical-specific information. To date, the AEGL Committee has published AEGL values for 271 chemicals on the AEGL priority list. Surprisingly, no statistical assessments have been performed on AEGL-approved empirical values of *n*. In the present study, we assess the statistical strength of default TLEs adopted by the AEGL Committee by performing a comprehensive analysis of empirically derived information about temporal extrapolation in the AEGL database, ten Berge's study, and the literature.

2. METHODS

2.1 Sources of toxic load exponents

Empirically supported and chemical-specific TLEs were extracted from three distinct sources. As the motivation for this study, we started by compiling data from ten Berge *et al.* and technical support documents (TSDs) for guideline levels prepared by the AEGL Committee. In effort to explore other relevant data and inhalation chemicals not included in the two aforementioned sources, we performed a review of literature to identify empirical data used to derive additional TLEs. For all sources, we documented what species were used in the study and categorized the study endpoint using AEGL definitions of: (1) reversible discomfort (e.g. mild headache), (2) irreversible disabling effect (e.g. incapacitation), or (3) life-threatening effect (e.g. lethality).

ten Berge et al. – The prominently cited article "Concentration-time mortality response relationship of irritant and systemically acting vapours and gases" was published in the *Journal of Hazardous Materials* in 1986. This article contains re-evaluation of raw mortality data from 20 volatile industrial chemicals utilizing probit analysis (Finney, 1947). Toxic load exponents published by ten Berge and co-authors were extracted and recalculated (when possible) to minimize the influence of rounding errors for our analysis.

AEGL – The AEGL database contains 271 chemicals for which AEGLs have been derived at the "*Finalized*," "*Interim*," and "*Proposed*" development stages. Technical support documents for each chemical were retrieved for review from the U.S. EPA AEGL *Chemical Data Portal* (http://www.epa.gov/oppt/aegl/pubs/humanhealth.htm). Two-hundred of the 271 chemicals had AEGL concentrations that were derived from either human observations and/or animal studies. Technical support documents for these 200

chemicals contained information on a point of departure (POD), which is the selection of the highest exposure level at which the effects that characterize an AEGL threshold level are not observed. Points of departures were either a no observed adverse effect level (NOAEL) or benchmark concentration (BMC). The other 71 chemicals in the database contained PODs that were cross-extrapolated from another structurally similar chemical. The 71 chemicals that lack experimental PODs were excluded from further review as unsupported by chemical-specific data. Technical support documents of the remaining 200 chemicals were then thoroughly reviewed to identify empirically supported TLEs that have been adopted or derived by the AEGL Committee. When available, raw data referenced within the TSDs for chemicals with empirically supported TLEs were re-evaluated to identify unrounded statistics.

Literature review – Journal articles were retrieved without foreign language restrictions using keyword searches of "*acute inhalation toxicity*," "LC_{50}", and "*inhalation exposure limits*" in Google Scholar and PubMed search engines. For each chemical, an *n* value was derived if an inhalation study identified by this search included two or more exposure durations accompanying the same endpoint. Toxic load exponents were then derived from these two points using the AEGL approved approach described in the next section. Literature search was also used to identify TLEs derived by other authors not included in ten Berge *et al.* or the AEGL database. If several appropriate studies were available for the same chemical, TLEs were derived from each of them and included in the database as separate entries.

2.2 Derivation of endpoint-dependent chemical toxic load exponents

Probit analysis was not applied to derive novel TLEs because our literature search was limited to already pre-processed laboratory data. For literature review chemicals, TLEs were derived using a simple linear regression fit to endpoint concentrations and corresponding exposure durations on the logarithmic scale. Logarithmic transformation of concentration and exposure duration linearizes the non-linear Eq. (1) (NRC, 2001):

$$C^n \times t = k \qquad \text{Eq. (1)}$$

$$\log C = (-1/n) \log t + (\log(k))/n \qquad \text{Eq. (2)}$$

where C is a regressed concentration that causes a health effect in a specified percentage of the population (typically LC_{50} or EC_{50}) at exposure duration of t; k is a determinant of the adverse health effect. Chemical-specific TLEs were then determined by solving $-1/n$ for n.

2.3 Identification of a chemical's designated toxic load exponent

Toxic load exponents can be derived for a chemical substance from studies employing different animal models as well as different endpoints. This is exemplified in ten Berge's study, where five different values of n are derived for nitrogen dioxide from five different animal lethality models (mouse, rat, guinea pig, rabbit and dog). For this instance, ten Berge and co-authors combined data from all species to derive a single n associated to nitrogen dioxide. For this study, we relied on the AEGL Committee's discretion for designating an n value to a particular chemical (i.e. one per chemical), if available. Toxic load exponents adopted or derived by the AEGL Committee undergo expert-validated reviews, some of which reject or adopt statistics derived by ten Berge and co-authors.

Therefore, all chemicals with AEGL Committee recommended TLEs were assigned such values for our analysis. Moreover, if TLEs were identified for multiple endpoint classifications for a single chemical substance, the most severe (i.e. highest lethality) derived TLEs were always assigned. This procedure was used because lethality is a well-defined tangible endpoint, unlike more subjective endpoints in the discomfort or disabling categories. Therefore, lethality-derived TLEs combined from these sources may demonstrate the strongest experimental integrity in revealing the true TLE distribution. Toxic load exponents derived from disabling endpoints were used if values of *n* could not be derived from lethality studies but appropriate non-lethality data was available. Finally, in attempt to increase data homogeneity, TLEs derived from rat animal models were used if values of *n* from multiple species were identified.

2.4 Testing homogeneity of toxic load exponents

To justify merger of TLE samples originating from different information sources, the Kolmogorov-Smirnov (KS, as implemented in SAS, Cary, NC Version 9.4) and Anderson-Darling (AD, Engmann & Cousineau, 2011) two sample tests were used. The tests were first applied to the data derived from the AEGL database and ten Berge *et al*. 1986 paper in an effort to detect if the these two sets of data come from different general populations. The tests do not require conjectures about normality of the data (i.e. they are a non-parametric test appropriate for assumption-free examination of the given data). Toxic load exponents adopted or derived by the AEGL Committee and remaining statistics from ten Berge's study were then compared to TLEs derived from our literature review using aforementioned tests. Similarly, the tests were used to determine if data samples of TLEs derived from lethal and non-lethal endpoints were drawn from different populations.

2.5 Grouping of toxic load exponents

To evaluate the impact of data set consolidation on distribution features of TLEs, we grouped the data by several attributes. Lethality derived TLEs published in ten Berge *at el.* and those lethality derived by the AEGL Committee were evaluated separately. A third cluster included the combination of the aforementioned groups of TLEs, with the exception of ten Berge TLEs not adopted by the AEGL Committee. A fourth group included all identified chemical substances with empirically supported TLEs from lethality studies only. Finally, a fifth group included all identified chemicals substances with empirically supported TLEs.

2.6 Parametric estimation

Log-normal, Weibull and gamma distributions were fitted to the data. For each group, the log-transformed data were tested for normality using the Shapiro-Wilk (SW) test and the Anderson-Darling (AD) test was used to evaluate Weibull and gamma distributions. When appropriate, fitted distribution parameters were used to derive percentiles of interest and their respective 95% confidence intervals. All these calculations were carried out using SAS 9.4.

2.7 Non-parametric estimation

The sizes of data groups analyzed in the present study are relatively small and maybe insufficient for confident inference about the form and parameters of the underlying general population, because of the type II error. To increase confidence in percentile estimation, non-parametric estimates were also derived. Generally, non-parametric methods are less powerful (i.e. less accurate on small samples) than parametric ones,

however, they are free of (potentially false) inferences about general population. As such, they are more robust against gross errors in the analysis and may be used for quality control of parametric results. In addition to calculating observed percentiles, non-parametric estimation of percentiles of interest and 95% confidence intervals on them were carried out using a bootstrap distribution of 10,000 samples. Bootstrap smoothing was attained by adding random noise (or a small variance) of $1/\sqrt{N}$ to each bootstrap sample, with a sampling size of *N*. A SAS macro was used for bootstrap re-sampling (Cassell, 2010). Bootstrap smoothing was performed because of our interest in non-parametric estimates of statistics in the upper and lower tails of the distribution. While smoothing yields little advantage when examining quantiles near the center of the distribution, this method has been shown to increase estimate precision for extreme low and high quantiles (Sheather & Marron, 1990; Silverman & Young, 1987).

3. RESULTS

3.1 Summary of toxic load exponents

In their study, ten Berge and co-authors published TLEs for 20 extremely hazardous airborne substances (*Table 1*), all of which have been derived from lethality animal models. Review of the AEGL TSDs identified the direct adoption of ten Berge *et al.* numbers for eight of these 20 substances (acrylonitrile, ammonia, bromine, crotonaldehyde, hydrogen chloride, tetrachloroethylene, nitrogen dioxide, and methyl-tertiary-butylether). Two chemicals from ten Berge's study (methylene chlorobromide and dibutylhexamethylenediamine) are not in the AEGL chemical database. For the remaining substances, TLEs derived by ten Berge and co-authors have not been adopted by AEGL Committee when performing temporal extrapolation. Further review of the AEGL TSDs identified an additional 65 substances whose TLEs have been derived by the AEGL Committee using empirically supported data corresponding to "*lethal*," "*disabling*" or "*discomfort*" endpoints (*Table 2*). Fifty-nine substances had AEGL-3 values developed using TLEs derived from lethality endpoints and six other substances had exponents derived from disabling or discomfort endpoints, four of which (adamsite, aniline, chlorine and diborane), the AEGL Committee adopted for AEGL-3 concentration-exposure duration extrapolation. Together, ten Berge *et al.* and the AEGL database provided 69 expert-validated chemical-specific TLEs derived from lethality studies.

Supplementary to substances included in ten Berge *et al.* and the AEGL database, 52 additional substances (39 not included in the AEGL chemical database) were identified from our literature review to have empirically supported TLEs (*Table 3*). Forty-seven substances had novel TLEs derived for this study using regression of endpoint concentration-exposure duration relationships found in literature and the remaining five were previously reported by other authors. Forty-one substances had TLEs derived from

lethality endpoints and 11 from disabling endpoints. In combined effort, we identified a total of 127 unique chemical substances with empirically supported TLEs: 110 derived from lethality endpoints; 14 derived from non-lethal endpoint; and three derived from discomfort endpoints (*Table 4/Figure 1*).

3.2 Homogeneity of toxic load exponents

The KS and AD two-sample tests did not suggest that TLEs from ten Berge *et al.* (N = 20) and the AEGL database (N = 65) were drawn from different statistical populations (KS: *p*-value = 0.1077, AD: *p*-value > 0.05) (*Figure 2*). Therefore, the similarities in the cumulative distribution functions of TLEs statistically supported data set consolidation from these two sources. Furthermore, pairwise comparisons of TLE distributions from our literature review (N = 52) and those from ten Berge *et al*. (KS: *p*-value = 0.4686, AD: *p*-value > 0.05) as well as the AEGL database (KS: *p*-value = 0.4690, AD: *p*-value > 0.05) also indicated homogeneity of the TLEs data between the three sources.

In addition to variability in the sources used to identify empirically supported TLEs, our data collection also contained unequal groups of TLEs derived from lethal (N = 110) and non-lethal (N = 17) endpoints. Toxic load exponents derived from non-lethal endpoints included the six AEGL chemicals where the AEGL Committee identified stronger empirical support for temporal extrapolation when using non-lethality studies over lethality data. Similarly, our review also identified 11 chemicals where TLEs could not be derived from lethality studies but appropriate non-lethality data was available. Even with a small number of substances with non-lethality derived TLEs, the cumulative distribution was nearly identical to that of substances with TLEs derived from lethality endpoints (*Figure 2*). Similarly to aforementioned results on grouping TLEs by source, KS and AD two-

sample tests did not suggest that the data samples of TLEs derived from lethal and non-lethal endpoints were drawn from different general populations (KS: p-value = 0.6704, AD: p-value >0.05). Together these results, statistically supported consolidation of all TLEs collected throughout review.

3.3 Group comparison of toxic load exponents for unique chemical substances

Our group comparison of TLEs for unique chemicals substances varied by their attributes on study endpoints (lethal/non-lethal) and sources (ten Berge *et al.*/AEGL/literature review). Group 1 (N = 20) and Group 2 (N = 59) included an independent analysis on ten Berge and AEGL chemical substances with lethality derived TLEs; Group 3 (N = 69) included the combination of the two previous groups, with the exclusion of ten Berge TLEs not adopted by the AEGL Committee; Group 4 (N = 110) included lethality derived TLEs from all sources; and Group 5 (N = 127) included all TLEs identified in our collective review (*Table 5*). Of the five different clusters of TLEs, the 20 chemical substances studied by ten Berge (Group 1) had the narrowest range of 0.84 to 3.50 for derived TLEs (*Table 5*). Additionally, the distribution of ten Berge's TLEs was slightly right-shifted, as indicated by the larger median (1.96) and mean (1.85), compared all other groups analyzed (*Table 5/Figure 3*). In fact, ten Berge's group was the only one in which the median was found to be larger than the mean (suggesting the presence of systematic bias). Toxic load exponents for chemical substances studied by ten Berge were found to follow a log-normal distribution (SW: p-value = 0.1573), however Weibull and gamma distribution fittings could also not be rejected for this group (*Supplementary Data*). Conversely, chemical substances with lethality derived TLEs developed by the AEGL Committee (Group 2) were only found to follow a log-normal distribution (SW: p-value =

0.1218). As expected, the combined chemical substances whose lethality-specific TLEs were validated by ten Berge *et al*. and the AEGL Committee (Group 3) also followed only a log-normal distribution (SW: *p*-value = 0.0894); as 86% (59/69) of the data points were associated to Group 2. Log-normality was formally rejected for larger groups of data using all lethality derived TLEs from all sources (Group 4) (SW: *p*-value = 0.0088) as well as all TLEs identified in our review (Group 5) (SW: *p*-value = 0.0045). Still, histograms and kernel density estimates suggested that TLEs, in general, approximately follow the log-normal distribution (*Figure 4*). These results are not too surprising as it is well-known that real-world samples of increasing size rarely exactly follow an ideal theoretical distribution. Usually, a fine structure that may originate from superposition of several ideal distributions or some sort of small systematic skew or kurtosis disrupt the idealized construct.

3.4 Percentile estimation (Parametric)

With normality of log-transformed TLEs, distribution-fitted percentile estimates indicated a 90 percentile range of 0.83 (95% CI: 0.55 – 1.05) and 3.45 (95% CI: 2.72 – 5.16) for ten Berge chemicals (*Table 6*). The current AEGL default values for temporal extrapolation (1 for short-to-long and 3 for long-to-short) were included within these confidence intervals (*Figure 5*). However, poor confidence in upper and lower bounds for the 90 percentile range may further support the distribution uncertainty associated with the small sample size of ten Berge chemical substances. Confidence intervals were more than halved when performing parametric estimates to 5^{th} and 95^{th} percentile points on data samples that included TLEs from the AEGL database (*Table 6*). Distribution-fitted percentile estimates indicated a 90 percentile range of 0.76 (95% CI: 0.63 – 0.88) and 3.00 (95% CI: 2.60 – 3.64) for AEGL derived TLEs from lethality studies (Group 2) and fitted

percentile estimates for the combined data set (Group 3) indicated a 90 percentile range with even narrower 95% confidence intervals on the upper and lower bounds (Table 6). Importantly, both Groups 2 and 3 suggested log-normal distribution and did not support the AEGL Committee's default *n* value of 1 for short-to-long term extrapolation within estimates for the 5th percentile (*Figure 5*). Normality of log-transformed TLEs included in Groups 4 and 5 were rejected. Therefore, determining distribution-fitted estimates for these groups based on log-normal distributions was inappropriate.

3.5 Percentile estimation (Non-parametric)

Ambiguity in the underlying distribution of TLEs observed as the group size was increasing suggested that parametric estimation was not the best option for the given data and that non-parametric estimations may be more appropriate. 90% of ten Berge's TLEs fell within 0.92 and 3.49, while bootstrapping suggested that 90% of the values were confined between 0.80 (95% CI: 0.52 – 1.07) and 3.35 (95% CI: 2.53 – 3.83) (*Table 7*). Thus, bootstrap estimation confirmed the parametric results. Smoothed bootstrap distributions were found to considerably improve the discrete nature of distributions produced from our finite samples by a simple bootstrap method; therefore increasing information in the tails of the distribution (*Supplemental data*). Similar to our findings using parametric estimates of ten Berge's TLEs, the AEGL Committee's default values for temporal extrapolation were also included within the non-parametric confidence interval estimations (*Figure 6*). However, large uncertainty was present around the 5th percentile estimate. Comparable to ten Berge's substances, 90% of lethality derived TLEs developed by the AEGL Committee (Group 2) fell within 0.85 and 3.46, and our bootstrap distribution estimated that 90% of the values were confined between 0.79 (95% CI: 0.65 – 0.92) and

3.36 (95% CI: 2.54 – 4.78) (*Table 5*). Sizeable improvements were produced in the confidence around the 5th percentile estimate when evaluating TLEs derived by the AEGL Committee. Consequently, the narrowing of the confidence interval of Group 2 did not include the AEGL Committee's default *n* value of 1 for short-to-long term extrapolation (*Figure 6*). Although the width of the confidence interval around the 5th percentile estimate did not change when comparing Group 3 to Group 4, substantial improvement in confidence around the 95th percentile estimate were produced when chemical substances with lethality derived TLEs identified in our literature search were added. For Group 4, 90% of the TLEs fell within 0.81 and 3.52 with our bootstrap estimation of 0.76 (95% CI: 0.64 – 0.88) and 3.59 (95% CI: 2.93 – 4.27) (*Table 5*). While the 90 percentile range for TLEs is slightly larger compared to only those validated by ten Berge *et al*. and the AEGL Committee, the 95% confidence interval on the upper bound was reduced by 0.67. Finally, small improvements in confidence intervals around the 5th and 95th percentile estimates were once more achieved when all TSFs identified in our collective review (Group 5) were evaluated non-parametrically. The 90 percentile range of TLEs was identical to the lethality derived data set but yielded slightly smaller 95% confidence intervals on the upper bound, 0.77 (95% CI: 0.66 – 0.88), and lower bound, 3.59 (95% CI: 3.03 – 4.32), as determined by our bootstrap estimation (*Table 5*). Importantly, non-parametric estimation for the 90 percentile range of all TLEs identified in our study failed to include the AEGL Committee's default *n* value of 1 for short-to-long term extrapolation and 3 for long-to-short term extrapolation at a 95% confidence level (*Figure 6*).

4. DISCUSSION

The current *Standing Operating Procedures* for developing AEGL values for hazardous substances embrace the adoption of an *n* of 1 for short-to-long term extrapolation and 3 for long-to-short. Adopted defaults for temporal extrapolation are justified, "as these two values encompassed over 90% of the *n* values calculated by ten Berge *et al.*, they represent conservative approaches" (Rusch, 2002). However, our analysis indicates that the distribution of ten Berge's TLEs is actually slightly wider, as 90% of unrounded values calculated by ten Berge actually ranged from 0.92 to 3.49. Bootstrap resampling using ten Berge's TLEs also suggested that point estimates for the 90 percentile range are wider, although, current defaults were contained in the confidence intervals. Importantly, the power associated to these non-parametric estimates is rather low (i.e. supply poor confidence) as a result of the small sample size. Our collective review of 127 chemicals with designated TLEs identified within literature and the AEGL database not only provides new information on concentration-exposure duration relationships for specific chemicals but it also increases our understanding of the true distribution of these relationships as a whole.

Most notably, when evaluating our entire database of 127 chemicals with designated TLEs, the current defaults of 1 and 3 used for temporal extrapolation only encompass just under 75% of the distribution (16^{th} and 89^{th} percentiles, respectively). Suggesting that these adopted values may not be as conservative as initially assumed. Failing to provide sufficient protectiveness when developing such AEGL values may hinder AEGL application to sensitive subpopulations (including infants, children, the elderly, persons with asthma and those with other illnesses), whom the threshold levels are developed (NRC, 2001). Our analysis suggests 0.75 and 3.5 as more appropriate defaults for concentration-exposure duration extrapolation (*Figure 7*). Based on the analysis, these

values more accurately represent a conservative approach (if the 90% of the distribution is believed to represent a conservative one) and are associated with stronger statistical support (i.e. narrow confidence intervals).

Using both parametric and non-parametric approaches, no grouping in our analysis (with the exception of ten Berge's data) contained the value of 1 in the 95% confidence interval of the lower bound of the 90 percentile range for TLEs. Increasing the chemical list to 127 also produced considerable improvements in confidence surrounding the lower bound of the 90 percentile range. Our non-parametric estimates were able to produce an approximately normal distribution around the 5th percentile (*Figure 7*), and suggested that 5% of the chemicals had values of *n* below 0.88, with 95% confidence. Therefore, unlike Haber's rule ($n = 1$), adopted by the AEGL Committee for short-to-long term extrapolation, our data suggest that chemical toxicity may be even more dependent on duration of exposure than the airborne concentration for a larger group of chemicals than has been previously thought. Exposures to such chemicals are suggested to be associated with the activation of adaptation systems at high doses or with increased reversibility of effects as a result of a short chemical half-life (Belkebir, 2011). Therefore, understanding such chemical properties can be imperative when extrapolations are made for longer durations from shorter endpoint studies. Consequently, AEGLs and other inhalation health guidance values that have been derived using a default *n* of 1 for short-to-long term extrapolation may be insufficiently protective and may need reexamination. Nitrogen mustard-1 (HN1) exposure thresholds exemplify the need for such AEGL reexamination. In this case, short-to-long term extrapolation to four exposure durations from a 20 minute study endpoint applies. As can be seen by our sensitivity analysis for short-to-long term extrapolation procedures (*Table 8*), a seemingly small difference in the default *n* value can result in nearly

a 3-fold difference in concentration at the 8-hour exposure period, suggesting that current default values may be sufficiently underproductive when applied in such practices.

Although not as extreme, the current default exponent of 3 for long-to-short term extrapolation was not embraced in the confidence interval of the upper bound of the 90 percentile range for TLEs. Increasing the chemical list to 127 identified a trend of the distribution shifting away from containing the current default. Again, our non-parametric estimates were able to produce a nearly normal distribution around the 95th percentile (*Figure 7*), and suggested that 5% of the chemicals had values of *n* above 3.03, with 95% confidence. Therefore, our data suggests that chemical toxicity may be even more dependent on the concentration than the exposure duration for a larger group of chemicals than previously identified in ten Berge *et al*. This type of concentration-exposure duration relationship are said to be associated with chemicals who's adsorption is affected by saturation of the metabolism, the enzymatic systems involved in toxicity are modified or when the detoxification process is saturated (Belkebir, 2011). As expressed with the default for short-to-long term extrapolation, AEGLs and other inhalation health guidance values that have been derived using a default *n* of 3 for long-to-term term extrapolation may also be insufficiently protective and may need reexamination. In the case of nitrogen mustard-2 (HN2), long-to-short term extrapolation was applied to three exposure durations from a 120 minute study endpoint. Sensitivity analysis for long-to-short term extrapolation for nitrogen musterd-2 indicates that small differences in concentration thresholds are produced when TLEs are adjusted from 3 to 3.5 (*Table 8*).

Remarkably, we are able to show that the temporal extrapolation method associated with the largest sensitivity (short-to-long) is complemented with the point estimate (0.75) with smallest uncertainty (0.66 to 0.88). On the other hand, the difference in extrapolated

thresholds is not as profound for long-to-short term extrapolation, for which the point estimate (3.5) was associated with larger uncertainty (3.03 to 4.32). Additionally, non-parametric estimates for the 95 percentile range indicated that the point estimate for the lower bound (0.69) and upper bound (4.12) were both confined to our estimated confidence intervals for corresponding upper and lower bounds of the 90 percentile range (*Supplemental data*). Thus, suggesting that the confidence intervals associated with our point estimates contain values for more conservative approaches (i.e. 95% confidence) for the short-to-long and long-to-short term extrapolation.

Though not included in our analysis, we often identified TLEs derived for a single chemical substance from studies employing different animal models as well as different endpoints. This is demonstrated by AEGL extrapolation for AEGL-2 and AEGL-3 values of allyl ammine, where the *n* used to derive AEGL-2 values was derived from cardiotoxicity studies in rats (Guzman, 1961) and the *n* used to derive AEGL-3 values was derived from lethality studies in rats (Hine, 1960). While we explained our rational for designating a single TLE to chemical substances in section *Methods 2.3*, statistical analysis of distributions for multiple TLEs per chemical may also be explored. Applying an identical non-parametric procedure to all TLEs identified in our search (i.e. more than one TLE per chemical) (N = 216), we saw that 90% of the values were confined between 0.73 (0.63 – 0.84) and 3.77 (3.37 – 4.30) (*data not shown*). Notably, this strengthens our support for suggesting new default values for temporal extrapolation because the point estimates (and their associated smaller confidence intervals) identified using all TLEs were also approximately centered around 0.75 and 3.5 and, most importantly, both estimates exclude 1 and 3 in their respective 95% confidence intervals. As not the purpose of the study, we did not further explore relationships between species-specific and endpoint-specific

derived TLEs identified in our search. However, this database contains valued information, and warrants further exploration, on whether meta-analysis of animal data from multiple animal models can be averaged when deriving chemical-specific TLEs (i.e. ten Berge *et al*.) or if endpoint specific trends in TLEs can be identified.

We recognize that the 47 novel TLEs derived for this study may be limited in validity as they were not subjected to interagency panel review like those derived by the AEGL Committee. Additionally, many of these novel TLEs were derived using values that only express concentration-exposure duration relationships at two unique time points. Therefore, judgments regarding the goodness of fit of the regressed line could not be made. With that said, this is not an uncommon practice among the AEGL Committee. For example, among others, an $n = 1.7$ that was used for temporal extrapolation for acetone was derived from 4- and 8-hour LC_{50} values for rats obtained by Pozzani *et al.* (1959). Furthermore, our derivation of novel TLEs was subjected to additional criteria not expressed by the AEGL Committee. All novel TLEs derived for this study contained experimental data on concentration-exposure duration relationships acquired by a single author. Although additional TLEs could have been derived using empirical information from multiple authors, they were excluded from our search due to uncertainty in experimental replication between authors. Again, this approach was conservative compared to TLEs derived by the AEGL Committee, where, for example, an $n = 2.0$ used for temporal extrapolation for the chemical substance dimethylsulfate was derived using LC_{50} values derived in rats from two exposure durations from two different authors; 1-hour (Hein, 1969) and 4-hour exposure (Kennedy & Graepel, 1991).

Regardless of the addition of novel TLEs derived for this study, the distribution of panel reviewed values derived by the AEGL Committee (Group 2) still suggest that 0.75

and 3.5 are most appropriate default values for short-to-long and long-to-short term extrapolation, respectively. Furthermore, all clusters of TLEs beyond just ten Berge's data (Groups 2-5) had point estimates that were centered around or included 0.75 and 3.5 in the confidence intervals for parametric and non-parametric estimates of the 90 percentile range. The same cannot be said for the current default exponents of 1 and 3.

5. CONCLUSION

In conclusion, our study was the first to review concentration-exposure duration relationships for acute exposure to hazardous substances on such a scale. Furthermore, this was the first study to compile valuable temporal extrapolation relationships identified by the AEGL Committee. Using such approaches, we were able to increase the chemical diversity and provide a more representative distribution of TLEs than previously described in ten Berge *et al*. Consequently, our estimation suggests 0.75 and 3.5 as more appropriate defaults for concentration-exposure duration extrapolation, if a conservative approach is desired. Therefore, AEGLs and other inhalation health guidance values that have been derived using defaults of 1 and 3 for extrapolation may be insufficiently protective and may need reexamination.

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TABLES

Table 1. Toxic load exponents derived by ten Berge *et al.*

#	Chemical (CAS)	*n*	Species	References
1	Acrylonitrile (107-13-1)	1.10	Rat	Dudley & Neal (1942), Appel (1981) [1]
2	Ammonia (7664-41-7)	2.00	Rat, Mouse	Appelman (1982), Kapeghian (1982), Silver & McGrath (1948) [1]
3	Bromine (7726-95-6)	2.17	Mouse	Bitron and Aharonson (1978) [1]
4	Carbon tetrachloride (56-23-5)	2.84	Rat	Adams (1952)
5	Chlorine (7782-50-5)	3.47	Mouse	Bitron & Aharonson (1978)
6	Chlorine pentafluoride (13637-63-3)	2.00	Monkey, Dog, Rat, Mouse	Darmer (1972)
7	Crotonaldehyde (15798-64-8)	1.16	Rat	Rinehart (1967) [1]
8	Dibutylhexamethylenediamine (4835-11-4) *	1.03	Rat	Kennedy & Chen (1984)
9	Ethylene dibromide (106-93-4)	1.16	Rat	Rowe (1952a)
10	Ethyleneimine (151-56-4)	1.10	Guinea Pig, Rat	Carpenter (1948)
11	Hydrogen chloride (7647-01-0)	1.00	Rat, Mouse	Darmer (1974) [1]
12	Hydrogen cyanide (74-90-8)	2.70	Monkey, Goat, Dog, Cat, Rabbit, Rat	Barcroft (1931)
13	Hydrogen fluoride (7664-39-3)	1.94	Guinea Pig, Rabbit	Machle (1934)
14	Hydrogen sulfide (7783-06-4)	2.17	Cat, Rabbit	Lehmann (1892)
15	Methylene chlorobromide (74-97-5) *	1.60	Rats	Torkelson (1960)
16	Methyl-tertiary-butylether (1634-04-4)	1.97	Mouse	Snam Progetti (1980) [1]
17	Nitrogen dioxide (10102-44-0)	3.50	Dog, Guinea Pig, Rabbit, Rat, Mouse	Hine (1970) [1]
18	Perfluoroisobutylene (382-21-8)	1.22	Rat	Smith (1982)
19	Tetrachloroethylene (127-18-4)	2.02	Rat	Rowe (1952b) [1]
20	Trichloroethylene (79-01-6)	0.84	Rat	Adams (1951)

* Chemical is not included in the AEGL chemical database
[1] *n* value adopted by AEGL Committee

Table 2. Toxic load exponents derived by the AEGL Committee

#	Chemical (CAS)	Endpoint	*n*	Species	References
1	1,1-Dimethylhydrazine (57-14-7)	Lethal	0.89	Rat	Weeks (1963)
2	Acetone (67-64-1)	Lethal	1.66	Rat	Pozzani (1959)
3	Acetonitrile (75-05-8)	Lethal	1.55	Rat	Pozzani (1959), Haguenoer (1975), UCC (1965), Monsanto (1986), Du Pont (1968)
4	Acrolein (107-02-8)	Lethal	1.21	Rat	Ballantyne (1989)
5	Acrylic acid (79-10-7)	Lethal	1.83	Rat	Hagan & Emmons (1988)
6	Adamsite (578-94-9)	Discomfort	0.71	Human	Lawson & Temple (1922), Craighill & Folkoff (1922) [1]
7	Allyl alcohol (107-18-6)	Lethal	0.95	Rat	Kirkpatrick (2008), Union Carbide and Carbon Corporation (1951), Smyth & Carpenter (1948), McCord (1932)
8	Allylamine (107-11-9)	Lethal	0.85	Rat	Hine (1960)
9	Aniline (62-53-3)	Disabling	1.00	Rat	Kim & Calrson (1986) [1]
10	Bromoacetone (598-31-2)	Lethal	1.26	Rat	Dow Chemical Company (1968)
11	Carbon monoxide (630-08-0)	Lethal	1.50	Human [a]	NRC (2010)
12	Carbon tetrachloride (56-23-5)	Lethal	2.53	Rat	Adams (1952), Dow Chemical Company (1960), Mellon Institute (1947)
13	Chlorine (7782-50-5)	Discomfort	1.90	Human	ten Berge & Vis van Heemst (1983) [1]
14	Chlorine pentafluoride (13637-63-3)	Lethal	1.86	Rat	Darmer (1972)
15	Chlorine trifluoride (7790-91-2)	Lethal	1.30	Monkey, Rat, Mouse	Horn & Weir (1955), MacEwen & Vernot (1970), Dost (1974)
16	Chloroacetaldehyde (107-20-0)	Lethal	1.21	Rat	Dow Chemical Company (1952)
17	Chloropicrin (76-06-2)	Lethal	2.31	Rat	Yoshida (1987)
18	Diborane (19287-45-7)	Disabling	1.09	Mouse	Nomiyama (1995), Uemura (1995) [1]
19	Dimethyl sulfate (77-78-1)	Lethal	2.00	Rat	Hein (1969), Kennedy & Graepel (1991)
20	Dimethylamine (124-40-3)	Lethal	2.81	Rat	Mezentseva (1956), Koch (1980)
21	Epichlorohydrin (106-89-8)	Lethal	0.87	Rat	Berdasco & Waechter (2012), Laskin (1980), Kobernick (1983), Grigorowa (1974), Kimmerle (1967)
22	Ethyl acrylate (140-88-5)	Lethal	1.27	Rat	Nachreiner & Dodd (1989), UCC (1989), Oberly & Tansy (1985)
23	Ethylbenzene (100-41-4)	Lethal	2.31	Human [b]	NRC (2009a)
24	Ethylene dibromide (106-93-4)	Lethal	1.41	Rat	Rowe (1952a)
25	Ethylene oxide (75-21-8)	Lethal	1.21	Rat	Nachreiner (1991), Nachreiner (1992), Jacobson (1956)

Table 2. Continued

#	Chemical (CAS)	Endpoint	*n*	Species	References
26	Ethyleneimine (151-56-4)	Lethal	1.13	Rat	Carpenter (1948) [1]
27	Fenamiphos (22224-92-6)	Lethal	4.78	Rat	Kimmerle (1972), Thyssen (1979)
28	Fluorine (7782-41-4)	Lethal	1.77	Mouse	Keplinger & Suissa (1968)
29	Hexafluoroacetone (684-16-2)	Lethal	0.93	Rat	Du Pont (1962), Du Pont (1965)
30	Hexafluoropropene (116-15-4)	Lethal	1.33	Rat	Du Pont (1960), Paulet & Debrousses (1965)
31	Hydrogen cyanide (74-90-8)	Lethal	2.59	Rat	Du Pont (1981)
32	Hydrogen fluoride (7664-39-3)	Lethal	1.90	Rat	Rosenholtz (1963)
33	Hydrogen sulfide (7783-06-4)	Lethal	4.35	Rat	Zwart (1990), MacEwen & Vernot (1972), Prior (1988), Tansy (1981)
34	Lewsite 1 (541-25-3)	Lethal	1.02	Dog	Armstrong (1923)
35	Methanol (67-56-1)	Lethal	1.21	Human [b]	NRC (2005)
36	Methyl bromide (74-83-9)	Lethal	1.23	Rat	Bakhishev (1973), Honma (1985), Kato (1986), Zwart (1988b)
37	Methyl iodide (74-88-4)	Lethal	1.81	Rat	Eastman Kodak Co. (1987), Reed (1995) U.S. EPA (2006)
38	Methyl isocyanate (624-83-9)	Lethal	1.01	Rat	Mellon Institute (1970)
39	Methylamine (74-89-5)	Lethal	1.85	Rat	IRDC (1992a)
40	Methylchloroform (71-55-6)	Lethal	3.01	Rat	Clark and Tinston (1982), Adams (1950), Calhoun (1988), Bonnet (1980)
41	Methyldichloroarsine (593-89-5)	Lethal	0.82	Dog	Allen (1922)
42	Methylene chloride (75-09-2)	Lethal	2.48	Human [b]	NRC (2012)
43	Methylhydrazine (60-34-4)	Lethal	0.97	Monkey	Haun (1970)
44	Nitrogen trifluoride (7783-54-2)	Lethal	1.02	Dog	Vernot (1973)
45	Oxamyl (23135-22-0)	Lethal	1.59	Rat	Du Pont (1969a), Du Pont (1969b), Kelly (2001)
46	Oxygen difluoride (7783-41-7)	Lethal	1.11	Rat	Lester & Adams (1965), Davis (1970)
47	Pentaborane (19624-22-7)	Lethal	1.30	Rat	Weir (1961), Weir (1964)
48	Peracetic acid (79-21-0)	Lethal	1.64	Rat	Janssen (1989), Janssen & Van Doorn (1994)
49	Perfluoroisobutylene (382-21-8)	Lethal	1.04	Rat	Smith (1982), Karpov (1977), Paulet & Bernard (1968)
50	Phosgene (75-44-5)	Lethal	1.00	Rat	Rinehart (1962), Rinehart & Hatch (1964)
51	Piperidine (110-89-4)	Lethal	1.51	Guinea Pig, Rat, Mouse	AIHA (2001), BG Chemie (2000), BASF (1980)
52	Propylene glycol dinitrate (6423-43-4)	Disabling	1.24	Human	Stewart (1974)
53	Propylene oxide (75-56-9)	Lethal	1.68	Rat	Rowe (1956)

Table 2. Continued

#	Chemical (CAS)	Endpoint	*n*	Species	References
54	Sarin (107-44-8)	Lethal	1.88	Rat	Mioduszewski (2000)
55	Styrene (100-42-5)	Lethal	1.24	Rat	BASF (1979), Bonnet (1982)
56	Sulfuric acid (7664-93-9)	Lethal	3.46	Mouse	Runkle & Hahn (1976)
57	Sulfur mustard (505-60-2)	Discomfort	1.11	Human	Reed (1918), Guild (1941), Anderson (1942)
58	Tear gas (532-27-4)	Lethal	0.70	Rat	McNamara (1969), Ballantyne & Callaway (1972), Ballantyne & Swanston (1978)
59	Titanium tetrachloride (7550-45-0)	Lethal	0.88	Rat	Kelly (1980)
60	Toluene (108-88-3)	Lethal	1.96	Human [b]	NRC (2014)
61	Trichloroethylene (79-01-6)	Lethal	1.51	Rat	Adams (1951)
62	Trifluorochloroethylene (79-38-9)	Lethal	1.37	Mouse	Walther & Fischer (1968)
63	Trimethoxy silane (2487-90-3)	Lethal	1.45	Rat	Nachreiner & Dodd (1988)
64	Trimethylamine (75-50-3)	Lethal	2.47	Rat	IRDC (1992), Koch (1980)
65	Xylenes (1330-20-7)	Lethal	1.98	Human [b]	NRC (2010)

[a] Corburn, Forster and Kane (CFK) model, [b] Physiologically based pharmacokinetic (PBPK) model
[1] *n* value adopted for AEGL-3 extrapolation

Table 3. Toxic load exponents from literature review

#	Chemical (CAS)	Endpoint	*n*	Species	References
1	1,1,2-Trichloroethane (79-00-5) *	Disabling	1.73	Mouse	Lazarev & Brusilovskaya (1934)
2	1,1,3-Trichlorotrifluoroacetone (79-52-7) *	Lethal	2.96	Rat	Borzelleca (1964)
3	1,1-Dichloro-1-nitroethane (594-72-9) *	Lethal	3.22	Rabbit	Machle (1945)
4	1,1-Dichloroethane (75-34-3) *	Disabling	3.28	Mouse	Lazarev & Brusilovskaya (1934)
5	1,3-Dichlorotetrafluoroacetone (127-21-9) *	Lethal	1.15	Rat	Borzelleca (1964)
6	1-Nitropropane (108–03–2) *	Lethal	1.59	Guinea pig	Machle (1940)
7	2,3-Dichlorohexafluorobutene-2 (303-04-8) *	Lethal	1.29	Rat	Raventos (1965)
8	2-Nitropropane (79-46-9) *	Lethal	1.35	Cat	Treon & Dutra (1952)
9	2-Pentanone (107-87-9) *	Lethal	1.33	Guinea pig	Yant (1936)
10	Allyl chloride (107-05-1)	Lethal	0.59	Rat	Adams (1940) [1]
11	Arsine (7784-42-1)	Lethal	1.18	Rat	IRDC (1985) [1]
12	Aviation Gasoline (308082-09-9) *	Disabling	4.82	Mouse	Lazarev & Brusilovskaya (1934)
13	Azinphos-methyl (86-50-0) *	Lethal	1.48	Rat	Bayer (1988)
14	Benzene (71-43-2)	Disabling	1.89	Mouse	Lazarev & Brusilovskaya (1934)
15	Carbon disulfide (75-15-0)	Lethal	1.42	Mouse	Lazarev & Brusilovskaya (1934)
16	Chloroform (67-66-3)	Disabling	2.04	Mouse	Lazarev & Brusilovskaya (1934)
17	Chloropentafluoroacetone (79-53-8) *	Lethal	1.12	Rat	Borzelleca (1964)
18	Cyanuric acid (108-80-5) *	Lethal	1.77	Rat	Ballantyne (1994), Blagden (1994), Higgins (1972) [2]
19	Cyclohexadiene (29797-09-9) *	Disabling	2.27	Mouse	Lazarev & Brusilovskaya (1934)
20	Cyclohexane (110-82-7) *	Disabling	2.45	Mouse	Lazarev & Brusilovskaya (1934)
21	Cyclosarin (329-99-7)	Lethal	1.26	Mini Pig	Hulet (2014)
22	Demeton (8065-48-3) *	Lethal	1.05	Rat	Kimmerle (1968)
23	Dicrotophos (141-66-2)	Lethal	0.72	Rat	NIOSH (1998)
24	Diglycidyl ether (2238-07-5) *	Lethal	0.64	Rat	Hine (1961)
25	Disulfoton (298-04-4) *	Lethal	0.88	Rat	U.S. EPA (1998)
26	Ethanol (64-17-5) *	Disabling	1.41	Mouse	Lazarev & Brusilovskaya (1934)
27	Ethyl silicate (78-10-4) *	Lethal	3.65	Guinea pig	Smyth & Seaton (1940)
28	Fensulfothion (115-90-2) *	Lethal	1.05	Rat	Kimmerle (1968)
29	Fenthion (55-38-9) *	Lethal	1.08	Rat	Bayer (1987a), Bayer (1987b)
30	Fonofos (944-22-9) *	Lethal	2.07	Rat	Weir (1982)
31	Furfural (98-01-1) *	Lethal	1.01	Rat	Terrill (1989)

Table 3. Continued

#	Chemical (CAS)	Endpoint	*n*	Species	References
32	Halothane (151-67-7) *	Lethal	3.43	Mouse	Moser (1985)
33	Heptane (142-82-5) *	Disabling	2.93	Mouse	Lazarev & Brusilovskaya (1934)
34	Hexachloroacetone (116-16-5) *	Lethal	1.14	Rat	Borzelleca (1964)
35	Hexamethylene diisocyanate (822-06-0) *	Lethal	2.32	Rat	Kimmerle (1971)
36	Hydrazine (302-01-2)	Lethal	4.26	Rat	Comstock (1954)
37	Ketene (463-51-4)	Lethal	1.41	Mouse	Treon (1949)
38	m-Xylene (108-38-3) *	Disabling	1.02	Mouse	Lazarev & Brusilovskaya (1934)
39	Nitrogen fluoride oxide (13847-65-9) *	Lethal	0.96	Rat	Lee (1968)
40	Nitromethane (75-52-5) *	Lethal	1.00	Rabbit	Weatherby (1955)
41	Parathion (56-38-2)	Lethal	1.08	Rat	Kimmerle (1968)
42	Parathion-methyl (298-00-0)	Lethal	2.71	Rat	Kimmerle (1968)
43	p-tert-Butyltoluene (98-51-1)	Lethal	1.10	Rat	Hine (1954)
44	p-Xylene (106-42-3) *	Disabling	1.15	Mouse	Lazarev & Brusilovskaya (1934)
45	sec-Butyl alcohol (78-92-2) *	Lethal	0.84	Mouse	Weese (1928)
46	Sulfotep (3689-24-5) *	Lethal	0.81	Rat	Kimmerle (1974)
47	Sulfur dioxide (7446-09-5)	Lethal	3.90	Mouse	Bitron & Aharonson (1978) [2]
48	Tetraethyl pyrophosphate (107-49-3) *	Lethal	1.13	Rat	Kimmerle (1968)
49	Tetrafluorohydrazine (10036-47-2) *	Lethal	0.63	Rat	Carson (1963)
50	Trimethylopropane phosphate (1005-93-2) *	Lethal	0.95	Rat	Kimmerle (1976)
51	Turpentine oil (8006-64-2) *	Lethal	3.52	Rat	Sperling (1967)
52	Vinyl chloride (75-01-4)	Lethal	2.38	Mouse	Mastromatteo (1960), Prodan (1975) [2]

* Chemical is not included in the AEGL chemical database
[1] Derived by Salmon *et al.* (2008), [2] Derived by Péry *et al.* (2009)

Table 4. Summary of toxic load exponents for each source and endpoint characteristics

Endpoint	*ten Berge*	AEGL	Literature Review	Total
Lethality	10	59	41	110
Disabling	0	3	11	14
Discomfort	0	3	0	3
Total	10	65	52	127

Table 5. Toxic load exponent group characteristics and descriptive statistics

Characteristic	Group 1	Group 2	Group 3	Group 4	Group 5
Data Source:					
ten Berge	+	-	+	+	+
AEGL	-	+	+	+	+
Literature Review	-	-	-	+	+
Endpoint:					
Lethal	+	+	+	+	+
Non-lethal	-	-	-	-	+
Descriptive Statistics:					
N	20	59	69	110	127
Mean (95%CI)	1.85 (1.47–2.23)	1.66 (1.45–1.87)	1.67 (1.48–1.86)	1.66 (1.50–1.83)	1.69 (1.53–1.85)
Median	1.96	1.45	1.50	1.34	1.37
Std. dev.	0.80	0.81	0.80	0.88	0.90
Range	0.84–3.50	0.70–4.78	0.70–4.78	0.59–4.78	0.59–4.82
Shapiro-Wilk (*p*-value)	*0.1573	*0.1218	*0.0894	0.0088	0.0045

* Normal distribution using Shapiro-Wilk test on log-transformed data ($\alpha = 0.05$)

Table 6. Parametric percentile estimates using log-normal distributions

Percentile Estimates	Group 1	Group 2	Group 3	Group 4	Group 5
5th (95% CI)	0.83 (0.55–1.05)	0.76 (0.63–0.88)	0.77 (0.65–0.88)	** Normal*	** Normal*
Δ 95% CI	0.50	0.25	0.23	*distribution*	*distribution*
95th (95% CI)	3.45 (2.72–5.16)	3.00 (2.60–3.64)	3.02 (2.64–3.59)	*assumption*	*assumption*
Δ 95% CI	2.44	1.04	0.95	*not met*	*not met*

* Shapiro-Wilk test on log-transformed data (p-value < 0.05)

Table 7. Non-parametric percentile estimates using smoothed bootstrap distributions (*N=10,000*)

Percentile Estimates	Group 1	Group 2	Group 3	Group 4	Group 5
Observed Percentiles:					
90th range	0.92–3.49	0.85–3.46	0.87–3.46	0.81–3.52	0.81–3.52
90% Smoothed Bootstrap					
5th (95% CI)	0.80 (0.52–1.07)	0.79 (0.65–0.92)	0.83 (0.71–0.95)	0.76 (0.64–0.88)	0.77 (0.66–0.88)
Δ 95% CI	0.55	0.27	0.24	0.24	0.22
95th (95% CI)	3.35 (2.53–3.83)	3.53 (2.54–4.74)	3.32 (2.50–4.51)	3.59 (2.93–4.27)	3.62 (3.03–4.32)
Δ 95% CI	1.30	2.20	2.01	1.34	1.29

Table 8. Toxic load exponent default sensitivity analysis for short-to-long term extrapolation (HN1) and long-to-short term extrapolation (HN2)

Interim AEGL-3 (mg/m^3): Nitrogen Mustard-1 HN1 (CAS: 538-07-8)

Default *n*	Exposure Duration			
	30 min	60 min	4 hr	8 hr
1.00	0.96	0.48	0.12	0.06
0.75	0.84	0.33	0.05	0.02
x-fold	**1.14**	**1.44**	**2.29**	**2.88**

Interim AEGL-3 (mg/m^3): Nitrogen Mustard-2 HN2 (CAS: 51-75-2)

Default *n*	Exposure Duration		
	10 min	30 min	60 hr
3.0	1.27	0.88	0.70
3.5	1.13	0.83	0.68
x-fold	**1.13**	**1.07**	**1.03**

Supplemental Table 1. Distribution fitting test for each group

Distribution	Group 1	Group 2	Group 3	Group 4	Group 5
Log-normal (Pr > A-Sq)	*0.106	*0.239	*0.165	<0.005	<0.005
Weibull (Pr > A-Sq)	*0.089	<0.010	<0.010	<0.010	<0.010
Gamma (Pr > A-Sq)	*0.099	0.016	0.010	<0.001	<0.001

* Normal distribution using Anderson-Darling statistic ($\alpha = 0.05$)

Supplemental Table 2. Comparison of non-parametric percentile estimates

Percentile Estimates	Group 1	Group 2	Group 3	Group 4	Group 5
Observed Percentiles:					
90th range	0.92-3.49	0.85-3.46	0.87-3.46	0.81-3.52	0.81-3.52
95th range	0.84-3.50	0.82-4.35	0.82-4.35	0.82-4.35	0.70-4.26
90% Simple Bootstrap					
5th (95% CI)	0.95 (0.84-1.10)	0.85 (0.70-0.93)	0.87 (0.82-0.97)	0.78 (0.64-0.88)	0.78 (0.64-0.88)
Δ 95% CI	0.26	0.23	0.15	0.24	0.24
95th (95% CI)	3.28 (2.44-3.50)	3.51 (2.53-4.78)	3.32 (2.48-4.35)	3.59 (2.96-4.26)	3.61 (3.01-4.35)
Δ 95% CI	1.06	2.25	1.87	1.30	1.34
90% Smoothed Bootstrap					
5th (95% CI)	0.80 (0.52-1.07)	0.79 (0.65-0.92)	0.83 (0.71-0.95)	0.76 (0.64-0.88)	0.77 (0.66-0.88)
Δ 95% CI	0.55	0.27	0.24	0.24	0.22
95th (95% CI)	3.35 (2.53-3.83)	3.53 (2.54-4.74)	3.32 (2.50-4.51)	3.59 (2.93-4.27)	3.62 (3.03-4.32)
Δ 95% CI	1.30	2.20	2.01	1.34	1.29
95% Smoothed Bootstrap					
2.5th (95% CI)	0.72 (0.38-1.03)	0.73 (0.57-0.88)	0.74 (0.59-0.87)	0.66 (0.53-0.80)	0.69 (0.58-0.81)
Δ 95% CI	0.65	0.31	0.28	0.27	0.23
97.5th (95% CI)	3.52 (2.63-3.99)	4.00 (2.68-4.87)	4.08 (2.81-4.86)	4.10 (3.47-4.75)	4.12 (3.44-4.79)
Δ 95% CI	1.36	2.19	2.05	1.28	1.35

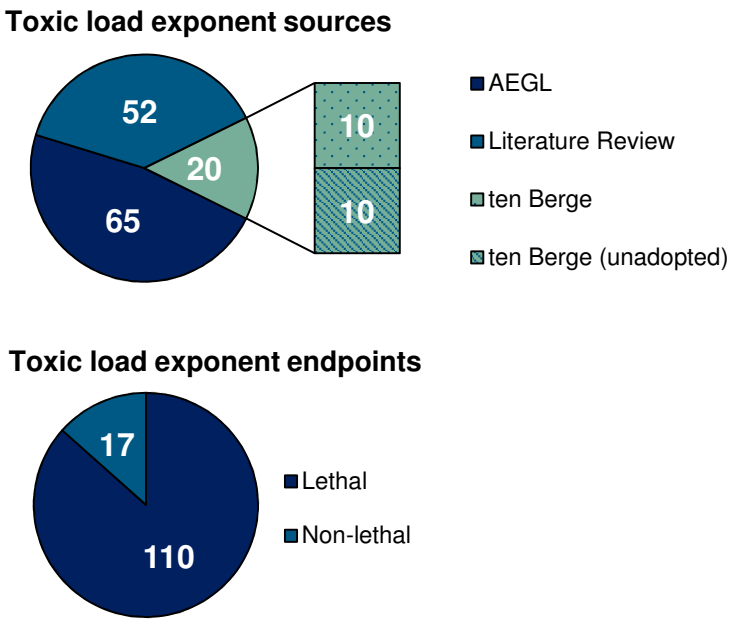


Figure 1. **Toxic load exponents by source and endpoint classification.** We identified a total of 127 unique chemical substances with empirically supported TLEs: 110 derived from lethality endpoints; 17 derived from non-lethal endpoints. Toxic load exponents for ten chemical substances from ten Berge *et al.* have not been adopted by the AEGL Committee. Instead, extrapolation has been carried out using TLEs derived by the Committee.

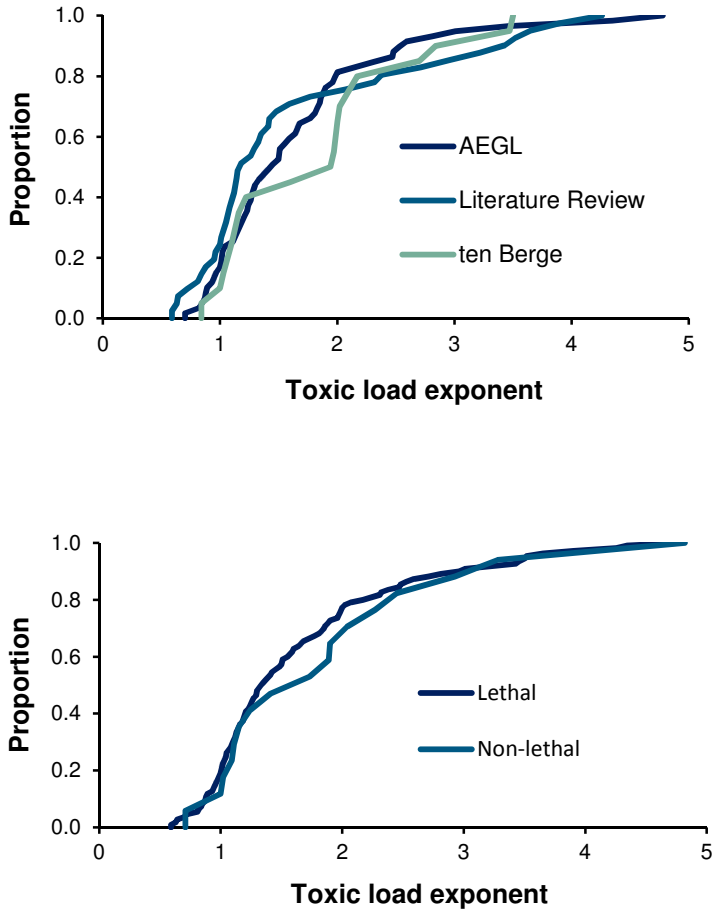


Figure 2. **Distribution homogeneity comparisons for toxic load exponents by source (*top*) and endpoint classification (*bottom*).** Pairwise Kolmogorov-Smirnov (KS) and Anderson-Darling (AD) two sample tests did not suggest that our data samples from: ten Berge (N = 20) and the AEGL Committee (N = 65) (KS: p-value = 0.1077, AD: p-value > 0.05); ten Berge (N = 20) and our literature review (N = 52) (KS: p-value = 0.4686, AD: p-value > 0.05); or the AEGL Committee (N = 65) and our literature review (N = 52) (KS: p-value = 0.4690, AD: p-value > 0.05) were drawn from different general populations. Likewise, Kolmogorov-Smirnov two sample test did not suggest that the data samples of TLEs derived from lethal (N = 110) and non-lethal (N = 17) endpoints were sampled from different populations (KS: p-value = 0.6704, AD: p-value > 0.05); thus, statistically supporting data set consolidation.

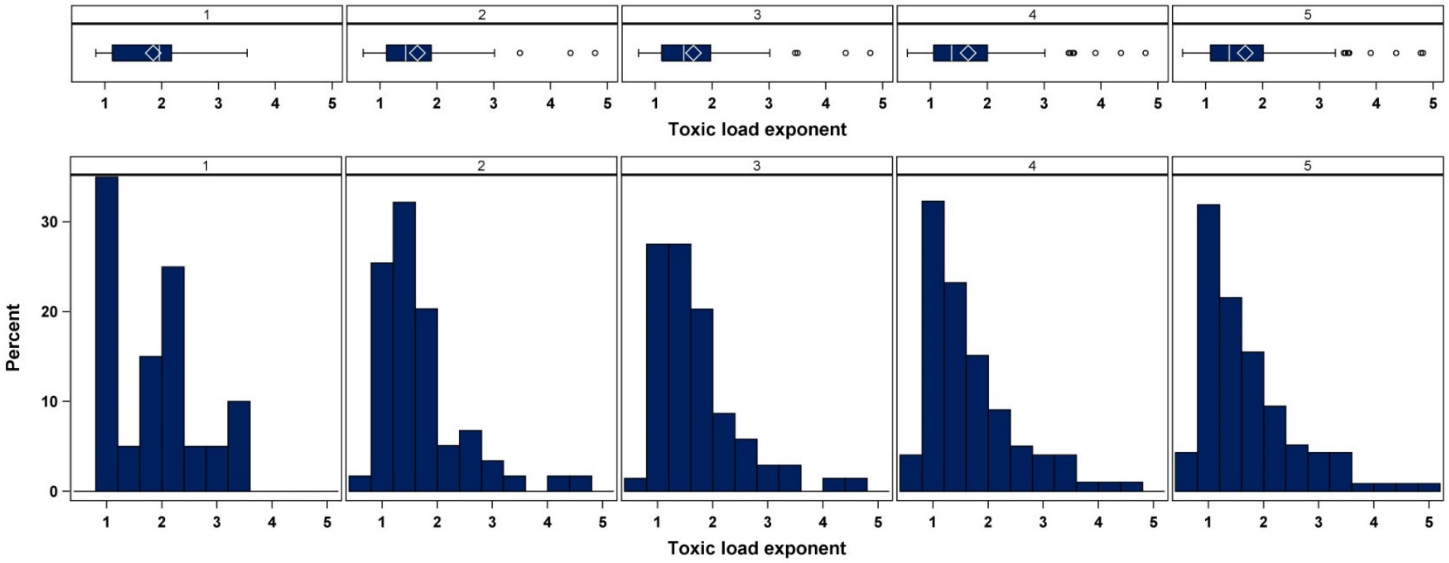


Figure 3. **Box plot and histogram of toxic load exponent distributions for each group.** Distribution of TLEs for Groups 2-5 (N = 65, 75, 110 and 127, respectively) indicate strong positive skew with peaks in the distributions centered around 1-2. The small sample size (N = 20) of ten Berge's TLEs (Group 1) limits its interpretation of the underlying distribution.

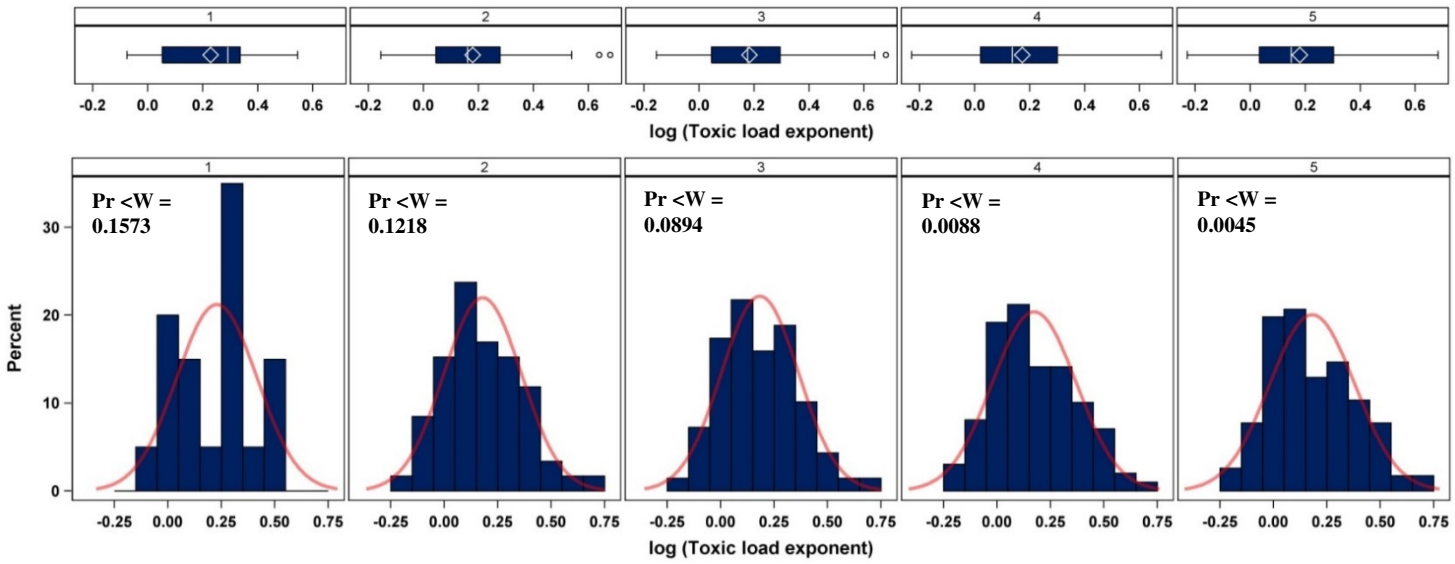


Figure 4. **Box plot and histogram of log-transformed toxic load exponent distributions for each group.** Shaprio-Wilk (SW) normality tests on log-transformed TLEs for Group 1 (SW: *p*-value = 0.1573), Group 2 (SW: *p*-value = 0.1218) and Group 3 (SW: *p*-value = 0.0894) all indicate their distributions follow a log-normal distribution (*red curve*). Log-normal distribution was not followed for Groups 4 (SW: *p*-value = 0.0088) and 5 (SW: *p*-value = 0.0045). However, the distributions do suggest that they follow approximately log-normal distributions.

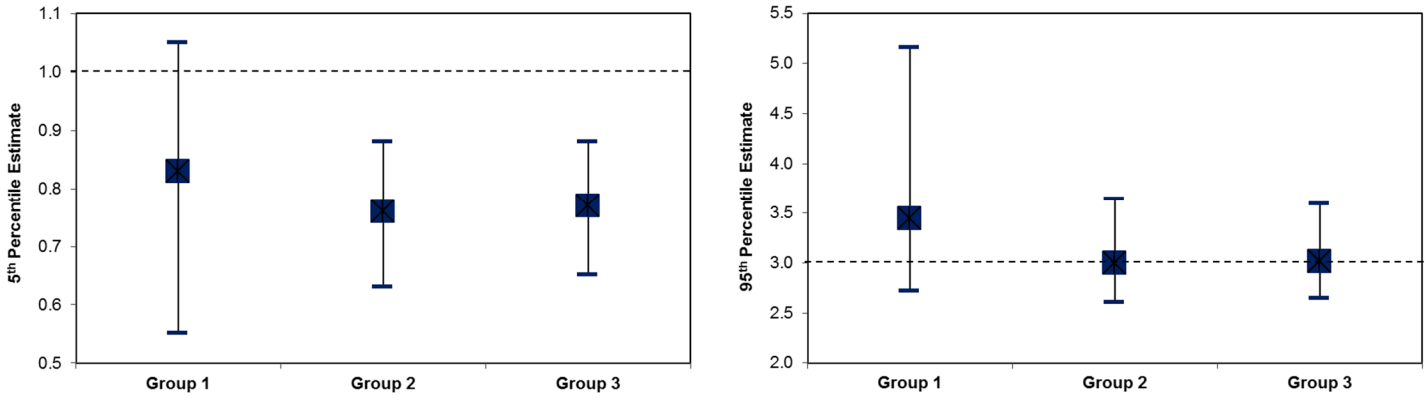


Figure 5. **Parametric percentile estimates using log-normal distributions.** Parametric estimates, assuming log-normality, indicated that the AEGL Committee's default *n* of 1 for short-to-long term extrapolation was not confined to 95% confidence intervals of the 5th percentile of TLE distributions from Groups 2 and 3 (*left*). The AEGL Committee's default *n* of 3 for long-to-short term extrapolation was confined to 95% confidence intervals of the 95th percentile for all distributions (*right*). Parametric estimates using log-transformed distributions TLEs for Groups 4 and 5 were not determined as the normality assumption was not met.

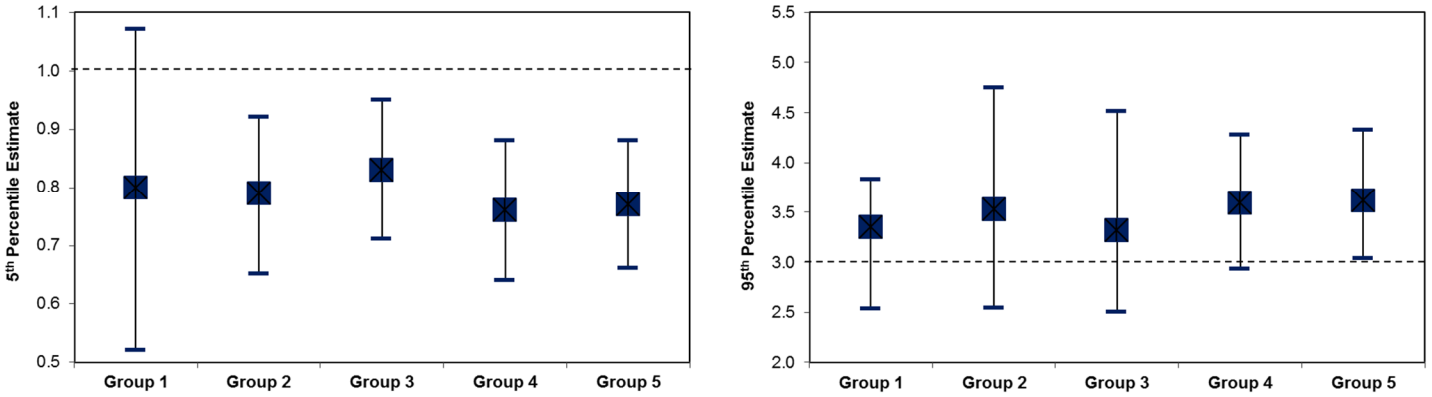


Figure 6. **Non-parametric percentile estimates using smoothed bootstrap distributions (*N=10,000*).** Non-parametric estimates, using smoothed bootstrap resampling (10,000 samples), indicated that the AEGL Committee's default *n* of 1 for short-to-long term extrapolation was not confined to 95% confidence intervals of the 5th percentile of TLE distributions from Groups 2-5 (*left*). The AEGL Committee's default *n* of 3 for long-to-short term extrapolation was confined to 95% confidence intervals of the 95th percentile for all distributions except when all data was used (Group 5) (*right*).

A

Extrapolation Method	Default (*n*)	95% CI
Short-to-long	0.75	0.66 – 0.88
Long-to-short	3.5	3.03 – 4.32

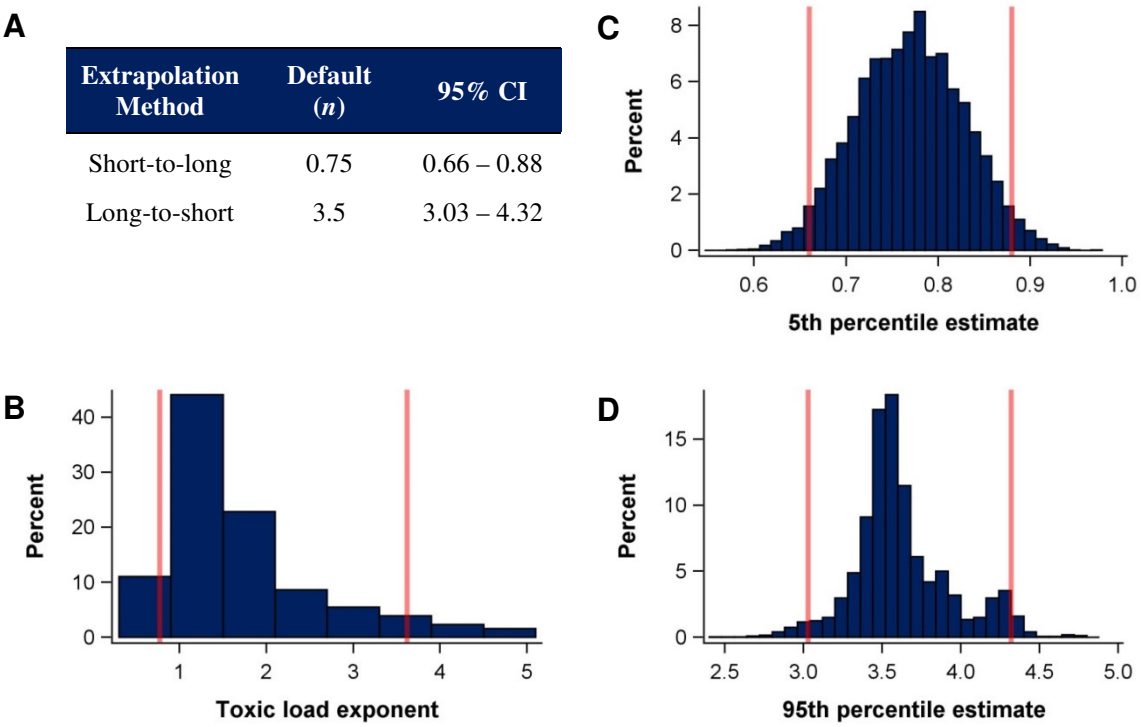
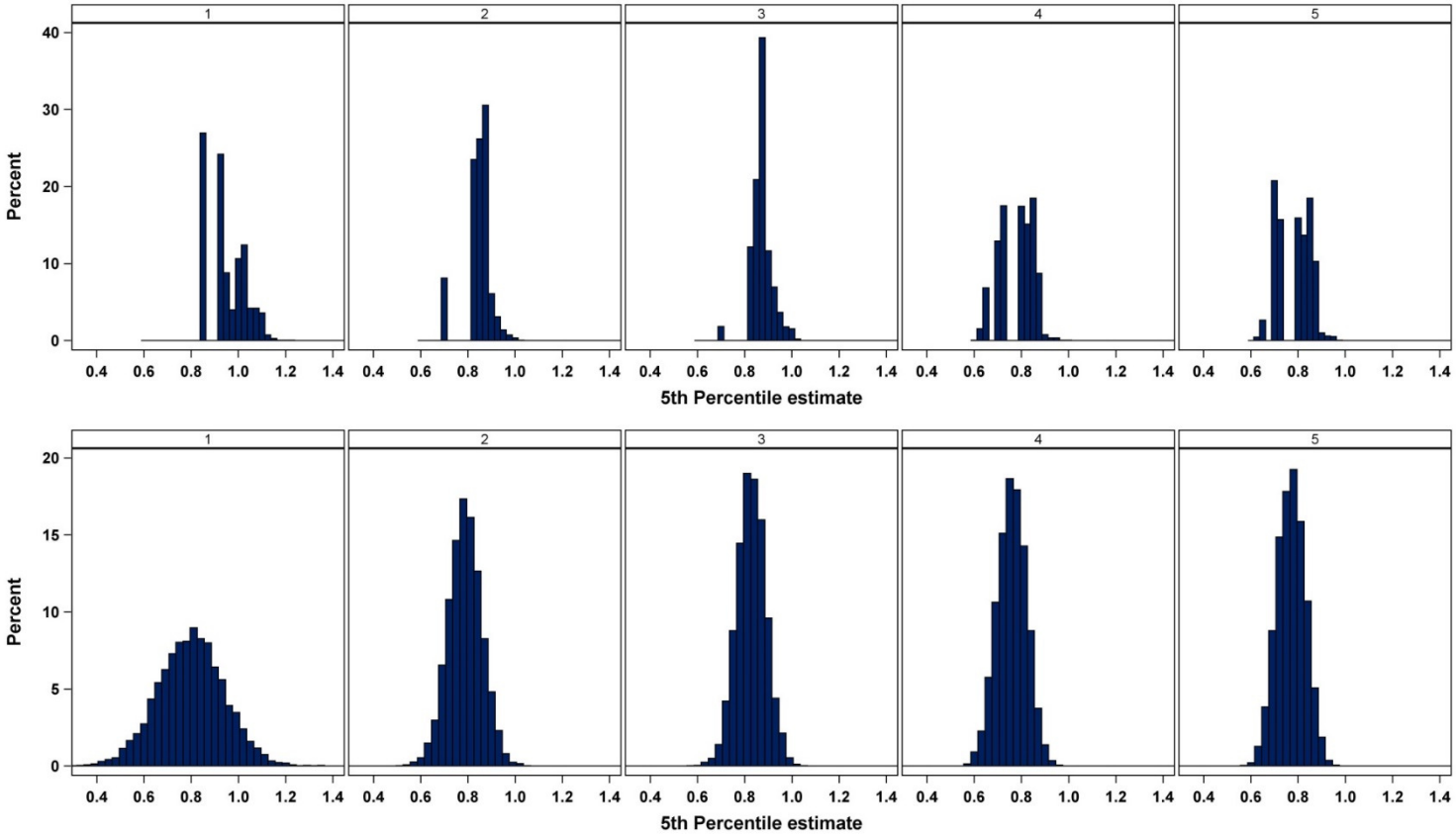
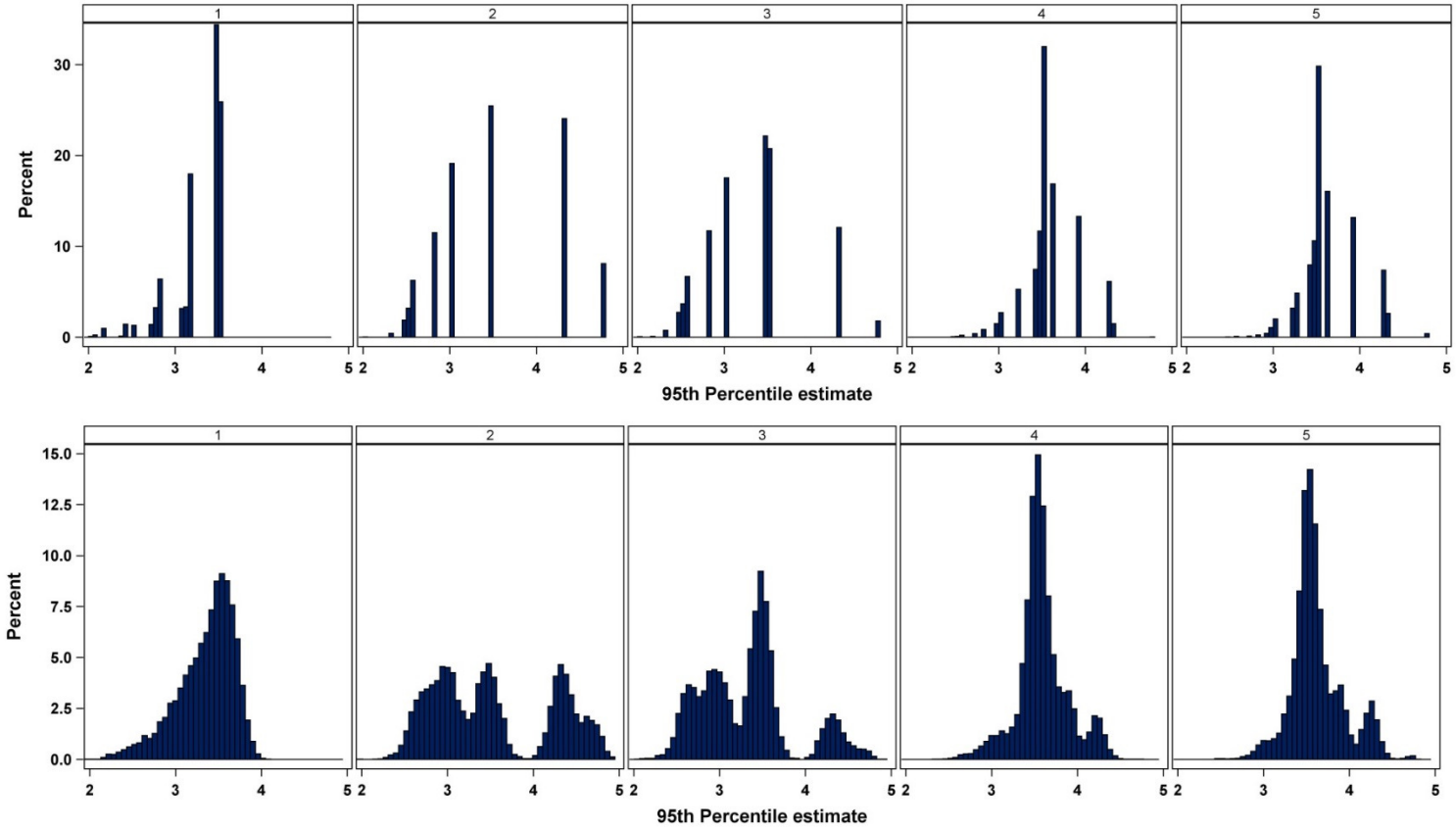


Figure 7. **Toxic load exponent distribution and smoothed bootstrap distributions for the 5th and 95th percentile estimates using all of the data points.** Our estimation, using the more appropriate non-parametric approach, suggests 0.75 and 3.5 as more suitable defaults for concentration-exposure duration extrapolation (*A*), as determined using the distribution of all 127 TLEs identified in our review (*red lines*) (*B*). Smoothed bootstrap resampling methods (10,000 samples) were able to produce approximately normal distribution around the 5th (*C*) and 95th (*D*) percentile points, in which 95% confidence intervals were determined (*red lines*).



Supplemental Figure 1. **Normal (*top*) and smoothed (*bottom*) bootstrap distributions for the 5th percentile estimates of each group.** Smoothed bootstrap distributions (sampling with a small variance of $1/\sqrt{N}$) were found to considerably improve the discrete nature of distributions produced from a simple bootstrap method; therefore increasing information in the tails of the distribution. Smoothed bootstrap resampling of the 5th percentile seemed to follow approximately normal distributions for all groups.



Supplemental Figure 2. **Normal (*top*) and smoothed (*bottom*) bootstrap distributions for the 95th percentile estimates of each group.** Smoothed bootstrap distributions (sampling with a small variance of $1/\sqrt{N}$) were found to considerably improve the discrete nature of distributions produced from a simple bootstrap method; therefore increasing information in the tails of the distribution. Smoothed bootstrap resampling of the 95th percentile seemed to follow approximately normal distributions when TLEs identified from our literature review (Groups 4-5) were added.

Chapter 3

Public Health Implications

Our study was able to build on ten Berge's discoveries on concentration-exposure duration response relationships of extremely hazardous airborne substances, first explored nearly 30 years ago. Inspired by his work, this study is the first to explore these relationships on such a scale and the first to compile expert-validated TLEs derived by the AEGL Committee. Our study showed, that increasing the chemical diversity and, therefore, providing a more representative distribution of TLEs may help further develop sufficiently protective procedures used in temporal extrapolation for inhalation exposure

Our findings show that the current *Standing Operating Procedures* for developing AEGL values for hazardous substances using an *n* of 1 for short-to-long term extrapolation and 3 for long-to-short term extrapolation are only approximately 75% protective. Therefore, AEGLs and other inhalation health guidance values that have been derived using defaults of 1 and 3 for extrapolation may be insufficiently protective and may need reexamination. Although this may not indicate an immediate hazard to a majority of the population, it could limit their application to sensitive subpopulations, such as infants, children, the elderly, persons with asthma and those with other illnesses.

Of the 200 AEGL chemicals derived from chemical-specific PODs, only 73 were associated with empirically supported TLEs. That means at least 127 AEGL chemicals have had AEGL values derived using default values of 1 for short-to-long term extrapolation and/or 3 for long-to-short and may be insufficiently protective. Our

estimation suggests 0.75 and 3.5 as more appropriate defaults for concentration-exposure duration extrapolation, if a conservative approach is desired. Contrary to previous procedures (supported by a sample size of only 20 chemicals), our estimates yield stronger statistical support, as they were derived using empirical information from 127 unique chemical substances.

Health guidance values should always be attuned to new and relevant information within the field. Here, we present suggestions for developing exposure limits for the general public for acute exposure to hazardous airborne chemicals. Adjusting default values used for temporal extrapolation to those suggested here not only decrease uncertainty but they represent a more conservative extrapolation approach. Such a balance in extrapolation and uncertainty are imperative in preventing morbidity and mortality to chemical emergency first responders and unprotected civilian populations.

Appendix

APPENDIX A. ABBREVIATIONS USED

AD	Anderson-Darling
AEGL	Acute Exposure Guideline Level
ATSDR	Agency for Toxic Substances and Disease Registry
BMC	Benchmark Concentration
EC_{50}	The concentration of a chemical that gives half-maximal response
KS	Kolmogorov-Smirnov
LC_{50}	Lethal concentration to 50% of the exposed population (in mg m^{-3} or ppm)
MRL	Minimal Risk Levels
NIOSH	National Institute for Occupational Health
NOAEL	No Observed Adverse Effect Level
NOC	Notices of Commencement of Manufacture or Import
NRC	National Research Council
OEHHA	Office of Environmental Health Hazard Assessment
POD	Point of Departure
RfC	Reference Concentrations
REL	Recommended Exposure Limits
SW	Shapiro-Wilk
TLE or *n*	Toxic Load Exponent
TSCA	U.S. EPA's Toxic Substances Control Act
TSD	Technical Support Document
U.S. EPA	United States Environmental Protection Agency

APPENDIX B. LIST OF "FINALIZED" AEGL CHEMICALS

167 hazardous chemicals have AEGLs that are published by the National Research Council, National Academy of Sciences (NRC/NAS) following NRC/NAS peer review. The NAS publications may differ slightly from the final AEGL technical support documents due to editorial changes. The chemicals are as follows:

CAS	Chemical
N/A	Magnesium aluminum phosphide
56-23-5	Carbon tetrachloride
57-14-7	1,1- Dimethyl hydrazine
60-34-4	Methyl hydrazine
62-53-3	Aniline
67-66-3	Chloroform
68-12-2	N,N-Dimethylformamide
74-83-9	Methyl bromide
74-87-3	Methyl chloride
74-90-8	Hydrogen cyanide
74-93-1	Methyl mercaptan
74-98-6	Propane
75-01-4	Vinyl chloride
75-05-8	Acetonitrile
75-08-1	Ethyl mercaptan
75-15-0	Carbon disulfide
75-21-8	Ethylene oxide
75-44-5	Phosgene
75-54-7	Methyl dichlorosilane
75-55-8	Propyleneimine
75-56-9	Propylene oxide
75-77-4	Trimethylchlorosilane
75-78-5	Dichlorodimethylsilane
75-79-6	Trichloromethyl silane
75-86-5	Acetone cyanohydrin
75-94-5	Vinyltrichlorosilane
77-81-6	Nerve Agent GA (Tabun)
78-82-0	Isobutyronitrile
78-93-3	Methyl ethyl ketone
78-95-5	Chloroacetone
79-11-8	Monochloroacetic acid

79-21-0	Peracetic Acid
80-10-4	Diphenyldichlorosilane
91-08-7	2,6-Toluenediisocyanate
95-63-6	1,2,4-Trimethylbenzene
96-64-0	Agent GD (Soman)
98-13-5	Phenyltrichlorosilane
100-47-0	Benzonitrile
103-71-9	Phenyl isocyanate
106-89-8	Epichlorohydrin
106-97-8	Butane
107-02-8	Acrolein
107-07-3	Ethylene chlorohydrin (2-Chloroethanol)
107-11-9	Allyl Amine
107-12-0	Propionitrile
107-13-1	Acrylonitrile
107-14-2	Chloroacetonitrile
107-15-3	Ethylene diamine
107-18-6	Allyl alcohol
107-19-7	Propargyl alcohol
107-20-0	Chloroacetaldehyde
107-30-2	Chloromethyl methyl ether
107-37-9	Allyltrichlorosilane
107-44-8	Agent GB (Sarin)
107-72-2	Amyltrichlorosilane
108-05-4	Vinyl acetate
108-67-8	1,3,5-Trimethylbenzene (Mesitylene)
108-88-3	Toluene
108-90-7	Chlorobenzene
108-91-8	Cyclohexylamine
108-95-2	Phenol
108-98-5	Phenyl Mercaptan
109-77-3	Malononitrile
109-90-0	Ethyl isocyanate
110-00-9	Furan
110-54-3	Hexane
110-89-4	Piperidine
111-36-4	n-Butyl isocyanate
112-04-9	Octadecyltrichlorosilane
115-21-9	Ethyltrichlorosilane

123-73-9	trans-Crotonaldehyde
124-63-0	Methansulfonyl chloride
124-70-9	Methylvinyldichlorosilane
126-98-7	Methacrylonitrile
141-57-1	Propyltrichlorosilane
151-56-4	Ethyleneimine
156-59-2	cis-1,2-Dichloroethylene
141-59-3	t-Octyl mercaptan
156-60-5	trans-1,2-Dichloroethylene
302-01-2	Hydrazine
329-99-7	Agent GF
353-50-4	Carbonyl fluoride
460-19-5	Cyanogen
463-51-4	Ketene
505-60-2	Sulfur Mustard
509-14-8	Tetranitromethane
526-73-8	1,2,3-Trimethylbenzene
540-73-8	1,2-Dimethyl hydrazine
541-25-3	Lewisite 1, including mixtures with Lewisite 2 (CAS No. 40334-69-8) and Lewisite 3 (CAS No. 40334-70-1)
542-88-1	Bis (chloromethyl) ether
556-61-6	Methyl isothiocyanate
584-84-9	2,4-Toluene Diisocyanate
594-42-3	Perchloromethyl mercaptan
598-31-2	Bromoacetone
624-83-9	Methyl isocyanate
630-08-0	Carbon monoxide
681-84-5	Tetramethoxy silane
684-16-2	Hexafluoroacetone
811-97-2	HFC 134A
928-65-4	Hexyltrichlorosilane
993-00-0	Methyl chlorosilane
1066-35-9	Dimethylchlorosilane
1305-99-3	Calcium phosphide
1314-84-7	Zinc phosphide
1330-20-7	Xylenes
1498-51-7	Ethylphosphorodichloridate
1558-25-4	Chloromethyltrichlorosilane
1717-00-6	HCFC 141b
1719-53-5	Diethyldichlorosilane

2487-90-3	Trimethoxysilane
2698-41-1	tear gas
3173-53-3	Cyclohexyl isocyanate
3282-30-2	Trimethyl acetyl chloride
4109-96-0	Dichlorosilane
4170-30-3	cis-Crotonaldehyde
4484-72-4	Dodecyltrichlorosilane
5283-66-9	Octyltrichlorosilane
5283-67-0	Nonyltrichlorosilane
6423-43-4	Propylene Glycol Dinitrate
6581-06-2	BZ
7446-09-5	Sulfur Dioxide
7521-80-4	Butyltrichlorosilane
7616-94-6	Perchloryl fluoride
7637-07-2	Boron trifluoride
7647-01-0	Hydrogen chloride
7664-39-3	Hydrogen fluoride
7664-41-7	Ammonia
7697-37-2	Nitric Acid
7719-12-2	Phosphorus Trichloride
7726-95-6	Bromine
7782-41-4	Fluorine
7782-50-5	Chlorine
7783-06-4	Hydrogen sulfide
7783-07-5	Hydrogen selenide
7783-41-7	Oxygen difluoride
7783-81-5	Uranium hexafluoride
7784-42-1	Arsine
7787-71-5	Bromine trifluoride
7789-30-2	Bromine pentafluoride
7790-91-2	Chlorine trifluoride
7791-25-5	Sulfuryl chloride
7803-51-2	Phosphine
8008-20-6	Jet Fuel (JP-5)
10025-78-2	Trichlorosilane
10025-87-3	Phosphorus oxychloride
10026-04-7	Tetrachlorosilane
10035-10-6	Hydrogen Bromide
10049-04-4	Chlorine dioxide

10102-43-9	Nitric oxide
10102-44-0	Nitrogen dioxide
10294-33-4	Boron tribromide
10544-72-6	Nitrogen tetroxide
12057-74-8	Magnesium Phosphide
12058-85-4	Sodium Phosphide
12504-13-1	Strontium Phosphide
13463-39-3	Nickel carbonyl
13463-40-6	Iron pentacarbonyl
13637-63-3	Chlorine pentafluoride
13863-41-7	Bromine chloride
19287-45-7	Diborane
20770-41-6	Potassium Phosphide
20859-73-8	Aluminum phosphide
27137-85-5	Dichlorophenyltrichlorosilane
50782-69-9	Agent VX
70892-10-3	Jet Fuel (JP-8)
106602-80-6	Otto Fuel (mainly Propylene Glycol Dinitrate 6423-43-4)
163702-07-6 and 163702-08-7	(HFE-7100) Methyl nonafluorobutyl ether (40%) and Methyl nonafluoroisobutyl ether (60%)

APPENDIX C. LIST OF "INTERIM" AEGL CHEMICALS

Interim AEGLs are established following review and consideration by the National Advisory Committee for AEGLs (NAC/AEGL) of public comments on Proposed AEGLs. Interim AEGLs are available for use by organizations while awaiting NRC/NAS peer review and publication of Final AEGLs. Changes to Interim values and Technical Support Documents may occur prior to publication of Final AEGL values. In some cases, revised Interim values may be posted on the U.S. EPA web site, but the revised Interim Technical Support Document for the chemical may be subject to change. The 92 chemicals with Interim AEGLs are as follows:

CAS	Chemical
50-00-0	Formaldehyde
51-75-2	Nitrogen Mustard-2
56-38-2	Parathion
67-56-1	Methanol
67-64-1	Acetone
71-43-2	Benzene
71-55-6	1,1,1-Trichloroethane
74-89-5	Methyl amine
75-04-7	Ethyl amine
75-07-0	Acetaldehyde
75-09-2	Methylene chloride
75-50-3	Trimethyl amine
76-06-2	Chloropicrin
77-78-1	Dimethyl sulfate
78-85-3	Methacrylaldehyde
78-94-4	Methyl vinyl ketone
79-01-6	Trichloroethylene
79-04-9	Chloroacetyl chloride
79-10-7	Acrylic acid
79-22-1	Methyl chloroformate
79-36-7	Dichloroacetyl chloride
79-38-9	Trifluorochloroethylene
79-41-4	Methacrylic acid
80-62-6	Methyl methacrylate
92-52-4	Biphenyl
98-82-8	Cumene
100-41-4	Ethylbenzene
100-42-5	Styrene

106-88-7	1,2-butylene oxide
106-93-4	Dibromoethane
106-99-0	1,3-Butadiene
107-05-1	Allyl chloride
108-23-6	Isopropyl chloroformate
109-61-5	Propyl chloroformate
116-14-3	Tetrafluoroethylene
116-15-4	Hexafluoropropylene
121-45-9	Trimethyl phosphite
121-75-5	Malathion
123-38-6	Propionaldehyde
123-91-1	1,4-Dioxane
124-40-3	Dimethylamine
127-18-4	Tetrachloroethylene
140-88-5	Ethyl acrylate
141-32-2	n-Butyl acrylate
143-33-9	Sodium cyanide
151-50-8	Potassium cyanide
298-00-0	Methylparathion
298-02-2	Phorate
382-21-8	Perfluoroisobutylene
463-58-1	Carbonyl Sulfide
501-53-1	Benzyl chloroformate
538-07-8	Nitrogen Mustard-1
541-41-3	Ethyl chloroformate
543-27-1	Isobutyl Chloroformate
555-77-1	Nitrogen Mustard-3
578-94-9	Adamsite
592-01-8	Calcium cyanide
592-34-7	n-Butyl chloroformate
593-89-5	Methyldichloroarsine
598-14-1	Ethyldichloroarsine
674-82-8	Diketene
696-28-6	Phenyl dichloroarsine
712-48-1	Diphenylchloroarsine
868-85-9	Dimethyl phosphite
1327-53-3	Arsenic trioxide
1634-04-4	Methyl-tertiary-butyl ether (MTBE)
1794-86-1	Phosgene oxime

1885-14-9	Phenyl chloroformate
2699-79-8	Sulfuryl fluoride
2937-50-0	Allyl chloroformate
2941-64-2	Ethylchlorothioformate
7439-97-6	Mercury Vapor
7440-43-9	Cadmium
7446-11-9	Sulfur trioxide
7550-45-0	Titanium tetrachloride
7664-93-9	Sulfuric acid
7719-09-7	Thionyl chloride
7782-65-2	Germane
7783-54-2	Nitrogen trifluoride
7783-61-1	Silicon tetrafluoride
7783-79-1	Selenium hexafluoride
7783-80-4	Tellurium hexafluoride
7790-94-5	Chlorosulfonic acid
7803-52-3	Stibine
7803-62-5	Silane
8014-95-7	Oleum
10025-67-9	Disulfur dichloride
10034-85-2	Hydrogen Iodide
17462-58-7	sec-Butyl chloroformate
19624-22-7	Pentaborane
20816-12-0	Osmium tetroxide
24468-13-1	2-Ethylhexylchloroformate

APPENDIX D. LIST OF "PROPOSED" AEGL CHEMICALS

Proposed AEGLs are published in the Federal Register for public comment following review and concurrence of Draft AEGLs by the NAC/AEGL. The comment period is 30 days from the date Proposed AEGLs are published in the Federal Register. The 12 chemicals with Proposed AEGLs are as follows:

CAS	Chemicals
62-73-7	Dichlorvos
74-88-4	Methyl iodide
116-06-3	Aldicarb
141-66-2	Dicrotophos
6923-22-4	Monocrotophos
7723-14-0	Red Phosphorus
8006-61-9	Gasoline
13171-21-6	Phosphamidon
10265-92-6	Methamidophos
16752-77-5	Methomyl
22224-92-6	Fenamiphos
23135-22-0	Oxamyl

APPENDIX E. LIST OF "ON HOLD" AEGL CHEMICALS

Holding Status AEGLs have been reviewed by the NAC/AEGL Committee and are on hold due to insufficient data to develop AEGL values. The 46 chemicals with Holding Status AEGLs are as follows:

CAS	Chemical
62-74-7	Sodium fluoroacetate
62-74-8	Fluoroacetate salts
75-36-5	Acetyl Chloride
75-74-1	Tetramethyl lead
76-02-8	Trichloroacetyl Chloride
77-10-0	Phencyclidine
80-12-6	Tetramethylene disulfotetramine
80-63-7	Methyl 2-chloroacrylate
97-02-9	2,4-Dinitroaniline
107-49-3	Tetraethyl pyrophosphate
110-78-1	n-Propyl isocyanate
144-49-0	Monofluoroacetic acid
151-38-2	Methoxyethyl mercuric acetate
371-62-0	Ethylene fluorohydrin
453-18-9	Methyl fluoroacetate
463-71-8	Thiophosgene
503-38-8	Diphosgene
506-77-4	Cyanogen chloride
556-64-9	Methyl thiocyanate
561-27-3	Diacetyl morphine
814-68-6	Acrylyl chloride
950-35-6	Methyl paroxon
993-43-1	Ethyl phosphonothioic dichloride
1303-28-2	Arsenic pentoxide
1498-40-4	Ethyl phosphonous dichloride
1609-86-5	t-butyl isocyanate
1737-93-5	3,5-dichloro-2,4,6-trifluoropyridine
1795-48-8	Isopropyl isocyanate
1873-29-6	Isobutyl isocyanate
2696-92-6	Nitrosyl chloride
354-32-5	Trifluoroacetyl chloride
4300-97-4	Chloropivaloyl chloride

4685-14-7	Paraquat
6427-21-0	Methoxymethyl isocyanate
7775-14-6	Sodium dithionite
7783-60-0	Sulfur tetrafluoride
7783-82-6	Tungsten hexafluoride
7784-34-1	Arsenic trichloride
7786-34-7	Mevinphos
7789-21-2	Fluorosulfonic acid
7803-49-08	Hydroxylamine
7803-54-5	Magnesium diamide
9009-86-3	Ricin
10294-34-5	Boron Trichloride
10544-73-7	Nitrogen trioxide
10545-99-0	Sulfur dichloride