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Concentration-Time Relationships for Short-Term Inhalation Exposures to Hazardous Substances

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Abstract

Concentration-Time Relationships for Short-Term Inhalation Exposures to Hazardous Substances

By Rajkumar Manimaran

Acute Exposure Guideline Levels (AEGLs) are developed by the USEPA AEGL committee to reduce the risk of acute exposures to airborne hazards. AEGLs are the threshold limits for once-in-a-lifetime or rare chemical exposures at five exposure durations (1/6, 1/2, 1, 4, 8h), across the three-health effect severity tiers (AEGL-1: mild, AEGL-2: disabling, and AEGL-3: life-threatening). They are derived from various published and unpublished experimental studies described in the Technical Support Documents prepared by the committee. An AEGL concentration (*C*) for duration (*t*) is extrapolated from available experimental data. The extrapolation is carried out using the Haber–ten Berge exponential function, $C^n * t = k$, where *n*, the temporal scaling factor (TSF), is chemical-specific. Preferably, TSF is derived experimentally, but so far only for a small number of chemicals the experimental TSFs have been derived. For most of 272 chemicals on the AEGL list, TSFs are unknown. For them, the AEGL committee carried out temporal extrapolation using expert-panel judgment. Thus, the AEGL database contains rich expert-validated chemical-specific information about temporal extrapolation.

The objective of the present study was to extract this information by four different approaches, analyze it, and derive statistically-justified guidelines for TSFs for chemicals without experimentally-derived TSFs. The AEGL values (concentrations) were log-transformed and regressed against the logarithm of time using SAS. TSFs were derived from regression slopes. For each chemical in the database, up to three TSFs were derived across the three AEGL health effect severity tiers.

TSFs derived using Approach 4 for chemicals, whose all AEGL values within a tier are different, were in agreement with AEGL Committee's empirically derived *n*-values and also with most of empirically derived *n*-values known from the literature. The range and mean of *n*-values derived in Approach 4 were in agreement with the range and mean of *n*-values published in the literature. Because the 95th percentile on *n*-values could not be reliably estimated from small datasets available in the past, the 90th percentile has been introduced in public health practice. A dataset analyzed in the present study is sufficiently large for reliable estimation of 95th and even 99th percentiles. Applying Approach 4 to these data, the 95th percentile for *n*-values was derived, which was estimated as $n = 3.5$ (95% CI: 2.8–4.4). Based on AEGL Committee practice of using uniform threshold concentrations across all durations in the AEGL-1 tier (i.e. using Approach 1), an *n*-value that maybe appropriate for this tier was estimated as 6.87 (95% CI: 6.45–7.35).

Thus, using an *n*-value of 3.5, a more health-protective scientifically-justified health guidance for acute severe airborne hazards can be implemented and for less-severe AEGL-1 hazards, however, even a higher TSF may be appropriate.

Keywords: Temporal scaling factor, AEGL, Haber-ten Berge, Acute inhalational exposure, airborne toxicity

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TABLE OF CONTENTS

Concentration-Time Relationships for Short-Term Inhalation Exposures to Hazardous Substances

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I. INTRODUCTION

To reduce the risk of inhalation exposures to hazardous chemical substances in humans, a USEPA-sponsored expert Committee has been developing the Acute Exposure Guideline Levels (AEGLs). AEGLs are the threshold exposure limits for once-in-a-lifetime, emergency (accidental), or rare exposures to acutely toxic chemicals for five short-term exposure durations (10 min, 30 min, 1 hr, 4 hr, and 8 hr)[7]. AEGLs have been grouped in three tiers as AEGL-1, AEGL-2, and AEGL-3 based on the varying degrees of severity of health effects in the general population, including susceptible individuals, such as infants, children, the elderly, and people with chronic diseases (e.g. cardiovascular disease or pulmonary disease) that may exacerbate upon exposures to hazardous substances. The AEGL values are used by government agencies, industry, and professional organizations for regulatory and non-regulatory purposes in affiliation with inhalational chemical emergency response, planning, and prevention programs. AEGL concentrations are expressed in units of parts per million (ppm) or milligrams per cubic meter (mg/m^3). The three tiers of AEGL values "provide much more information than a single value because the series indicates the slope of the dose-response curve"[12].

The characterization of the three tiers of AEGL is based on the definitions for the community emergency exposure levels (CEELs) published by the National Research Council (NRC) as follows[7] :

- AEGL-1 is the airborne concentration of an acutely toxic chemical above which it is anticipated that the general population, including susceptible individuals, could

experience discomfort, sensory irritation, or asymptomatic non-sensory effects that is not disabling and temporary and is reversible upon termination of exposure to the chemical.

- AEGL-2 is the airborne concentration of an acutely toxic chemical above which it is anticipated that the general population, including susceptible individuals, could develop serious adverse health effects that are irreversible, long lasting, or may result in impairment of the ability of an individual to escape from the exposure scene.
- AEGL-3 is the airborne concentration of an acutely toxic chemical above which it is anticipated that the general population, including susceptible individuals, could experience dangerous life-threatening health effects or mortality.

Hence, each chemical may be assigned up to fifteen AEGL values in total. For instance, the AEGL Committee assigned health guidance values (HGVs) to boron trifluoride is shown in Table 1[7].

The USEPA AEGL database lists 272 chemicals found in the Final, Interim and Proposed stages of AEGL development. To derive the AEGL values, the AEGL Committee has established a comprehensive Standing Operating Procedure (SOP) guidance, which adheres to the NRC guidelines. For each chemical in the AEGL database, the AEGL committee develops a Technical Support Document (TSD) that contains a thorough analysis of the source data, methods, scientific rationale, and other aspects that apply to derivation of AEGL values.

Development of AEGL values involves, gathering of relevant published and unpublished experimental data (from peer-reviewed journals, government databases, published and unpublished information from the public and private sectors), which are evaluated by prominent scientists with expertise in toxicology, chemistry, and relevant fields. Most of these primary data originate from controlled animal-based experiments, which are extrapolated to the context of

human environmental health to derive the AEGL values. Since for many chemicals complete data are unavailable, extrapolation methods and Committee's scientific expert judgment are often applied to derive the AEGL values. When the data are inadequate or incomplete, the Committee may not establish an AEGL value.

The methodology AEGL development involves the following categories[7] :

- The "key study" – toxicity data gained from a primary source, which could be a human observation and/or animal study, from which the AEGL values are derived.
- Toxicological endpoints relevant to the chemical-specific thresholds of each of the three AEGL severity levels.
- A point of departure (POD), that is the selection of highest exposure level at which the effects that characterize an AEGL threshold level are not observed, which could be either a no observed adverse effect level (NOAEL) or benchmark concentration (BMC) when appropriate data are available.
- Uncertainty factors (UFs) used to extrapolate an AEGL value from the POD. UFs address the variability observed across species (inter-species variability), among the same species (intra-species variability), insufficient information about the chemical or its mechanism of action, multiple exposure study used to calculate AEGL value, and other factors that may affect the scientific judgment.
- Modifying factor to account for uncertainties in the overall chemical-specific database or for known distinctions in the toxicity among structurally analogous (congeneric) chemicals.
- Temporal scaling factor (TSF) is used for duration adjustments.

i. Temporal Scaling Factor (TSF):

As stated above, AEGLs are derived for 10 min, 30 min, 1 hr, 4 hr, and 8 hr exposure durations to accommodate a broad range of safety protection needs. However, data available from animal studies, controlled human exposures, and chemical release incidents generally comprise exposure durations and concentrations distinct from those particularized for AEGLs. Therefore, the AEGL committee often extrapolates the particularized AEGL values from an available exposure-duration and chemical-concentration information using a predefined set of rules for temporal extrapolation.

Several models that relate a chemical concentration and duration of exposure to health effects are known from the literature. Historically, duration adjustments have been carried out using Haber's rule[14]:

$$C \times (t_f - t_i) = K_{EP}, \qquad (1)$$

which states that a product of exposure concentration, C (that yields a given toxicological effect, E, in a given percentage of the population, P) and duration of exposure that begins at the initial time t_i and ends at the final time t_f, $(t_f - t_i)$, is a constant K_{EP}. Haber's rule assumes that the toxicological effect is a function of only the total inhaled dose (cumulative dose), regardless of whether the dose is delivered via a long exposure to low concentration or short exposure to high concentration. The original Haber's rule implies a constant concentration of the chemical. Adapted to non-steady-state conditions, this rule prescribes that the instantaneous concentration shall be integrated with respect to time[14]:

$$\int_{t_i}^{t_f} C(t)\, dt = K_{EP} \qquad (2)$$

Eq. 2 is an extension of Haber's rule. It states that for any time-varying chemical concentration function, *C(t),* beginning at the initial time t_i and ending at the final time t_f, that yields a given toxicological effect, *E*, in a given percentage of the population, *P*, the integral of the instantaneous concentration across the exposure duration is a constant K_{EP}.

This idealized concept has been proposed by the inventor of chemical warfare Fritz Haber (1868-1934). It has been deduced to imply that the severity of a health effect produced from an exposure to any chemical is linear with respect to both the concentration and duration of exposure. Validity of Haber's rule has been assessed for acute toxicity of some chemicals and in particular cases like cumulative or carcinogenic chemicals[5, 8, 10], yet many toxicologists including the US Environmental Protection Agency have continued using this duration adjustment as a default factor for chronic exposure conditions[1]. This is because using Haber's rule for temporal extrapolation generally gives a lower critical dose than unadjusted dose yielding an extra margin of safety for public health[2].

Haber's rule suggests that a chemical exposure to both short-term, high concentration and long-term, low concentration shall result in equivalent biological effects. Even though this assumption may be true for some chemicals across exposure durations of interest, generally, it is does not hold for all chemicals. For instance, for a particular substance irrespective of duration of exposure, typically, there is a concentration at which no observable effects will be experienced. Laboratory animal experiments have demonstrated that Haber's rule does not apply to a number of chemical warfare agents, such as sarin (GB), soman (GD), cyclosarin (GF), and distilled sulfur mustard (HD)[14].

Given the same cumulative dose of several warfare chemicals, such as, GB, GD, GF and HD, the severity of health effects is greater in laboratory animals exposed to short rather than long

durations[14]. A likely reason for this is due to physiological processes of elimination and detoxification of the chemical within the body over a course of long period of exposure.

To account for these discrepancies the toxic load framework has been proposed. In this framework the population response is described by a logarithmic function of "toxic load" (TL) rather than dosage[4], where the TL is defined as[14] :

$$C^n \times (t_f - t_i) = K_{TL,} \quad (3)$$

The TL value, K_{TL}, is a determinant of the adverse health effect in a specified percentage of the population. A value of the TL exponent, n, is determined in animal experiments using various exposure scenarios. Ten Berge et al. (1986) have shown that the concentration and time of exposure can be reasonably approximated by an exponential function of concentration, and thus for steady-state conditions:

$$C^n \, x \, t = K_{TL}, \quad (4)$$

Analysis of LC_{50}, carried out by ten Berge et al. (1986) for 20 structurally different chemicals, reveals that chemical-specific relationships between exposure concentration and exposure duration are often exponential, where n is a chemical-specific exponent greater than zero. Essentially, this equation expresses the relationship in the form of linear regression on the log-log transformed plot of exposure concentration versus exposure duration. Eq. (4) reduces to Haber's rule when $n = 1$. In the ten Berge et al. (1986) study, empirically derived n values range from 0.8 to 3.5[13]. When $n = 1$, the toxicity of a substance is equally dependent on exposure concentration and exposure duration; when $n < 1$, the toxicity is more dependent on the duration of exposure than on the concentration, and conversely when $n > 1$. Preferably, TSF is derived experimentally by evaluating the concentration versus health effect relationships for several different exposure durations, but so far, such information is available only for a limited number of chemical substances.

A study conducted by California EPA Office of Environmental Health Hazard Assessment (OEHHA) states that Haber's rule does not apply to many sensory irritants but Eq. (4) yields reasonably good results[11]. The value of *n* increases, as the exposure concentration becomes the more important factor in contribution to the TL and a value of $n \geq 3$ suggest a strong influence of concentration over time[6].

"Guidelines for Developing Spacecraft Maximum Allowable concentrations for space Station Contaminants" released by the toxicology committee of the National Research Council [3], mentions the desirability of applying a power law over Haber's rule by stating that a more general expression for analyzing relationships between concentration, time, and the TL constant is given by $C^a \times T^b = K_{TL}$, where the exponents *a* and *b* are estimated from experimental data. This relationship is appropriate when the exposure concentration and exposure duration do not equally contribute to the observed adverse health effects.

It is also essential to note that the value of the TL TSF derived from animal experiment is carried on with exposures to steady-state chemical concentrations[9]. Hence, as in the case of Haber's rule, experimental basis for the TL model is determined based on constant concentration exposures only.

In real-life exposure scenarios, however, the concentration is rarely constant. Non-steady-state conditions have been considered in several extensions of the TL model, but none are experimentally validated[4]:

- Integrated Concentration Toxic Load Model[14] :

  This model was proposed by ten Berge and va`n Heemst in 1983 which extends equation (2) by applying a time integral over the instantaneous concentration elevated to the power of TL exponent.

$$\int_{t_i}^{t_f} C\,(t)^n dt = TL_{integrated} \qquad (5)$$

- Average Concentration Toxic Load Model[14] :

  This is a different approach to applying the TL model to time varying substance concentration by replacing the steady concentration in equation (3) with the average concentration over the exposure duration. The average concentration, C_μ, is calculated as follows,

$$C_\mu = \frac{\int_{t_i}^{t_f} C\,(t)^n dt}{t_f - t_i} \qquad (6)$$

  Substitution of C_μ in equation (3) results in average concentration of the TLmodel with an assumption that a time-varying chemical concentration can be reasonably approximated by a constant average concentration[14]:

$$C_\mu{}^n \times (t_f - t_i) = \left(\frac{\int_{t_i}^{t_f} C\,(t)^n dt}{t_f - t_i}\right)^n \times (t_f - t_i) = TL_{average} \qquad (7)$$

ii. Temporal extrapolation by AEGL committee:

The AEGL committee's temporal extrapolation relies on the exponential TL model (3), in which the exponential temporal scaling factor (TSF), *n*, is chemical and health-effect specific. Generally, toxicity data for any or all of the AEGL-specific exposure durations are not available. Therefore, duration adjustment is necessary to derive scientifically credible values for the

AEGL-particularized time points. The use of both the appropriate supporting data and scientific judgment determines the extent of temporal extrapolation and its validity in AEGL derivations. The greater is the difference between an experimental exposure duration and AEGL-specific duration, the greater is the uncertainty on the developed AEGL value due to extrapolation errors, including the estimation of the *n* value. Thus, extrapolation to a 4 hr or 8 hr AEGL value from a 10 min exposure data needs more supporting information than extrapolation to a 30 min value. Similarly, extrapolation to 10 min AEGL value from 4 hr or 8 hr exposure data requires more supporting information and assumptions than to 1 hr. Therefore, a 30 min AEGL value is assigned to a10 min AEGL duration in absence of strong supporting data[7].

AEGL committee applies the following tiered approach to time scaling[7],

- If toxicity data are available for all AEGL-particularized exposure durations, the AEGL committee uses this empirical data directly to derive AEGL values and therefore, there is no need to derive the *n* value.
- If adequate empirical exposure concentration/exposure duration relationship data for a specific toxicity endpoint, including mortality, are available for durations other than the AEGL-specified exposure durations, AEGL committee uses the available data to derive scientifically more credible TSF and extrapolate the AEGL values using eq. (3) rather than a default value of $n = 1$.

  The first step in deriving the TSF is the selection of an appropriate health effect endpoint consistent with the AEGL tier under examination. After that, qualitative and quantitative evaluation of the empirical data appropriate for derivation of TSF is carried out. The concentration-duration relationship is defined by the slope of a curve obtained by at least two empirical data points but the scientific validity of the slope and the estimated values for TSF improves with increasing number of empirical data points given that there is a

reasonable fit of these empirical points. Plotting the log transformed concentration data in Y-axis and duration data in X-axis points and running a simple linear regression on the data forms the linear equation of the nonlinear $C^n \times t = k$ equation as follows[7]:

$$\log C = (-1/n) \log t + (\log k)/n$$

Where, C is regressed concentration to result a health effect at exposure duration of t.

$(\log k)/n$ = the Y intercept of the plot of log C against log t, and

$-1/n$ = the slope of the plot of log C against log t.

The log-transformation of the nonlinear $C^n \times t = k$ equation to a linear equation form is as follows[7]:

$$C^n \times t = k \quad (1)$$

$$\log (C^n \times t) = \log k \quad (2)$$

$$n \log C + \log t = \log k \quad (3)$$

$$n \log C = \log k - \log t \quad (4)$$

$$\log C = (\log k)/n - (\log t)/n \quad (5)$$

$$\log C = (-1/n) \log t + (\log k)/n \quad (6)$$

Thus, the slope suggests a general interpretation of how the two plotted variables (concentration and duration of exposure) are related. The regression coefficient or slope, $-1/n$, which is the rate of change along the regression line is the distance between the log C values of the two points divided by the distance between their respective log time values. The regression coefficient is calculated as[7],

$$-1/n = \frac{N\sum (\log t)(\log C) - (\sum \log t)(\sum \log C)}{N\sum (\log t)^2 - (\sum \log t)^2}$$

Where, N = the number of observations.

Solving the above gives TSF.

For example, plotting logarithm of pentaborane concentration against the logarithm of the exposure time (Table 2, Figure 1) gives a TSF of pentaborane[7],

Slope = -0.7703

-1/n = -0.7703

Therefore, *n* value of pentaborane = -1/-0.7703 = 1.3

Specific steps to derive AEGL-2 values of pentaborane for the AEGL-specific durations are as follows[7]:

- Key study chosen: Weir, F.W., V.M. Seabaugh, M.M. Mershon, et al. 1964. Short exposure inhalation toxicity of pentaborane in animals. Toxicol. Appl. Pharmacol. 6: 121-131.
- AEGL-2 relevant health effects: CNS effects.
- POD: NOAEL for single 60 min exposure to 1.4 ppm.
- Total uncertainty factor used is 10 (Interspecies and Intraspecies)
- Modifying factor: None
- Time-scaling: $C^{1.3} \times t = k$

  $(1.4 \text{ ppm})^{1.3} \times 60 \text{ min} = 93 \text{ ppm-min}$
- Calculation of AEGL-2 values (NRC, 2001):

  10-min AEGL-2: $C^{1.3} \times 10 \text{ min} = 93 \text{ ppm-min}$; C = 5.6 ppm

  5.6 ppm /10 = 0.56 ppm (1.4 mg/m^3)

  30-min AEGL-2: $C^{1.3} \times 30 \text{ min} = 93 \text{ ppm-min}$; C = 2.4 ppm

  2.4 ppm /10 = 0.24 ppm (0.62 mg/m^3)

  1-hour AEGL-2: C = 1.4 ppm

1.4 ppm /10 = 0.14 ppm (0.36 mg/m^3)

4-hour AEGL-2: $C^{1.3} \times 240$ min = 93 ppm-min; C = 0.48 ppm

0.48 ppm /10 = 0.048 ppm (0.12 mg/m^3)

8-hour AEGL-2: $C^{1.3} \times 480$ min = 93 ppm-min; C = 0.28 ppm

0.28 ppm /10 = 0.028 ppm (0.072 mg/m^3)

The degree of correlation among the varied concentration and duration data points utilized to form the line and the equation determines validity of the derived values of *n*. Generally coefficient of determination (r^2) is used to describe how well a regression line fits a set of data points. But in this case the use of r^2 is depreciated as the number of data points usually available are only in the range of 3 or 4 values. Hence, the AEGL committee applies informed professional judgment based on careful review, evaluation, and discussion of all available data. Although deriving the value of *n* from empirical data that describes the exposure concentration-time relationship, the AEGL Committee evaluates the resultant AEGL values if it fits the supporting data to determine the validity of the extrapolated values.

- If no empirical data of exposure concentration-exposure duration relationship for a toxicity endpoint is available to generate a TSF, the AEGL committee initially tests tentative AEGL values by using a value of *n* = 1 for a short-to-long term extrapolation and a value of *n* = 3 for long-to-short term extrapolation. As per the work of ten Berge et al. (1986), *n* = 1 is an estimate of the lower boundary of the *n* value and the value of *n* = 3, is an estimate of the upper boundary of the *n* value . This approach results in less rapid rates of decrease and increase in estimated effect concentrations when extrapolated to longer and shorter exposure periods, respectively. Approximately 90% of *n* values of the chemicals analyzed by ten Berge et al. (1986) range from 1 to 3.

Evaluation of the scientific validity of the choice of the estimated lower and upper boundaries of *n* (1 and 3) is carried out by comparing all the supporting data with the estimated AEGL values.

- In absence of supporting data to evaluate estimated values of *n*, AEGL committee selects a default value of *n* = 1 for short-to-long term extrapolation and a default value of *n* = 3 for long-to-short extrapolation and considers the estimated AEGL values to be protective and scientifically credible.

Thus, the AEGL database contains rich expert-validated chemical-specific information about temporal extrapolation. The objective of the present study was to derive the TSFs using the AEGL database and analyze this information.

II. MATERIALS AND METHODS:

i. Database development:

The AEGL database contains 272 chemicals for which AEGLs have been derived at the Final, Interim, or Proposed AEGL development stages. The chemical-specific AEGL concentration values at the three severity tiers and five exposure durations were extracted from USEPA AEGL Chemical Data website (http://www.epa.gov/oppt/aegl/pubs/ humanhealth.htm) and compiled in Microsoft Excel spreadsheet.

ii. Method of analysis:

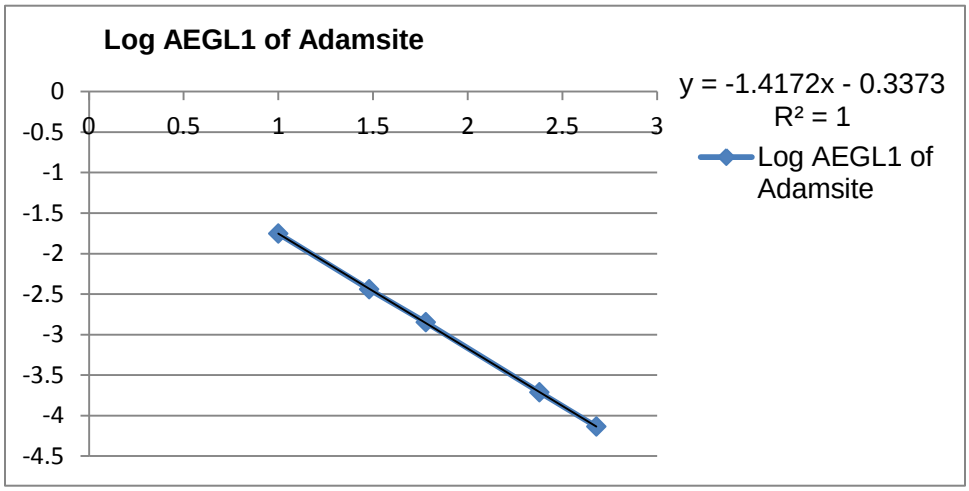
A method used to derive TSFs was similar to the AEGL committee method of TSF derivation when empirical exposure concentration-exposure duration data are available. The AEGL concentration values across the three-health effect severity levels (AEGL-1, AEGL-2 and AEGL-3) of each chemical and the five time durations (10 min, 30 min, 1 hr, 4 hr, and 8 hr) were log transformed. The logarithm of AEGL concentration was regressed against the logarithm of time

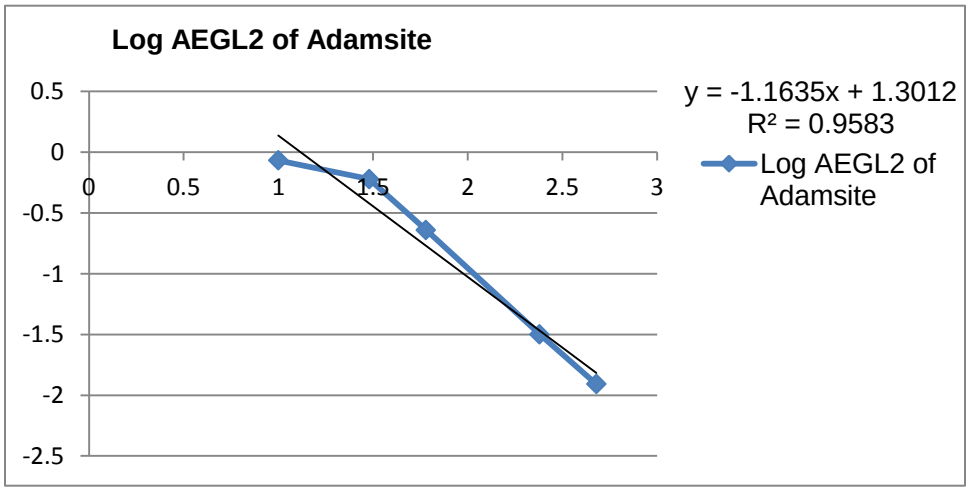
for every chemical across the three severity tiers. A simple linear regression was ran in SAS and then was solved to obtain the *n* value (see below). For each chemical in the database across the three AEGL health effect levels, at least three surrogate values of *n* were derived.

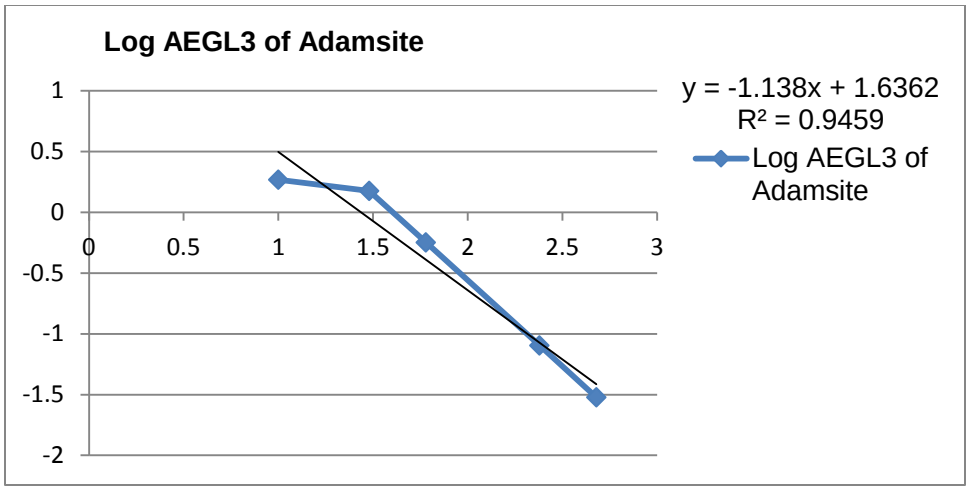
For example, TSF of adamsite was derived from its AEGL values (Table 3) as follows,

The logarithm of the concentration was plotted against the logarithm of the exposure time as shown in Figure 2. :

Figure 2.







Therefore *n* = 1/*a*, where *a* is a slope of the line.

Hence, *n* values of adamsite are,

AEGL-1 = 1/1.4 = 0.706 (95% CI 0.698–0.714)

AEGL-2 = 1/1.2 = 0.859 (95% CI 0.621–1.394)

AEGL-3 = 1/1.1 = 0.879(95% CI 0.611–1.567)

The derivation of empirical *n* value 0.71 of adamsite is based on the analysis of the average response of human tolerance limit in 1 to 6 subjects[7]. The same *n* value was used for all AEGL tiers due to the progression of effects (irritation to epithelial tissue injury) noticed for adamsite appears to be the consequence of a similar mode of action. Adamsite's empirical TSF derived by the AEGL committee lies within the 95% confidence interval of the study derived TSF in all the three health severity levels.

Four different approaches were applied to AEGL data to derive tier-dependent TSFs (*n1*, *n2* and *n3* are TSFs for AEGL-1, AEGL-2 and AEGL-3, respectively) as follows:

- Approach 1. Using mean log AEGLs averaged over all chemicals for a given severity tier (AEGL-1, AEGL-2 and AEGL-3) and duration (1/6, 1/2, 1, 4, 8 hrs). This approached

produced three TSFs averaged over all data in the AEGL database, including chemicals with identical AEGL values across all exposure durations within a severety tier.

- Approach 2. Using up to 5 AEGL concentration values for each chemical within a severety tier with at least one or more different AEGL value(s) across the 5 exposure durations.
- Approach 3. Using the AEGL data for each chemical within a severity tier, 5 exposure duration points were split in half:

  (3a.) 10 min, 30 min, 1 hr (short-term – $n_1 1$, $n_1 2$ and $n_1 3$) and

  (3b.) 1 hr, 4 hr, 8 hr (long-term – $n_2 1$, $n_2 2$ and $n_2 3$), with at least one or more different AEGL value(s) across the 3 exposure durations.

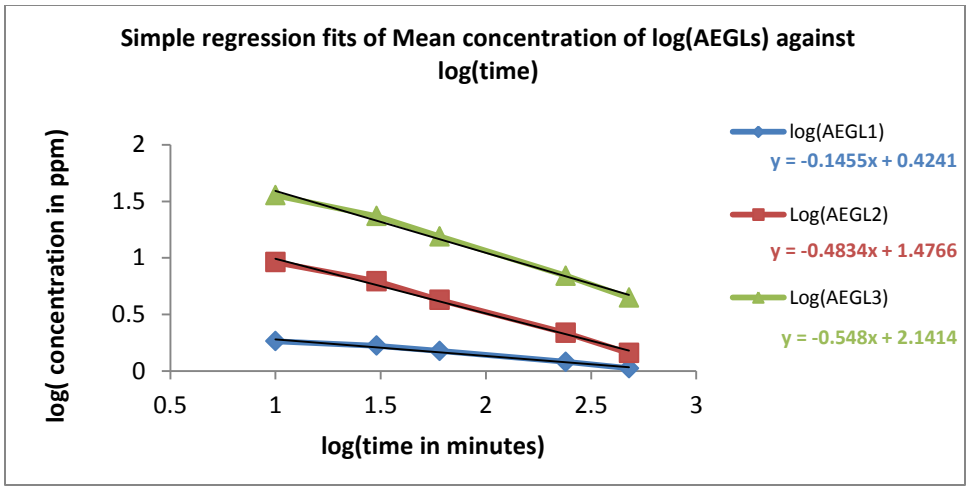
  This approach was used to examine a possible effect of short-to-long and long-to-short exposure duration extrapolation.
- Approach 4. Using chemicals whose all 5 AEGLs were different. For each chemical, a TSF was calculated for each of the 3 health effects severity tiers.

To derive the TSF, the chemical that had identical AEGL values across all 5 duration points were ignored in Approaches 2, 3 and 4 to form the equation of the line with its slope. This is because the slope of the line gives the general interpretation of the relationship of the AEGL concentration value and duration.

III. RESULTS:

i. Approach 1. TSF statistics were derived using averaged log AEGLs.

Figure 3. Simple regression fits of mean concentration of log (AEGLs) against log (time)



As seen in table 4, within a health effect severity tier, means ranged from 0.02 to 0.26 for log AEGL-1 values (sample size = 164–167), 0.16 to 0.96ppm for log AEGL-2 values (sample size = 262–269), and 0.65 to 1.55ppm for log AEGL-3 values (sample size = 257–263) across all five durations. Within a severity tier, the mean log AEGL concentration values decreased with increasing durations. Across the severity tiers, mean log AEGL values increased with increasing health effect severity.

A relationship between TSF for mild/reversible (*n1*=6.87 (95% CI 6.45–7.35), AEGL-1 tier), disabling/irreversible (*n2*=2.07 (95% CI 2.02–2.12), AEGL-2 tier), and life-threatening effects (*n3*=1.82 (1.80–1.85), AEGL-3 tier) was *n1* > *n2* > *n3*. Using this approach, chemicals with identical AEGL values across exposure durations within a severity tier were accounted for. Such chemicals could not be analyzed using other approaches described in the present report.

ii. Approach 2. TSF statistics were derived using a set of TSFs calculated individually for each chemical within each health effects severity tier. In this approach, only chemicals that had at least one or more different AEGL values within a tier were used. Histograms of non-log-transformed and log-transformed AEGL-derived *n* values derived following Approach 2 are

shown in Fig. 4. Both the non-log-transformed and log-transformed *n* values did not follow a normal distribution for *n2* and Log*n2* with a sample size of 245(*n2* – Shapiro-Wilk W = 0.666198, Pr < 0.0001, Log*n2* – Shapiro-Wilk W = 0.942643, Pr < 0.0001), *n3* and Log*n3* with a sample size of 252 (*n3* – Shapiro-Wilk W = 0.741556, Pr < 0.0001, Log*n3* – Shapiro-Wilk W = 0.935437, Pr < 0.0001). The log transformed TSF of AEGL-1 passed a normality test, perhaps, due a smaller size of 51 (*n1* – Shapiro-Wilk W = - 0.890728, Pr = 0.0002, Log*n1* – Shapiro-Wilk W = - 0.978546, Pr = 0.4791). Hence a non-parametric SAS statistical procedure PROC UNIVARIATE was used to find median *n* and its confidence interval.

A relationship between median TSFs for mild/reversible (*n1*=2.88, 95% CI [2.00, 3.41], sample size=51; AEGL-1 tier), disabling/irreversible (*n2*=2.00, 95% CI [1.72, 2.07], sample size=245; AEGL-2 tier), and life-threatening effects (*n3*=1.77, 95% CI [1.50, 2.01], sample size=252; AEGL-3 tier) was $n1 > n2 \approx n3$ (Table 9).

iii. Approach 3. Similar to Approach 2 but the 5 exposure duration points were split in half in 10 min, 30 min, 1 hr subgroup 3a (short-term – $n_1 1$, $n_1 2$ and $n_1 3$) (Figure 5a) and 1 hr, 4 hr, 8 h subgroup 3b (long-term – $n_2 1$, $n_2 2$ and $n_2 3$) (Figure 5b). Using these subgroups, two TSFs were calculated for each chemical: a short- and long-term one. This approach tested whether extrapolations involving the AEGL Committee rules, which are different for short-to-long and long-to-short durations extrapolations, affect TSF statistics.

Histograms of non-log-transformed and log-transformed AEGL-derived n values derived following Apporach 3a and 3b are shown in Fig. 5a and 5b respectively. Both the non-log-transformed and log-transformed n values did not follow a normal distribution for $n_1 1$ and Log$n_1 1$ (AEGL-1short-term) with a sample size of 50 ($n_1 1$ – Shapiro-Wilk W = 0.861646; Pr <0.0001, Log$n_1 1$ – Shapiro-Wilk W = 0.90377; Pr =0.0006), $n_1 2$ and Log$n_1 2$ (AEGL-2 short-term) with a sample size of 237 ($n_1 2$ – Shapiro-Wilk W = 0.799203 Pr <0.0001, Log$n_1 2$ –

Shapiro-Wilk W = 0.914498 Pr <0.0001), $n_2 2$ and Log$n_2 2$ (AEGL-2 long-term) with a sample size of 239 ($n_2 2$ – Shapiro-Wilk W = 0.890504; Pr <0.0001, Log$n_2 2$ – Shapiro-Wilk W = 0.931843; Pr <0.0001), $n_1 3$ and Log$n_1 3$ (AEGL-3 short-term) with sample size of 251 ($n_1 3$ – Shapiro-Wilk W = 0.796874; Pr <0.0001, Log$n_1 3$ – Shapiro-Wilk W = 0.910686; Pr <0.0001), $n_2 3$ and Log$n_2 3$ (AEGL-3 long-term) with sample size of 249 ($n_2 3$ – Shapiro-Wilk W = 0.867328; Pr <0.0001, Log$n_2 3$ – Shapiro-Wilk W = 0.951932; Pr <0.0001). Both $n_2 1$ and Log$n_2 1$ (AEGL-1 long-term), passed normality test due to a smaller sample size of 49 ($n_2 1$ – Shapiro-Wilk W = -0.963603; Pr = 0.1333, Log$n_2 1$ – Shapiro-Wilk W = - 0.958277; Pr = 0.0805). Similar to approach 2, a non-parametric SAS statistical procedure PROC UNIVARIATE was used to find the median and its confidence interval of the n value raw (non-log-transformed) data.

Short-term: A relationship between median TSFs for mild/reversible ($n_1 1$=3.04, 95% CI [2.99, 7.55], sample size=50; AEGL-1 tier), disabling/irreversible ($n_1 2$=2.86, 95% CI [2.50, 2.98, sample size=237; AEGL-2 tier), and life-threatening effects ($n_1 3$=2.91, 95% CI [2.25, 3.00], sample size=251; AEGL-3 tier) was $n_1 1 > n_1 2 \approx n_1 3$ (Table 9).

Long-term: A relationship between median TSFs for mild/reversible ($n_2 1$=2.01, 95% CI [1.93, 2.40], sample size=49; AEGL-1 tier), disabling/irreversible ($n_2 2$=1.93, 95% CI [1.87, 2.01], sample size=239; AEGL-2 tier), and life-threatening effects ($n_2 3$=1.62, 95% CI [1.45, 1.87], sample size=249; AEGL-3 tier) was $n_2 1 > n_2 2 > n_2 3$ (Table 9).

Iv Approach 4. Only chemicals, whose all 5 AEGL values within a severity tier were different, were used:

Histograms of non-log-transformed and log-transformed AEGL-derived *n* values derived following Apporach 4 are shown in Fig. 6. Both the non-log-transformed and log-transformed *n* values did not follow a normal distribution for *n2* and Log*n2* with a sample size of 118(*n2* – Shapiro-Wilk W = 0.870155, Pr < 0.0001, Log*n2* – Shapiro-Wilk W = 0.961515, Pr < 0.0019), *n3*

and LOG*n3* with a sample size of 125 (*n3* – Shapiro-Wilk W = 0.857757, Pr < 0.0001,Log*n3* – Shapiro-Wilk W = 0.953951, Pr < 0.0003). The log transformed TSF of AEGL-1 passed a normality test, perhaps, due a smaller size of 20 (*n1* – Shapiro-Wilk W = - 0.880695, Pr = 0.0182, Log*n1* – Shapiro-Wilk W = - 0.975898, Pr = 0.81).Similar to Approach 2 and 3, median and its confidence interval was obtained using a non-parametric SAS statistical procedure PROC UNIVARIATE.

A relationship between median TSFs for mild/reversible (*n1*=1.69, 95% CI [1.33, 2.19], sample size=20; AEGL-1 tier), disabling/irreversible (*n2*=1.41, 95% CI [1.40, 1.70], sample size=118; AEGL-2 tier), and life-threatening effects (*n3*=1.41, 95% CI [1.40, 1.70], sample size=125; AEGL-3 tier) was $n1 \approx n2 \approx n3$ (Table 9).

IV. DISCUSSION:

In this paper TSF statistics were calculated using data from the AEGL database. Four different approaches were used. Using these statistics recommendations for temporal extrapolation of inhalation toxicity data may be developed. Generally, an empirically derived chemical-specific value for the exponent *n* available is preferred for temporal extrapolation. This value is estimated by evaluating the concentration versus response relationship for several different exposure durations and it is used to parameterize an exponential toxic load model (3) described in the Introduction. However, only for a small number of chemicals the empiric information is available. ten Berge et al (1986) report a 0.8–3.5 range for empirically-derived TSFs, which have been observed on only 20 chemicals. When empiric values of *n* are not available, AEGL committee uses a value of $n = 1$ to extrapolate from shorter to longer exposure durations and a value of $n = 3$ to extrapolate from longer to shorter durations. These rules are based off of the ten Berge et al (1986) data, which encompass approximately 90% of chemical *n* values in the 1–3 range.

In the present study, only TSFs estimated using Approach 4 were in agreement with AEGL Committee's empiric *n*-values (Table 5) and with many OEHHA and ten Berge's empiric *n*-values[6] (Table 6), but this was not true in the case of many TSFs estimated using Approach 2 and 3 except for the chemicals with all different AEGL values within a severity tier.

When an empiric *n*-value is available for a chemical, AEGL committee uses it, in most cases, for temporal extrapolation across different health-effects severity tiers. For example, ammonia's *n* value is 2.0 [13], and it has been used for estimating AEGL-2 and AEGL-3 values. Similarly, an AEGL committee-derived empirical *n* value of oxamyl is 1.6, and it has been used across all three health-effect tiers to derive the oxamyl AEGL values. Approach 4's result shows that the median *n*-values are approximately equal to 1.5 (Table 9) across AEGL-1, AEGL-2, and AEGL-3, but this is not seen in the results of other Approaches.

As seen in Table 8, *n* values derived using Approach 4 range from 0.8 to 4.7, which is in agreement with published OEHHA-derived values for *n* shown in range from 0.8 to 4.6[6]. The mean value 1.8 in this range is approximately equal to OEHHA's mean 2; the interquartile range (25%–75%) is 1.2–2.1, which is also close to OEHHA's interquartile range 1.0–2.2[6]. A distribution-free median of all TSFs derived using Approach 4 is close to 1.5 (Table 7), which is in agreement with a median of each health-effect severity level TSF (Table 9). Therefore, Approach 4 appears to be better suited for temporal extrapolation of AEGL data.

AEGL committee concluded that it is more appropriate to use a value of $n = 3$, which approximates the 90th percentile of the range of values reported by ten Berge et al (1986) to extrapolate from a longer to shorter duration. According to the present study, the 90th percentile of the range of Approach 4's *n* value (Table 7) is 2.6 (95% CI 2.4–3.5), which is statistically identical to the ten Berge and OEHHA recommended value of 3 for extrapolation from longer to shorter duration. The study derived 95th percentile of the range of approach 4's n value (Table

7) is 3.5 (95% CI 2.8–4.4). The use of n value 3.5 to extrapolate from longer to shorter duration would yield a more conservative chemical threshold concentration and provide an additional margin of safety for public health.

Approach 1's *n1* value (6.87) was much greater as compared to other approaches due to inclusion of chemicals with identical values across all 5 exposure durations. Most of such chemicals are found in the AEGL-1 tier (115 compounds). Many of the AEGL-1 critical effects are sensory irritations (non-systemic). As such, their magnitude often depends on concentration but not a mass transferred over specified time. Therefore, AEGL Committee often does not apply AEGL-2 and -3 *n*-values to the AEGL-1 tier and, accordingly, the Approach 1 *n1* value reflects this fact. Taking into account the AEGL Committee practice, a higher than 3 default *n*-value may be appropriate for the AEGL-1 tier.

V. CONCLUSIONS AND RECOMMENDATIONS:

This study examined a relationship between exposure concentration and time for three health-effect levels to derive TSFs by four different approaches. Results summarized in the present report are still preliminary. The ideal method to derive TSF is by regressing experimental values. As the experimental data are limited, concentration values and time periods from the USEPA AEGL database were used in the present study to estimate the TSFs. TSFs derived using Approach 4 were in agreement with AEGL Committee's empirically derived TSFs and also with most of Cal/EPA Office of Environmental Health Hazard Assessment (OEHHA) and ten Berge's empirically derived TSF. A range and mean of TSFs derived by Approach 4 were in agreement with the range and mean of published and OEHHA derived TSFs. In the present study, 90^{th}, 95^{th}, and 99^{th} percentiles of TSF values were derived using Approach 4. They are 2.6 (90% CI: 2.4–3.5), 3.5 (95% CI: 2.8–4.4), and 4.4 (99% CI: 3.6–4.7), respectively. Hence, a higher than 3

default value of TSF may be appropriate for extrapolation from long to short term durations. A case-by-case approach should be undertaken to evaluate the validity of the TSFs for each chemical. More experimental data for other chemicals on concentration-time-response would be valuable for expanding our knowledge about TSFs. An extensive literature search for such information would be useful in the future, which would increase scientific credibility of modern approaches to temporal extrapolation of air-borne toxicity data.

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VII. TABLES /FIGURES:

Table 1. AEGL values for boron trifluoride, [mg/m^3].

	10 min	30 min	60 min	4 hr	8 hr
AEGL-1	2.5	2.5	2.5	2.5	2.5
AEGL-2	37	37	29	18	9.3
AEGL-3	110	110	88	55	28

Table 2. Empirical Concentration and exposure duration of pentaborane.

Time (Minutes)	Concentration (ppm)	Log Time	Log Concentration
5	66.6	0.6990	1.8235
15	31.2	1.1761	1.4942
30	15.2	1.4771	1.1818
60	10.4	1.7782	1.0170

Table 3. AEGL values for adamsite, [mg/m^3].

Time	10 min	30 min	1 hr	4 hr	8 hr
AEGL-1	0.20	0.041	0.016	0.0022	0.00083

AEGL-2	9.7	6.8	2.6	0.36	0.14
AEGL-3	21	17	6.4	0.91	0.34

Table 4. Descriptive statistics of log AEGL-1, AEGL-2 and AEGL-3 values across five exposure durations (10mins, 30mins, 1 hr, 4 hr, and 3 hr) (Approach 1)

Log AEGLs (sample size)	Mean(SD)
AEGL-1 – 10mins (167)	0.26(1.48)
AEGL-1 – 30mins (167)	0.22(1.49)
AEGL-1 – 1 hr (167)	0.18(1.50)
AEGL-1 – 4 hr (164)	0.08(1.54)
AEGL-1 – 8 hr (164)	0.02(1.56)
AEGL-2 – 10mins (269)	0.96(1.44)
AEGL-2 – 30mins (265)	0.79(1.46)
AEGL-2 – 1 hr (265)	0.63(1.48)
AEGL-2 – 4 hr (262)	0.34(1.53)
AEGL-2 – 8 hr (262)	0.16(1.58)
AEGL-3 – 10mins (263)	1.55(1.40)

AEGL-3 – 30mins(260)	1.37(1.41)
AEGL-3 – 1 hr (260)	1.19(1.42)
AEGL-3 – 4 hr (257)	0.84(1.45)
AEGL-3 – 8 hr (257)	0.65(1.49)

Table 5. Comparison of AEGL committee's n-value with Approach 4 estimated n-value:

Chemical	AEGL	n1 (CI*)	n2 (CI*)	n3 (CI*)
Adamsite	0.71	0.705 (0.697–0.713)	0.859 (0.621–1.393)	0.878 (0.610–1.567)
Ethyleneimine	0.9(n2) 1.1(n3)		0.909 (0.906–0.911)	1.094008 (1.080–1.107)
Fenamiphos	4.8		4.686 (4.143–5.394)	4.736 (4.192–5.443)
Oxamyl	1.6	1.595 (1.559–1.633)	1.592 (1.539–1.650)	1.585 (1.546–1.626)
Oxygendifluoride	1.1		1.103 (1.086–1.120)	1.095 (1.089–1.101)
Pentaborane	1.3		1.290 (1.283–1.297)	1.290 (1.283–1.297)
Sodium cyanide	2.0(n1) 2.6(n3)		2.008 (1.972–2.046)	2.617 (2.189–3.254)
Trimethoxysilane	1.45		1.446 (1.401–1.494)	1.449 (1.429–1.470)
Hydrogen Cyanide	2.1(n2) 2.6(n3)		2.007 (1.961–2.055)	2.647 (2.222–3.274)

*95% Confidence Interval

Table 6. Comparison of OEHHA and Ten Berge's n-values[6] with Approach 4 estimated n-values:

Chemical	OEHHA/ten Berge**	*n1* (CI*)	*n2* (CI*)	*n3* (CI*)
Acrylonitrile**	1.1		1.094 (1.072–1.116)	1.213 (1.147–1.287)
Benzene	2.0	1.5 (1.170–1.923)	1.756 (1.423–2.292)	1.764 (1.412–2.350)
Bromine**	2.2		2.208 (2.172–2.245)	2.189 (2.098–2.288)
Carbon tetrachloride**	2.8		2.438 (2.229–2.689)	2.431 (2.339–2.530)
Ethyleneimine**	1.1		0.909 (0.906–0.911)	1.094 (1.080–1.107)
Hydrazine	2.0		1.396 (0.953–2.607)	1.399 (0.964–2.546)
Hydrogen cyanide**	2.7		2.007 (1.961–2.055)	2.647 (2.222–3.274)
Methyl hydrazine	1.0		1.000 (0.978–1.024)	1.001 (0.986–1.017)
Methyl isocyanate	1.1		0.995 (0.968–1.024)	0.998 (0.994–1.002)
Nitrogen dioxide	3.5		3.520 (3.365–3.689)	3.471 (3.236–3.742)
Toluene	2.5		2.563 (1.931–3.809)	2.450 (1.733–4.181)

*95% Confidence Interval

**ten Berge derived n value

Table 7. Descriptive statistics of all (AEGL-1, AEGL-2 and AEGL-3) the TSFs stratified by Approaches (2, 3a, 3b and 4)

	Approach 2 (n=548)	Approach 3a (n=538)	Approach 3b (n=537)	Approach 4 (n=263)
50% (CI*)	1.98 (1.76–2.04)	2.91 (2.86–2.99)	1.88 (1.83–1.91)	1.41 (1.41–1.75)
75% (CI*)	2.91 (2.87–3.07)	5.89 (4.65–7.88)	2.42 (2.38–2.46)	2.07 (1.99–2.36)
90% (CI*)	3.59 (3.47–3.88)	8.87 (8.48–8.87)	2.85 (2.81–2.98)	2.61(2.37–3.50)
95% (CI*)	4.40 (3.94–5.07)	9.16 (8.87–9.54)	3.20 (3.02–3.80)	3.51 (2.77–4.43)
Range	0.71–14.17	0.71–18.79	0.70–6.19	0.81–4.71

*95% Confidence Interval

Table 8. Comparison of descriptive statistics of published/OEHHA[6] estimated and Approach 4 derived TSF.

	OEHHA	Approach 2	Approach 3a	Approach 3b	Approach 4
Range	0.8–4.6	0.7 –14.2	0.7–18.8	0.7–6.2	0.8–4.7
Mean	2.0	2.4	3.8	1.9	1.8
Interquartile range	1.0–2.2	1.4–2.9	1.3–5.9	1.2–2.4	1.2–2.1

Table 9. Distribution free median and 95% confidence interval (CI) of Approach 2, 3a, 3b and 4 derived TSF of AEGL-1, AEGL-2 and AEGL-3.

	Approach 2	Approach 3a	Approach 3b	Approach 4
AEGL-1 Median(CI)	2.88 (2.00–3.41)	3.04 (2.99–7.55)	2.01 (1.93–2.40)	1.69 (1.33–2.19)
AEGL-2 Median(CI)	2.00 (1.72–2.07)	2.86 (2.50–2.98)	1.93 (1.87–2.01)	1.41 (1.40–1.70)
AEGL-3 Median(CI)	1.77 (1.50–2.01)	2.91 (2.25–3.00)	1.62 (1.45–1.87)	1.41 (1.40–1.70)

Figure 1. Simple regression fits of pentaborane log (AEGLs) against log (time)

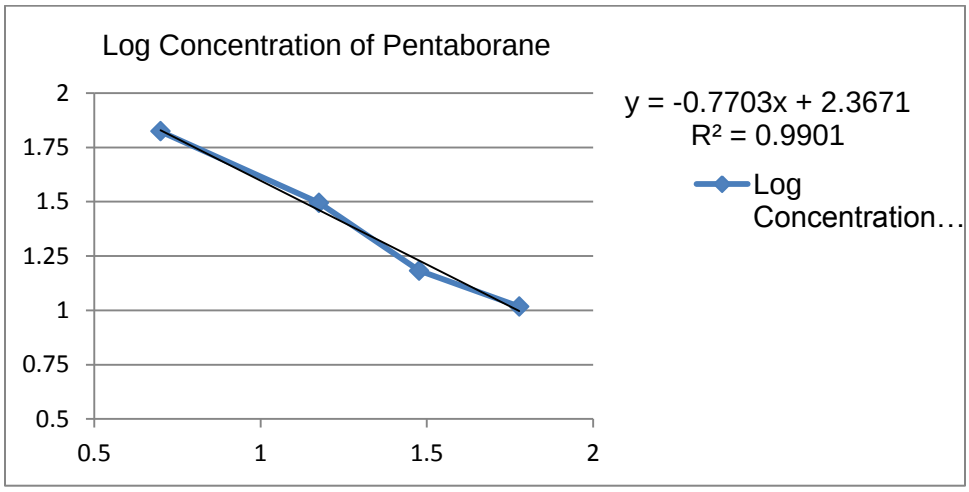

Figure 4. Approach 2: Histograms of non-log-transformed and log-transformed AEGL-derived *n* values

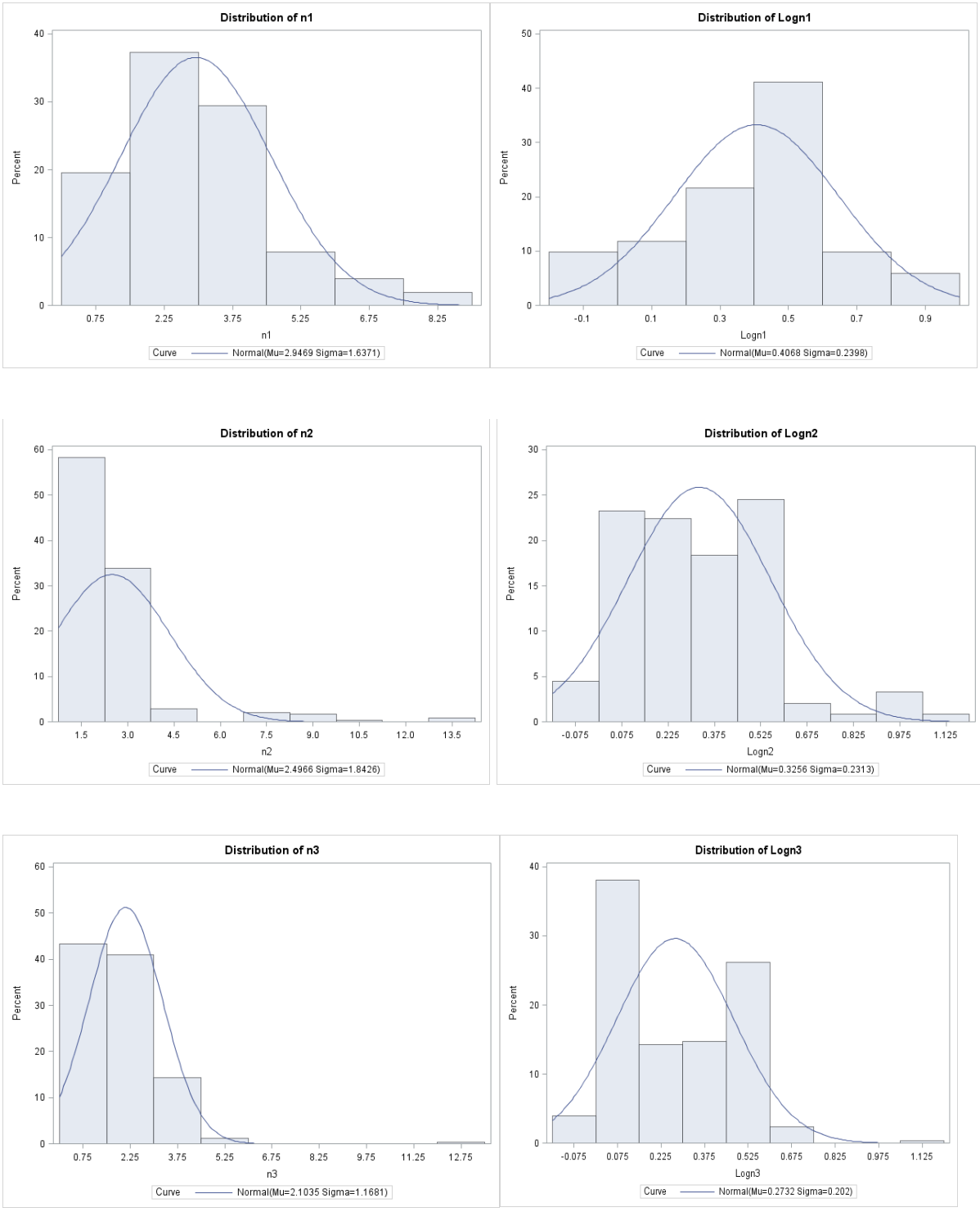

Figure 5. Approach 3: Histograms of non-log-transformed and log-transformed AEGL-derived *n* values

Figure 5a. Short-term exposure (Approach 3a)

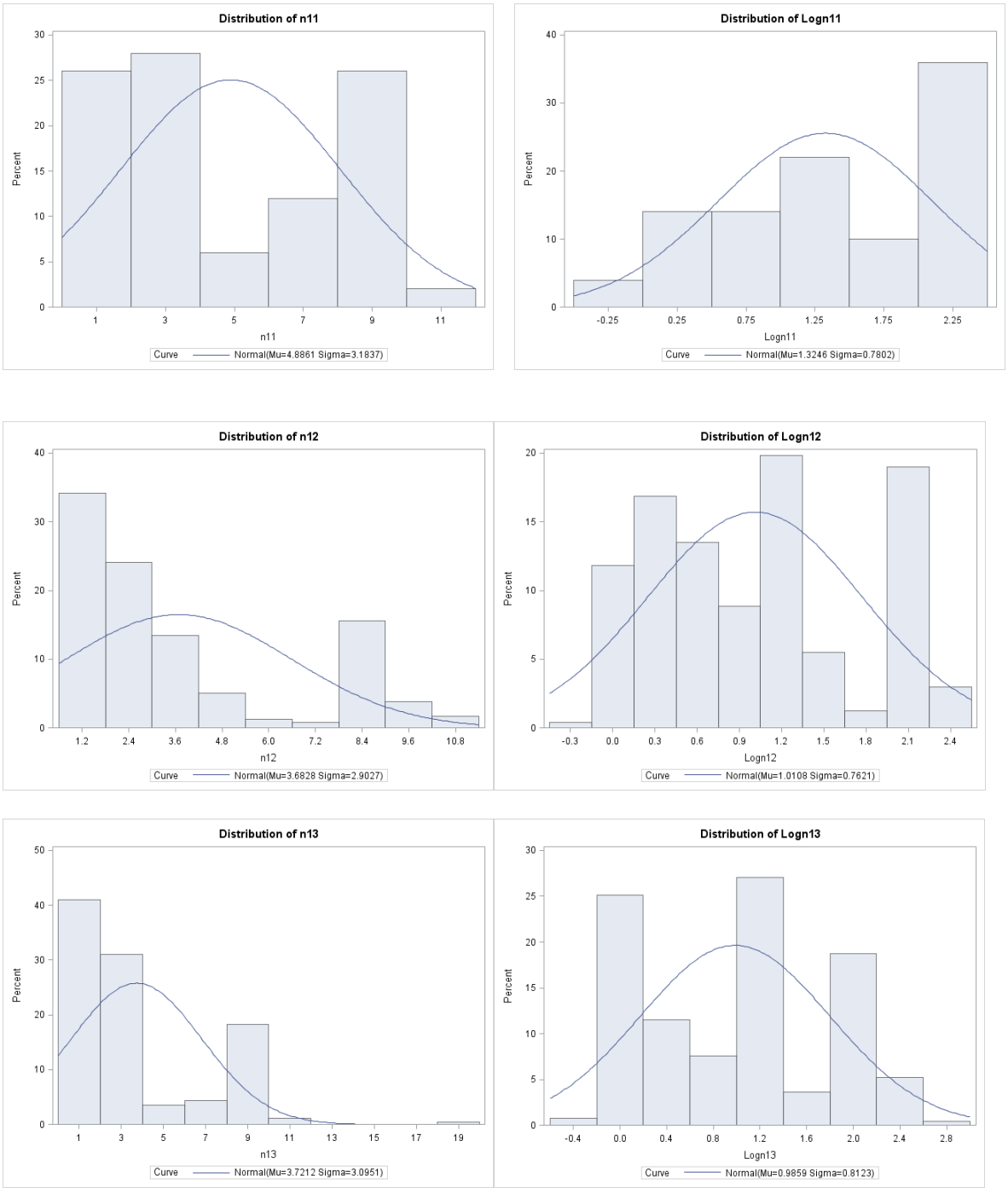

Figure 5b. Long-term exposure (Approach 3b)

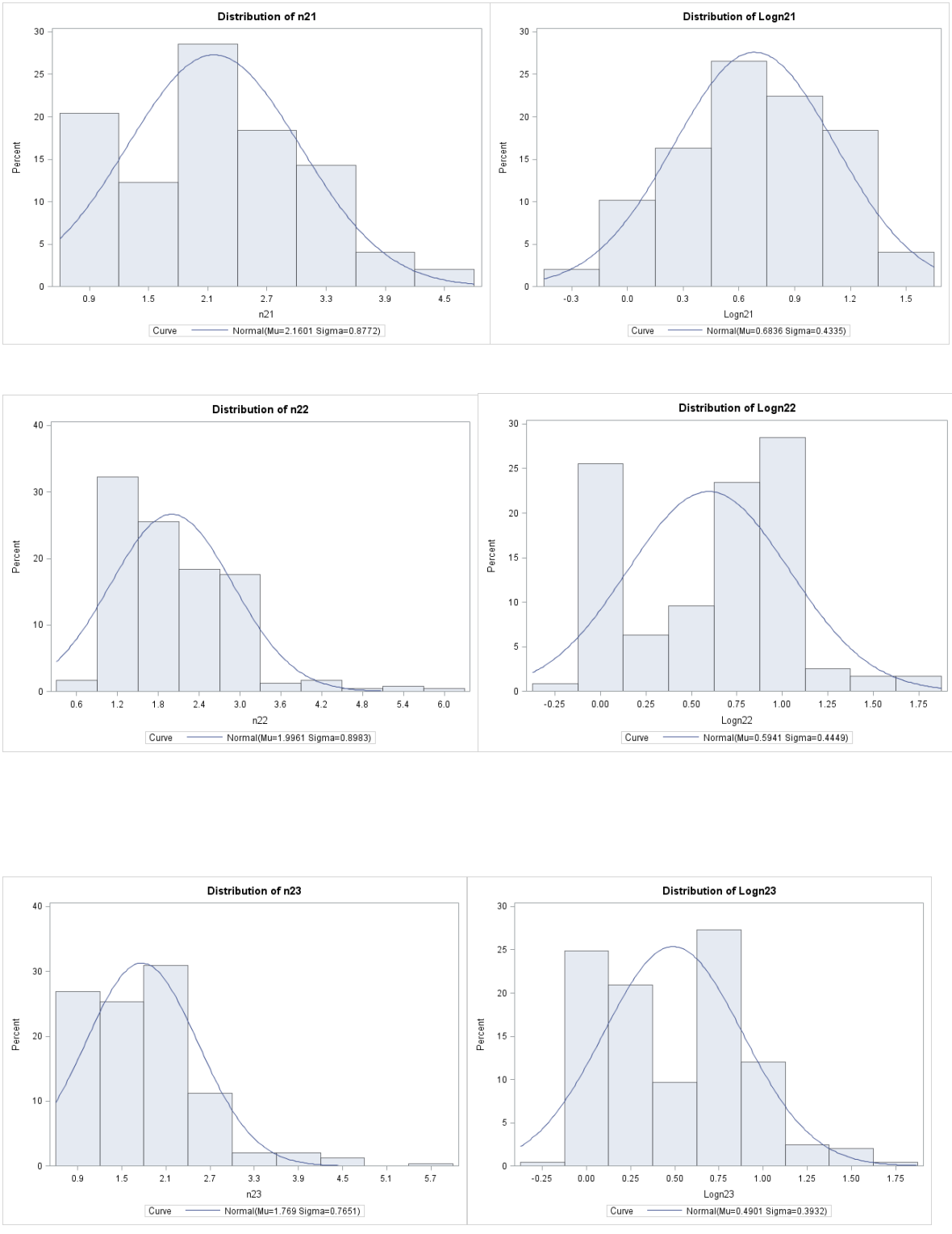

Figure 6. Approach 4: Histograms of non-log-transformed and log-transformed AEGL-derived *n* values