

ABSTRACT

New human estimates for chlorine inhalation lethality as a function of exposure duration were derived via a review and statistical analysis of existing mammalian lethality data. Such estimates are needed to support risk assessments and casualty predictions involving airborne releases of chlorine. At present, casualty predictions for such releases are at odds with what has been observed historically; the predicted downwind hazard area has often been much larger than what was actually observed. Either the present estimates for median lethal dosages (LCT_{50}) are too low, the currently popular atmospheric transport and dispersion (ATD) models cannot adequately model chlorine releases, or both.

LCT_{50} and quantal response data were analyzed for eight species (mouse, rat, guinea pig, rabbit, cat, dog, goat and sheep), for exposure durations from 8 to 235 minutes. The base 10 probit slope (concentration) was estimated via the weighted average of experimentally measured slopes in mammalian lethality studies. Resulting human lethality (military) estimates as a function of exposure duration were expressed via the toxic load model. General population estimates were derived from the military estimates using the mathematical method of Crosier (2007).

Previous human estimates were reviewed and compared to the new general population estimate. The impact of the new estimate was evaluated through a series of transport and dispersion modeling runs for the catastrophic accidental release of 50 tons of chlorine from a tanker car. The sensitivity of downwind hazard distances was also investigated as a function of median lethal toxic load (TL), toxic load exponent and probit slope values.

INTRODUCTION

Chlorine is a greenish-yellow, highly reactive halogen gas that has a pungent, suffocating odor. Because of its extensive industrial use and toxicity, it has been the subject of many toxicological studies, and a number of human toxicity estimates have been derived. Several previous efforts centered on toxicity estimates for protecting a

population from accidental releases. However, many risk assessment applications require an objective estimate of the actual toxicity and not a conservative, protective estimate. At present, casualty predictions for accidental chlorine releases are at odds with what has been observed historically. Either the present toxicity estimates are too low (*i.e.* potency is over estimated), 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 (IH) exposures involving a healthy (military-type) human population. An allometric modeling approach was used to extrapolate a human estimate from applicable mammalian toxicity data. The estimate also provides a probit slope for a healthy adult population. General population estimates were developed from the military estimates using Crosier (2007).

STATISTICAL BACKGROUND

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 fitted constant (West *et al.*, 1997). 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.

In inhalation toxicology, the dose received by an animal is directly related to the amount of air inhaled (Phalen, 1984, Salem, 1987, Snipes, 1988). Minute volume (V_M) is a commonly used respiratory measurement, which equals the volume of air inspired per minute. A relatively recent review (and analysis) of mammalian V_M data (and species body mass, M) is available from Bide *et al.* (2000). [Table 1 lists some of their average V_M and M values.] Based upon allometric scaling law, V_M should scale to the 0.75 power, but they found that V_M scales to the 0.809 power for non-anesthetized, adult mammals:

Review and Assessment of Chlorine Mammalian Lethality Data and the Development of a Human Estimate

Douglas R. Sommerville
US Army Edgewood Chemical
Biological Center (ECBC)
douglas.sommerville@us.army.mil

John J. Bray
Optimetrics, Inc.
jbray@omi.com

Sharon A. Reutter-Christy
US Army ECBC
s.reutterchristy@us.army.mil

Raymond E. Jablonski
Chemical Security Analysis
Center
ray.jablonski@dhs.gov

Erin E. Shelly
US Army ECBC
erin.shelly@us.army.mil

APPLICATION AREAS:
WG-2: Nuclear Biological
Chemical Defense; WG-5:
Homeland Security,
Homeland Defense and
Civil Support; WG-17:
Casualty Estimation and
Force Health Protection

OR METHODOLOGIES:
Applied Statistics (Linear
regression, probit analysis,
allometric modeling);
Probabilistic Operations
Research (Simulation with
atmospheric transport and
dispersion (ATD) models)

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

Table 1. Summary of Minute Volumes (Non-Anaesthetized Animals)*.

Species	Mass (kilograms)	Minute Volume Expt. Average (liters)	Minute Volume Allometric Model Fit (liters)	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

* adapted from Bide *et al.*, 2000

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

where V_M is in liters/min and M is in kg. Using Equation [2], they calculated a V_M of 15.5 liters/min for 70 kg man engaged in mild activity—not a resting volume. This V_M is very close to the standard V_M of 15 liters/min used by DoD as a basis for their toxicity estimates for a 70 kg soldier (US Army Chemical School, 2005).

For typical whole body exposures, the exact inspired amount is usually not measured. In its place, a nominal dose (mg) can be calculated by multiplying the lethal inhalation dosage, (mg-min/m³) (estimated from experimental toxicology data) by the minute volume (m³/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.

Toxicity is a function of many factors, and some of these (*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 Equation [4]. A human estimate can be obtained from mammalian data by extrapolating to a 70 kg human.

$$\begin{aligned} LD_{50} &= X_0 M^b \\ \text{or} \\ \log(LD_{50}) &= \log(X_0) + b \log(M) \end{aligned} \quad [4]$$

In Equation [4], both the regressor term (LD_{50}) and the predictor term (M) are highly correlated with the parameter, V_M . Controversy, dating back to 1897 (Pearson, 1897), exists over regressions involving predictor and regressor variables sharing a common term, and continues to this day (Albrecht *et al.*, 1993; Bradshaw & Radbill, 1987; Dunlap *et al.*, 1997; Firebaugh, 1986, 1988; Firebaugh & Gibbs, 1985, 1987; Kraft, 1987; Kuh & Meyer, 1955; Macmillan & Daft, 1980; Prairie & Bird, 1989; Smith, 2005; Vanderburgh, 1998; Yule, 1910)—it is thought that such regressions return spurious correlations. 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 (Firebaugh & Gibbs, 1985, 1987; Prairie & Bird, 1989).

Inhalation Dose-Response Statistics and the Toxic Load

The statistical properties of dose-response distribution have been extensively reviewed (Finney, 1971; Neumann & Kimmel, 1998) and summarized (Salem, 1987; Crosier & Sommerville, 2002). Inhalation dosage traditionally has been expressed as the product of vapor concentration (C) and duration (T), or CT . The distribution of effective CT s for a homogeneous population is usually lognormal and described by:

$$Z = m [\log(LCT_{XX}) - \log(LCT_{50})] \quad [5]$$

where Z is the standard normal random variable, m is the probit (or Bliss) slope (and equal to inverse of the standard deviation), LCT_{XX} and LCT_{50} are the CTs that will produce lethality in XX% and 50%, respectively, of the exposed individuals. Z is a function of the cumulative probability, with the 16, 50 and 84% response level corresponding to Z equal to -1, 0 and 1, respectively (Box *et al.*, 1978; Hine & Montgomery, 1990; MINITAB® Statistical Software, 2006). Toxicologists traditionally use base 10 logarithms to calculate the probit (Bliss) slope (Bliss, 1934; Finney, 1971), while engineers often use natural logarithms (Fairhurst & Turner, 1993; Ferguson & Hendershot, 2000; The Major Hazards Assessment Panel, 1988; Yee, 1996a).

When the LCT_{50} is constant with respect to T , it is said to obey Haber's Rule (Haber, 1924). However, Haber's Rule is more of an exception than a true rule. Thus, a new term, Toxic Load (TL), has been developed and extensively used in inhalation toxicology to account for time-dependent toxicity (Mannan, 2005; Ride, 1995; Sommerville *et al.*, 2005; Yee, 1996b; Yee & Yee, 1996). TL is normally expressed as C^nT , with n being the toxic load exponent (TLE). LTL_{50} refers to the TL that will produce lethality in 50% of exposed individuals. When $n = 1$, the chemical follows Haber's Rule (Sommerville *et al.*, 2005). For acute inhalation of irritant gases, n tends to be greater than unity and is often of the order of two in value (Mannan, 2005). The same statistical theory used for dosages (Finney, 1971) has also been adopted for use with toxic load (Fairhurst & Turner, 1993; Griffiths, 1991; Schubach, 1995, 1997; Withers & Lees, 1985a,b; Yee, 1996a,b).

Although the normal distribution is continuous, quantal data (response *versus* no response) are used to fit Equation [5] (Finney, 1971, 1978), through the use of probit analysis and maximum likelihood estimation (MLE) (Fairhurst & Turner, 1993; Finney, 1971; Fox, 1997). The following equation is fitted via probit analysis/MLE for vapor toxicity studies (Fairhurst & Turner, 1993; Finney, 1971; Yee, 1996a,b):

$$Y_N = (Y_P - 5) = k_0 + k_C \log C + k_T \log T \quad [6]$$

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. The constants k_C and k_T are the probit slopes for concentration and time, respectively. The TLE (n) equals the ratio of these two slopes, or (k_C / k_T). Some studies report a probit slope for the TL (Fairhurst & Turner, 1993; Franks *et al.*, 1996; Marshall, 1989; Poblete & Lees, 1984; ten Berge & van Heemst, 1983; Withers & Lees, 1985a,b).

When fitting Equation [6], all variability in the data will contribute to the estimate for m , be it from variance due to individual susceptibilities (the true goal), batch effects, experimental error, differences in durations, compilation from many sources (Franks *et al.*, 1996), *etc.* The heterogeneity introduced by outside sources of variance will artificially lower the probit slope. The precision of slope estimation typically improves as more experimental subjects are used. For studies involving more than one exposure duration, fitting Equation [6] with T treated as a factor (instead of as a covariate) will produce the best overall probit slope estimate for the whole study (Benton *et al.*, 2007; Hulet *et al.*, 2006). Equation [6] can also be written in the following form:

$$Y_N = k_0 + k_{TL} \log(TL) \quad [7]$$

with k_0 and k_{TL} being fitted coefficients, and k_{TL} being the probit slope on a toxic load basis. Also, k_{TL} equals the probit slope for time, k_T .

The TL relationship is empirical, rather than theoretical (Fairhurst & Turner, 1993; Griffiths, 1991; Yee, 1996a,b). Thus, Equations [6] and [7] needs to be empirically derived on an individual toxicant basis from experiments where both C and T are varied (ten Berge *et al.*, 1986). The value for n may offer some insight into the influence of underlying toxicological mechanisms (Griffiths, 1991). For instance, it can be argued that if $n > 1$, then significant detoxification may be occurring during the exposure, since the required effective dosage is increasing as the dosage is incurred over a longer duration.

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

$$\log(LD_{50}) = \log(Y_0) + k_M \log(M) + k_T \log(T) \quad [8]$$

Using Equations [3] and [8], it can be shown algebraically that the TLE (n) equals $[1 / (1 - k_T)]$. After the appropriate substitutions, Equation [8] can be written in a TL form (Equation [7]).

Statistical Treatment of Historical Data

Proper evaluation of historical data is critical. The studies were often done in different decades, by different researchers in different laboratories. With linear regression analysis, the use of weights technically permits assigning a numerical value to the quality of a datum, but how does the analyst properly estimate the values for weighting? A solution to this problem is the use of one of many robust regression methods that have been developed (Box & Draper, 1987; Fox, 1997; Myers & Montgomery, 1995).

For the present study, the iteratively re-weighted least squares (IRLS) method (Box & Draper, 1987; Fox, 1997; Myers & Montgomery, 1995) 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 from the previous iterative step. Often, the standardized residual is used (Box & Draper, 1987), but for this study the studentized deleted residual was used instead. The studentized deleted 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).

Military Subpopulation *versus* General Population in Toxicity Sensitivity

It is assumed that only healthy animals were used in the reviewed studies. Consequently, when scaling from smaller mammals up to humans, the derived estimate should correspond to a healthy human subpopulation, defined in this case as being healthy and fit enough for mil-

itary service. However, this does not address the issue of the more vulnerable portions of the general population. Several studies have attempted to account for such sensitivity differences in different populations (Eisenberg *et al.*, 1975; Harris & Moses, 1983; MHAP, 1988; NRC, 2004; ten Berge & van Heemst, 1983; Withers & Lees, 1985a,b). For this study, it is assumed that the sensitive subpopulation can be adequately modeled using Equation [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 estimates that were derived using the mammalian data.

In a series of reports (Crosier & Sommerville, 2002; Crosier, 2003, 2007), ECBC has developed a mathematical method for the conversion from one population basis to another, with Crosier (2007) presenting the final version of the method. The premise of the approach is that mathematically the distribution of $\log(\text{doses})$ 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 of Crosier (2007) is that it reduces the amount of subjectivity that has been used in the past in accounting for population differences.

Military Chemical Warfare Defense and the Toxic Load Model

Use of the Toxic Load Model is a recent development in military toxicology, being officially adopted by the Department of Defense (DoD) in 2005 (US Army Chemical School, 2005). The demise of the offensive chemical warfare (CW) program (and the resulting change in mission) necessitated such a course. Using Haber's Rule was sufficient for offensive CW operations, where the exposure durations of interest were from 2 to 10 minutes. However, CW defense is now the primary focus. Both short and long exposure durations (from a few minutes to hours) need to be considered—for example:

- Protective equipment tested against the higher effective concentrations associated with short exposure durations
- Decontamination standards (among other items) based on the lower effective concentrations associated with longer exposure durations

Proper risk optimization involving levels of CW protection requires an accurate knowledge of the TLE. The issue is illustrated in Figure 1, with a comparison of two different LCT_{50} time relationships: Haber's Rule agent ($n = 1$) versus a TL agent having an $n > 1$. Decision making using Haber's rule for a TL agent (or *vice versa*) may produce an inaccurate assessment.

HISTORICAL CHLORINE DATA AND HUMAN TOXICITY ESTIMATES

Toxic Action of Chlorine Inhalation on Animals and Humans

Chlorine is an acute respiratory irritant in both animals and humans and produces a simi-

lar spectrum of toxic responses (from minor irritation to death), in all species, as the exposure concentration increases (MHAP, 1988; Mannan, 2005; NRC, 2004; Turner & Fairhurst, 1990). Chlorine 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 (NRC, 2004). 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 (MHAP, 1988; Mannan, 2005).

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 (2005), as well as the 1987 monograph by the MHAP sponsored by the Institution of Chemical Engineers. Human estimates from five previous studies were investigated for comparison with the present work:

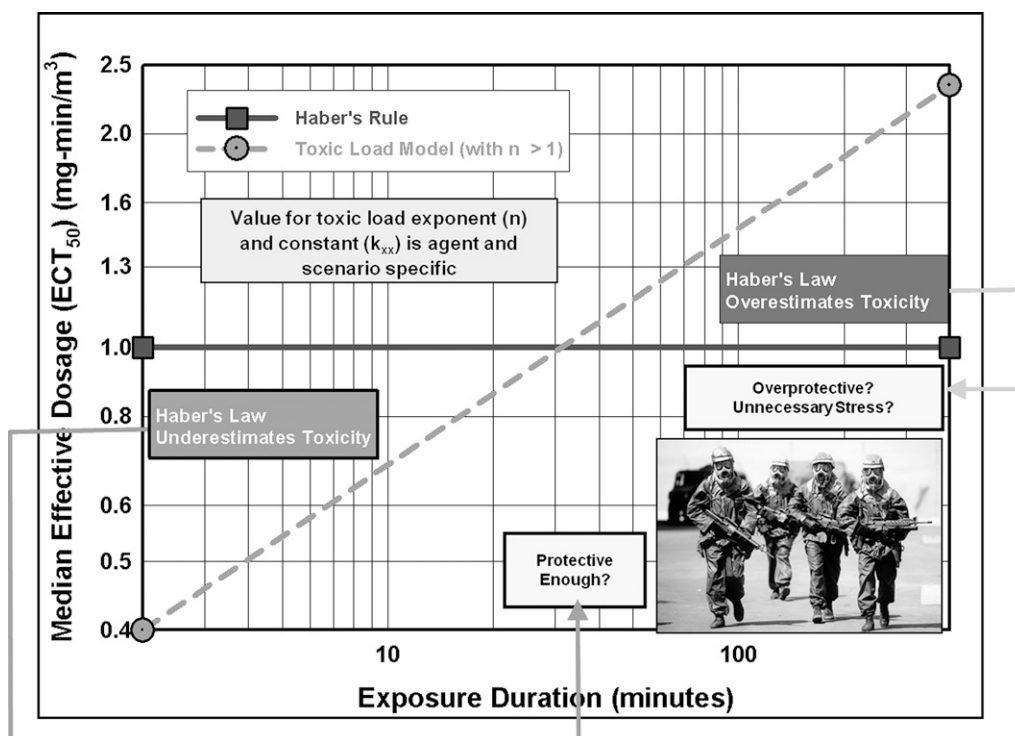


Figure 1. Importance of Establishing the Time Dependence of IH Toxicity.

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

- (1) Eisenberg *et al.* (1975)
- (2) Perry & Articola (1980)
- (3) ten Berge & van Heemst (1983)
- (4) Rijnmond Report (1982)/Harris & Moses (1983)
- (5) Withers & Lees (1985a,b)

All five studies recognized that chlorine inhalation toxicity varies with duration and used the TL model to describe the relationship (see "Inhalation Dose-Response Statistics and the Toxic Load"). Nonetheless, these studies do differ in their philosophies on how to best extrapolate from animal data to a human toxicity estimate. Although some (MHAP, 1987; Withers & Lees, 1985a) 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.

Eisenberg *et al.* (1975) and Perry & Articola (1980) are related works that were written in support of the US Coast Guard's Vulnerability Model—chlorine was one of many chemicals for which human toxicity estimates were collected or derived. These human estimates lie well below the LCT_{50} s of the underlying experimental animal data, and several authors do not recommend their estimates for risk assessment (Harris & Moses, 1983; MHAP, 1987; ten Berge & van Heemst, 1983; Withers & Lees, 1985a,b).

ten Berge & van Heemst (1983) assumed that humans can be modeled as being as sensitive as the average mammal, which would place the human between the mouse (most sensitive) and the dog (least sensitive). Their estimate of the human response variability was for a general population. The toxicity time dependence was based upon mouse data of Bitron & Aharonson (1978) and human volunteer irritation dose-response relationship reported by Anglen (1981).

Harris & Moses (1983) did not make any explicit statement on what animal model they used to base their estimates. Since their human estimate curve is very similar to that of ten Berge & van Heemst (1983) it may be inferred that Harris & Moses assumed that human toxicity can be equated to that of an average experimental animal. Harris & Moses believed that more variability exists in the human general population response (based upon the historical record) than was originally estimated by the

US Coast Guard studies. However, the Harris & Moses estimate for response variability is less than that of ten Berge & van Heemst. Thus, although the predicted LCT_{50} s 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. Harris & Moses and the Rijnmond Report (1982) have identical human estimates and are treated as synonymous by Mannan (2005).

Withers & Lees (1985a,b) gave greatest weight to the dog data of Underhill (1920) in the development of their human estimate, but did not neglect to interpret the dog data in light of the other animal data. They also 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 and 12 liters/min, respectively). All of the Withers & Lees estimates are lower than those for the general population estimates from ten Berge & van Heemst (1983) and Harris & Moses (1983), with the difference increasing as the duration increases.

HISTORICAL RECORD OF CHLORINE RELEASES

The historical record of chlorine industrial accidents has been well documented (Harris & Moses, 1983; MHAP, 1987; Mannan, 2005; Marshall, 1977). The most notable statistic for the reported incidents of accidental outdoor releases (with release amounts up to 50 metric tons) is that fatalities (with one exception) occur within about 400 meters of the actual point of release, and more often within 250 meters (MHAP, 1987; Mannan, 2005). The largest number of fatalities for an outdoor chlorine release is around 60 and resulted from a ruptured storage tank in Romania in 1939 (Marshall, 1977). It has been estimated that there are (on average) 0.3 to 0.8 fatalities per metric ton of an accidental industrial release (Harris & Moses, 1983; MHAP, 1987; Marshall, 1977).

Marshall (1977) made the anecdotal observation that no civilian casualties were reported

from the first large scale chemical warfare attack at the Second Battle of Ypres on 22 April 1915 in World War I (Heller, 1984). The Germans released 168 tons of chlorine over a four mile front, producing an estimated 5000 military fatalities. The distance between the German and Allied lines were roughly 200 to 600 meters in the vicinity of the attack. The Allied lines were located about four miles (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.

It is well known that ATD models, in general, often greatly overestimate the downwind hazard resulting from chemical releases, and modeling of chlorine is no exception (Mannan, 2005). There are many possible factors for this: inadequacy of ATD model algorithms (for dense gas releases, terrain effects, etc.); incomplete knowledge of the atmospheric chemistry of chlorine; the source term for the chlorine gas cloud; and the toxicity estimates.

Based upon the above historical record, any chlorine toxicity estimate that predicts a significant number of fatalities farther than a kilometer downwind from the release point should be considered suspect. A significant number of predicted fatalities between 500 and 1000 meters should be cause for concern. A case in point is that of Franks *et al.* (1996). Using a toxicity estimate from the Health and Safety Executive (UK) (Turner & Fairhurst, 1990), Franks *et al.* predicted via ATD modeling that the downwind range of a LC₉₅ would be from 400 to 800 meters for a chlorine puff release of 1000 kg (a small amount for an industrial-type accident), and for the LC₅₀, from 650 to 1100 meters.

DATA ACQUISITION

An extensive literature review was conducted to find existing LCT₅₀ estimates for acute inhalation exposures to chlorine. Whenever possible, the underlying raw quantal response data were also obtained. For the initial identification of relevant studies, three reference works were consulted: the Acute Exposure Guideline

Levels (AEGL) for chlorine (NRC, 2004); the Third Edition of Lee's Loss Prevention in the Process Industries ("Toxic Releases", Chapter 18) (Mannan, 2005); and the Chlorine Toxicity Monograph published by the Major Hazards Assessment Panel (MHAP, 1988). The search was subsequently expanded beyond this point.

A total of 29 individual LCT₅₀s were collected (or derived from raw data) from 18 studies and sources for eight species [see Table 2]. Whenever possible, original sources were found for each LCT₅₀. In some cases, data were discovered in previously uncited US Army technical reports (Armstrong *et al.*, 1923; Beebe, 1924; Marshall, 1917 a,b; McElroy *et al.*, 1943). Finally, previously derived human toxicity estimates for chlorine were also reviewed and collected (NRC, 2004; Perry & Articola, 1980; Rijnmond Public Authority, 1982; ten Berge & van Heemst, 1983; Withers & Lees, 1985a,b).

[Some of the LCT₅₀s in Table 2 do not exactly correspond to what was originally reported. Probit analysis (Finney, 1971) with modern computer software was not always available, and many older studies had to use graphical methods (Litchfield & Wilcoxon, 1949). Where the original response data were available, the originally reported LCT₅₀ was updated via probit analysis.]

Only studies where mammals were exposed for a defined duration and then removed from the chamber for observation were used in the subsequent statistical analysis (See "DATA ANALYSIS AND RESULTS"). Studies that exposed the animals continuously until death were omitted. [The latter studies generally produced higher LCT₅₀s relative to fixed duration and observed studies. An example of an exposure to death study is Weedon *et al.* (1940), which is cited by many reviews of chlorine toxicity (MHAP, 1988; Mannan, 2005, NRC, 2004) and was not included in the dataset for this study.]

Many sources give incomplete information about what their "lethal" values truly signify (*i.e.* is it 1% lethality or 50% lethality?), so only LCT₅₀s were used in the present study. If an LCT₅₀ could not be estimated from any reported quantal response data, that study's "lethal" value was not used. Also, no LCT₅₀ was included unless the exposure duration was given.

Every effort was made to verify that each LCT₅₀ was an independent measurement. For

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

Table 2. Experimental IH LCT₅₀s and Other Parameter Values.

Study (Authors)	Report Date	Raw Data	Method	Probit Slope	Slope SE	Time (min)	LCT ₅₀ (mg-min/m ³)	LD ₅₀ (mg)
Mouse								
Silver, McGrath	1942	Yes	Probit	7.32	0.52	10	13150	0.41
Silver, McGrath, Ferguson	1942	Yes	Probit	7.83	1.05	10	19430	0.60
Zwart, Woutersen	1988	Yes	Probit	10.04	2.01	10	30620	0.95
Alarie	1980	No				10	8752	0.27
Bunting	1945	No				10	15200	0.47
Lipton, Rotariu	1941	No				10	18199	0.56
Bitron, Aharonson	1978	Yes	MLE	10.63	1.02	11	9245	0.29
Schlagbauer, Henschler	1967	Yes	Probit	6.18	1.23	30	10682	0.33
Zwart, Woutersen	1988	Yes	Probit	6.82	3.68	30	49300	1.53
Bitron, Aharonson	1978	Yes	MLE	10.63	1.02	55	27096	0.84
Back <i>et al.</i> & Vernot <i>et al.</i>	1972 & 1977	No				60	23822	0.74
Rat								
Zwart, Woutersen	1988	Yes	Probit	15.84	3.33	5	77850	15.80
Zwart, Woutersen	1988	Yes	Probit	15.84	3.33	10	61160	12.42
Zwart, Woutersen	1988	Yes	Probit	15.84	3.33	30	54810	11.13
Zwart, Woutersen	1988	Yes	Probit	15.84	3.33	60	83820	17.02
Vernot <i>et al.</i>	1977	No				60	50947	10.34
Guinea Pig								
Lehmann	1882	Yes	MLE			30	290000	52.78
Rabbit								
Marshall	1917(a)	Yes	MLE			30	21580	31.36
Barrow, Smith	1975	Yes	MLE			30	30479	44.29
Lehmann	1882	Yes	MLE			190	300000	435.90
Cat								
Lehmann	1882	Yes	MLE			235	390000	329.55
Dog								
Armstrong	1923	Yes	Probit	7.51	2.83	10	58340	246.78
Marshall	1917(a)	Yes	Probit	3.12	1.45	30	47010	198.85
Underhill	1920	Yes	Probit	3.45	0.81	30	49380	208.88
Marshall	1917(b)	No				30	75000	317.25
Beebe	1924	No				30	90000	380.70
Sheep								
Batchinsky <i>et al.</i>	2006	No				30	24343	338.37
Goat								
McElroy <i>et al.</i>	1943	Yes	MLE			18.5	51500	494.40
McElroy <i>et al.</i>	1943	Yes	MLE			8.5	16500	158.40

instance, both Back *et al.* (1972) and Vernot *et al.* (1977) report the same data for mouse (attributed to Back *et al.* in Table 2) and rat (attributed to Vernot *et al.* in Table 2).

DATA REDUCTION

Prior to use, several calculation procedures were used to reduce the collected data. First, when possible, probit analysis was used to estimate both k_C and the LCT₅₀ (via the binary logis-

tic regression routine in MINITAB®). If a study included more than one exposure duration, duration was treated as a factor (not a covariate) in the calculations (see “Inhalation Dose-Response Statistics and the Toxic Load”), thereby producing a best estimate for the true slope for the whole study (which was the case with Zwart & Woutersen, 1988). However, in many cases, only LCT₅₀s (and no other data) were given.

For four studies (Barrow & Smith, 1975; Lehmann, 1882; Marshall, 1917a; McElroy, 1943)

basically only limited quantal response data were recorded; which was not sufficient for use in a traditional probit analysis. No k_C or LCT_{50} s were originally reported. For these sets, a one-factor MLE analysis (see Fox, 1997 or Hulet *et al.*, 2006 for examples) with a probit link function was used to estimate the LCT_{50} .

After collection or estimation, the LCT_{50} s were converted into nominal LD_{50} s using Equation [4] and the species appropriate M and V_M (expt. avg.) values from Table 1. All the values shown in Table 2 were used in the final model fit of Equation [8]. The LCT_{50} s, as well as the previous general population estimates listed in "Previous Human Lethality Estimates for Chlorine Inhalation Toxicity", are shown in Figure 2. The LCT_{50} versus Time relationships for the Rijnmond Report (1982) and ten Berge & van Heemst (1983) are essentially identical, although the ten Berge & van Heemst curve is slightly higher.

DATA ANALYSIS AND RESULTS

Probit Slope Estimation

Slope Estimation via a Weighted Average. A weighted average (Speigel, 1961) was taken of the experimental probit slopes listed in Table 2. The inverses of the variances (the squares of the standard errors (SE)) of the probit slope estimates were used for the weights. The probit slopes from two WWI era studies (Marshall, 1917a; Underhill, 1920) were not used due to concerns about the quality of their probit slopes. It was found that the weighted average equals 7.96 with 95% confidence interval of 7.21 to 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.

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 3. All were developed for use in modeling chlorine toxicity within the general population; although in the case of Withers & Lees (1985a,b), 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. To derive their equation [see Table 3], a fit was made to these points. Withers & Lees also 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 typically used. For chlorine, the conversion is $[mg/m^3] = [ppm] \times (2.898)$. Table 4 presents the probit slopes (k_C) for the references given in Table 3.

Linear Regression Analysis

Using Equation [8] and IRLS with MINITAB®, the following model fit was obtained:

$$\log(LD_{50}) = (0.515) + (0.869)\log(M) + (0.630)\log(T) \quad [9]$$

A plot of Equation [9] (with associated 95% confidence limits) is shown in Figure 3 with the individual experimental LD_{50} s for comparison.

For the IRLS process, an initial unweighted model fit to Equation [8] was performed using MINITAB®; studentized deleted residuals were calculated for the set of observations. From these residuals, a set of weights was created for the next iteration. Iterations continued until a specific tolerance level was reached.

Weights (W) were calculated as follows (based on recommendations of Box & Draper, 1987):

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

$$\begin{array}{ll} \text{convergence} & \text{for each } j : (W_{i+1,j} - W_{i,j}) \\ \text{criteria} & \leq 1 \times 10^{-6} \end{array} \quad [10]$$

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 defined as having been

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

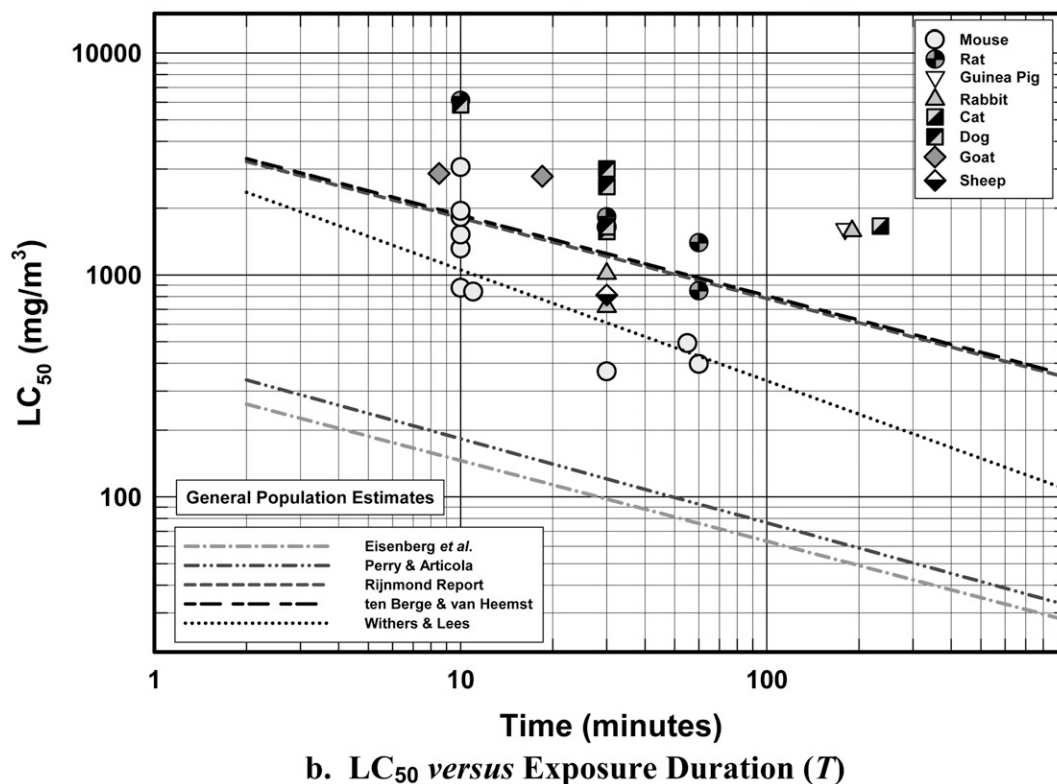
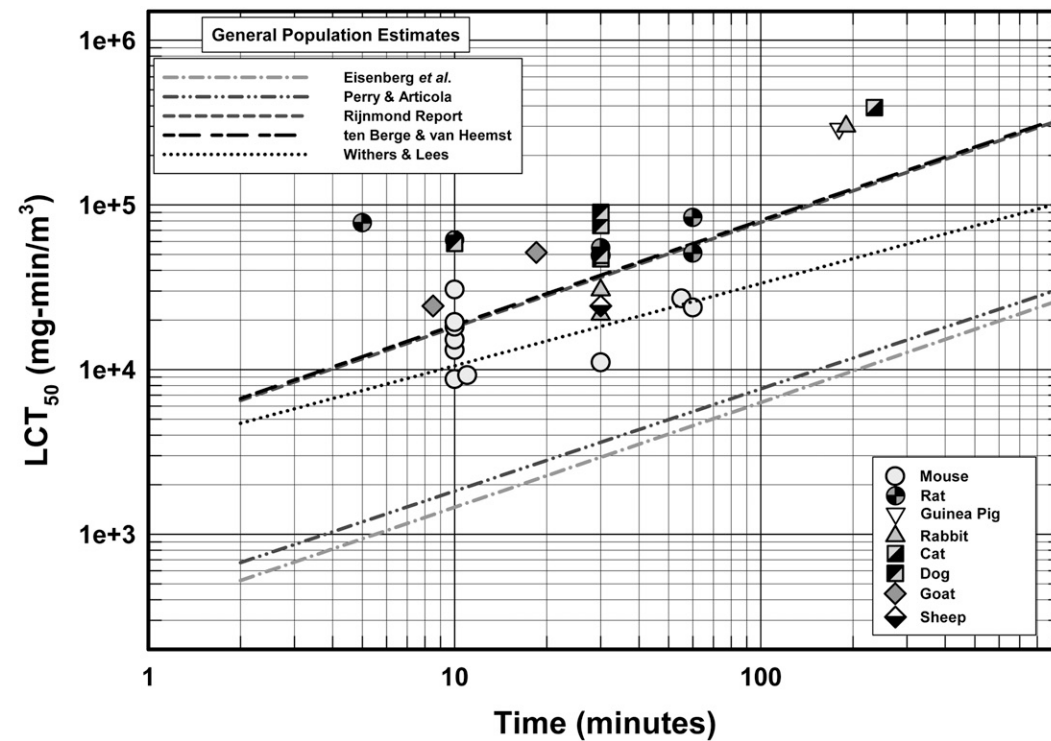


Figure 2. Animal Data and Previous Human Estimates for Chlorine IH Lethality as a Function of Exposure Duration.

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

Table 3. Equations for Human Chlorine Inhalation LCT₅₀s.

Reference	Year	Original Published Equation *	Converted Equation**
Withers, Lees	1985	_____	$Y_N (\text{Normit}) = -11.697 + 1.675 \text{ LOG } (C^{2.00} T)$
Eisenberg, Lynch, Breeding	1975	$Y_P (\text{Probit}) = -17.10 + 1.69 \text{ Ln } (C^{2.75} T)$	$Y_N (\text{Normit}) = -27.045 + 3.891 \text{ LOG } (C^{2.75} T)$
Perry, Articola	1980	$Y_P (\text{Probit}) = -36.45 + 3.13 \text{ Ln } (C^{2.64} T)$	$Y_N (\text{Normit}) = -50.242 + 7.207 \text{ LOG } (C^{2.64} T)$
ten Berge, van Heemst	1983	$Y_P (\text{Probit}) = -5.04 + 0.50 \text{ Ln } (C^{2.75} T)$	$Y_N (\text{Normit}) = -11.503 + 1.151 \text{ LOG } (C^{2.75} T)$
Rijnmond Report (Harris, Moses)	1982	$Y_P (\text{Probit}) = -11.40 + 0.82 \text{ Ln } (C^{2.75} T)$	$Y_N (\text{Normit}) = -18.799 + 1.888 \text{ LOG } (C^{2.75} T)$
		* The concentration "C" is measured in parts per million	** The concentration "C" is measured in milligrams per cubic meter

reached when for each W_j successive iterations (i and $i + 1$) produced estimates that agreed to the sixth decimal place.

Chlorine toxicity correlates (with $p < 0.001$) with species body mass (M). On an absolute nominal dose basis, LD₅₀ scales to $M^{0.87}$. Thus, for larger animals a greater agent dose—on an absolute basis, is required for lethality. However, on a per kg of body mass basis, larger mammals are more sensitive to chlorine than smaller mammals [LD₅₀ (mg/kg) scales to $M^{0.13}$].

Toxic Load Exponent and Time-Concentration Relationship

Estimation from Allometric Modeling of Historical Database. Based on Equation [8], n equals $[1 / (1 - k_T)]$. From the LD₅₀ fit (Equation [9]), k_T equals (0.630); thus, the TLE equals 2.70. For a healthy human, the minute-volume for light activity is assumed to equal 0.015 m³/min, and the military standard mass is assumed to be 70 kilograms (US Army Chemical School, 2005). Using the above information and Equation [7], the following relation is obtained (shown also in Figure 4):

$$C^{(2.70)} T = 4.39 \times 10^{10} \quad [11]$$

The standard error (SE = 0.059) for the fitted coefficient, k_t from Equation [9] can be used to produce approximated 95% confidence intervals for n . Random k_t values were generated by us-

ing a normal distribution with mean equal to the fitted k_t and a standard deviation equal to the SE of the fitted k_t . Using the relationship, $[1 / (1 - k_T)]$, the corresponding random n values were calculated. The 95% confidence intervals correspond to the 2.5 and 97.5 percentiles of the random n values, for a confidence interval of 2.06 to 3.96 in this case. This low precision is possibly due to the relatively narrow range of exposure durations represented in the historical data, with the bulk of them ranging from 10 to 60 minutes. The presence of random error between the various studies could also decrease the precision in the TLE estimate. Thus, another approach was investigated to develop a more precise estimate for the TLE (see below).

Estimation from Individual Studies. Only two studies listed in Table 2 involved exposures at several durations: Bitron & Aharonson (1978) and Zwart & Woutersen (1988).

Table 4. General Population Probit Slopes [(Base 10) on Concentration].

Reference	Probit Slope (with respect to Concentration)
Withers, Lees	3.3
Eisenberg <i>et al.</i>	10.7
Perry, Articola	19.0
ten Berge, van Heemst	3.2
Rijnmond Report	5.2

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

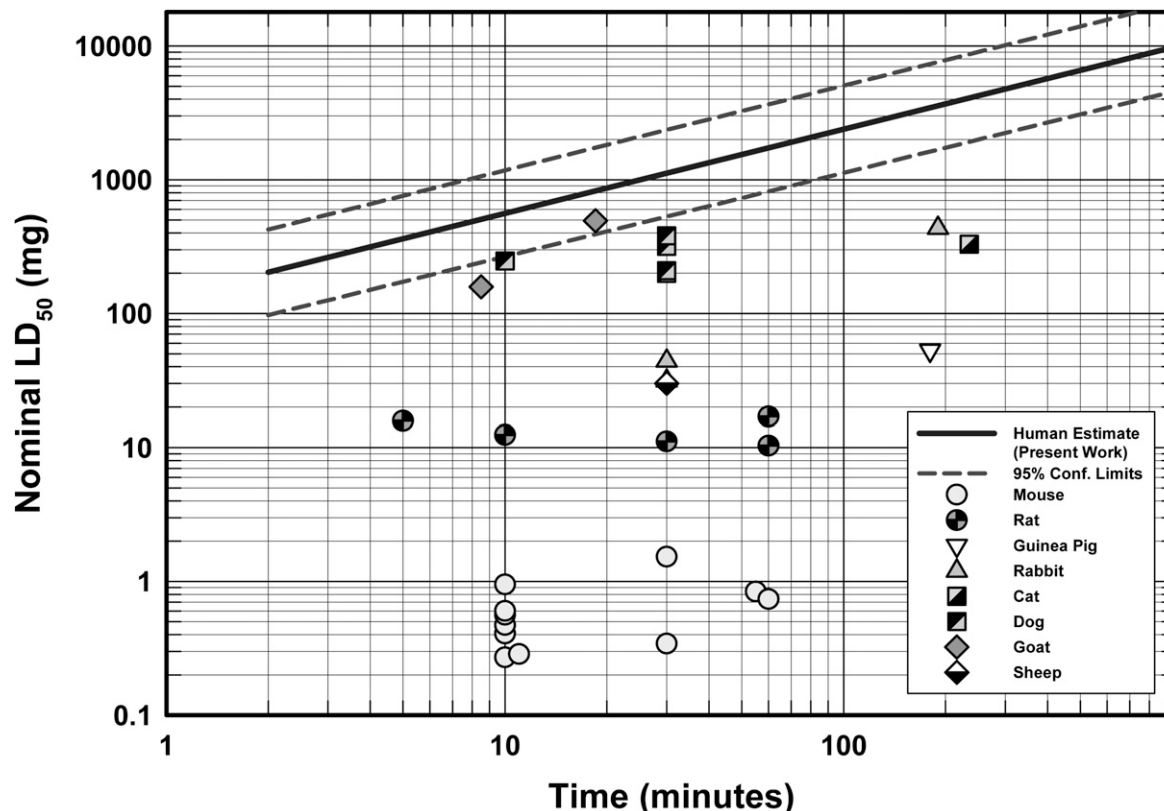


Figure 3. Allometric Model Fit of Nominal IH LD₅₀ for Healthy Human Adults Exposed to Chlorine.

Bitron & Aharonson (1978) exposed 476 male mice at two constant vapor concentrations over a range of exposure durations [13 to 160 minutes for 170 ppm (16 runs), and 6 to 30 minutes for 290 ppm (18 runs)]. 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 n was not originally reported, but ten Berge & van Heemst (1983) subsequently calculated a value of 3.5 (with 95% CI of 2.5 to 4.5) from this dataset.

Zwart & Woutersen (1988) exposed male and female mice and rats to several chlorine concentrations at four exposure durations. Two hundred twenty rats were used for exposures of 5, 10, 30 and 60 minutes; 100 mice were used for exposures of 10 and 30 minutes. For each exposure, 10 animals (five of each gender) were exposed in a common chamber. Unfortunately, the response results were not broken down by gender. [Gender differences often exist

in the responses of rodents to toxicants—see Benton *et al.*, 2007]. Also, this dataset is not as well balanced, particularly for the rat, as that of Bitron & Aharonson (1978). It is interesting to note that Mannan (2005), in his extensive review of the existing chlorine toxicity data, did not mention the results of Zwart & Woutersen. Considering the relative merits of the two studies, the data of Bitron & Aharonson are superior to that of Zwart & Woutersen for estimating n .

For this study, response results as a function of chlorine vapor concentration and duration were extracted from the graphical representations shown in Figures 9 and 11 of Bitron & Aharonson (1978). Using the binary logistic regression routine in MINITAB®, a multifactor probit analysis was then performed on the data. It was found that the TLE equals 3.18 with 95% CI of 2.90 to 3.46. This confidence interval is considerably narrower than was originally calculated by ten Berge & van Heemst (1983).

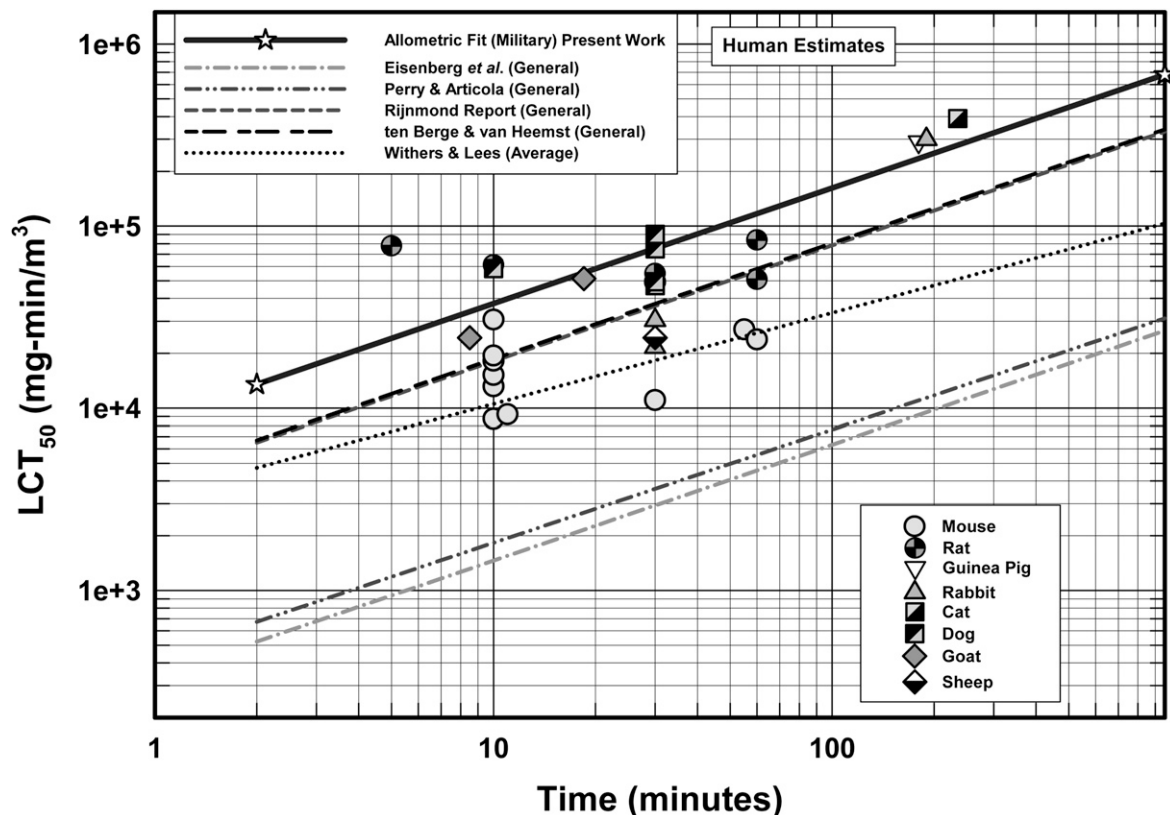


Figure 4. Comparison of Human (Military) Estimate for Chlorine IH Lethality from Allometric Fit to Previous Human Estimates and Experimental Animal Data.

Human Lethality Estimates for Chlorine Inhalation

Three parameters are needed to mathematically define a final inhalation toxicity estimate (as represented in Equation [7]: (1) a probit slope to describe the range of individual sensitivities to the toxicant (k_{TL}); (2) the LCT_{50} (or toxic load) at some reference duration (k_0 when Y_N is set equal to zero); and a TLE (n) to describe how the toxicity changes with duration.

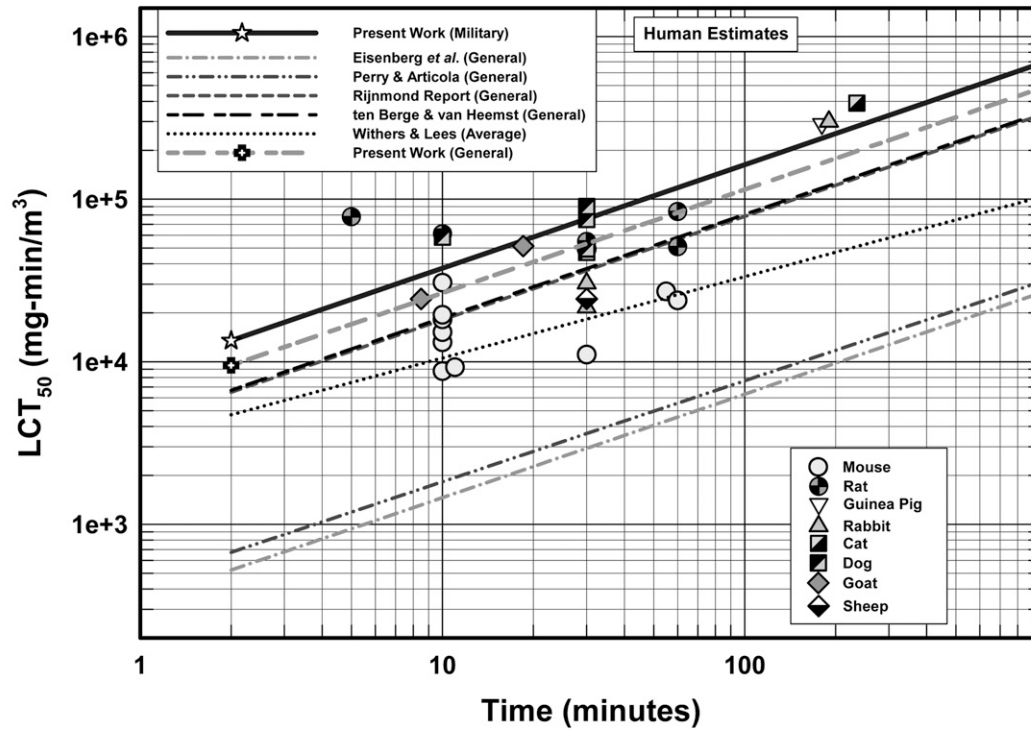
In the following two sections, the derivation of the final human estimates is described for both a military subpopulation and the general population. These estimates are shown in Figure 5 in comparison to previous estimates and the existing mammalian database. The final military subpopulation estimate is slightly different from what was derived via allometric scaling (Equation [11]) for reasons explained in greater detail below.

Military Subpopulation

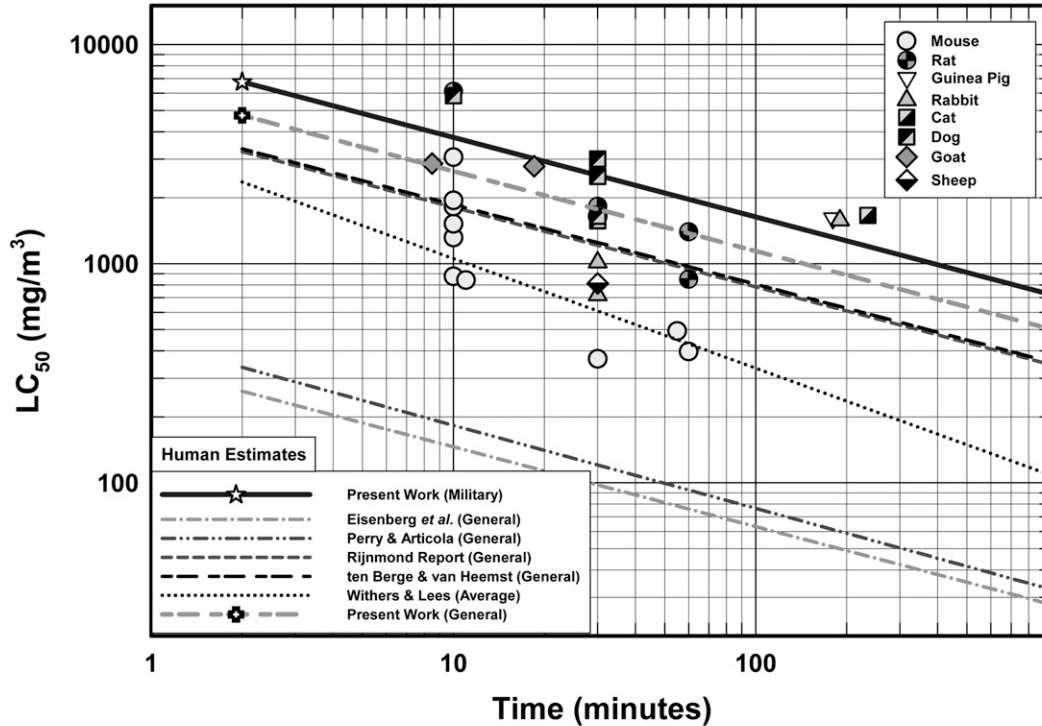
Probit Slope. For the probit slope, a weighted average from the available data (see Table 2) yielded an estimate of 8.0 (rounded from 7.96), with 95% CI of 7.2 to 8.7. It is assumed that this estimate is appropriate for a healthy (military) human subpopulation.

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 2). In Figure 4, the allometric fit (Equation [9]) is shown in comparison to estimates previously derived by other researchers. The allometric fit of the estimates derived herein is higher than that for previous estimates, with those of ten Berge & van Heemst (1983) and the Rijnmond Report (1982) being closest to these revised estimates. Because of faulty assumptions

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



a. LCT_{50} versus Exposure Duration (T)



b. LC_{50} versus Exposure Duration (T)

Figure 5. Comparison of Final Human Estimates Chlorine IH Lethality with Previous Human Estimates and Experimental Data.

used in their derivations, the estimates of Eisenberg *et al.* (1975) and Perry & Articola (1980) can be dropped from consideration.

There are two reasons for the difference between Equation [9] and ten Berge & van Heemst and the Rijnmond Report. First, Equation [9] is meant for use with a healthy (military) subpopulation, while the other two are for the general population. [This issue is further addressed below.] Second, Equation [9] is based on the fact that both the LD₅₀ (absolute) and LC₅₀ increase as a function of increasing species body mass (as demonstrated by statistical analysis in the present study), but both ten Berge & van Heemst and the Rijnmond Report assumed that a human estimate can be modeled on an average for all mammals. So, as a starting point for a human general population estimate, the human healthy (military) LCT₅₀ for a two minute exposure was taken from Equation [9], or 13,500 mg-min/m³.

Toxic Load Exponent. For deriving the TLE, past approaches have been somewhat subjective. ten Berge & van Heemst (1983) took an average of the lethality study of Bitron & Aharonson (1978) ($n = 3.5$) and the olfactory irritation study of Anglen (1981) ($n = 1.9$) to arrive at 2.75. This may be a case of obtaining a correct answer via incorrect methods: it is unlikely that the toxic mechanisms and their corresponding n values are the same for lethality and nuisance effects. Thus, an average of the two is not the proper approach for obtaining a lethal TLE.

Harris & Moses (1983) concluded that the Coast Guard reports (Eisenberg *et al.*, 1975; Perry & Articola, 1980) have the TLE correct at 2.75. It is not readily evident how the Coast Guard arrived at this estimate, but it appears that instead of basing it on the available mammalian data, they performed an empirical fit of previous human estimates.

The MHAP (1988) also concluded that 2.75 was a reasonable estimate for the TLE. They reasoned that the evidence for this value is much stronger than for the lower values derived by others (such as Withers & Lees, 1985a,b). They believed that the value of 2.75 is advantageous because it results in conservative assessments for short exposures (less than ten minutes), for which there is considerable uncertainty in the dose-response relationship.

Withers & Lees (1985a) based their estimate ($n = 2$) on a review of Weedon *et al.* (1940) and Bitron & Aharonson (1978). Others (Franks *et al.*, 1996; Turner & Fairhurst, 1990) have used the same value—but for different reasons. Withers & Lees felt that these were the only available studies from which to estimate n for chlorine. A major difference between Weedon *et al.* and Bitron & Aharonson is the number of animals used in each study, 24 and 476, respectively: In essence, Withers & Lees took an unweighted average of the n values from these studies. All other factors being equal, more weight should have been given to the Bitron & Aharonson value, since it is based upon a larger number of animals. If a weighted average is taken (using the number of animals for the weights), an n of 2.94 is obtained.

In summary, this study is in agreement with both ten Berge & van Heemst (1983) and Withers & Lees (1985a) on the importance of Bitron & Aharonson (1978). The results of Bitron & Aharonson support a higher value (in the range of 3 to 3.5) for the TLE than has been used previously. Of the available experimental studies, Bitron & Aharonson have the best set of lethality data involving multiple durations, but this is only one study which has not yet been reproduced. As a result, caution is required with respect to TLE recommendation. Setting the TLE value too high will underestimate the toxic effects for longer 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 Equation [9]) and on the upper end by this study's estimate of n from the data of Bitron & Aharonson ($n = 3.18$). Thus, for a human estimate, a TLE of 2.75 was chosen (as a conservative estimate) for generating a final human (military) toxicity-time relationship. This favors the bulk of the historical database (Table 2) and previous estimates for the exponent value made by previous researchers (Eisenberg *et al.*, 1975; Harris & Moses, 1983; MHAP, 1988; Perry & Articola, 1980; Rijnmond Public Authority, 1982; ten Berge & van Heemst, 1983). However, this TLE should be re-evaluated in the light of any applicable future mammalian studies.

Human (Military) Lethality Relationship from Allometric Fit. From the previous discussion, the final human

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

toxicity estimate for healthy (military) individuals, based upon allometric scaling, is defined by Equation [12] (see Figure 5a):

$$Y_N = (-31.52) + (2.91)\log(C^{2.75}T) \\ \text{or} \\ L(C^{2.75}T)_{50} = 6.79 \times 10^{10} \quad [12]$$

where C is in mg/m^3 and T is in minutes.

General Population. Toxicity estimates for the general population were generated from the estimate for the military subpopulation (Equation [12]) via the method of Crosier (2007) (as previously discussed). Using this method, the following values were obtained:

$$\text{Probit slope (general population)} (k_C) = 6.0 \\ \text{LCT}_{50} \text{ for two minutes (general population)} = 9,500 \text{ mg-min}/\text{m}^3$$

For the TLE, mathematical considerations require that both a subpopulation and the general population must have identical exponent values (*ex.* differing values for n can produce the paradoxical situation where the LCT_{50} for the general population could exceed that of the military subpopulation). Putting these three parameters together produces the probit relation for the general population:

$$Y_N = (-22.698) + (2.18)\log(C^{2.75}T) \\ \text{or} \\ L(C^{2.75}T)_{50} = 2.58 \times 10^{10} \quad [13]$$

where C is in mg/m^3 and T is in minutes.

HPAC Modeling Results

A series of modeling runs was conducted, using the Defense Threat Reduction Agency's (DTRA) Hazard Prediction and Assessment Capability (HPAC, 2003). 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 the person be exposed to these concentration-time profiles.

HPAC Model Inputs and Outputs. The scenario modeled was for a catastrophic release of 50 tons

(~45,500 kg) of chlorine liquid. This is based on the largest release reported by Mannan (2005) in his review of chlorine industrial/transportation accidents.

Model inputs were kept fairly simple. Flat terrain was assumed. Meteorological conditions were kept at a steady-state, fixed wind direction and speed during the simulations. The HPAC model estimates the amount of chlorine that initially pools, but all the liquid evaporated very quickly. Since meteorological conditions can produce significant differences in hazard prediction results, three different weather conditions were modeled:

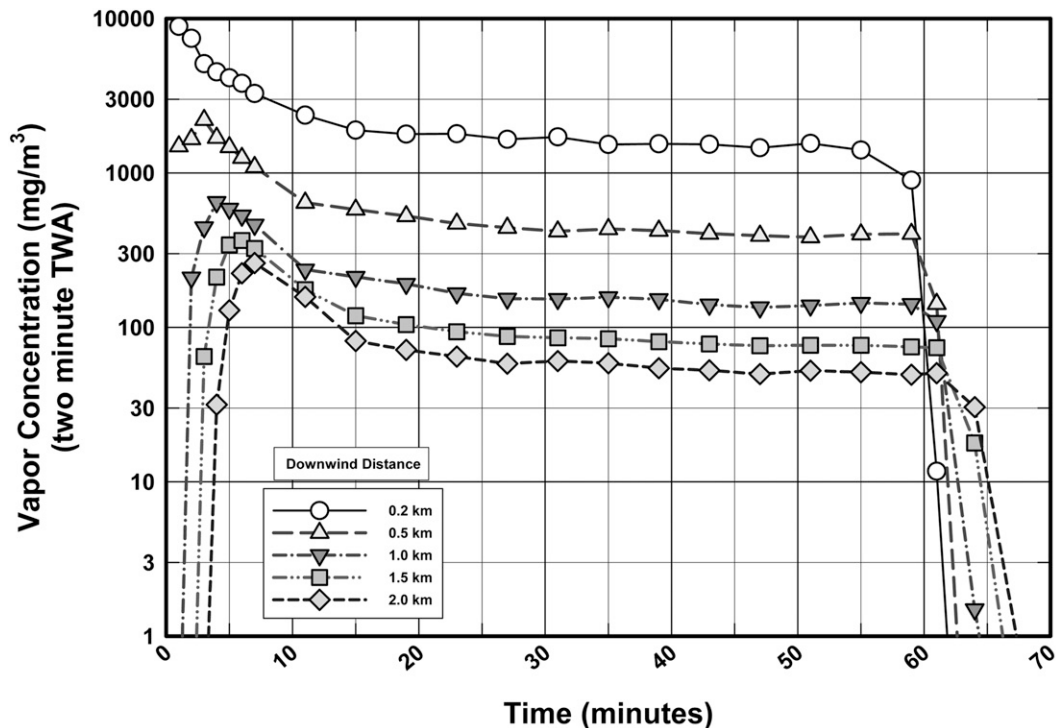
- Low wind (1 m/sec), clear sky, nighttime (2am), "stable" condition (Pasquill Stability (PST) Class F—Pasquill, 1961)
- Moderate wind (5 m/sec), cloudy day, "neutral" condition (PST Class D)
- Low wind (2 m/sec), clear sky, daytime (2pm), "unstable" condition (PST Class B).

The HPAC model provided numeric output of concentration time history for each model run at downwind distances of 0.2, 0.5, 1.0, 1.5 and 2.0 km. The concentration time histories were then numerically integrated using several different human toxicity estimates from Table 3 and Equation [13] to calculate the probability of lethality at each downwind sampler location.

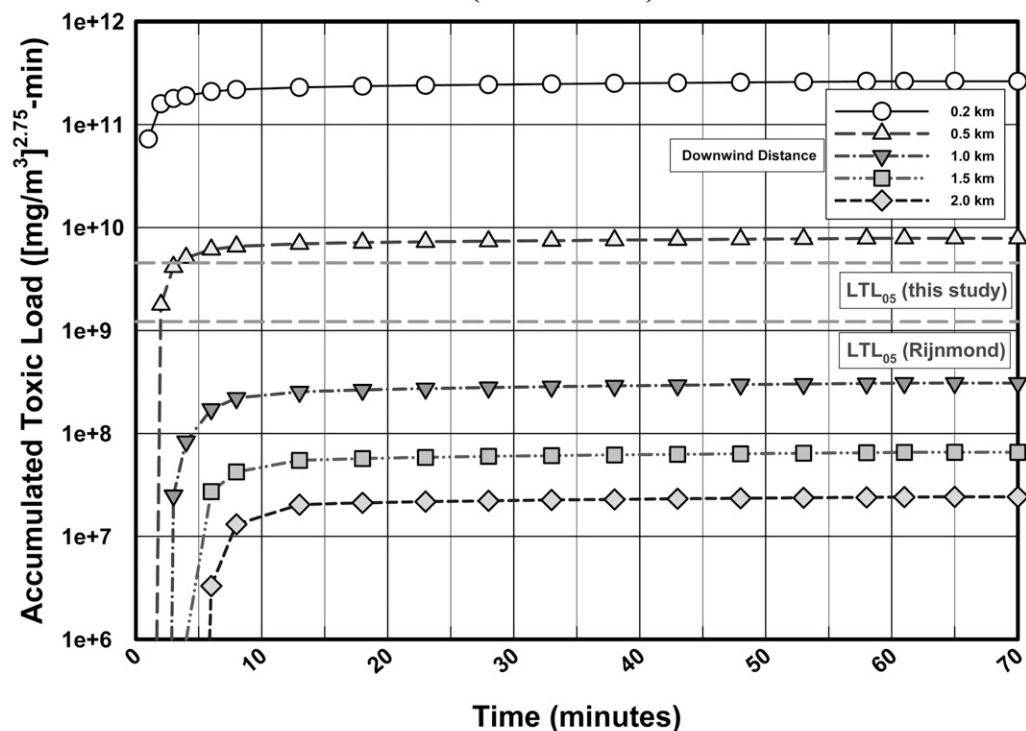
Samples of some of the concentration-time and TL-time outputs as a function of downwind distance are shown in Figures 6a and 6b for the PST Class D HPAC runs. The peak concentration values were observed rather quickly, from essentially instantaneous at 0.2 km to about 7 minutes for 2 kms downwind. The peaks roughly correspond to the point where the accumulated TL had reached about 90 to 95% of its final value for a particular downwind location. If the accumulated TL had not reached lethal levels within a few minutes after the observed peak concentration, it was very unlikely that it will do so. Of the five downwind locations, only 0.2 and 0.5 km had an accumulated TL that was in excess of the LTL_{05} from either this study (Equation [12]) or the Rijnmond Report (see Table 3).

Sensitivity of HPAC Model Predictions to Changes in Toxicity Estimate Parameters. Not surprisingly, as demonstrated in Figure 7 using the HPAC

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



a. Concentration (2 min TWA) versus Time Profile



b. Toxic Load versus Time Profile

Figure 6. Output Profiles from HPAC as a Function of Downwind Distance for Chlorine (Pasquill Stability Category D).

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

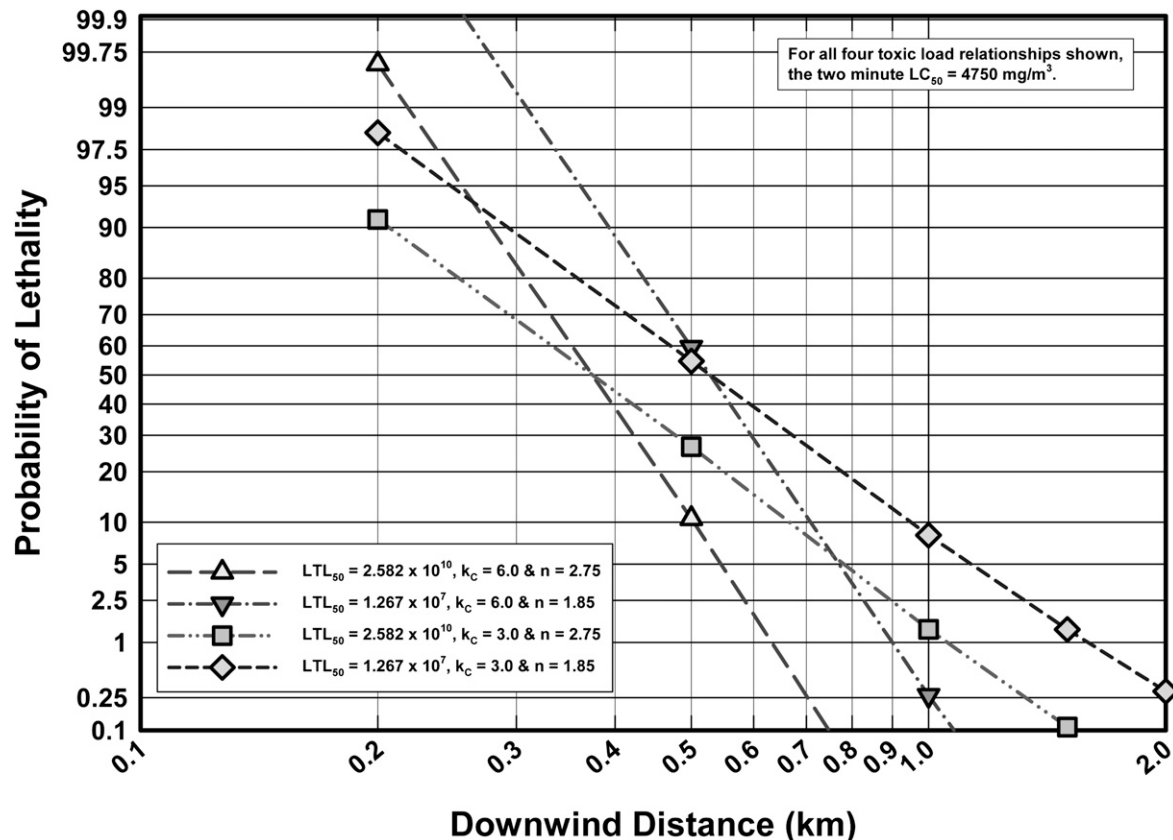


Figure 7. Probability of Lethality *versus* Downwind Distance as a Function of Toxic Load Expression (Pasquill Stability Category F).

concentration-time profile generated under night time conditions (PST Class F), the relationship of the probability of lethality as a function of downwind distance is dependent on the toxicity estimate used. 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} of $4,750 \text{ mg/m}^3$ at two minutes. Equation [13] (for the general population) is represented by the curve labeled $k_C = 6$ and $n = 2.75$.

An increase in the TLE value shifts the line to the left, with the new curve still parallel to the original line [when plotted on a probability *versus* $\log(\text{distance})$ scale]. An increase in k_C rotates the new line clockwise 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 one moves closer or further from the point of intersection between the two lines. These trends from Figure 7 are better highlighted in Figure 8.

Comparison of Human Toxicity Estimates in Predicting Lethality Probabilities from HPAC Model Predictions. In Figure 9, the probability-distance profile based upon Equation [13] is compared to profiles generated using the human toxicity estimates in Table 3 for the HPAC concentration-time profile generated for night time conditions (PST Class F). For probabilities below 10%, the downwind distance predicted by Equation [13] is less than what is predicted by Withers & Lees (1985b), Rijnmond Report (1982)/Harris & Moses (1983) and ten Berge & van Heemst (1983). Distances predicted by Haber's Rule (using a LCT_{50} of $9,300 \text{ mg-min/m}^3$ and a probit

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

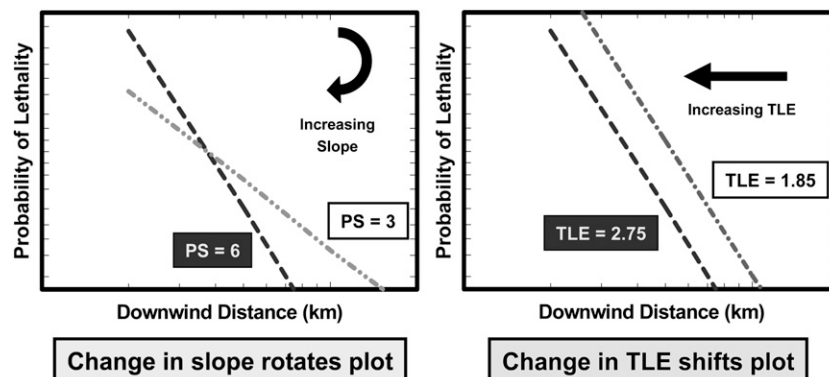


Figure 8. Trends in Lethality Probability *versus* Downwind Distance as a Function of Probit Slope (Concentration) and Toxic Load Exponent (TLE).

slope of 6) were also calculated. Considering the historical record (see **HISTORICAL RECORD OF CHLORINE RELEASES**), 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).

Of the other three studies, the Rijnmond Report curve is the closest in location and orientation to that of Equation [13]. The probit slope and TLE values from the Rijnmond Report ($k_{TL} = 1.89$ and $n = 2.75$) are very similar to that of Equation [13] ($k_{TL} = 2.18$ and $n = 2.75$). The difference between the two curves is mainly due to differences in the LCT_{50} used in the two estimates. Both Withers & Lees and ten Berge & van Heemst estimated smaller probit slopes than Equation [13] and the Rijnmond Report, and their prediction curves are, thus, rotated counter-clockwise relative to Equation [13] and the Rijnmond Report. In Figure 10, the same toxicity relationships used for Figure 9 are used for the HPAC concentration-time profile generated for day time conditions (PST Class B).

In Figure 11, the previous plots for Equation [13], ten Berge & van Heemst and the Rijnmond Report are shown for both day and night time conditions (plots for overcast conditions--PST Class D) are very similar to those of night time). Any proposed toxicity estimate/ATD model combination should produce downwind prediction curves consistent with the historical record (maximum fatality downwind distance of 400 meters). Under daytime conditions, the plots for Equation [13], ten Berge & 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 meters downwind (from 40 to 75%). From this point downwind, probabilities from both Equation [13] and the Rijnmond Report fall off quickly as a function of distance relative to that predicted by ten Berge & van Heemst. It is possible that deaths have not been seen at 500 meters (despite the high predicted probabilities) due to other factors (*i.e.* more time available for escape/sheltering in place at the longer downwind distances, night time accidents may not be that frequent relative to day time, not all releases are 50 tons, *etc.*). At 1 km, there is still a 3% probability of lethality with ten Berge & van Heemst, while the other two are both below 0.2%. This greater distance, on the part of ten Berge & 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).

DISCUSSION/CONCLUSIONS

The development of a human toxicity estimate for chlorine 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 estimates. Some (Harris & Moses, 1983; Richmond Public Authority, 1982; ten Berge & van Heemst, 1983; Withers & Lees, 1985a,b) have been more successful than others (Eisenberg *et al.*, 1975; Perry & Articola,

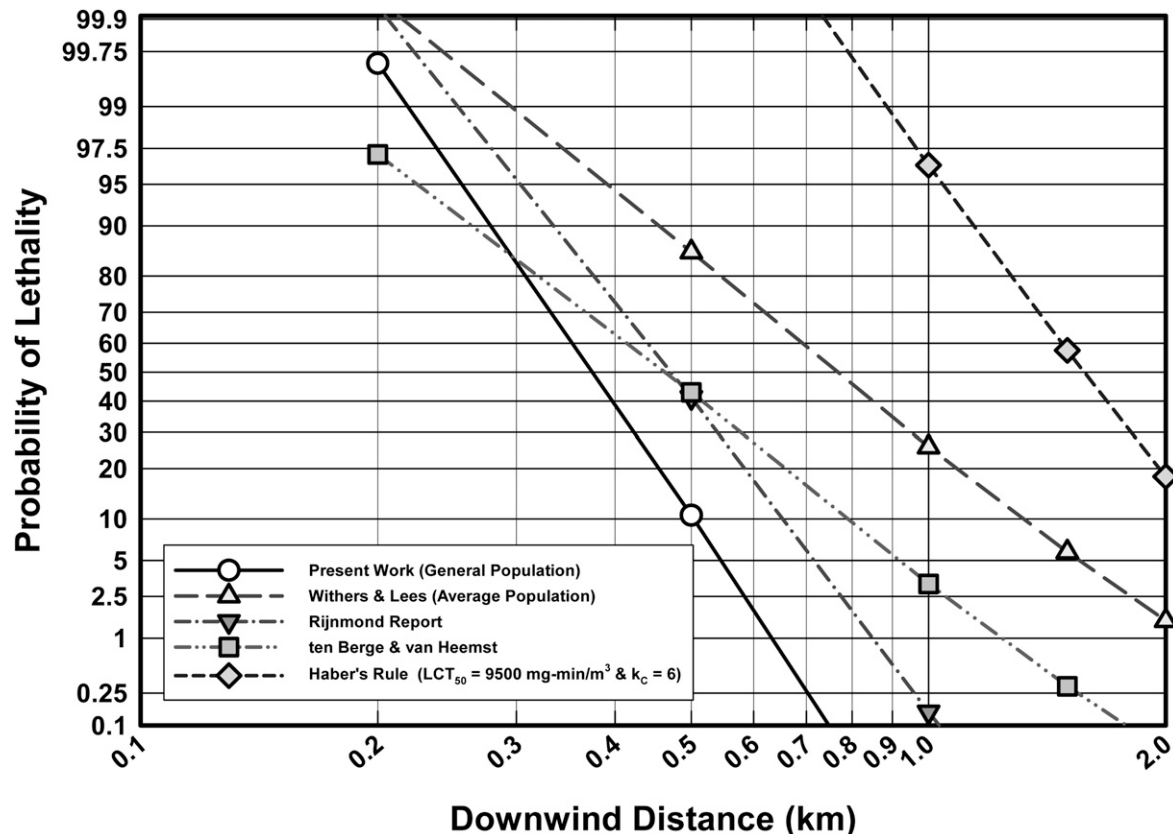


Figure 9. Probability of Lethality versus Downwind Distance for Several Human Lethality Estimates for Chlorine (Pasquill Stability Category F).

1980). 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/under analyzed lethality data (Armstrong *et al.*, 1923; Barrow & Smith, 1975; Beebe, 1924; Lehmann, 1882; Marshall, 1917a,b; McElroy *et al.*, 1943). Because of significant shortcomings in the chlorine lethality data, one should not be dogmatic about the human estimate. Thus, the human toxicity estimates from the present study (for both military and general population) are offered as qualitative (rather than quantitative) improvements over estimates from previous investigators (Harris & Moses, 1983; Richmond Public Authority, 1982; ten Berge & van Heemst, 1983; Withers & Lees, 1985a,b). 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.

Variability in Human Response

It has been recognized by many that the general human population is likely to have more inhalation response variance than healthy laboratory animals (Crosier, 2003, 2007; Crosier & Sommerville, 2002; Mannan, 2005; MHAP, 1988; Richmond Public Authority, 1982; Salem, 1987; Schubach, 1997; Sommerville *et al.*, 2005; ten Berge & van Heemst, 1983; Withers & Lees, 1985a,b). The problem has been how to best extrapolate probit slopes from a laboratory animal to a general human basis.

In the present study, more statistical rigor was employed. This was done by using probit

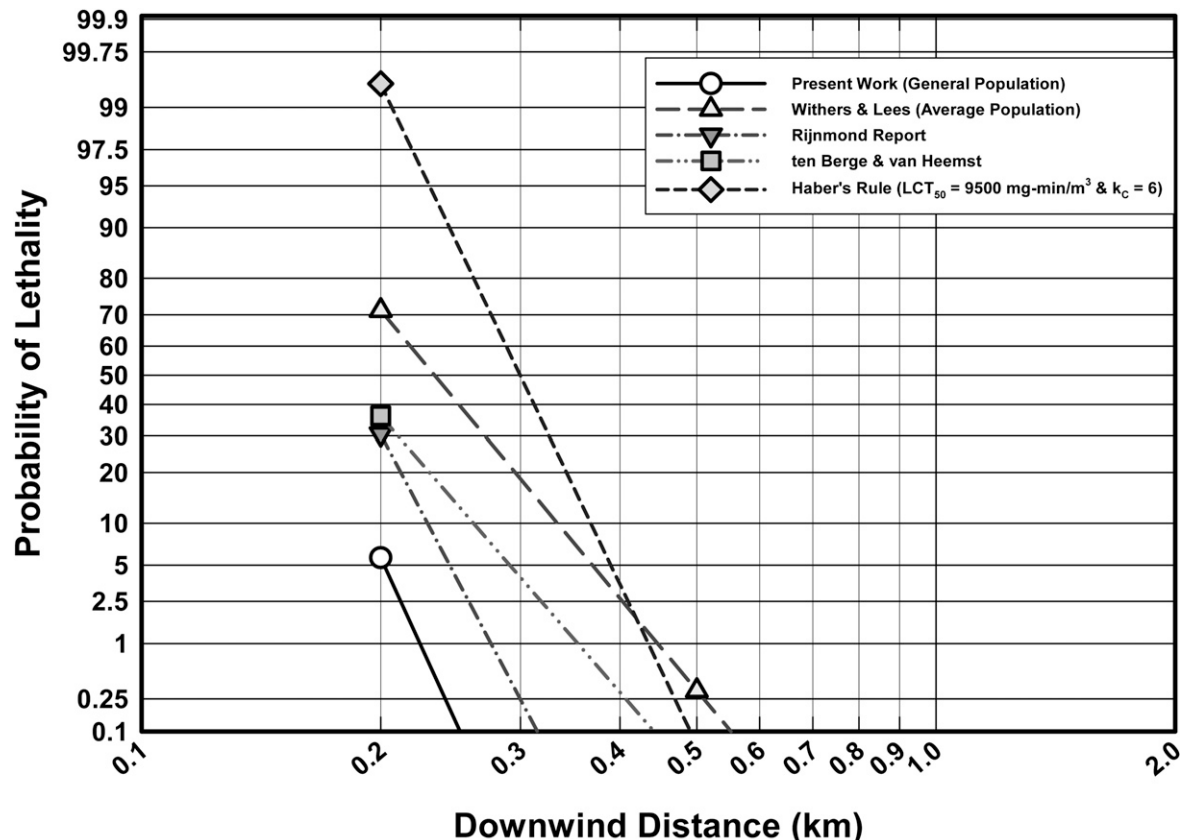


Figure 10. Probability of Lethality *versus* Downwind Distance for Several Human Lethality Estimates for Chlorine (Pasquill Stability Category B).

analysis to generate probit slopes and associated standard errors from the original experimental data. 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 study animals. It was reasonably assumed that healthy humans were equivalent in their variability to laboratory animals. An estimate for the general population was generated by using a mathematical model of the relationship between a subpopulation and the whole population developed by Crosier (2007). Of the previous estimates for the probit slope of the general population, the estimate of the present study ($k_C = 6$) is in closest agreement to that of the Rijnmond Report ($k_C = 5.2$). The other important studies (ten Berge & van Heemst and Withers & Lees) arrived at lower probit slopes (indicating more response variability).

Time Dependence of Chlorine Inhalation Toxicity

Previous researchers (ten Berge & van Heemst, 1983; Withers & Lees, 1985a,b) have recognized the futility of calculating an estimate for the TLE based on the existing lethality database. Instead, the individual findings of four experimental toxicity studies (Anglen, 1981; Bitron & Aharonson, 1978; Weedon *et al.*, 1940; Zwart & Woutersen, 1988) were cited as the basis for a human lethality exponent value by several studies (ten Berge & van Heemst, 1983; Withers & Lees, 1985a,b; Zwart & Woutersen, 1988). Although their work has been misapplied in the past, the present study has concluded that only Bitron & Aharonson is suitable for use in developing a toxic load exponent for lethality (see **Human Lethality Estimates for Chlorine Inhalation**). The proper use of Bitron &

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

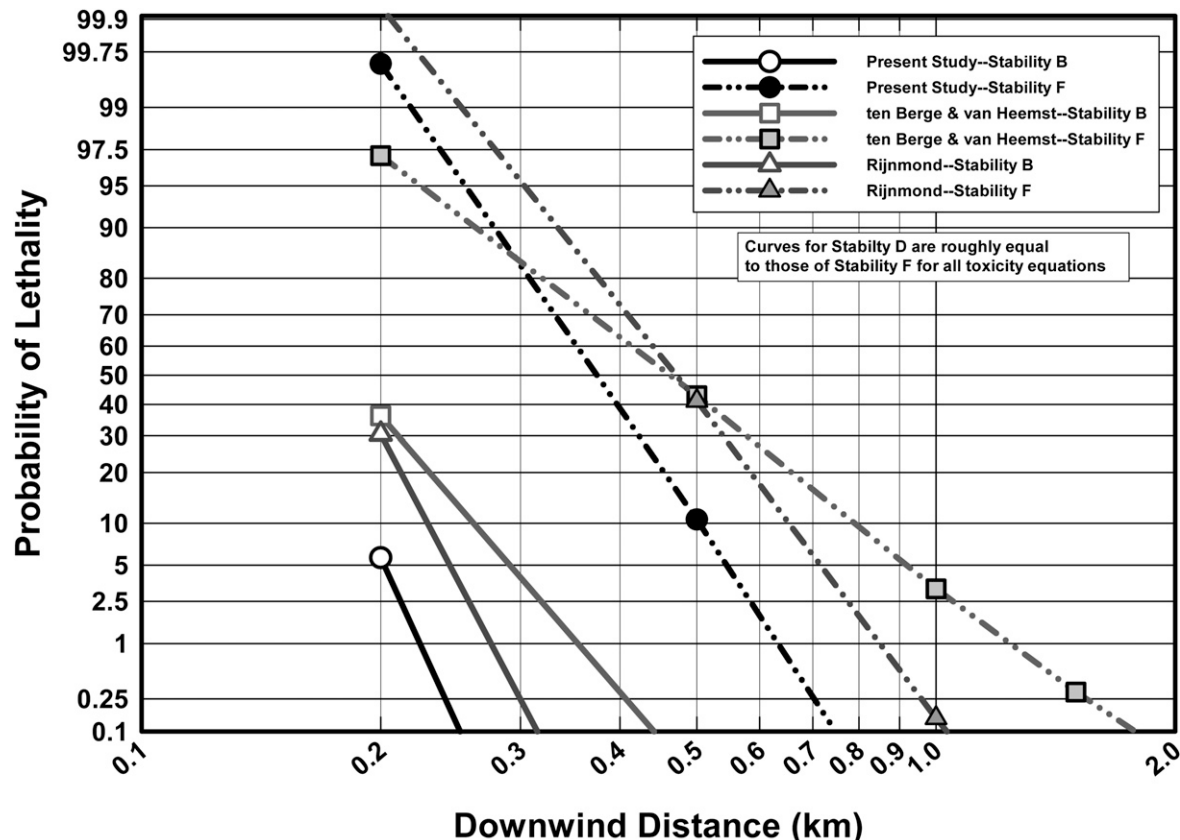


Figure 11. Probability of Lethality *versus* Downwind Distance for Several Human Lethality Estimates for Chlorine (Pasquill Stability Categories B and F).

Aharonson leads to a TLE ranging from 3 to 3.4. However, allometric modeling and consideration of the database as a whole support the slightly lower exponent of about 2.75. The “truth” probably lies somewhere between the two extremes. The lower exponent (2.75) is recommended for two reasons: (1) there is no collaborating study confirming Bitron & Aharonson; and (2) it is desirable to avoid underestimating toxicity at longer durations by using a TLE that is too large.

Median Lethal Dosage (LCT_{50})

With respect to LCT_{50} , the basic philosophy for extrapolating from animals to humans has been to assume that humans are equivalent to the average mammal (Harris & Moses, 1983; Rijnmond Public Authority, 1982; ten Berge & van Heemst, 1983; Withers & Lees, 1985a,b).

However, although the exact reason has been debated (MHAP, 1988; Withers & Lees, 1985a), it has been recognized that the chlorine inhalation LCT_{50} does increase as body mass increases. An allometric fit of the data in the present study found that the LCT_{50} was slightly dependent on the body mass (with statistical significance), with both the nominal LD_{50} (absolute) and LCT_{50} increasing as the body mass increases. However, the large amount of random error present in the mammalian database (Table 2) decreases the confidence in allometric-based extrapolation from this database to arrive at a human estimate. Thus, the “true” answer probably lies in-between the two philosophies.

Final Human Lethality Estimates

Of the five previous human estimates reviewed (see Table 3), the Rijnmond Report (1982) /Harris & Moses (1983) comes the closest

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

to the general population estimate of the present work (Equation [13]) in terms of downwind hazard predictions (see **HPAC Modeling Results**). Both have identical TLEs (2.75) and similar probit slopes (k_C) (6 *versus* 5.2).

The HPAC modeling runs (see **HPAC Modeling Results**) confirms the often observed disconnect between the historical record (see **HISTORICAL RECORD OF CHLORINE RELEASES**) and the overly pessimistic predictions from ATD models (Mannan, 2005). There are three possible explanations for this conflict. Either, the ATD models are over-predicting the downwind transport of chlorine; the human lethality estimates are over-predicting 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), TLE (n), and reference LCT_{50}), the general population estimate from Equation [13] is in better agreement with the Rijnmond Report than with the other previous estimates, particularly for k_C and n . The constant difference in LCT_{50} s is due to differences in extrapolation philosophies (average mammal (Rijnmond) *versus* allometric scaling (present

study)). The LCT_{50} estimate of Equation [13] 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 Equation [13] 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 Equation [13], and the lower estimate is defined 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) from its value of 5.2 equal to that of the slope in Equation [13] ($k_C = 6.0$), and then a two minute reference dosage of 6,500 mg-min/m³ (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 two minute general population LCT_{50} from Equation [13] equals 9,500 mg-min/m³. These estimates are shown below in Equations [13] and [14] and in tabular form in Table 5.

$$\begin{aligned} \text{upper estimate} \quad Y_N &= (-22.698) + (2.18)\log(C^{2.75}T) \\ \text{(adjusted allometric fit)} \quad \text{or} \quad L(C^{2.75}T)_{50} &= 2.58 \times 10^{10} \end{aligned} \quad [13]$$

Table 5. General and Military Populations Dosage and Concentration Estimates

	Modified Rijnmond General Population Equation [14]			General Population Equation [13]			Military Population Equation [12]		
	LCT_{50}	LC_{50}	LC_{50}	LCT_{50}	LC_{50}	LC_{50}	LCT_{50}	LC_{50}	LC_{50}
Time (mg-min / m ³)	(mg / m ³)	(mg / m ³)	(ppm)	(mg-min / m ³)	(mg / m ³)	(ppm)	(mg-min / m ³)	(mg / m ³)	(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

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

lower estimate (modified Rijnmond) $Y_N = (-21.710) + (2.18)\log(C^{2.75}T)$ or $L(C^{2.75}T)_{50} = 9.09 \times 10^9$ [14]

To evaluate the relative merits of Equations [13] and [14], it is recommended that a more extensive sensitivity study with ATD models be conducted (beyond the scope of the present work). If ATD models continue to overstate the hazard (even when using the higher estimate of Equation [13]), 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 an inadequate lethality estimate. A general population median lethality estimate higher than Equation [13] cannot be justified using the current lethality database (Table 2).

RECOMMENDATIONS

To better refine the human lethality estimates for chlorine toxicity, future toxicity studies should address the following issues: First, there is currently only one experimental study (Bitron & Aharonson, 1978) that provides a defensible estimate for the lethality TLE (n). The reproducibility of this result should be confirmed (over a range of durations from several minutes to several hours), preferably in multiple mammalian species. Second, the usefulness of allometric scaling can be strengthened by choosing larger species (*i.e.* rabbit, swine or goat) for the 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.

ACKNOWLEDGEMENTS

This study was funded by the Department of Homeland Security, Chemical Security Analysis Center, Aberdeen Proving Ground, MD, under Contract SP0700-00-D-3180. The study is documented in the following technical report:

Sommerville DR, Bray JJ, Reutter-Christy SA, Jablonski RE and Shelly EE, *Review and Assess-*

ment of Chlorine Mammalian Lethality Data and the Development of a Human Estimate, CBRNIAC-SS3-628. Department of Homeland Security, Chemical Security Analysis Center, Aberdeen Proving Ground, MD, 23 January 2008.

Acronyms

ATD	Atmospheric transport and dispersion modeling
CT	Concentration-time
DoD	Department of Defense
DHS	Department of Homeland Security
DTRA	Defense Threat Reduction Agency
ECBC	Edgewood Chemical Biological Center
HPAC	Hazard Prediction and Assessment Capability
IH	Inhalation
IRLS	Iteratively reweighted least squares
LCT ₅₀	Lethal concentration-time to 50% of exposed individuals
LD ₅₀	Lethal dosage to 50% of exposed individuals
LTL ₅₀	Lethal toxic load 50% of exposed individuals
MHAP	Major Hazards Assessment Panel
MLE	Maximum Likelihood Estimation
PST	Pasquill Stability
SE	Standard error
TL	Toxic load
TLE	Toxic load exponent
TWA	Time Weighted Average
WW1	World War One

Descriptors

Chlorine, Inhalation, Toxicity, Atmospheric Transport & Dispersion (ATD) Models, Iteratively Reweighted Least Squares (IRLS), Allometric Modeling, Subpopulation Statistics, HPAC

REFERENCES

- Alarie, Y, *Toxicological Evaluation of Airborne Chemical Irritants and Allergens Using Respiratory Reflex Reactions*, **Proceedings of Symposium on Inhalation Toxicology and Technology**. Ann Arbor Science Symposium, Ann Arbor, Michigan, 1980.
- Albrecht, GH; Gelvin, BR; and Hartman, SE, *Ratios as a Size Adjustment in Morphometrics*,

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

- American Journal of Physical Anthropology.** 91: 441–468, 1993.
- Anglen, DM, **Sensor Response of Human Subjects to Chlorine in Air.** Thesis, University of Michigan, Ann Arbor, MI, 1981.
- Armstrong, GC; Eldridge, WA; and Baldwin, JA, *Toxicity of Chlorine on Dogs – Ten-Minute Exposures*, **EA-MRD-17.** U.S. War Department, Chemical Warfare Service, Edgewood Arsenal, MD, 1923, UNCLASSIFIED Report, AD# B954958.
- Back, NC; Thomas, AA; and MacEwen, JD, *Reclassification of Materials Listed as Transportation Hazards*, **Report TSA-20-72-3.** US Air Force Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH, 1972.
- Barrow, RE and Smith, RG, *Chlorine-Induced Pulmonary Function Changes in Rabbits*, **American Industrial Hygiene Association Journal.** 36: 398–403, 1975.
- Batchinsky, AI; Martini, DK; Jordan, BS; Dick, EJ; Fudge, J; Baird, CA; Hardin, DE; and Cancio, LC, *Acute Respiratory Distress Syndrome Secondary to Inhalation of Chlorine Gas in Sheep*, **Journal of Trauma Injury, Infection, and Critical Care.** 60(5): 944–957, May 2006.
- Beebe, CH; *Important Constants of Fourteen Common Chemical Warfare Agents*, **EA-CD-328.** U.S. War Department, Chemical Warfare Service, Edgewood Arsenal, MD, 1924, UNCLASSIFIED Report, AD# B958296.
- Benton, BJ; McGuire, JM; Sommerville, DR; Dabisch, PA; Jakubowski, EM; Crosier, RB; Mioduszeewski, RJ; Thomson, SA; Crouse, KL; and Crouse, CL, *Effects of Whole-Body VX Vapor Exposure on Lethality in Rats*, **ECBC-TR-525.** US Army Edgewood Chemical Biological Center, Aberdeen Proving Ground, MD, January 2007, UNCLASSIFIED Report, AD# A462960.
- Bide, RW; Armour, SJ; Yee, E, *Allometric Respiration/Body Mass Data for Animals to be Used for Estimates of Inhalation Toxicity to Young Adult Humans*, **Journal of Applied Toxicology.** 20: 273–290, 2000.
- Bitron, MD and Aharonson, EF, *Delayed Mortality of Mice Following Inhalation of Acute Doses of Formaldehyde, Sulfur Dioxide, Chlorine, and Bromine*, **American Hygiene Association Journal.** 39(2): 129–138, 1978.
- Bliss, CI, *The Method of Probits*, **Science.** 79: 38–39, 1934.
- Box, GE and Draper, NR, **Empirical Model-Building and Response Surfaces.** John Wiley and Sons, New York, 1987.
- Box, GEP; Hunter, WG; and Hunter, JS, **Statistics for Experimenters.** John Wiley & Sons, New York, 1978.
- Bradshaw, Y and Radbill, L, *Method and Substance in the Use of Ratio Variables*, **American Sociological Review.** 52(1): 132–135, 1987.
- Bunting, H, *The Toxicity of Inhaled Chlorine Gas*, Chapter 2 in **Fasciculus on Chemical Warfare Medicine—Volume II: Respiratory Tract.** Committee on Treatment of Gas Casualties, Division of Medical Sciences, National Research Council, Washington, DC, pp. 18–23, 1945, UNCLASSIFIED Report.
- Crosier, RB, *Mathematical Limits on Differences between a Population and a Subpopulation*, **ECBC-TR-337.** US Army Chemical Biological Center, Aberdeen Proving Ground, MD, August 2003, UNCLASSIFIED Report, AD# 417162.
- 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.
- Crosier, RB and Sommerville, DR, *Relationship Between Toxicity Values for the Military Population and Toxicity Values for the General Population*, **ECBC-TR-224.** US Army Edgewood Chemical Biological Center, Aberdeen Proving Ground, MD, 2002, UNCLASSIFIED Report, AD# A400214.
- Dunlap, WP; Dietz, J; and Cortina, JM, *The Spurious Correlation of Ratios that have Common Variables: a Monte Carlo Examination of Pearson's Formula*, **Journal of General Psychology.** 124: 182–193, 1997.
- Eisenberg, NA; Lynch, CJ; Breeding, RJ, *Vulnerability Model: A Simulation System for Assessing Damage Resulting from Marine Spills*, **Report # CG-D-136-75.** Enviro Control Incorporated, Rockville, MD, 1975.
- Fairhurst, S and Turner, RM, *Toxicological Assessments in Relation to Major Hazards*, **Journal of Hazardous Materials.** 33: 215–227, 1993.
- Ferguson, JS and Hendershot, DC, *The Impact of Toxicity Dose-Response Relationships on*

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

- Quantitative Risk Analysis Results, **Process Safety Progress**. 19(2): 91–97, 2000.
- Finney, DJ, **Probit Analysis**. The University Press, Cambridge, Great Britain, 1971.
- Finney, DJ, **Statistical Methods in Biological Assay**. Charles Griffin, London, 1978.
- Firebaugh, G, *Is the Density-Fertility Relation a Statistical Artifact?—A Reply to Eric Jensen*, **Demography**. 23(2): 285–289, 1986.
- Firebaugh, G, *The Ratio Variables Hoax in Political Science*, **American Journal of Political Science**. 32(2): 523–535, 1988.
- Firebaugh, G and Gibbs, JP, *User's Guide to Ratio Variables*, **American Sociological Review**. 50(5): 713–722, 1985.
- Firebaugh, G and Gibbs, JP, *Defensible and Indefensible Commentaries*, **American Sociological Review**. 52(1): 136–141, 1987.
- Fox, J, *Applied Regression Analysis, Linear Models, and Related Methods*. SAGE Publications, Thousand Oaks, CA, 1997.
- Franks, AP; Harper, PJ; and Bilo, M, *The Relationship Between Risk of Death and Risk of Dangerous Dose for Toxic Substances*, **Journal of Hazardous Materials**. 51: 11–34, 1996.
- Griffiths, RF, *The Use of Probit Expressions in the Assessment of Acute Population Impact of Toxic Releases*, **Journal of Loss Prevention in the Process Industries**. 4: 49–57, 1991.
- Haber, FR, *Zur Geschichie des gaskrieges*, in **Fünf Vortrage aus Jahren 1920–1923**. Springer, Berlin, 1924.
- Harris, NC and Moses, AM, *The Use of Acute Toxicity Data in the Risk Assessment of the Effect of Accidental Release of Toxic Gases*, **Fourth International Symposium on Loss Prevention and Safety Promotion in the Process Industries**. Institution of Chemical Engineers, Rugby 1: I–36, 1983.
- Hazard Prediction and Assessment Capability (HPAC) User Guide Version 4.0.4 9. **HPACUGUIDE-01-RBC1**. prepared for Defense Threat Reduction Agency (DTRA), Contract No. DSWA01-98-C-0110, by: Science Applications International Corporation, Advanced Systems Development & Integration Operation, 10260 Campus Point Drive, San Diego, CA 92121, May 2003.
- Heller, CE, *Chemical Warfare in World War I: The American Experience, 1917–1918*, **Leavenworth Papers No. 10**. Combat Studies Institute, US Army Command and General Staff College, Fort Leavenworth, KS, September 1984.
- Hines, WW and Montgomery, DC, **Probability and Statistics in Engineering and Management Science**. Third Edition, John Wiley & Sons, New York, 1990.
- Hulet, SW; Sommerville, DR; Jakubowski, EM; Benton, BJ; Forster, JS; Dabisch, PA; Scotto, JA; Crosier, RB; Muse, WT; Gaviola, BI; Burnett, DC; Reutter, SA; Mioduszewski, RJ; and Thomson, SA, *Estimating Lethal and Severe Toxic Effects in Minipigs Following 10, 60, and 180 Minutes of Whole-Body GB Vapor Exposure*, **ECBC-TR-451**. US Army Edgewood Chemical Biological Center, Aberdeen Proving Ground, MD, March 2006, UNCLASSIFIED Report, AD# A462852.
- Kraft, M, *On User's Guide to Ratio Variables*, **American Sociological Review**. 52(1): 135–136, 1987.
- Kuh, E and Meyer, JR, *Correlation and Regression Estimates when the Data are Ratios*, **Econometrica**. 23(4): 400–416, 1955.
- Lehmann, KB, *Experiment on Chlorine*, **Arch f. Hygiene**. Wurtzburg, 1882.
- Lipton, MA and Rotariu, GJ, *The Toxicity of Chlorine Gas for Mice*, **UCTLR-1**. The University of Chicago Toxicity Laboratory, Chicago, IL, 1941, UNCLASSIFIED Report.
- Litchfield, JT; and Wilcoxon, F; *A Simplified Method of Evaluating Dose-Effect Experiments*, **Journal of Pharmacology and Experimental Therapeutics**. 96(2): 99–113, 1949.
- Macmillan, A and Daft, RL, *Relationships among Ratio Variables with Common Components: Fact or Artifact*, **Social Forces**. 58(4): 1109–1128, 1980.
- Mannan, S, ed. **Lee's Loss Prevention in the Process Industries**, Chapter 18 (*Toxic Release*), Volume 2; Elsevier, Butterworth, Heinemann, Burlington, MA, 2005.
- Marshall, EK, *Pharmacological and Research Detection Monographs; Chlorine*, **Report # 4**. War Department Chemical Warfare Service, Research Division, American University Experiment Station, Washington, DC, 1917a.
- Marshall, EK, *A Comparison of the Toxicity and Action of Chlorine, Phosgene, Superpalite*,

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

- Chlorpicrin, and Hydrocyanic Acid on Dogs*, Report # 12. War Department Chemical Warfare Service, Research Division, American University Experiment Station, Washington, DC, 1917b.
- Marshall, VC, *How Lethal are Explosions and Toxic Escapes*, **The Chemical Engineer (London)**. 323: 573–577, 1977.
- Marshall, VC, The Predictions of Human Mortality from Chemical Accidents with Special Reference to the Lethal Toxicity of Chlorine, **Journal of Hazardous Materials**. 22: 13–56, 1989.
- McElroy, OE; Shils, ME; Ginsburg, TH; Neville, GA; and Gish, FB; *The Concentration of Sugar in the Blood of Animals Exposed to Chemical Warfare Agents*, MD(EA) Memorandum Report 91. Medical Department Research Center, Office of the Surgeon General, Washington, DC, 24 May 1943, UNCLASSIFIED Report.
- MINITAB® Statistical Software. Releases 13 and 15, MINITAB Incorporated, State College, PA, 2000 and 2006.
- Myers, RH and Montgomery, DC, Response Surface Methodology—Process and Product Optimization Using Designed Experiments. John Wiley and Sons, New York, 1995.
- National Research Council, Committee on Toxicology, *Chlorine Acute Exposure Guideline Levels, Acute Exposure Guideline Levels for Selected Airborne Chemicals—Volume 4: The National Academies Press*, Washington, DC, 2004.
- Neumann, DA and Kimmel, CA, **Human Variability in Response to Chemical Exposures**. International Life Sciences Institute, CRC Press, Boca Raton, FL, 1998
- Pasquill, F, *The Estimation of the Dispersion of Windborne Material*, **The Meteorological Magazine**. 90(1063): 33–49, 1961.
- Pearson, K, Mathematical Contributions to the Theory of Evolution—On a Form of Spurious Correlation which may Arise when Indices are Used in the Measurement of Organs, **Proceedings of the Royal Society (London)**. 60: 489–498, 1897.
- Perry, W and Articola, W, US Department of Transportation Report: Study to Modify the Vulnerability Model of the Risk Management System. Office of Research and Development, Washington, DC, February 1980.
- Phalen, RF, **Inhalation Studies: Foundations and Techniques**. CRC Press, Boca Raton, FL, pp 211–242, 1984.
- Poblete, BR and Lees, FP, The Assessment of Major Hazards: Estimation of Injury and Damage Around a Hazard Source Using an Impact Model Based on Inverse Square Law and Probit Relations, **Journal of Hazardous Materials**. 9: 355–371, 1984.
- Prairie, YT and Bird, DF, Some Misconceptions about the Spurious Correlation Problem in the Ecological Literature, **Oecologia**. 81: 285–288, 1989.
- Ride, DJ, A Practical Method of Estimating Toxic Loads in the Presence of Concentration Fluctuations, **Environmetrics**. 6: 643–650, 1995.
- Rijnmond Public Authority, Risk Analysis of Six Potentially Hazardous Industrial Objects in the Rijnmond Area, A Pilot Study. Reidel, Dordrecht, 1982.
- Salem, H, *Factors Affecting Toxicity*, in Salem H (ed), **Inhalation Toxicology; Research Methods, Applications and Evaluation**. Marcel Dekker, New York, pp. 35–58, 1987.
- Salem, H, *Principles of Inhalation Toxicology*, in Salem, H, ed. **Inhalation Toxicology: Research Methods, Applications, and Evaluation**. Marcel Dekker, Inc., New York, pp 1–33, 1987.
- Schlagbauer, M and Henschler, D, **Toxicity of Chlorine and Bromine with Single and Repeated Inhalation**. International. Arch. Gewerbepathol. Gewerbehyg, 23: 91–98, 1967.
- Schubach, S, *Comparison of Probit Expressions for the Prediction of Lethality due to Toxic Exposure*, **Journal of Loss Prevention in the Process Industries**. 8(4): 197–204, 1995.
- Schubach, S, A Measure of Human Sensitivity in Acute Inhalation Toxicity, **Journal of Loss Prevention in the Process Industries**. 10: 309–315, 1997.
- Silver, SD and McGrath, FP, *Chlorine – Median Lethal Concentration for Mice*, **EATR Report # 351**. War Department Chemical Warfare Center, Edgewood Arsenal, MD, 1942, UNCLASSIFIED Report, AD# B955268.
- Silver, SD; McGrath, FP; and Ferguson, RL; *Chlorine – Median Lethal Concentration for Mice (II)*, **EATR Report # 373**. War Department

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

- Chemical Warfare Center, Edgewood Arsenal, MD, 1942, UNCLASSIFIED Report, AD# B955266.
- Smith, RJ, Relative Size versus Controlling for Size—*Interpretation of Ratios in Research on Sexual Dimorphism in the Human Corpus Callosum*, **Current Anthropology**. **46**(2): 249–273, 2005.
- Snipes, MB, *Species Comparisons for Pulmonary Retention of Inhaled Particles*, in McClelland, RO, and Henderson, RF, eds., **Concepts in Inhalation Toxicology**. 1st edition, Hemisphere Publishing, New York, p 196, 1988.
- Sommerville, DR; Park, KH; Kierzewski, MO; Dunkel, MD; Hutton, MI; and Pinto, NA, *Toxic Load Modeling*, Chapter 8 in Salem, H, and Katz, SA, eds., **Inhalation Toxicology**. 2nd Edition, CRC Press, New York, 2005.
- Spiegel, MR, *Theory and Problems of Statistics—Schaum's Outline Series*. McGraw-Hill Book Company, New York, 1961.
- ten Berge, WF and van Heemst, MV, *Validity and Accuracy of a Commonly Used Toxicity Assessment Model in Risk Analysis*, **Fourth International Symposium on Loss Prevention and Safety Promotion in the Process Industries**. Institution of Chemical Engineers, Rugby 1: I-1 to I-12, 1983.
- ten Berge, WF; Zwart, A; and Appelman, LM, Concentration-Time Mortality Response Relationship of Irritant and Systemically Acting Vapours and Gases, **Journal of Hazardous Materials**. **13**: 301–309, 1986.
- The Major Hazards Assessment Panel (Kletz, TA, Chair), **Chlorine Toxicity Monograph**. Toxicity Working Party for Chlorine, Institution of Chemical Engineers, Rugby, 1988.
- Turner, RM and Fairhurst, S, **Toxicology of Substances in Relation to Major Hazards—Chlorine**. Health and Safety Executive, London, 1990.
- Underhill, FB, **The Lethal War Gases: Physiology and Experimental Treatment**. Yale University Press, New Haven, CT, 1920.
- 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.
- Vanderburgh, PM, Two Important Cautions in the Use of Allometric Scaling: The Common Exponent and Group Difference Principles, **Measurements in Physical Education and Exercise Science**. **2**(3): 153–163, 1998.
- Vernot, EH; MacEwen, JD; Haun, CC; and Kinkead, ER, *Acute Toxicity and Skin Corrosion Data for Some Organic and Inorganic Compounds and Aqueous Solution*, **Toxicology and Applied Pharmacology Journal**. **42**: 417–423, 1977.
- Weedon, FR; Hartzell, A; and Setterstrom, C, *Toxicity of Ammonia, Chlorine, Hydrogen Cyanide, Hydrogen Sulfide, and Sulphur Dioxide Gases—V. Animals*, **Contributions from Boyce Thompson Institute**. **11**: 365–385, 1940.
- West, GB; Brown, JH; and Enquist, BJ, *A General Model for the Origin of Allometric Scaling Laws in Biology*, **Science**. **276**: 122–26, 4 April 1997.
- 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, 1985a.
- 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, 1985b.
- Yee, E, A Rational Basis for Accounting for the Impact of Concentration on Toxicological Assessment and Estimation of Injury Resulting from the Release of Chemical and Biological Warfare Agents, **SR-634**. Defence Research Establishment Suffield, Alberta, Canada, 1996a, AD# A304587.
- Yee, E, A Non-Linear Dose-Response Model with an Application to the Reconstruction of the Human Mortality Response Surface from Acute Inhalation Toxicity with Sarin, **SM-1476**. Defence Research Establishment Suffield, Alberta, Canada, 1996b, AD# A309486.
- Yee, E and Ye, H, Military Casualty Estimation for Realistic Chemical and Biological Warfare Agent Cloud Concentration Challenges, **SR-661**. Defence Research Establishment Suffield, Alberta, Canada, 1996, AD# 322185.
- Yule, GU, *On the Interpretation of Correlations Between Indices or Ratios*, **Journal of the Royal Statistical Society**. **73**(6/7): 644–647, 1910.
- Zwart, A and Woutersen, RA, Acute Inhalation Toxicity in Rats and Mice: Time-Concentration-Mortality Relationships and Effects on Respiration, **Journal of Hazardous Materials**. **19**: 195–208, 1988.