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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

BY

Eugene Yee

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A RATIONAL BASIS FOR ACCOUNTING FOR THE IMPACT OF CONCENTRATION FLUCTUATIONS ON TOXICOLOGICAL ASSESSMENT AND ESTIMATION OF INJURY RESULTING FROM THE RELEASE OF CHEMICAL AND BIOLOGICAL WARFARE AGENTS

by

Eugene Yee

PCN No. 051SP

ABSTRACT

A rational, consistent, and simple methodology for the estimation of the degree of injury or damage to exposed military personnel around a chemical or biological warfare (CBW) agent release is developed. The proposed hazard analysis methodology places particular emphasis on the following important factors: (1) recognition that the toxicity of rapidly acting inhaled toxic materials is usually highly nonlinear, and use of a nonlinear toxic load to quantify this effect; (2) recognition that realistic estimates for toxicological assessment must explicitly account for the fluctuating concentration in a dispersing plume, and development of a simple model for incorporation of these effects into the ensemble-averaged (mean) nonlinear toxic load; (3) recognition of the importance of identifying the relevant time scale for the application (i.e., the time scale appropriate for the response of the human lungs); and, (4) recognition of the variability in the exposed population to a specific toxic load of material, and use of probit relationships to model this varying susceptibility. Example calculations performed using the proposed methodology demonstrated the importance of accounting for concentration fluctuations in the hazard assessment. It is shown that failure to do so under realistic situations could lead to a serious underestimation of the severity of the toxic effects and of the crosswind and downwind extents of the hazard zones generated by the CBW agent release.

EXECUTIVE SUMMARY

Introduction: The existing methodology for military hazard assessment is based on using standard atmospheric dispersion methods (e.g., Gaussian plume or puff models) for estimating the mean concentration of a chemical or biological warfare (CBW) agent, and coupling this information with the concept of a linear dosage for determination of the toxic effect on the exposed population. Although the severe limitations of this method for hazard assessment has been understood for over a decade, it is still nevertheless used to estimate the adverse effects that would be felt by an exposed group of people. The widespread use of the current hazard analysis methodology despite its serious limitations derives from a phenomenon that has been termed the availability error. The latter is nothing more than a strong disposition to make judgements or evaluations in light of the first available thing that comes to mind (or is "available" to the mind). In the case of military hazard assessment, the ready availability of toxic gas models that predict the mean concentration, used in conjunction with the dosage-effect correlation that has been observed for some toxic materials, has led to the widespread use of the present hazard analysis methodology.

However, military hazard assessments that use only the mean concentration and a linear dosage ignore several important factors that may lead to serious errors: (1) the toxic effects produced by CBW agents are usually nonlinear with the important consequence that the toxic effects produced by these agents are dependent on the level of concentration as well as the dosage (viz., for these agents a high peak concentration felt for a short duration, followed by a period of zero concentration, can cause a greater adverse effect than a low concentration felt for a longer time even though the dosage is the same in both exposures); (2) CBW agent concentrations in plumes dispersing in the atmosphere are inherently random variables because of their dependence on the fluctuations of a variety of meteorological (turbulence) and emission variables; and, (3) the varying susceptibility in the exposed personnel to the toxic agent has not been properly accounted for. In view of these serious deficiencies in the current military CBW agent hazard assessment methodology, the purpose of this study is to develop a rational, yet simple, methodology for hazard assessment that overcomes the deficiencies cited. In particular, a model to account for the essentially statistical nature of atmospheric dispersion as it relates to the determination of

an appropriate degree of injury function for exposure to CBW agents is developed.

Results: A rational, consistent, and simple methodology for the estimation of the degree of injury or damage for exposed military personnel around a CBW agent release is developed. The hazard analysis procedure consists of a number of steps which can be summarized as follows. Firstly, the use of a nonlinear toxic load is advocated as a measure of the level of damage resulting from exposure to many harmful substances for which the interaction of concentration and exposure time is nonlinear. Evidence from a number of toxicological experiments supporting the use of the toxic load as an appropriate measure of the level of damage for a wide variety of toxic materials is summarized. Secondly, the importance of concentration fluctuations in determination of the toxic load is emphasized. Using an extensive new data set of instantaneous plume concentration measurements from the CONFLUX project, it is shown how various statistical characteristics can be determined and assigned to the fluctuating concentrations, and how the latter information can be utilized to provide a simple, practical method for estimating the ensemble-averaged (mean) toxic load in the presence of concentration fluctuations. Thirdly, the importance of identifying the relevant time scale of concentration fluctuations (e.g., a time scale relevant to the smoothing imposed by the human lungs) for the toxicological assessment is noted. Fourthly, the mathematical basis of probit relationships is reviewed, and their use in modelling the variability in individual toxic gas susceptibility is described. Fifthly, it is shown how by combining the ensemble-averaged toxic load and the probit method, it is possible to determine the fraction of an exposed population that would be affected by a given CBW agent event. The latter procedure simultaneously takes into account the intensity and frequency of concentration fluctuations in determination of the toxic load and the response of a population of varying susceptibility to this toxic load.

Significance of Results: With few exceptions, CBW agent dispersion models have been limited to the prediction of dosage or ensemble mean concentrations averaged over time scales of tens of minutes, hours, or more. While this scheme can be used successfully for predicting cumulative effects of nuclear radiation (e.g., radioactive isotopes), it is much less satisfactory for many CBW agents for which the interaction between concentration and exposure time is nonlinear. For example, the toxicity of many CBW agents may be increased by the existence of pockets of high concentration within the plume because the

damage function (the so-called toxic load) is of the form C^nT, where n is an index (the so-called toxic load exponent) that is usually greater than 1 (typically in the range from 1 to 4), C is the concentration, and T is the exposure duration. In this case, the use of a time-averaged dosage could lead to a dangerous underestimation of the hazard with respect to both the severity of the toxic effect and the size or extent of the hazard zone.

In particular, actual measurements have shown that the fluctuation intensity (i.e., the ratio of the standard deviation of concentration to mean concentration) perceived at a time scale of about 1 s (e.g., a time scale comparable to the response of the human lungs) varies in the range from about 0.5 to 10 depending on plume position. For toxic load exponents ranging from between 1 to 3.5 (viz., a range which covers that observed for a wide variety of toxic gases) and for the range of fluctuation intensities expected to be encountered in a dispersing plume, the ensemble-averaged toxic load ratio (viz., a ratio that measures the enhancement in the toxic response due to a fluctuating concentration over that provided by a steady, average concentration whose value is the mean of the fluctuating one) was found to vary from about 1 to greater than 1000. The enhancement in the toxic load predicted by the new model reinforces the importance of paying careful attention to plume meandering effects that can reduce mean-plume concentrations while increasing peak fluctuation levels at the plume fringes. These results provide compelling evidence for using probabilistic/statisical methods for military hazard assessment, rather than traditional deterministic methods.

Future Goals: With regard to the problem addressed in this paper, there is one significant area where further modelling work is required for practical application. The ensemble-averaged (mean) toxic load was used for making quantitative estimates for biological response to toxic materials, largely because our current state of knowledge of quantities required for the prediction of the mean toxic load is relatively certain. However, a more complete scheme for hazard assessment would need to account for the inherent or natural variability in the nonlinear toxic load resulting from the concentration fluctuations. A difficult statistical problem that remains unsolved concerns the determination of the relationship between the statistical properties of the toxic load to those of the fluctuating concentration. In particular, an ambitious line of future research would be to develop a model for the probability distribution of the toxic load itself, and use this information in the toxicological assessment rather than the mean toxic load used here. However, it is important to

note that the latter problem is extremely difficult because the probability distribution of the toxic load is not expressible in terms of the one-point probability distribution of the instantaneous concentration itself (for which reliable information is available at present), since it requires a knowledge about what is happening at many points in the plume simultaneously and, hence, of joint probability distributions of concentration (for which no information is available at present).

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INTRODUCTION

The assessment of hazards likely to be caused by the release of chemical warfare (CW) and biological warfare (BW) agents is a problem of great practical military importance. The assessment of the potential effects of such releases is necessary for the formulation of operational and design strategies for managing the consequences of the hazard, as well as for providing answers to political and military concerns such as: What is the hazard range, that is, the maximum distance downwind that might be reached by a militarily significant concentration of CBW agent under particular release conditions?; What is the size and shape of the area affected by the CBW agent release, and what is the expected toxicological effect on military personnel located within the hazard range?; Are present CBW agent detection systems adequate to forwarn against the arrival of the dispersing cloud of contaminant?; How effective are available protective equipment (such as respiratory protective devices and suits) against the instantaneous concentration field arising from a particular CBW release?; etc. Indeed, the answers to these and many related questions are required in order to develop an effective defence against CBW agent attack. In particular, these answers will provide decision makers with an rational assessment of the likely magnitude of the militarily significant downwind hazard produced by a particular release of CBW agent. In turn, this information can be used to give numerical advice to commanders and NBC advisors in the field, and enable realistic risk-taking procedures to be explored and developed.

Downwind hazard distance data are usually obtained from mathematical modelling. The consequences in terms of concentration at particular distances and times are provided by turbulent diffusion calculations, and this information has to be translated subsequently into specified levels of harm to exposed military personnel. Indeed, the entire process of hazard assessment is extremely complex. Despite this complexity, assessing the likely damage from the use of CBW agents involves basically three principal components. Firstly, the characteristics of the source must be known, and these include typically input information such as the kind of material released, the quantity of material released, the duration of the release, release position, the initial spatial and temporal distribution of material, etc. Indeed, the geometry of the source may take many forms and the initial momentum may be significant. In most cases of military concern, the source characteristics are not well-defined

and, as a consequence, modelling may be required to determine their likely values if *a priori* knowledge (e.g., military intelligence) on the nature of the release is inadequate. Secondly, it is required to determine the transport and diffusion of the material (contaminant) through the turbulent atmosphere. On a fundamental level, this involves modelling the advection by the mean wind and dilution by the atmospheric turbulence, but because of the diversity of CBW agents, this stage may frequently involve other processes as well (e.g., for CW agents, the process of formation of gaseous clouds may involve two-phase phenomena with significant thermodynamic effects, frequently leading to negative buoyancy (or, dense gas) effects; for BW agents, a number of non-conservative processes may be involved such as gravitational settling, wet and dry deposition, biological activity agent decay, etc.). Thirdly, it is required to estimate the effects (e.g., toxic or infective effects as a function of distance) on military personnel exposed to the CBW agent release.

It is clear that CBW agent hazard assessment is an interdisciplinary science requiring, as such, the expertise of toxicologists, epidemiologists, atmospheric and aerosol physicists, fluid mechanicians, and statisticians. Obviously, a CBW agent hazard assessment requires the synergistic combination of two basic models: namely, a physical sciences model which can be used to predict the physical consequences of a CBW agent release (e.g., the intensity of the physical effect such as concentration and persistence of the agent at a point downwind of the release); and, a biological sciences model which can be used to predict the probability of injury to exposed military personnel as a function of the physical intensity (e.g., percentage of the exposed personnel which might be incapacitated, infected, killed, etc). The purpose of the present study is to show how a rational, practical, and operational statistical methodology can be developed for the assessment of hazards resulting from the release of CBW agents.

In this paper, we do not try to quantify all sources of uncertainty in the hazard assessment process. Rather, we assume that the CBW agent source is well-characterized, and focus our attention on estimation of the effects of 3 major sources of variability in the hazard assessment process: namely, (1) the inherent uncertainty in the atmospheric dispersion process arising from the naturally induced fluctuations of concentration in the atmosphere; (2) the nonlinearity of the response of the biological receptor for CBW agents; and, (3) the variability in the response of an exposed population to a specific dose of CBW agent. How the latter 3 effects can be accounted for in a military hazard assessment is the subject of the present study. In so doing, we show how a rational, practical and operational

statistical method for the assessment of hazards due to dispersing CBW agent clouds can be developed. In addition, we show how such a method can be used for evaluating the probabilities and consequences of possible outcomes resulting from releases of CBW agents into the atmosphere.

BIOLOGICAL MODEL: TOXIC LOAD AND PROBIT METHOD

THE CONCEPT OF TOXIC LOAD

Information on the acute inhalation toxicity of toxic gases and aerosols (e.g., various CBW agents) is required for the purposes of hazard assessment. For acutely toxic gases and aerosols, the factor which correlates with the degree of injury (e.g., incapacitation, death, etc.) is not necessarily the intensity of the physical effect (e.g., concentration of the toxic material), but rather some functional of this. For example, for many toxic materials, the functional that correlates with injury is the integrated time-varying concentration, frequently with concentration or time raised to some power. It is standard practice to use a linear time-integrated concentration, or dosage, to predict mortality or infectivity response relationships. Indeed, the use of dosage as the basis for estimating injury from exposure to CBW agents appears to be an accepted principle in military hazard assessment. In consequence, its general applicability for risk/benefit analysis in military decision making with regard to all CBW agents is almost never questioned. The method was first proposed by Haber (see [1]), who found that for certain poison gases (e.g., phosgene) used in the First World War, the toxic effects appeared to be correlated with the dosage, which for a constant concentration exposure is simply defined as the product of the concentration C and the exposure duration T (e.g., the so-called CT value). Implicit in the dosage concept proposed by Haber is the reciprocal trade-off between C and T for toxic gases, so that the toxic effect is assumed to remain unchanged if, for example, the concentration is doubled and the exposure time is halved (e.g., the so-called Haber's rule). There are toxic materials for which Haber's rule is valid. For example, dosages have been used successfully for predicting the cumulative effects of heavy metal (e.g., lead) poisoning and nuclear radiation.

Unfortunately, the simple concept of dosage as the determinant of injury in a biological receptor has been found to be inadequate for many acutely-toxic gases and aerosols. Here, one is interested in materials that produce an acute response, where "acute" means

"occurring in a time that is short compared to the duration of sampling". For these materials, it is generally the case that the influence of concentration is more pronounced than that of exposure time. In other words, a high concentration for a short period has a more severe effect than a low concentration for a longer time. In consequence, the simple definition of the dosage as the product of exposure time and time-mean concentration is not in general a good measure of the degree of injury.

Indeed, Haber [2] had already noted that the level of damage for certain poison gases (e.g., chlorine, hydrogen cyanide, etc.) did not correlate well with the dosage or CT value. The dependence of toxicity of certain war gases on the concentration level was conclusively demonstrated during the Second World War by Japanese military toxicologists [3]. In particular, the Japanese conducted animal experiments in which various species of animals were exposed to intermittent concentrations of a number of toxic gases (e.g., hydrogen cyanide) for a constant exposure time. In these careful experiments, it was found that the higher (and, hence, more intermittent) concentrations produced the most severe toxic effects, despite the fact that the dosage in each exposure was kept constant. It is interesting to note that the discovery by the Japanese military toxicologists [3] of the nonreciprocal tradeoff between concentration and exposure time for many war gases has been largely ignored within the military hazard assessment community until relatively recently.

The concept that the biological response to many toxic gases and aerosols is nonlinear (e.g., a high peak concentration applied for a short time, followed by a period where the concentration is zero, induces a greater adverse effect than a low concentration applied for a longer time, even though both exposures yield the same mean concentration and dosage), was rediscovered in the 1970s and 1980s by industrial toxicologists and hygienists. In particular, for many acutely-toxic materials (e.g., industrial gases), it has been found recently (cf. studies such as Larsen, Gardner, and Coffin [4,5]; ten Berge [6]; ten Berge, Zwart, and Appelman [7]; Zwart and Woutersen [8]; etc.) that dosage provides a poor measure of the level of damage. Rather, it was demonstrated that the functional of concentration that correlates well with the degree of injury is the product C^nT, where C is the (constant) concentration, T is the exposure time, and n is an index (the so-called toxic load exponent) that depends on the particular gas or aerosol. In general, for most gases for which experiments have been conducted, n was found to be greater than one. The causative (or injury) factor in which the nonlinear effect of concentration peaks on the biological response is accounted for by the simple expedient of raising the concentration to some exponent n became known

as the the toxic load, TL. It is defined for a constant concentration exposure as follows:

$$TL \equiv C^n T. \tag{1}$$

The toxic load exponent, n, characterizes the nonlinearity of the biological response to the material. Obviously, if $n = 1$, then the toxic load, TL, simply reduces to the usual dosage, $D \equiv CT$.

The objective of the toxicological assessment is to define all combinations of concentration C and exposure time T that would produce a specified level of effect (SLOE) of interest (e.g., SLOE may correspond to a specific lethal or incapacitating effect in the population exposed to the material). In view of the fact that the damage produced by many toxic materials appears to be related to the toxic load, this objective can be met by consideration of the equation $TL = K$, where K is a constant. The latter equation essentially embodies all sets of exposure conditions that could give rise to the SLOE of interest. Different numerical values for the constant K then correspond to different levels of injury for any particular toxic gas or aerosol. It is important to emphasize that the toxic load defined in Equation (1) is not derived from any fundamental biological principles per se. Rather, the measure is based entirely on empirical observations usually involving exposures of small mammals to differing constant concentrations C, for differing exposure times T. Nevertheless, the toxic load is as good a measure of the level of damage in a biological receptor as is currently available. However, it should be noted that other parametrizations for the toxic load are certainly possible and, in this regard, Zwart and Woutersen [8] suggest a more complicated function of C and T for TL.

It has been found that responses of animals to many locally irritant and systemically acting toxic gases are highly nonlinear. Correlations of existing toxicity data for these materials by ten Berge, Zwart, and Appelman [7] show that the toxic load exponent, n, in Equation (1) lies in the range from about 1 to 3.5. For example, ten Berge, Zwart, and Appelman [7] report toxic load exponent values of 1.2, 2.2, 2.7, and 3.5 for perfluoroisobutylene (PFIB), hydrogen sulfide (H_2S), hydrogen cyanide (HCN), and chlorine (Cl_2) gas, respectively. Hence, the index n varies considerably depending on the toxic material, and may be considerably greater than one. Because of the latter fact, the use of dosage as a measure of damage would be highly inappropriate. As a example, for HCN which has $n = 2.7$, a factor of two increase in concentration will produce the same level of toxicity in about one-sixth the exposure time, and not one-half the exposure time as would be predicted with a linear

dosage relationship.

Although the evidence is more sparse, there have been suggestions that exposure to toxic aerosols (e.g., BW agents, coal and silicaeous dust, etc.) can also elicit nonlinear biological responses. Wright [9] pointed out that despite the evidence supporting the use of a linear dosage, several authorities in the field believe that high concentrations of airborne toxic particles over short periods can make significantly greater contributions to lung burden than do the average concentration. This belief is based on the assumption that the deposition of a large number of particles in the lung in a brief period impairs the efficiency of the clearance mechanisms. In addition, Reisner [10] has cited evidence from which he concludes that it is not out of the question that high concentrations of toxic aerosols can have effects exceeding those expected on the basis of a linear dosage alone. Finally, Roach [11] found that for airborne particles which produce an acute response, the presence of peak concentrations during an exposure duration may be of real significance. In particular, he assumed that the body burden x from exposure to a contaminant built up in a simple exponential fashion,

$$x = kC/a + \big(x_0 - (kC/a)\big)\exp(-aT),$$

where C is concentration of the airborne contamination; T is exposure time; k is the product of the volume of air inhaled per unit time (i.e., tidal volume per unit time) and the fraction of inhaled contaminant that is deposited in the body; x_0 is the body burden at time $t = 0$; and, a is an elimination rate which is related to the half-life $t_{1/2}$ of the substance in the body by $a = \ln 2/t_{1/2}$. Under these circumstances, Roach showed that if x_0 is negligible, $x \propto CT$ when $t_{1/2}$ is very long and $T \ll t_{1/2}$, but $x \propto C$ (i.e., body burden is dependent on the concentration level) when $t_{1/2}$ is very short and a is very large. In the latter case, it is obvious that the inhalation hazard will be increased by the presence of peak concentrations (e.g., by the existence of pockets of high concentration within the plume or cloud).

It is important to note that the empirical relationship embodied in Equation (1) is based mainly on laboratory studies of toxic effects on small mammals such as mice and rats for exposures to different *constant* concentrations, C, for different exposure times, T. In the case of actual concentration-time histories such as those experienced at receptor points in a dispersing atmospheric plume or cloud, the concentration will vary with time during any particular exposure. In the latter situation, it is conceivable that the relationship of

Equation (1) can be generalized to accomodate a time-varying concentration as follows:

$$TL = \int_0^T \chi^n(t)\, dt, \tag{2}$$

where $\chi(t)$ is the time-varying concentration. In the case of exposure to a dispersing cloud, we will identify $\chi(t)$ in Equation (2) with the instantaneous concentration of a contaminant measured at a fixed receptor point as the cloud passes by.

Finally, it is important to emphasize that the toxic load does not account for two other basic effects that may be important in any particular episode of gas poisoning; namely, the rate of uptake and the rate of detoxification. Obviously, man does not remain passive in the face of a toxic threat—the reaction to the threat will entail some form of activity to escape the threat. This enhanced activity will result in the inhalation of larger volumes of contaminated air, and effect of the enhanced inhalation rate would be to enhance the toxic response. On the other hand, any detoxification mechanism through metabolic processes will remove toxic material from the system. The application of toxic load for measuring the degree of injury implicitly assumes that the exposure time is much shorter than a characteristic time for detoxification for the biological receptor. This assumption is probably reasonable for acute intoxication for many toxic materials (e.g., chlorine, hydrogen cyanide, hydrogen sulfide, etc.).

THE PROBIT METHOD

For each individual in an exposed population, there will be a certain value of the toxic load (cf. Equations (1) or (2)) that will be required to produce a SLOE of interest. This specific value of the toxic load may vary from individual to individual due to the varying susceptibility among individuals in a population to an exposure of a particular material. Hence, in any population of people or animals, there will be varying degrees of susceptibility to the adverse effects from toxic gas or aerosol exposure, and this source of variability needs to be accounted for. In acute-toxic gas inhalation studies on laboratory animals, it has been found that variation in susceptibility among members in a population to exposure to toxic materials tends to follow a lognormal distribution. With this type of distribution, and expressing probability in units of standard deviation, the varying susceptibility among individuals in a population can be conveniently expressed in the form of a probit (probability-unit) equation having the following general form:

$$Y = k_1 + k_2 \ln(TL), \tag{3}$$

where Y is the probit; and, k_1 and k_2 are numerical constants that depend on the stressing agent and, in consequence, must be determined from experimental tests. Note that in Equation (3), the toxic load TL is used as a measure for the injury or causative factor of the harmful agent. The combination of toxic load (rather than linear dosage) with the probit method is a relatively recent development apparently first advocated by Lees [12].

The probit value Y is a measure related to the percentage of an exposed population that suffers a SLOE of interest. In view of its relationship to the lognormal distribution, this implies that the probability P that an individual in a specified population experiences a given adverse effect from a toxic load TL is

$$P = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{Y} \exp(-u^2/2)\, du. \tag{4}$$

It should be noted that Equation (4) differs from the usual probit relation originally defined by Finney [13] (who used it in tests on the effectiveness of insecticides) in the sense that the (arbitrary) value of 5 has not been added to Y in order to eliminate negative values of the probit. Hence, in our definition, the probit Y is a normally distributed random variable with a mean of 0 (rather than 5) and a standard deviation of 1. In other words, the value of 0 for Y corresponds to the median value of the effect being studied (viz., the value at which 50% of the exposed population experiences the SLOE), whereas probit values of $1, 2, \ldots$ correspond to $1, 2, \ldots$ standard deviations above and probit values of $-1, -2, \ldots$ correspond to $1, 2, \ldots$ standard deviations below the median.

Note that the probit Y and probability of injury, P, are completely determined once we have specified the coefficients k_1 and k_2. These coefficients can be determined once we have data at two or more levels of response. Indeed, denote by $(TL)_{50}$ the toxic load that would cause 50% of the exposed population to experience the SLOE of interest (i.e., $(TL)_{50}$ is the median toxic load). From the definition of Y in Equation (4), the fractional effect is 0.5 (i.e., $P = 0.5$) at $Y = 0$. From Equation (3), this implies

$$k_1 = -k_2 \ln(TL)_{50}, \tag{5}$$

so

$$Y = k_2 \ln\left(\frac{TL}{(TL)_{50}}\right). \tag{6}$$

Hence, inserting Equation (6) in Equation (4) and evaluating the integral leads to the

following explicit result:

$$P = \frac{1}{2}\left(1 + \mathrm{erf}\left(\frac{\ln(TL/(TL)_{50})}{\sqrt{2}S_L}\right)\right), \tag{7}$$

where

$$S_L \equiv 1/k_2, \tag{8}$$

and $\mathrm{erf}(x)$ is the error function. In Equation (8), we defined a parameter S_L which can be interpreted simply as the logarithmic standard deviation of the susceptibility of the exposed population. A large value of S_L occurs when the exposed population contains a wide range of individual susceptiblity to the adverse effect, and a small value implies a more homogeneous population. Hence, the probit coefficients k_1 and k_2 can be expressed in terms of $(TL)_{50}$ and S_L. Finally, it is important to note that the probit relationship exhibited in Equations (6), (7), and (8) suffers from the defect that the (lognormal) distribution is unbounded, with the deleterious effect that it predicts that there is a finite probability that an individual will survive or die from a toxic load no matter how large or small, respectively.

Finally, given the probability of injury P, and the distribution of exposed personnel in the area around the CBW hazard source, the number of people injured may be estimated from the following relationship:

$$N(z_s;T) = \int\int_A \rho(x,y)P(x,y,z_s;T)\,dx\,dy,$$

where $P(x,y,z;T)$ is the probability of injury (cf. Equation (7)) at a receptor point with Cartesian coordinates (x,y,z) for an exposure duration T; $\rho(x,y)$ is the density of exposed personnel at (x,y) in the hazard area A; z_s is the exposure height (e.g., typically z_s is chosen to be the nose height); and, $N(z_s;T)$ is the number of exposed personnel affected (e.g., incapacitated, killed, etc.).

PHYSICAL MODEL: ACCOUNTING FOR CONCENTRATION FLUCTUATIONS

Effects of fluctuating concentration on toxic response

In the previous section, we described the components of the biological model required for determining the toxicological hazard (incapacitation, lethality, etc.) resulting from the

release of a CBW agent into the atmosphere. The basis of the biological model involved combining the toxic load which characterizes the nonlinearity of the dose-time response of a biological receptor to the toxic substance, with the probit method which accounts for the variability in the response in a population of biological receptors to a specific load of the toxic substance. In accordance to Equation (2), the quantitative estimation of the degree of intoxication requires explicit knowledge of the time history of the concentration to which the biological receptor is exposed. Indeed, the degree of injury for a nonlinear material (viz., a material with $n > 1$) depends on the concentration time-history during the exposure, with different time-histories giving rise to different toxic loads, even though the dosages may be the same for each of these time-histories.

The dependence of the toxic load (and, by implication, the toxic response) on the concentration time-history was first recognized by Griffiths and Megson [14] who considered the effect of two rather artificial concentration time-histories with equal dosages; one composed of a steady concentration C applied for time T, and the other composed of a series of blocks of non-zero concentration C_p applied for a total time T_p, with each block separated by gaps with zero concentration for a total time T_0, where $T_p + T_0 = T$. From this *gedanken* experiment, Griffiths and Megson [14] demonstrated the extreme sensitivity of the toxic load to periods of peak concentration. In so doing, they quantified the enhanced toxicity resulting from an intermittent concentration. Ride [15] confirmed the latter effect by using a simple physical model based on spherical eddies of constant concentration separated by regions of uncontaminated air.

These seminal investigations demonstrated the importance of accounting for concentration fluctuations when one is concerned with nonlinear toxic substances for which the injury function is a toxic load TL of the form C^nT, with n an index that is greater than one. The significance of concentration fluctuations for toxic gas hazard assessment can be demonstrated also using concentration time series measured in full-scale field experiments. Figure 1 displays 1800 s of a sample concentration time series measured by a fast-response concentration detector located approximately at the mean-plume centerline of a dispersing plume at a downwind distance $x = 60$ m. The concentration detector used for the measurement was a photoionization sensor with a frequency response of about 300 Hz (Chandler [16]) and sampled concentration at 4000 samples per second. Note that the concentration time series exhibited in Figure 1 provides a strong visual indication of the wide range of timescales that are responsible for the complex concentration patterns resulting from a

plume exposure at any fixed receptor downwind of the release. In particular, observe that the plume concentrations exhibit a highly intermittent structure in which concentration variability is composed of a series of bursts of high concentration interspersed with periods of zero concentration. Indeed, the concentration time series in Figure 1 clearly shows the two distinctly different mechanisms that produce fluctuations: namely, plume meandering in which turbulent eddies larger than the plume move it bodily back and forth over the receptor point to produce the intervals of zero concentration; and, in-plume turbulent fluctuations in which turbulence on smaller scales than the instantaneous plume width produce rapidly varying concentrations and fine-scale in-plume concentration structure.

To show the effects of naturally induced fluctuations in the atmospheric concentrations of toxic vapors on biological response, it is convenient to measure the ratio of the toxic load in the fluctuating plume concentration to that in a constant concentration exposure whose value is the mean of the fluctuating one. To this end, let us define the toxic load ratio, TLR, as follows:

$$TLR \equiv \frac{\int_0^T \chi^n(t)\,dt}{C^n T} = \frac{1}{T}\int_0^T \left(\frac{\chi(t)}{C}\right)^n dt, \tag{9}$$

where C is the mean concentration (time-averaged over the exposure time T) corresponding of the instantaneous (fluctuating) concentration $\chi(t)$. Now an indication of the effects of concentration fluctuations on the severity of the toxic response can be obtained by evaluating the TLR defined in Equation (9) along the measured concentration time series shown in Figure 1. The results are summarized in Figure 2, using a range of values for the toxic load exponent n between 1 and 4. Recall that n for toxic gases appears to range from 1 to 3.5 [7]. Figure 2 shows that for the concentration pattern exhibited in Figure 1, the toxic hazard is increased by a factor of between about 3 and 30 for n between 1.5 and 2.25. The increase in the toxicity appears to be extremely sensitive to the precise value of n chosen, with the toxic response increasingly dramatically for highly nonlinear materials (e.g., materials such as chlorine gas with $n > 3$).

Importance of averaging time

While the relative trends exhibited in Figure 2 appear to be correct, it is important to emphasize that the absolute values for the increased toxic hazard displayed here appear to be unrealistic (or, at least implausible), especially at the higher values for n. The large values

for the TLR summarized in Figure 2 arise because the concentration pattern (cf. Figure 1) used to determine these values is that perceived by a high-resolution concentration detector. The latter can resolve very large, short-duration concentration peaks that are probably not very important in the toxicological assessment for a biological receptor. In particular, these high concentrations of very short duration cannot be resolved by the human body because breathing rates have a finite time scale. Indeed, the finite response of the human lungs must impose some physical averaging time (typically about 3 s) on the fluctuations in concentration. Consequently, the concentration time series used to evaluate the toxic load ratio for toxicological assessment should actually be the distribution of concentration fluctuations as *perceived* by the human lungs, and not by a high resolution concentration detector. The former typically have time scales of between about 1 to 10 s depending on the level of physical activity. In any case, for a toxic material, concentration fluctuations with time scales shorter than about 1 s are unlikely to be significant because of averaging in the lungs.

Figure 3 shows the effect of averaging time for the concentration time series exhibited in Figure 1. In this example, a simple block average with an averaging time of 3 s was applied to the time series of Figure 1 to simulate a time series that would have been *perceived* by a detector (e.g., a biological receptor) with a temporal response of 3 s. Note that at this slower response time, the gross features of the original concentration time series have been retained, but the fine-scale structure of rapid fluctuations has been drastically smoothed out. In particular, the concentration peaks have been reduced by a factor of 10 or more. Figure 4 exhibits the TLR for the 3 s time-averaged concentration pattern shown in Figure 3. Note that the TLR is reduced for the time-averaged concentration pattern, the more so for higher values of the toxic load exponent. In particular, the TLR is about 90 at $n = 3.5$ (e.g., a value of n appropriate for chlorine) for the 3 s time-averaged concentration pattern of Figure 3; and, in contrast, the TLR is about 2000 at $n = 3.5$ for the unfiltered concentration pattern of Figure 1.

The concomitant effect of averaging time on the toxic load ratio value is exhibited in Figure 5. Here, the averaging time of the concentration time series shown in Figure 1 was varied by smoothing with a running mean, and the block-averaged time series were used to compute the toxic load ratios for three values of n; namely, $n = 1.2$, 2.7, and, 3.5 which are appropriate for PFIB, HCN, and Cl_2, respectively [7]. Depending on the averaging time, the toxic load ratio (which represents the factor by which the toxic response is enhanced

by the concentration fluctuations beyond that provided by a constant concentration whose value is the mean of the fluctuating one) can vary by a factor of about 1000 for Cl_2, a toxic material that produces a highly nonlinear toxic response, but only by a factor of 2 or less for PFIB, a toxic material that is nearly linear (i.e., it nearly conforms to Haber's rule). Human breathing typically has a time scale of between about 1 and 10 s, but even over this range of time scales, the toxic hazard can be increased by a factor of between about 10 and 100 for Cl_2 and about 5 and 30 for HCN for the example shown.

In consequence, for toxicological assessment we require the distribution of concentration fluctuations as *perceived* by the body. From this viewpoint, the toxic load TL defined in Equation (2) is more correctly expressed as follows:

$$TL = \int_0^T \chi_{\tau_{av}}^n(t)\, dt, \tag{10}$$

where τ_{av} is some measure of the time averaging with which $\chi(t)$ must be specified for the purpose of determination of the injury factor. In particular, the constant τ_{av} should represent the averaging characteristics of the human lungs for some prescribed physical activity level. Equation (10) implies that the determination of the toxic load TL requires the prediction of the complete concentration time history $\chi_{\tau_{av}}(t)$ for an averaging time scale of τ_{av}, a task which is impossible given our current understanding of the problem. Furthermore, since $\chi(t)$ is a stochastic process, so is $\chi_{\tau_{av}}(t)$ and TL. An extremely difficult statistical problem, which will not be considered here, is to relate the statistical properties of TL to those of $\chi(t)$. Ultimately, we would like to be able to model the probability density function (pdf) of TL. The latter task is extremely difficult because this pdf must necessarily depend on the joint pdf of the time-averaged concentration for all times in the exposure interval.

Ensemble-averaged toxic load

Rather than attempt to determine the full statistical description of TL, we consider here instead the use of an ensemble-averaged toxic load and toxic load ratio defined as follows:

$$\langle TL \rangle = \int_0^T \langle \chi_{\tau_{av}}^n(t) \rangle\, dt, \tag{11a}$$

and

$$\langle TLR \rangle = \frac{\int_0^T \langle \chi_{\tau_{av}}^n(t) \rangle\, dt}{C^n T} \equiv \frac{1}{T} \int_0^T \left\langle \left(\frac{\chi_{\tau_{av}}(t)}{C} \right)^n \right\rangle dt. \tag{11b}$$

Angle brackets are used here to denote ensemble averages. In Equation (11b), C is identified with the ensemble mean concentration (viz., $\langle \chi_{\tau_{av}} \rangle \equiv C$). Furthermore, in the case of a plume generated from a point source that is emitting at a constant rate into a "stationary" atmosphere, the plume concentration measured at a fixed receptor point downwind of the release can be considered to be a stationary random process (i.e., its statistical properties do not depend on absolute time t), with the result that Equations (11a) and (11b) reduce, in this case, to

$$\langle TL \rangle = T \langle \chi^n_{\tau_{av}} \rangle, \tag{12a}$$

and

$$\langle TLR \rangle = \left\langle \left(\frac{\chi_{\tau_{av}}(t)}{C} \right)^n \right\rangle. \tag{12b}$$

For hazard assessment purposes, we propose using the ensemble-averaged toxic load (or, equivalently, the ensemble-averaged toxic load ratio) for determination of the degree of injury. In view of Equations (11a) and (11b) (or, Equations (12a) and (12b) for the steady-state case), this requires the prediction of the n-th concentration moment for an averaging time of τ_{av} (viz., $\langle \chi^n_{\tau_{av}}(t) \rangle$), a task that is considerably simpler than the prediction of the actual concentration time history required for Equation (10). In spite of this, however, it is important to note that even the prediction of the distribution of the n-th concentration moment in a dispersing plume or cloud is still an extremely difficult problem. At present, atmospheric dispersion models exist only for the prediction of the first- and second-order concentration moments (i.e., the mean and mean-squared concentration), whereas the ensemble-averaged toxic load or toxic load ratio for a material with toxic load exponent n requires knowledge of the n-th concentration moment. In general, n does not necessarily have to equal either 1 or 2.

Relationships between higher concentration moments

Because concentration moments higher than the second cannot be estimated reliably at present, it is necessary to consider an alternative procedure for the determination of the ensemble-averaged TL (or, TLR) required for the biological model. To this purpose, we will try to ascertain whether there are any relationships between the higher-order moments of concentration. In particular, we will investigate whether the second concentration moment (e.g., the mean-squared concentration which can be predicted reasonably well) exhibits any relationships with the higher concentration moments. A theoretical investigation of

the relationships between the higher concentration moments is not possible at our current knowledge level of the problem. Consequently, we will try to determine these relationships (if they exist at all) using experimental observations of turbulent dispersion that cover a wide range of downwind distances and atmospheric stabilities.

To this purpose, we will use a comprehensive concentration fluctuation data set that covers a very wide range of experimental conditions in order to test various relationships between the higher moments of concentration. A comprehensive set of tracer experiments studying concentration fluctuations in plumes and clouds dispersing near the surface was undertaken using fast-response photoionization detectors (cf. Chandler [16]) as the concentration analyzer. The latter set of experiments formed part of a cooperative Concentration Fluctuation Experiments (CONFLUX) project involving defence research establishments in the United States, United Kingdom, and Canada. The overall scientific objective of the field campaigns was the detailed study of the fine-scale structure and dynamics in dispersing plumes in relationship with the turbulence structure of the atmosphere. All field experiments were conducted near Tower Grid on U.S. Army Dugway Proving Ground, Utah (40°06' N, 112°59' W), about 2 km west of Camel Back Ridge on the edge of the Great Salt Lake Desert. The terrain was uniform and homogeneous, covered with short grass interspersed with a few low shrubs that are less than 0.5 m in height, providing an upwind fetch that is absolutely uniform and unobstructed for 5 km or more.

The data that we will use for studying the relationships between the higher concentration moments were collected during the September 1991, November 1992, May 1993, and May 1994 phases of the CONFLUX project. The results of the concentration data analysis from the CONFLUX project have been described in detail in a series of papers ([17], [18], [19], [20], [21], [22], [23], [24], [25]) to which the reader is referred for more detail. For the present study, we extracted 1107 individual CONFLUX concentration time series from a large number of different experiments covering a very wide range of atmospheric conditions. All the experiments considered here involved the continuous and controlled release of propylene (C_3H_6) tracer gas into the atmosphere. The measurements were made at downwind fetches x of between 12.5 and 1000 m from the source, under moderately convective to extremely stable atmospheric conditions in which mechanical turbulence was suppressed by the stable stratification. The concentration time series were measured over a wide range of receptor positions in both lateral and vertical cross-sections through the plume—lateral plume positions varied from the mean-plume centerline at $y/\sigma_y = 0$ to the extreme plume

fringes at $y/\sigma_y \approx \pm 4$, where y is the crosswind distance from the mean-plume centerline and σ_y is the mean-plume dispersion; and, vertical plume positions ranged from 0.5 to 16 m height above ground. The source was placed at heights above ground ranging from 1 to 5 m. The sampling time for the concentration data ranged from 16 to 64 min for the experiments conducted in September 1991, and 30 or 35 min for the experiments conducted in November 1992, May 1993, and May 1994.

We consider here the various moments of the normalized concentration, χ/C, where χ is the instantaneous concentration and C is the mean concentration. Let M_n denote the n-th moment of the normalized concentration, viz.

$$M_n \equiv \left\langle \left(\frac{\chi}{C}\right)^n \right\rangle .$$

Note that $M_1 = 1$, and $M_2 = i^2 + 1$ where $i \equiv \sigma_\chi/C$ is the relative fluctuation intensity, and σ_χ is the concentration standard deviation. Figure 6 presents scatterplots of various higher-order concentration moments M_n (n = 3, 4, 5, 6, 7, and 8) versus the second-order concentration moment M_2 obtained from the 1107 CONFLUX concentration time series selected for this analysis. Notice in Figure 6 that there is more scatter in the plots of M_n versus M_2 for the higher values of n. This scatter appears to be random, and is most likely attributed to the difficulty of measuring higher moments due to enhanced sampling errors (viz., the standard errors of the measured moments rapidly increase with order). Nevertheless, each of these scatterplots appears to exhibit a collapse of the data onto a single curve. It is noteworthy that the collapse here occurs over five decades in M_2. The remarkably systematic dependencies of M_n ($n > 2$) on M_2, exhibited by the data in Figure 6, is all the more interesting because it covers a very large range in plume positions and atmospheric stratification. In particular, the collapse of M_n ($n > 2$) on M_2 provides compelling evidence that the concentration pdf can be represented (approximately or better) with 2 parameters; namely, one for location (e.g., mean concentration) and one for scale (e.g., root-mean-squared (rms) concentration).

It is of interest to compare the moment relationships between M_n ($n > 2$) and M_2 shown in Figure 6 with a simple model for these relationships, namely, the exponential pdf model. The exponential pdf for intermittent concentrations is a two-parameter pdf that has the following form:

$$f(\chi) = \frac{\gamma^2}{C} \exp\left(-\frac{\gamma\chi}{C}\right) + (1-\gamma)\delta(\chi), \qquad (13)$$

where $\delta(\chi)$ is the Dirac delta function, and γ is the intermittency factor defined as the fraction of the total time that non-zero concentrations are observed. Hence, the discrete part of the distribution in Equation (13) arises from the fact that χ admits the value 0 with probability $(1-\gamma)$. The concentration pdf exhibited in Equation (13) is composed of a mixed fluid part (e.g., the exponential function) that models the in-plume mixing of eddies that contain the scalar contaminant, and an unmixed ambient fluid part (e.g., the Dirac delta function) that models the plume meandering contribution that produces the intermittent periods of zero concentration for a fraction of time $(1-\gamma)$. The relationship between the higher concentration moments and the second concentration moment for the exponential pdf can be summarized as follows:

$$\left\langle \left(\frac{\chi}{C}\right)^n \right\rangle = \frac{\Gamma(n+1)}{2^{n-1}} \left\langle \left(\frac{\chi}{C}\right)^2 \right\rangle^{n-1}, \qquad n > 2, \tag{14}$$

where $\Gamma(x)$ is the gamma function.

The present experimental data (cf. Figure 6) clearly show that there are strong correlations between the various normalized higher-order concentration moments and the normalized second-order concentration moment (e.g., normalized mean-squared concentration). To test whether the exponential pdf model can be used to predict the observed relationships between the various higher concentration moments and the second concentration moment, we have plotted in Figure 6 the moment relationships predicted by the exponential pdf model (cf. Equation (14)). It is noteworthy that the exponential pdf appears to provide a very good fit to the concentration moment relationships over the full range of behavior covered by the observed concentration data. Hence, the present experimental data clearly show that there are strong correlations between the various normalized higher-order concentration moments and the normalized second-order concentration moment (e.g., the normalized mean-squared concentration), and that these relationships can be adequately modeled using the simple exponential pdf model.

The results of Figure 6 show clearly that the higher-order concentration moment relationships provided by the exponential pdf (cf. Equation (14)) are valid (approximately or better) for the unfiltered concentration data. However, the prediction of the ensemble-averaged toxic load and toxic load ratio (cf. Equations (11) and (12)) requires information on the concentration moment relationships as perceived by the body (viz., the concentration moment relationships as measured with an averaging time τ_{av}). In consequence, the

question that needs to be addressed is as follows: Are the concentration moment relationships provided by the exponential pdf model (cf. Equation (14)) valid for the time-averaged concentration data? To address this question, we have computed the n-th order normalized concentration moments,

$$M_n(\tau_{\rm av}) \equiv \left\langle \left(\frac{\chi_{\tau_{\rm av}}}{C} \right)^n \right\rangle ,$$

for the CONFLUX concentration time series obtained by smoothing them using a running mean with averaging time $\tau_{\rm av}$. Figure 7 illustrates scatterplots of the various higher moments of concentration $M_n(\tau_{\rm av})$ $(n = 3, 4, \ldots, 8)$ versus the second moment of concentration $M_2(\tau_{\rm av})$ for 3 different averaging times $\tau_{\rm av}$; namely, for $\tau_{\rm av} = 0.1$, 1, and, 3 s. Also, displayed in Figure 7 are the predictions for these moment relationships provided by the exponential pdf model; namely,

$$\left\langle \left(\frac{\chi_{\tau_{\rm av}}}{C} \right)^n \right\rangle = \frac{\Gamma(n+1)}{2^{n-1}} \left\langle \left(\frac{\chi_{\tau_{\rm av}}}{C} \right)^2 \right\rangle^{n-1}, \qquad n > 2. \tag{15}$$

Figure 7 shows that the relationships between the various higher moments of concentration remain invariant with respect to the averaging time. In particular, the exponential pdf model summarized in Equation (15) appears to provide a good fit to the moment relationships as perceived over a range of averaging times (and, certainly for averaging times $\tau_{\rm av}$ that are approximately less than or equal to the integral time scale $T_{\rm c}$ of the concentration fluctuations). Hence, although with increasing averaging time the structure of the concentration time series becomes progressively smoothed out resulting in reductions in the higher moments of concentration, the general indications suggest that smoothing tends to preserve the relationships between the higher concentration moments (e.g., at least for $\tau_{\rm av} \lesssim T_{\rm c}$). Using this fact, the ensemble-averaged toxic load ratio can be represented now as follows on insertion of Equation (15) into Equation (11b):

$$\begin{aligned} \langle TLR \rangle = \frac{1}{T} \int_0^T \left\langle \left(\frac{\chi_{\tau_{\rm av}}(t)}{C} \right)^n \right\rangle dt &= \frac{\Gamma(n+1)}{2^{n-1}} \frac{1}{T} \int_0^T \left\langle \left(\frac{\chi_{\tau_{\rm av}}(t)}{C} \right)^2 \right\rangle^{n-1} dt, \\ &= \frac{\Gamma(n+1)}{2^{n-1}} \frac{1}{T} \int_0^T \left(i^2_{\tau_{\rm av}}(t) + 1 \right)^{n-1} dt, \end{aligned} \tag{16}$$

where $i_{\tau_{\rm av}}$ denotes the relative fluctuation intesity determined for the averaging time $\tau_{\rm av}$. Once the ensemble-averaged TLR is determined in accordance to Equation (16), the ensemble-averaged TL can be determined as

$$\langle TL \rangle = \langle TLR \rangle C^n T. \tag{17}$$

In other words, the actual toxic load is the simply the toxic load determined with the mean concentration and multiplied by the toxic load ratio or enhancement factor, the latter of which accounts for the effect of concentration fluctuations.

Procedure for estimation of toxic load and adverse effects

We summarize the procedure for estimation of toxic load and adverse effects in the form of an algorithm:

1. Specify the source characteristics (e.g., material properties, release rate, source location, source size, etc.) and the meteorological characteristics (e.g., wind speed at a reference height, roughness length, atmospheric stability class, etc.).

2. Calculate the mean concentration and concentration variance fields for the given release using an atmospheric dispersion model.

3. Specify an appropriate averaging time τ_{av} (e.g., averaging time imposed by the human lungs), and calculate the effect of the averaging time on the concentration variance determined in step 2.

4. Use Equation (16) to determine the ensemble-averaged toxic load ratio.

5. Use Equation (17) to determine the ensemble-averaged toxic load.

6. Use the result determined in step 5 to calculate the fraction of an exposed population that will suffer a specified adverse effect. The latter is obtained from the probit relationship summarized in Equation (7).

We emphasize that the ensemble-averaged TLR can be determined from a knowledge of only the normalized mean-squared concentration as measured with an averaging time of τ_{av}, with the latter time scale chosen to match some characteristic of the human lungs. This requires that three components be explicitly specified: namely, the mean concentration, the mean-squared concentration, and the mean-squared concentration obtained with an averaging time of τ_{av}. Our current understanding of turbulent diffusion enables all three of these components to be modelled.

Gaussian plume (or puff) models are available for the determination of the mean concentration field in a dispersing plume. As the name implies, a Gaussian form for the mean

concentration is assumed with the horizontal and vertical spreads of the plume (or puff) taken from empirical formulae for their dependence on downwind distance (or travel time), atmospheric stability, surface roughness, etc. (see Pasquill and Smith [26]). Another popular type of model that can be used to estimate the mean concentration field is that of random walks which attempt to mimic the motion of individual "marked" particles in turbulence through an assumed Markov process. The discovery of the well-mixed criterion by Thomson [27] has provided a rigorous technique for the prediction of the mean concentration field in both homogeneous and inhomogeneous turbulence.

Concentration variance (or, equivalently, mean-squared concentration) can be modelled using a meandering version of the Gaussian plume model in which the instantaneous cross-section of concentration and a distribution for plume meandering are assumed (e.g., Gifford [28], Sawford and Stapountzis [29], Yee *et al.* [30]). Sykes *et al.* [31] applied a second-order closure model for prediction of the concentration variance in a dispersing plume. A practical model for atmospheric dispersion based on simplifications of a second-order closure model along with a Gaussian shape assumption has been described by Sykes *et al.* [32]. The latter model provides a prediction of the statistical variance in the concentration field in addition to the mean concentration.

Finally, the effect of averaging time on the concentration variance has been considered by Wilson and Simms [33] who made the assumption that the concentration fluctuations follow a Markov process, and used this to show that

$$\frac{\langle \chi'^2_{\tau_{av}} \rangle}{\langle \chi'^2 \rangle} = \frac{1}{(1 + \tau_{av}/T_c)}, \tag{18}$$

where $\chi' \equiv (\chi - C)$ is the concentration fluctuation, $\langle \chi'^2 \rangle$ is the concentration variance, and $\langle \chi'^2_{\tau_{av}} \rangle$ is the concentration variance perceived at an averaging time of τ_{av}. In Equation (18), T_c is the integral time scale of the concentration fluctuations defined by

$$T_c = \int_0^\infty R(\tau)\, d\tau,$$

where $R(\tau)$ is the autocorrelation function of the concentration fluctuations (τ is the correlation lag time). A parameterization of the integral time scale for the surface concentration fluctuations has been suggested by Sykes [34]. It is noted that the averaging imposed by the human lungs on concentration fluctuations depends critically on the concentration integral time scale. For example, at short range in unstable conditions, the highest concentration

peaks have very short durations (and, hence, small integral time scales), and may consequently not be very important in practical applications because concentration fluctuations shorter than about 1 s are averaged in the lungs. However, under stable conditions, the peak concentrations have much longer durations and are also higher relative to the mean concentration (e.g., fluctuation intensities are higher). Under the latter condition, the integral time scales of concentration are longer and, as a consequence, the concentration fluctuations would not be smoothed out in the lungs to the same extent.

A NUMERICAL EXAMPLE

How does the added realism of including the effects of concentration fluctuations in the toxic load estimates change the hazard resulting from a CBW agent release? The best way to answer this question is to consider a simple example calculation. Typically, it has been found that relative fluctuation intensities of concentration in a dispersing plume fall within the range from about 0.5 to 10, for averaging times of about 1 s ([17], [19], [23], [35]). Lateral cross-sections of fluctuation intensity increase from a value of about 1 at the mean-plume centerline to about 10 towards the edge or fringe of the plume as the mean concentration decreases more rapidly than the concentration variance ([17], [19]). In the alongwind direction, the fluctuation intensity on the plume centerline decreases rapidly with distance close to source, but then approaches an apparently near-constant, non-zero value (e.g., about 1) at longer range [35].

We have computed the ensemble-averaged toxic load ratio (cf. Equation (16)) for $0.5 \lesssim i_{\tau_{av}} \lesssim 10$ for 3 different values of the toxic load exponent n; namely, $n = 1.2$, 2.7, and 3.5 which are appropriate for PFIB, HCN, and Cl_2 gas, respectively. The latter range of values for n roughly spans the range from 1 to 3.5 measured for a wide variety of toxic gases [7]. Figure 8 shows the ensemble-averaged TLR for this calculation and, in essence, summarizes the enhancement factor in the toxic response due to concentration fluctuations over the range of fluctuation intensities in concentrations expected within a dispersing plume and over the range of values for n measured for most toxic gases.

Near the mean-plume centerline where $i_{\tau_{av}} \approx 1$, the results of Figure 8 indicate that the increase in toxicity lies between about 1 and 10 for a range of n between about 1 and 3.5. However, towards the plume fringes where $i_{\tau_{av}}$ is large (typically between about 5 and 10), an increase in toxicity of more than 1000 times over that of the constant concentration

case is possible for high n. The net effect of these results is that toxicological assessment based on mean concentration only will result in a serious underestimation of the severity of the toxic effect for highly nonlinear toxic materials. Furthermore, including the effects of concentration fluctuations in the toxicological assessment would increase the hazard area produced by the atmospheric release of CBW agent. In particular, the influence of crosswind meandering is evident from the results of Figure 8. Large crosswind meandering will bring high centerline peak concentrations over to receptor points far off the mean-plume axis, causing a considerable widening of the toxic load contours at a SLOE.

SUMMARY AND CONCLUSIONS

In a hazard assessment which is taken to the point of determining specific effects to military personnel that are exposed to a release of CBW agents, it is frequently necessary to estimate injury (e.g., incapacitation, lethality, etc.) in the area around the CBW agent source. In order to accomplish this difficult task, it is necessary to be able to estimate first the intensity of the physical effect (e.g., toxic load as a function of distance), and then the probability of injury as a function of this physical intensity. In this study, we present a simple, rational methodology for estimating toxic effects of CBW agents that accounts for the following: (1) nonlinearity of the dose-time response of biological receptors; (2) natural variability of CBW agent dispersion in a turbulent atmosphere which will produce a range of mean and fluctuating values in concentration; and, (3) response of an exposed population of varying susceptibility to the toxic load.

In this paper, we have shown that many basic statistical ideas are central both for a scientific understanding of atmospheric dispersion required for estimating the intensity of the physical effect (e.g., the physical sciences model), and for the proper quantification of the relationship between the causative, or injury, factor and the probability of injury required for determination of the fraction of an exposed population that would be affected by a given release (e.g., the biological sciences model). Special emphasis has been placed here on developing quantitative methods for dealing with the effect of a fluctuating concentration on the nonlinear toxic load used for predicting adverse human response. In particular, it is shown that prediction of the nonlinear toxic load requires explicit knowledge of the statistical distribution of the fluctuating concentration in a dispersing plume. We have shown, using an extensive new data set of instantaneous concentration measurements from the CONFLUX project, how various statistical characteristics can be determined and assigned

to the fluctuating concentrations and how the latter information can be utilized to provide a simple, practical method for estimating the ensemble-averaged toxic load in the presence of concentration fluctuations.

The example calculations using the simple model have shown that peak concentrations caused by plume meander and inhomogeneous in-plume mixing play an important role in determining the degree of injury for toxic materials with a nonlinear biological response behavior. In particular, actual measurements have shown that the fluctuation intensity (i.e., the ratio of the standard deviation of concentration to mean concentration) perceived at a time scale of about 1 s (e.g., a time scale comparable to the response of the human lungs) varies in the range from about 0.5 to 10 depending on plume position. For toxic load exponents ranging from between 1 to 3.5 (viz., a range which covers that observed for a wide variety of toxic gases) and the range of fluctuation intensities expected to be encountered in a dispersing plume, the ensemble-averaged toxic load ratio predicted by the model was found to vary from about 1 to greater than 1000. The enhancement in the toxic load predicted by the model reinforces the importance of paying careful attention to plume meandering effects that can reduce mean-plume concentrations while increasing peak fluctuation levels at the plume fringes. The latter effects can increase significantly both the crosswind and downwind extents of hazard zones for certain CBW agents.

We contend that the above results show the scientific case for using probabilistic/statisical methods for military hazard assessment, rather than traditional deterministic methods. With regard to the problem addressed in this paper, there is one significant area where further modelling work is required for practical application. The ensemble-averaged (mean) toxic load was used for making quantitative estimates for biological response to toxic materials, largely because our current state of knowledge of quantities required for the prediction of the mean toxic load is relatively certain. However, a more complete scheme for hazard assessment would need to account for the inherent or natural variability in the nonlinear toxic load resulting from the concentration fluctuations. A difficult statistical problem that remains unsolved is determination of the relationship between the statistical properties of the toxic load to those of the fluctuating concentration. In particular, an ambitious line of future research would be to develop a model for the probability distribution of the toxic load itself, and use this information in the toxicological assessment in place of the mean toxic load used here. However, it is important to note that the latter problem is extremely difficult because the probability distribution of the toxic load is not expressible in

terms of the one-point probability distribution of the instantaneous concentration itself (for which reliable information is available at present), since it requires a knowledge about what is happening at many points in the plume simultaneously and, hence, of joint probability distributions of concentration (for which no information is available at present).

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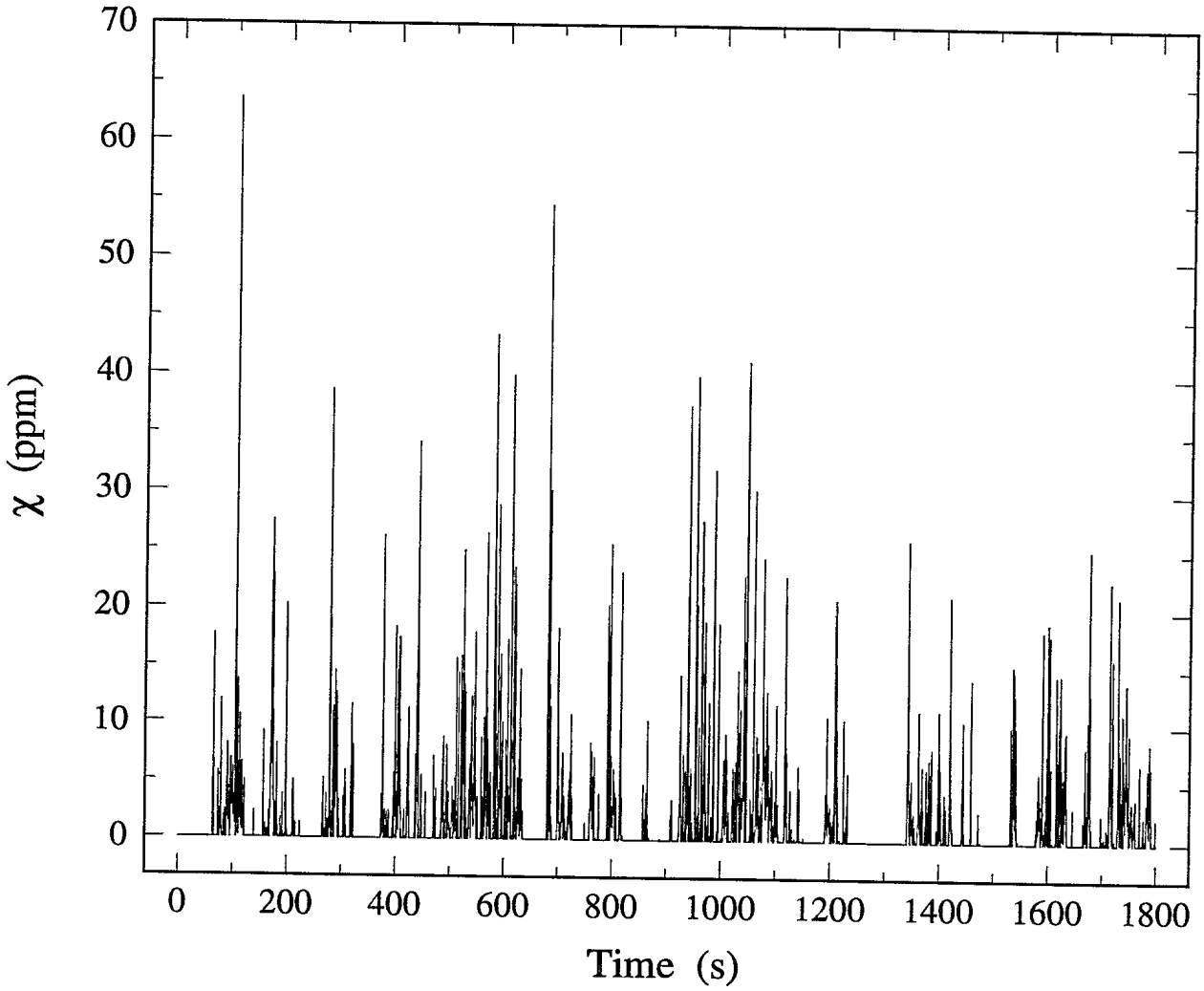

Figure 1

An example of 30 min of a concentration time series illustrating plume intermittency (periods of zero concentration) and in-plume fluctuations (fine-scale internal structure). The time series was measured near the mean-plume centerline at a downwind distance of 60 m for a source at 2.5 m height.

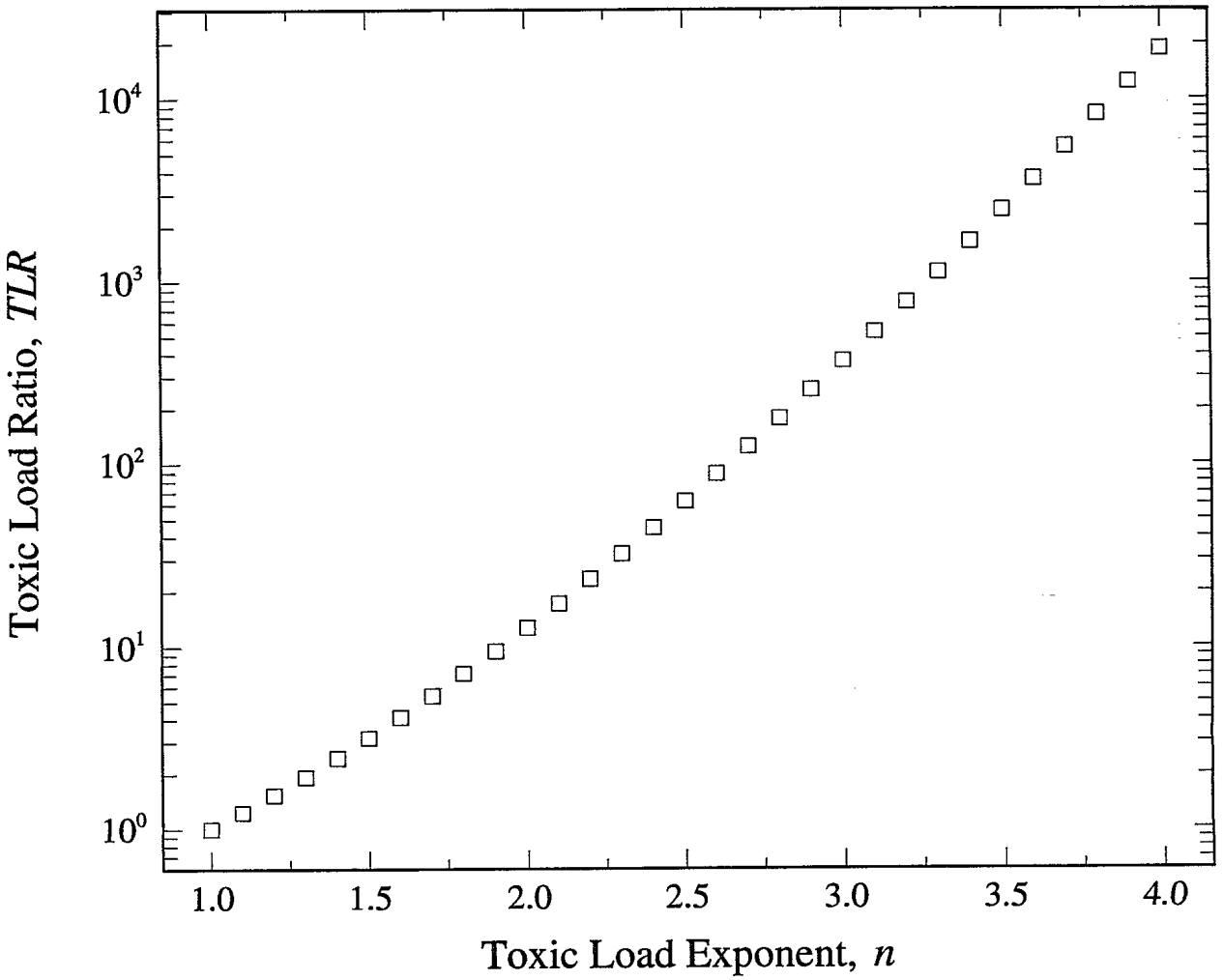

Figure 2

Toxic load ratio, TLR, plotted against the toxic load exponent, n, for exposure to the concentration pattern exhibited in Figure 1.

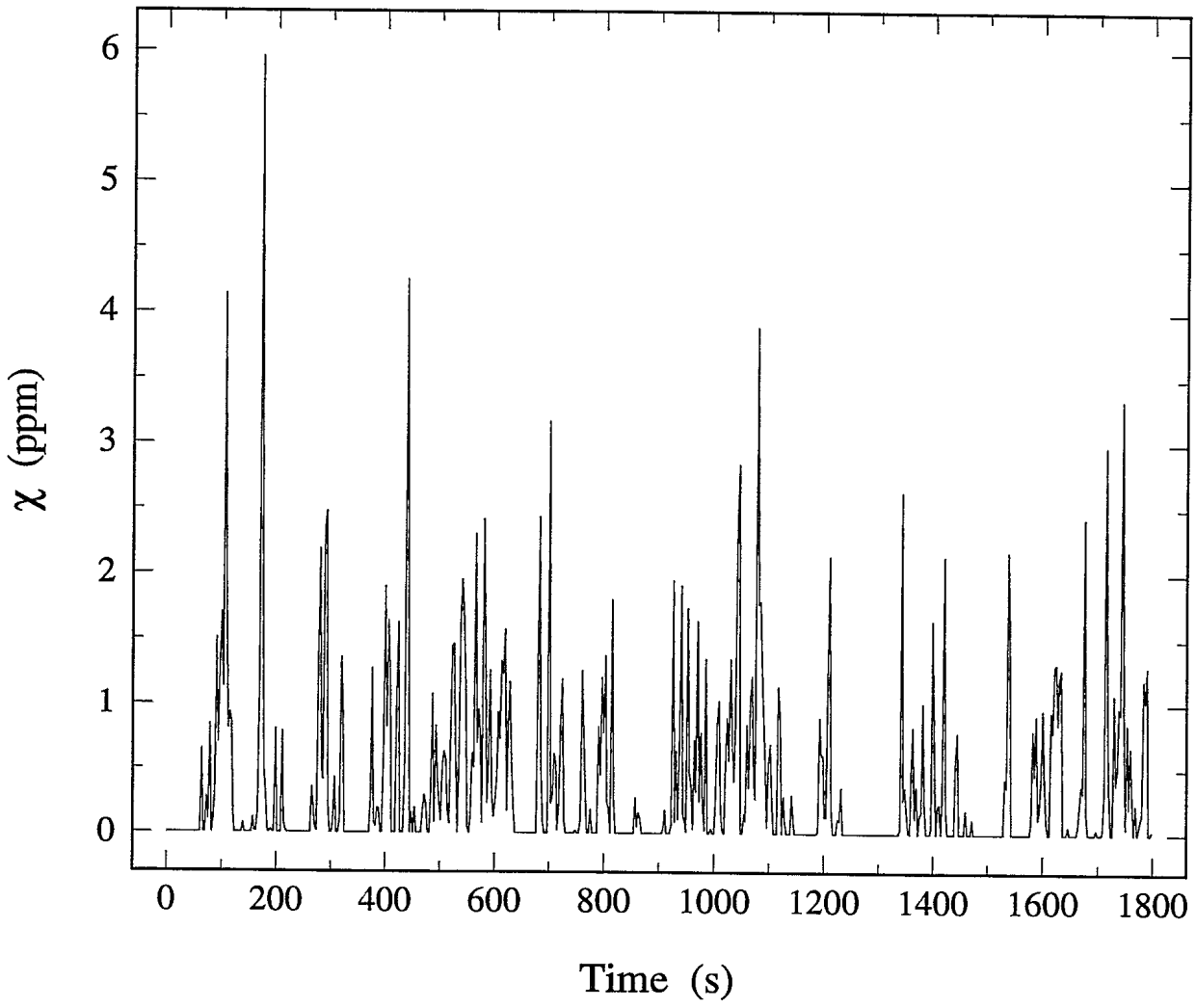

Figure 3

Sample concentration time series of Figure 1 smoothed with a running mean with an averaging time of 3 s.

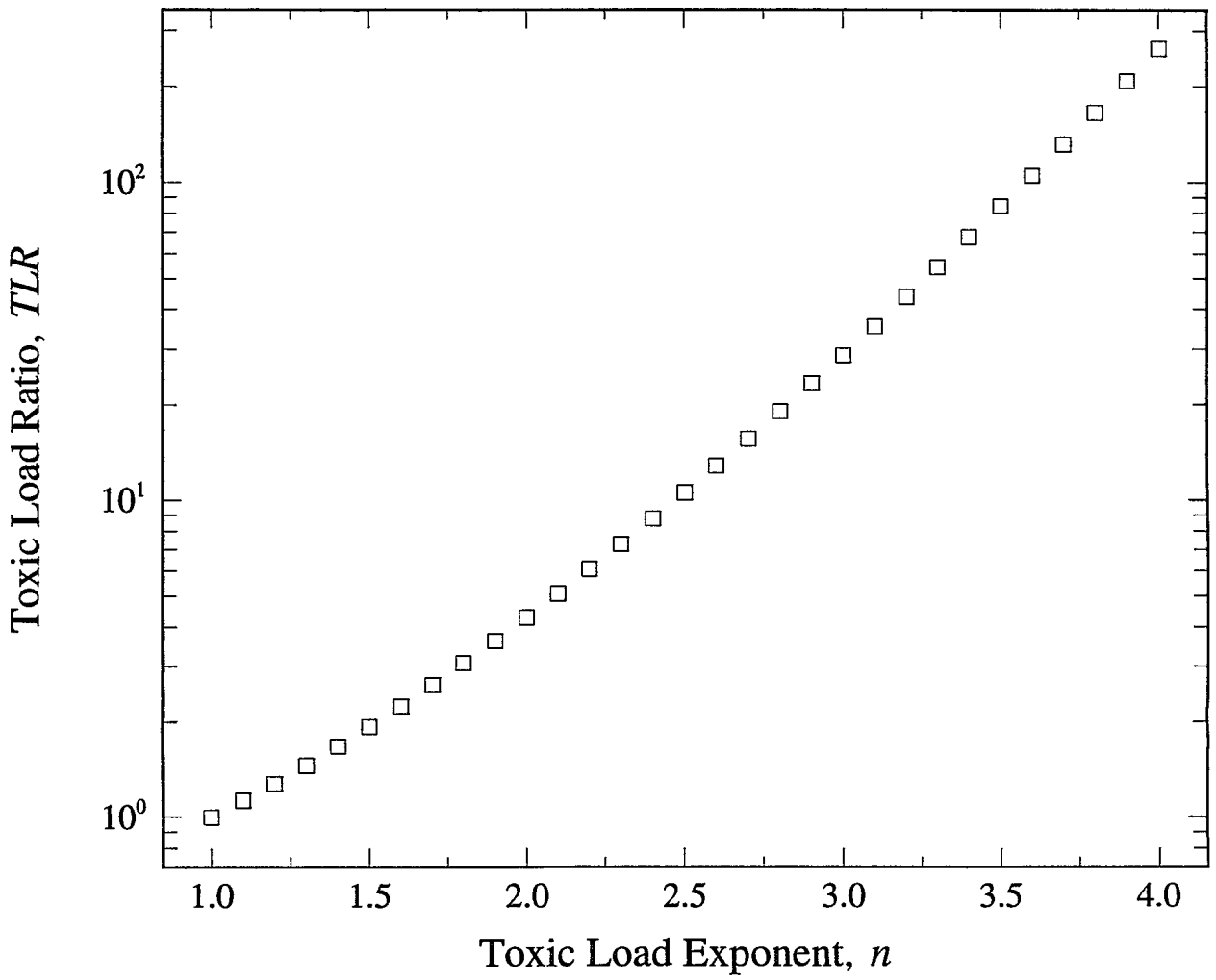

Figure 4

Toxic load ratio, TLR, plotted against the toxic load exponent, n, for exposure to the time-averaged concentration pattern exhibited in Figure 3.

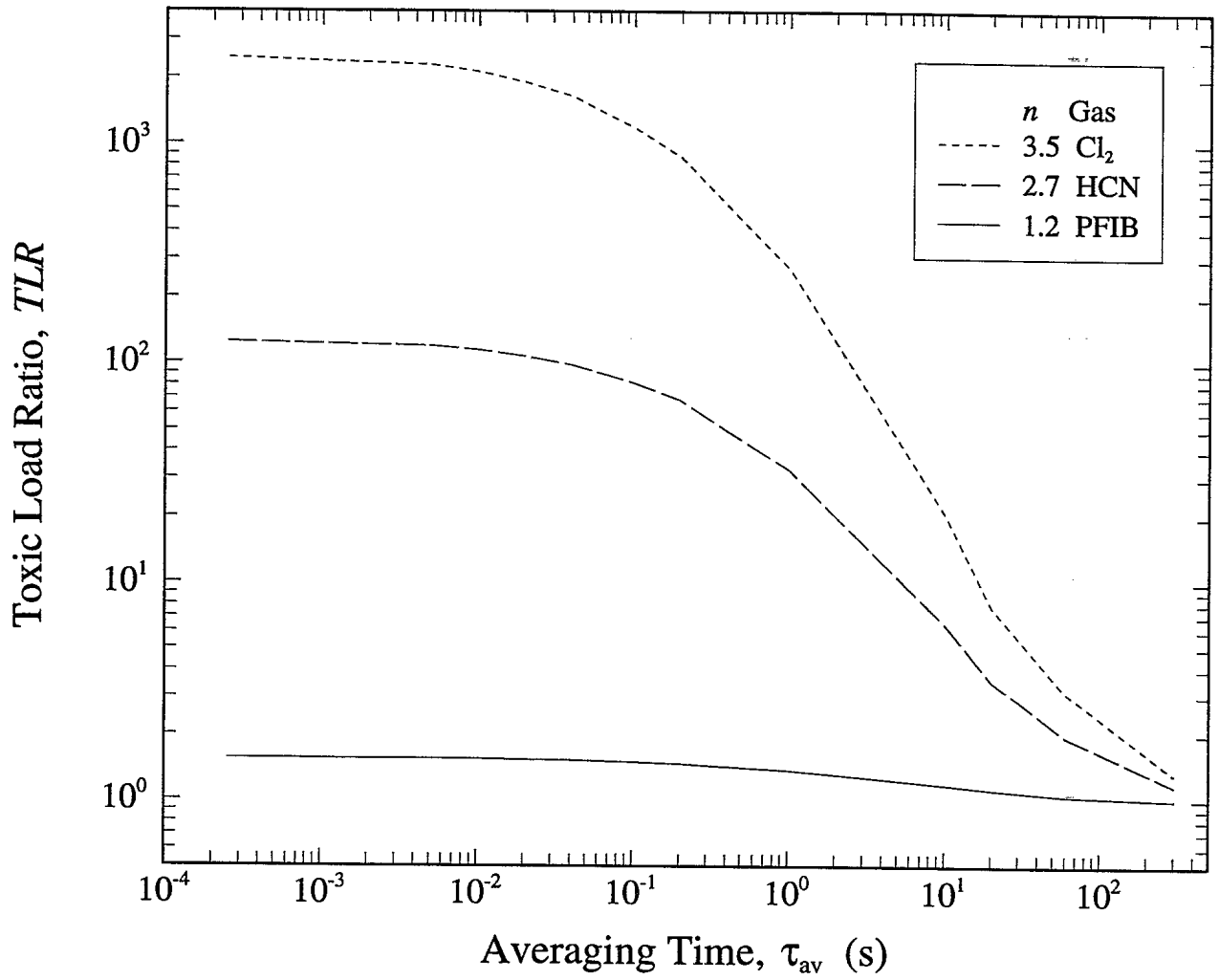

Figure 5

Toxic load ratio, TLR, plotted against the averaging time, τ_{av}, for three different values of the toxic load exponent n. The results were obtained by smoothing the concentration time series shown in Figure 1 with a series of running mean filters with averaging times of τ_{av} s.

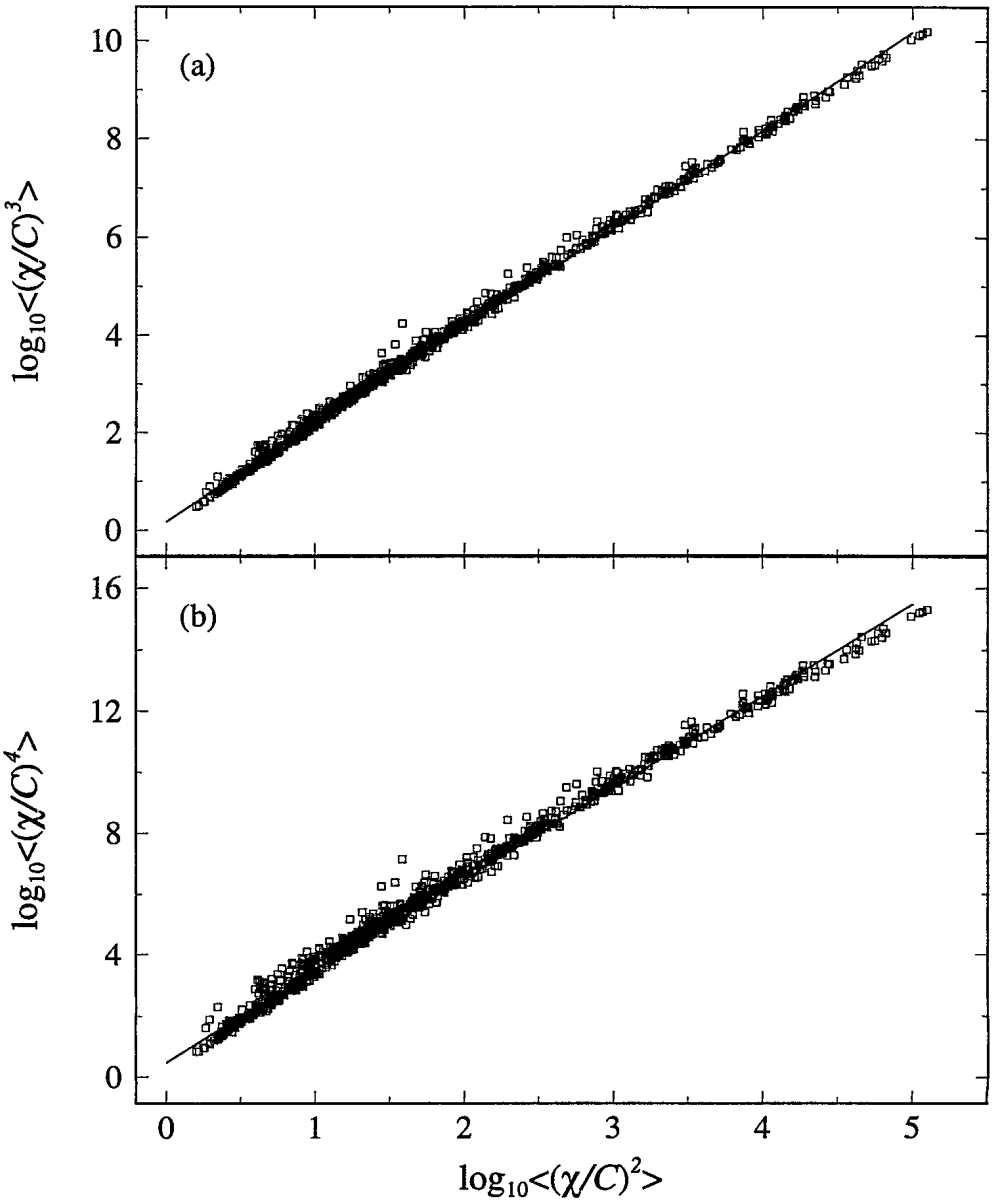

Figure 6

Double logarithmic scatterplots of (a) M_3 versus M_2 and, (b) M_4 versus M_2. The solid curves show the analytically predicted relationships between these normalized concentration moments provided by the exponential pdf model.

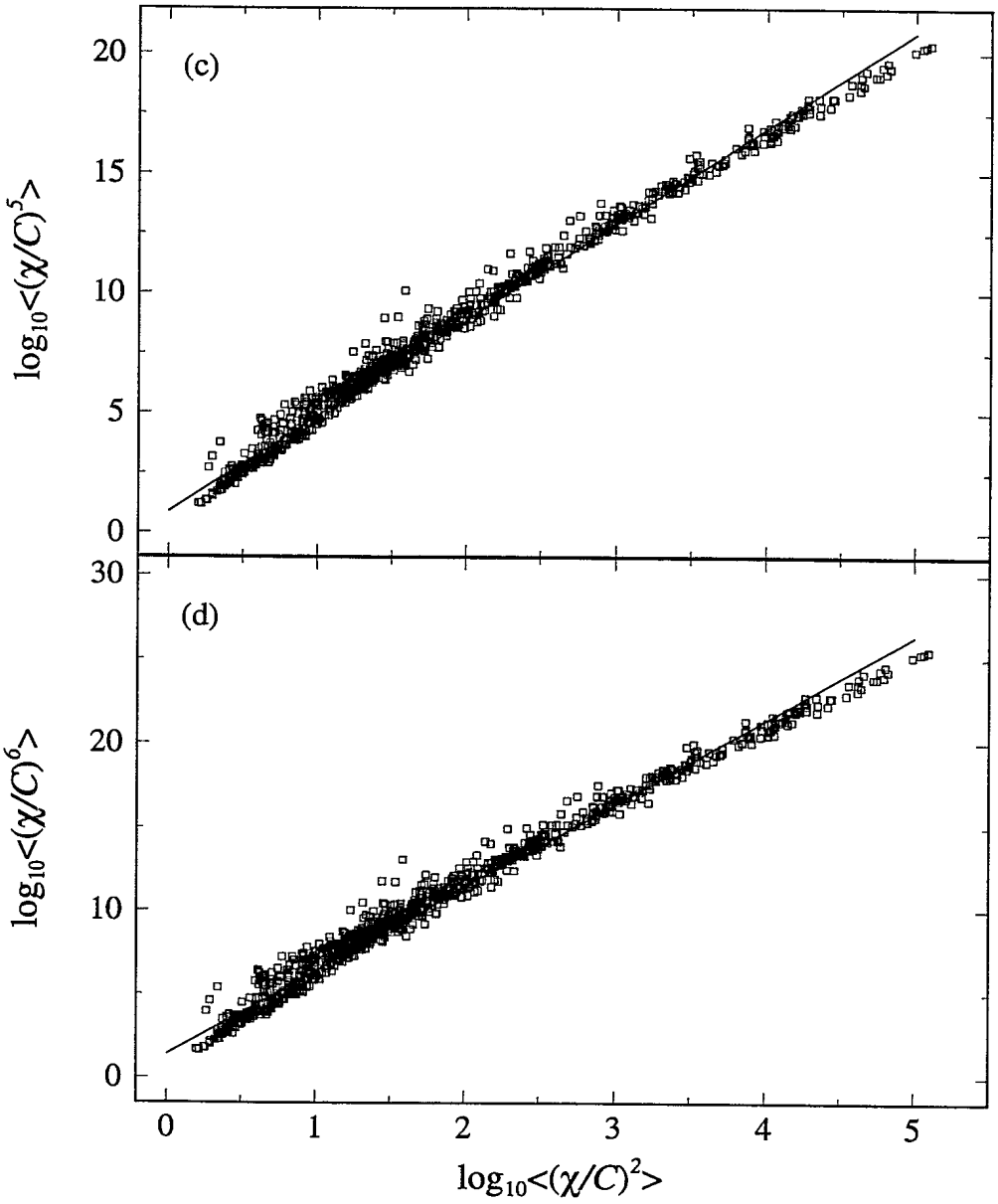

Figure 6

Double logarithmic scatterplots of (c) M_5 versus M_2 and, (d) M_6 versus M_2. The solid curves show the analytically predicted relationships between these normalized concentration moments provided by the exponential pdf model.

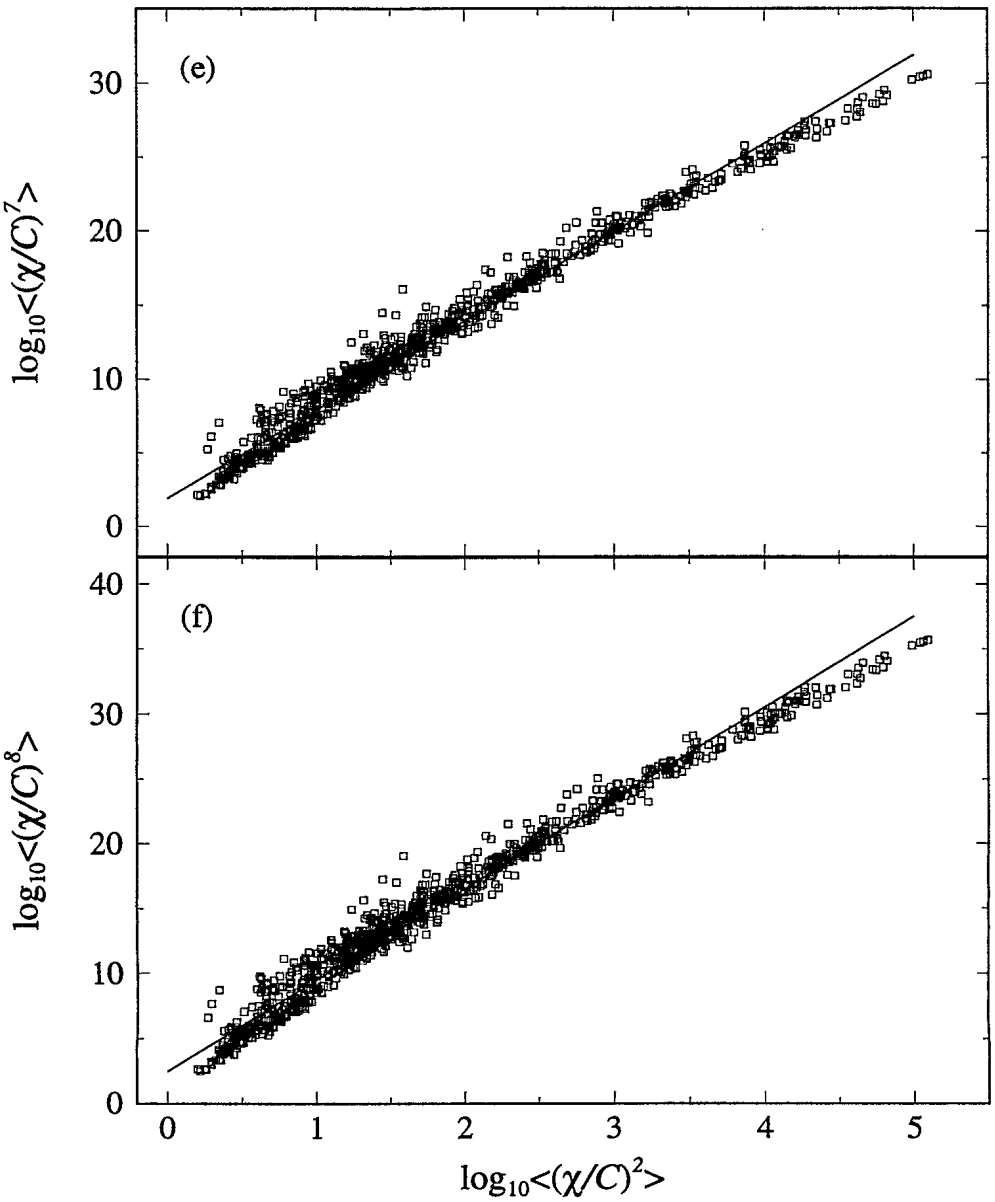

Figure 6

Double logarithmic scatterplots of (e) M_7 versus M_2 and, (f) M_8 versus M_2. The solid curves show the analytically predicted relationships between these normalized concentration moments provided by the exponential pdf model.

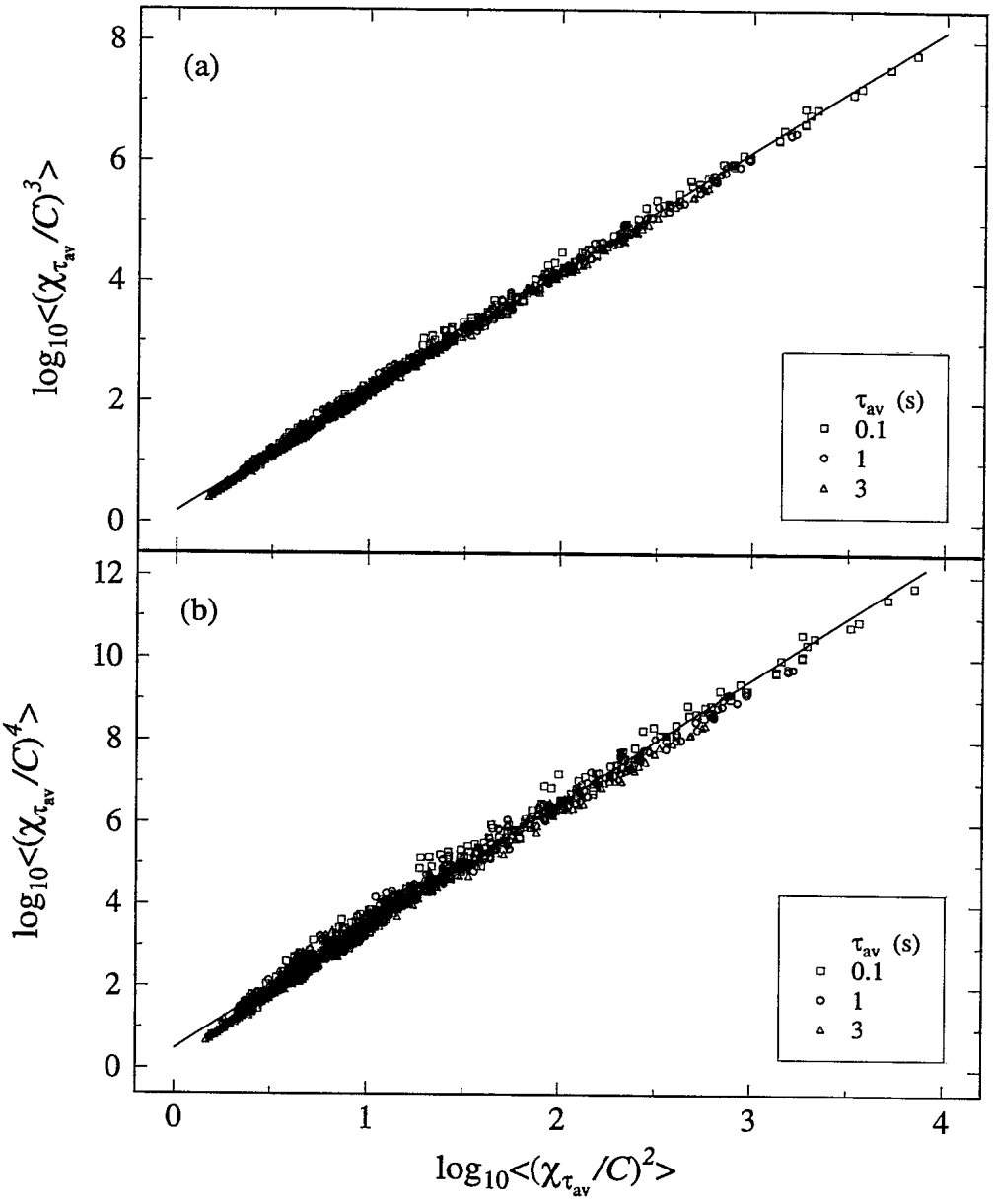

Figure 7

Double logarithmic scatterplots of (a) M_3 versus M_2 and, (b) M_4 versus M_2 for 3 different averaging times τ_{av}. The solid curves show the analytically predicted relationships between these normalized concentration moments provided by the exponential pdf model.

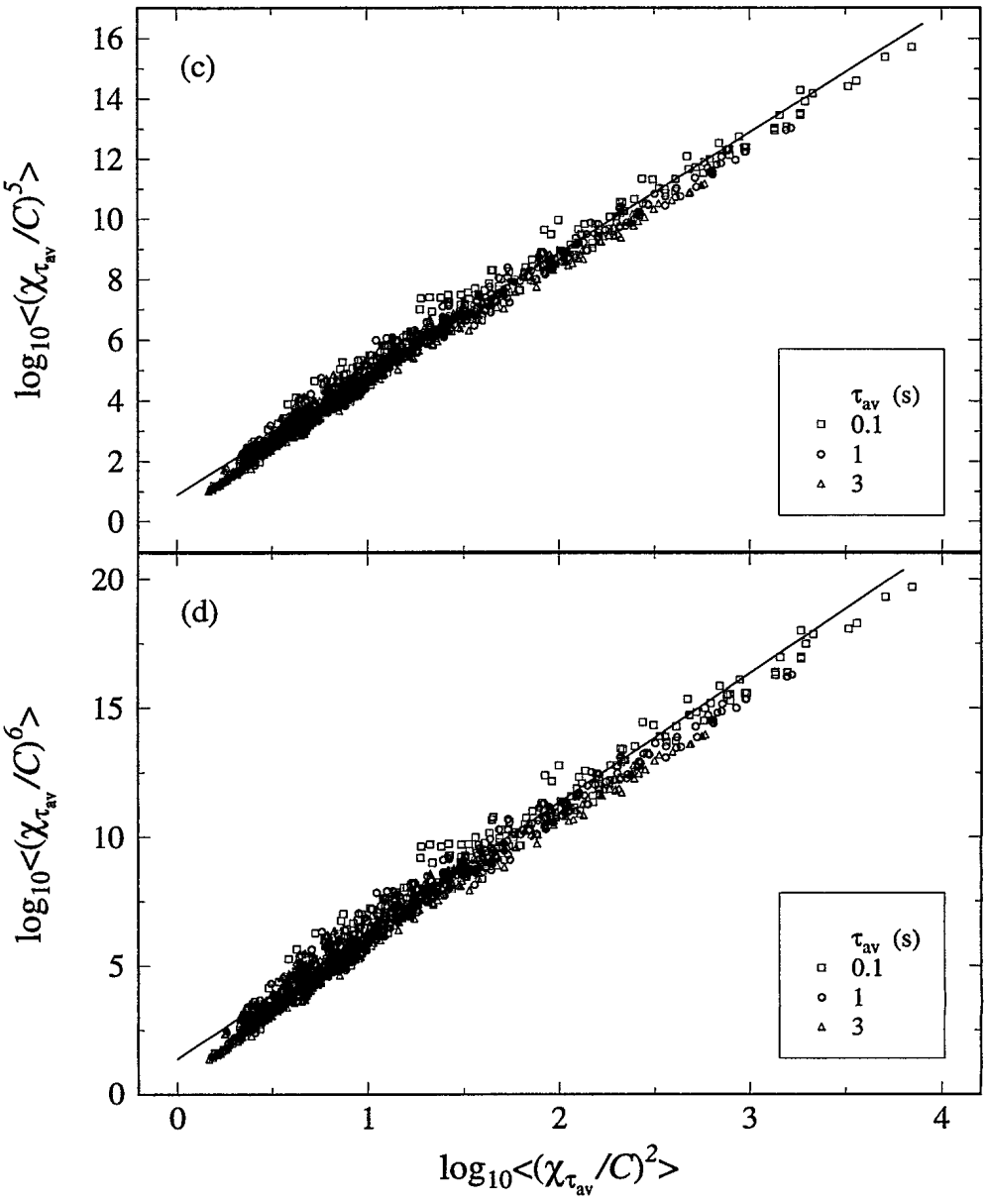

Figure 7

Double logarithmic scatterplots of (c) M_5 versus M_2 and, (d) M_6 versus M_2 for 3 different averaging times τ_{av}. The solid curves show the analytically predicted relationships between these normalized concentration moments provided by the exponential pdf model.

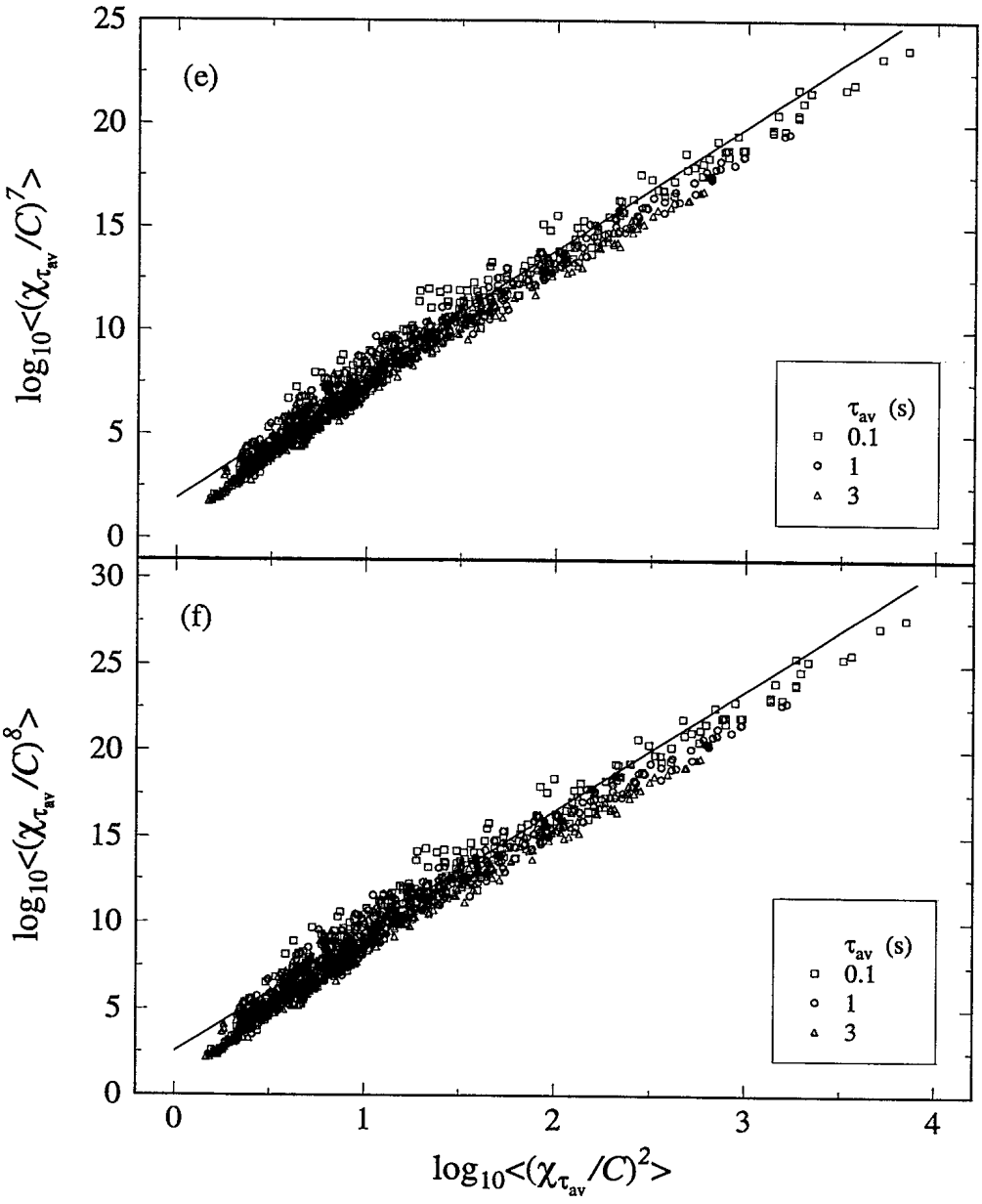

Figure 7

Double logarithmic scatterplots of (e) M_7 versus M_2 and, (f) M_8 versus M_2 for 3 different averaging times τ_{av}. The solid curves show the analytically predicted relationships between these normalized concentration moments provided by the exponential pdf model.

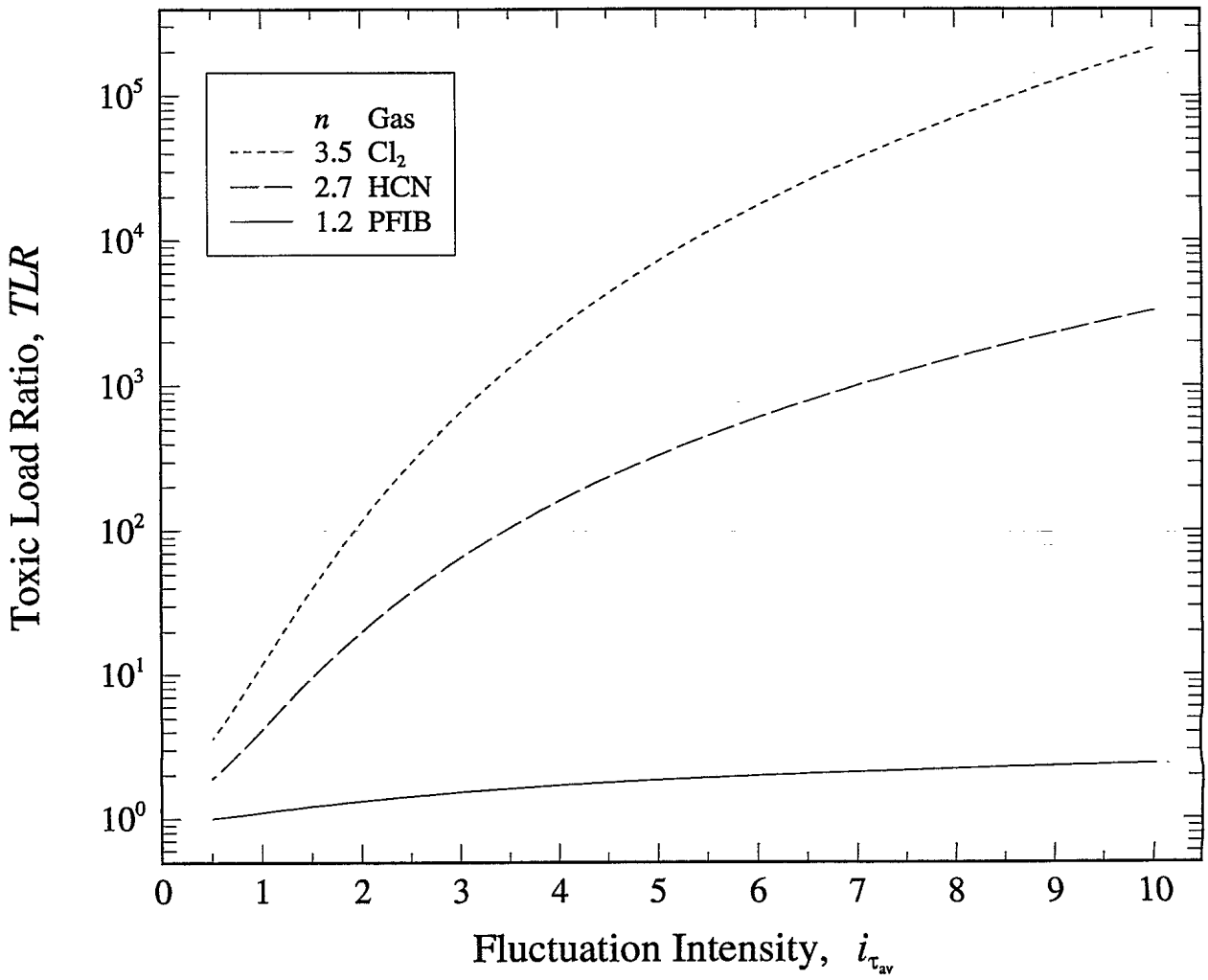

Figure 8

Plot of the toxic load ratio TLR as a function of the fluctuation intensity $i_{\tau_{av}}$ for three different values of the toxic load exponent, n. The range of values of $i_{\tau_{av}}$ shown here are appropriate for an averaging time τ_{av} of about 1 s, which corresponds roughly to the time scale appropriate for the response of the human lungs.

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A rational, consistent, and simple methodology for the estimation of the degree of injury or damage to exposed military personnel around a chemical or biological warfare (CBW) agent release is developed. The proposed hazard analysis methodology places particular emphasis on the following important factors: (1) recognition that the toxicity of rapidly acting inhaled toxic materials is usually highly nonlinear, and use of a nonlinear toxic load to quantify this effect; (2) recognition that realistic estimates for toxicological assessment must explicitly account for the fluctuating concentration in a dispersing plume, and development of a simple model for incorporation of these effects into the ensemble-averaged (mean) nonlinear toxic load; (3) recognition of the importance of identifying the relevant time scale for the application (i.e., the time scale appropriate for the response of the human lungs); and, (4) recognition of the variability in the exposed population to a specific toxic load of material, and use of probit relationships to model this varying susceptibility. Example calculations performed using the proposed methodology demonstrated the importance of accounting for concentration fluctuations in the hazard assessment. It is shown that failure to do so under realistic situations could lead to a serious underestimation of the severity of the toxic effects and of the crosswind and downwind extents of the hazard zones generated by the CBW agent release.

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