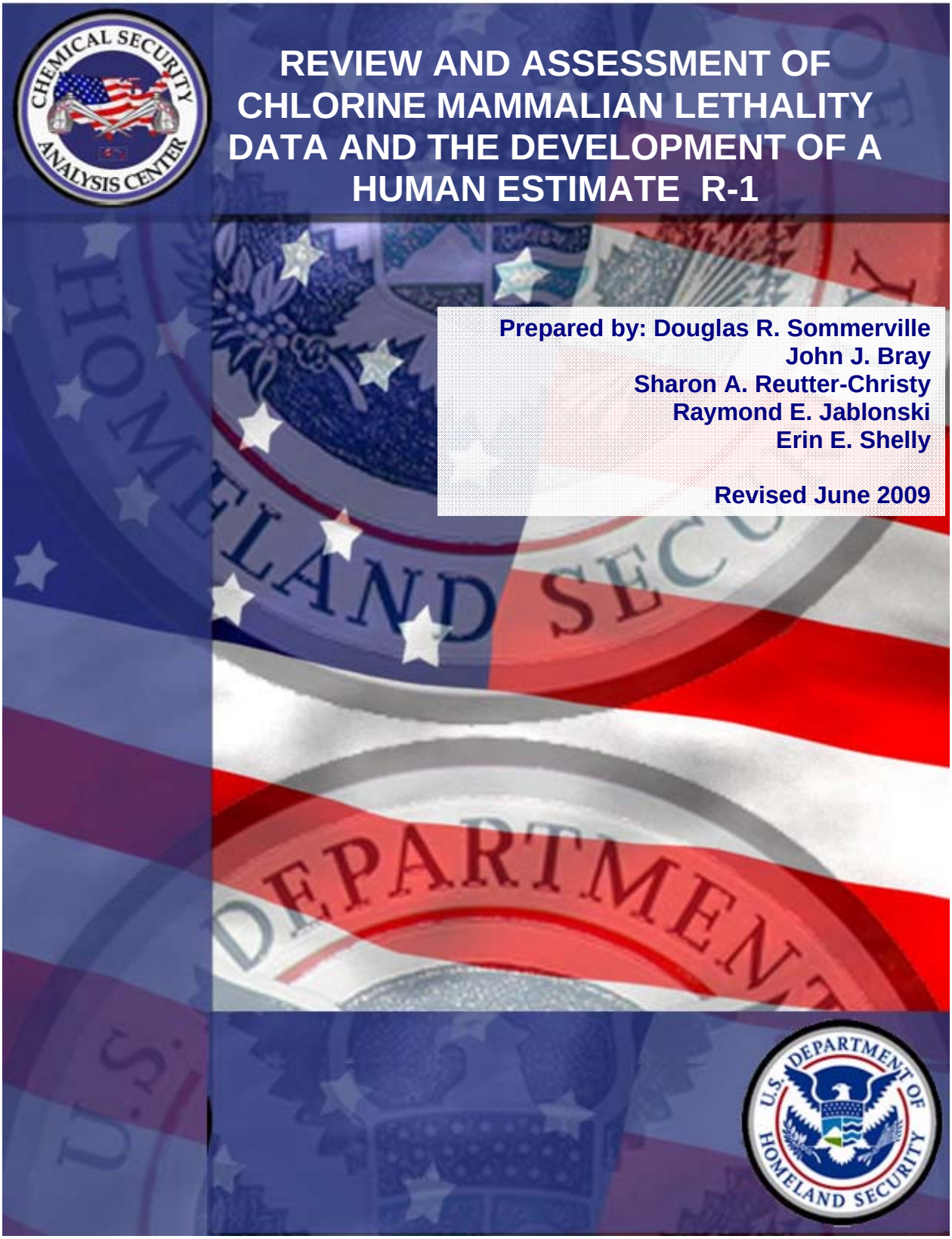

REVIEW AND ASSESSMENT OF CHLORINE MAMMALIAN LETHALITY DATA AND THE DEVELOPMENT OF A HUMAN ESTIMATE R-1

Prepared by: Douglas R. Sommerville
John J. Bray
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Raymond E. Jablonski
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Prepared by:

Douglas R. Sommerville
Sharon A. Reutter-Christy
Erin E. Shelly
Research and Technology Directorate
US Army Edgewood Chemical Biological Center
Aberdeen Proving Ground, MD

John J. Bray
OptiMetrics, Inc.
Abingdon, MD 21009

Raymond E. Jablonski
Chemical Security Analysis Center
U.S. Department Of Homeland Security
Aberdeen Proving Ground, MD

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Douglas R. Sommerville
John J. Bray
Sharon A. Reutter-Christy
Raymond E. Jablonski
Erin E. Shelly

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14. ABSTRACT
New human estimates for chlorine inhalation lethality as a function of exposure duration (for a healthy subpopulation and the general population) were derived via a review and statistical analysis of existing mammalian lethality data. Median lethal dosage and quantal response data were found and analyzed for eight species (mouse, rat, guinea pig, rabbit, cat, dog, goat and sheep) and for durations (T) from 8 min to 235 min. Resulting human estimates were expressed via the toxic load model, $L(C^nT)_{50} = k$, where n = 2.75 and k = 6.79×10^{10} (military) or 2.58×10^{10} (general), with C in mg/m^3 and T in minutes. For 2-min exposures, LCT_{50} equals 13,500 and 9500 mg-min/m^3, for military and general population, respectively. The base 10 probit slope (concentration) was estimated to equal 8.0 (military) and 6.0 (general). Previous human estimates were reviewed, and one study identified as corresponding to the lower confidence limit for the new estimate. The impact of the new estimate was evaluated through a series of transport and dispersion modeling runs using the general population estimate. The predicted downwind hazard distances were consistent with what has been witnessed historically.

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ABBREVIATIONS AND ACRONYMS

Abbreviation and Acronym	Definition
AEGL	Acute Exposure Guideline Level
ALOHA	Areal Locations of Hazardous Atmospheres
ATD	atmospheric transport and dispersion
AFMIC	Armed Forces Medical Intelligence Center
APG	Aberdeen Proving Ground
ASHRAE	American Society of Heating, Refrigerating, and Air-Conditioning Engineers
ATD	atmospheric transport and dispersion
BA	blood agent
CA	chemical agent
CATS	Consequence Assessment Toolset
CBRN	Chemical, Biological, Radiological, Nuclear
CBRNE	Chemical, Biological, Radiological, Nuclear, Explosives
CDC	Centers for Disease Control
CDS	Civil Defense Simultest
cfm	cubic feet per minute
CI	confidence interval
CIA	Central Intelligence Agency
cm	centimeter
CMS	Chip Measurement Systems
CSAC	Chemical Security Analysis Center
CT	concentration time (effective dose)
CTRA	Chemical Threat Risk Assessment
CWA	chemical warfare agent
DHS	Department of Homeland Security
DoD	Department of Defense
DTRA	Defense Threat Reduction Agency
EC_{xx}	effective concentration producing effects in xx% of exposed population
ECBC	Edgewood Chemical Biological Center
ED_{xx}	effective dosage producing effects in xx% of exposed population
EOD	explosives ordnance disposal
EPA	Environmental Protection Agency
eq	equation
ERDEC	Edgewood Research and Development Engineering Center
ERPG	Emergency Response Planning Guidelines
ETV	Environmental Technology Verification
FacDAC	Facilities Weapons of Mass Destruction Decision Analysis Capability
FBI	Federal Bureau of Investigation
ft	feet or foot
h	hour

Abbreviation and Acronym	Definition
HHS	Health and Human Services
HPAC	Hazard Prediction and Assessment Capability
HSE	Health and Safety Executive
ICT_{xx}	incapacitating concentration (dosage) producing incapacitation in xx% of exposed population
ICD	improvised chemical device
in	inch
IRLS	iteratively reweighted least squares
L	liter
LANL	Los Alamos National Laboratory
lb	pound
LCT_{xx}	lethal concentration (dosage) producing lethality in xx% of exposed population
LD_{xx}	lethal dose producing lethality in xx% of exposed population
LT_{xx}	lethal toxicity producing lethality in xx% of exposed population
LTL_{xx}	lethal toxic load producing lethality in xx% of exposed population
kg	kilogram
km	kilometer
m	meter
mgd	millions of gallons per day
mg/m^3	milligram per meter cubed
mi	mile
min	minute
MHAP	Major Hazards Assessment Panel
mL	milliliter
MLE	maximum likelihood estimation
M/T	metric ton
MW	molecular weight
n	toxic load exponent
NATO	North Atlantic Treaty Organization
NHSRC	National Hazardous Substance Research Center
NIAID	National Institute of Allergies and Infectious Diseases
NIH	National Institutes of Health
NOAA	National Oceanic and Atmospheric Administration
pdf	probability density function
PPE	personal protective equipment
ppm	parts per million
RDECOM	Research Development and Engineering Command
s	second
SBCCOM	Soldier Biological and Chemical Command

Abbreviation and Acronym	Definition
SCIPUFF	Second-order Closure Integrated Puff
SE	standard error
SME	Subject Matter Expert
SNL	Sandia National Laboratories
SSD	sum of squared differences
T	time (exposure duration)
TEEL	Temporary Emergency Exposure Limits
TL	toxic load
U.S.	United States
USACHPPM	U.S. Army Center for Health Promotion and Preventive Medicine
USAMRICD	U.S. Army Medical Research Institute of Chemical Defense
WINPAC	Weapons Intelligence Non-Proliferation and Arms Control Center
wk	week
WW	World War

EXECUTIVE SUMMARY

New human estimates for chlorine inhalation lethality as a function of exposure duration (for a healthy subpopulation and the general population) were derived via a review and statistical analysis of existing mammalian lethality data. Median lethal dosage and quantal response data were found and analyzed for eight species (mouse, rat, guinea pig, rabbit, cat, dog, goat, and sheep) and for durations (T) from 8 min to 235 min. Resulting human estimates were expressed via the toxic load model, $L(C^nT)_{50} = k$, where n = 2.75 and $k = 6.79 \times 10^{10}$ (military) or 2.58×10^{10} (general), with C in mg/m^3 and T in minutes. For 2-min exposures, LCT_{50} equals 13,500 and 9500 mg-min/m^3, for military and general population, respectively. The base 10 probit slope (concentration) was estimated to equal 8.0 (military) and 6.0 (general). Previous human estimates were reviewed, and one study identified as corresponding to the lower confidence limit for the new estimate. The impact of the new estimate was evaluated through a series of transport and dispersion modeling runs using the general population estimate. The predicted downwind hazard distances were consistent with what has been witnessed historically.

REVIEW AND ASSESSMENT OF CHLORINE MAMMALIAN LETHALITY DATA AND THE DEVELOPMENT OF A HUMAN ESTIMATE

STATISTICAL ANALYSIS OF CHLORINE LETHALITY DATA

1.0 Introduction

Chlorine is a greenish-yellow, highly reactive halogen gas that has a pungent, suffocating odor. It is widely used in industry and as a biocide in water and waste treatment plants. Because of its extensive use and toxicity, it has been the subject of many toxicological studies, human toxicity estimates (ranging from threshold mild effects to lethality for various populations) and other general reviews and commentary. Many of these previous efforts have focused on creating toxicity estimates that would be appropriate for protecting a human population from an accidental chlorine release. However, many risk assessment applications require an accurate estimate of a chemical's actual toxicity and thus should not be conservative just to be on the safe side. At present, casualty predictions for accidental chlorine releases are at odds with what has been observed historically. Either the present human toxicity estimates are too low, the currently popular atmospheric transport and dispersion (ATD) models cannot adequately model chlorine releases, or both.

The purpose of this study is to reevaluate the human lethality estimate as a function of duration for chlorine inhalation exposures involving a healthy human population. These estimates are meant for use in performing risk assessments involving chlorine airborne releases. To accomplish this, an allometric modeling approach was used to extrapolate a human estimate from suitable data in the existing mammalian toxicity database. Included in the analysis is the estimate of a probit slope for a healthy (military-type) adult population. In addition, estimates for the general population were also developed based upon the military-type estimates using the mathematical method of Crosier (2007).[1] General population estimates are compared to those of previous researchers.

2.0 Statistical Background

The development of human toxicity estimates is often a multidisciplinary endeavor. In this section, several important topics are presented that aid in understanding the development of a human toxicity estimate for chlorine.

2.1 Allometric Modeling

The dependence of a biological variable X on body mass M is typically characterized by an allometric scaling law of the form:

$$X = X_0 M^b \quad (1)$$

where b is the scaling exponent and X_0 a constant that is characteristic of the kind of organism involved.[2] These two coefficients can be estimated via the linear regression fit of X versus M on a log-log scale, where the slope and y-intercept of the resulting line equal b and $\log(X_0)$, respectively. For biological parameters (such as blood volume and oxygen diffusing capacity) that scale as a function of the volume of the animal, b is predicted and generally observed (from experimental data) to equal one.[2]

In inhalation toxicology, the dose received by an animal is directly related to the amount of air inhaled.[3,4,5] Minute volume (V_M)[a] is a commonly used respiratory measurement, and Bide *et al.*[6] have reviewed the existing mammalian minute volume data (as well as species body mass) for the purpose of supporting inhalation toxicology research. Table 2–1 lists some average minute volume and species body mass values for non-anesthetized mammals. An empirical relationship (for both anesthetized and nonanesthetized animals) of the minute volume as a function of M has also been developed.[6] Based upon allometric scaling law, V_M should scale to the 0.75 power, but Bide *et al.*[6] found that V_M scales to the 0.809 power based upon the available experimental data for nonanesthetized, adult mammals:

$$V_M = (0.499) M^{(0.809)} \quad (2)$$

where V_M is in L/min and M is in kg. Bide *et al.* calculated a value of 15.5 L/min for a 70 kg man from eq 2. This is very close to the standard value of 15 L/min for light activity used by DoD as a basis for their toxicity estimates for a 70 kg soldier.[7] Bide *et al.* further note that their equation is for normally breathing, nonanesthetized mammals engaged in mild activity; it is not a resting value.

Table 2–1. Summary of mammalian (nonanesthetized) minute volume values from Bide *et al.* (2000)

SPECIES	MASS (KILOGRAMS)	MINUTE VOLUME EXPT. AVERAGE (LITERS)	MINUTE VOLUME ALLOMETRIC MODEL FIT (CUBIC METERS)	V_M RATIO (EXPT./FIT)
Mouse	0.0207	0.0310	0.0217	1.431
Rat	0.261	0.203	0.168	1.206
Guinea Pig	0.323	0.182	0.200	0.910
Rabbit	2.77	1.453	1.138	1.277
Cat	3.36	0.845	1.330	0.635
Dog	13.0	4.230	3.975	1.064
Goat	36.9	9.600	9.243	1.039
Sheep	52.6	13.90	12.31	1.129
Human (Male)*	70	15	15.5	0.967

* US Army Chemical School, *Potential Military Chemical/Biological Agents and Compounds*, FM 3-11.9. US Army Training and Doctrine Command, Fort Monroe, VA, 10 January 2005.

[a]Minute volume equals the tidal volume multiplied by the number of breaths per minute. The tidal volume equals the volume of air inspired or expired during each breath.

For typical whole body exposures, the exact dosage inspired by an individual animal is usually not measured. In place of the exact dosage, a nominal dose (mg) can be calculated by multiplying the lethal inhalation dosage, (mg-min/m^3) (estimated from experimental toxicology data) by the minute volume (m^3/min):

$$LD_{50} = V_M \times LCT_{50} \quad (3)$$

where LD_{50} is the nominal dose lethal to 50% of exposed individuals and LCT_{50} is the lethal concentration-time (or inhalation dosage) to 50% of exposed individuals. If the LD_{50} is expressed on a per unit mass basis (or 0.809 – 1), then it will scale to the -0.19 power based upon eq 2 and eq 3 [and assuming that the observed LCT_{50} values (at some set duration) do not vary between different species for a particular toxicant]. So, in such a situation, larger mammals are more sensitive than smaller mammals.

However, many other factors influence toxicity, and some of these factors (i.e., metabolic, circulatory, etc.) may also scale allometrically in their effect. Allometric modeling can be used to empirically account for the cumulative effect of these factors and scale the nominal LD_{50} (mg) as a function of species body mass, as shown in eq 4. A human estimate can then be obtained from mammalian data by extrapolating to a 70 kg human.

$$LD_{50} = X_0 M^b \quad \text{or} \quad \log(LD_{50}) = \log(X_0) + b\log(M) \quad (4)$$

In eq 4, both the regressor term (LD_{50}) and the predictor term (M) are both highly correlated with the parameter, V_M. Controversy exists over regressions involving predictor and regressor variables sharing a common term, which dates back to 1897[8] and has continued to this day.[9-22] The common charge is that such regressions return spurious correlations. It is not within the scope of the present work to address this controversy in detail. The statistical community has rejected the notion that these types of regression are statistically invalid, but many individuals in the greater scientific community have not kept abreast of these statistical advances.[9,10,13]

Nonetheless, care still must be taken with these types of regressions. According to Prairie and Bird,[13] the correlation between such composite variables is always legitimate provided: (1) they satisfy the assumptions of correlation analysis; (2) the variables are meaningful, that is they represent the concepts of interest and not just a component of them; and (3) the variables do not share a large measurement error term. In the present work, the first point is addressed in the data analysis and results sections of this report. The second point is satisfied—the variables do properly represent concepts of interest for this problem. For the last point, the measurement error is vastly overshadowed by the amount of random error present in the values for LCT_{50} (and hence the nominal LD_{50}), M, and V_M. Also, though V_M is correlated with M, these parameters are (in practice) measured separately and independently of each other—they do not share a measurement error term.

As a further precaution, LC_{50} was substituted for LD_{50} in eq 4. Predictions from this fit were then compared to the LD_{50} fit as a check of the appropriateness of the LD_{50} model.

2.2 Inhalation Dose-Response Statistics and the Toxic Load

For each individual, there is a dose or dosage that is just sufficient to produce a specified biological response. These just-sufficient dosages are called effective dosages (ED) to distinguish them from administered dosages. The statistical properties of this response distribution have been extensively reviewed[23,24] and summarized.[25,26] One of the more important aspects of effective dosages is that the distribution of effective dosages for a homogeneous population is usually lognormal. The severity and probability of effects experienced depends primarily on the amount of toxic material received. When the just-sufficient dosage for an effect is relatively insensitive to exposure duration, the calculation of the probability of effect is straightforward. However, when the effective dosages are a function of exposure duration, a different approach is required. Instead of quantifying the amount of toxic material in terms of dosage, a new term, toxic load (TL), has been developed and extensively used in inhalation toxicology to predict the probability and severity of the response.[27-34] Toxic load is normally expressed as some function of vapor concentration (C) and exposure duration (T), with toxic load

equaling C^nT being a typical form and n being the toxic load exponent. Sommerville *et al*.[33] provide a summary of the theory and application of the toxic load model.

The same statistical theory used for measures of dose and dosages[23] has also been adopted for use with toxic load.[29-31,35-40] The following discussion has been largely extracted from a brief review by Crosier and Sommerville[25] of the statistical theory behind dose response. Where the substitution of toxic load for dosage is not straightforward, it is specifically noted.

A plot of the density function for the normal distribution of log(effective dosage), produces the well-known bell-shaped curve.[41] The two parameters most often used to characterize a normal distribution are its mean μ and variance σ^2 (or standard deviation, σ).[42] Using these two parameters, every normally distributed random variable X can be standardized to a standard normal random variable Z:

$$Z = \frac{(X - \mu)}{\sigma} \qquad (5)$$

In toxicology, X is usually the common logarithm of the dosage.

Although statisticians typically describe the lognormal distribution of effective dosages by the mean and variance of log(ED), toxicologists usually describe the distribution by the median effective dosage, ED_{50}, and the probit (or Bliss) slope, m:

$$ED_{50} = \text{antilog}(\eta) \qquad (6)$$

$$m = 1/\sigma \qquad (7)$$

where η is the median of log(effective dosage). The median effective dosage, $ED_{50,}$ is the dosage at which 50% of the exposed individuals will exhibit a specified biological response. For vapor exposures, the equivalent dosage term is the 50% effective concentration (EC_{50}) or the product of the exposure concentration and exposure time (ECT_{50}).[25] Median effective dosages are in the original units, not in logarithms of the original units, and hence are easier to interpret than μ. Although the mean μ and median η of a normal distribution are the same ($\mu = \eta$), this property does not hold for a lognormal distribution.

Effective dosages for response levels other than 50% can be calculated from μ and σ, by solving for X in eq 1 and using the Z value corresponding to the cumulative probability of interest. The 50% response level corresponds to a Z value of zero. Tables of cumulative probabilities and their corresponding Z values are found in standard statistical textbooks[41,42] or obtained using statistical software.[43]

Toxicologists traditionally use base 10 logarithms to calculate the probit (Bliss) slope,[23,44] while engineers often use natural logarithms.[30,31,35,37] Probit slopes based on both natural and base 10 logarithms are found in the literature. Care must be exercised when comparing probit slopes from different sources.

The probit slope equals the number of standard deviations (ΔZ) corresponding to a factor of either 10 or e (= 2.718 . .) change in ED.[45] Thus, a probit slope (base 10) of six means that a factor of 10 change in ED corresponds to six standard deviations (ΔZ = 6). For the normal distribution, a range of Z from negative four (very sensitive individuals) to four (highly tolerant individuals) (or ΔZ = 8) encompasses over 99.99% of the total population. If the toxicant has a probit slope of eight, a factor of 10 separates the effective dosages for these two Z values. The higher the probit slope, the closer the two tails of the distribution are in terms of ED (in other words, there is less variance in the effective dosages of the population).

Though the normal distribution is continuous, quantal data (response versus no response) are used to estimate the parameters (median and probit slope) of the distribution of effective dosages.[23,46] Probit analysis and maximum likelihood estimation (MLE) are used to estimate these parameters from experimental data.[23,29,47] The following equation is fitted via probit analysis/MLE for vapor toxicity studies:[23,29,30,31]

$$Y_N = (Y_p - 5) = k_o + k_c \, logC + k_t \, logT \qquad (8)$$

where Y_N is a normal probability unit (or normit), Y_P is a probability unit (or probit), the k's are fitted coefficients, C is vapor concentration, and T is exposure time. Normit values of -2, -1, 0, 1 and 2 correspond to percent effect probabilities of 2.3, 15.9, 50.0, 84.1 and 97.7%, respectively. The constants k_c and k_t are the probit slopes for

concentration and time, respectively. The toxic load exponent (n) equals the ratio of these two slopes, or (k_c/k_t). Often, experiments are conducted with exposure time held constant, which reduces eq 8 to the traditional probit equation.[23] Thus, the probit slope for a vapor exposure usually refers to the slope on vapor concentration ($m = k_c$) instead of the slope on exposure duration. Some studies report a probit slope for the toxic load.[29,39,40,48-51] Thus, when comparing probit slope values from various studies, a common basis has to be used.

When fitting eq 8 or similar probit model, all variability in the data will contribute to the estimate for m, be it from variance due to individual susceptibilities, batch effects, experimental error, differences in exposure durations, etc. Thus, there is an experimental bias towards producing lower-than-actual slope estimates. The precision of the probit slope estimation generally improves as more subjects are used. Probit analysis performed on a compilation of data from many sources will not produce an accurate measure of variance among individuals due to the heterogeneity introduced by differences among the studies (e.g., experimental procedures, type of animals used, etc.).[49] The effect of such heterogeneity will be to lower the probit slope. Also, using a compilation of data from many sources can complicate the accurate estimation of the toxic load exponent.[29] For studies involving more than one exposure duration, fitting eq 8 with T treated as a factor (instead of as a covariate) will produce the best overall probit slope estimate for the whole study.[52,53]

A straight comparison between slope values can be misleading because of the large variability among experimental studies (e.g., a study based on 100 animals probably has a more precise estimate than a study based on 30 animals). In the present work, a different approach was taken towards the issue of obtaining an average probit slope value from among several studies (considering all the potential pitfalls mentioned above). For each study where the original quantal response data were available, a probit slope estimate with its corresponding standard error was generated via probit analysis. Then, a weighted average of all the individual probit slope estimates was taken using the standard errors of the individual slope values as the basis to generate the weights (see Section 5.1.1).

When toxic load is being used as the measure of toxicant amount received by an individual, eq 8 is usually written in the following form:

$$Y_N = k_o + k_{TL} \log TL \qquad (9)$$

with k_o and k_{TL} being fitted coefficients, and k_{TL} being the probit slope on a toxic load basis.

It should be recognized that the toxic load relationship (in eq 9) is based more on empirical observations rather than on basic biological theories.[29,30,31,35] As a result, eq 9 needs to be derived empirically on an individual toxicant basis from acute toxicity experiments where both vapor concentration and exposure duration are varied.[54] However, the value for the toxic load exponent can offer some insight into the influence of underlying toxicological mechanisms (i.e., metabolic detoxification) involved in a particular toxicant exposure.[35] For instance, it can be argued that if the toxic load exponent is greater than one for a particular chemical exposure, then significant detoxification may be occurring during the exposure, since in this situation the required effective dosage is increasing as the dosage is incurred over a longer exposure duration. Slowing the rate of dosage administration gives any existing detoxification mechanism a chance to function, thereby causing an increase in the ECT_{50} as a function of time.

When performing an allometric regression fit of inhalation dose data, eq 4 is expanded to the following form to account for the time dependency of the toxicity:

$$\log(LD_{50}) = \log(Y_0) + k_m \log(M) + k_t \log(T) \qquad (10)$$

Using eq 10, it can be shown algebraically that the toxic load exponent (n) equals [1 / (1 – k_t)]. Once the appropriate values for M and V_M are substituted into the equation, eq 10 can be written in a toxic load form (eq 9).

Fluctuations in the concentration-time profile can have a major impact on toxic load calculations. Unfortunately, their exact impact cannot be accurately determined due to the absence of experimental dose-population response curve data taken under such conditions (see Sommerville *et al.*[33] for a review of the issue). The theorized impact for chemicals with $n > 1$ is that fluctuations will increase the toxic effect of the inhalation exposure. Fluctuations are usually more

pronounced in the area around the point of release and are less of an issue further downwind. So, the potential impact of the currently perforce assumption of toxicity being independent of concentration fluctuations will likely decrease in magnitude as the downwind distance increases.

2.3 Statistical Treatment of Historical Data

An important issue when analyzing historical data is how to properly judge and quantify the quality of data that was collected over a span of decades, by many different researchers, and among a wide variety of experimental facilities. It is difficult to be truly objective with such a task. With linear regression analysis, the use of weights technically permits putting a numerical value on the quality of a datum, but how does the analyst properly estimate the weight's value? Often,a measured response does have an estimated error associated with it, and this can be used as the basis for calculating a weight. However, this type of error term is more a measure of precision than of accuracy, and who is to say which laboratory was more accurate 50 years ago even though they may have been less precise? A solution to this problem is the use of one of many robust regression methods that have been developed.[47,55,56]

For the present study, the iteratively reweighted least squares (IRLS)[47,55,56] method was used. The IRLS method does not involve making an *a priori* decision on what weight values to use. Instead, through an iterative process, the weight of a datum is calculated as some function of its residual (i.e., the difference between the actual value and that predicted from the regression fit) from the previous iterative step. Often, the standardized[b] residual (a residual divided by an estimate of its standard deviation) is used,[55] but for this study the studentized deleted residual was used instead. The studentized deleted[c] residual of an observation uses a predicted value from a regression fit omitting the observation, and it is more sensitive to outliers than the standardized residual. Weights based on deleted residuals will be less than those based on standardized residuals (all other factors being equal).

2.4 Military Subpopulation versus General Population in Toxicity Sensitivity

It is assumed that only healthy animals were used in the studies reviewed for this work. Consequently, when scaling from smaller mammals up to humans, the derived estimate should correspond to a healthy human sub-population. In this case, a healthy subpopulation is being defined as being healthy and fit enough to serve in the military (which would be healthier than what would qualify for the working subpopulation). However, this does not address the issue of the more vulnerable portions of the general population. Several studies have attempted to account for this difference in population sensitivity[34,39,40,51,57-59] in the formulation of their toxicity estimates. For this study, it is assumed that the vulnerable subpopulation can be adequately modeled using eq 5 if a probit slope and median effective dose for the general (or whole) population were used. The vulnerable subpopulation would be accounted for by using the lower tail of the bell distribution. Thus, the key is to change the basis (from healthy subpopulation to general population) of the probit slope and median effective dose values that were derived using the mammalian data.

In a series of three technical reports,[1,26,60] Edgewood Chemical Biological Center (ECBC) has developed a mathematical method for the conversion from one population basis to another, with Crosier[1] presenting the final version of the method. The premise of the approach (see Appendix I for a more detailed description) is that mathematically the distribution of log(doses) for a healthy subpopulation is located completely within the distribution formed by the general population (i.e., the smaller bell curve is inside the larger bell curve). A major advantage to Crosier[1] is that it reduces the amount of subjectivity that has been used in the past in accounting for population differences.

[b] Also known as an internally studentized residual.
[c] Also known as a deleted t or externally studentized residual.

3.0 Historical Chlorine Data and Human Toxicity Estimates

3.1 Toxic Action of Chlorine Inhalation on Animals and Humans

Chlorine is an acute respiratory irritant in both animals and humans, producing a similar spectrum of toxic responses (from minor irritation to death) as the exposure concentration increases.[27,34,58,61] It reaches the lungs because it is only moderately soluble in water, and it is not totally absorbed in the upper respiratory tract at high concentrations.[58]

In animal studies, the cause of death for acute exposures is almost always recorded as pulmonary edema, probably due to damage to the alveolar membranes.[27,34] Occasionally, reports relating to very high concentrations of chlorine over short exposure durations list other causes of death, such as broncho-constriction, shock, and immediate respiratory arrest. Postmortem examinations of fatalities resulting from accidental or wartime human exposure to chlorine have revealed pulmonary edema, with or without cardiac complications, as the cause of death. The effect of edema is to cause a reduction in the supply of oxygen from the lungs to the blood. Death can occur within hours or may not occur for a couple of days post-exposure. Delayed deaths can be due to secondary pneumonia. Thus, effects of acute inhalation are qualitatively similar in animals and humans.

It has been concluded by the Major Hazards Assessment Panel (MHAP) that there is little basis for supposing that the sensitivity of humans to chlorine is significantly different from that of small mammals.[27,34] They noted several factors:

(1) The alveolar membranes between humans and mammals are not likely to differ significantly in their intrinsic sensitivity to chlorine.

(2) The volume of air breathed per unit time, per unit body weight for mice or rats at rest is approximately ten times that for humans at rest, suggesting that small animals may deliver a higher proportion of a given dose of chlorine to their lungs and thus be more sensitive than humans. However, active humans (in an escape scenario) have a breathing rate that will reduce this ratio (when compared to subdued rodents in experiments) to approximately two or less. Thus, differences in species breathing rates are likely to have little impact.

(3) Rodents are obligate nose breathers, whereas dogs and humans are not. The nose has the potential for removing chlorine before it can make it to the lungs. However, Alarie[62] found that the LC_{50} for tracheally cannulated mice was about two times lower in the LC_{50} for normal mice. The MHAP concluded that this factor difference is unlikely to lead to a significant difference between rodents and humans.

3.2 Previous Human Lethality Estimates for Chlorine Inhalation Toxicity

There are several excellent reviews of the body of chlorine inhalation toxicity information available. One of the more recent is Mannan,[27] as well as the 1987 monograph by the MHAP sponsored by the Institution of Chemical Engineers.[34] Human estimates from five previous studies were investigated for comparison with the results of the present work:

(1) Eisenberg *et al.*[57]

(2) Perry and Articola[63]

(3) ten Berge and van Heemst[51]

(4) Rijnmond Report/Harris and Moses[59,64]

(5) Withers and Lees[39,40]

All five studies recognized that the inhalation toxicity of chlorine varies with exposure duration, and they used the toxic load model to describe the relationship (see Section 2.2). Nonetheless, these studies do differ in their philosophies on how to best extrapolate from animal data to produce a final human estimate.

Eisenberg *et al.*[57] and Perry and Articola[63] are related works that were written in support of the U.S. Coast Guard's Vulnerability Model, with chlorine being one of many chemicals for which human toxicity estimates were collected or derived. They reviewed the existing mammalian toxicity database but used only the data for estimating the variability of individual toxic responses and disregarded the absolute concentration values.[34] Though not explicitly stated, their absolute levels were ultimately based upon the publication by Flury and Zernick.[34,65] Their human estimates lie well below the experimental

animal data, and several papers do not recommend their estimates for risk assessment.[34,39,40,51,59]

The other three studies[39,40,51,59,64] also reviewed the existing mammalian toxicity database, as well. However, unlike Eisenberg *et al*. and Perry and Articola, they used the database for estimating both response variability and absolute levels of concentration. As a result, more realistic estimates were produced.

ten Berge and van Heemst[51] assumed that humans can be modeled to be as sensitive as the average mammal, which meant placing the human estimate between that of the mouse (more sensitive) and the dog (less sensitive). Their estimate of the human response variability was for a general population basis. The toxicity time dependence was based upon mouse data[66] and human volunteer irritation dose-response relationship.[67]

Harris and Moses[59,d] took the work of Eisenberg *et al*. and Perry and Articola and then proceeded to make reasonable adjustments to account for the absolute levels of concentration from the mammalian database (which was previously neglected by Eisenberg *et al*. and Perry and Articola). However, Harris and Moses did not make any explicit statement on what animal model they based their adjustments on. Since their human estimate curve is very similar to that of ten Berge and van Heemst, it may be inferred that Harris and Moses assumed that human toxicity can be equated to that of an average mammal. As for human response variability, Harris and Moses believed that more variability exists in the human general population response (based upon the historical record) than was originally estimated by the U.S. Coast Guard studies. However, the Harris and Moses estimate for response variability is less than that of ten Berge and van Heemst. Thus, though the predicted median lethal dosages from the two estimates are practically identical (for all exposure durations), predicted dosages for percent effect levels other than 50% will increasingly differ as the two extremes (zero and 100% response) are approached.

Withers and Lees[39,40] gave greater weight to the dog chlorine data in the development of their human estimate, while not neglecting to interpret the dog data in light of the other animal experimental data. Also, they developed human estimates as a function of the type of human population (regular, average and vulnerable) and two levels of physical activity (base and standard, corresponding to minute volumes of 6 L/min and 12 L/min, respectively). All of the Withers and Lees estimates are lower than those for the general population estimates from ten Berge and van Heemst[51] and Harris and Moses,[59] with the difference increasing as the exposure duration increases.

Though some[34,39] have observed that the LC_{50} varied as a function of species size, there are no known studies that have actually attempted allometric modeling of the existing database.

[d] Harris and Moses and the Rijnmond Report have identical human estimates and are treated as synonymous by Mannan.[27]

4.0 Historical Record of Chlorine Releases

The historical record of chlorine industrial accidents has been discussed in several sources.[27,34,59,68] The most notable statistic for the reported incidents of outdoor releases (with release amounts up to 50 metric tons) is that fatalities (with one exception) occur within about 400 m of the actual point of release, and more often within 250 m.[27,34,51] The largest number of fatalities for an outdoor chlorine release is around 60 from a ruptured storage tank in Romania in 1939.[68] Furthermore, it has been estimated that there are (on average) 0.3 to 0.8 fatalities per metric ton of an accidental industrial release.[34,59,68]

In addition to the above, Marshall[68] makes the anecdotal observation that no civilian casualties were reported as a result of the first large-scale chemical warfare attack at the Second Battle of Ypres on 22 April 1915 in World War (WW) I. The Germans released 168 tons of chlorine over a 4-mi front, which inflicted an estimated 5000 military fatalities. The distance between the German and Allied lines were roughly 200 m to 600 m apart in the vicinity of the attack. The Allied lines were located about 4 mi (or 6 km) upwind from the town of Ypres, which was still occupied by many civilians. It might be inferred from the lack of evidence that the chlorine cloud never reached the town, since it is likely wartime propaganda would have made the most of any civilian deaths had they occurred.

Also from the WWI era, a chlorine attack was qualitatively assessed to have a persistency of approximately 10 min in the open and 3 h in woods under calm weather conditions.[69] High temperatures and wind velocities decrease persistency, and low temperatures and wind velocities increased it. Considering the size of chlorine releases from WW I, these observations suggest that chlorine releases have a range more limited than what is predicted by the current ATD models.

In developing a human chlorine toxicity estimate, the historical record must be considered. It is well known that ATD models in general often greatly overestimate the downwind hazard resulting from chemical releases.[27] Many factors are likely culprits for this situation,[e] with the toxicity estimates being high on the list. Any chlorine toxicity estimate that predicts a significant number of predicted fatalities located further than a kilometer downwind from the release point should be considered suspect based upon the above historical record. A significant number of predicted fatalities between 500 m and 1000 m should be cause for concern. A case in point is that of Franks *et al*.[49] Using a human toxicity estimate from the Health and Safety Executive (UK),[61] Franks *et al*. produced ATD modeling results that predicted that the downwind range of a LC_{95} would be from 400 m to 800 m for a chlorine puff release of 1000 kg (a small amount for an industrial-type accident), and for the LC_{50}, from 650 m to 1100 m (see Section 7.5.4 for more details).

[e] Other factors being the adequacy of the algorithms used in the ATD models (for dense gas releases, terrain effects, *etc*.), possible significant atmospheric decay rates of the released chlorine gas due to its reactivity, and incomplete information about the actual dispersion of chlorine gas clouds from the accidental releases.

5.0 Data Acquisition

An extensive literature review was conducted to locate experimentally measured median lethal dosage values for mammalian acute inhalation exposures to chlorine. Whenever possible, the underlying raw quantal response data were also obtained if available. For the initial identification of relevant studies, three reference works were consulted: the background material supporting the Acute Exposure Guideline Levels (AEGL) for chlorine;[58] the Third Edition of Lee's Loss Prevention in the Process Industries ("Toxic Releases," Chapter 18);[27] and the Chlorine Toxicity Monograph published by the MHAP.[34] The search was subsequently expanded beyond this point.

A total of 29 individual median lethal inhalation dosage (LCT_{50}) values were collected (or derived from raw data) from 18 studies and sources for eight mammalian species (see Table 5–1) for a summary of the collected data). Whenever possible, original sources were found (and cited) for each LCT_{50} value. In some cases, data were discovered in previously uncited U.S. Army technical reports[70-74] and were subsequently included in the final dataset. In addition to the collection of experimental data, previously derived human toxicity estimates for chlorine were also reviewed and collected.[39,40,51,57,63,64]

Some of the LCT_{50} values in Table 5–1 do not exactly correspond to what was originally reported. Many older studies used the Litchfield and Wilcoxon method[75] for calculating median effective dosages and probit slopes from binary response data. The method is graphical in nature and was originally developed as a means for rapid calculations in the days before widespread computer usage. Probit analysis[23] with modern computer software is more accurate and quicker than the Litchfield and Wilcoxon method. Where the original response data were available, the originally reported LCT_{50} value was updated via probit analysis.

Besides the collected LCT_{50} values, average species body mass and minute volume values from Bide *et al.*[6] for nonanesthetized mammals were used in the present analysis (see Table 2–1). For a healthy human, an average body mass of 70 kg and minute volume of 15 L/min (for light activity) were assumed.

For this study, vapor concentration values are expressed in units of mg/m^3. In a majority of the cited studies, concentrations are expressed in parts per million (ppm). The following was used to convert from ppm to mg/m^3 for chlorine: $1.0\ mg/m^3 = 1\ ppm \times (2.898)$.

Only studies where mammals were exposed for a set period of time and then removed from the chamber for observation were used in the subsequent statistical analysis (Section 7). Studies that exposed the animals continuously until death was observed were not used. Such studies generally produced higher LCT_{50} values relative to fixed duration and observe studies. An example of an exposure to death study is Weedon *et al.*,[88] which is cited by many reviews of chlorine toxicity[27,34,58] and was not included in the dataset for this study.

In addition, many sources give incomplete information about what their "lethal" values truly signify (i.e., is it 1% lethality or 50% lethality?). Only LCT_{50} values were included in the allometric modeling of the present study. If an LCT_{50} value could not be estimated from any reported quantal response data, that study's "lethal" value was not included in the present dataset. Also, due to the recognized importance of time on chlorine toxicity, no LCT_{50} value was included unless a duration value was associated with it.

Significant statistical advances have occurred since most of the reviewed reports were published. Many of the reports were published on or before the WWII era. Some even resulted from observed WWI era data but were primary qualitative in nature. The approaches used by the authors of these reports were not discernable through the set of documents gathered, and the methods used may not have been nearly as sophisticated as those that are now in place (e.g., an LCT_{50} may have been simply reported for a dosage that marked the demise of one half of the subjects in an experiment).

Table 5–1. Data and calculations

STUDY (AUTHORS)	REPORT DATE	REF NUMBER	RAW DATA	METHOD	PROBIT SLOPE	SLOPE ERROR	TIME (min)	LCT_{50} (mg-min/m^3)	LD_{50} (mg)
Mouse									
Silver, McGrath	1942	76	Yes	Probit	7.3207	0.5184	10	13150	0.41
Silver, McGrath, Ferguson	1942	77	Yes	Probit	7.8260	1.0520	10	19430	0.60
Zwart, Woutersen	1988	78	Yes	Probit	10.0410	2.0060	10	30620	0.95
Alarie	1980	62	No				10	8752	0.27
Bunting	1945	79	No				10	15200	0.47
Lipton, Rotariu	1941	80	No				10	18199	0.56
Bitron, Aharonson	1978	66	Yes	MLE	10.6300	1.0160	11	9245	0.29
Schlagbauer, Henschler[f]	1967	81	Yes	Probit	6.1790	1.2280	30	10682	0.33
Zwart, Woutersen	1988	78	Yes	Probit	6.8240	3.6750	30	49300	1.53
Bitron, Aharonson	1978	66	Yes	MLE	10.6300	1.0160	55	27096	0.84
Back, Thomas, MacEwen[g]	1972	82, 83	No				60	23822	0.74
Rat									
Zwart, Woutersen	1988	78	Yes	Probit	15.8410	3.3290	5	77850	15.80
Zwart, Woutersen	1988	78	Yes	Probit	15.8410	3.3290	10	61160	12.42
Zwart, Woutersen	1988	78	Yes	Probit	15.8410	3.3290	30	54810	11.13
Zwart, Woutersen	1988	78	Yes	Probit	15.8410	3.3290	60	83820	17.02
Vernot, MacEwen, Haun[g]	1977	82,83	No				60	50947	10.34
Guinea Pig									
Lehmann	1882	84	No	MLE			30	290000	52.78
Rabbit									
Marshall	1917(a)	70	Yes	MLE			30	21580	31.36
Barrow, Smith	1975	85	Yes	MLE			30	30479	44.29
Lehmann	1882	84	Yes	MLE			190	300000	435.90
Cat									
Lehmann	1882	84	Yes	MLE			235	390000	329.55
Dog									
Armstrong	1923	71	Yes	Probit	7.5120	2.8290	10	58340	246.78
Marshall	1917(a)	70	Yes	Probit	3.1170	1.4460	30	47010	198.85
Underhill	1920	86	Yes	Probit	3.4514	0.8053	30	49380	208.88
Marshall	1917(b)	72	No				30	75000	317.25
Beebe	1924	73	No				30	90000	380.70
Sheep									
Batchinsky, Martini, Jordan	2006	87	No				30	24343	338.37
Goat									
McElroy, Shils, Ginsburg	1943	74	Yes	MLE			18.5	51500	494.40
McElroy, Shils, Ginsburg	1943	74	Yes	MLE			8.5	16500	158.40

[f]Schlagbauer and Henschler also collected data for 3-h and 6-h exposures, but their quantal response data did not bracket the 50% level, which was unsuitable for calculating LCT_{50} values at these durations.
[g]Back *et al*. and Vernot *et al*. report the same data for both mouse and rat.

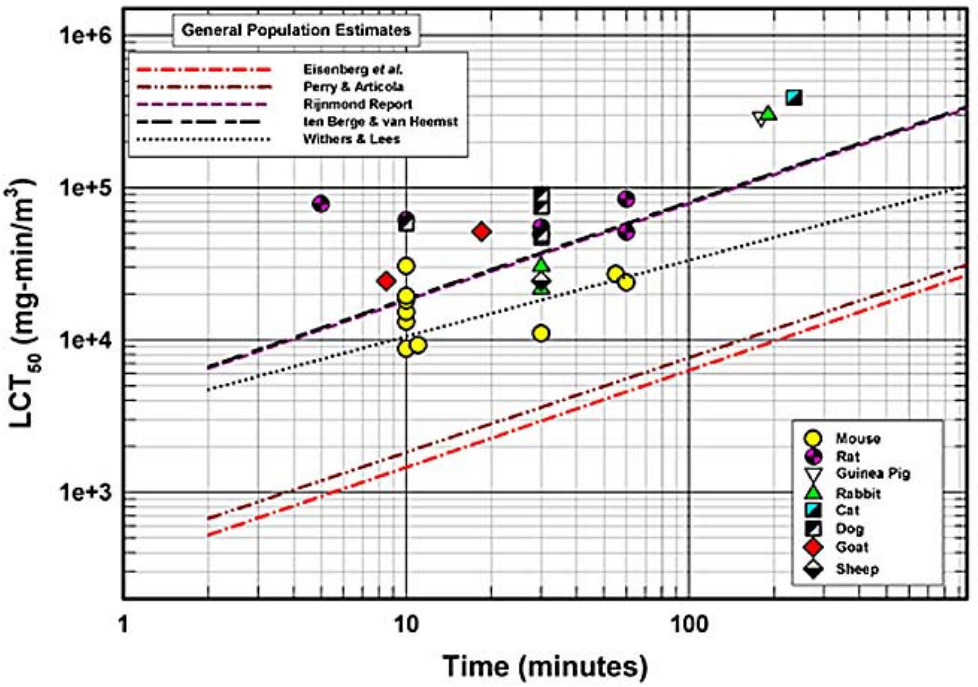
6.0 Data Reduction

The collected data were subjected to several calculation procedures prior to use for the final model fit. First, if sufficient quantal response data were available from an individual study, both the probit slope (with respect to concentration) and the LCT_{50} were estimated via probit analysis.[23] The calculation was performed using the binary logistic regression routine in Minitab® Statistical Software, and the standard error of the probit slope recorded (see Appendix A for an example probit analysis). If more than one exposure duration was used within a study, the duration was treated as a factor (not a covariate) in the calculations (see Section 2.2), thereby producing a best estimate for the true probit slope for the whole study (which was the case with Zwart and Woutersen).[78] However, in many cases, only LCT_{50} values were explicitly given in the publications reviewed.

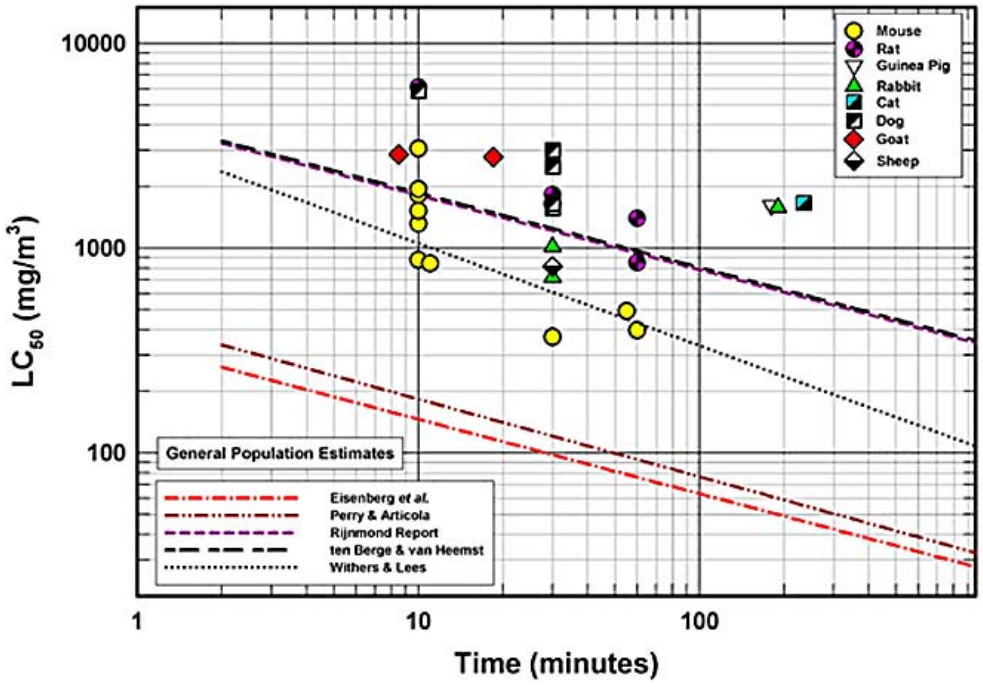
For four studies,[70,74,84,85] only limited quantal response data were recorded for the most part, which was not sufficient for use in a traditional probit analysis. No probit slope or LCT_{50} values were originally reported. For these datasets, a one-factor MLE analysis[47,53] with a probit link function was used to estimate the LCT_{50}. An example of the one-factor MLE analysis is shown in Appendix B. The MLE calculations for Lehmann[84] and McElroy *et al.*[74] are shown in Appendix C.

Once the LCT_{50} values had been collected or estimated, they were converted into nominal lethal doses using eq 4 and the species appropriate average experimental minute volume values from Bide, *et al.*[6] Table 5–1 displays the name and year of the study, reference number, species, availability of raw data, the method of LCT_{50} estimation (if appropriate), exposure duration, the value of the collected or estimated LCT_{50} value, and estimated probit slope value with associated standard error.

A more complete table that provides all data—both observed and computed—is given in Appendix D. All the values shown in Table 5–1 were used in the final model fit of eq 10. The mammalian LCT_{50} values are shown in Figure 6–1, as well as the previous general population estimates listed in Section 3.2.



a. Median lethal dosage (LCT_{50}) versus exposure duration (*T*)



b. Median lethal concentration (LC_{50}) versus exposure duration (*T*)

Figure 6–1. Mammalian experimental data and previous human estimates for chlorine inhalation lethality as a function of exposure duration[h]

[h]The plots for the Rijnmond Report and ten Berge and van Heemst are essentially identical, though ten Berge and van Heemst is very slightly higher.

7.0 Data Analysis And Results

7.1 Probit Slope Estimation

7.1.1 Slope Estimation via a Weighted Average

As explained in Section 2.2, the derivation of an appropriate human probit slope from mammalian data is not a trivial matter. A weighted average was taken of the experimental probit slopes listed in Table 5–1. The inverse of the variances (the squares of the standard errors) of the probit slope estimates were used for the weights. Thus, smaller weights were objectively assigned to less precise slope estimates. The probit slopes from two WWI era studies (Marshall[70] and Underhill[86]) were not used in this analysis. As mentioned in Section 2.2, other factors besides variability in individual sensitivities contribute to the probit slope value and can "artificially" suppress the slope value. It was judged that such was the case with the slopes from these two studies.

The weighted average of the probit slope values equals:[89]

$$\bar{S} = \frac{\sum_{i=1}^{n} w_i S_i}{\sum_{i=1}^{n} w_i} \qquad (11)$$

where $\bar{S}$ is the weighted average probit slope, S_i are the individual probit slope estimates, and w_i are the weights. The variance of the weighted average (when the weights are based on the individual variances) equals:[89]

$$\sigma_{\bar{S}}^2 = \frac{1}{\sum_{i=1}^{n} w_i} \qquad (12)$$

where $\sigma_{\bar{S}}^2$ is the variance of the weighted average.

Table 7–1 presents the step-by-step process in developing both the point estimate of the slope and the variance. Below the chart are the supplemental calculations for the 95% confidence interval (based upon $\sigma_{\bar{S}}^2$) for the probit slope.

The computations are as follows: Weighted average for probit slope becomes (using eq 11):

$$\bar{S} = \frac{\sum_{i=1}^{n} w_i S_i}{\sum_{i=1}^{n} w_i} = \frac{(54.07633)}{(6.794295)} = 7.96$$

The weighted variance is simply the inverse of the sum in the next to last column (see eq 12), which equals 0.147182. Thus, the 95% confidence interval for the weighted slope average becomes:

$$(7.96) - (1.96)\sqrt{(0.147182)} \le S \le (7.96) + (1.96)\sqrt{(0.147182)}$$

or

$$7.21 \le S \le 8.71$$

It is assumed that the above weighted average for the probit slope is a reasonable estimate for the probit slope for a healthy (i.e., military) human subpopulation.

Table 7–1. Probit slope computational scheme

REF #	COUNT	PROBIT SLOPE ESTIMATE	STANDARD ERROR	VARIANCE (= SE²)	WEIGHT (= 1/V)	PRODUCT (= Wᵢ * Sᵢ)
		(S_i)	(SE)	(V)	(w_i)	
76	1	7.3207	0.5184	0.268739	3.721089	27.240974
77	2	7.8260	1.0520	1.106704	0.903584	7.071448
78	3	10.0410	2.0060	4.024036	0.248507	2.495256
66	4	10.6300	1.0160	1.032256	0.968752	10.297833
81	5	6.1790	1.2280	1.507984	0.663137	4.097524
78	6	6.8240	3.6750	13.505625	0.074043	0.505271
78	7	15.8410	3.3290	11.082241	0.090234	1.429404
71	8	7.5120	2.8290	8.003241	0.124949	0.938620
	Column Sums			40.53083	6.794295	54.07633

7.1.2 Slope Estimation From Other Sources

Several probit equations for human lethality have been developed or estimated within the past 30 years. Five such relations are listed in Table 7–2.[27,39,40,51,57,59,63,64] All five were developed for use in modeling chlorine toxicity within the general population, though in the case of Withers and Lees,[40] no probit relation was originally reported for the general (or their average) population. Instead, they reported estimated concentrations for 10%, 50%, and 90% lethality for two separate exposure durations. A fit was then made to these points to derive their equation in Table 7–2. Also, Withers and Lees developed probit equations for the healthy and vulnerable subpopulations.

Four of the five equations were originally reported using probit units, natural logarithms and concentrations expressed in ppm. For ECBC risk assessment and toxicological applications, normit units, base 10 logarithms and concentrations expressed in mg/m^3 are normally used. Also, the probit slope based on concentration (k_c) is commonly used by ECBC and others rather than a slope based on toxic load (k_{TL}). So, these equations were transformed from the published form to the construct used for this analysis as shown below. The resulting relations are also listed in Table 7–2.

$$\ln(x) = \ln(10) \times \log(x), \quad (13)$$

$$C \text{ (ppm)} = 0.34507 \times C \text{ (mg/m}^3\text{)}, \text{ and} \quad (14)$$

$$Y_P \text{ (Probit)} = Y_N \text{ (Normit)} + 5. \quad (15)$$

Given an original equation in the form:

$$Y_P = k_o + k_{TL} \ln (C^n T), \quad (16)$$

where k_o is the constant, k_{TL} is the probit slope (relative to the toxic load), and n is the toxic load coefficient, the construct of the transformed equation becomes:

$$Y_N + 5 = k_o + k_{TL} \{(\ln(10) \times \log[(0.34507\ C_{mg/m3})^n\ T]\}$$

$$Y_N + 5 = k_o + k_{TL} \ln(10) \{\log [(0.34507\ C_{mg/m3})^n] + \log[T]\}$$

$$Y_N + 5 = k_o + k_{TL} \ln(10) \{n \log[(0.34507\ C_{mg/m3})] + \log[T]\}$$

$$Y_N + 5 = k_o + k_{TL} \ln(10) \{n \log[0.34507] + n \log[C_{mg/m3})] + \log[T]\}$$

$$Y_N + 5 = k_o + n\ k_{TL} \ln(10) \log (0.34507) + k_{TL} \ln(10) [n \log(C) + \log(T)]$$

where the concentration C is now expressed in mg per m^3. Continuing,

$$Y_N + 5 = k_o + n\ k_{TL} \ln(10) \log (0.34507) + k_{TL} \ln(10) [\log(C^n) + \log(T)]$$

$$Y_N + 5 = k_o + n\ k_{TL} \ln(10) \log(0.34507) + k_{TL} \ln(10) [\log(C^n T)]$$

$$Y_N = [k_o - 5 + n\ k_{TL} (\ln(10)) \log(0.34507)\ ] + [k_{TL} (\ln(10))] \log(C^n T)$$

or in simplified notation:

$$Y_N = k_o' + k_{TL}' \log(C^n T) \quad (17)$$

Table 7–2. Human lethality equations from other sources

REFERENCE	REF #	ORIGINAL PUBLISHED EQUATION*	CONVERTED EQUATION**
Withers, Lees	39,40	————————	Y_N (Normit) = -11.697 + 1.675 log($C^{2.00}$ T)
Eisenberg, Lynch, Breeding	57	Y_P (Probit) = -17.10 + 1.69 ln($C^{2.75}$ T)	Y_N (Normit) = -27.045 + 3.891 log($C^{2.75}$ T)
Perry, Articola	63	Y_P (Probit) = -36.45 + 3.13 ln($C^{2.64}$ T)	Y_N (Normit) = -50.242 + 7.207 log($C^{2.64}$ T)
ten Berge, van Heemst	51	Y_P (Probit) = -5.04 + 0.50 ln($C^{2.75}$ T)	Y_N (Normit) = -11.503 + 1.151 log($C^{2.75}$ T)
Rijnmond Report (Harris, Moses)	59, 64	Y_P (Probit) = -11.40 + 0.82 ln($C^{2.75}$ T)	Y_N (Normit) = -18.799 + 1.888 log($C^{2.75}$ T)
		*The concentration "C" is measured in parts per million	**The concentration "C" is measured in milligrams per cubic meter

Reformatting the converted equations in Table 7–2:

$$Y_N = k_o' + k_{TL}' \log(C^n T)$$

$$= k_o' + k_{TL}' \log(C^n) + k_{TL}' \log(T)$$

$$= k_o' + nk_{TL}' \log(C) + k_{TL}' \log(T)$$

$$= k_o' + nk_{TL}' \log(C) + k_{TL}' \log(T) + nk_{TL}' \log(T) - nk_{TL}' \log(T)$$

$$= k_o' + nk_{TL}' \log(C) + nk_{TL}' \log(T) + k_{TL}' \log(T) - nk_{TL}' \log(T)$$

$$= k_o' + nk_{TL}' \log(CT) + k_{TL}' (1 - n) \log(T)$$

The important element of this configuration is nk_{TL}', with equals the probit slope (base 10) relative to concentration (k_c), differentiated from the previously discussed probit slope relative to toxic load (k_{TL}). It also turns out that the probit slope for time (k_t—see eq 8) equals k_{TL}.

Table 7–3 presents the probit slopes (k_c) for the references given in Table 7–2.

7.2 Linear Regression Analysis

7.2.1 Fit of Mammalian LD_{50} Values

Using eq 10 (see Section 2.2) and IRLS (see Section 2.3) with Minitab®, the following model fit was obtained:

$$\log(LD_{50}) = (0.515) + (0.869)\log(M) + (0.630)\log(T) \quad (18)$$

The details of the model fit are described in Appendix F. A plot of eq 18 (with associated 95% confidence limits) is shown in Figure 7–1 with the individual experimental mammalian LD_{50} values for comparison.

For the IRLS process[55] an initial unweighted model fit to eq 10 was performed using Minitab®, with the studentized deleted residuals being calculated for the set of observations. From these residuals, a set of weights were created for the next iteration. Iterations continued until a specific tolerance level was reached.

Table 7–3. Probit slopes (base 10) on concentration from other sources for the general population

REFERENCE	PROBIT SLOPE (WITH RESPECT TO CONCENTRATION)
Withers, Lees[39,40]	3.3
Eisenberg *et al.*[57]	10.7
Perry, Articola[63]	19.0
ten Berge, van Heemst[51]	3.2
Rijnmond[59,64]	5.2

Weights (W) were calculated as follows:

$$W_{i,j} = \frac{2}{\left[1 + TRES_{i-1,j}^2\right]}$$

$$\boxed{\text{convergence criteria}} \quad \text{for each j}: \left(W_{i+1,j} - W_{i,j}\right) \le 1 \times 10^{-6} \quad (19)$$

where the counter "i" represents i[th] iteration, and commences at 2 since the first regression run is unweighted, "j" is the index for the j^{th} observation, and $TRES_{i,j}$ is the studentized deleted residual for the j^{th} observation within the i^{th} iteration. Convergence was considered reached when, for each W_j successive iteration (i and i + 1), estimates were produced that agreed to the sixth decimal place

Appendix E presents the procedure within a flow diagram context, detailing the IRLS process used in this effort. Appendix F gives an extract of the IRLS session that culminated in the regression equation result for this analysis.

7.2.2 Fit of Mammalian LC_{50} Values

Other models can be used to fit the data, and two such expressions were also investigated based upon using eq 10 (see Section 2.2) to solve for LC_{50} (instead of LD_{50}). For the first fit, $\log(LC_{50})$ was regressed against $\log(M)$ and $\log(T)$, with no attempt to model the nominal respiratory dose.

In the second fit, $\log(LC_{50})$ was regressed against $\log(M)$, $\log(T)$, and $\log(V_{ratio})$. The minute volume ratio, V_{ratio}, equals the experimental average of V_M values for a species (see Table 2–1) divided by V_M from the allometric model fit of Bide *et al.*[6] (see eq 2). Conceptually, V_{ratio} empirically represents a shape factor of sorts—how much a species respiratory geometry differs from the norm. Theoretically, V_{ratio} should not be correlated with M as the number of species represented in a particular dataset increases. However, for the species represented in the present dataset, there is a correlation between $\log(M)$ and $\log(V_{ratio})$. Thus, in the final model fit with both $\log(M)$ and $\log(V_{ratio})$, $\log(M)$ was found to be statistically insignificant, and it was dropped from the final fit.

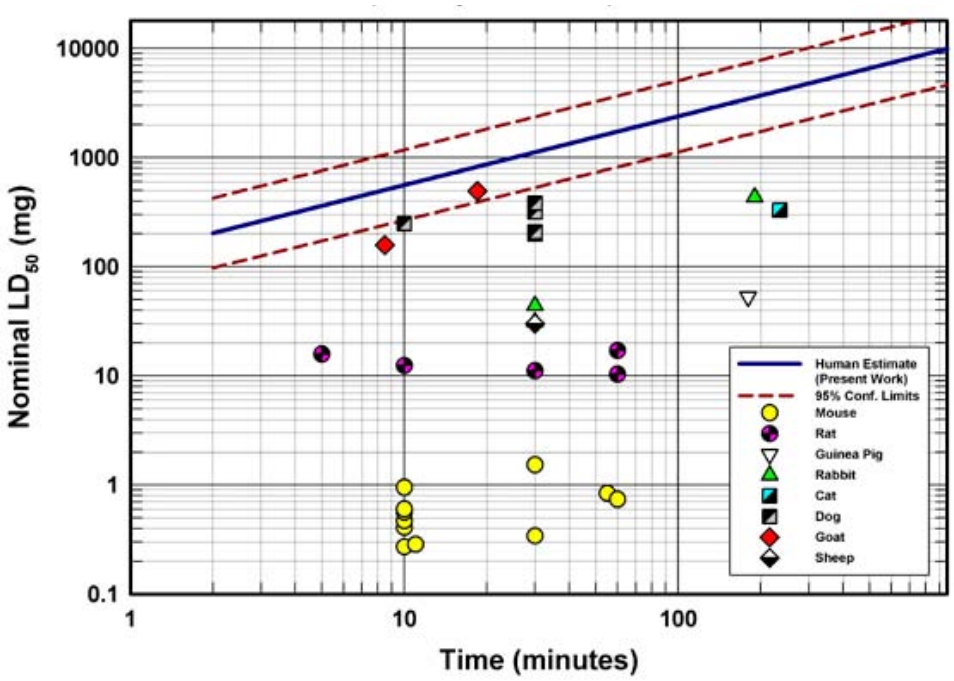


Figure 7–1. Allometric model fit of nominal inhalation LD_{50} for healthy adult humans as a function of exposure duration

Using IRLS (see Section 2.3), the following model fits were obtained (with weights calculated using eq 19):

$$\log(LC_{50}) = (3.62) + (0.0976)\log(M) + (-0.278)\log(T) \quad (20)$$

$$\log(LC_{50}) = (4.31) + (-3.03)\log(V_{ratio}) + (-0.627)\log(T) \quad (21)$$

More details of the above model fits are listed in Appendix G. A plot of eq 20 and eq 21 (with associated 95% confidence limits) are shown in Figure 7–2 along with the LD_{50} fit (eq 19) and the individual experimental mammalian LC_{50} values for comparison. The 95% confidence intervals for eq 20 and eq 21 are roughly equivalent to those for eq 19, with the ranking of relative width (from narrowest to widest) being eq 21 < eq 19 < eq 20. eq 19 was converted from an LD_{50} to LCT_{50} basis (see Section 7.3) for its plot in Figure 7–2.

7.2.3 Summary of Linear Regression Fits

Chlorine toxicity does correlate (with statistical significance, p-value < 0.001) with species body mass. On an absolute nominal dose basis, LD_{50} scales to $M^{0.87}$. Thus, lethality for larger animals requires a greater agent dose on an absolute basis. However, on a per kg of body mass basis, larger mammals are more sensitive to chlorine than smaller mammals [LD_{50} (mg/kg) scales to $M^{-0.13}$].

The LC_{50} scales to $M^{0.10}$ (with a p-value = 0.011)—the LC_{50} is not a very strong function of species body mass. In practical terms, this relationship predicts that the healthy human LC_{50} value is a factor of 2.25 higher than the mouse and just barely greater than the LC_{50} value of the dog (a factor of 1.18) or the goat (a factor of 1.07).

The regression fit of LC_{50} as a function of V_{ratio} (with a p-value < 0.001) qualitatively suggests that species respiratory geometry may play a factor in predicting chlorine inhalation toxicity. However, due to the database composition (where V_{ratio} is inadvertently correlated with M), a quantitative conclusion cannot be reached at this time.

Based upon the final weight assignments from the IRLS procedure for the LD_{50} fit (see Appendix F), the least valuable data are: the 5-min and 10-min rat LCT_{50} values from Zwart and Wourterson;[78] the 30-min mouse LCT_{50} value from Schlagbauer and Henschler;[81] and the 30-min sheep LCT_{50} values from Batchinsky *et al.*[87] All of these received weight values less than 0.65. The most valuable data are: the 18.5-min goat LCT_{50} value from McElroy *et al.*;[74] and the 10-min mouse LCT_{50} value from Bunting.[79] Both are close to the maximum value of 2 and are greater than 1.95 in value.

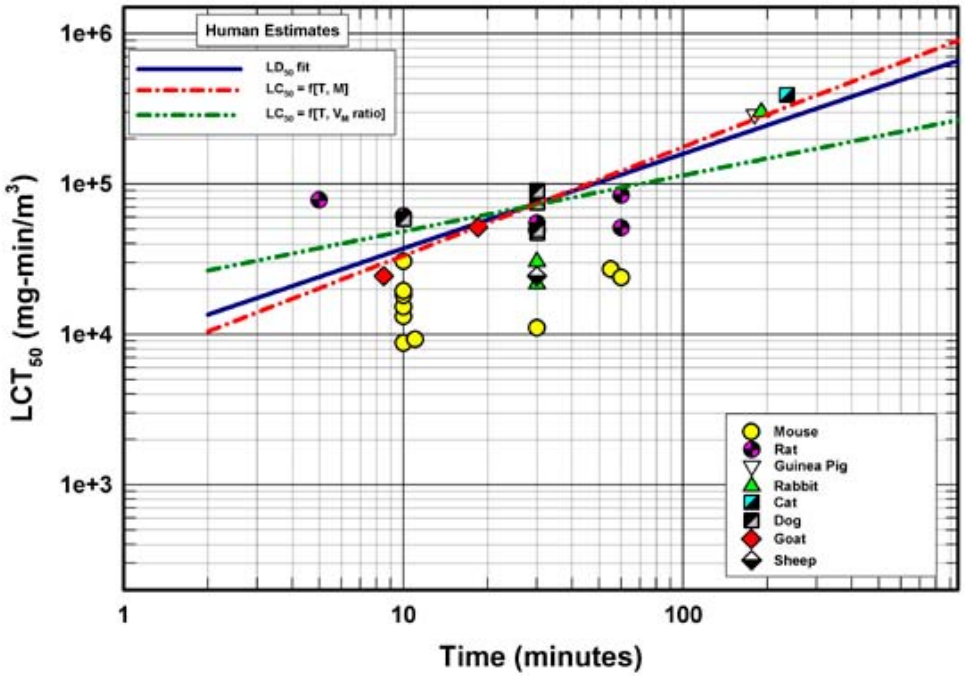


Figure 7–2. Comparison of human estimates (military personnel) from various model fits in the present study

7.3 Toxic Load Exponent and Time-Concentration Relationship

7.3.1 Estimation from Allometric Modeling of Historical Database

Using eq 3 and eq 10, a reformulation is used to derive the toxic load exponent.

$$\log(LD_{50}) = \log(LCT_{50}) + \log(V_M) = k_o + k_m \log(M) + k_t \log(T)$$

$$\log(C) + \log(T) = k_o + k_m \log(M) - \log(V_M) + k_t \log(T)$$

$$\log(C) + \log(T) - k_t \log(T) = k_o + k_m \log(M) - \log(V_M)$$

$$\log(C) + \log(T) - k_t \log(T) = k_o + k_m \log(M) - \log(V_M)$$

$$\log(C) + (1 - k_t) \log(T) = k_o + k_m \log(M) - \log(V_M)$$

$$(1/[1 - k_t]) \log(C) + \log(T) = (1/[1 - k_t]) (k_o + k_m \log[M] - \log[V_M])$$

$$\log(C^{(1/[1-k_t])}) + \log(T) = (1/[1 - k_t])k_o + k_m \log[M] - \log[V_M])$$

$$\log(C^{(1/[1-k_t])}) = (1/[1-k_t])k_o + k_m \log[M] - \log[V_M])$$

Written in this form, the toxic load exponent equals $1/[1 - k_t]$. The relationship between the concentration and the duration of exposure is given by this last equation.

For the LD_{50} fit (eq 19), substituting the value of $k_t = 0.62960$; the toxic load exponent becomes $1/(1 - 0.62960)$ or approximately 2.70.

For a healthy human being, the minute-volume for light activity is assumed to equal 0.015 m^3/min, and the standard military mass is 70 kg.[7]

The right-hand side of the equation becomes:

$$(1/[1 - k_t]) \times (k_o + k_m \log[M] - \log[MV]) =$$

$$(2.69978) \times [0.5147 + 0.86908 \log(70) - \log(0.015)] = 10.64293$$

These quantities produce the relationship (shown also in Figure 7–3):

$\log(C^{2.7}T) = 10.64293$, resulting in the toxic load equation:

$$C^{2.7}T = 4.39 \times 10^{10} \quad (22)$$

From the linear regression fit for eq 19, an estimate can be obtained for the standard error (SE = 0.05939) for the fitted coefficient, k_t (see Appendix F). It is possible to construct 95% confidence intervals for k_t from its SE ($k_t \pm (1.96)SE$). The 95% confidence intervals for the toxic load exponent (n) can be generated by substituting the upper and lower limits for k_t into

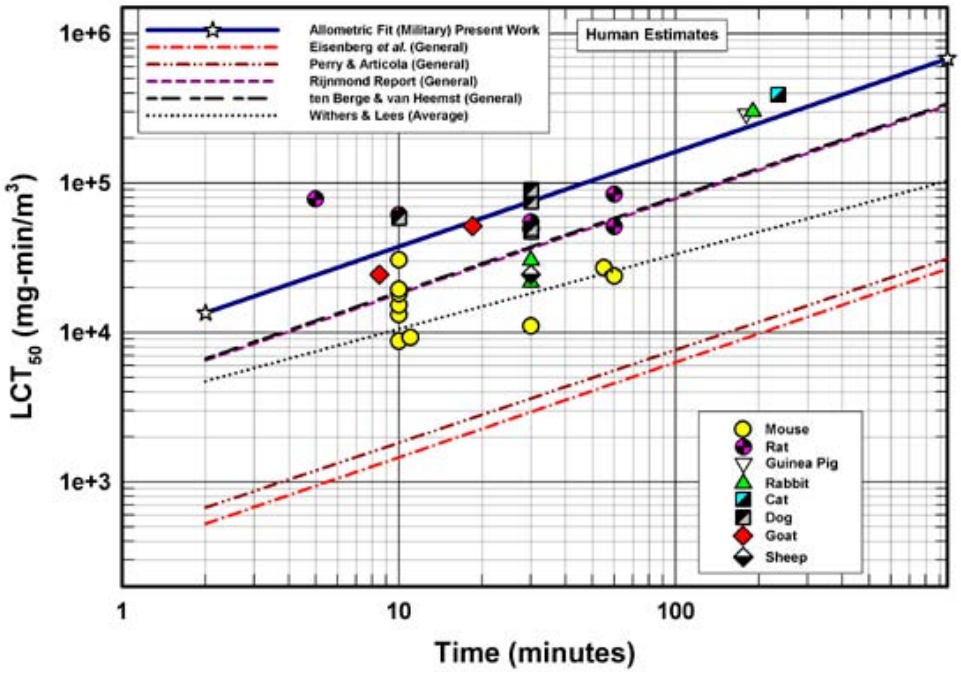


Figure 7–3. Comparison of human estimates from allometric fit to previous human estimates and experimental mammalian data

the relationship, $\{1/[1 - k_t]\}$. The fitted value for k_t and the calculated value for n are listed in Table 7–4, along with their 95% confidence intervals.

Since the 95% confidence bounds of the toxic load exponent do not include the value of one, Haber's Rule—where n equals 1 or, equivalently, that the value of a LCT_{50} (or ECT_{50}) is constant with respect to exposure duration—is not applicable for chlorine. Therefore, the true relationship between chlorine concentration and time of exposure is appropriately given by the toxic load model ($L(C^nT)_{50}$ = constant). However, the precision for n is very low, with the 95% confidence intervals for the toxic load exponent ranging from 1.7 to 6.0. A possible explanation for this is the relatively narrow range of exposure durations that have been investigated historically, with the bulk of the exposure durations ranging from 10 min to 60 min.

Table 7–4. Toxic load exponent estimate from allometric model fit

	POINT ESTIMATE	LOWER BOUND (95% CI)	UPPER BOUND (95% CI)
k_t (coefficient of duration time)	0.63	0.43	0.83
n (toxic load exponent)	2.70	1.74	5.97

Also, the presence of random error between the various studies could decrease the lack of precision in the toxic load exponent. Thus, another approach was investigated in the development of an estimate for the toxic load exponent in a human toxicity relationship was investigated (see Section 7.3.2).

7.3.2 Estimation from Individual Studies

If random error among several studies is an issue in estimating the toxic load exponent, then a review of individual studies that investigated several exposure durations can be helpful. This was the approach taken by ten Berge and van Heemst[51] and ten Berge *et al.*[54] However, only two studies represented in Table 5–1 (page 5–2) involved exposures at several exposure durations: Bitron and Aharonson[66] and Zwart and Woutersen.[78]

Bitron and Aharonson[66] exposed male mice to a range of exposure durations at two constant vapor concentrations (durations of 13 min to 160 min for 170 ppm, and 6 min to 30 min for 290 ppm). For each experimental run, 14 mice were exposed (with each mouse in his own chamber connected to a central air/chlorine vapor source). There were 16 runs using 170 ppm and 18 runs using 290 ppm, for a grand total of 476 mice. The dataset is well balanced, with a good distribution of percent response values that cover at least 5% to 95%

range for each concentration. A value for the toxic load exponent was not originally reported, but ten Berge and van Heemst[51] subsequently calculated a value of 3.5 [with 95% confidence interval (CI) of 2.5 to 4.5] from the data of Bitron and Aharonson.

Zwart and Woutersen[78] exposed both male and female animals to several concentrations at four exposure durations (5 min, 10 min, 30 min, and 60 min) for rats and at two durations (10 min and 30 min) for mice. Ten animals (five of each gender) were exposed in a common chamber. There were 22 runs with the rats (220 rats total) and 11 runs with the mice (100 mice total). However, they did not break down their response results by gender. It is known that there can be gender differences in the toxic response of rodents[52] to toxicants in general. Also, their dataset is not as well balanced as that of Bitron and Aharonson, particularly for the rat. The 5-min and 10-min durations response data are sparse on responses that are not 0% or 100%, and the rat LCT_{50} values at 5 min and 10 min are higher than the value at 30 min (or a toxic load exponent less than one for the range of 5 min to 30 min). It is interesting to note that Mannan[27] does not mention the results of Zwart and Woutersen in his extensive review of the existing chlorine toxicity data. Considering the relative merits of the two studies, the data of Bitron and Aharonson is superior to that of Zwart and Woutersen for estimating the toxic load exponent.

Response results as a function of chlorine vapor concentration and exposure duration were extracted from the graphical representations shown in Bitron and Aharonson.[66] A multifactor probit analysis was then performed on the data using the binary logistic regression routine in Minitab®. It was found that the toxic load exponent equals 3.36 with 95% CI of 2.99 to 3.73. This confidence interval is considerably narrower than was originally calculated by ten Berge and van Heemst.[51] However, there was statistically significant lack of model fit. Two outliers were identified as having a high leverage on the final model fit. When these outliers were dropped from the analysis, the toxic load exponent was found to equal 3.18 with 95% CI of 2.90 to 3.46, which is not drastically different from the model fit with the outliers. Also, the lack of model fit disappeared per the results of the Hosmer-Lemeshow lack of fit test. See Appendix J for a complete description of the statistical analysis.

Thus, an examination of the three allometric-based toxicity fits (eqs 18, 20, and 21) shown in Figure 7–2 finds that the calculated toxic load exponent from Bitron and Aharonson is in better agreement with the exponent values from eqs 18 and 20. The fit (eq 21) using the minute volume ratio (V_M) produces an exponent value that is too low.

7.4 Human Chlorine Inhalation Toxicity Estimates

Three parameters are needed to mathematically define a final inhalation toxicity estimate (as represented in eq 23 below): (1) a probit slope to describe the range of individual sensitivities to the toxicant (k_{TL}); (2) the median lethal dosage (or toxic load) at some reference exposure duration (k_o when Y_N is set equal to zero); and a toxic load exponent (n) to describe how the toxicity changes with exposure duration.

$$Y_N = k_o + k_{TL} \log(C^n T) \qquad (23)$$

In the following two sections, the derivation of the final human estimates is described for both a military subpopulation and the general population. These are shown in Figure 7–4 in comparison to previously derived estimates and the existing mammalian database. The final military sub-population estimate is slightly different from what was derived via allometric scaling (eq 22) for reasons explained in greater detail below.

7.4.1 Military Subpopulation

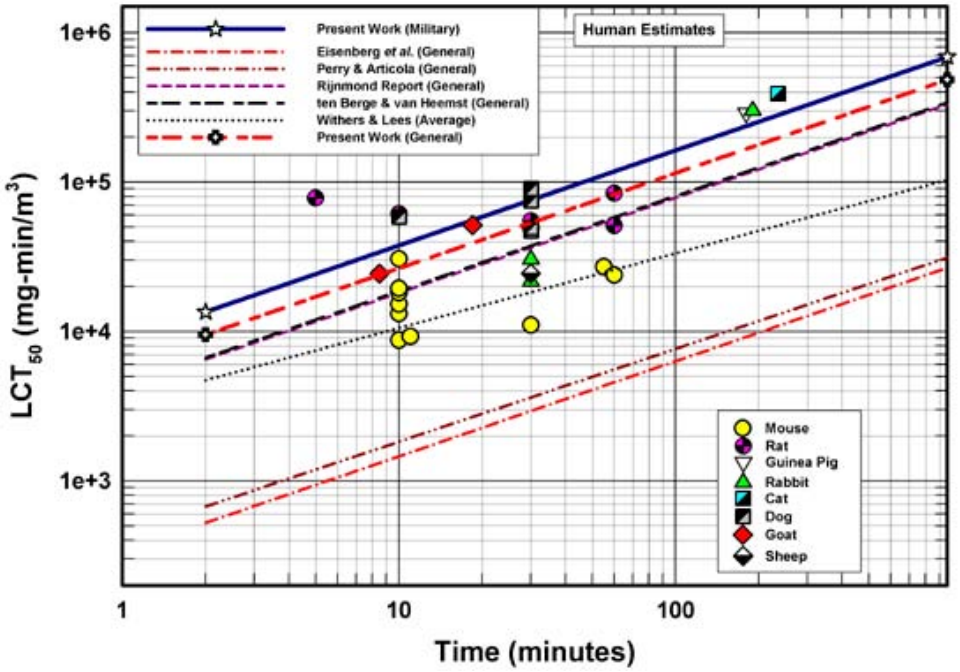
7.4.1.1 Probit Slope

For the probit slope, a weighted average from the available experimental data (see Section 7.1.1) for healthy laboratory animals produced a value of 8.0 (rounded from 7.96), with 95% CI of 7.2 to 8.7. It is assumed that this is an appropriate estimate for healthy (military) human subpopulation.

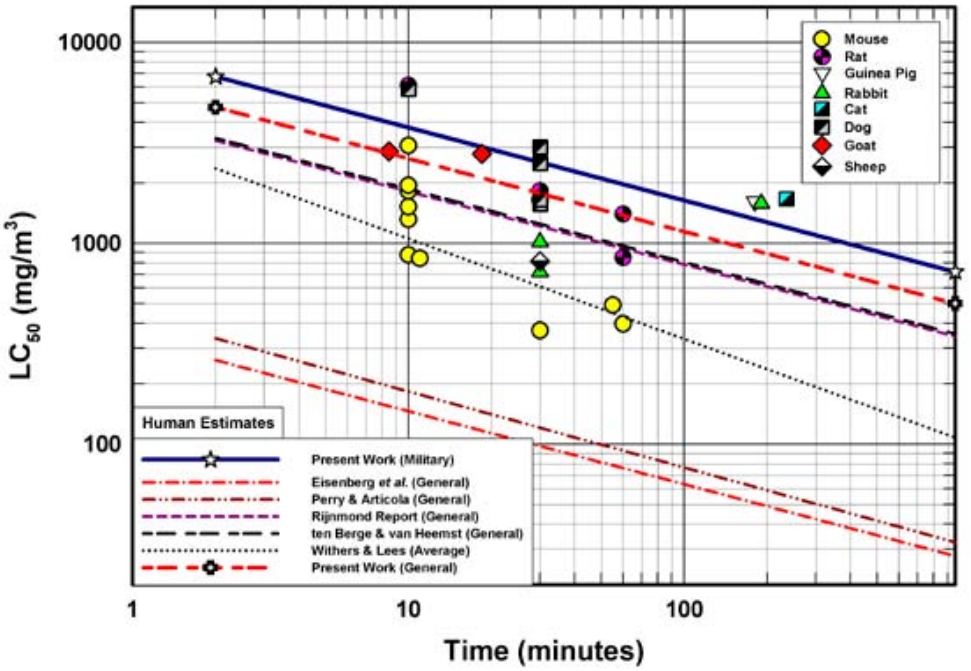
7.4.1.2 Reference Median Lethal Dosage

For the median lethal toxic load, there is some leeway for a recommended value due to the large amount of random error present among the various experimental studies (see Table 5–1, page 5–2). In Figure 7–3, the allometric fit (eq 18) is shown in comparison to previously derived estimates by other researchers. The allometric fit is higher than all of the previous estimates, with those of ten

Berge and van Heemst[51] and the Rijnmond Report[59,64] being the closest. Eisenberg *et al.*[57] and Perry and Articola[63] can be dropped from consideration due to the faulty assumptions used in their derivations.[27,34,39,40,51] There are two reasons for the difference between eq 18 and ten Berge and van Heemst and the Rijnmond Report. First, eq 18 is meant for use with a healthy (military) subpopulation, while the other two are for the general population. This issue is further addressed



a. Median lethal dosage (LCT_{50}) versus exposure duration (T)



b. Median lethal concentration (LC_{50}) versus exposure duration (T)

Figure 7–4. Comparison of human estimates (military and general) with previous human estimates and experimental mammalian data

in Section 7.4.2. Second, eq 18 is based on the fact that both LD_{50} (absolute) and LC_{50} increase as a function of increasing species body mass (as demonstrated by statistical analysis in the present study). Both ten Berge and van Heemst and the Rijnmond Report assumed that a human estimate can be modeled on an average for all mammals (see Section 3.2). So, as a starting point for a human general population estimate, the human healthy (military) LCT_{50} for a 2-min exposure was taken from eq 18, or 13,500 mg-min/m^3.

7.4.1.3 Toxic Load Exponent

For the toxic load exponent, past approaches have been somewhat subjective. ten Berge and van Heemst[51] took an average of Bitron and Aharonson[66] (n = 3.5) and Anglen[67] (n = 1.9) to arrive at 2.75. This may be a case of a correct answer being obtained by incorrect methods. Bitron and Aharonson was a lethality study, while Anglen investigated chlorine vapor concentrations that cause olfactory irritation. The toxic mechanisms are likely different between lethality (from irritation of the lungs) and nuisance effects (due to local irritation of the nasal mucous membranes). Thus, the toxic load exponent values for the two phenomena are likely not equal, and so, the use of an average of the two is not the proper approach to obtain an estimate for the lethal toxic load exponent.

Harris and Moses (1983), in their subjective review of existing animal data, concluded that Coast Guard reports[57,63] have the toxic load exponent correct at 2.75. However, it is not readily evident how the Coast Guard arrived at their estimate, though it appears that they performed an empirical fit of previous human estimates instead of basing it on the available mammalian data.

Withers and Lees[39] based their estimate (n = 2) on an examination of the LCT_{50} values for several exposure durations reported by Weedon *et al.*[88] and Bitron and Aharonson.[66] Others have used the same value, though for different reasons.[49,61] Withers and Lees did note a major problem with Weedon *et al.* (the gas until death exposure protocol), which made its use less than desirable. Also, they had a concern about the unusually low proportion of acute deaths in Bitron and Aharonson. However, Withers and Lees felt that these were the only two studies available from which to justify the effect on exposure duration on chlorine toxicity. A major difference between Weedon *et al.* and Bitron and Aharonson is the number of animals used in each study: Weedon *et al.* used eight rats and four mice for each LCT_{50} estimate (for a total of 16 rats and 8 mice); and Bitron and Aharonson used 476 mice (roughly equally divided between their two LCT_{50} estimates). Withers and Lees took the six LCT_{50} values from the two reports and calculated values of $L(CT^{(1/n)})$ for several values for (1/n)—0.4, 0.5, and 0.6. They concluded that a value of 0.5 produced $L(CT^{(1/n)})$ values that were in the best agreement with one another. A subsequent reexamination by this study of their approach found that an exponent value of 0.33 (or n = 3) works best for the Bitron and Aharonson values and an exponent value of 0.55 (or n = 1.82) for Weedon *et al.* values. All other factors being equal, more weight should have been given by Withers and Lees to the Bitron and Aharonson value, since it is based upon the response of 476 mice versus the 24 rodents used in Weedon *et al.* If a weighted average is taken of 0.33 and 0.55 (using the number of animals for the weights), a value of 0.34 (or n = 2.94) is obtained.

The MHAP also concluded that 2.75 was a reasonable estimate for the toxic load exponent in their development of a threshold severe effects level.[34] They reasoned that the evidence for this value is much stronger than for the lower values derived by others (such as 2.0 by Withers and Lee[39,40]). They believed that the value of 2.75 is advantageous because it results in conservative assessments for short exposures (less than 10 min) where there is considerable uncertainty in the dose-response relationship.

In summary, this study is in agreement with both ten Berge and van Heemst[51] and Withers and Lees[39] on the importance of Bitron and Aharonson.[66] The results of Bitron and Aharonson support a higher value (in the range of 3 to 3.5) for the toxic load exponent than has been used in the previous human estimates. Of the available experimental studies, Bitron and Aharonson have the best set of lethality data involving multiple exposure durations. Yet, this is only one study, which has not yet been reproduced.

Considering all of this, some caution is in order with respect to recommending a toxic load exponent value, since setting the toxic load

exponent value too high will underestimate the toxicity for longer exposure durations. The range of reasonable values to choose from can be defined on the low end by the allometric fit from this study (n = 2.70 from eq 18) and on the upper end by this study's estimate of n from the data of Bitron and Aharonson (n = 3.35). Thus, for a human estimate, a toxic load exponent of 2.75 was chosen (as a conservative estimate) for generating a final human (military) toxicity time relationship. This favors (for the moment) the bulk of the historical database (Table 5–1) and previous human estimates for the exponent value.[34,51,57,59,63,64] However, this toxic load exponent should be reevaluated in the light of any applicable future mammalian studies.

7.4.1.4 Human (Military) Lethality Relationship from Allometric Fit

Based upon the discussion of the previous sections, the healthy (military) human toxicity estimate based upon allometric scaling (Section 7.2) is defined by eq 24 (see also Figure 7–4a):

$$Y_N = (-31.52 + (2.91)\log(C^{2.75}T)$$

or (24)

$$L(C^{2.75}T)_{50} = 6.79 \times 10^{10}$$

where C is in mg/m^3 and T is in minutes. In Table 7–5, a listing is given of LC_{50} and the LCT_{50} values for select exposure durations.

7.4.2 General Population

Estimates for the general population were generated from the allometric scale-based estimate for the military subpopulation (eq 24) via the method of Crosier[1] (see Section 2.4). Using this method, the following values were obtained:

Probit slope (general population) (k_c) = 6.0

LCT_{50} for 2 min (general population) = 9500 mg-min/m^3

For the toxic load exponent, mathematical considerations require that both a subpopulation and the general population must have identical toxic load exponent values (e.g., differing values for n can produce the paradoxical situation where the median lethal dosage for the general population could exceed that of the military subpopulation). Putting these three parameters together produces the probit relation for the general population:

$$Y_N = (-22.698) + (2.18)\log(C^{2.75}T)$$

or (25)

$$L(C^{2.75}T)_{50} = 2.58 \times 10^{10}$$

where C is in mg/m^3 and T is in minutes. A listing is given of LC_{50} and the LCT_{50} values for select exposure durations in Table 7–6 (see also Appendix H).

7.5 HPAC Modeling Results

To provide a sanity check for the new human estimates, a series of modeling runs were conducted using the Hazard Prediction and Assessment Capability (HPAC) model (see

Table 7–5. LCT_{50} and LC_{50} values from military chlorine toxicity estimate (eq 24)

EXPOSURE DURATION (min)	MILITARY SUBPOPULATION	
	Probit Slope (k_c) = 8.0	
	LCT_{50} (mg-min/m^3)	LC_{50} (mg/m^3)
2	13500	6750
10	37600	3760
30	75700	2520
60	118000	1960
120	183000	1520
240	284000	1180
360	368000	1020
480	442000	920
960	687000	720

Table 7–6. LCT_{50} and LC_{50} values from general population chlorine toxicity estimate (eq 25)

EXPOSURE DURATION (min)	WHOLE POPULATION SINGLE TRUNCATION	
	Probit Slope (k_c) = 6.0	
	LCT_{50} (mg-min/m^3)	LC_{50} (mg/m^3)
2	9500	4750
10	26400	2640
30	53200	1780
60	82700	1380
120	129000	1080
240	200000	830
360	259000	720
480	311000	650
960	483000	500

Appendix I). For a typical large-scale accidental release of chlorine, vapor concentration versus time profiles were generated for several locations downwind. Then several human (general population) toxicity estimates were used to estimate the probability of an exposed individual dying should they be exposed to these concentration-time profiles.

7.5.1 HPAC Model Inputs and Outputs

The scenario modeled was for a catastrophic release of 50 tons (~45,500 kg) of chlorine liquid. Ninety tons is the typical amount for a standard rail tank car. However, a release of 50 tons was used as input into HPAC, since this is the largest release reported by Mannan[27] in their review of chlorine industrial/transportation accidents. Literature commentary on the downwind location of fatalities (see Section 4) uses this accident database as its reference. Thus, modeling results for the 50-ton release were used for comparison to the different toxicity methodologies.

Model inputs were kept fairly simple for these simulations. Flat terrain was assumed. Meteorological conditions were kept at a steady-state, fixed-wind condition (same wind direction and wind speed assumed through the simulation). The chlorine release was assumed to be a catastrophic, instantaneous release of the liquid. HPAC make estimates of the amount of chlorine that initially pools, but all liquid evaporated very quickly. Since meteorological conditions can produce significant differences in hazard prediction results, three different weather conditions were modeled. These three conditions were:

- Low wind (1 m/s), clear sky, nighttime (2 a.m.), "stable" condition (Pasquill[90] Stability Category F).
- Moderate wind (5 m/s), cloudy day, "neutral" condition (Pasquill Stability Category D).
- Low wind (2 m/s), clear sky, daytime (2 p.m.), "unstable" condition (Pasquill Stability Category B).

The HPAC model provided numeric output of concentration time history for each model run at downwind distances of 0.2 km, 0.5 km, 1.0 km, 1.5 km, and 2.0 km. The concentration time histories were then numerically integrated using several different human toxicity estimates from Table 7–2 and eq 25 to calculate the probability of lethality at each downwind sampler location.

In the course of this exercise, it was discovered that HPAC cannot properly display LTL_{XX} contours in its graphical output though it can properly calculate exposure toxic loads (see Appendix I for a more detailed discussion). This is why a numeric output of the concentration-time history was subsequently used for this section.

7.5.2 Sensitivity of HPAC Model Predictions to Changes in Toxicity Estimate Parameters

Not surprisingly, the relationship of the probability of lethality as a function of downwind distance is dependent on the toxicity estimate used. The nature of this relationship is demonstrated in Figure 7–5 using the HPAC concentration-time profile generated using nighttime conditions (Pasquill Stability Class F). Four curves were generated using a two by two matrix of k_c (3 and 6) and n (1.85 and 2.75) values. All four curves share an identical LC_{50} value of 4750 mg/m^3 at 2 min. Equation 25 (for the general population) is represented by the curve labeled k_c = 6 and n = 2.75.

A decrease in the toxic load exponent value (with everything else constant) shifts the line to the right, with the new curve still being parallel to the original line (when plotted on a probability versus log(distance) scale). A decrease in the probit slope (concentration), k_c, (with everything else constant) rotates the new line counterclockwise relative to the original line. Changing both k_c and n both shifts and rotates the new line compared to the original. Since a probit slope change rotates the line, the differences in downwind distances between the old and new lines is a function of the lethality probability, with the difference increasing as you move closer or further from the point of intersection between the two lines.

7.5.3 Comparison of Human Toxicity Estimates in Predicting Lethality Probabilities from HPAC Model Predictions

In Figure 7–6, the probability-distance profile based upon eq 25 is compared to profiles generated using previously derived human estimates (see Table 7–2) for the HPAC concentration-time profile generated for nighttime conditions (Pasquill Stability Class F). For probabilities below 10%, the

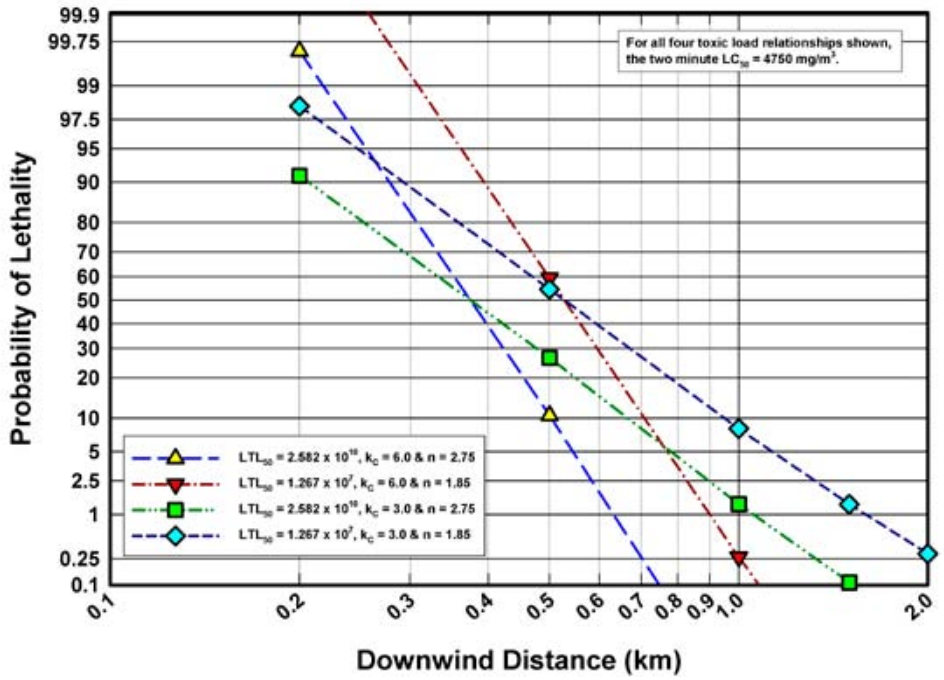


Figure 7–5. Probability of lethality versus downwind distance as a function of toxic load expression (Pasquill Stability Category F)

downwind distance predicted by eq 25 is less than what is predicted by Withers and Lees,[40] Rijnmond Report/Harris and Moses[59,64] and ten Berge and van Heemst.[51] Distances predicted by Haber's Rule (using a LCT_{50} of 9300 mg-min/m^3 and a probit slope of 6) were also calculated. Considering the historical record (see Section 4), the downwind distances predicted by Haber's Rule are very unrealistic (i.e., a 20% chance of lethality at a downwind distance of 2 km).

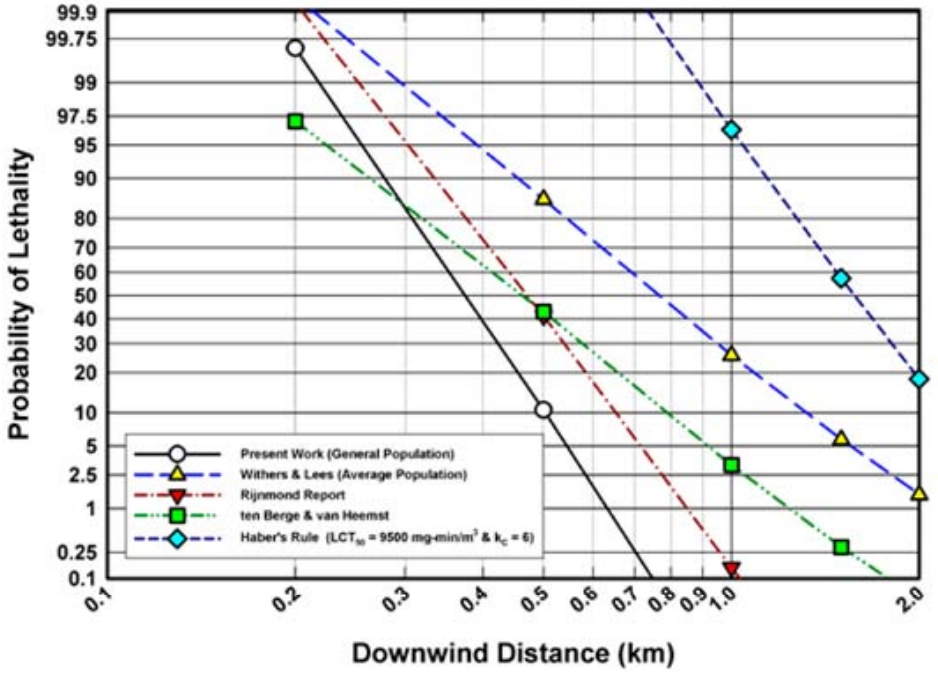


Figure 7–6. Probability of lethality versus downwind distance for several human chlorine lethality estimates (Pasquill Stability Category F)

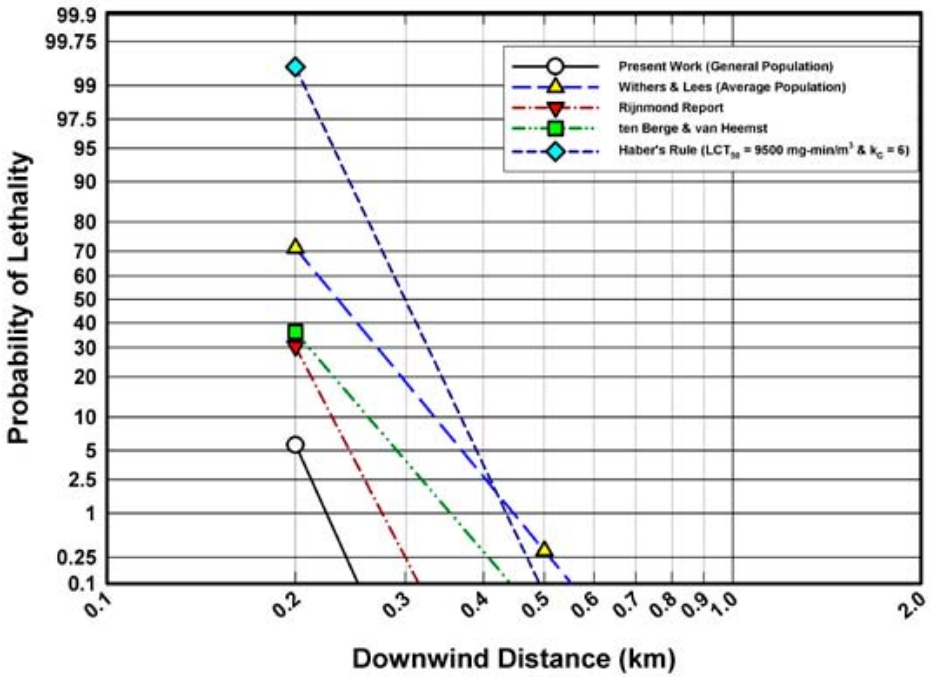


Figure 7–7. Probability of lethality versus downwind distance for several human chlorine lethality estimates (Pasquill Stability Category B)

Of the other three studies, the downwind prediction curve from the Rijnmond Report comes the closest in location and orientation to that of eq 25. The probit slope and toxic load exponent values from the Rijnmond Report (k_{TL} = 1.89 and n = 2.75) are very similar to that of eq 25 (k_{TL} = 2.18 and n = 2.75). The difference between the two curves is mainly due to differences in the median lethal toxic load used in the two toxicity estimates. Both Withers and Lees and ten Berge and van Heemst

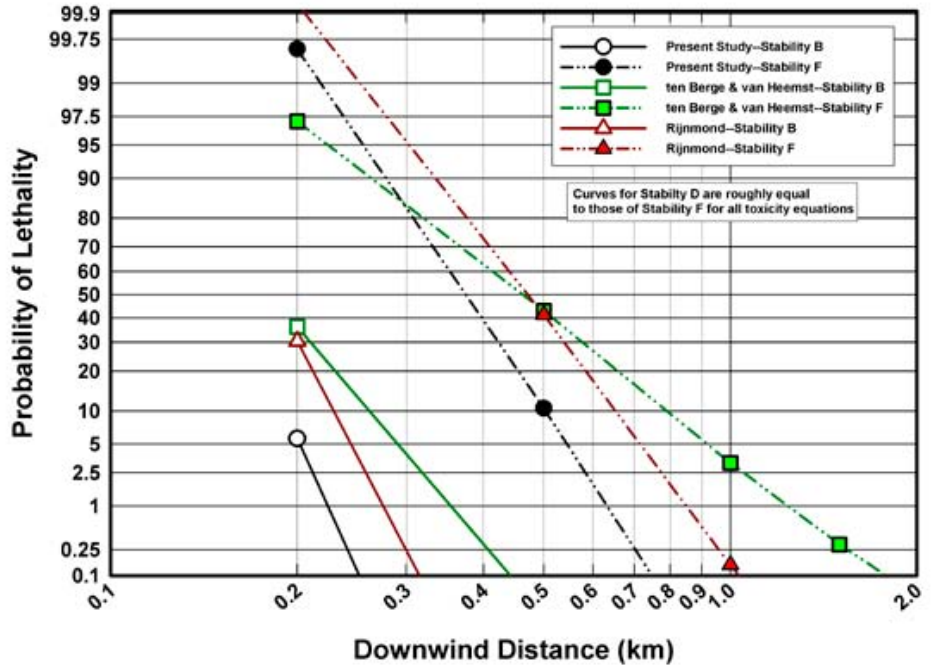


Figure 7–8. Probability of lethality versus downwind distance for several human chlorine lethality estimates (Pasquill Stability Categories B and F)

have smaller probit slope values than eq 25 and the Rijnmond Report, and thus, their predictions curves are rotated counterclockwise relative to eq 25 and the Rijnmond Report (per the observations of the sensitivity study in the previous paragraph). In Figure 7–7, the same toxicity relationships used for Figure 7–6 are used for the HPAC concentration-time profile generated for day time conditions (Pasquill Stability Class B).

In Figure 7–8, the previous plots for eq 25, ten Berge and van Heemst and the Rijnmond Report are shown for both day and nighttime conditions [plots for overcast conditions (Pasquill Stability Class D) are very similar to those of nighttime]. As previously mentioned in Section 4, most fatalities from industrial/transportation accidents involving chlorine have occurred with 250 m of the point of release (even when considering large 20-ton to 50-ton releases), and the maximum distance is 400 m (with one exception). So, any proposed general population toxicity estimate should produce downwind prediction curves that are consistent with the historical record (assuming that the ATD model is adequately predicting vapor dispersion). Under daytime conditions, the plots for eq 25, ten Berge and van Heemst and the Rijnmond Report are consistent with the historical record. However, for nighttime conditions, all three toxicity estimates still produce significant lethality probabilities at 400 m downwind (from 40% to 75%). From this point downwind, probabilities from both eq 25 and the Rijnmond Report fall off quickly as a function of distance relative to that predicted by ten Berge and van Heemst. Is possible that deaths have not been seen at 500 m (despite the high predicted probabilities) due to other factors (i.e., more time available for escape/sheltering in place at the longer downwind distances, nighttime accidents may not be that frequent relative to daytime, not all releases are 50 tons, *etc*.). For distances further than 500 m, the 10% lethal probability is reached at 500 m with eq 25, 650 m with the Rijnmond Report, and 800 m with ten Berge and van Heemst. At 1 km, there is still a 3% lethal probability with ten Berge and van Heemst, while the other two are both below 0.2%. This greater distance on the part of ten Berge and van Heemst is due primarily to its shallower probit slope (k_c = 3.2 versus 5.19 and 6 for the other two toxicity estimates).

7.5.4 Comparison of HPAC Modeling Results to that of Franks et al. (1996)

Franks *et al*.[49] used a ATD model to evaluate the downwind hazard from various chlorine release scenarios (see also Section 4). For puff releases, they investigated puff sizes ranging from 500 kg to 5000 kg [or 0.5 metric tons (M/T) to 5 metric tons] in size, using a human toxicity estimate from the Health and Safety Executive (HSE) (UK).[61] The toxicity estimate was based on the mouse 30-min LC_{50} value of Schlagbauer and Henschler,[81] a probit slope (k_c) of 6.67 (base 10), and a toxic load of 2 to extrapolate to other exposure durations. The LCT_{50} as a function of T for this relationship is parallel to that of Withers and Lees (see Figure 1a)[39,40] with the LCT_{50} of Withers and Lees being a factor of 1.6 higher. The underlying assumption of the HSE human estimate is that man is equivalent to the most sensitive mammal—the mouse in this case.

The largest puff (5 metric tons) investigated by Franks *et al*. is about a factor of 10 lower than the 50-ton release used for the HPAC runs described above. Even so, their 5-metric ton release has the LC_{50} extending from 1400 m to 1800 m downwind. For the worse case scenario in the HPAC runs (see Figure 7–6 through Figure 7–8), the furthest the LC_{50} extended was 750 m using the toxicity estimate of Withers and Lees (if the unrealistic Haber's Rule is ignored).

8.0 Discussion/Conclusions

The development of a human chlorine toxicity estimate has been hampered by the lack of appropriate and accurate toxicity data. As a result, various investigators have had to resort to various degrees of subjective "hand-waving" to produce appropriate human toxicity estimates. Some[39,40,51,59,64] have been more successful than others.[57,61,63] The present study improved upon the previous work by applying novel approaches (i.e., allometric modeling, weighted average of experimental probit slopes, statistical analysis of original response data, mathematical modeling of relationship between subpopulation and the general population, *etc*.) to the problem and introducing previously unknown[70-74]/underanalyzed[74,84,85] mammalian lethality data. However, even with these additional objective methods, the final human estimate is only as good as the underlying original mammalian data that it is based upon. Because of significant shortcomings in the mammalian chlorine lethality data, being dogmatic about the final human estimate should be avoided. Thus, the human estimates (for both military and general population) developed in the present study are offered as a qualitative (rather than quantitative) improvement over estimates from previous investigators.[39,40,51,57,59,63,64] The following is a brief review of the salient issues addressed in the present study and how they differentiate the recommendations of the present study from those of the previous efforts.

8.1 Variability in Human Response

It has been recognized by many that the general human population is likely to have more variance in its response to chlorine inhalation than healthy laboratory animals.[1,25,27,33,34,38-40,45,51,59,60,64] The problem has been how to best extrapolate probit slope values from a laboratory animal to a general human basis.

In the present study, more statistical rigor was employed. This was done by first using probit analysis on the original response data from the experimental studies to generate probit slope values and associated standard errors. Then, a weighted average of the probit slopes was calculated, and this was assumed to be the best estimate for variability in the response among test mammals. It was reasonably assumed that healthy humans were equivalent in their variability to that of healthy laboratory mammals. An estimate for the general population was generated by using a mathematical model of the relationship between a subpopulation and the whole population (see Section 7.4).[1] Of the previous estimates for the probit slope of the general population, the estimate of the present study (k_c = 6) is closest agreement to that of the Rijnmond Report (k_c = 5.2). The other important studies (ten Berge and van Heemst and Withers and Lees) arrived at lower (more response variability) probit slope values.

8.2 Time Dependence of Chlorine Inhalation Toxicity

Previous researchers[39,40,51] have recognized (and the present study has further confirmed—see Sections 7.3.1 and 7.4.1.3) the futility of calculating a precise estimate for the toxic load exponent based on the existing lethality database in total. Instead, the individual findings of four experimental studies[66,67,78,88] have been cited[39,40,51,78] as the basis for a human lethality exponent value. Of these four, the present study has concluded that only Bitron and Aharonson[66] is suitable for use in developing a lethality exponent value (see Section 7.4.1.3). However, the findings of Bitron and Aharonson have been misapplied to the problem.[39,40,51] A proper use of Bitron and Aharonson would lead to a toxic load exponent value in the range of 3 to 3.4. Allometric modeling and considering the database as a whole support a slightly lower value of about 2.75. The "truth" probably lies somewhere between the two extremes. At present, a lower value (2.75) is recommended for two reasons: (1) there is no collaborating study confirming Bitron and Aharonson; and (2) the desire to avoid underestimating toxicity at longer exposure durations by using too high a value for the toxic load exponent.

8.3 Median Lethal Dosage

The basic philosophy for extrapolating from mammal to human with respect to median lethal dosage has been to assume that humans are equivalent to the average mammal.[39,40,51,59,64] However, it has been recognized that the LC_{50} does increase as the species' body mass increases, though the exact reason for this has been debated.[34,39] An allometric fit of the data in the present study found that the median lethal dosage was slightly dependent on the body mass (with

statistical significance), with both the nominal LD_{50} (absolute) and LC_{50} increasing as the species' body mass increases. However, the large amount of random error present in the mammalian database (Table 5–1) prevents a precise allometric-based extrapolation from this database to arrive at a human estimate. Thus, the "true" answer probably lies inbetween the two philosophies.

8.4 Final Human Lethality Estimates

Of the five previous human estimates reviewed (see Table 7–2), the Rijnmond Report[64]/Harris and Moses[59] comes the closest to the general population estimate of the present work (eq 25) in terms of downwind hazard predictions (see Section 7.5.3). This is driven mainly by the identical toxic load exponent values (2.75) and similar probit slope (k_c) values (6 for the present study versus 5.2 for the Rijnmond Report). However, in terms of the median lethal dosage, the relationship from ten Berge and van Heemst[51] is equivalent to that of the Rijnmond Report.

The HPAC modeling runs (Section 7.5) confirm the often observed disconnect between the historical record (Section 4) and the overly pessimistic predictions from ATD models.[27] There are three possible explanations for this conflict. Either the ATD models are overpredicting the downwind transport of chlorine, the human lethality estimates are overpredicting the toxicity, or a combination of both of these factors. There is a temptation to be biased towards using larger LCT_{50} estimates to achieve more reasonable casualty predictions from the current ATD models. However, future improvements in the ATD models (and/or the knowledge of the atmospheric chemistry of chlorine) could leave such a biased lethality estimate "out of position."

For the three important toxicity estimate parameters (probit slope (k_c), toxic load exponent (n), and reference median lethal dosage), the general population estimate from eq 25 is in better agreement with the Rijnmond Report than with the other previous human estimates, particularly for k_c and n. The constant difference in LCT_{50} values is due to differences in extrapolation philosophies [average mammal (Rijnmond) versus allometric scaling (present study)]. The LCT_{50} estimate of eq 25 is about a factor of 1.5 higher than that from the Rijnmond Report, which is not much above the random noise in the data. The true three parameter fit for general population toxicity is probably bracketed by eq 25 and the Rijnmond Report.

In summary, the following upper and lower general population estimates for chlorine lethality are presented for consideration. The upper estimate is defined by eq 25, and lower estimate by a modified form of the Rijnmond Report expression (see Table 4). The Rijnmond Report expression was modified by changing the original probit slope (k_c) value equal to the slope in eq 25 (a change from 5.2 to 6.0), and then a 2-min reference dosage of 6500 mg-min/m^3 (calculated from the Rijnmond estimate) was used as the basis for a toxic load expression (with no change in the value of n). In comparison, the 2-min general population LCT_{50} value from eq 25 equals 9500 mg-min/m^3. These estimates are shown below in eq 25 and eq 26 and in tabular form in Table 8–1.

Upper estimate (adjusted allometric fit)

$$Y_N = (-22.698) + (2.18)\log\left(C^{2.75}T\right) \quad \text{or} \quad L\left(C^{2.75}T\right)_{50} = 2.58 \times 10^{10} \tag{25}$$

Lower estimate (modified Rijnmond)

$$Y_N = (-21.710) + (2.18)\log\left(C^{2.75}T\right) \quad \text{or} \quad L\left(C^{2.75}T\right)_{50} = 9.09 \times 10^{9} \tag{26}$$

To evaluate the relative merits of eq 25 and eq 26, it is recommended that a more extensive sensitivity study with ATD models be conducted (which was beyond the scope of the present work). If ATD models continue to overstate the hazard (even when using the higher estimate of eq 25), then it is very likely that the problem lies with the algorithms of the ATD models (and/or inadequate knowledge of cloud transport or chlorine atmospheric chemistry) rather than in an inadequate lethality estimate. A general population median lethality estimate higher than eq 25 cannot be justified using the current lethality database (Table 5–1).

An important perforce assumption behind eq 24 to eq 26 is that the predicted toxic response is independent of fluctuations around the mean vapor concentration value in the concentration-time history profile (see Section 2.2). If this should be shown in the future not to be the case, it is likely (based on theory) that eq 24 to eq 26 will increasingly underestimate the toxicity as the

Table 8–1. Final general and military populations dosage and concentration estimates

TIME (min)	MODIFIED RIJNMOND GENERAL POPULATION			GENERAL POPULATION EQUATION 25			MILITARY POPULATION EQUATION 24		
	LCT_{50} (mg-min/m^3)	LC_{50} (mg/m^3)	LC_{50} (ppm)	LCT_{50} (mg-min/m^3)	LC_{50} (mg/m^3)	LC_{50} (ppm)	LCT_{50} (mg-min/m^3)	LC_{50} (mg/m^3)	LC_{50} (ppm)
2	6500	3250	1120	9500	4750	1640	13500	6750	2320
10	18100	1810	630	26400	2640	910	37600	3760	1300
30	36400	1210	420	53200	1780	610	75700	2520	870
60	56600	940	330	82700	1380	480	118000	1960	680
120	88000	730	250	129000	1080	370	183000	1520	530
240	137000	570	200	200000	830	290	284000	1180	410
360	177000	490	170	259000	720	250	368000	1020	359
480	213000	440	150	311000	650	220	442000	920	320
960	330000	340	120	483000	500	170	687000	720	250

magnitude of the fluctuations increases, since $n > 1$ for chlorine. Operationally, fluctuations usually become less pronounced as the distance increases from the point of release.

9.0 Recommendations

To better refine the human chlorine lethality estimates, possible future toxicity studies should concentrate on the following issues. First, there is currently only one study[66] that was properly and accurately conducted that provides a defensible estimate for the lethality toxic load exponent (n). The reproducibility of this result should be confirmed (over a range of exposure durations from several minutes to several hours), preferably in multiple mammalian species. Second, the usefulness and appropriateness of allometric scaling can be strengthened by choosing larger species (i.e., rabbit, swine or goat) for the previously mentioned toxicity time-dependency studies. Lastly, comprehensive sensitivity studies using ATD models should be conducted to evaluate against the historical record casualty predictions from all toxicity estimate candidates.

Independent of the recommendations with respect to chlorine toxicity, steps should be taken to improve the capability of HPAC to graphically display LTL_{XX} contours in its plume plots (see Appendix I for a detailed discussion). Also, the effect of concentration fluctuations on the toxicity of chemicals as a function of the toxic load exponent and magnitude of the fluctuations needs to be investigated via mammalian inhalation studies. As mentioned in Section 2.2, there is currently no experimental toxicity data available for guidance on this issue.

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APPENDIX A: PROBIT ANALYSIS EXAMPLE

The data from Silver, McGrath, and Ferguson[1] is used below (Table A–1) to illustrate the application of probit analysis to raw quantal data in order to estimate probit slopes. In this lethality study, mice were exposed to chlorine for a period of 10 min.

A probit equation is now achieved through the use of Minitab® Statistical Software. The number of deaths was imputed as "successes," and the link function utilized was the "normit." This normit function assumes the conventional normal distribution for the common logarithm of the concentration. In other situations, the common logarithm of the dosage (concentration x time of exposure) is also modeled by the normal distribution, and the normit is used as the link for statistical analysis within Minitab®. Binary logistic regression is the specific routine utilized.

The equation that is derived is in the form:

$$Z = A + B \log(C) \qquad (A1)$$

Where B is the probit slope, A is the intercept, C is the concentration [milligrams per cubic meter (mL/m^3)], and Z is the Z-score from the standard normal distribution.

Binary Logistic Regression: Number Deaths, Number Trials versus Log(C)

Link Function: **Normit**

Response information:

Variable	Value	Count
Number D	Success	157
	Failure	143
Number T	Total	300

See logistic regression table (Table A–2)

Table A–2. Logistic regression table

	PREDICTOR COEF.	SE COEF.	Z	P
Constant	-25.735	3.477	-7.40	0.000
Log(C)	7.826	1.052	7.44	0.000

Table A–1. Chlorine lethality data for mice from Silver, et al. (1942)

TIME (min)	CONCENTRATION (mg/m^3)	NUMBER OF TRIALS	NUMBER OF DEATHS	log(C)	log(T)
10	1100	20	2	3.04139	1
10	1590	20	9	3.20140	1
10	1590	20	5	3.20140	1
10	1690	20	1	3.22789	1
10	1830	20	8	3.26245	1
10	1850	20	9	3.26717	1
10	2000	20	3	3.30103	1
10	2050	20	12	3.31175	1
10	2060	20	11	3.31387	1
10	2160	20	14	3.33445	1
10	2300	20	15	3.36173	1
10	2360	20	20	3.37291	1
10	2440	20	8	3.38739	1
10	2520	20	20	3.40140	1
10	2580	20	20	3.41162	1

Log-Likelihood = -170.220

Test that all slopes are zero: G = 74.795, DF = 1, P-value = 0.000

Goodness-of-Fit Tests:

Method	Chi-Square	DF	P
Pearson	58.241	12	0.000
Deviance	68.052	12	0.000
Hosmer-Lemeshow	22.634	5	0.000

The remainder of the calculations uses the equation produced to calculate the median lethal concentration (LCT). This is accomplished by setting the Z-score to zero, and solving for "C."

$Z = -25.735 + 7.826 \log(LC_{50})$

$0 = -25.735 + 7.826 \log(LC_{50})$

$\log(LC_{50}) = 25.735/7.826$

$\log(LC_{50}) = 3.288398$

$LC_{50} = 1943$

The median lethal dosage (LD) is then estimated by multiplying the median lethal concentration by the duration of exposure. The result, in units of milligram-minutes per cubic meter (mg-min/m^3), is posted to the data table the main text.

LCT_{50} = 10 min x 1943 mg/m^3 = **19430 mg-min/m^3**

A1.0 References

[1] Silver, SD; McGrath, FP; and Ferguson, RL; *Chlorine – Median Lethal Concentration for Mice (II),* **EATR Report # 373**. War Department Chemical Warfare Center, Edgewood Arsenal, MD, 1942, UNCLASSIFIED Report, AD# B955266.

APPENDIX B: BINARY AND ORDINAL PROBIT MODELS AND THE METHOD OF MAXIMUM-LIKELIHOOD ESTIMATION—Douglas R. Sommerville

B1.0 Introduction

Traditionally, median effective dosages (ED) are determined via the use of probit analysis.[1,2] In conventional probit analysis of binary response data, two parameters are estimated simultaneously from experimental quantal data using the method of maximum likelihood estimation (MLE):[3-8] the median effective stress, μ; and the standard deviation of effective stresses, σ. In toxicology, the effective stress is the base-10 logarithm of the effective dosage. Thus, the base-10 logarithm of the median effective dosage, $\log_{10}(ECT_{50})$, corresponds to μ, while the probit slope equals the inverse of σ. The probit model can also be extended for use with ordinal response data [categorical data that have three or more possible levels with a natural ordering (example, mild, moderate, and severe)].[1,3] For the ordinal probit model, there are individual μ's for each category, but the σ's for each category are assumed to equal each other.

The efficiency of the MLE procedure with the probit model is dependent on the sample size. Larger sizes provide unbiased and minimum variance estimates of both μ and σ, but this is not the case for small sample sizes. It has been shown that when solving for both μ and σ with small sample sizes that estimates for μ are unbiased (for all practical purposes), but estimates for σ are biased (with estimates for σ being too small on average).[3,8,9] Furthermore, the probability of MLE solution instability increases as sample size decreases when trying to solve for both μ and σ. Thus, for small sample sizes, a more pragmatic approach is commonly taken by fixing σ at some set value (based on historical knowledge of the system under study) while solving for μ. This is an underlying principle of the up-and-down method for estimating median effective stresses/dosages.[6]

The following are examples of both a binary and ordinal probit model applied to the male pig GB ordinal data (severe effects and lethality) for ten minutes exposures from the present study. The probit slope ($1/\sigma$ or m) was held constant throughout the computations.

B2.0 Binary Probit Model

B2.1 MLE Algorithm for Binary Probit Model

For each trial condition, i, there is a likelihood, L_I, of the observed result occurring:

$$L_i = p_i^{x_i} (1 - p_i)^{n_i - x_i} \qquad \text{(B1a)}$$

$$\log_e(L_i) = x_i [\log_e p_i] + (n_i - x_i) [\log_e (1 - p_i)] \qquad \text{(B1b)}$$

where p_i is the event probability for test condition i, n_i is the number of independent trials under the i-th condition, and x_i is the number of successes in n_i. The likelihoods for all test conditions are then multiplied together to arrive at the likelihood, L. The values of the p_i's that are most supported by the quantal data are the values for which L is the largest. For ease of calculation, the natural logarithm of the likelihood is often used.

For a normal distribution, p_i is defined by the following relations:

$$p_i = \int_{-\infty}^{Z_i} f(Z)\, dZ \qquad \text{(B2)}$$

$$f(Z) = \left[\frac{1}{\sqrt{2\pi}}\right] \exp\left[\frac{-Z^2}{2}\right] \qquad \text{(B3)}$$

where Z, is the standard normal random variable and $f(Z)$ is the probability density function (pdf) of a standard normal distribution. In toxicology, the values of the individual p_i's are a function of the applied dosages, $(CT)_i$, used in an experiment and their respective distances from the median effective dosage, ECT_{50}. This is reflected in the following definition of Z_i:

$$Z_i = \frac{\{s_i - \mu\}}{\sigma} = m\,\{\log_{10}(CT)_i - \log_{10}(ECT_{50})\} \qquad \text{(B4)}$$

where s_i is the applied stress for trial condition i and m is the probit slope (equal to $1/\sigma$). The 50% response level (or $p = 0.5$) corresponds to a Z value of zero. The MLE estimate of $\log(ECT_{50})$ is the value of $\log(ECT_{50})$ that is found to maximize L in eq B1.

For the MLE calculations, the first and second derivatives of $\log_e(L_i)$ with respect to μ are used:[3,7,8]

$$\left(\frac{\partial \log_e(L_i)}{\partial \mu}\right) = \left(\frac{f(Z_i)}{\sigma}\right)\left\{(-x_i)\left[\frac{1}{p_i}\right] + (n_i - x_i)\left[\frac{1}{(1-p_i)}\right]\right\} \quad \text{(B6)}$$

$$\left(\frac{\partial^2 \log_e(L_i)}{\partial \mu^2}\right) = \left(\frac{f(Z_i)}{\sigma^2}\right)\left\{(-x_i)\left[\frac{Z_i}{p_i} + \frac{f(Z_i)}{p_i^2}\right] + (n_i - x_i)\left[\frac{Z_i}{(1-p_i)} - \frac{f(Z_i)}{(1-p_i)^2}\right]\right\} \quad \text{(B7)}$$

To reach convergence at the value of $\log(ECT_{50})$ that maximizes $\log_e L$, a Newton-Raphson (or Newton's Method) algorithm (or similar procedure) can be used.[3,7,8,10] Using the Newton-Raphson method for the present system of equations (eq B1b, eq B6, and eq B7), the following equation is used to determine the next guess for $\log(ECT_{50})$, as well as to check on convergence at the MLE for $\log(ECT_{50})$:

$$\mu_{next} = \mu_o - \left(\frac{\partial \log_e L}{\partial \mu_o}\right) \Big/ \left(\frac{\partial^2 \log_e L}{\partial \mu_o^2}\right) \quad \text{(B8)}$$

where μ_o is the current guess for μ (or $\log(ECT_{50})$), μ_{next} is the next guess for μ, and

$$\left(\frac{\partial \log_e L}{\partial \mu}\right) = \sum_{i=1}\left(\frac{\partial \log_e(L_i)}{\partial \mu}\right) \quad \text{(B9)}$$

$$\left(\frac{\partial^2 \log_e L}{\partial \mu^2}\right) = \sum_{i=1}\left(\frac{\partial^2 \log_e(L_i)}{\partial \mu^2}\right) \quad \text{(B10)}$$

The first and second derivatives for $\log_e L$ are evaluated at μ_o. $\text{Log}_e L$ is maximized when its first derivative with respect to μ equals zero. Convergence is achieved when the absolute difference between μ_o and μ_{next} is less than a predetermined value.

Thus, the following algorithm is used to find the MLE estimate for ECT_{50}:

(1) Set the probit slope (m) equal to some fixed value for the duration of the algorithm.

(2) Make an initial guess, μ_o, for μ (or $\log(ECT_{50})$).

(3) Calculate Z_i , $f(Z_i)$ and p_i for each test condition i, corresponding to some $(CT)_i$ exposure using eq B2, eq B3, and eq B4.

(4) Using eq B1, calculate the individual likelihoods, L_i.

(5) Multiply the L_i's (or add the $\log_e(L_i)$'s) together to estimate the total likelihood, L (or $\log_e L$), of the MLE estimate.

(6) Calculate the first and second derivatives for $\log_e L$ (evaluated at μ_o) using eq B6, eq B7, eq B9, and eq B10.

(7) Check to verify whether the maximum value of L has been obtained. If not, go back to Step (3) with a new guess, μ_{next}, for μ (or $\log(ECT_{50})$ using eq B8.

After the final $\log(ECT_{50})$ estimate, $\hat{\mu}$, is obtained, there are three common and general methods for obtaining approximate confidence limits for the estimate:[3] Wald test, likelihood-ratio test, and the score (or Lagrange-multiplier) test. These approximations grow more accurate as the sample size gets larger.

In the present study, the Wald test was used to calculate confidence limits. Limits from the Wald test can be readily obtained from calculations performed as part of the Newton-Raphson algorithm used for finding the maximum value for L. However, the likelihood-ratio test required additional Newton-Raphson algorithm iterations.

In the present study, the following equation was used (based on the Wald test) to calculate the 95% asymptotic confidence interval for μ or the $\log(ECT_{50})$:[3]

$$\hat{\mu} - \frac{(1.96)}{\sqrt{\frac{-d^2 \log_e L(\hat{\mu})}{d\mu^2}}} \le \mu \le \hat{\mu} + \frac{(1.96)}{\sqrt{\frac{-d^2 \log_e L(\hat{\mu})}{d\mu^2}}} \quad \text{(B11)}$$

where the second derivatives for $\log_e L$ are evaluated at $\hat{\mu}$ using eq B7 and eq B10.

B2.2 Example of Application of Binary Probit Model with Fixed Probit Slope

Table B–1 provides the binary data for the 10-min exposures of the male pig to GB vapor from Hulet *et al.* (2006).[11] Dosage is in units of mg-min/m^3.

For this example, test condition i will only have one pig. So, for eq B1, n will equal one for each test condition. The values for x_i correspond to the absence or presence of lethality in the exposed pig.

Table B–1. Male pig GB ordinal data (10-min exposure duration)—binary data

PIG	DOSAGE (CT)	$\log_{10}$(CT)	OUTCOME	x_i
1	53.5	1.728354	< severe	0
2	59.0	1.770852	severe	0
3	67.0	1.826075	death	1
4	74.5	1.872156	severe	0
5	94.0	1.973128	death	1
6	95.0	1.977724	death	1

Steps (1) and (2): Probit slope and initial guess for $\log_{10}(ECT_{50})$ for iteration one

For Step (1) of the algorithm, the probit slope is set equal to 10, which was used as the step size for the up-and-down method employed in the present study. For Step (2), the initial guess for the $\log_{10}(ECT_{50})$ is 1.85304.

Step (3): Calculation of Z_i's and p_i for iteration one using eq B2, eq B3, and eq B4

$Z_1 = [1.72835) - 1.85304)]/(1/10) = -1.24685$ ===> $p_1 = 0.10623$

$Z_2 = [1.77085) - 1.85304)]/(1/10) = -0.82187$ ===> $p_2 = 0.20558$

$Z_3 = [1.82608) - 1.85304)]/(1/10) = -0.26964$ ===> $p_3 = 0.39372$

$Z_4 = [1.87216) - 1.85304)]/(1/10) = 0.19117$ ===> $p_4 = 0.57580$

$Z_5 = [1.97313) - 1.85304)]/(1/10) = 1.20089$ ===> $p_5 = 0.88510$

$Z_6 = [1.97772) - 1.85304)]/(1/10) = 1.24685$ ===> $p_6 = 0.89377$

Steps (4) and (5): Calculation of L_i's and L for iteration one using eq B1

$\log_e(L_1) = (0)\ (\log_e(0.10623)) + (1 - 0)\ (\log_e(1 - 0.10623)) = -0.11230$

$\log_e(L_2) = (0)\ (\log_e(0.20558)) + (1 - 0)\ (\log_e(1 - 0.20558)) = -0.23014$

$\log_e(L_3) = (1)\ (\log_e(0.39372)) + (1 - 1)\ (\log_e(1 - 0.39372)) = -0.93212$

$\log_e(L_4) = (0)\ (\log_e(0.57580)) + (1 - 0)\ (\log_e(1 - 0.57580)) = -0.85756$

$\log_e(L_5) = (1)\ (\log_e(0.88510)) + (1 - 1)\ (\log_e(1 - 0.88510)) = -0.12205$

$\log_e(L_6) = (1)\ (\log_e(0.89377)) + (1 - 1)\ (\log_e(1 - 0.89377)) = -0.11230$

Sum of the above $\log_e(L_i)$'s (or $\log_e(L)$) equals -2.36647.

Step (6): Calculate the first and second derivatives for $\log_e L$ (evaluated at μ_o) using eq B6, eq B7, eq B9, and eq B10

$d[\log_e(L_1)]/d[\mu_o] = 2.05162$

$d[\log_e(L_2)]/d[\mu_o] = 3.58246$

$d[\log_e(L_3)]/d[\mu_o] = -9.77094$

$d[\log_e(L_4)]/d[\mu_o] = 9.23437$

$d[\log_e(L_5)]/d[\mu_o] = -2.19159$

$d[\log_e(L_6)]/d[\mu_o] = -2.05162$

Sum of the above $d[\log_e(L_1)]/d[\mu_o]$'s equals 0.85430.

$d^2[\log_e(L_1)]/d[\mu_o]^2 = -29.790$

$d^2[\log_e(L_2)]/d[\mu_o]^2 = -42.277$

$d^2[\log_e(L_3)]/d[\mu_o]^2 = -69.125$

$d^2[\log_e(L_4)]/d[\mu_o]^2 = -67.620$

$d^2[\log_e(L_5)]/d[\mu_o]^2 = -31.122$

$d^2[\log_e(L_6)]/d[\mu_o]^2 = -29.790$

Sum of the above $d^2[\log_e(L_1)]/d[\mu_o]^2$'s equals -269.72.

Step (7): Check for convergence on maximum L value and new guess for $\log(ECT_{50})$ for iteration two using eq B8

After the first iteration, the next guess for μ is found to equal:

$\mu_{next} = 1.85304 - (0.85430)/(-269.72) = 1.85304 - (-0.00317) = 1.85621$

Convergence was nearly reached after the first iteration, as seen above with only a difference of -0.00317 between μ_{next} and μ_o. After the second iteration, the difference falls further to 2.1×10^{-7}.

Thus, the final estimate for $\log_{10}(ECT_{50})$ is 1.85621 (or (ECT_{50}) = 71.8 mg-min/m^3), and the final $\log_e(L)$ value was -2.36512. The denominators of eq B11 were found to equal the square root of 269.7. With this value for the denominators, the corresponding 95% asymptotic confidence interval for $\log_{10}(ECT_{50})$ equals 1.73686 to 1.97556, or for ECT_{50}, the interval is 54.6 to 94.5 mg-min/m^3.

B3.0 Ordinal Probit Model

B3.1 MLE Algorithm for Ordinal Probit Model

To model an ordinal ternary response, eq B1 is modified as follows for each trial condition *i*:

$$L_i = p_{1,i}^{x_{1,i}} \; p_{2,i}^{x_{2,i}} (1 - p_{1,i} - p_{2,i})^{n_i - x_{1,i} - x_{2,i}} \qquad \text{(B12a)}$$

$$\log_e(L_i) = x_{1,i}[\log_e p_{1,i}] + x_{2,i}[\log_e p_{2,i}] + (n_i - x_{1,i} - x_{2,i})[\log_e (1 - p_{1,i} - p_{2,i})] \qquad \text{(B12b)}$$

where $p_{1,i}$ and $p_{2,i}$ are the event probabilities for responses of categories one and two, respectively, for test condition *i*, n_i is the number of independent trials under the *i*-th condition, and $x_{1,i}$ and $x_{2,i}$ are the number of responses of categories one and two, respectively, in n_i. As before with the binary model, the likelihood, *L*, is obtained by multiplying together the individual likelihoods (for all test conditions).

The ordinal categories are in order of increasing severity, with Category Two being more severe than Category One. For this example, Category Two corresponds to lethality, while Category One corresponds to severe effects. Two normal distributions are represented in eq 12, and are defined as follows for the i^{th} condition:

$$p_{2,i} = \int_{-\infty}^{Z_{2,i}} f(Z)\,dZ \qquad \text{(B13)}$$

$$p_{1,i} + p_{2,i} = \int_{-\infty}^{Z_{1,i}} f(Z)\,dZ \qquad \text{(B14)}$$

The values of the individual $p_{1,i}$'s and $p_{2,i}$'s are a function of the applied dosages, $(CT)_i$, used in an experiment and their respective distances from their corresponding median effective dosages: for category one, μ_1 or ECT_{50} (severe); and for category two, μ_2 or LCT_{50} (lethality). This is reflected in the following definitions of the Z_i's for each *i*-th condition:

$$Z_{1,i} = \frac{\{s_i - \mu_1\}}{\sigma} = m\,\{\log_{10}(CT)_i - \log_{10}(ECT_{50})\} \qquad \text{(B15)}$$

$$Z_{2,i} = \frac{\{s_i - \mu_2\}}{\sigma} = m\,\{\log_{10}(CT)_i - \log_{10}(LCT_{50})\} \qquad \text{(B16)}$$

where $\mu_2 > \mu_1$ and σ (or *m*) is assumed to be the same for both distributions. MLE is now used to simultaneously obtain estimates for both the ECT_{50} (severe) and LCT_{50}. However, some modifications are needed to eq B6 and eq B7 to account for the first and second derivatives of $\log_e(L_i)$ with respect to μ_1 and μ_2, respectively:

$$\left(\frac{\partial \log_e(L_i)}{\partial \mu_1}\right) = \left(\frac{f(Z_{1,i})}{\sigma}\right)\left\{(-x_{1,i})\left[\frac{1}{p_{1,i}}\right] + (n_i - x_{1,i} - x_{2,i})\left[\frac{1}{p_{0,i}}\right]\right\} \qquad \text{(B17)}$$

$$\left(\frac{\partial^2 \log_e(L_i)}{\partial \mu_1^2}\right) = \left(\frac{f(Z_{1,i})}{\sigma^2}\right)\left\{(-x_{1,i})\left[\frac{Z_{1,i}}{p_{1,i}} + \frac{f(Z_{1,i})}{p_{1,i}^2}\right] + (n_i - x_{1,i} - x_{2,i})\left[\frac{Z_{1,i}}{p_{0,i}} - \frac{f(Z_{1,i})}{p_{0,i}^2}\right]\right\} \qquad \text{(B18)}$$

$$\left(\frac{\partial \log_e(L_i)}{\partial \mu_2}\right) = \left(\frac{f(Z_{2,i})}{\sigma}\right)\left\{(x_{1,i})\left[\frac{1}{p_{1,i}}\right] + (-x_{2,i})\left[\frac{1}{p_{2,i}}\right]\right\} \qquad \text{(B19)}$$

$$\left(\frac{\partial^2 \log_e(L_i)}{\partial \mu_2^2}\right) = \left(\frac{f(Z_{2,i})}{\sigma^2}\right)\left\{(x_{1,i})\left[\frac{Z_{2,i}}{p_{1,i}} - \frac{f(Z_{2,i})}{p_{1,i}^2}\right] + (-x_{2,i})\left[\frac{Z_{2,i}}{p_{2,i}} + \frac{f(Z_{2,i})}{p_{2,i}^2}\right]\right\} \qquad \text{(B20)}$$

where $p_{0,i}$ equals $(1 - p_{1,i} - p_{2,i})$. Also, the partial derivative of $\log_e(L_i)$ with respect to both μ_1 and μ_2, is required:

$$\left(\frac{\partial^2 \log_e(L_i)}{\partial \mu_1 \partial \mu_2}\right) = \left(\frac{f(Z_{1,i})\,f(Z_{2,i})}{\sigma^2}\right)\left[\frac{x_{1,i}}{p_{1,i}^2}\right] \qquad \text{(B21)}$$

To reach convergence at the values for μ_1 (or ECT_{50} (severe)) and μ_2 (or LCT_{50} (lethality)) that maximizes $\log_e L$, a Newton-Raphson (or Newton's Method) algorithm (or similar procedure) can be used.[3,7,8,10] Using the Newton-Raphson method for the present system of equations (eq B17 to eq B21), the following simultaneous equations are used to determine the next guess for the median effective dosages, as well as to check on the convergence of the solution:

$$-\left(\frac{\partial \log_e(L)}{\partial \mu_1}\right) = \left(\frac{\partial^2 \log_e(L)}{\partial \mu_1^2}\right)\Delta\mu_1 + \left(\frac{\partial^2 \log_e(L)}{\partial \mu_1 \partial \mu_2}\right)\Delta\mu_2 \qquad \text{(B22)}$$

$$-\left(\frac{\partial \log_e(L)}{\partial \mu_2}\right) = \left(\frac{\partial^2 \log_e(L)}{\partial \mu_1 \partial \mu_2}\right)\Delta\mu_1 + \left(\frac{\partial^2 \log_e(L)}{\partial \mu_2^2}\right)\Delta\mu_2 \qquad \text{(B23)}$$

where $\Delta\mu_1 = (\mu_{next} - \mu_o)_1$ and $\Delta\mu_2 = (\mu_{next} - \mu_o)_2$ for median effective dosages 1 (severe) and 2 (lethal), respectively, and

$$\left(\frac{\partial \log_e L}{\partial \mu_j}\right) = \sum_{i=1}\left(\frac{\partial \log_e (L_i)}{\partial \mu_j}\right) \quad \text{(B24)}$$

$$\left(\frac{\partial^2 \log_e L}{\partial \mu_j^2}\right) = \sum_{i=1}\left(\frac{\partial^2 \log_e (L_i)}{\partial \mu_j^2}\right) \quad \text{(B25)}$$

$$\left(\frac{\partial^2 \log_e L}{\partial \mu_1 \partial \mu_2}\right) = \sum_{i=1}\left(\frac{\partial \log_e (L_i)}{\partial \mu_1 \partial \mu_2}\right) \quad \text{(B26)}$$

where, j equals 1 and 2 for severe and lethality, respectively. The above derivatives for $\log_e L$ are evaluated at $\mu_{1,o}$ and $\mu_{2,o}$. $\text{Log}_e L$ is maximized when its first derivatives with respect to the two μ's equal zero. Convergence is achieved when the absolute difference between μ_o and μ_{next} is less than a predetermined value. After convergence is reached, the asymptotic variance-covariance matrix of the maximum likelihood estimate can be calculated by taking the inverse of the matrix of second derivatives of $\log_e L$:[3,7,8]

$$V(\mu_1, \mu_2) = \begin{bmatrix} \left(\frac{\partial^2 \log_e (L)}{\partial \mu_1^2}\right) & \left(\frac{\partial^2 \log_e (L)}{\partial \mu_1 \partial \mu_2}\right) \\ \left(\frac{\partial^2 \log_e (L)}{\partial \mu_1 \partial \mu_2}\right) & \left(\frac{\partial^2 \log_e (L)}{\partial \mu_2^2}\right) \end{bmatrix}^{-1} \quad \text{(B27)}$$

Thus, the following algorithm is used to find the MLE estimate for ECT_{50}:

(1) Set the probit slope (m) equal to some fixed value for the duration of the algorithm.

(2) Make initial guesses for $\log(ECT_{50})$ and $\log(LCT_{50})$: $\mu_{1,o}$ and $\mu_{2,o}$, respectively.

(3) Calculate $Z_{i,j}$, $f(Z_{i,j})$ and $p_{i,j}$ for each test condition i and mean dosage j, corresponding to some $(CT)_i$ using eq B3 and eq B13 to eq B16.

(4) Using eq B12, calculate the individual likelihoods, L_i.

(5) Multiply the L_i's (or add the $\log_e(L_i)$'s) together to estimate the total likelihood, L (or $\log_e L$), of the MLE estimate.

(6) Calculate the first and second derivatives for $\log_e L$ (evaluated at μ_o) for each mean dosage j, using eq B17 to eq B20. Also, calculate the derivative for $\log_e L$ with respect to both $\mu_{1,o}$ and $\mu_{2,o}$ using eq B21.

(7) Check to verify whether the maximum value of L has been obtained. If not, go back to Step (3) with new guesses, $\mu_{1,next}$ and $\mu_{2,next}$, for μ_1 and μ_2, respectively, by solving eq B22 and eq B23, simultaneously.

In some instances with Step (7), poor initial guesses for μ_1 and μ_2 may produce the situation where $\mu_{1,next} > \mu_{2,next}$, a violation of a key boundary condition. A simple resolution for this problem is to artificially reduce (for this iteration) the values of $\Delta\mu_1$ and $\Delta\mu_2$ by some set factor.

After the final $\log(ECT_{50})$ and $\log(LCT_{50})$ estimates, $\hat{\mu}_1$ and $\hat{\mu}_2$, are obtained, there are three common and general methods for obtaining approximate confidence limits for these estimates:[3] Wald test, likelihood-ratio test, and the score (or Lagrange-multiplier) test. As with the binary probit model (see Section B2.0), these approximations grow more accurate as the sample size gets larger.

In the present study, the Wald test was used to calculate confidence limits. Limits from the Wald test can be readily obtained from calculations performed as part of the Newton-Raphson algorithm used for finding the maximum value for L. However, the likelihood-ratio test required additional Newton-Raphson algorithm iterations.

In the present study, the following equation was used (based on the Wald test) to calculate the 95% asymptotic confidence interval for each μ_j [with j = 1 for $\log(ECT_{50})$ and 2 for $\log(LCT_{50})$]:[3,7,8]

$$\hat{\mu}_j - \frac{(1.96)}{\sqrt{\text{var}(\mu_j)}} \le \mu_j \le \hat{\mu}_j + \frac{(1.96)}{\sqrt{\text{var}(\mu_j)}} \quad \text{(B28)}$$

where $\text{var}(\mu_j)$ is the variance for μ_j. The values for the variances and covariance are calculated using eq B27.

B3.2 Example of Application of Ordinal Probit Model with Fixed Probit Slope

Table B–2 provides the quantal data for the 10-min exposures of the male pig to GB vapor from Hulet *et al.* (2006).[11] Dosage is in units of mg-min/m^3.

For this example, test condition *i* will only have one pig. So, *n* will equal one for each test condition for eq B12. The values for x_1 and x_2 correspond to the absence or presence of a maximum effect: x_1 equals one if the maximum effect observed was severe effects (and equals zero otherwise); and x_2 equals one if the maximum effect was lethality (and equals zero otherwise).

Steps (1) and (2): Probit slope and initial guesses for $\log_{10}(ECT_{50})$ and $\log_{10}(LCT_{50})$ for iteration one.

For Step (1) of the algorithm, the probit slope is set equal to 10, which was used as the step size for the up and down method employed in the present study. For Step (2), the initial guesses for $\log_{10}(ECT_{50})$ and $\log_{10}(LCT_{50})$ are 1.68 and 1.83, respectively.

Steps (3), (4) and (5): Calculation of $Z_{i,j}$, $f(Z_{i,j})$ and $p_{i,j}$ using eq B3 and eq B13 to eq B16 and of L_i's and L Using eq B12 for iteration one.

Table B–3 shows the calculated values for each pig. The sum of the individual $\log_e L_i$ equals -3.8212.

Step (6): Calculate the various derivatives for $\log_e L$ (evaluated at $\mu_{1,o}$ and $\mu_{2,o}$) for each mean dosage *j*, using eq B17 to eq B21.

Table B–4 shows the calculated values for each pig. Pigs showing severe effects make contributions to all five derivatives, whereas those pigs having less than severe effects or that have died only contribute to two of the five derivatives.

Step (7): Check for convergence on maximum *L* value and new guesses for $\log(ECT_{50})$ and $\log(LCT_{50})$ for iteration two using eq B22 and eq B23.

Solving eq B22 and eq B23 simultaneously produces values of 0.03283 and 0.03087 for $\Delta\mu_1$ and $\Delta\mu_2$, respectively. So, the next guesses for μ_1 and μ_2 are 1.71283 and 1.86087, respectively. After the third iteration, the absolute values for both $\Delta\mu_1$ and $\Delta\mu_2$ are less than 1×10^{-5}. At which point, the final values for μ_1 and μ_2 are 1.71203 and 1.86015, respectively. Thus, the final estimates for ECT_{50} and LCT_{50} are 51.5 and 72.5 mg-min/m^3, respectively. The final $\log_e(L)$ value was -3.6478. The final variance-covariance matrix equals:

$$V(\mu_1, \mu_2) = \begin{bmatrix} 0.005449 & 0.001100 \\ 0.001100 & 0.003642 \end{bmatrix}$$

Using the above information with eq B28, the corresponding 95% asymptotic confidence interval for $\log_{10}(ECT_{50})$ equals 1.56735 to 1.85671, or for ECT_{50}, the interval is 36.9 to 71.9 mg-min/m^3. For lethality, the confidence interval for $\log_{10}(LCT_{50})$ equals 1.74186 to 1.97845, or for LCT_{50}, the interval is 55.2 to 95.2 mg-min/m^3.

Table B–2. Male pig GB ordinal data (10-min exposure duration)—quantal data

PIG	DOSAGE (CT)	$\log_{10}$(CT)	OUTCOME	x_1	x_2
1	53.5	1.728354	< severe	0	0
2	59.0	1.770852	severe	1	0
3	67.0	1.826075	death	0	1
4	74.5	1.872156	severe	1	0
5	94.0	1.973128	death	0	1
6	95.0	1.977724	death	0	1

Table B–3. Values of $Z_{i,j}$, $f(Z_{i,j})$ and $p_{i,j}$ for first iteration

PIG	Z_1	Z_2	$f(Z_1)$	$f(Z_2)$	p_1	p_2	$\log_e L_i$
1	0.48354	-1.01646	0.35493	0.23799	0.53094	0.15470	-1.15720
2	0.90852	-0.59148	0.26404	0.33492	0.54110	0.27710	-0.61420
3	1.46075	-0.03925	0.13727	0.39864	0.44361	0.48434	-0.72500
4	1.92156	0.42156	0.06297	0.36502	0.30934	0.66333	-1.17330
5	2.93128	1.43128	0.00543	0.14324	0.07449	0.92382	-0.07920
6	2.97724	1.47724	0.00474	0.13398	0.06835	0.93019	-0.07240

Table B–4. Values of $\log_e L$ derivatives for first iteration

PIG	$\left(\frac{\partial \log_e(L_i)}{\partial \mu_1}\right)$	$\left(\frac{\partial^2 \log_e(L_i)}{\partial \mu_1^2}\right)$	$\left(\frac{\partial \log_e(L_i)}{\partial \mu_2}\right)$	$\left(\frac{\partial^2 \log_e(L_i)}{\partial \mu_2^2}\right)$	$\left(\frac{\partial^2 \log_e(L_i)}{\partial \mu_1 \partial \mu_2}\right)$
1	11.2906	-72.8829	0	0	0
2	-4.8798	-68.1456	6.1896	-74.9220	30.2039
3	0	0	-8.2304	-64.5089	0
4	-2.0355	-43.2572	11.8000	-89.4952	24.0191
5	0	0	-1.5505	-24.5966	0
6	0	0	-1.4404	-23.3522	0
Total	4.3753	-184.2857	6.7683	-276.8749	54.2231

B4.0 Other Useful Relationships

For simplicity, many of the derivative equations are presented without benefit of showing intermediate steps. The following is a listing of relationships that were useful in arriving at the final relations.

B4.1 Binary Probit Model

$$\frac{\partial p_i}{\partial \mu} = \frac{-f(Z_i)}{\sigma} \quad \textbf{(B29)}$$

$$\frac{\partial f(Z)}{\partial \mu} = \left[\frac{f(Z)Z}{\sigma}\right] \quad \textbf{(B30)}$$

$$\frac{\partial Z_i}{\partial \mu} = -\left(\frac{1}{\sigma}\right) \quad \textbf{(B31)}$$

B4.2 Ordinal Probit Model

$$\frac{\partial p_{1,i}}{\partial \mu_1} = \frac{-f(Z_{1,i})}{\sigma} \quad \textbf{(B32)}$$

$$\frac{\partial p_{2,i}}{\partial \mu_1} = 0 \quad \textbf{(B33)}$$

$$\frac{\partial p_{1,i}}{\partial \mu_2} = -\left(\frac{\partial p_{2,i}}{\partial \mu_2}\right) = \frac{f(Z_{2,i})}{\sigma} \quad \textbf{(B34)}$$

$$\frac{\partial p_{2,i}}{\partial \mu_2} = \frac{-f(Z_{2,i})}{\sigma} \quad \textbf{(B35)}$$

$$\frac{\partial f(Z_1)}{\partial \mu_1} = \left[\frac{f(Z_1)Z_1}{\sigma}\right] \quad \textbf{(B36)}$$

$$\frac{\partial f(Z_2)}{\partial \mu_2} = \left[\frac{f(Z_2)Z_2}{\sigma}\right] \quad \textbf{(B37)}$$

$$\frac{\partial f(Z_2)}{\partial \mu_1} = \frac{\partial f(Z_1)}{\partial \mu_2} = 0 \quad \textbf{(B38)}$$

$$\frac{\partial Z_1}{\partial \mu_1} = \frac{\partial Z_2}{\partial \mu_2} = -\left(\frac{1}{\sigma}\right) \quad \textbf{(B39)}$$

$$\frac{\partial Z_1}{\partial \mu_2} = \frac{\partial Z_2}{\partial \mu_1} = 0 \quad \textbf{(B40)}$$

B5.0 References

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APPENDIX C: MAXIMUM LIKELIHOOD ESTIMATION CALCULATIONS OF LCT_{50} VALUES FOR DATA OF LEHMANN (1882) AND McELROY ET AL. (1943)—Douglas R. Sommerville

C1.0 Introduction

The literature search for this study discovered two datasets for which LCT_{50} values were not originally reported: Lehmann (1882)[1] and McElroy *et al.* (1943).[2] In both cases, the data are insufficient for traditional probit analysis to provide a LCT_{50} estimate. However, if a one-parameter MLE analysis is used instead of the two-parameter traditional probit analysis, it is possible to obtain LCT_{50} values from these datasets. The data from these studies and the resulting MLE calculations and LCT_{50} estimates are presented in this appendix.

C2.0 Experimental Data

The experimental data of Lehmann [(1882)[1] (as reported by the Major Hazards Assessment Panel (1987)][3] and McElroy *et al.* (1943)[2] are listed in Tables C–1 through C–4. The data from Lehmann are also shown in Figures C–1 through C–3 (pages C–3 and C–4).

Table C–1. Individual response data (72-h basis) for cats exposed to chlorine in Lehmann (1882)

CONCENTRATION		TIME (min)	CT (mg-min/m³)	C^2T (mg²-min/m⁶)	OUTCOME
ppm	mg/m³				
10	28.98	450	13000	3.78E+05	survived
130	377	630	237000	8.94E+07	survived
180	522	300	156000	8.16E+07	survived
330	956	390	373000	3.57E+08	survived
450	1300	210	274000	3.57E+08	died
430	1250	300	374000	4.66E+08	survived
660	1910	240	459000	8.78E+08	survived
3100	8980	180	1617000	1.45E+10	died
3300	9560	90	861000	8.23E+09	died
4500	13000	60	782000	1.02E+10	died

Table C–2. Individual response data (72-h basis) for rabbits exposed to chlorine in Lehmann (1882)

CONCENTRATION		TIME (min)	CT (mg-min/m³)	C^2T (mg²-min/m⁶)	OUTCOME
ppm	mg/m³				
180	522	300	156000	8.16E+07	survived
330	956	390	373000	3.57E+08	survived
400	1160	210	243000	2.82E+08	died
430	1250	300	374000	4.66E+08	died
660	1910	240	459000	8.78E+08	survived
3100	8980	180	1617000	1.45E+10	died
3300	9560	90	861000	8.23E+09	died
4500	13000	60	782000	1.02E+10	died

Table C–3. Individual response data (72-h basis) for guinea pigs exposed to chlorine in Lehmann (1882)

CONCENTRATION		TIME (min)	CT (mg-min/m³)	C^2T (mg²-min/m⁶)	OUTCOME
ppm	mg/m³				
180	522	300	156000	8.16E+07	survived
330	956	390	373000	3.57E+08	died
450	1300	210	274000	3.57E+08	survived
430	1250	300	374000	4.66E+08	survived
660	1910	240	459000	8.78E+08	died
3200	9270	180	1670000	1.55E+10	died
3300	9560	60	574000	5.49E+09	died
4500	13000	60	782000	1.02E+10	died

Table C–4. Individual response data (72-h basis) for goats exposed to chlorine in McElroy *et al.* (1943)

CONCENTRATION	TIME (min)	CT (mg-min/m³)	C^2T (mg²-min/m⁶)	OUTCOME
mg/m³				
3000	20	60000	1.80E+08	died
3000	20	60000	1.80E+08	survived
2500	17.5	43750	1.09E+08	died
2500	17.5	43750	1.09E+08	survived
2500	17.5	43750	1.09E+08	survived
2600	10	26000	6.76E+07	died
1900	8	15200	2.89E+07	died
1900	8	15200	2.89E+07	survived
1900	8	15200	2.89E+07	survived

C3.0 Data Reduction and Analysis

The data from Lehmann (1882) were grouped by species, and a MLE analysis (see Appendix A) was applied separately to each. The probit slope was assumed to equal 10. It was assumed based on the total historical dataset that chlorine toxicity follows a toxic load type model for time dependence. With this in mind, the binary response was analyzed against the logarithm (base 10) of two forms of the toxic load: C^2T and C^3T. It was found that the final estimate was relatively insensitive to the value of the toxic load exponent being used (two versus three). Thus, for the final estimate, C^2T was used for the toxic load model. After the median lethal C^2T was determined, the geometric mean of all the individual exposure durations (T) was then calculated for each species dataset. The $L(C^2T)_{50}$ was assumed to be associated with this geometric mean time, which was found to equal 235 min for the cat, 190 min for the rabbit and 180 min for the guinea pig. The LC_{50} and LCT_{50} was then calculated from the $L(C^2T)_{50}$ values using these mean times.

The data from McElroy *et al.* (1943)[2] was split into two exposures groups: short-time durations (8 min and 10 min) and long-time durations (17.5 min and 20 min). MLE analysis was then used on each set separately. The geometric mean of all of the individual exposure durations (T) within each set was taken. As with the Lehmann datasets, $L(C^2T)_{50}$ values were assumed to be associated with the appropriate geometric mean times. For the short-time duration, the geometric mean is 8.5 min, and for the long duration, it was 18.5 min. The LC_{50} and LCT_{50} was then calculated from the $L(C^2T)_{50}$ values using these mean times.

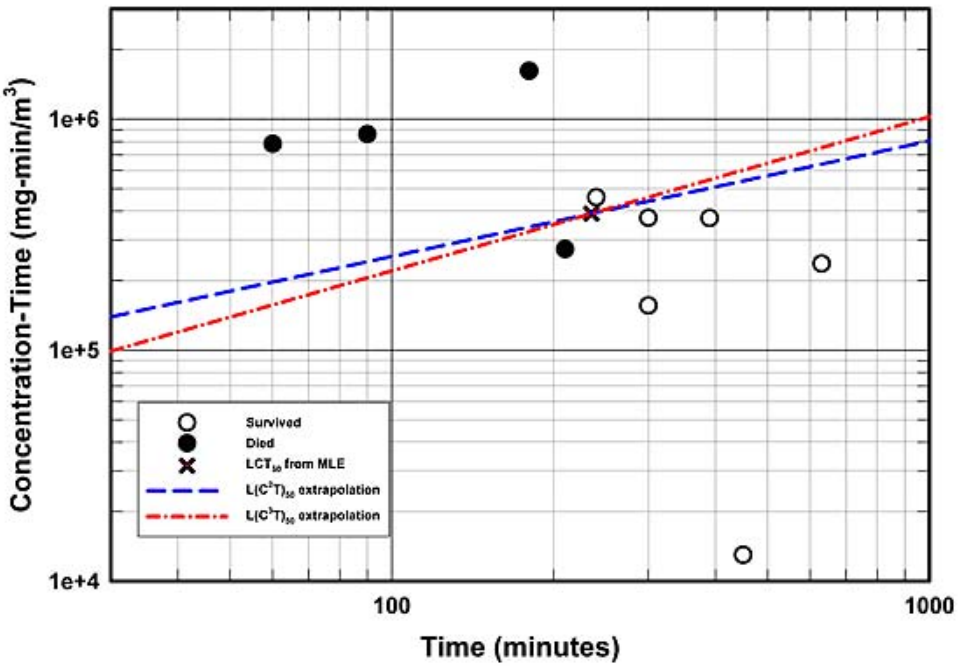

Figure C–1. Binary response data for chlorine inhalation exposures for cats from Lehmann (1882)

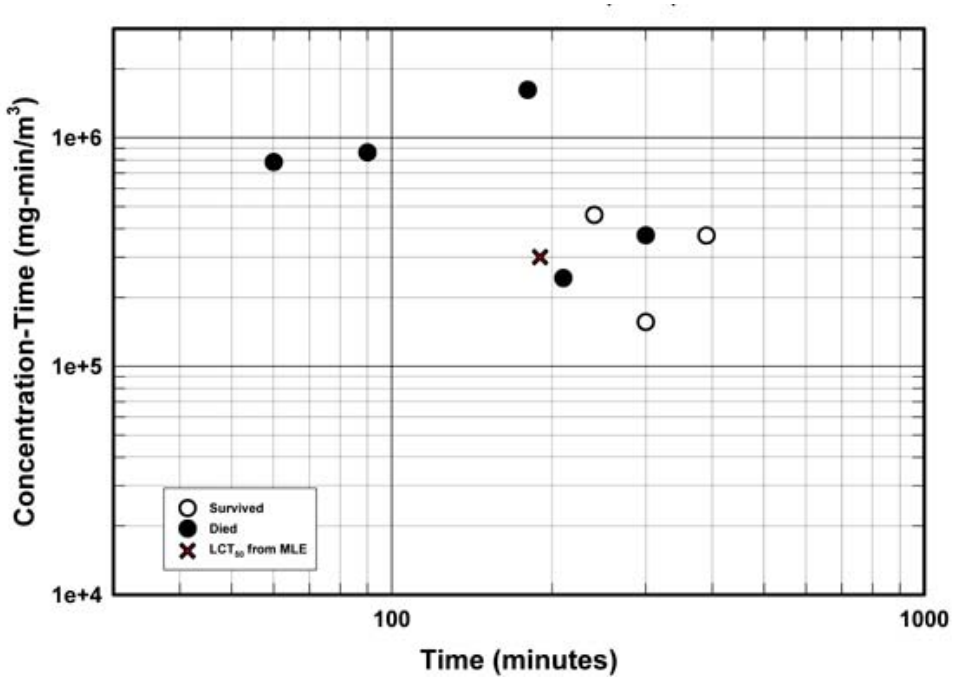

Figure C–2. Binary response data for chlorine inhalation exposures for rabbits from Lehmann (1882)

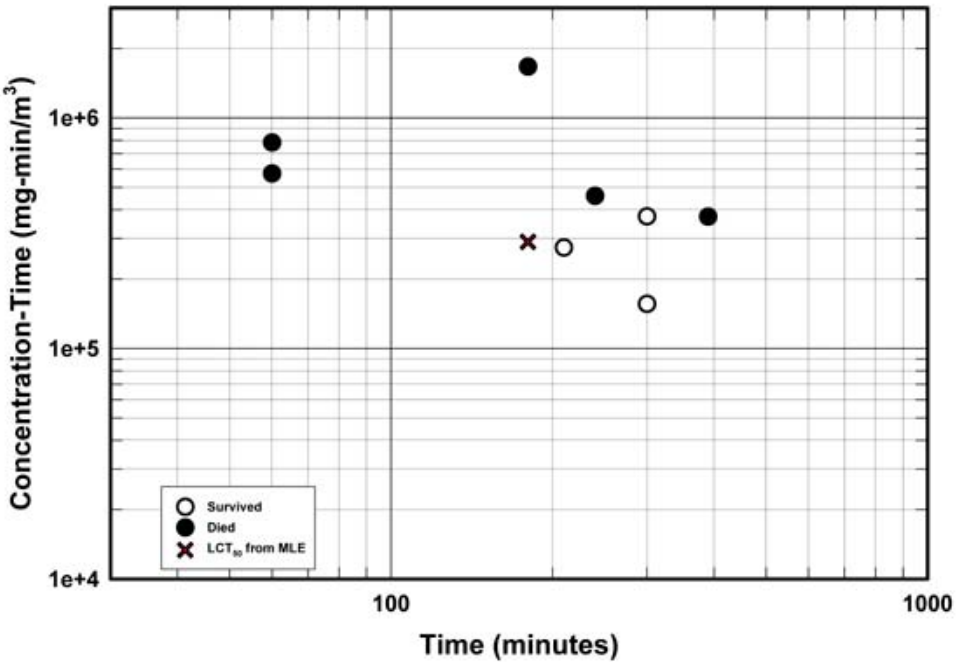

Figure C–3. Binary response data for chlorine inhalation exposures for guinea pigs from Lehmann (1882)

C4.0 Discussion and Results

The estimated LCT_{50} values for both Lehmann (1882)[1] and McElroy *et al.* (1943)[2] are listed in Table C–5 (with approximate 95% confidence intervals), and the values for the Lehmann dataset are shown in Figures C–1 to C–3.

Based upon the ratio of the 95% confidence limits, the LCT_{50} estimates for McElroy *et al.* dataset are more precise than those for Lehmann. This is probably due to McElroy *et al.* having more animals exposed at some fixed duration (or small duration interval) than Lehmann. In the case of Lehmann, it was infrequent for him to have more than one exposure for a particular duration.

For best results, a one-parameter MLE analysis should be used with one-dimensional datasets. This is usually the case with response data collected for a series of different vapor concentrations at one exposure duration. With McElroy *et al.* (1943),[2] this was readily accomplished (see above) through judicious grouping. For Lehmann (1882),[1] this could not be done, and at first glance, the data appear to be two-dimensional, with both concentration and duration being varied simultaneously. However, the coordinates for the test conditions do roughly stay within a narrow band and thus are one-dimensional. This band is more or less perpendicular to the toxic load model extrapolation from the estimated LCT_{50} value. This is demonstrated in Figure C–1 using Lehmann's cat data. Two different toxic load extrapolations are shown: n =2 and n = 3. With a proper MLE application, the estimated median effective dosage/toxic load should be a demarcation point between two groups: one predominated by lethal outcomes (above the median effective toxic load) and the other by nonlethal outcomes (below the median effective toxic load). For the Lehmann data, such an effect is seen. Also, there is no difference in how the $L(C^2T)_{50}$ and $L(C^3T)_{50}$ curves split the test coordinates, which is why the MLE estimate for the median effective dosage is insensitive (in this case) to the assumed value for the toxic load exponent (n).

Prior to a MLE analysis approach, it was not possible to derive estimated LCT_{50} values for either Lehmann or McElroy *et al.* using traditional probit analysis methods. Thus, MLE analysis can "retrieve" additional median lethal toxicity information from previously ignored data sources.

Table C–5. LCT_{50} estimates from MLE analysis of datasets from Lehmann (1882) and McElroy *et al.* (1943)

SPECIES	TIME (min)	LCT_{50} (mg-min/m^3)	APPROXIMATE 95% CONFIDENCE INTERVAL		RATIO OF UL TO LL	STUDY
			LOWER LIMIT	UPPER LIMIT		
Goat	8.5	16500	13900	19500	1.40	McElroy *et al.*
Goat	18.5	51500	44500	59000	1.33	McElroy *et al.*
Cat	235	390000	290000	520000	1.79	Lehmann
Rabbit	190	300000	225000	385000	1.71	Lehmann
Guinea Pig	180	290000	210000	390000	1.86	Lehmann

C5.0 References

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APPENDIX D: COMPLETE TABLE OF DATA AND COMPUTATIONS

Table D–1. Table of data and calculations

STUDY (AUTHORS)	REPORT DATE	REFERENCE NUMBER	RAW DATA	METHOD	TIME (min)	LCT_{50} (mg-min/m^3)	PROBIT SLOPE	SLOPE ERROR	MV (L)	MV (m^3)	MASS (kg)	LETHAL DOSE (mg)	LOG (LD)	LOG(M)	LOG(T)
MOUSE															
Silver, McGrath	1942	1	Yes	Probit	10	13150	7.3207	0.5184	0.031	0.000031	0.0207	0.40765	-0.3897	-1.6840	1.0000
Silver, McGrath, Ferguson	1942	2	Yes	Probit	10	19430	7.8260	1.0520	0.031	0.000031	0.0207	0.60233	-0.2202	-1.6840	1.0000
Zwart, Woutersen	1988	3	Yes	Probit	10	30620	10.0410	2.0060	0.031	0.000031	0.0207	0.94922	-0.0226	-1.6840	1.0000
Alarie	1980	4	No		10	8752			0.031	0.000031	0.0207	0.27131	-0.5665	-1.6840	1.0000
Bunting	1945	5	No		10	15200			0.031	0.000031	0.0207	0.47120	-0.3268	-1.6840	1.0000
Lipton, Rotariu	1941	6	No		10	18199			0.031	0.000031	0.0207	0.56417	-0.2486	-1.6840	1.0000
Bitron, Aharonson	1978	7	Yes	MLE	11	9245	10.6300	1.0160	0.031	0.000031	0.0207	0.28660	-0.5427	-1.6840	1.0414
Schlagbauer, Henschler	1967	8	Yes	Probit	30	10682	6.1790	1.2280	0.031	0.000031	0.0207	0.33114	-0.4800	-1.6840	1.4771
Zwart, Woutersen	1988	3	Yes	Probit	30	49300	6.8240	3.6750	0.031	0.000031	0.0207	1.52830	0.1842	-1.6840	1.4771
Bitron, Aharonson	1978	7	Yes	MLE	55	27096	10.6300	1.0160	0.031	0.000031	0.0207	0.83998	-0.0757	-1.6840	1.7404
Back, Thomas, MacEwen	1972	9	No		60	23822			0.031	0.000031	0.0207	0.73848	-0.1317	-1.6840	1.7782
RAT															
Zwart, Woutersen	1988	3	Yes	Probit	5	77850	15.8410	3.3290	0.203	0.000203	0.2610	15.80355	1.1988	-0.5834	0.6990
Zwart, Woutersen	1988	3	Yes	Probit	10	61160	15.8410	3.3290	0.203	0.000203	0.2610	12.41548	1.0940	-0.5834	1.0000
Zwart, Woutersen	1988	3	Yes	Probit	30	54810	15.8410	3.3290	0.203	0.000203	0.2610	11.12643	1.0464	-0.5834	1.4771
Zwart, Woutersen	1988	3	Yes	Probit	60	83820	15.8410	3.3290	0.203	0.000203	0.2610	17.01546	1.2308	-0.5834	1.7782
Vernot, MacEwen, Haun	1977	10	No		60	50947			0.203	0.000203	0.2610	10.34224	1.0146	-0.5834	1.7782
GUINEA PIG															
Lehmann	1882	11	Yes	MLE	180	290000			0.182	0.000182	0.3230	52.78000	1.7225	-0.4908	2.2553

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Table D–1. Table of data and calculations

STUDY (AUTHORS)	REPORT DATE	REFERENCE NUMBER	RAW DATA	METHOD	TIME (min)	LCT_{50} (mg-min/m^3)	PROBIT SLOPE	SLOPE ERROR	MV (L)	MV (m^3)	MASS (kg)	LETHAL DOSE (mg)	LOG (LD)	LOG(M)	LOG(T)
RABBIT															
Marshall	1917(a)	12	Yes	MLE	30	21580			1.453	0.001453	2.7700	31.35574	1.4963	0.4425	1.4771
Barrow, Smith	1975	13	Yes	MLE	30	30479			1.453	0.001453	2.7700	44.28599	1.6463	0.4425	1.4771
Lehmann	1882	11	Yes	MLE	190	300000			1.453	0.001453	2.7700	435.90000	2.6394	0.4425	2.2788
CAT															
Lehmann	1882	11	Yes	MLE	235	390000			0.845	0.000845	3.3600	329.55000	2.5179	0.5263	2.3711
DOG															
Armstrong	1923	14	Yes	Probit	10	58340	7.5120	2.8290	4.230	0.004230	13.0000	246.77820	2.3923	1.1139	1.0000
Marshall	1917(a)	12	Yes	Probit	30	47010	3.1170	1.4460	4.230	0.004230	13.0000	198.85230	2.2985	1.1139	1.4771
Underhill	1920	15	Yes	Probit	30	49380	3.4514	0.8053	4.230	0.004230	13.0000	208.87740	2.3199	1.1139	1.4771
Marshall	1917(b)	16	No		30	75000			4.230	0.004230	13.0000	317.25000	2.5014	1.1139	1.4771
Beebe	1924	17	No		30	90000			4.230	0.004230	13.0000	380.70000	2.5806	1.1139	1.4771
SHEEP															
Batchinsky, Martini, Jordan	2006	18	No		30	24343			13.900	0.013900	52.6000	338.36770	2.5294	1.7210	1.4771
GOAT															
McElroy, Shils, Ginsburg	1943	19	Yes	MLE	18.5	51500			9.600	0.009600	36.9000	494.40000	2.6941	1.5670	1.2672
McElroy, Shils, Ginsburg	1943	19	Yes	MLE	8.5	16500			9.600	0.009600	36.9000	158.40000	2.1998	1.5670	0.9294

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D1.0 References

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APPENDIX E: ITERATIVELY REWEIGHTED LEAST SQUARES (IRLS)

i = 1 (Establish iteration counter, where i = 1, 2, . . .m, and "m" is the total number of iterations needed for convergence.

↓

↓

Derive first (i = 1) regression equation. The initial regression is unweighted, since the weights are a function of the studentized residuals that will occur after the first model is attempted. The residuals from any iteration will generate the weights for producing the subsequent iteration (if one is needed). The form of the model is:

$$\log(\text{Dose}) = k_o + k_m \log(\text{Mass}) + k_t \log(\text{Time})$$

↓

↓

Calculate the studentized residual for each observed value. The residual for the i^{th} observation is calculated by a comparison of the full model with a model with the i^{th} observation removed. These quantities are labeled as $TRES_{1,j}$ where:

j = 1, 2, ... n, and "n" is the number of observations.

↓

↓

Calculate the set of "weights" to be applied to the observations in the second iteration.

$W_{2,j} = 2/(1 + [TRES_{1,j}]^2)$ where j = 1, 2, ... n, and "n" is the number of observations.

↓

↓

Derive second (i = 2) regression equation.

↓

↓

Calculate t-values for the second set of standardized residuals for use in the third iteration ($[TRES_{2,j}]^2$)

↓

↓

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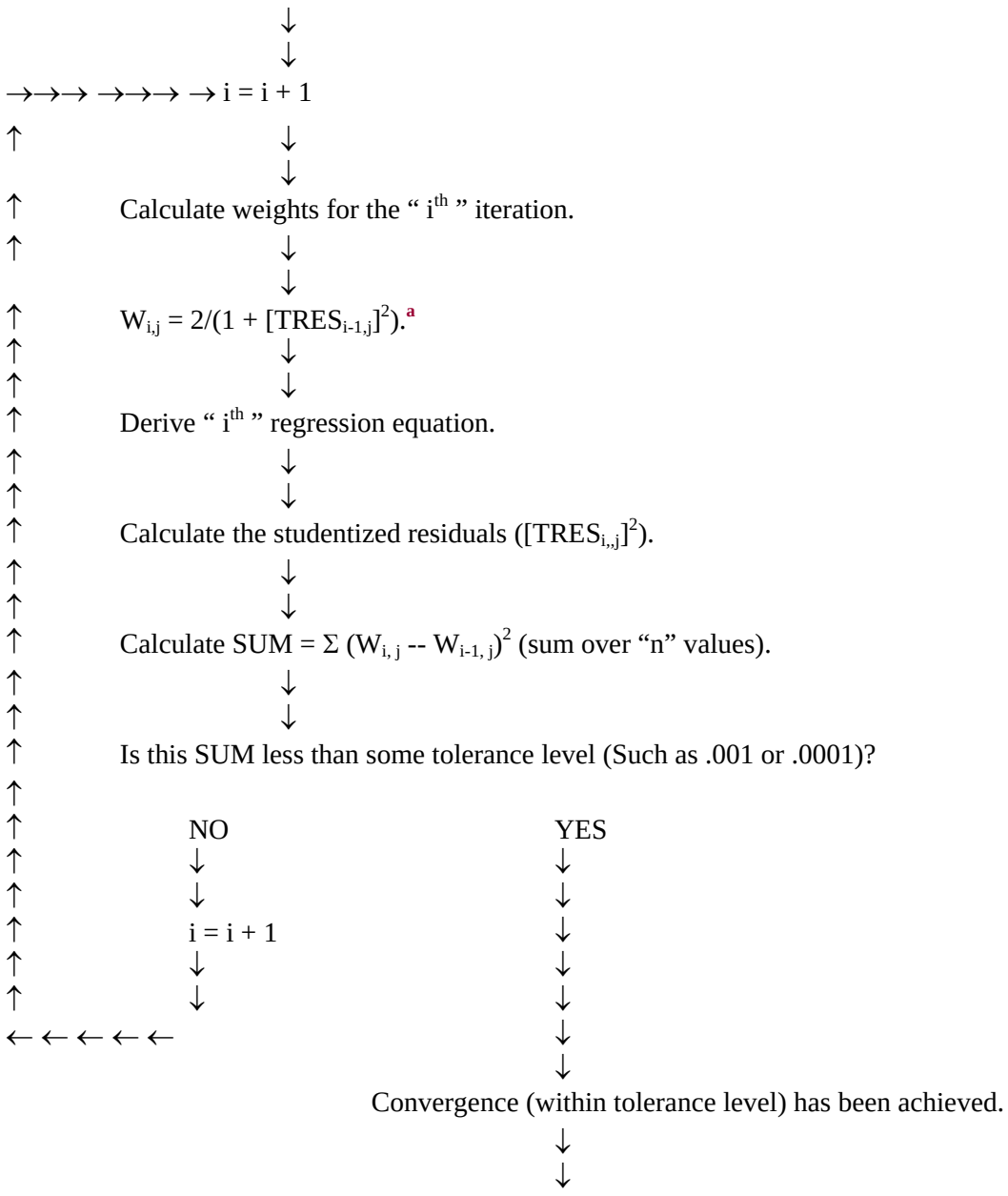

[a] A supplemental approach that was used in the weighted regression runs for this project incorporates an averaging process. Weights are calculated as a result of the studentized residuals, as presented above. These values can be referred to as "preliminary" weights. This new set of weights is averaged with the weights used in the run immediately prior to form the "applied" weights for the current model. That is,

$W_{i,\,j\ (applied)} = [\ W_{i,\,j\ (preliminary)} + W_{i-1,\,j\ (applied)}\ ]/2$

This process, though optional, may induce an earlier convergence and a quicker adherence to the stated tolerance level.

APPENDIX F: MINITAB® SESSION IRLS ANALYSIS FOR LOG(LD_{50}) AS A FUNCTION OF LOG(TIME) AND LOG(MASS)

Regression analysis: log(LD_{50}) versus log(M), log(T)

Unweighted regression:

The regression equation is:
Log(LD_{50}) = 0.642 + 0.873 log(M) + 0.543 log(T)

Predictor	Coef	SE Coef	T	P	VIF
Constant	0.6420	0.1874	3.43	0.002	
Log(M)	0.87255	0.04281	20.38	0.000	1.0
Log(T)	0.5433	0.1259	4.32	0.000	1.0

S = 0.2812
R-Sq = 94.9%
R-Sq(adj) = 94.5%
PRESS = 2.63845
R-Sq(pred) = 93.50%

Analysis of variance

Source	DF	SS	MS	F	P
Regression	2	38.530	19.265	243.63	0.000
Residual error	26	2.056	0.079		
Lack of fit	15	1.578	0.105	2.42	0.072
Pure error	11	0.478	0.043		
Total	28	40.586			

13 rows with no replicates

Source	DF	Seq SS
Log(M)	1	37.057
Log(T)	1	1.473

No evidence of lack of fit (P > 0.1)

Establish the weight for the second regression run.

Let W2 = 2/(1 + (TRES1)**2)

Regression analysis: log(LD_{50}) versus log(M), log(T)

Weighted regression analysis using weights in W2:

The regression equation is:
Log(LD_{50}) = 0.548 + 0.873 log(M) + 0.606 log(T)

Predictor	Coef	SE Coef	T	P	VIF
Constant	0.5479	0.1505	3.64	0.001	
Log(M)	0.87308	0.03153	27.69	0.000	1.1
Log(T)	0.6060	0.1010	6.00	0.000	1.1

S = 0.2327
R-Sq = 97.4%
R-Sq(adj) = 97.1%
PRESS = 1.70162
R-Sq(pred) = 96.80%

Analysis of variance

Source	DF	SS	MS	F	P
Regression	2	51.785	25.893	478.14	0.000
Residual error	26	1.408	0.054		
Lack of fit	15	0.930	0.062	1.43	0.279
Pure error	11	0.478	0.043		
Total	28	53.193			

13 rows with no replicates

Source	DF	Seq SS
Log(M)	1	49.837
Log(T)	1	1.948

Durbin-Watson statistic = 1.80
No evidence of lack of fit (P > 0.1)

Establish the weight for the third regression run.

Let W3 – Pre = 2/(1 + (TRES3)**2)
Let W3 = (W3 – Pre + W2)/2

Regression analysis: log(LD_{50}) versus log(M), log(T)

Weighted regression analysis using weights in W3:

The regression equation is:
$Log(LD_{50}) = 0.547 + 0.872\ log(M) + 0.608\ log(T)$

Predictor	Coef	SE Coef	T	P	VIF
Constant	0.5472	0.1551	3.53	0.002	
Log(M)	0.87183	0.03344	26.07	0.000	1.1
Log(T)	0.6077	0.1039	5.85	0.000	1.1

S = 0.2399

R-Sq = 97.1%

R-Sq(adj) = 96.8%

PRESS = 1.83254

R-Sq(pred) = 96.40%

Analysis of variance

Source	DF	SS	MS	F	P
Regression	2	49.448	24.724	429.52	0.000
Residual error	26	1.497	0.058		
Lack of fit	15	1.035	0.069	1.65	0.205
Pure error	11	0.461	0.042		
Total	28	50.945			

13 rows with no replicates

Source	DF	Seq SS
Log(M)	1	47.478
Log(T)	1	1.971

Durbin-Watson statistic = 1.81

No evidence of lack of fit (P > 0.1)

Calculate the sum of squared differences of the last two weights, and compare to tolerance level.

Let DIFF (W3 – W2)**2 = (W3 – W2)**2

Sum of DIFF (W3 – W2)**2 = 0.48642

The first difference of successive weights occurred after the third run was made. The difference of the second weight (used for the 2nd regression run but produced by the 1st regression model) and the third weight (used for the 3rd regression run but produced by the 2nd regression model) was squared for each observation. The sum of the squared differences (SSD) was found to equal 0.53764. Iterations of model building will be continued until the SSD does not exceed a predetermined "tolerance."

As a result of the 7th run, the SSD attained a value of 0.000572. Several more runs were made to acquire a finer level of accuracy. The final regression run is provided below.

Regression analysis: log(LD_{50}) versus log(M), log(T)

Weighted regression analysis using weights in W 30:

The regression equation is:
$Log(LD_{50}) = 0.515 + 0.869\ log(M) + 0.630\ log(T)$

Predictor	Coef	SE Coef	T	P	VIF
Constant	0.5147	0.1526	3.37	0.002	
Log(M)	0.86908	0.03347	25.97	0.000	1.1
Log(T)	0.6296	0.1015	6.20	0.000	1.1

S = 0.2373

R-Sq = 97.1%

R-Sq(adj) = 96.9%

PRESS = 1.79176

R-Sq(pred) = 96.43%

Analysis of variance

Source	DF	SS	MS	F	P
Regression	2	48.747	24.373	432.79	0.000
Residual error	26	1.4642	0.056		
Lack of fit	15	1.012	0.067	1.64	0.206
Pure error	11	0.453	0.041		
Total	28	50.211			

13 rows with no replicates

Source	DF	Seq SS
Log(M)	1	46.581
Log(T)	1	2.165

Durbin-Watson statistic = 1.81

No evidence of lack of fit (P > 0.1)

Predicted values for new observations:

New Obs	Fit	SE Fit	95.0% CI	95.0% PI
1	2.3078	0.1555	(1.9881, 2.6275)	(1.7246, 2.8910)
2	2.7479	0.1016	(2.5390, 2.9567)	(2.2172, 3.2785)
3	3.0483	0.0815	(2.8807, 3.2158)	(2.5325, 3.5640)
4	3.2378	0.0821	(3.0691, 3.4065)	(2.7216, 3.7539)
5	3.4273	0.0933	(3.2356, 3.6191)	(2.9032, 3.9514)
6	3.6168	0.1120	(3.3867, 3.8470)	(3.0775, 4.1562)
7	3.7277	0.1251	(3.4706, 3.9848)	(3.1763, 4.2791)
8	3.8064	0.1350	(3.5288, 4.0839)	(3.2451, 4.3676)
9	3.9959	0.1606	(3.6657, 4.3261)	(3.4069, 4.5849)

Values of predictors for new observations:

New Obs	log(M)	log(T)
1	1.85	0.30
2	1.85	1.00
3	1.85	1.48
4	1.85	1.78
5	1.85	2.08
6	1.85	2.38
7	1.85	2.56
8	1.85	2.68
9	1.85	2.98

Mean square error = 0.0563163

"X-prime X" inverse matrix:

0.413737	0.029592	-0.264750
0.029592	0.019892	-0.016512
-0.264750	-0.016512	0.183084

Variance-covariance matrix:

0.023300	0.001667	-0.014910
0.001667	0.001120	-0.000930
-0.014910	-0.000930	0.010311

Tables F–1 through F–3 summarize the data in Appendix F.

Table F–1. Raw data, input quantities, and output results

						MODEL INPUT			MODEL OUTPUT				
Species	Time (min)	Minute Volume (m^3/min)	Observed LCT_{50}	Mass (kg)	Observed LD_{50}	Observed Log (LD_{50})	Log(Time)	Log(Mass)	Last Applied Weight	Standardized Residuals	Studentized Residuals	Predicted log (LD_{50})	Predicted LD_{50}
Mouse	10	0.000031	8752	0.0207	0.271	-0.56653	1.00000	-1.68403	0.94547	-1.05376	-1.05610	-0.31923	0.48
Mouse	10	0.000031	13150	0.0207	0.408	-0.38971	1.00000	-1.68403	1.71066	-0.41800	-0.41126	-0.31923	0.48
Mouse	10	0.000031	15200	0.0207	0.471	-0.32679	1.00000	-1.68403	1.99537	-0.04911	-0.04815	-0.31923	0.48
Mouse	10	0.000031	18199	0.0207	0.564	-0.24859	1.00000	-1.68403	1.70972	0.41878	0.41204	-0.31923	0.48
Mouse	10	0.000031	19430	0.0207	0.602	-0.22017	1.00000	-1.68403	1.54100	0.55328	0.54576	-0.31923	0.48
Mouse	10	0.000031	30620	0.0207	0.949	-0.02263	1.00000	-1.68403	0.82988	1.17818	1.18743	-0.31923	0.48
Mouse	11	0.000031	9245	0.0207	0.287	-0.54273	1.04139	-1.68403	0.94091	-1.05839	-1.06094	-0.29317	0.51
Mouse	30	0.000031	10682	0.0207	0.331	-0.47999	1.47712	-1.68403	0.58394	-1.51625	-1.55724	-0.01883	0.96
Mouse	30	0.000031	49300	0.0207	1.528	0.18421	1.47712	-1.68403	1.08060	0.92506	0.92240	-0.01883	0.96
Mouse	55	0.000031	27096	0.0207	0.840	-0.07573	1.74036	-1.68403	1.00725	-0.99305	-0.99278	0.14690	1.40
Mouse	60	0.000031	23822	0.0207	0.738	-0.13166	1.77815	-1.68403	0.81079	-1.20036	-1.21108	0.17070	1.48
Rat	5	0.000203	77850	0.2610	15.804	1.19875	0.69897	-0.58336	0.37091	1.97110	2.09574	0.44781	2.80
Rat	10	0.000203	61160	0.2610	12.415	1.09396	1.00000	-0.58336	0.59063	1.50514	1.54474	0.63734	4.34
Rat	30	0.000203	54810	0.2610	11.126	1.04636	1.47712	-0.58336	1.51078	0.57659	0.56905	0.93774	8.66
Rat	60	0.000203	50947	0.2610	10.342	1.01461	1.77815	-0.58336	1.47646	-0.60301	-0.59548	1.12727	13.41
Rat	60	0.000203	83820	0.2610	17.015	1.23084	1.77815	-0.58336	1.52633	0.56461	0.55707	1.12727	13.41
G Pig	180	0.000182	290000	0.3230	52.780	1.72247	2.25527	-0.49080	1.00815	0.99220	0.99189	1.50811	32.22
Rabbit	30	0.001453	21580	2.7700	31.356	1.49632	1.47712	0.44248	0.76964	-1.25005	-1.26436	1.82927	67.49
Rabbit	30	0.001453	30479	2.7700	44.286	1.64627	1.47712	0.44248	1.16420	-0.85193	-0.84730	1.82927	67.49
Rabbit	190	0.001453	300000	2.7700	435.900	2.63939	2.27875	0.44248	0.79205	1.22266	1.23494	2.33398	215.76
Cat	235	0.000845	390000	3.3600	329.550	2.51792	2.37107	0.52634	1.77546	0.36176	0.35563	2.46498	291.73
Dog	10	0.004230	58340	13.0000	246.778	2.39231	1.00000	1.11394	0.85391	1.15097	1.15852	2.11243	129.55
Dog	30	0.004230	47010	13.0000	198.852	2.29853	1.47712	1.11394	1.46279	-0.61352	-0.60601	2.41283	258.72
Dog	30	0.004230	49380	13.0000	208.877	2.31989	1.47712	1.11394	1.58236	-0.52118	-0.51375	2.41283	258.72
Dog	30	0.004230	75000	13.0000	317.250	2.50140	1.47712	1.11394	1.60787	0.50119	0.49384	2.41283	258.72
Dog	30	0.004230	90000	13.0000	380.700	2.58058	1.47712	1.11394	1.21177	0.81200	0.80652	2.41283	258.72
Goat	8.5	0.009600	16500	36.9000	158.400	2.19976	0.92942	1.56703	0.87852	-1.12388	-1.12984	2.46176	289.57
Goat	18.5	0.009600	51500	36.9000	494.400	2.69408	1.26717	1.56703	1.96713	0.13179	0.12927	2.67441	472.51
Sheep	30	0.013900	24343	52.6000	338.368	2.52939	1.47712	1.72099	0.63676	-1.43210	-1.46319	2.94040	871.77

Table F–2. Human dose and dosage estimates with respect to exposure time from allometric fit

TIME (min)	LOG(DOSE) (LD_{50})			DOSE (LD_{50}) (mg)			DOSAGE (LCT_{50}) mg-min/m^3		
	POINT ESTIMATE	LOWER BOUND	UPPER BOUND	POINT ESTIMATE	LOWER BOUND	UPPER BOUND	POINT ESTIMATE	LOWER BOUND	UPPER BOUND
2	2.30779	1.98810	2.62748	203	97	424	13500	6500	28300
10	2.74786	2.53901	2.95671	560	346	905	37300	23100	60300
30	3.04826	2.88071	3.21581	1118	760	1644	74500	50700	110000
60	3.23779	3.06905	3.40652	1729	1172	2550	115000	78200	170000
120	3.42732	3.23557	3.61906	2675	1720	4160	178000	115000	277000
240	3.61685	3.38673	3.84696	4139	2436	7030	276000	162000	469000
360	3.72771	3.47065	3.98478	5342	2956	9656	356000	197000	644000
480	3.80638	3.52882	4.08393	6403	3379	12132	427000	225000	809000
960	3.99591	3.66572	4.32609	9906	4631	21188	660000	309000	1145000

Table F–3. Human concentration estimates with respect to exposure time from allometric fit

TIME (min)	CONCENTRATION (LC_{50}) (mg/m^3)			CONCENTRATION (LC_{50}) (ppm)		
	POINT ESTIMATE	LOWER BOUND	UPPER BOUND	POINT ESTIMATE	LOWER BOUND	UPPER BOUND
2	6770	3240	14100	2340	1120	4880
10	3730	2310	6030	1290	800	2080
30	2480	1690	3650	860	580	1260
60	1920	1300	2830	660	450	980
120	1490	960	2310	510	330	800
240	1150	680	1950	400	230	670
360	990	550	1790	340	190	620
480	890	470	1690	310	160	580
960	690	320	1190	240	110	410

APPENDIX G: MINITAB® SESSION IRLS ANALYSIS FOR LOG(LC_{50}) AS A FUNCTION OF LOG(TIME), LOG(MASS) AND LOG(MVRATIO)

Regression analysis: log(LC_{50}) versus log(M), log(T)

Unweighted regression:

The regression equation is:
log(LC_{50}) = 3.78 + 0.103 log(M) – 0.393 log(T)

Predictor	Coef	SE Coef	T	P	VIF
Constant	3.7846	0.2024	18.70	0.000	
Log(M)	0.10310	0.04624	2.23	0.035	1.0
Log(T)	-0.3932	0.1360	-2.89	0.008	1.0

S = 0.3037

R-Sq = 30.2%

R-Sq(adj) = 24.8%

PRESS = 3.08666

R-Sq(pred) = 10.15%

Analysis of variance

Source	DF	SS	MS	F	P
Regression	2	1.03660	0.51830	5.62	0.009
Residual error	26	2.39859	0.09225		
Lack of fit	15	1.92066	0.12804	2.95	0.038
Pure error	11	0.47793	0.04345		
Total	28	3.43518			

13 rows with no replicates

Source	DF	Seq SS
Log(M)	1	0.26498
Log(T)	1	0.77161

Durbin-Watson statistic = 1.69

The same iterative procedure demonstrated in Appendix F, and described in Appendix E, was employed here. A weight was calculated for each iteration, and the process was curtailed when the individual SSD of two consecutive sets of weights (from two consecutive regression runs) became close to zero.

The final run is depicted below.

Regression analysis: log(LC_{50}) versus log(M), log(T)

Weighted regression analysis using weights in W30:

The regression equation is:
log(LC_{50}) = 3.62 + 0.0976 log(M) – 0.278 log(T)

Predictor	Coef	SE Coef	T	P	VIF
Constant	3.6208	0.1670	21.68	0.000	
Log(M)	0.09764	0.03575	2.73	0.011	1.1
Log(T)	-0.2780	0.1125	-2.47	0.020	1.1

S = 0.2554

R-Sq = 29.2%

R-Sq(adj) = 23.8%

PRESS = 2.08444

R-Sq(pred) = 13.02%

Analysis of variance

Source	DF	SS	MS	F	P
Regression	2	0.69982	0.34991	5.36	0.011
Residual error	26	1.69658	0.06525		
Lack of fit	15	1.22493	0.08166	1.90	0.142
Pure error	11	0.47165	0.04288		
Total	28	2.39639			

13 rows with no replicates

Source	DF	Seq SS
Log(M)	1	0.30115
Log(T)	1	0.39867

Durbin-Watson statistic = 1.72

Predicted values for new observations:

New Obs	Fit	SE Fit	95.0% CI	95.0% PI
1	3.7172	0.1685	(3.3709, 4.0636)	(3.0882, 4.3463)
2	3.5229	0.1088	(3.2994, 3.7465)	(2.9522, 4.0936)
3	3.3903	0.0873	(3.2108, 3.5697)	(2.8353, 3.9452)
4	3.3066	0.0891	(3.1235, 3.4897)	(2.7505, 3.8626)
5	3.2229	0.1027	(3.0118, 3.4339)	(2.6570, 3.7888)
6	3.1392	0.1242	(2.8838, 3.3945)	(2.5553, 3.7231)
7	3.0902	0.1392	(2.8042, 3.3762)	(2.4923, 3.6881)
8	3.0555	0.1504	(2.7463, 3.3647)	(2.4461, 3.6648)
9	2.9718	0.1792	(2.6034, 3.3401)	(2.3304, 3.6132)

No evidence of lack of fit (P > 0.1)

Values of predictors for new observations:

New Obs	log(M)	log(T)
1	1.85	0.30
2	1.85	1.00
3	1.85	1.48
4	1.85	1.78
5	1.85	2.08
6	1.85	2.38
7	1.85	2.56
8	1.85	2.68
9	1.85	2.98

Mean square error = 0.0652529

"X-prime X" inverse matrix:

0.427454	0.029429	-0.277259
0.029429	0.019586	-0.016489
-0.277259	-0.016489	0.193902

Variance-covariance matrix:

0.027893	0.001920	-0.018092
0.001920	0.001278	-0.001076
-0.018092	-0.001076	0.012653

Regression analysis: log(LC_{50}) versus log(M), log(MVratio), log(T)

Unweighted regression:

The regression equation is:

$\log(LC_{50}) = 4.24 - 0.0098 \log(M) - 2.85 \log(MVratio) - 0.574 \log(T)$

Predictor	Coef	SE Coef	T	P	VIF
Constant	4.2391	0.2393	17.72	0.000	
Log(M)	-0.00976	0.05681	-0.17	0.865	2.0
Log(MVratio)	-2.8534	0.9962	-2.86	0.008	2.5
Log(T)	-0.5742	0.1359	-4.23	0.000	1.3

S = 0.2688

R-Sq = 47.4%

R-Sq(adj) = 41.1%

PRESS = 3.15099

R-Sq(pred) = 8.27%

Analysis of variance

Source	DF	SS	MS	F	P
Regression	3	1.62924	0.54308	7.52	0.001
Residual error	25	1.80594	0.07224		
Lack of fit	14	1.32802	0.09486	2.18	0.099
Pure error	11	0.47793	0.04345		
Total	28	3.43518			

13 rows with no replicates

Source	DF	Seq SS
Log(M)	1	0.26498
Log(MVratio)	1	0.07459
Log(T)	1	1.28966

The inclusion of species mass, specifically the variable log(Mass), does not contribute to the regression equation. Log(Mass) has attained a high p-value, indicating minimal or no value in predicting log(LC_{50}) given the other variables in the model. The presence of log(MVratio) negates the need for the mass variable to also be included. Additional runs are made without log(Mass). See Table G–1 for the concentration, dosage, and dose estimates regression with log(LC_{50}) versus log(M) and log(T) data.

Table G–1. Concentration, dosage, and dose estimates regression with log(LC_{50}) versus log(M) and log(T)

TIME (min)	LOG [CONCENTRATION (LC_{50})] (mg/m^3)			CONCENTRATION (LC_{50}) (mg/m^3)		
	POINT ESTIMATE	LOWER BOUND	UPPER BOUND	POINT ESTIMATE	LOWER BOUND	UPPER BOUND
2	3.71724	3.37091	4.06358	5210	2350	11580
10	3.52291	3.29935	3.74646	3330	1990	5580
30	3.39025	3.21078	3.56972	2460	1620	3710
60	3.30655	3.12345	3.48965	2030	1330	3090
120	3.22286	3.01184	3.43388	1670	1030	2720
240	3.13916	2.88378	3.39455	1380	770	2480
360	3.09020	2.80416	3.37624	1239	640	2380
480	3.05546	2.74627	3.36466	1140	560	2320
960	2.97177	2.60343	3.34011	940	400	2190

TIME (min)	LOG [CONCENTRATION (LC_{50})] (ppm)			DOSAGE (LCT_{50}) (mg-min/m^3)		
	POINT ESTIMATE	LOWER BOUND	UPPER BOUND	POINT ESTIMATE	LOWER BOUND	UPPER BOUND
2	1800	810	3990	10400	4700	23200
10	1150	690	1920	33300	19900	55800
30	850	560	1280	73700	48700	111000
60	700	460	1070	122000	79700	185000
120	580	350	940	200000	123000	326000
240	480	260	860	331000	184000	595000
360	420	220	820	443000	229000	856000
480	390	190	800	545000	268000	1111000
960	320	140	760	900000	385000	2101000

Regression analysis: log(LC_{50}) versus log(MVratio), log(T)

Unweighted regression:

$\log(LC_{50}) = 4.23 - 2.73 \log(MVratio) - 0.570 \log(T)$

Predictor	Coef	SE Coef	T	P	VIF
Constant	4.2260	0.2225	18.99	0.000	
Log(MVratio)	-2.7347	0.7041	-3.88	0.001	1.3
Log(T)	-0.5696	0.1307	-4.36	0.000	1.3

S = 0.2637

R-Sq = 47.4%

R-Sq(adj) = 43.3%

PRESS = 2.53042

R-Sq(pred) = 26.34%

Analysis of variance

Source	DF	SS	MS	F	P
Regression	2	1.62711	0.81355	11.70	0.000
Residual error	26	1.80808	0.06954		
Lack of fit	15	1.33015	0.08868	2.04	0.118
Pure error	11	0.47793	0.04345		
Total	28	3.43518			

13 rows with no replicates

Source	DF	Seq SS
Log(MVratio)	1	0.30663
Log(T)	1	1.32047

Durbin-Watson statistic = 2.05

No evidence of lack of fit (P > 0.1)

The same iterative procedure demonstrated in Appendix F, and described in Appendix E, was employed here. A weight was calculated for each iteration, and the process was curtailed when the individual squared differences (SSD) of two consecutive sets of weights (from two consecutive regression runs) became close to zero.

The final run is depicted below.

Regression analysis: log(LC_{50}) versus, log(MVratio), log(T)

Weighted regression analysis using weights in W30

The regression equation is:
log(LC_{50}) = 4.31 – 3.03 log(MVratio) – 0.627 log(T)

Predictor	Coef	SE Coef	T	P	VIF
Constant	4.3117	0.1913	22.54	0.000	
Log(MVratio)	-3.0292	0.5721	-5.29	0.000	1.3
Log(T)	-0.6272	0.1131	-5.55	0.000	1.3

S = 0.2182

R-Sq = 60.2%

R-Sq(adj) = 57.1%

PRESS = 1.69334

R-Sq(pred) = 45.57%

Analysis of variance

Source	DF	SS	MS	F	P
Regression	2	1.87288	0.93644	19.66	0.000
Residual error	26	1.23841	0.04763		
Lack of fit	15	0.80505	0.05367	1.36	0.306
Pure error	11	0.43336	0.03940		
Total	28	3.11129			

13 rows with no replicates

Source	DF	Seq SS
Log(MVratio)	1	0.40779
Log(T)	1	1.46509

Durbin-Watson statistic = 2.04

No evidence of lack of fit (P > 0.1)

Predicted values for new observations:

New Obs	Fit	SE Fit	95.0% CI	95.0% PI
1	4.1229	0.1591	(3.7959, 4.4499)	(3.5677, 4.6780)
2	3.6845	0.0898	(3.4999, 3.8690)	(3.1994, 4.1696)
3	3.3852	0.0589	(3.2642, 3.5062)	(2.9206, 3.8498)
4	3.1964	0.0597	(3.0737, 3.3191)	(2.7313, 3.6615)
5	3.0076	0.0773	(2.8487, 3.1665)	(2.5316, 3.4835)
6	2.8187	0.1035	(2.6060, 3.0315)	(2.3223, 3.3152)
7	2.7083	0.1206	(2.4603, 2.9563)	(2.1957, 3.2209)
8	2.6299	0.1333	(2.3560, 2.9039)	(2.1043, 3.1556)
9	2.4411	0.1647	(2.1026, 2.7797)	(1.8791, 3.0031)

Values of predictors for new observations:

New Obs	log(MVratio)	log(T)
1	0.000000	0.30
2	0.000000	1.00
3	0.000000	1.48
4	0.000000	1.78
5	0.000000	2.08
6	0.000000	2.38
7	0.000000	2.56
8	0.000000	2.68
9	0.000000	2.98

Mean square error = 0.0476312

"X-prime X" inverse matrix:

0.76816	-1.53853	-0.43372
-1.53853	6.87194	0.67487
-0.43372	0.67487	0.26853

Variance-covariance matrix:

0.036588	-0.073282	-0.020659
-0.073282	0.327319	0.032145
-0.020659	0.032145	0.012790

See Table G–2 for the concentration, dosage, and dose estimates regression with log(LC_{50}) versus log(MVratio) and log(T) data.

Table G–2. Concentration, dosage, and dose estimates regression with log(LC_{50}) versus log(MVratio) and log(T)

TIME (min)	LOG [CONCENTRATION (LC_{50})] (mg/m^3)			CONCENTRATION (LC_{50}) (mg/m^3)		
	POINT ESTIMATE	LOWER BOUND	UPPER BOUND	POINT ESTIMATE	LOWER BOUND	UPPER BOUND
2	4.12288	3.79587	4.44990	13300	6250	28200
10	3.68446	3.49990	3.86902	4840	3160	7400
30	3.38520	3.26419	3.50620	2430	1840	3210
60	3.19638	3.07371	3.31905	1570	1180	2080
120	3.00756	2.84866	3.16647	1020	710	1470
240	2.81875	2.60604	3.03146	660	400	1080
360	2.70830	2.46034	2.95625	510	290	900
480	2.62993	2.35601	2.90386	430	230	800
960	2.44112	2.10256	2.77967	280	130	600
TIME (min)	CONCENTRATION (LC_{50})] (ppm)			DOSAGE (LCT_{50}) (mg-min/m^3)		
	POINT ESTIMATE	LOWER BOUND	UPPER BOUND	POINT ESTIMATE	LOWER BOUND	UPPER BOUND
2	4580	2160	9720	26500	12500	56400
10	1670	1090	2550	48400	31600	74000
30	840	630	1110	72800	55100	96200
60	540	410	720	94300	71100	125000
120	350	240	510	122000	84700	176000
240	230	140	370	158000	96900	258000
360	180	100	310	184000	104000	326000
480	150	80	280	205000	109000	385000
960	100	40	210	265000	122000	578000

APPENDIX H: EXTRAPOLATION OF HUMAN CHLORINE LETHALITY ESTIMATE FROM A MILITARY SUBPOPULATION TO GENERAL POPULATION BASIS USING THE METHOD OF CROSIER (2007)—John J. Bray and Douglas R. Sommerville

H1.0 Introduction

It is widely believed that the general population is more susceptible to toxicants than the military population is and that the general population has more variability in susceptibility to toxicants than the military subpopulation does.[1-9] In the absence of data relevant to the soldier-to-civilian adjustment, a subjective estimate must be used. In a series of three technical reports,[1-3] ECBC has developed a mathematical method for the conversion from one population basis to another, with Crosier[3] presenting the final version of the method. The premise of the approach is that mathematically the distribution of log(doses) for a healthy subpopulation is located completely within the distribution formed by the general population (i.e., the smaller bell curve is inside the larger bell curve). Previously, Sommerville *et al.*[9] formulated toxicity estimates for chemical warfare agents (CWAs) using an earlier version[2] of the extrapolation model. The reader is referred to Crosier[3] for a more detailed description of the method.

H2.0 Model Parameter Inputs

The Crosier method[3] requires the following parameter inputs are required when extrapolating toxicity estimates from a subpopulation basis to that of a general population:

(1) Size of the subpopulation (as a percent of the whole population)

(2) Median effective dose/dosage

(3) Probit slope (base 10), annotated m_{sub}

It is assumed that the military subpopulation comprises 30% of the total population. The military subpopulation is defined as anyone in the general population who meets the age, health, and physical fitness requirements for military service. The 30% figure is subject to debate, and Crosier[3] does provide solutions for percent sizes from 5% to 75%. If a smaller size is chosen, this will increase the difference in median effective dosages between subpopulation and whole population, while the reverse is true for a larger size.

From Section 7.4.1.4, the military subpopulation probit slope for chlorine inhalation lethality was estimated to equal 8.0, and the LCT_{50} was estimated to equal 13,500 mg-min/m^3.

H3.0 Model Assumptions

Crosier[3] modeled the subpopulation as either being based upon a double truncation or single truncation of the whole population. The basis for use of double truncation is that age is the covariate, and young adults correspond to some age range, say 18 yr to 35 yr. As pointed out by Crosier,[3] using double truncation will result in children being more resistant to toxicants than young adults are, which is not acceptable for risk assessment. For single truncation, the basis is health, and it is assumed that the military will not reject someone for being too healthy. Single truncation is a more logical assumption for the present application.

There is a region of feasible values for a subpopulation's mean log(dose) and standard deviation relative to the whole population where the distribution of the subpopulation's log(doses) can still be adequately represented by a normal distribution. This is demonstrated in Crosier's[3] Figure 5. For risk assessment purposes, the maximum difference in median effective dosages is desired, and for the single truncation subpopulation, this point is represented by a circle in his Figure 5.

H4.0 Model Outputs

From Crosier,[3] the following parameter values were obtained for a single truncation subpopulation with a size of 30% of the general population:

(1) mean δ_T equals 0.900

(2) ε_T (standard deviation factor) equals 0.744

These parameters are then used in the following equations to arrive at parameter estimates for the general population for a 2-min inhalation exposure to chlorine vapor.

$$m_{whole} = \varepsilon_T\, m_{sub} = (0.744)(8.0) = 5.952 \qquad \text{(H1)}$$

$$\text{Ratio} = (-1)\frac{\delta_T}{m_{whole}} = (-1)\frac{(0.900)}{(5.952)} = (-0.151) \qquad \text{(H2)}$$

$$(LCT_{50})_{whole} = 10^{Ratio}\,(LCT_{50})_{sub}$$
$$= 10^{(-0.151)}(13500) \quad \text{(H3)}$$
$$= 9500 \text{ mg-min/m}^3$$

A toxic load exponent value of 2.75 was then used to extrapolate to other LCT_{50} values from the two minute value. For other percent effect levels, a round probit slope value of 6.0 is recommended. See Table H–1 for a listing of subpopulation toxicity values for several selected exposure durations. The toxic load equations are shown below for both military (eq H4) and general (eq H5) populations.

$$Y_N = (-31.52) + (2.91)\log\left(C^{2.75}T\right)$$
$$\text{or} \quad \text{(H4)}$$
$$L\left(C^{2.75}T\right)_{50} = 6.79 \times 10^{10}$$

$$Y_N = (-22.698) + (2.18)\log\left(C^{2.75}T\right)$$
$$\text{or} \quad \text{(H5)}$$
$$L\left(C^{2.75}T\right)_{50} = 2.58 \times 10^{10}$$

Table H–1. Chlorine inhalation median lethal dosages and probit slope for the general population

Agent:	Chlorine	SINGLE TRUNCATION CALCULATIONS	
Nomenclature:	Cl_2	Standard Deviation (for single truncation)	=0.744
Type of Exposure:	Inhalation/Ocular	m (slope) whole population (subpopulation slope x standard deviation)	= 5.952
Form:	Vapor	Z (for mean single truncation)	= 0.900
Level:	Lethal	Ratio (-z/m whole)	= -0.151
Toxic Load Exponent:	2.75	Conversion Factor [antilog (ratio)]	= 0.706
Temperature:	None Specified		

EXPOSURE DURATION (MIN)	MILITARY SUBPOPULATION		WHOLE POPULATION SINGLE TRUNCATION	
	PROBIT SLOPE = 8.0		PROBIT SLOPE = 6.0	
	LCT_{50} (mg-min/m³)	LC_{50} (mg/m³)	LCT_{50} (mg-min/m³)	LC_{50} (mg/m³)
2	13500	6750	9500	4750
10	37600	3760	26400	2640
30	75700	2520	53200	1770
60	118000	1970	82700	1380
120	183000	1530	129000	1080
240	284000	1180	200000	830
360	368000	1020	259000	720
480	442000	920	311000	650
960	687000	720	483000	500

H5.0 References

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[3] Crosier, RB, *New Model for Population-Subpopulation Differences*, **ECBC-TR-534**. US Army Edgewood Chemical Biological Center, Aberdeen Proving Ground, MD, February 2007, UNCLASSIFIED Report, AD# A465827.

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[6] Withers, RMJ and Lees, FP, *The Assessment of Major Hazards: The Lethal Toxicity of Chlorine, Part I—Review of Information on Toxicity*, **Journal of Hazardous Materials**. **12**: 231-282, 1985.

[7] Withers, RMJ and Lees, FP, *The Assessment of Major Hazards: The Lethal Toxicity of Chlorine, Part II—Model of Toxicity to Man*, **Journal of Hazardous Materials**. **12**: 283-302, 1985.

[8] National Research Council, Committee on Toxicology, *Chlorine Acute Exposure Guideline Levels*, **Acute Exposure Guideline Levels for Selected Airborne Chemicals. 4**: The National Academies Press, Washington, DC, 2004.

[9] Sommerville, DR, Reutter, SA, Crosier, RB, Shockley, EE, and Bray, JJ, *Chemical Warfare Agent Toxicity Estimates for the General Population*, **ECBC-TR-442**. US Army Edgewood Chemical Biological Center, Aberdeen Proving Ground, MD, June 2005, UNCLASSIFIED, AD# B311889.

APPENDIX I: CHLORINE HAZARD PREDICTION—Raymond E. Jablonski and Douglas R. Sommerville

I1.0 Introduction

For this report, a series of computer simulations were conducted of a large chlorine spill release for eventual comparison to the toxicity methodologies discussed in this report. Initially, two atmospheric transport and dispersion (ATD) models were used: the EPA/NOAA Areal Locations of Hazardous Atmospheres (ALOHA)[1] and Defense Threat Reduction Agency's (DTRA's) Hazard Prediction Assessment Capability (HPAC) models.[2] Both of these models were part of a recent evaluation of dense gas dispersion models (along with four other models) involving the simulation of three railroad accidents involving the bulk release of chlorine vapor.[3] The predictions from both ALOHA and HPAC were found to be in "good agreement" with the predictions of the other four ATD models. Only the HPAC model provided numeric output of concentration time history needed for the toxic load analysis discussed in Section 7.5 in the main body of the report. A summary of the simulations and results produced by both models are discussed in this appendix.

I2.0 Model Description

The following model descriptions are largely extracted from their respective user's manuals.[1,2]

I2.1 HPAC

The Hazard Prediction and Assessment Capability (HPAC)[2] automated software system provides the means to accurately predict the effects of hazardous material releases into the atmosphere and its impact on civilian and military populations. The system uses integrated source terms, high-resolution weather forecasts and particulate transport analyses to model hazard areas produced by military or terrorist incidents and industrial accidents. HPAC and its companion tools [e.g., Consequence Assessment Toolset (CATS)] provide actionable information to support consequence assessment and management of CBRNE hazards, the impact on personnel and operations, and resource requirements for response and recovery.

The transport and diffusion sub-model embedded within HPAC is the Second-order Closure Integrated Puff (SCIPUFF) model. SCIPUFF is an atmospheric dispersion model with a wide range of application. The turbulent diffusion parameterization is based on second-order turbulence closure theory, which relates the dispersion rate to velocity fluctuation statistics. In addition to the average concentration value, the closure model provides a prediction of the statistical variance in the concentration field resulting from the random fluctuations in the wind field. The variance is used to estimate a probability distribution for the predicted value.

SCIPUFF uses a collection of Gaussian puffs to represent an arbitrary three-dimensional, time-dependent concentration field, and incorporates an efficient scheme for splitting and merging puffs. Wind shear effects are accurately modeled, and puffs are split when they grow too large for single-point meteorology to be representative. These techniques allow the puff model to describe complex flow effects on dispersion, such as terrain-driven circulations.

SCIPUFF has been developed with a flexible interface, to describe many types of source geometries and material properties. Solid particles, liquid droplets, and gaseous materials are represented, with both primary and secondary evaporation mechanisms that produce vapor puffs as the droplets evaporate in the air or after deposition on the ground. Precipitation washout effects are also included for particles and droplets. SCIPUFF describes dynamic effects of buoyant rise due to thermal release or lighter-than-air materials and also the effects of a dense cloud near the ground surface. The model also uses several types of meteorological input, including surface and upper air observations or three-dimensional grid data. Planetary boundary layer turbulence is represented explicitly in terms of surface heat flux and shear stress using parameterized profile shapes. The HPAC system also has embedded climatology or historical weather data for use when planning incidents beyond the normal time associated with credible weather forecast data. One-kilometer terrain data and supporting wind-flow models calculate the local winds field in the area of concern. Other weather sources are also available upon request to DTRA. The HPAC system can also help answer the question, "How good is the prediction?" by providing probabilistic

calculations. The hazard area feature estimates the weather uncertainty and turbulence effects on possible plume trajectories and calculates the areas of hazard impact and the degree of confidence of the prediction.

I2.2 ALOHA

ALOHA[1] is a computer program designed especially for use by people responding to chemical releases, as well as for emergency planning and training. ALOHA models key hazards—toxicity, flammability, thermal radiation (heat), and overpressure (explosion blast force)—related to chemical releases that result in toxic gas dispersions (i.e., how a toxic gas cloud might disperse in the atmosphere after an accidental chemical release), fires, and/or explosions.

ALOHA runs quickly on small computers/laptops that are easily transportable. It is designed to be easy to use so that a user can operate it successfully during high-pressure situations. Its chemical library contains information about the physical properties of approximately 1000 common hazardous chemicals. Its computations represent a compromise between accuracy and speed; ALOHA has been designed to produce good results quickly enough to be of use to responders. ALOHA is designed to minimize operator error. It checks information that the user enters and warns the user when he/she makes a mistake. ALOHA's on-screen help offers you quick access to explanations of ALOHA's features and computations, as well as background information to help you interpret its output.

ALOHA models three hazard categories: toxic gas dispersion, fires, and explosions. ALOHA employs several different models, including an air dispersion model that it uses to estimate the movement and dispersion of chemical gas clouds. From this model, ALOHA is able to estimate the toxic gas dispersion, the overpressure values from a vapor cloud explosion, or the flammable areas of a vapor cloud.

I2.3 Chlorine Scenario Modeled

The scenario modeled was for a catastrophic release of either 90 tons (~81,000 kg) or 50 tons (~45,500 kg) of chlorine liquid. Ninety tons is the typical amount for a standard rail tank car. However, a release of 50 tons was used as input into HPAC, since this is the largest release reported by Mannan[4] in their review of chlorine industrial/transportation accidents. Literature commentary on the downwind location of fatalities (see Section 4) uses this accident database as its reference. Thus, modeling results for the 50-ton release were used for comparison to the different toxicity methodologies.

Model inputs were kept fairly simple for these simulations. Flat terrain was assumed. Meteorological conditions were kept at a steady-state, fixed wind condition (same wind direction and wind speed assumed through the simulation). The chlorine release was assumed to be a catastrophic, instantaneous release of the liquid. Both ALOHA and HPAC make estimates of the amount of chlorine that initially pools, but all liquid evaporated very quickly. Since meteorological conditions can produce significant differences in hazard prediction results, three different weather conditions were modeled. These three conditions were:

- Low wind (1 m/s), clear sky, nighttime (2 a.m.), "stable" condition (Pasquill[5] Stability Category F)
- Moderate wind (5 m/s), cloudy day, "neutral" condition (Pasquill Stability Category D)
- Low wind (2 m/s), clear sky, daytime (2 p.m.), "unstable" condition (Pasquill Stability Category B)

I2.4 Critical Importance of Proper Toxicity Effects Definition

One of the major concerns within the chemical/biological defense community is whether current hazard prediction models are producing reliable and "accurate" results. A number of current models have been reviewed, and there is agreement that the methodology used within these models is "state of the art." Six dense gas models were recently compared to three actual chlorine railcar accidents and these models compared well with one another.[3] One of the major conclusions of the study was that estimation of the source term is important for good results. The same can be said for determining casualty estimates. Although a number of toxicity definitions exist (AEGLs, ERPGs, TEELs, ICT_{50}, LCT_{50}, etc.), these definitions and the data points they represent for a specific chemical must be in

sync with current hazard prediction model calculations.

An important problem with many of the current toxicity estimates is that they are currently used in the ATD models with a Haber's Rule mindset—that an effective dosage (concentration-time or CT) is constant with respect to time. This is ironic, since many of these toxic estimates (including chlorine) were developed with the acknowledgement that Haber's Rule is often inadequate. The toxic load model is a possible alternative but only if the result is used with a toxic load mindset. This issue is explored further in Section I3.1.

Based on results from this brief analysis, there may be some question whether the necessary synchronization currently exists. The following sections provide several examples and identify some questions to consider for further investigation.

I3.0 Results

I3.1 HPAC Model Runs

I3.1.1 Initial Plots

The differences in plume shape and downwind hazard extent are depicted in the HPAC contour plots [Figure I–1 through Figure I–3 (high resolution) and Figure I–4 through Figure I–6 (low resolution)] for the three different meteorological conditions. Note that the nighttime release will produce the largest hazard area, while the daytime release will produce the smallest.

Figure I–1 through Figure I–3 (pages I–4 and I–5) display dosage contour plots using LCT_{50} values from eq 25 of the main body of the report (corresponding to exposure durations from 2 min to 60 min). Figure I–4 through Figure I–6 (pages I–5 and I–6) display dosage contour plots across a range of toxicity effects definitions. These include the old military LCT_{50} and ICT_{50} values[6] (19,000 mg-min/m^3 and 1800 mg-min/m^3, respec-tively—which are independent of exposure duration) and a series of chlorine AEGL effects levels[7] for different exposure times (10 min to 60 min). It should be noted that similar AEGL definitions (i.e., AEGL1, AEGL2, AEGL3) at different exposure times do produce significantly different contour areas. These plots show the criticality of proper model input for source term, meteorological data and toxicity estimate definition.

Another important observation from Figure I–1 through Figure I–6 is that the plume contours were generated by HPAC using a Haber's Rule mindset. This is demonstrated by the paradox of having the plume size decrease as a function of an increase in the duration basis for the plotted dosage contour [i.e., the plume size for LCT_{50} (2 min) is larger than LCT_{50} (60 min) in Figure I–1 through Figure I–3—the same is true with the AEGL values as wel] The reason for this is that HPAC currently plots the dosage contour without reference to the predicted duration value that was used to produce the dosage value for that contour.[j] In all likelihood, the duration associated with the LCT_{50} (2 min) contour is on the order of 10 min to 60 min, in which case this LCT_{50} value is meaningless. It has been demonstrated in the main body of this report and elsewhere that the LCT_{50} for chlorine increases as a function of exposure duration. In the future, a solution for this problem would be to modify HPAC to permit the plotting of toxic load contours (see Section I3.1.2)

I3.1.2 HPAC Sampler Output

Because of the problem in the HPAC plotting routine (see Section I3.1.1), model results for five "sampler" locations were also produced so that the necessary calculations could be made independent of the misleading HPAC plots. These "samplers" were located 0.2 km, 0.5 km, 1.0 km, 1.5 km, and 2.0 km downwind of the source release. Sampler output data from HPAC included time history (at 1-min intervals), mean concentration (in kg/m^3), concentration variance and correlation time scale (in seconds). The primary output needed for the toxicity methodology comparison was the time history and mean concentration at the five locations. An example of the numeric output data is provided in Figure I–7 (page I–7).

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[a] Acute Exposure Guideline Levels (AEGLs); Emergency Response Exposure Limits (TEELs); incapacitating dosage for 50% of the exposed population (ICT_{50}); and lethal dosage (CT) for 50% of the exposed population (LCT_{50})

[b] Phone conversation, Mr. Sommerville with Dr. R. Ian Sykes, L-3 Titan Corporation, Princeton, NJ, October 2007. Author's Note: HPAC can presently perform toxic load calculations for casualty assessment; it just cannot graphically present the results of such calculations in an easily understandable manner.

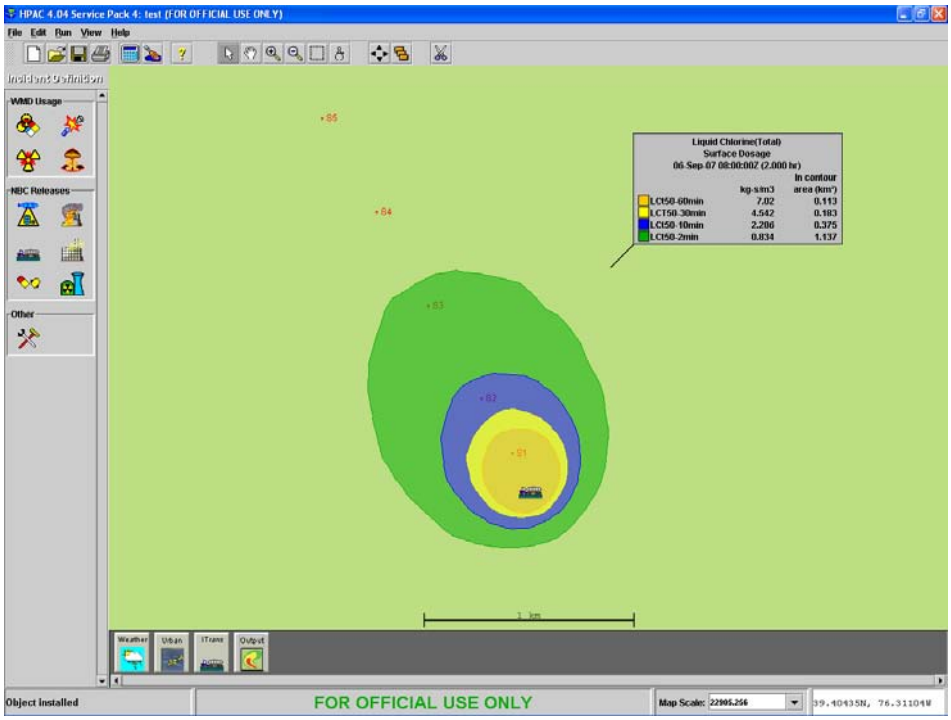

Figure I–1. HPAC plumes (high resolution) for low wind (1 m/s), clear sky, nighttime (2 a.m.), "stable" condition (Pasquill Category F)

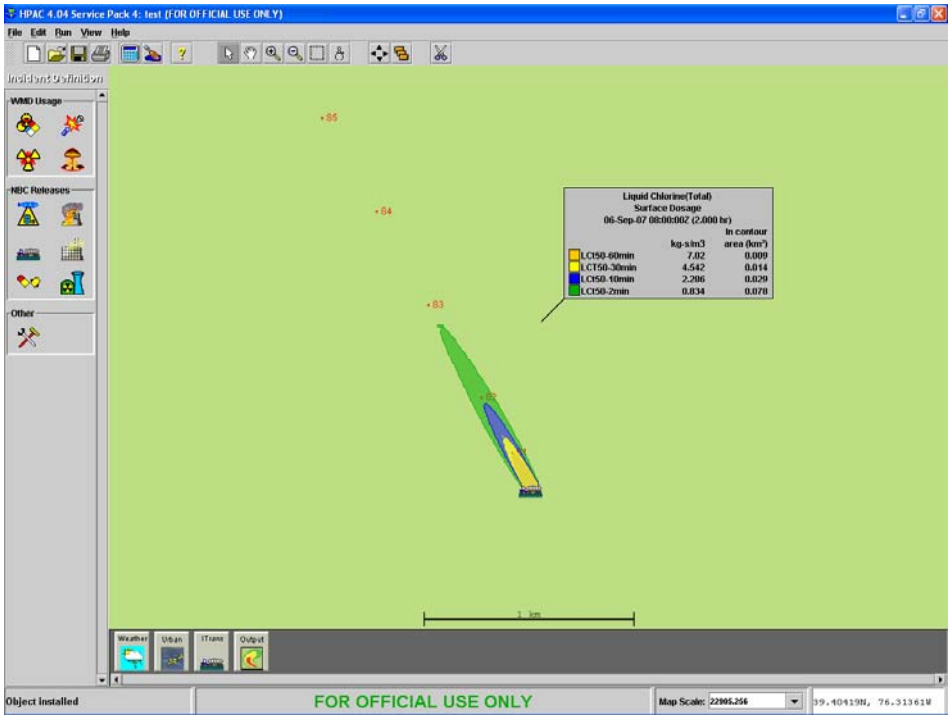

Figure I-2. HPAC plumes (high resolution) for moderate wind (5 m/s), cloudy day, "neutral" condition (Pasquill Category D)

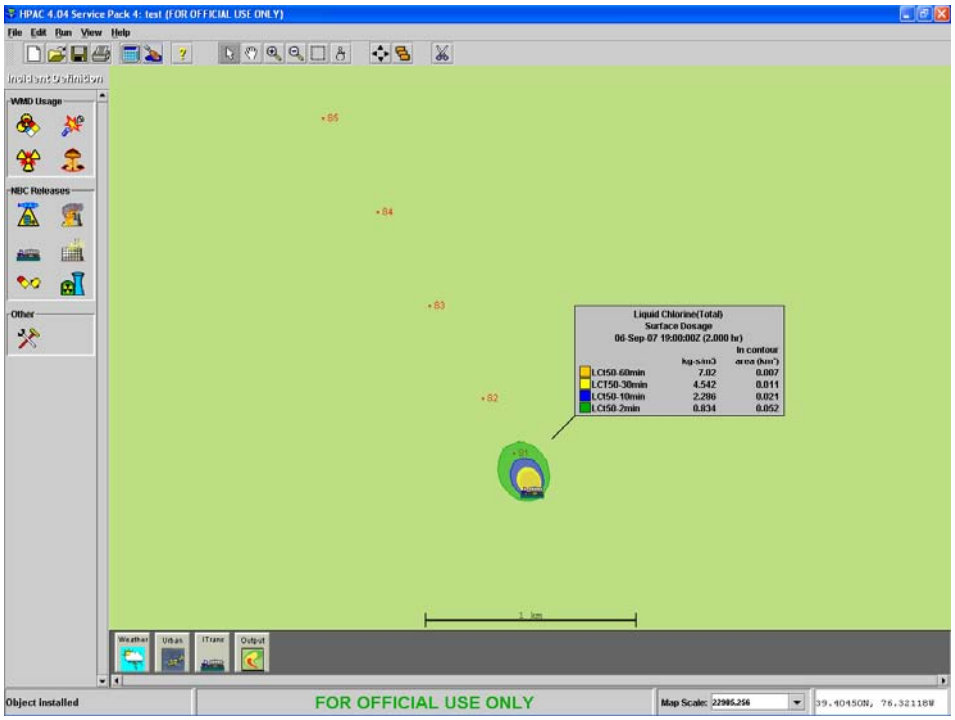

Figure I–3. HPAC plumes (high resolution) for low wind (2 m/s), clear sky, daytime (2 p.m.), "unstable" condition (Pasquill Category B)

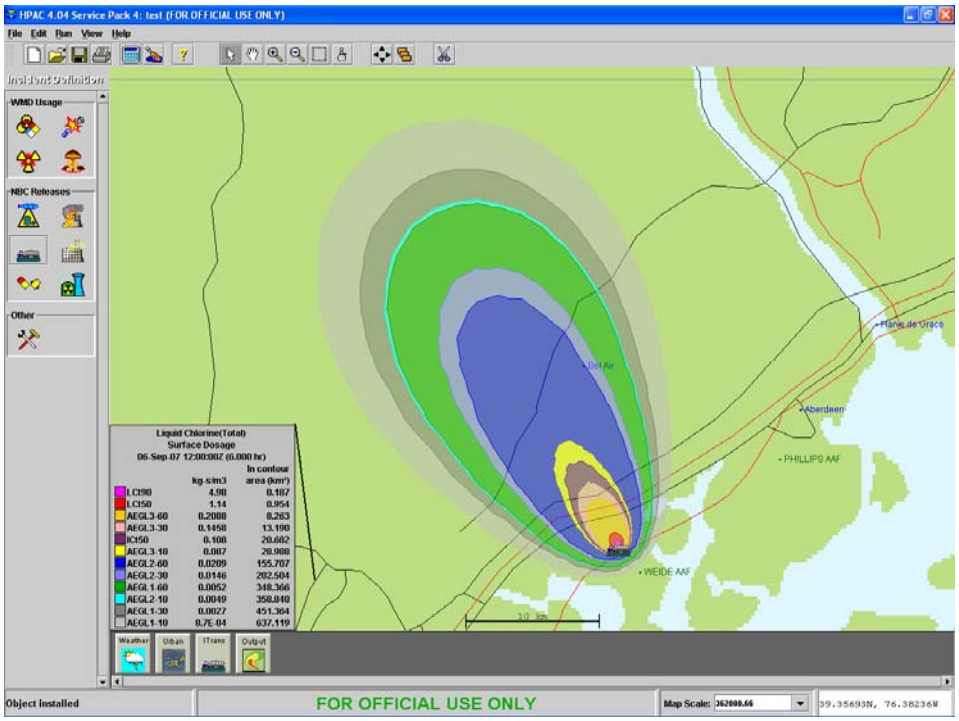

Figure I–4. HPAC plumes (low resolution) for low wind (1 m/s), clear sky, nighttime (2 a.m.), "stable" condition (Pasquill Category F)

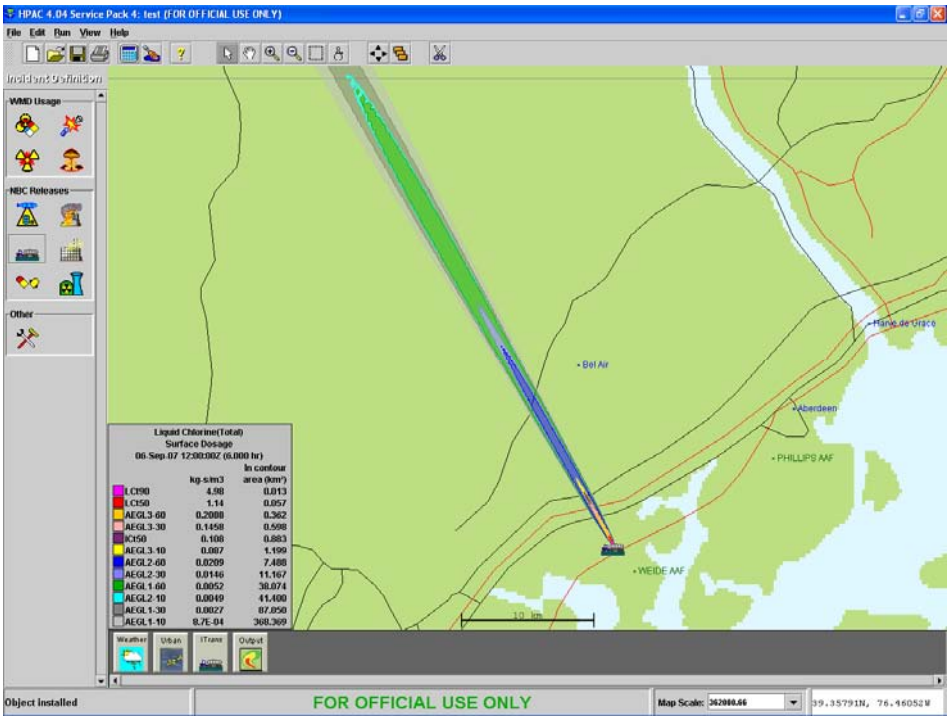

Figure I–5. HPAC plumes (low resolution) for moderate wind (5 m/s), cloudy day, "neutral" condition (Pasquill Category D)

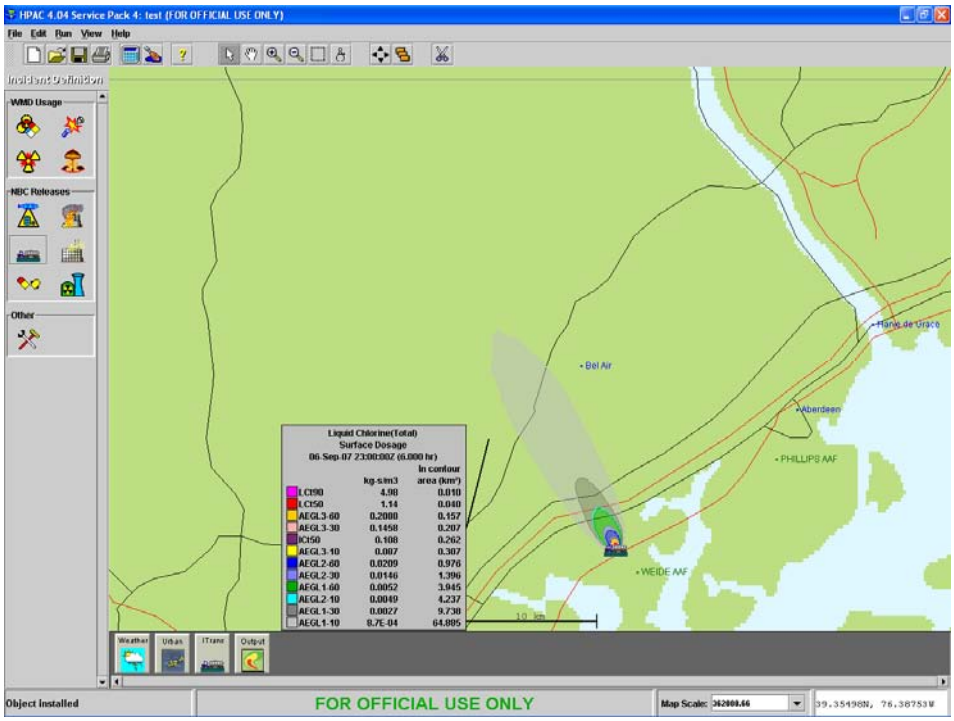

Figure I–6. HPAC plumes (low resolution) for low wind (2 m/s), clear sky, daytime (2 p.m.), "unstable" condition (Pasquill Category B)

CL2_LIQ	0.2 km			0.5 km			1.0 km			1.5 km			2.0 km		
Time (sec)	C001	V001	T001	C002	V002	T002	C003	V003	T003	C004	V004	T004	C005	V005	T005
60	2.32E-04	7.37E-07	73.77158	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
120	3.27E-03	1.15E-05	83.03574	1.41E-09	5.00E-12	82.92215	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
180	6.53E-03	2.32E-05	96.51088	1.08E-06	3.85E-09	96.45029	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
240	6.75E-03	2.48E-05	110.0538	7.20E-05	2.54E-07	98.25278	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
300	7.79E-03	2.47E-05	140.8548	3.55E-04	9.06E-07	110.8229	4.39E-10	1.12E-12	110.7804	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
360	6.80E-03	2.07E-05	152.7631	6.99E-04	1.71E-06	116.8192	9.21E-08	2.22E-10	114.6809	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
420	6.67E-03	1.96E-05	177.1167	9.93E-04	2.11E-06	136.8604	1.44E-06	2.68E-09	126.4517	3.88E-12	7.22E-15	126.4504	0.00E+00	0.00E+00	0.00E+00
480	6.87E-03	2.11E-05	216.371	1.24E-03	2.44E-06	146.8682	8.16E-06	1.31E-08	130.3253	4.58E-10	7.35E-13	130.1885	0.00E+00	0.00E+00	0.00E+00
540	5.98E-03	1.97E-05	262.2555	1.38E-03	2.64E-06	161.7596	2.49E-05	3.88E-08	138.9023	1.11E-08	1.72E-11	137.818	0.00E+00	0.00E+00	0.00E+00
600	5.73E-03	2.08E-05	303.2225	1.50E-03	2.94E-06	184.2696	5.61E-05	8.16E-08	148.3181	1.24E-07	1.74E-10	145.4408	7.52E-12	1.06E-14	145.3966
660	4.66E-03	1.74E-05	315.9564	1.55E-03	3.11E-06	201.078	1.03E-04	1.68E-07	163.9132	3.80E-07	6.18E-10	163.7983	4.74E-11	7.71E-14	163.7983
720	4.37E-03	1.77E-05	319.8347	1.54E-03	2.83E-06	227.9767	1.63E-04	2.14E-07	170.7958	1.83E-06	2.39E-09	169.7338	1.20E-09	1.57E-12	169.7334
780	4.10E-03	1.76E-05	334.0078	1.49E-03	2.67E-06	252.1395	2.21E-04	2.63E-07	179.9559	5.72E-06	6.66E-09	176.3739	1.33E-08	1.55E-11	176.3606
840	3.82E-03	1.52E-05	342.6748	1.35E-03	2.49E-06	273.0671	2.35E-04	2.54E-07	192.6898	1.05E-05	1.06E-08	183.24	6.13E-08	6.18E-11	183.0771
900	3.81E-03	1.65E-05	375.3797	1.28E-03	2.20E-06	284.6122	2.81E-04	2.86E-07	213.8385	2.00E-05	1.81E-08	201.6943	2.56E-07	2.31E-10	201.1393
960	4.15E-03	2.26E-05	420.948	1.23E-03	2.00E-06	294.3638	3.20E-04	2.97E-07	223.8518	3.32E-05	2.66E-08	208.9149	8.09E-07	6.38E-10	207.4989
1020	3.59E-03	1.58E-05	415.4004	1.12E-03	1.83E-06	305.4799	3.46E-04	2.98E-07	237.3021	4.78E-05	3.33E-08	217.0268	1.94E-06	1.30E-09	214.1958
1080	3.34E-03	1.44E-05	446.0834	1.02E-03	1.58E-06	324.2372	3.55E-04	2.84E-07	248.2217	6.51E-05	4.19E-08	225.4892	4.10E-06	2.53E-09	222.3149
1140	3.12E-03	1.26E-05	474.8366	9.70E-04	1.57E-06	346.1641	3.61E-04	2.80E-07	264.5752	7.91E-05	4.75E-08	236.5932	6.94E-06	3.92E-09	230.2961
1200	3.18E-03	1.36E-05	512.9303	9.24E-04	1.42E-06	359.1628	3.68E-04	2.60E-07	275.9481	9.58E-05	5.05E-08	249.2097	1.12E-05	5.37E-09	241.5921
1260	3.07E-03	1.18E-05	540.1797	8.72E-04	1.27E-06	372.6974	3.55E-04	2.45E-07	286.3101	1.03E-04	5.36E-08	262.6485	1.47E-05	6.91E-09	254.9859
1320	2.94E-03	1.12E-05	548.9271	7.96E-04	1.14E-06	389.4146	3.59E-04	2.43E-07	299.7686	1.17E-04	6.25E-08	291.972	1.98E-05	8.91E-09	287.5628
1380	2.84E-03	1.10E-05	578.7224	7.60E-04	1.07E-06	418.1495	3.47E-04	2.15E-07	306.0931	1.32E-04	6.25E-08	291.0547	2.74E-05	1.10E-08	285.9475
1440	3.19E-03	1.33E-05	607.0953	7.50E-04	1.03E-06	442.3345	3.49E-04	1.98E-07	318.8276	1.49E-04	6.36E-08	302.5255	3.64E-05	1.32E-08	297.1932
1500	2.74E-03	1.00E-05	609.5892	7.20E-04	9.71E-07	459.1912	3.44E-04	1.87E-07	330.7391	1.64E-04	6.57E-08	312.7029	4.71E-05	1.59E-08	305.4526
1560	2.68E-03	1.00E-05	623.8851	7.03E-04	9.19E-07	487.0183	3.32E-04	1.76E-07	338.6996	1.63E-04	6.54E-08	323.4315	5.03E-05	1.70E-08	321.0647
1620	3.00E-03	1.21E-05	637.3651	6.83E-04	8.87E-07	513.3849	3.09E-04	1.56E-07	352.7653	1.62E-04	5.93E-08	334.4287	5.79E-05	1.78E-08	331.2895
1680	2.56E-03	9.24E-06	636.8289	6.47E-04	8.46E-07	530.1002	3.04E-04	1.47E-07	367.7075	1.71E-04	5.70E-08	344.7525	6.86E-05	1.92E-08	338.7609
1740	2.52E-03	9.32E-06	646.0638	6.34E-04	8.07E-07	549.9619	2.93E-04	1.35E-07	384.3856	1.66E-04	5.37E-08	359.158	6.96E-05	1.90E-08	355.8243
1800	2.83E-03	1.12E-05	654.7936	6.26E-04	7.87E-07	565.1236	2.86E-04	1.25E-07	395.5575	1.72E-04	5.21E-08	365.1847	7.87E-05	2.01E-08	363.7718

Figure I–7. Example of numeric output data from HPAC

In Figure I–8 through Figure I–10, the concentration-time profiles associated with the three meteorological conditions are shown as a function of downwind distance along the centerline of the plume. From these profiles, the accumulated toxic load was calculated via the rectangle method for numerical integration of the concentration-time profiles using the below algorithm.

$$TL = \int_0^T C^n \, dt \approx \sum_{i=1}^{i=120} \left(\tfrac{1}{2}\right)\left(C_i^n + C_{i-1}^n\right) \Delta t \qquad (I1)$$

where TL is the total toxic load, C is the predicted mean vapor concentration from HPAC (converted from the original units of kg/m^3 to mg/m^3), T is the event time (in minutes), n is the toxic load exponent and Δt equals 1 min.

The toxic load values (for $TL = (C^{2.75}T)$) as a function of time are shown in Figure I–11 through Figure I–13 corresponding to the concentration-time profiles in Figure I–8 through Figure I–10). A toxic load exponent (n) of 2.75 was chosen since this value is common to several toxicity estimates (Rijnmond Report[8]/Harris and Moses,[9,k] ten Berge and van Heemst,[10] and this report's eq 25). See Table I–1 for a listing of the lethality estimates investigated in this appendix (which were extracted report). For comparison, the 5% lethal toxic load (or LTL_{05}) estimates from eq 25 (upper dashed red line) and the Rijnmond Report (bottom dashed red line) are also shown in Figure I–11 through Figure I–13. A plume contour of a LTL_{XX} is independent of exposure duration, and it is recommended that this useful capability be introduced into a future version of HPAC.

The behavior of the TL versus time profiles is interesting. The total TL reaches a plateau value at about the instance when the initial "pulse" of the chlorine cloud passes by a downwind location.

Table I–1. Human lethality equations from main body of this report

REFERENCE	CONVERTED EQUATION**
Withers, Lees	Y_N (Normit) = -11.697 + 1.675 log($C^{2.00}$ T)
ten Berge, van Heemst	Y_N (Normit) = -11.503 + 1.151 log($C^{2.75}$ T)
Rijnmond Report (Harris, Moses)	Y_N (Normit) = -18.799 + 1.888 log($C^{2.75}$ T)
Equation 25	Y_N (Normit) = -22.698 + 2.182 log($C^{2.75}$ T)

**The concentration "C" is measured in mg/m^3

cHarris and Moses and the Rijnmond Report have identical human estimates and are treated as synonymous by Mannan.[4]

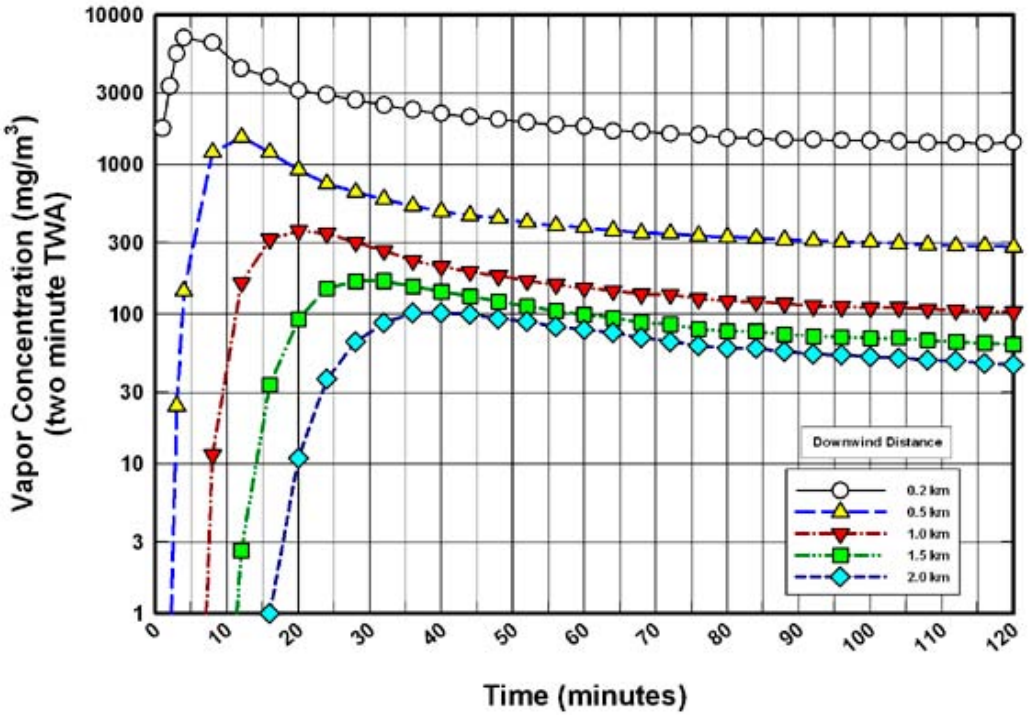

Figure I–8. Mean vapor concentration (2-min TWA) versus time and downwind distance—HPAC predictions for Pasquill Category F release scenario

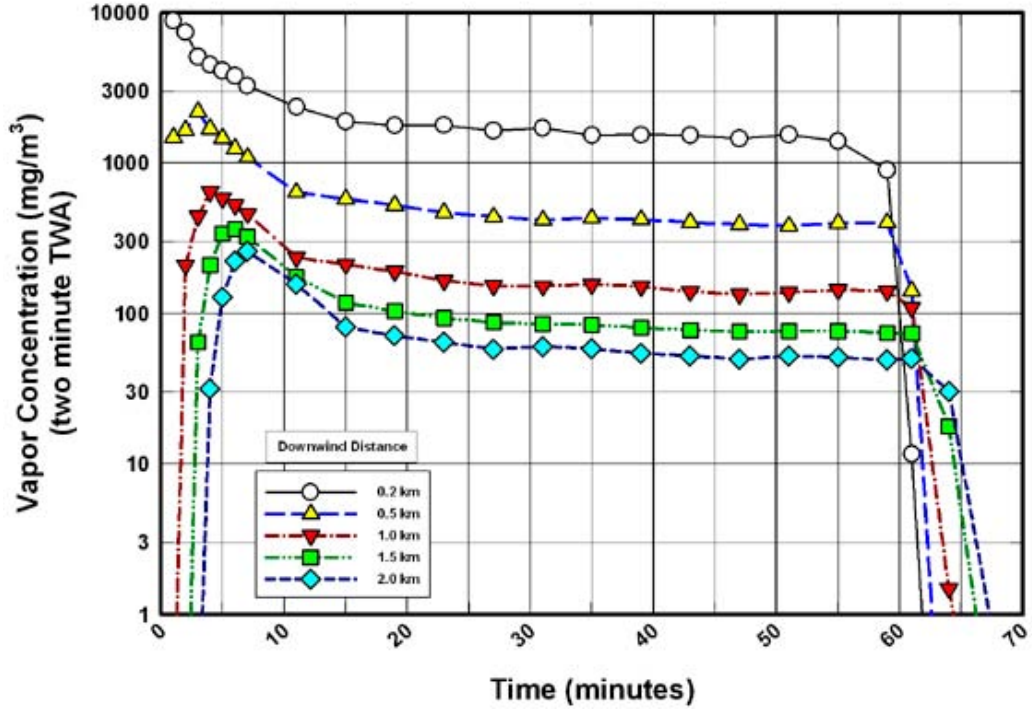

Figure I–9. Mean vapor concentration (2-min TWA) versus time and downwind distance—HPAC predictions for Pasquill Category D release scenario

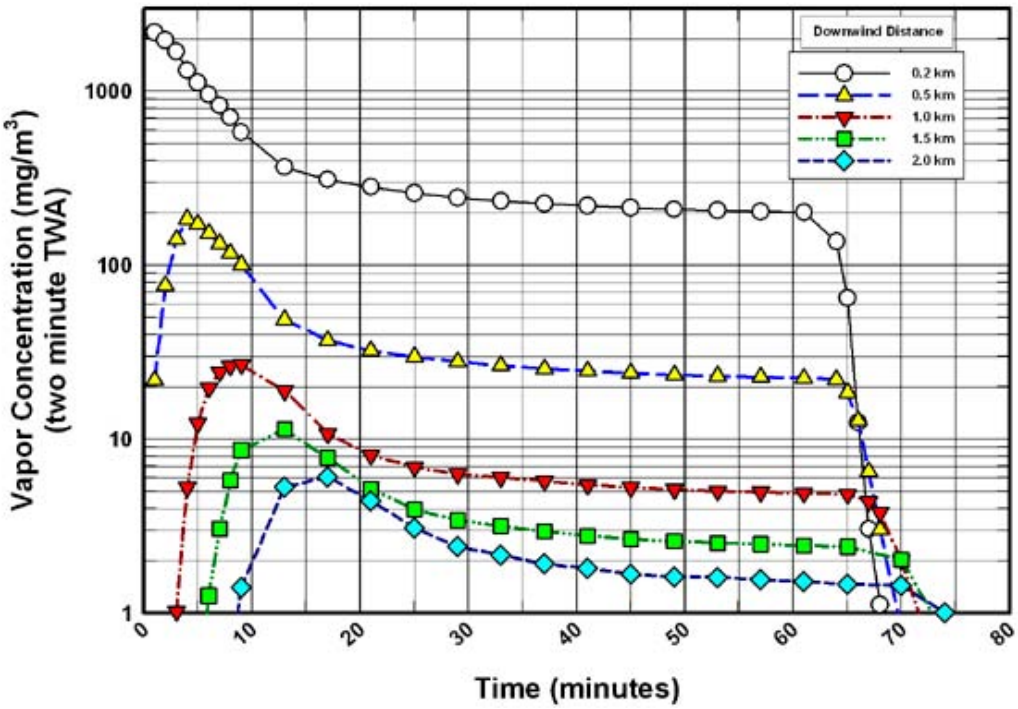

Figure I–10. Mean vapor concentration (2-min TWA) versus time and downwind distance—HPAC predictions for Pasquill Category B release scenario

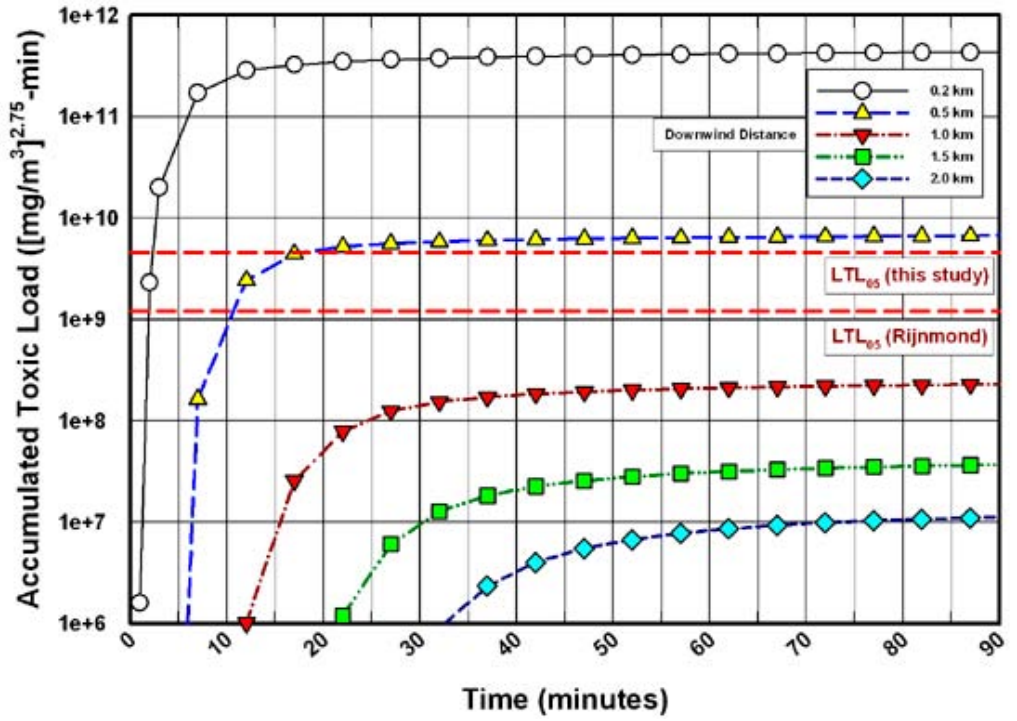

Figure I–11. Accumulated toxic load versus time and downwind distance—HPAC predictions for Pasquill Category F release scenario

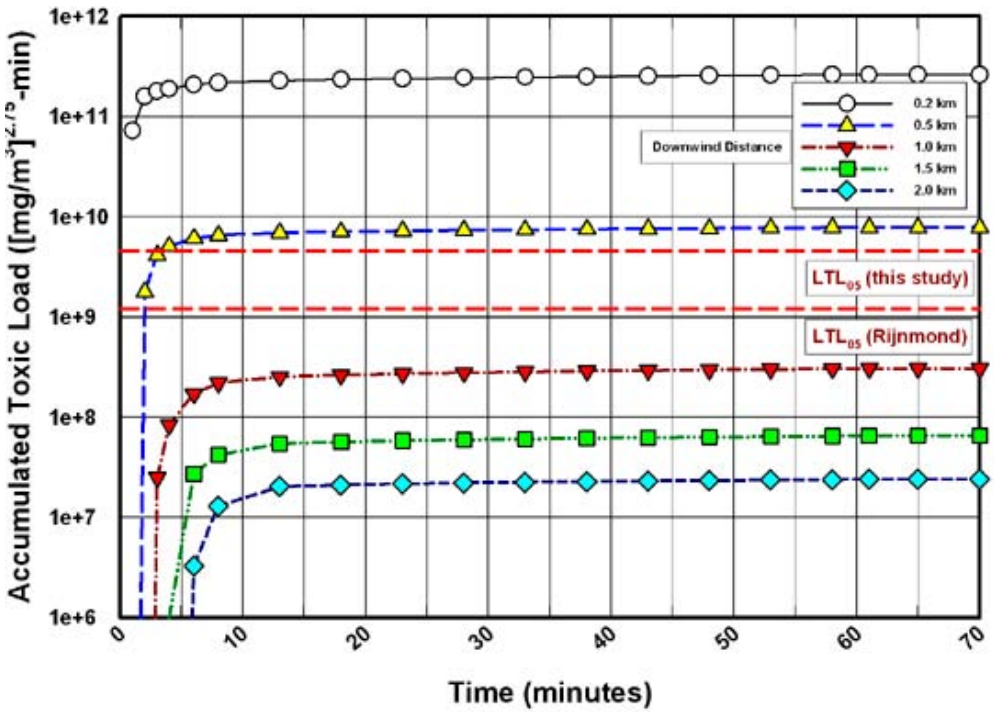

Figure I–12. Accumulated toxic load versus time and downwind distance—HPAC predictions for Pasquill Category D release scenario

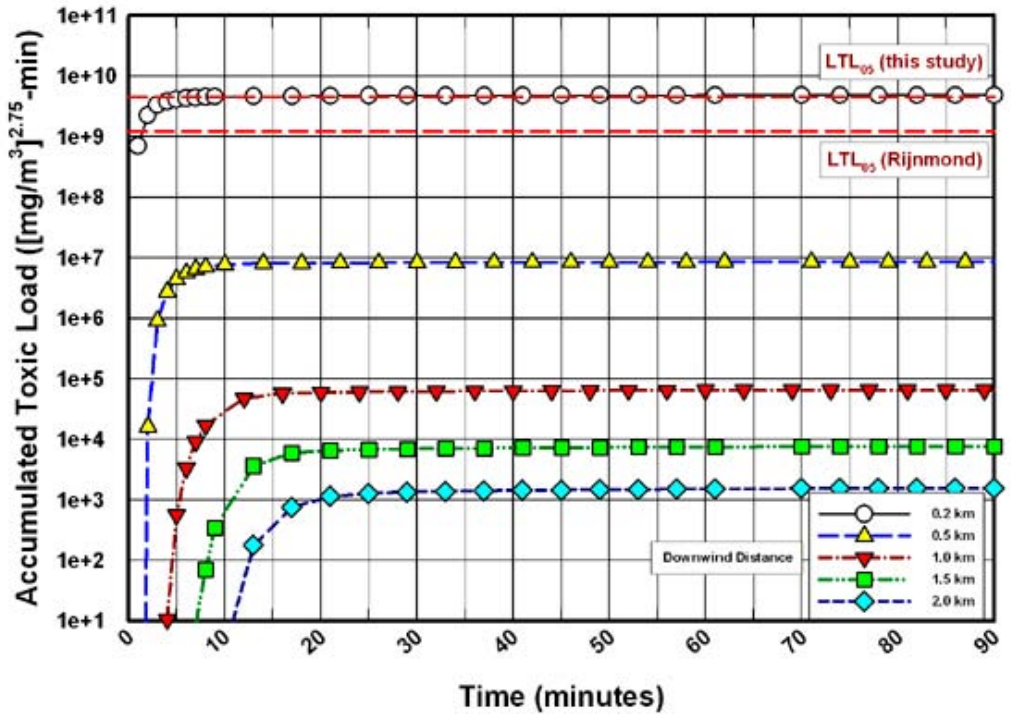

Figure I–13. Accumulated toxic load versus time and downwind distance—HPAC predictions for Pasquill Category B release scenario

Thus, for chlorine (for n = 2.75), most of the lethal toxic load has already been received within 10 min to 30 min (depending on atmospheric conditions and whether lethal toxic load levels have been reached) post-arrival of the initial pulse. For sub-lethal effects (which are not addressed in this report), the critical post-arrival period is probably longer than 30 min [particularly if n (nonlethal) is less than n (lethal)]. Thus, effective sheltering in place measures during that critical period is essential if evacuation prior to the cloud's arrival is not possible.

The percent probability of lethality was then estimated from the toxic load estimates using several of the probit relationships[4,8-12] from Table I–2, as well as using Haber's Rule based upon the 2-min LCT_{50} value from eq 25 (n = 1, k_c = 6 and LCT_{50} = 9500 mg-min/m^3). The percent probability values (and their associated normit values) are listed in Table I–2 through Table I–4 as a function of atmospheric conditions and down-wind distance. Some of these results are also plotted in Figures 7–6 to 7–8 in the main body of this report. Of the lethality probit relationships studied, the probability of lethality versus downwind distance profiles from eq 25 and the Rijnmond Report[8,9] are the most consistent with what has been observed historically in chlorine accidents.[4] See Section 7.5 of the main body of the report for a more detailed discussion.

A sensitivity analysis was also performed on how changes in the toxic load exponent and probit slope (concentration) affect the probability of lethality versus downwind distance profile. The concentration-time profile from Figure I–8 (page I–8) was used. The toxic load equation parameter inputs and the final results of the analysis are discussed in Section 7.5.2 in the main body of the report.

Table I–2. Lethality probabilities as a function of lethality expression and distance from release point—nighttime conditions (Pasquill Category D)

	PRESENT STUDY (EQ 25)	RIJNMOND	TEN BERGE & VAN HEEMST	WITHERS & LEES	HABER'S RULE
Lethal Toxic Load (LTL_{50})	2.582E+10	9.059E+09	9.861E+09	9.662E+06	9.500E+03
Toxic Load Exponent (n)	2.75	2.75	2.75	2.00	1.00
Probit Slope with respect to Toxic Load PS (TL)	2.18	1.89	1.15	1.68	6.00
Probit Slope with respect to Concentration PS (CT)	6.00	5.19	3.17	3.35	6.00
Distance (kilometers)	Prob (%)	Prob (%)	Prob (%)	Prob (%)	Prob (%)
0.2	98.6	99.7	94.9	99.7	100.0
0.5	13.0	45.4	45.5	81.3	100.0
1.0	0.00	0.28	4.2	22.8	73.9
1.5	0.00	0.00	0.61	5.6	18.4
2.0	0.00	0.00	0.13	1.7	2.9
Distance (kilometers)	Normits	Normits	Normits	Normits	Normits
0.2	2.1989	2.7644	1.6397	2.7351	6.7584
0.5	-1.1263	-0.1160	-0.1130	0.8881	3.4215
1.0	-4.1952	-2.7744	-1.7305	-0.7468	0.6397
1.5	-5.6619	-4.0450	-2.5036	-1.5884	-0.9001
2.0	-6.6061	-4.8629	-3.0012	-2.1257	-1.8925

Table I–3. Lethality probabilities as a function of lethality expression and distance from release point—nighttime conditions (Pasquill Category F)

	PRESENT STUDY (EQ 25)	RIJNMOND	TEN BERGE & VAN HEEMST	WITHERS & LEES	HABER'S RULE
Lethal Toxic Load (LTL_{50})	2.582E+10	9.059E+09	9.861E+09	9.662E+06	9.500E+03
Toxic Load Exponent (n)	2.75	2.75	2.75	2.00	1.00
Probit Slope with respect to Toxic Load PS (TL)	2.18	1.89	1.15	1.68	6.00
Probit Slope with respect to Concentration PS (CT)	6.00	5.19	3.17	3.35	6.00
Distance (kilometers)	Prob (%)	Prob (%)	Prob (%)	Prob (%)	Prob (%)
0.2	99.7	99.9	97.2	99.9	100.0
0.5	10.6	41.2	43.0	85.4	100.0
1.0	0.00	0.15	3.2	25.7	96.5
1.5	0.00	0.00	0.30	5.8	57.6
2.0	0.00	0.00	0.04	1.5	18.1
Distance (kilometers)	Normits	Normits	Normits	Normits	Normits
0.2	2.7047	3.2026	1.9063	3.2669	> 7.9347
0.5	-1.2486	-0.2220	-0.1774	1.0523	4.7386
1.0	-4.4246	-2.9732	-1.8514	-0.6516	1.8131
1.5	-6.1237	-4.4450	-2.7470	-1.5723	0.1907
2.0	-7.2132	-5.3888	-3.3213	-2.1727	-0.9113

Table I–4. Lethality probabilities as a function of lethality expression and distance from release point—nighttime conditions (Pasquill Category B))

	PRESENT STUDY (EQ 25)	RIJNMOND	TEN BERGE & VAN HEEMST	WITHERS & LEES	HABER'S RULE
Lethal Toxic Load (LTL_{50})	2.582E+10	9.059E+09	9.861E+09	9.662E+06	9.500E+03
Toxic Load Exponent (n)	2.75	2.75	2.75	2.00	1.00
Probit Slope with respect to Toxic Load PS (TL)	2.18	1.89	1.15	1.68	6.00
Probit Slope with respect to Concentration PS (CT)	6.00	5.19	3.17	3.35	6.00
Distance (kilometers)	Prob (%)	Prob (%)	Prob (%)	Prob (%)	Prob (%)
0.2	5.7	30.5	36.2	71.3	99.4
0.5	0.00	0.00	0.02	0.31	0.07
1.0	0.00	0.00	0.00	0.00	0.00
1.5	0.00	0.00	0.00	0.00	0.00
2.0	0.00	0.00	0.00	0.00	0.00
Distance (kilometers)	Normits	Normits	Normits	Normits	Normits
0.2	-1.5806	-0.5096	-0.3524	0.5616	2.5312
0.5	-7.5900	-5.7152	-3.5199	-2.7349	-3.2057
1.0	-12.2020	-9.7103	-5.9508	-5.2169	-7.3497
1.5	-14.2462	-11.4811	-7.0282	-6.3283	-9.2310
2.0	-15.7481	-12.7821	-7.8198	-7.1263	-10.5361

I3.2 ALOHA Model Runs

Figure I–14 through Figure I–16 are examples of the ALOHA output. ALOHA does have the convenience of producing quick graphic results, including time history plots. But, numeric time history output is not available from ALOHA. Results also tend to be more conservative, especially when plotting to the AEGL concentration levels. The following plots used the general population chlorine toxicity estimates from this report at the 2-min exposure interval (see Table 7–6 of the main body). The ALOHA model does seem to predict more pronounced heavy-gas effects compared to the HPAC results. ALOHA also has an embedded 1-h or 10-km cut-off in its calculations, which accounts for the flat cut-off features in the contour plots shown. The rationale for this cut-off is that meteorological uncertainties cannot provide a reliable prediction after 1 h or beyond 10 km after the event has occurred.

I4.0 Summary

A very brief and limited set of simulations were conducted for use as input to a comparison of various chlorine lethality estimates (see Table I–1, page I–7). Results can vary greatly based on the ATD model used (and the methodology assumptions assumed within the model), input parameters assumed and the definition of toxicological effects used to determine population effects, casualties and/or fatalities. Another important observation is that the graphical output from neither HPAC or ALOHA can adequately display toxicity estimates that are based on a toxic load model for time-dependence. When the toxic load is properly calculated from numerical HPAC output, it was found that some lethality relationships do produce probability of lethality, downwind distance profiles that are consistent with the historical record for accidental chlorine releases. It is recommended that the developers of HPAC seriously consider the addition of a toxic load contour option to HPAC graphical output.

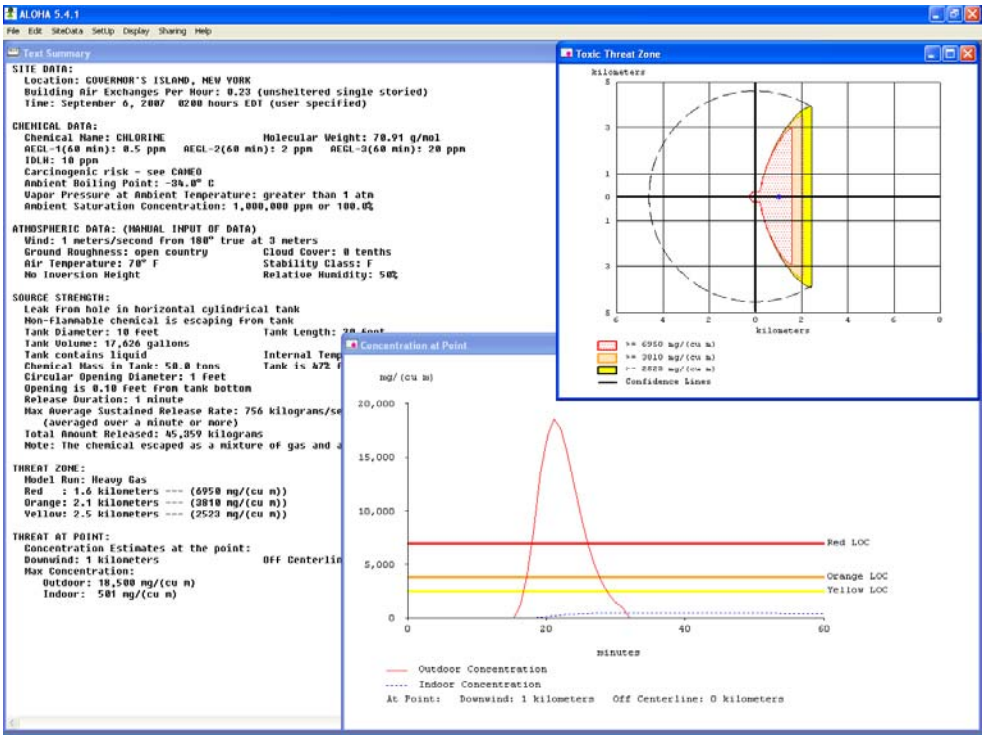

Figure I–14. ALOHA predictions for low wind (1 m/s), clear sky, nighttime (2 a.m.), "stable" condition (Pasquill Category F)

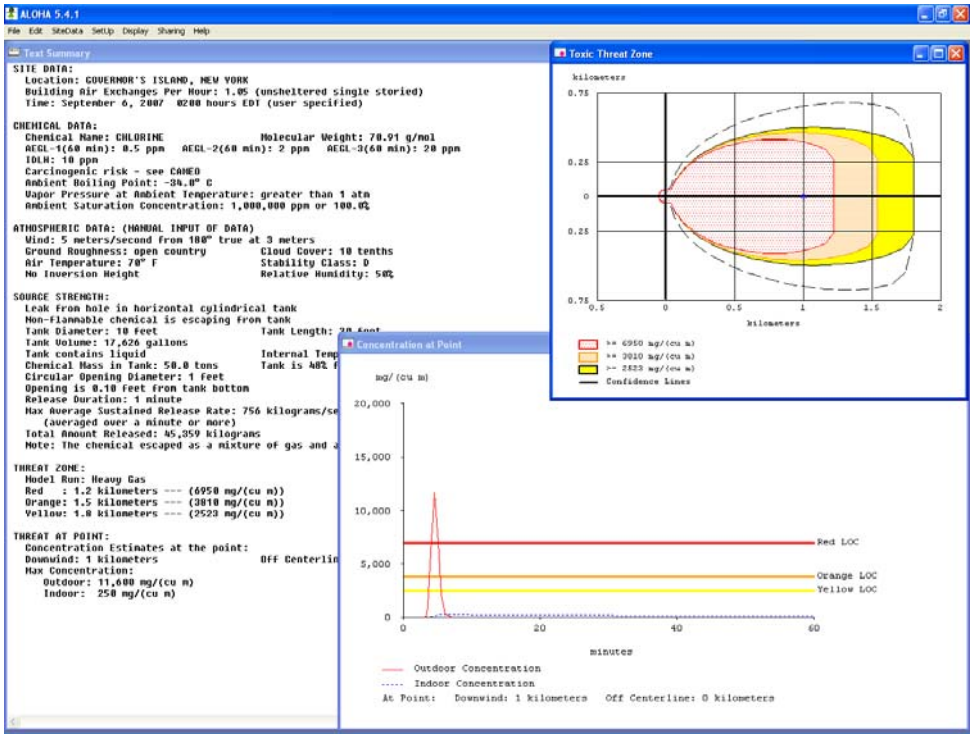

Figure I–15. ALOHA predictions for moderate wind (5 m/s), cloudy day, "neutral" condition (Pasquill Category D)

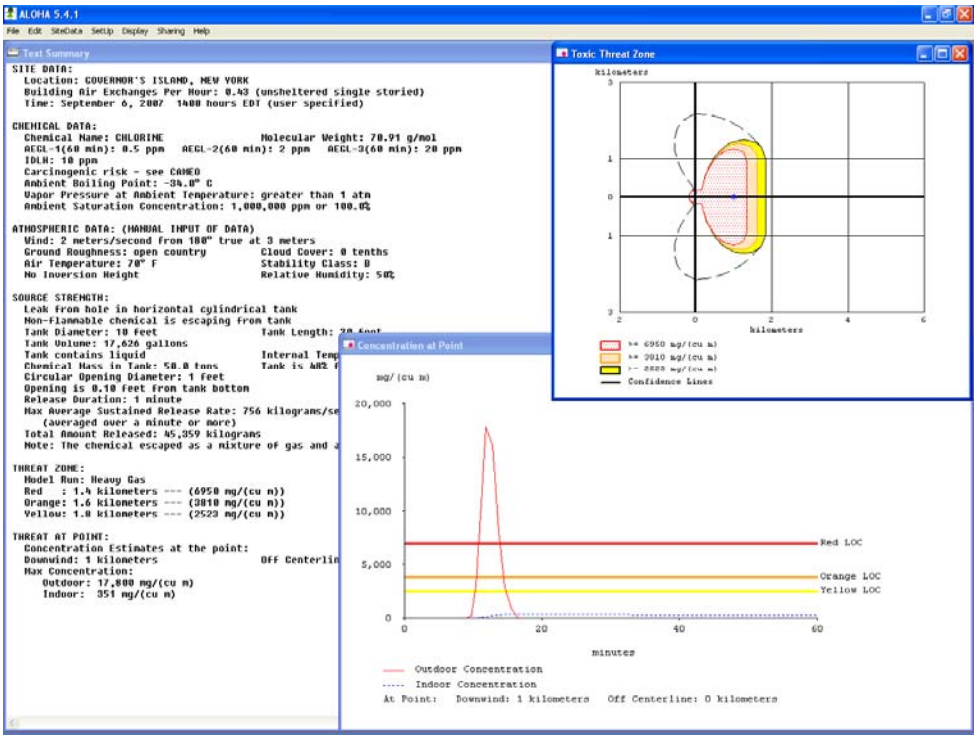

Figure I–16. ALOHA predictions for low wind (2 m/s), clear sky, daytime (2 p.m.), "unstable" condition (Pasquill Category B)

I5.0 References

[1] **ALOHA (Areal Locations of Hazardous Atmospheres) User's Manual**. US Environmental Protection Agency Office of Emergency Management, Washington, D.C., and National Oceanic and Atmospheric Administration Office of Response and Restoration/Hazardous Materials Response Division, Seattle, Washington, February 2007.

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[11] Withers, RMJ and Lees, FP, The Assessment of Major Hazards: The Lethal Toxicity of Chlorine, Part I—Review of Information on Toxicity, **Journal of Hazardous Materials**. **12**: 231-282, 1985.

[12] Withers, RMJ and Lees, FP, The Assessment of Major Hazards: The Lethal Toxicity of Chlorine, Part II—Model of Toxicity to Man, **Journal of Hazardous Materials**. **12**: 283-302, 1985.

APPENDIX J: STATISTICAL ANALYSIS OF MICE CHLORINE LETHALITY DATA OF BITRON AND AHARONSON (1978)—Douglas R. Sommerville

J1.0 Introduction

Mouse chlorine lethality data from Bitron and Aharonson[1] were subjected to a statistical analysis. Bitron and Aharonson exposed 476 mice (in groups of 14) about evenly divided between either of two concentrations (C) of chlorine vapor (170 ppm or 290 ppm) and for varying periods of time (T) (from 14 min to 160 min for 170 ppm and from 6 min to 31 min for 290 ppm). Their data was reevaluated in this analysis using modern statistical methods in order to better model how the median lethal dosage (LCT_{50}) varied as a function of exposure duration. Originally, Bitron and Aharonson did not report a mathematical expression for the time-dependence of the toxicity. However, subsequent researchers[2-4] have fitted a toxic load expression ($L(C^nT)_{50}$ = a constant)[5,6] using the two LT_{50} values that were reported (11 min. for 290 ppm and 55 min for 170 ppm). A toxic load exponent (n) value of 3.5 has been reported by ten Berge and van Heemst[2] and a value of 3 from the method[a] used by Withers and Lees.[3] These estimates are both based upon an incomplete picture of the data. ten Berge and van Heemst used a multifactor probit fit on a select portion of the original data, and Withers and Lees depended on the reported median lethal dosages instead of analyzing the original binary response data. To address this deficiency, the complete response dataset of Bitron and Aharonson was subjected to a multifactor probit analysis[8] using the binary logistic regression routine in Minitab®[9] From this fit, the values of the toxic load exponent and other important parameters were estimated, along with 95% confidence intervals.

J2.0 Data Collection and Reduction

The individual percent response values are not listed separately in the original report. Instead, these values must be extracted from the graphical representations shown in the Bitron and Aharonson report, Figures 9 and 11. In their Figure 9, the overall mortalities for individual grouping of three to four exposure durations each were plotted as a function of days post-exposure. In their Figure 11, the percent response is plotted versus the exposure millimeter ruler was then used to determine the coordinates of each symbol relative to the origin of the plot. Their coordinates were then converted into values for numbers of deaths per exposure group for some value of C and T using the appropriate map scale for the enlarged figure. For the response data at 290 ppm, there are five experiments of 100% mortality that were omitted from their Figure 11. So, the response data was reconstructed in the best manner possible. As a check of the reconstructed data, the total percent mortality in their Figure 9 for each grouping of durations was consulted and also subjected to a regression analysis. The collected data are shown in Table J–1 and Table J–2. A summary of percent mortality values per exposure duration group from their Figure 9 is listed in Table J–3.

[a]Originally, Withers and Lees calculated an average toxic load exponent value using median toxic load values from Bitron and Aharonson and Weedon *et al.*[7] If only the data of Bitron and Aharonson is subjected to the Withers and Lees calculation algorithm, a toxic load exponent value of 3 is obtained.

Table J-1. Mouse chlorine inhalation lethality data from Figure 11 of Bitron and Aharonson for 170 ppm of chlorine vapor

C (ppm)	T (min)	DEATHS	NUMBER OF MICE EXPOSED	PERCENT LETHALITY	DURATION GROUP IN FIGURE 9 (min)
170	13	0	14	0.0	22
170	16	4	14	28.6	22
170	18	1	14	7.1	22
170	29	1	14	7.1	22
170	39	4	14	28.6	52
170	41	3	14	21.4	52
170	42	9	14	64.3	52
170	49	10	14	71.4	52
170	57	13	14	92.9	52
170	57	4	14	28.6	52
170	57	3	14	21.4	52
170	81	10	14	71.4	120
170	100	10	14	71.4	120
170	112	13	14	92.9	120
170	121	12	14	85.7	120
170	163	8	14	57.1	120

Table J–2. Mouse chlorine inhalation lethality data from Figure 11 of Bitron and Aharonson for 290 ppm of chlorine vapor

C (ppm)	T (min)	DEATHS	NUMBER OF MICE EXPOSED	PERCENT LETHALITY	DURATION GROUP IN FIGURE 9 (min)
290	6	0	14	0.0	6
290	6	0	14	0.0	6
290	7.5	4	14	28.6	9
290	8.5	7	14	50.0	9
290	9.25	7	14	50.0	9
290	10.25	4	14	28.6	9
290	13	7	14	50.0	15
290	13	11	14	78.6	15
290	13	11	14	78.6	15
290	13	14	14	100.0	15
290	14	10	14	71.4	15
290	16.25	14	14	100.0	15
290	20.5	12	14	85.7	25
290	23.5	12	14	85.7	25
290	19	14	14	100.0	25
290	31	14	14	100.0	25
290	25	14	14	100.0	25
290	25	14	14	100.0	25

Table J–3. Summary of mouse chlorine inhalation mortality from Figure 9 of Bitron and Aharonson

C (ppm)	DURATION GROUP (min)	DEATHS	NUMBER OF MICE EXPOSED	NUMBER OF EXPERIMENTS	PERCENT MORTALITY
170	22 ± 8	6	56	4	10.7
170	52 ± 13	46	98	7	46.9
170	120 ± 40	53	70	5	75.7
290	6	0	28	2	0.0
290	9 ± 1	22	56	4	39.3
290	15 ± 2	67	84	6	79.8
290	25 ± 6	80	84	6	95.2

J3.0 Statistical Analysis of Binary Response Data

The following are the Minitab® printouts for the multifactor probit analysis of the mouse chlorine inhalation lethality data. Examples are presented on how various final parameter values (median effective dosages, dosage ratio of severe and lethal effects, etc.) are calculated from these printouts.

J3.1 Nomenclature

C	Concentration of chlorine vapor in ppm (1 mg/m^3 = 2.898 x 1 ppm) (used as a covariate)
Conc	Concentration treated as a factor
Deaths	Number of deaths
logC	Log base 10 of vapor concentration
logCT	Log base 10 of vapor concentration multiplied by exposure duration
logT	Log base 10 of exposure duration
n	Toxic load exponent
Number	Number of mice exposed to indicated row values of C and T
SE	Standard error of coefficient
T	Exposure duration (in minutes)
Time	Duration treated as a factor
Z	Normit (Z = 0 for 50% response, -1 for 16% response and 1 for 84% response)

J3.2 Toxic Load Exponent Estimation

To estimate the toxic load exponent, a multifactor probit analysis was performed on logC and logT for two sets of data: (1) data from Table J–1 and Table J–2; and (2) data from Table J–3. The ratio of the fitted coefficients for logC and logT (or k_c/k_t) equals the toxic load exponent.[6]

J3.2.1 Binary Response from Table J–1 and Table J–2 Versus LogC and LogT

Link Function: Normit

Response Information

Variable	Value	Count
Deaths	Event	274
	Non-event	202
Number	Total	476

Logistic Regression Table

Predictor	Coef	SE Coef	Z	P
Constant	-29.2194	2.75200	-10.62	0.000
logC	10.6318	1.01580	10.47	0.000
logT	3.16473	0.303112	10.44	0.000

Log-Likelihood = -240.542

Test that all slopes are zero: G = 167.860, DF = 2, P-Value = 0.000

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	89.6501	24	0.000
Deviance	81.4549	24	0.000
Hosmer-Lemeshow	18.3257	7	0.011

Variance-Covariance Matrix for Fit

Constant	logC	logT
7.57348	-2.78459	-0.729094
-2.78459	1.03185	0.255530
-0.72909	0.25553	0.091877

The LT_{50} values from this fit for concentrations of 170 ppm and 290 ppm are 55 min and 9.1 min, respectively. Bitron and Aharonson originally reported 55 min and 11 min using the Litchfield and Wilcoxon method[11] to analyze their data. The probit slope (k_c) for this fit equals 10.6 with 95% fiducial limits of 8.64 to 12.62.

There is statistically significant lack of fit, based upon three statistical tests (Pearson, Deviance and Hosmer-Lemeshow). A review of the standardized Pearson residuals identified two outliers: (1) 16 min at 170 ppm (4 deaths out of 14); and (2) 163 min at 170 ppm (8 deaths out of 14). A second regression without the two outliers produces the following fit.

Link Function: Normit

Response Information

Variable	Value	Count
Deaths	Event	262
	Non-event	186
Number	Total	448

* NOTE * 32 cases were used

* NOTE * 2 cases contained missing value

Logistic Regression Table

Predictor	Coef	SE Coef	Z	P
Constant	-38.5843	3.54588	-10.88	0.000
logC	13.9054	1.29500	10.74	0.000
logT	4.37248	0.399308	10.95	0.000

Log-Likelihood = -205.765

Test that all slopes are zero: G = 196.574, DF = 2, P-Value = 0.000

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	41.3492	22	0.007
Deviance	47.7748	22	0.001
Hosmer-Lemeshow	5.5522	5	0.352

Variance-Covariance Matrix for Fit

Constant	logC	logT
12.5733	-4.57879	-1.29129
-4.5788	1.67702	0.45500
-1.2913	0.45500	0.15945

For the second fit, at least one test (Hosmer-Lemeshow) returned a p-value greater than 0.05 signifying that there is no lack of fit. The LT_{50} values from this fit for concentrations of 170 ppm and 290 ppm are 54 min and 9.9 min, respectively. This is not drastically different from the regression fit that included the outliers.

The probit slope (k_c) for this fit equals 13.9 with 95% fiducial limits of 11.4 to 16.4. This is higher than for the fit that included the outliers. This is not surprising, since the probit slope is a measure of variance and the remove of outliers will usually reduce the variance in the data.

The present of statistically significant curvature was tested for by introducing a $(logT)^2$ term into the model. This term was found to be statistically significant for the dataset in Table J–1 and Table J–3, with and without the previously identified outliers. Curvature in the logC and logT fit is not unheard of, but the result is difficult to use in atmospheric transport and dispersion models.[12]

J3.2.2 Binary Response from Table J–3 Versus LogC and LogT

Link Function: Normit

Response Information

Variable	Value	Count
Deaths	Event	274
	Non-event	202
Number	Total	476

Logistic Regression Table

Predictor	Coef	SE Coef	Z	P
Constant	-32.2629	2.83110	-11.40	0.000
logC	11.6873	1.04248	11.21	0.000
logT	3.49093	0.309412	11.28	0.000

Log-Likelihood = -234.041

Test that all slopes are zero: G = 180.861, DF = 2, P-Value = 0.000

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	19.6929	4	0.001
Deviance	25.0251	4	0.000
Hosmer-Lemeshow	10.7637	4	0.029

Variance-Covariance Matrix for Fit

Constant	logC	logT
8.01514	-2.93985	-0.769620
-2.93985	1.08676	0.269349
0.26935	-0.76962	0.095736

The LT_{50} values from this fit for concentrations of 170 ppm and 290 ppm are 59 min and 9.9 min, respectively. Bitron and Aharonson originally reported 55 min and 11 min using the Litchfield and Wilcoxon method[11] to analyze their data.

There is statistically significant lack of fit, based upon three statistical tests (Pearson, Deviance and Hosmer-Lemeshow). A review of the standardized Pearson residuals identified two outliers: (1) 120 min at 170 ppm (53 deaths out of 70); and (2) 6 min at 290 ppm (zero deaths out of 28). Omitting either of the outliers will remove the lack of fit. However, there is a big difference between the resulting toxic load exponent values depending on which datum is chosen for omission (2.95 versus 3.59).

The presence of statistically significant curvature was tested for by introducing a $(logT)^2$ term into the model. This term was found to be statistically

significant, a result identical to that of Section J3.2.1.

J3.2.3 Calculation of the Toxic Load Exponent

The following is a step by step example of calculating the toxic load exponent and associated confidence limits.

(1) Calculation of toxic load exponent for first dataset (Table J–1 and Table J–2):

$$n = \frac{k_c}{k_t} = \frac{(10.6318)}{(3.16473)} = 3.36 \qquad \text{(J1)}$$

(2) The standard error of a ratio needs to be calculated. From Mood et al. (1974), the following is given:[10]

$$\text{var}(a/b) = \left[\frac{a^2}{b^2}\right]\left[\frac{\text{var}(a)}{a^2} + \frac{\text{var}(b)}{b^2} - \frac{(2)\text{cov}(a,b)}{ab}\right] \qquad \text{(J2)}$$

$$\text{StndError} = \sqrt{\text{var}(a/b)}$$

(3) Using values from the variance-covariance matrix, the variance of the numerator, var(num) or var(k_c), equals 1.03185. For k_t, the variance equals 0.091877.

(4) Using values from the variance-covariance matrix, the covariance of the numerator and the denominator, cov(k_c, k_t), equals 0.255530.

(5) Thus, the standard error (using eq A3) equals:

$$\text{var}(a/b) = \left[\frac{(10.6318)^2}{(3.16473)^2}\right]\left[\frac{(1.03185)}{(10.6318)^2} + \frac{(0.091877)}{(3.16473)^2} - \frac{(2)(0.255530)}{(10.6318)(3.16473)}\right] \qquad \text{(J3)}$$

$$\text{StndError} = \sqrt{\text{var}(a/b)} = 0.187$$

(6) The approximate 95% confidence limits for the toxic load exponent now equal:

$$\hat{\mu}_j - (1.96)(\text{StndErr}) \le n \le \hat{\mu}_j + (1.96)(\text{StndErr})$$

or

$$3.359 - (1.96)(0.187) \le n \le 3.359 + (1.96)(0.187) \qquad \text{(J4)}$$

or

$$2.992 \le \text{Ratio} \le 3.727$$

The above calculations were repeated for the fit of Section J3.2.1 (without two outliers). The toxic load exponent was found to equal 3.18 with 95% CI of 2.90 to 3.46. For the fit from Section J3.2.2, the exponent was found to equal 3.35 with 95% CI of 3.01 to 3.68.

J3.3 Probit Slope (k_t) Estimation

To estimate the probit slope for exposure duration (k_t), a multifactor probit analysis was performed on covariate logT nested with the factor *Conc* for two sets of data: (1) data from Table J–1 and Table J–2; and (2) data from Table J–3. The estimates for k_t are shown in Table J–4, along with the originally reported values from Bitron and Aharonson. The reverse analysis (covariate logC nested with the factor *Time*) could not be performed, due to having only two unique values for concentration (170 ppm and 290 ppm). Thus, for a k_c estimate, one of the approaches shown in Section J3.2 must be used.

For the fit of logT nested within *C*, there was no lack of fit for any of the datasets analyzed. Also, for both datasets, the probit slope values are different from each other with statistical significance. This is consistent with the significant curvature found in the logC and logT fit of Section J3.2. There is agreement between the probit slope estimates from this appendix and what was originally reported by Bitron and Aharonson.

J4.0 Discussion and Summary

The presence of significant curvature in the logC and logT fit (see Section J3.2) is problematic. However, the curvature could be an artifact of an improperly designed test matrix. The probit slope is a measure of all variance present in a study, not just of the variability in individual toxic responses. For example, if all the runs for each concentration were performed together (i.e., all the 170-ppm experiments were performed before any of the 290-ppm experiments), then there could be a batch

Table J–4. Summary of probit slope (exposure duration) estimates from mouse chlorine inhalation mortality of Bitron and Aharonson

DATASET	*C* (ppm)	PROBIT SLOPE (k_t) (BASE 10)	95% FIDUCIAL LIMITS
Tables J1&J2	170	2.20	1.55 to 2.84
	290	5.67	4.40 to 6.94
Table J3	170	2.56	1.85 to 3.27
	290	5.25	4.12 to 6.37
Bitron and Aharonson	170	2.5	NR
	290	4.7	NR

effect due to changes in laboratory procedures (i.e., different animal handlers, different batches of chlorine, seasonal effects, etc.). Also, only two concentration values were investigated, preventing the testing for curvature as a function of concentration. So, for the moment, a simplified approach (assuming linearity in the logC and logT fit) is warranted until such curvature is reproduced in a future study.

Using three different datasets (Table J–1 and Table J–2; Table J–1 and Table J–2 with two outliers removed, and Table J–3), remarkably similar values for the toxic load exponent were obtained. For a final estimate for both the toxic load exponent and the probit slope (k_c), the fit (with the two outliers) in Section J3.2.1 should be used for two reasons:

(1) The original notes from Bitron and Aharonson are not available, thus identification of suspect experiments would be difficult. Omitting one outlier over another can greatly influence the final estimate for the toxic load exponent.

(2) The exposure duration values in Table J–3 are averages of the actual durations that were used, which would artificially reduce the lethal response variance.

From the logC and logT fit (Section J3.2.1), the toxic load exponent equals 3.36 with 95% confidence interval of 2.99 to 3.73. The probit slope (k_c) equals 10.6 with 95% fiducial limits of 8.64 to 12.62.

J5.0 References

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