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Toxic load modeling for naturally fluctuating concentration exposures

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Abstract

The toxic load model is widely used in hazard assessment involving the release of toxic gases into the atmosphere. The underlying basis of this model consists of laboratory experiments in which various animal species are exposed to constant concentrations of a toxic gas for a fixed exposure duration. However, natural variability (fluctuations) in the concentration of a toxic gas at a point in a plume dispersing in the atmosphere is a ubiquitous feature that must be properly incorporated into the toxic load model for noxious gases which do not vary linearly with the concentration and exposure time. Towards this purpose, the statistical characteristics of the toxic load (or, equivalently, the toxic load ratio) have been explicitly derived from the statistical properties of the exposure concentration on which it depends for three different models. In particular, the ensemble average and variance of the toxic load (and the related toxic load ratio) have been determined assuming that the probability density function of either the exposure concentration or dosage is well characterised using a clipped-normal distribution.

Although these three models give the same predictions of the toxic load for constant concentration exposures, it is shown that predictions of the statistical characteristics (ensemble average and variance) of the toxic load ratio appropriate for a naturally fluctuating concen-tration exposure differ for the three models over a wide range of combinations of parame-ters on which the models depend (e.g., uptake time constant, exposure time, integral time scale of concentration fluctuations, and higher-order moments of exposure concentration or dosage). Owing to the fact that there is no experimental data that can be used to assess the prediction efficacy of these three toxic load models for a random fluctuating concentration, a simple toxicity experiment is proposed involving a series of constant concentration pulses. An analysis of this proposed experiment with reference to the three toxic load models is provided.

Résumé

Le modèle de charge toxique est largement utilisé pour l'évaluation des risques posés par le rejet de gaz toxiques dans l'atmosphère. La base sous-jacente de ce modèle est constituée d'expériences en laboratoire au cours desquelles diverses espèces animales sont exposées à des concentrations constantes d'un gaz toxique pendant une durée fixe. Toutefois, la variabilité naturelle (fluctuation) de la concentration d'un gaz toxique à un point donné d'un panache se dispersant dans l'atmosphère est une caractéristique ubiquiste qui doit être correctement incorporée dans le modèle de charge toxique pour des gaz nocifs qui ne varient pas linéairement avec la concentration et la durée d'exposition. À cette fin, les caractéristiques statistiques de la charge toxique (ou, de manière équivalente, le rapport de charge toxique) ont été dérivées explicitement des propriétés statistiques de la concentration d'exposition, dont elles dépendent pour trois modèles différents. En particulier, la moyenne d'ensemble et la variance de la charge

toxique (et le rapport de charge toxique relié) ont été déterminées en assumant que la fonction de densité de la concentration d'exposition ou du dosage est bien caractérisée au moyen d'une loi normale partielle.

Bien que ces trois modèles conduisent aux mêmes prédictions de la charge toxique pour des expositions à concentration constante, nous avons montré que les prédictions des caractéristiques statistiques (moyenne d'ensemble et variance) du rapport de la charge toxique appropriée pour une exposition à une concentration fluctuant naturellement diffèrent pour les trois modèles sur une large gamme de combinaisons de paramètres desquelles le modèle dépend (p. ex. constante de la durée d'absorption, durée de l'exposition, échelle de temps intégrée des fluctuations de la concentration et moments d'ordre supérieur de la concentration ou du dosage d'exposition. Étant donné que nous ne disposons d'aucune donnée expérimentale pouvant être utilisée pour évaluer l'efficacité de prédiction de ces trois modèles de charge toxique pour une concentration fluctuant aléatoirement, nous proposons une simple expérience de toxicité mettant en jeu une série d'impulsions de concentration constantes. Une analyse d'une telle expérience proposée avec référence aux trois modèles de charge toxique est fournie.

Executive summary

Toxic load modeling for naturally fluctuating concentration exposures

E. Yee; DRDC Suffield TR 2012-052; Defence R&D Canada – Suffield August, 2012

Background: For some noxious substances, the toxic effects resulting from inhalational exposure depend in a linear fashion on both the concentration of the substance, C, and the exposure duration, t_e , i.e. the same toxic effect would result if one quantity were doubled and the other halved, and *vice versa*. For such substances, one can even predict the toxic effect of a varying concentration, provided that the instantaneous concentration over the exposure period is known. However, the toxic effects for most substances (including, in particular, the nerve agents) depend on the concentration of the substance in a nonlinear fashion. In such cases, it has been found that, if the concentration remains fixed over an exposure period, toxic effects will depend on the product $C^n t_e$, the "toxic load", where n is determined empirically through animal testing and varies from substance to substance. For example, the toxicity of hydrogen cyanide varies approximately as $C^{2.7} t_e$, so increasing the concentration two-fold results in the same level of toxicity in about one-sixth the exposure time.

While the toxic load model has been shown to provide good predictions of the toxic effects of noxious substances which depend nonlinearly on concentration when the exposure concentration is fixed, there is currently no accepted toxicity model for such substances when the concentration varies over time. This is a significant gap, as the concentration in a plume of noxious pollutant dispersing in the atmosphere inevitably exhibits large fluctuations owing to irregular motion of the wind currents. As a result, the assessment of hazards resulting from releases of toxic materials is not as reliable as would be desirable.

Principal results: To address this deficiency, three different toxicity models extending the toxic load model to address irregular and fluctuating concentrations have been developed. Although each model will give the same prediction for any constant concentration exposure, analysis demonstrates that they will predict different effects for irregular and fluctuating concentrations. As no experimental data exists that could be used to assess the prediction efficacy of these models, a conceptually simple toxicity experiment to permit this has also been devised.

Significance of results: The fundamental basis for generalization of toxic load models to accommodate fluctuating concentrations has been developed, marking a significant step towards addressing a gap in assessing the hazard posed by atmospheric releases of noxious substances, whether deliberate or accidental.

Future work: No further work by DRDC is planned due to resource constraints.

Sommaire

Toxic load modeling for naturally fluctuating concentration exposures

E. Yee ; DRDC Suffield TR 2012-052 ; R & D pour la défense Canada – Suffield; Août 2012

Contexte: pour certaines substances nocives, les effets toxiques résultant d'une inhalation dépendent de manière linéaire de la concentration de la substance, C, et de la durée de l'exposition, te , c.-à-d. que le même effet toxique serait constaté si une quantité était doublée et l'autre réduite de moitié, et vice versa. Pour de telles substances, on peut même prédire l'effet toxique d'une concentration variable, à la condition que la concentration instantanée pendant la période d'exposition soit connue. Toutefois, les effets toxiques de la plupart des substances (y compris en particulier ceux des agents neurotoxiques) dépendent de la concentration de la substance de manière non linéaire. Dans de tels cas, on a trouvé que, si la concentration reste fixe pendant une période d'exposition, les effets toxiques dépendront du produit Cnte, la « charge toxique », dans lequel n est déterminé empiriquement au moyen de tests sur des animaux et varie d'une substance à l'autre. Par exemple, la toxicité de l'acide cyanhydrique varie approximativement selon C2,7te, un doublement de la concentration conduit donc au même effet toxique en environ un sixième du temps d'exposition.

Alors qu'on a montré que le modèle de charge toxique peut fournir de bonnes prédictions des effets toxiques de substances nocives qui dépendent de manière non linéaire de la concentration quand la concentration d'exposition est fixe. Il n'existe pas actuellement de modèle de toxicité accepté pour de telles substances quand la concentration varie avec le temps. Ceci constitue une lacune importante, la concentration dans un panache de polluant nocif se dispersant dans l'atmosphère exhibant inévitablement de grandes fluctuations dues au mouvement irrégulier des courants d'air. L'évaluation des risques résultant de rejets de matières toxiques n'est donc pas aussi fiable que ce qui serait souhaitable.

Principaux résultats: pour le présent rapport, nous proposons trois différents modèles pour l'extension du modèle de charge toxique afin de traiter les concentrations irrégulières et fluctuantes. Bien que chaque modèle conduira à la même prédiction pour toute exposition à une concentration constante, l'analyse montre qu'ils prédiront des effets différents pour des concentrations irrégulières et fluctuantes. Comme il n'existe aucune donné expérimentale qui pourrait être utilisée pour évaluer l'efficacité de prédiction de ces modèles, une expérience simple de toxicité a aussi été conçue pour permettre cette évaluation.

Importance des résultats: nous avons développé la base fondamentale pour généraliser l'utilisation des modèles de charge toxique aux concentrations fluctuantes. Ceci constitue une étape importante pour remédier à la lacune existant pour l'évaluation des risques posés par des rejets atmosphériques de substances nocives, délibérés ou accidentels.

Travail future: aucun travail ultérieur n'est prévu à RDDC en raison de contraintes de ressources.

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1 Introduction

Information on the acute inhalation toxicity of toxic gases and vapours [e.g., toxic industrial chemicals (TICs), chemical warfare agents (CWAs), etc.] is required for the purpose of hazard or consequence assessment. For volatile toxic materials, the toxicity depends on two factors; namely, the exposure concentration C in the air and the duration of exposure t_e. The factor which correlates with the degree of injury (e.g., incapacitation, death) corresponds to some functional relationship $f(C, t_e)$ between C and t_e, with a given level set of this functional [viz., $f(C, t_e) = k$, where k is a constant] correlating to a specified level of toxicity (SLOT).

For some toxic gases, the functional f that correlates with injury (damage) is the time-integrated concentration, or dosage D [viz., $D = f(C, t_e) = Ct_e$ assuming that the concentration C remains constant over the exposure duration t_e]. The application of dosage as the basis for estimating injury from exposure to TICs and CWAs is commonly used in hazard assessment. The method was first proposed by Haber [1] who found that for certain poison gases (e.g., phosgene) used in the First World War, the toxic effects appear to correlate well with the dosage. Of course, the implication in the correlation of dosage with injury or damage is that there is a reciprocal trade-off between C and t_e for these types of toxic gases, so that the toxic effect remains unchanged if, for example, the concentration is doubled and the exposure time is halved, a relationship referred to as Haber's rule.

While Haber's rule is simple, it has been observed that for most toxic gases the use of dosage as the determinant of injury or damage in a biological receptor is wholly inadequate. Indeed, as early as 1938, Busvine [2] noted that the toxicity of an insecticide (ethylene oxide) for four different species of insects correlated well with the following functional form for C and t_e; namely, with $f(C, t_e) = C^n t_e$ where n is an exponent that is constant for a given toxic agent. Later, this particular functional form for C and t_e became known as the toxic load L_n (viz., $L_n \equiv C^n t_e$, where n is known as the toxic load exponent). Indeed, the toxic load concept has been applied subsequently to characterize the injury (damage) arising from exposure to many industrial and military gases (including studies conducted by Larsen et al. [3], ten Berge [4], Zwart and Woutersen [5], and Yee [6] with respect to the evaluation of the toxic effects of nitrogen dioxide, methyisocyanate, chlorine, and sarin, respectively).

A comprehensive study conducted by ten Berge et al. [7] showed that the response of animals to many locally irritant and systemically acting gases is nonlinear (viz., $n > 1$) in the toxic load relationship, implying that Haber's rule is not valid. More specifically, correlations of existing (historical) toxicity data for these acutely toxic gases analyzed by ten Berge et al. showed that the toxic load exponent, n, lies in the range from about 1 to 3.5 with the most common values for n being between 2 and 3. For example, these investigators report toxic load exponents of 1.2, 2.2, 2.7, and 3.5 for perfluoroisobutylene, hydrogen sulfide (H_2S), hydrogen cyanide (HCN), and chlorine (Cl_2) gas, respectively. In summary, it was found that the exponent n can vary considerably depending on the toxic material, and frequently is considerably greater than one. Because of this observation, it is seen that the use of dosage as a measure of damage or injury for many (if not most)

toxic agents is highly inappropriate. As an example, 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 as would be predicted with the linear dosage relationship implicit in Haber's rule.

For an individual in an exposed population, there will be a certain value of the toxic load L_n for a given noxious gas that will be required to produced a SLOT of interest. The specific value of the toxic load will vary from individual to individual owing to the varying susceptibility among individuals in a population to exposure to the given material. In experiments involving acute exposures of animals to a toxic gas, it has been found that variation in susceptibility among members in a population to exposure to toxic materials tends to follow a lognormal distribution. Using this distribution and expressing probability in units of standard deviation, the varying susceptibility among individuals in an exposed population can be conveniently expressed in the form of a probit (probability unit) equation with the following general form:

$$\mathrm{Pr} = k_1 + k_2 \log(L_n), \tag{1}$$

where Pr is the probit and k_1 and k_2 are numerical constants that depend on the toxic agent. These numerical constants can be determined from experimental tests involving the exposure of animals to the toxic agent. In particular, the parameters n, k_1, and k_2 in the probit relationship given by Eq. (1) can be obtained by fitting experimental data using the method described by Finney [8]. The probit was originally introduced by Bliss [9] in 1934 using the dosage D as the injury or damage factor. The probit relationship in Eq. (1) generalizes the result of Bliss by using the toxic load L_n, instead of the dosage D, as the measure for the injury or causative factor of the harmful agent.

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

$$P = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\mathrm{Pr}-5} \exp\left(-\frac{u^2}{2}\right) du = \frac{1}{2}\left(\mathrm{erf}\left(\frac{\mathrm{Pr}-5}{\sqrt{2}}\right) + 1\right), \tag{2}$$

where $\mathrm{erf}(x)$ denotes the error function. It is noted that Pr is a normally distributed random variable with a mean of 5 and a standard deviation of 1. In other words, a value of 5 for Pr corresponds to the median value of the effect being investigated (viz., the value at which 50% of the exposed population experiences the SLOT), whereas probit values of 6, 7, ... correspond to 1, 2, ... standard deviations above and probit values of 4, 3, ... correspond to 1, 2, ... standard deviations below the median. More specifically, the duration of exposure is t_e and the coefficients k_1 and k_2 in the probit relationship [cf. Eq. (1)] express the positions of families of mortality or incapacitation levels (e.g., LCt_5, LCt_{50}, LCt_{95}, etc. which are lethal or incapacitating dosages responsible for 5, 50, and 95% mortality or incapacitation, respectively) on a graph of C versus t_e. In the relationship of P to Pr in Eq. (2), for a population of biological receptors exposed to certain combinations of C and t_e, the fractional mortality (or, incapacitation) is approximately 0.16 for $\mathrm{Pr} = 4$, 0.5 for

Pr = 5, 0.84 for Pr = 6, and so forth. Finally, note that $Y \equiv \mathrm{Pr} - 5$ is the normit (viz., quantiles of a standard normal distribution with zero mean and unit variance).

The basis of the toxicity model for CWAs and TICs involves combining the toxic load L_n which characterizes the nonlinearity of the dose-time response of a biological receptor to the toxic substance, with the probit method [cf. Eqs. (1) and (2)] which accounts for the variability in the response in a population of biological receptors to a specific toxic load. These toxicity relationships are invariably inferred from animal experiments involving exposing animals to *constant* concentrations C for different exposure times t_e. However, it needs to be stressed that challenge concentrations of toxic gases arising from dispersion in the atmosphere are not constant concentrations. Rather, toxic gas concentrations in the atmosphere will be expected to fluctuate on a range of scales in both time and space that is reflective of the complex processes responsible for dispersion in the atmospheric boundary layer. It is expected that the degree of injury for a nonlinear toxic material (viz., a material with $n > 1$) will depend on the concentration fluctuations in the dispersing plume during the exposure, with different realizations of fluctuating concentrations giving rise to different toxic loads, even though the mean dosage (defined here as the product of the ensemble mean concentration and the exposure time) may be the same for each realization of the fluctuating concentration.

The dependence of the toxic load on concentration fluctuations has been recognized as early as the Second World War and, more particularly, in the 1940s Japanese military toxicologists conducted animal experiments in which various animal species were exposed to intermittent concentrations of a number of toxic gases for a fixed exposure time [10]. In this seminal work, it was found that higher (and, hence, more intermittent) concentrations produced the most severe toxic effects providing the first evidence of the toxicity enhancement due to a fluctuating concentration.

More recently, a number of researchers have used various (idealized) forms of fluctuating concentration time series in attempts to try to quantify the effect of fluctuations on the toxicity. Griffiths and Megson [11] and Griffiths and Harper [12] considered the effect of two rather artificial fluctuating concentrations with equal dosages; one composed of a constant concentration C applied for exposure time t_e, and the other composed of a series of blocks of non-zero constant concentration C_p applied for total time $t_{e,p}$, with each block separated by gaps with zero concentration for a total time $t_{e,0}$, where $t_{e,p} + t_{e,0} = t_e$. Using this idealized form for concentration fluctuations, these investigators demonstrated the extreme sensitivity of the toxic load to periods of peak concentration. From these *gedanken* experiments, Griffiths and various colleagues quantified the enhanced toxicity for exposure to an intermittent concentration in comparison to that of a constant concentration. Ride [13] confirmed this enhanced toxicity for noxious materials by using a simple physical model for fluctuating concentrations based on spherical eddies of concentration separated by regions of uncontaminated air. Later, Hilderman et al. [14] demonstrated the enhanced toxicity arising from a fluctuating concentration using a more realistic stochastic model for generation of plume concentration time series. In addition, Hilderman et al. have also included receptor dependent factors such as an uptake time constant, a recovery time constant, and a saturation concentration into their toxicity model.

It is evident that the extension of the toxic load to accommodate concentration fluctuations is not straightforward and appears to be fraught with a number of difficulties. What is clear, however, is the enhancement in the toxicity of a noxious substance arising from the exposure to a fluctuating concentration. How to estimate this enhancement is the *key* problem that needs to be addressed. In this report, rather than using specific models for fluctuating concentration time series (e.g., constant concentration pulses interspersed with periods of zero concentration, spherical eddies of constant concentration separated by regions of clean air, stochastic models for concentration time series generation, etc.) in the determination of the enhanced toxic load, we will instead determine explicitly the relationship between the statistical characteristics of the toxic load and of the fluctuating concentration from which it is derived. The objective is to derive the statistical properties of the toxic load directly from the known statistical characteristics of the underlying plume concentration fluctuations, but it will be shown that even this exercise raises some ambiguous results in the sense that three different forms of the toxic load, all of which are exactly equivalent for a constant concentration exposure, lead to different statistical properties of the toxic load for a fluctuating concentration.

2 Toxic load for fluctuating concentrations

It is now generally accepted through observations that the ratio of the root-mean-square to mean concentration in a plume dispersing in the atmosphere is of order one and, hence, knowledge of the mean concentration only is not adequate to address many of the problems that are important to air quality control and the regulation of hazards posed by the release of highly toxic, flammable, or malodorous materials (e.g., Jones [15]; Sawford [16]; Mylne and Mason [17]; Yee et al. [18–20]; Yee and Biltoft [21]). However, while the need to develop probabilistic models for the description of potential hazards resulting from the accidental or deliberate release of toxic or flammable materials into the atmosphere has been recognized for quite some time (Csanady [22]; Chatwin [23]), experimental studies of fluctuating atmospheric plume concentrations have been hampered until recently by the lack of suitable fast-response instrumentation for the quantitative measurement of the statistics of concentration fluctuations. In this section, we use known statistical characteristics of atmospheric plume concentration fluctuations (obtained from various full-scale tracer experiments in the atmosphere) to deduce the statistical properties of the toxic load derived from the given concentration fluctuations. To this purpose, three different models for the statistical properties of the toxic load are described. Furthermore, these models are appropriate for acute exposures with exposure durations less than about 60 min. These exposure time durations are short enough that repair or recovery processes are not important and, hence, do not need to be accounted for in the toxic load model.

2.1 Toxic load model 1

Recall that for a constant concentration C and exposure time t_e, the toxic load for a noxious substance with toxic load exponent n is defined simply as $L_n = C^n t_e$. Naturally, for exposure to a fluctuating or time-varying instantaneous concentration $\chi(t)$ at a fixed

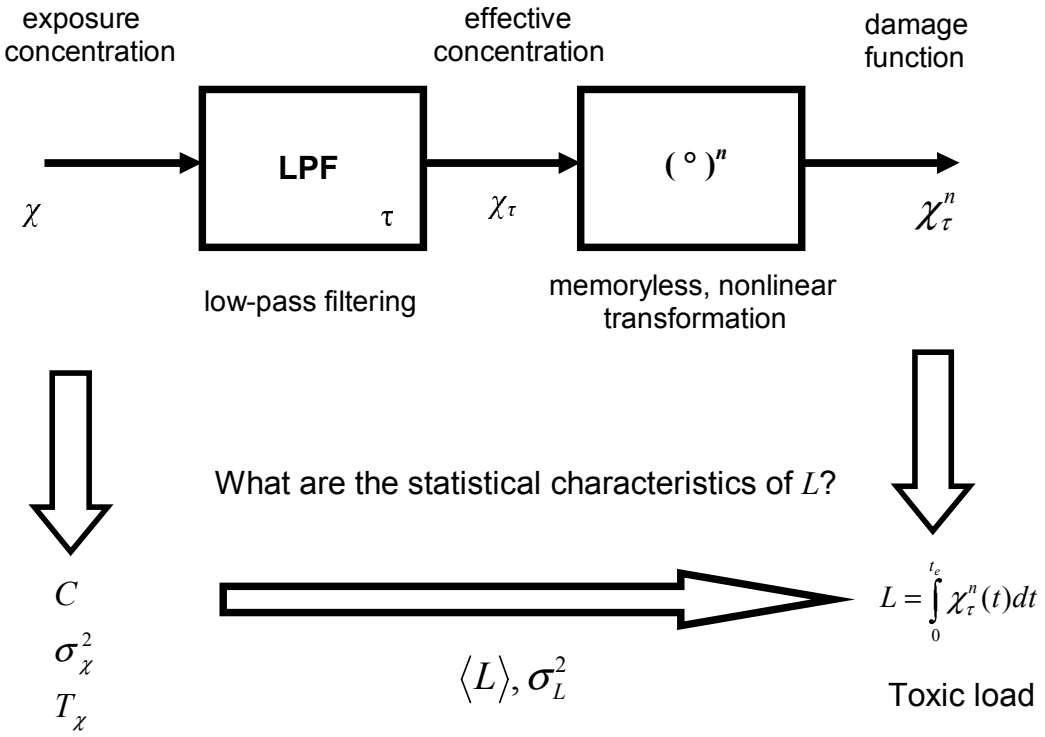


Figure 1: *Relationship of the toxic load L to the fluctuating concentration $\chi(t)$ upon which it depends. The sequence of operations shown here provides the basis for an operational definition of the toxic load that is appropriate for a fluctuating concentration.*

receptor point $\mathbf{x}$ in space, the definition of the toxic load can be generalized as follows (see, Ride [13] and ten Berge et al. [7]):

$$L_n \equiv L \equiv \int_0^{t_e} \chi^n(t)\, dt. \tag{3}$$

Note in Eq. (3) that L_n and L will be used henceforth interchangeably, with the latter simpler notational form used when the value of n is assumed to be explicitly understood from the problem context. Although this extension of the toxic load definition for fluctuating concentrations seems plausible, it does not take into account the finite time required for the uptake of the toxic gas into the body (viz., the uptake of the toxic gas into the body cannot be instantaneous). In view of this, the definition of the toxic load is perhaps better defined (formulated) using the sequence of operations displayed in Figure 1.

In Figure 1, the external challenge (exposure) concentration at a fixed receptor location is $\chi(t)$.[1] There is a finite time τ associated with the uptake of a toxic gas, corresponding as such to the fact that for a (locally) irritant chemical the finite response of the human

1. The instantaneous concentration field resulting from the release of a toxic agent into the turbulentatmosphere for a given set of external conditions can be considered to be a realization of a specific random or stochastic process (random field). An ensemble is a collection of all possible realizations of a naturally fluctuating concentration field generated by a specific stochastic process. Let (Ω, F, P) be some fixed

lungs must impose some physical averaging time (typically about 3 s) on the fluctuations in the exposure concentration $\chi(t)$. Moreover, if the toxic gas is a systemically acting chemical that affects an internal organ (other than the lungs), the averaging (uptake) time τ is even longer and is associated with the characteristic time required for the transport and absorption of the toxic material through the alveolar regions of the lungs and into the blood, tissue, and the internal organs of the body [24]. Consequently, owing to the finite uptake rate of a toxic gas, the relevant concentration for evaluation of the toxic load is the effective concentration $\chi_\tau(t)$, where $\chi_\tau(t)$ is a low-pass filtered (LPF) version of the exposure concentration $\chi(t)$ obtained by imposing an effective averaging time τ on $\chi(t)$. The injury or damage function perceived by the body correlates with $\chi_\tau^n(t)$ [involving a memoryless, nonlinear transformation of $\chi_\tau(t)$] and, as a result, the toxic load L needs to be defined as follows:

$$L \equiv \int_0^{t_e} \chi_\tau^n(t)\, dt, \tag{4}$$

where τ is the uptake time constant that determines some measure of the time averaging that must be imposed on $\chi(t)$ for the purpose of determination of the injury (damage) factor.

Given the sequence of operations illustrated in Figure 1, the statistical properties of L in Eq. (4) can (in principle) be deduced from a knowledge of the statistical characteristics of the fluctuating exposure concentration $\chi(t)$. However, the statistical properties of L will require a complete knowledge of the higher-order multi-time statistics of $\chi(t)$. Clearly, such complete information is never available, and in practice, one must settle for reduced information. In the subsequent development, we assume that the only statistical information that is available concerning $\chi(t)$ are: (1) ensemble mean concentration $C \equiv \langle \chi \rangle$, where $\langle \cdot \rangle$ denotes an ensemble average (or, mathematical expectation); (2) concentration variance σ_χ^2; and, (3) integral time scale of concentration fluctuations T_χ. It should be noted that modern atmospheric dispersion models can make predictions of the ensemble mean concentration, concentration variance, and an integral time scale of concentration fluctuations for the instantaneous concentration χ associated with a scalar released into the turbulent atmosphere. For example, the Hazard Prediction and Assessment Capability (HPAC) developed by Defense Threat Reduction Agency (DTRA) uses a second-order closure scheme for turbulence to make predictions of these three statistical properties of the instantaneous concentration [25]. Given these statistical characteristics of the exposure concentration, it is possible to use this information to determine the two lowest-order moments of the (random) toxic load L given by Eq. (4); namely, the ensemble mean $\langle L \rangle$ and variance σ_L^2 of the toxic load (see Figure 1). The effects of the exposure duration t_e and the uptake time constant τ (or, averaging time) on the apparent statistical properties of L are of great importance, and a rigorous accounting for these two effects on the statistical characteristics of L will be provided below.

probability space, where Ω is a sample space (set of outcomes), $\mathcal{F}$ is a σ-algebra of subsets of Ω (set of events), and $\mathcal{P}$ is a probability measure (function that assigns probabilities to events). Each point $\omega \in \Omega$ corresponds to a specific realization of the fluctuating concentration, so the concentration field is characterized by $\chi(\mathbf{x}, t\,; \omega)$ that depends on the position vector $\mathbf{x}$ and on the time t. For simplicity of notation, since we consider the concentration at a fixed position, we use $\chi(t)$ to refer to a specific realization of the concentration time history at a fixed location $\mathbf{x}$.

To emphasize the toxicity enhancement due to a (random) fluctuating concentration χ, it is useful to define the toxic load ratio $LR_n \equiv LR$ as follows (see, Ride [26]):

$$LR_n \equiv LR \equiv \frac{\int_0^{t_e} \chi_\tau^n(t)\,dt}{\int_0^{t_e} \langle \chi_\tau(t)\rangle^n\,dt} = \frac{\int_0^{t_e} \chi_\tau^n(t)\,dt}{\int_0^{t_e} C^n(t)\,dt}. \tag{5}$$

Note in Eq. (5) that we have used that fact the $\langle \chi_\tau(t)\rangle = \langle \chi(t)\rangle \equiv C(t)$ [viz., the ensemble mean of the time-averaged effective concentration $\chi_\tau(t)$ is identical to the ensemble mean of the instantaneous exposure concentration $\chi(t)$]. Furthermore, note that LR is simply the ratio of the toxic load for the fluctuating effective concentration to the toxic load that would have been obtained using the ensemble mean concentration C. For a linear toxic gas for which $n = 1$, the ensemble mean of the toxic load ratio is identically unity. However, for a nonlinear toxic gas with $n > 1$, the ensemble-averaged toxic load ratio is greater than unity and can be interpreted as a measure of the toxicity enhancement arising from the nonlinear effects of the concentration fluctuations.

2.1.1 Ensemble mean toxic load

The ensemble mean toxic load ratio $\langle LR\rangle$ follows directly from Eq. (5) and is given by

$$\langle LR\rangle = \frac{\int_0^{t_e} \langle \chi_\tau^n(t)\rangle\,dt}{\int_0^{t_e} C^n(t)\,dt}. \tag{6}$$

From this result, the ensemble mean toxic load $\langle L\rangle$ [which should not be confused with the toxic load determined from using the ensemble mean concentration which appears as the denominator of Eq. (5)] can be determined as follows:

$$\langle L\rangle = \int_0^{t_e} \langle \chi_\tau^n(t)\rangle\,dt = \langle LR\rangle \times \int_0^{t_e} C^n(t)\,dt. \tag{7}$$

For the case of a continuous source emitting at a constant (steady) rate into a statistically stationary atmosphere, $\chi(t)$ is a stationary random process whose moments are independent of time. For this case, the ensemble mean toxic load ratio and toxic load simplify to

$$\langle LR\rangle = \frac{\langle \chi_\tau^n\rangle}{C^n} = \left\langle \left(\frac{\chi_\tau}{C}\right)^n \right\rangle, \tag{8}$$

and

$$\langle L\rangle = \langle \chi_\tau^n\rangle t_e. \tag{9}$$

These ensemble-averaged quantities are determined completely by knowledge of the n-th order moment of the effective concentration χ_τ.

To determine the statistical properties of χ_τ which, in turn, define the ensemble mean toxic load ratio and toxic load [cf. Eqs. (8) and (9)], it is necessary to express the statistical moments of χ_τ in terms of those of χ, for it is the two lowest-order moments of the latter quantity that is assumed to be known *a priori*. Firstly, as noted previously, time averaging such as that imposed by the rate of uptake of a toxic gas into the body does not affect

the ensemble mean concentration C (viz., C is invariant to a time-averaging operation, so $\langle \chi_\tau \rangle = \langle \chi \rangle = C$). However, the time averaging inherent in the finite uptake of a chemical into the body will affect the concentration variance. More specifically, the concentration variance of the effective concentration χ_τ will differ from the concentration variance of the exposure concentration χ, owing to the fact that time averaging imposed by the uptake time constant τ will smooth out the fine structure of rapid fluctuations in the exposure concentration χ. The expected reduction in the concentration variance of the effective concentration arising from the finite uptake rate of a toxic gas can be estimated as follows.

The process of averaging the exposure concentration χ over a duration τ to give the effective concentration χ_τ can be represented as follows:

$$\chi_\tau(t) = \frac{1}{\tau} \int_{t-\tau/2}^{t+\tau/2} \chi(t')\, dt'. \tag{10}$$

The convolution kernel associated with this time averaging is the box or top-hat filter defined as follows: $G(t-t') = 1/\tau$ if $|t-t'| \leq \tau/2$; and, $G(t-t') = 0$, otherwise. The frequency response (or, transfer) function $\hat{G}$ for this box or top-hat time low-pass filter is obtained as the Fourier transform of G:[2]

$$\hat{G}(f) = \frac{\sin\big(\pi f \tau\big)}{\big(\pi f \tau\big)}, \tag{11}$$

where f is the frequency. This implies that the variance contributed by the frequency f in the exposure concentration χ is reduced by a factor of $|\hat{G}(f)|^2 = \sin^2(\pi f \tau)/(\pi f \tau)^2$ (modulus squared of the transfer function) of its original value in the effective (time-averaged) concentration χ_τ (see Figure 2).

Let $F(f)$ denote the normalized power spectral density function for the exposure concentration. We note that $F(f)$ denotes the fractional contribution to the total concentration variance of χ for frequencies between f and $f + df$, so

$$\int_0^\infty F(f)\, df = 1. \tag{12}$$

Furthermore, the absolute power spectral density function for the exposure concentration χ is given by $S(f) = \sigma_\chi^2 F(f)$, so that

$$\int_0^\infty S(f)\, df = \sigma_\chi^2. \tag{13}$$

The normalized power spectral density function for the effective concentration χ_τ [obtained from applying the time-averaging operation of Eq. (10) on χ] is given by $F_{\text{out}}(f) =$

2. This can be seen easily if we consider the variation in $\chi(t')$ as a superposition of sinusoidal components, with the variation associated with frequency f represented as $\chi(t') = A\sin(2\pi f t')$. The process of averaging this sinusoidal variation in Eq. (10) over the uptake time interval τ gives $\chi_\tau(t) = A\big(\sin(\pi f\tau)/(\pi f\tau)\big)\sin(2\pi f t)$.

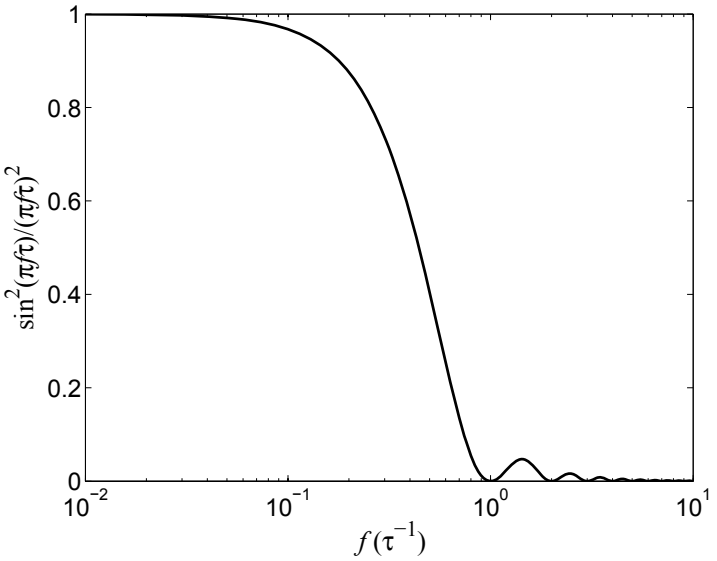


Figure 2: *Modulus squared of the transfer function* $\hat{G}(f) = \sin(\pi f\tau)/(\pi f\tau)$ *for a box or top-hat time low-pass filter. The frequency* f *is measured in units of* τ^{-1} *(inverse of the uptake time scale).*

$F(f)|\hat{G}(f)|^2$. Using this result in conjunction with Eq. (13), it can be seen that the concentration variance $\sigma^2_{\chi,\tau}$ of the effective concentration χ_τ is related to the concentration variance σ^2_χ of the exposure concentration χ by the following relationship:

$$\sigma^2_{\chi,\tau} = \sigma^2_\chi \int_0^\infty F(f)|\hat{G}(f)|^2\, df = \sigma^2_\chi \int_0^\infty F(f)\frac{\sin^2\big(\pi f\tau\big)}{\big(\pi f\tau\big)^2}\, df. \tag{14}$$

Note that the power spectral density of χ in Eq. (14) is attenuated by a weighting function $|\hat{G}(f)|^2$ whose functional form is depicted in Figure 2. Obviously, as the uptake time constant τ increases, more of the power spectral density $F(f)$ of χ is cut off by the weighting function and, as a consequence, $\sigma^2_{\chi,\tau}$ is reduced more significantly with respect to σ^2_χ.

To provide an explicit relationship between σ^2_χ and $\sigma^2_{\chi,\tau}$, we require an explicit formulation of a functional form for $F(f)$. To this purpose, we will assume that $F(f)$ has the following simple spectral form:

$$F(f) = \frac{4T_\chi}{1 + \big(2\pi T_\chi f\big)^2}, \tag{15}$$

where T_χ is the integral time scale of concentration fluctuations in χ. Indeed, it is straightforward to show that the inverse Fourier transform of $F(f)$ given by Eq. (15), which corresponds to the autocorrelation function for χ, has the following exponential form $\mathcal{R}(t) = \exp\big(-t/T_\chi\big)$, from which it is readily apparent that T_χ is the integral time scale of concentration fluctuations as defined by

$$T_\chi = \int_0^\infty \mathcal{R}(t)\, dt. \tag{16}$$

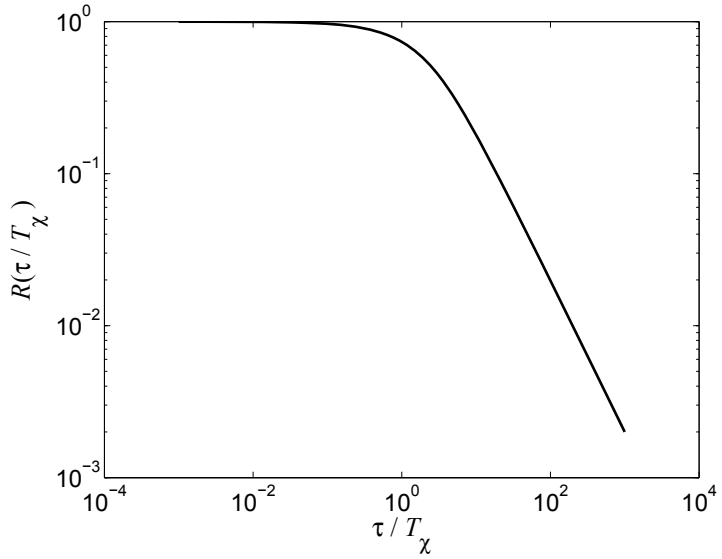


Figure 3: *The fractional reduction $R(\tau/T_\chi)$ in the concentration variance due to averaging of the exposure concentration χ (having an integral time scale T_χ) with an averaging time τ (uptake time constant).*

Substitution of the functional form for $F(f)$ given by Eq. (15) into Eq. (14) leads to the following explicit relationship between σ_χ^2 and $\sigma_{\chi,\tau}^2$:

$$\sigma_{\chi,\tau}^2 = 2\sigma_\chi^2 \left(\frac{T_\chi}{\tau}\right)^2 \left[\exp\left(-\frac{\tau}{T_\chi}\right) + \frac{\tau}{T_\chi} - 1\right] \equiv \sigma_\chi^2 R\left(\frac{\tau}{T_\chi}\right). \tag{17}$$

Note from Eq. (17) that $R(\tau/T_\chi)$ is defined as

$$R\left(\frac{\tau}{T_\chi}\right) \equiv 2\left(\frac{T_\chi}{\tau}\right)^2 \left[\exp\left(-\frac{\tau}{T_\chi}\right) + \frac{\tau}{T_\chi} - 1\right]. \tag{18}$$

Although a specific functional form for $F(f)$ was used to derive Eq. (17), it is expected that this relationship between σ_χ^2 and $\sigma_{\chi,\tau}^2$ is insensitive to wide variations in the assumed shape of $F(f)$ owing to the fact that $F(f)$ occurs as the integrand in Eq. (14).

The form of the reduction factor $R(\tau/T_\chi)$ for the concentration variance arising from time averaging [given by Eq. (18)] is shown Figure 3. It is seen that the reduction in the concentration variance tends asymptotically to a variation with τ^{-1} for a long uptake time constant relative to the integral time scale of concentration fluctuations. More quantitatively, it is seen that $\lim_{\tau\to\infty} \sigma_{\chi,\tau}^2 \tau \to 2\sigma_\chi^2 T_\chi$, so the reduced concentration variance $\sigma_{\chi,\tau}^2$ of the effective concentration χ_τ tends asymptotically to a variation with τ^{-1} (inverse of the uptake time constant).

2.1.2 Toxic load variance

The toxic load ratio defined in Eq. (5) is random owing to the fluctuating exposure concentration χ [which determines the effective concentration χ_τ through the time-averaging

operation of Eq. (10)]. In consequence, it is necessary (at the very least) to also provide an estimate of the variance of the toxic load ratio in order to provide the simplest measure of the variability that can be expected in this quantity between two realizations of the dispersion. To this purpose, starting from the random variable LR given by Eq. (5), it follows that the variance $\sigma^2_{LR}(t_e)$ of the toxic load ratio can be determined as follows:

$$\begin{aligned}\sigma^2_{LR}(t_e) &\equiv \frac{\int_0^{t_e}\int_0^{t_e}\langle \chi'^n_\tau(t_1)\chi'^n_\tau(t_2)\rangle\, dt_1\, dt_2}{\left(\int_0^{t_e} C^n(t)\, dt\right)^2} \\ &= \frac{2\int_0^{t_e} dt_1 \int_0^{t_1} ds \langle \chi'^{2n}_\tau(t_1)\rangle \mathcal{R}(\chi^n_\tau; t_1, s)}{\left(\int_0^{t_e} C^n(t)\, dt\right)^2},\end{aligned} \tag{19}$$

where $\chi'^n_\tau(t) \equiv \left(\chi^n_\tau(t) - \langle\chi^n_\tau(t)\rangle\right)$ is the fluctuating injury (damage) function involving a departure from the mean and

$$\mathcal{R}(\chi^n_\tau; t_1, s) \equiv \frac{\langle \chi'^n_\tau(t_1)\chi'^n_\tau(t_1+s)\rangle}{\langle\left(\chi'^n_\tau(t_1)\right)^2\rangle} \tag{20}$$

is the autocorrelation function for χ^n_τ. The first part of Eq. (19) is simply the definition of the variance of a quantity, and the second part of Eq. (19) follows readily from the first part on noting that this integral is symmetric under the interchange of t_1 and t_2 from which it follows that the integration over the rectangular region $0 \le t_1, t_2 \le t_e$ can be replaced by twice the integration over the triangular region given by $0 \le t_1 \le t_e$, $0 \le s \equiv (t_1 - t_2) \le t_1$. In view of Eq. (19), the toxic load variance $\sigma^2_L(t_e)$ is given by

$$\sigma^2_L(t_e) = \sigma^2_{LR}(t_e) \times \left(\int_0^{t_e} C^n(t)\, dt\right)^2. \tag{21}$$

In general, it should be noted that for exposure to a diffusing cloud at a fixed point in space in either a stationary or nonstationary atmosphere, $\chi(t)$ and (by implication) $\chi_\tau(t)$ are non-stationary processes. In consequence, the autocorrelation is a function of the (absolute) diffusion time t_1, as well as of the lag time s. Again, for the case of a steady continuous source emitting into a statistically stationary atmosphere (which is the case of interest here), the general results for the variance of the toxic load ratio and toxic load can be simplified as follows. In this case, the autocorrelation function for $\chi^n_\tau(t)$ depends only on the lag time s, so that $\mathcal{R}(\chi^n_\tau; t_1, s) = \mathcal{R}(\chi^n_\tau; s)$. Furthermore, if we perform an integration by parts with respect to t_1 in Eq. (19) and if we note that the mean concentration C is independent of time for this case, we get the following result for the toxic load ratio variance:

$$\sigma^2_{LR}(t_e) = \frac{2\langle\left(\chi'^n_\tau\right)^2\rangle \int_0^{t_e}(t_e - s)\mathcal{R}(\chi^n_\tau; s)\, ds}{\left(C^n t_e\right)^2}, \tag{22}$$

from which the toxic load variance is given by

$$\sigma^2_L(t_e) = \sigma^2_{LR}(t_e) \times \left(C^n t_e\right)^2. \tag{23}$$

For its full exploitation, an explicit form will be required for $\mathcal{R}(\chi_\tau^n; s)$ in Eq. (22). To this purpose, it will be assumed that the autocorrelation function of χ_τ^n has the following exponential form:

$$\mathcal{R}(\chi_\tau^n; s) = \exp\left(-\frac{|s|}{T_{\chi,\tau}^{(n)}}\right), \tag{24}$$

where $T_{\chi,\tau}^{(n)}$ is identified with the integral time scale for the $\chi_\tau^n(t)$ process (viz., the random process associated with the effective concentration raised to the n-th power). Substitution of this functional form for the autocorrelation function into Eq. (22) leads to the following explicit expression for the toxic load ratio variance:

$$\sigma_{LR}^2(t_e) = \frac{2\langle\left(\chi_\tau'^n\right)^2\rangle T_{\chi,\tau}^{(n)2}\left[\exp\left(-t_e/T_{\chi,\tau}^{(n)}\right) + t_e/T_{\chi,\tau}^{(n)} - 1\right]}{\left(C^n t_e\right)^2}, \tag{25}$$

which implies a toxic load variance given by

$$\sigma_L^2(t_e) = 2\langle\left(\chi_\tau'^n\right)^2\rangle T_{\chi,\tau}^{(n)2}\left[\exp\left(-t_e/T_{\chi,\tau}^{(n)}\right) + t_e/T_{\chi,\tau}^{(n)} - 1\right]. \tag{26}$$

In order to provide a practical method for estimation of either $\sigma_{LR}^2(t_e)$ [Eq. (25)] or $\sigma_L^2(t_e)$ [Eq. (26)], we require an explicit estimate for the integral time scale $T_{\chi,\tau}^{(n)}$ of the n-th power of the effective concentration. To this purpose, the key analysis for accomplishing this objective was provided by Yee [27] who showed that taking the n-th power of $\chi(t)$ (exposure concentration process) has a general "whitening" effect on $\chi(t)$ in the sense that the spectrum of $\chi^n(t)$ occupies a greater bandwidth than the spectrum of $\chi(t)$. Generalizing the methodology used by Sykes [28] for estimating the integral time scale T_χ of plume concentration χ from a knowledge of the Eulerian velocity scale, Yee [27] showed that the integral time scale of the n-th power of χ is related to the integral time scale of χ as follows:

$$\frac{T_\chi^{(n)}}{T_\chi} = \frac{\langle(\chi/C)^2\rangle}{\langle(\chi/C)^{2n}\rangle} \cdot \frac{\log\left[1 + 2\langle(\chi/C)^{2n}\rangle\right]}{\log\left[1 + 2\langle(\chi/C)^2\rangle\right]}. \tag{27}$$

However, what is required is the relationship of the integral time scale of the n-th power of χ_τ to the integral time scale of χ_τ (effective concentration). It will be assumed that this relationship is exactly the same as that exhibited in Eq. (27), except for the fact that (χ/C) is replaced by (χ_τ/C). This gives the following result for the ratio of $T_{\chi,\tau}^{(n)}$ to $T_{\chi,\tau}$:

$$\frac{T_{\chi,\tau}^{(n)}}{T_{\chi,\tau}} = \frac{\langle(\chi_\tau/C)^2\rangle}{\langle(\chi_\tau/C)^{2n}\rangle} \cdot \frac{\log\left[1 + 2\langle(\chi_\tau/C)^{2n}\rangle\right]}{\log\left[1 + 2\langle(\chi_\tau/C)^2\rangle\right]}. \tag{28}$$

To complete the estimate of $T_{\chi,\tau}^{(n)}$, we need to relate $T_{\chi,\tau}$ to T_χ because it is the latter integral time scale that is assumed *a priori* to be known. Applying the same reasoning as

used to derive Eq. (27), it is straightforward to relate the integral time scale of the effective concentration to that of the exposure concentration as follows:

$$\frac{T_{\chi,\tau}}{T_\chi} = \frac{\langle(\chi/C)^2\rangle}{\langle(\chi_\tau/C)^2\rangle} \cdot \frac{\log\Big[1+2\langle(\chi_\tau/C)^2\rangle\Big]}{\log\Big[1+2\langle(\chi/C)^2\rangle\Big]}. \tag{29}$$

2.2 Toxic load model 2

In the toxic load model 1 for fluctuating concentrations, the starting point for the development was the generalization of the toxic load for a constant concentration C in the form $L = C^n t_e$ to the more general form given by Eq. (4). However, for a constant concentration, the toxic load definition can be recast as $L = C^n t_e = (Ct_e)^n t_e^{1-n} = D^n t_e^{1-n}$, where D is the dosage. Now, the expression for the toxic load (which for a constant concentration is mathematically equivalent to the standard definition) can be used as the basis for generalization to accommodate a fluctuating concentration. Towards this objective, this form for the toxic load can be generalized to accommodate a fluctuating exposure concentration χ (and concomitant effective concentration χ_τ) as follows:

$$L = \left(\int_0^{t_e} \chi_\tau(t)\,dt\right)^n t_e^{1-n} \equiv D_\tau^n(t_e) t_e^{1-n}, \tag{30}$$

where we have used $D_\tau(t_e)$ to denote the effective dosage for an exposure time t_e (viz., dosage determined using the effective concentration χ_τ). This form of the toxic load for a fluctuating concentration is referred sometimes to as the "average concentration method" [29]. Finally, the toxic load ratio corresponding to Eq. (30) can be defined as [in analogy to Eq. (5)]

$$LR = \frac{\left(\int_0^{t_e} \chi_\tau(t)\,dt\right)^n t_e^{1-n}}{\int_0^{t_e} C^n(t)\,dt}. \tag{31}$$

Note again that the toxic load ratio involves normalization of the toxic load by the mean concentration toxic load determined by the ensemble-average concentration $\langle\chi_\tau(t)\rangle = C(t)$.

Owing to the fact that t_e is a deterministic quantity, the statistical properties of L given by Eq. (30) are entirely determined by the statistical characteristics of $D_\tau(t_e)$. Given this observation, the remainder of this section will be focussed on the determination of the two lowest-order moments of $D_\tau(t_e)$, which in turn determines the two lowest-order moments of L [as defined by Eq. (30)] providing as such the ensemble mean and variance of L [or, equivalently, of LR defined by Eq. (31)]. As in the previous section, the results will be derived for the case of a continuous source emitting tracer at a constant rate into a stationary atmosphere. In this case, the statistical properties of all quantities are independent of time t [and, more specifically, the denominator of Eq. (31) simplifies to $C^n t_e$].

Firstly, let us focus on the ensemble-averaged toxic load ratio and toxic load, with LR and L given by Eqs. (31) and (30), respectively. To begin with, note that $\langle D_\tau(t_e)\rangle = Ct_e$ so

$$\langle LR\rangle = \frac{\langle D_\tau^n(t_e)\rangle t_e^{1-n}}{C^n t_e} = \frac{\langle D_\tau^n(t_e)\rangle t_e^{1-n}}{\langle D_\tau(t_e)\rangle^n t_e^{1-n}} = \frac{\langle D_\tau^n(t_e)\rangle}{\langle D_\tau(t_e)\rangle^n} = \left\langle \left(\frac{D_\tau(t_e)}{\langle D_\tau(t_e)\rangle}\right)^n \right\rangle. \tag{32}$$

Note from Eq. (32) that the ensemble-averaged toxic load ratio for model 2 is determined by the n-th moment of the normalized effective dosage $D_\tau(t_e)$ (i.e., effective dosage normalized by the ensemble-averaged effective dosage). From this result, it is readily seen that the ensemble-averaged toxic load for model 2 is given by

$$\langle L \rangle = \langle LR \rangle \times \langle D_\tau(t_e) \rangle^n t_e^{1-n}. \tag{33}$$

Secondly, let us now determine the variance of the toxic load ratio and toxic load for model 2. Starting from Eq. (31), it is straightforward to show that

$$\sigma_{LR}^2(t_e) = \left\langle \left(\frac{D_\tau(t_e)}{\langle D_\tau(t_e) \rangle} \right)^{2n} \right\rangle - \left\langle \left(\frac{D_\tau(t_e)}{\langle D_\tau(t_e) \rangle} \right)^{n} \right\rangle^2, \tag{34}$$

from which it follows that

$$\sigma_L^2(t_e) = \sigma_{LR}^2(t_e) \times \langle D_\tau(t_e) \rangle^{2n} t_e^{2(1-n)}. \tag{35}$$

To complete the formulation of the toxic load model 2, we need to be able to express the moments of the effective dosage, D_τ, in terms of the moments of the exposure concentration χ (owing to the fact that it is only the latter moments that are assumed to be known *a priori*). To this end, applying the same line of reasoning that was used to derive Eq. (17), it can be readily shown that the normalized variance of the effective dosage $\sigma_{D_\tau}^2(t_e)/\langle D_\tau(t_e) \rangle^2$ can be expressed in terms of the normalized second-order moment of the effective concentration χ_τ as follows:

$$\frac{\sigma_{D_\tau}^2(t_e)}{\langle D_\tau(t_e) \rangle^2} = 2 \left(\left\langle \left(\frac{\chi_\tau}{C} \right)^2 \right\rangle - 1 \right) \frac{T_{\chi,\tau}^2}{t_e^2} \left[\exp\left(-\frac{t_e}{T_{\chi,\tau}} \right) + \frac{t_e}{T_{\chi,\tau}} - 1 \right]. \tag{36}$$

The second-order moment of χ_τ can be determined in terms of the second-order moment of χ using Eq. (17). To be more explicit, Eq. (17) implies that

$$\left\langle \left(\frac{\chi_\tau}{C} \right)^2 \right\rangle = \left(\left\langle \left(\frac{\chi}{C} \right)^2 \right\rangle - 1 \right) R\left(\frac{\tau}{T_\chi} \right) + 1. \tag{37}$$

Finally, the integral time scale of χ_τ in Eq. (36) can be determined in terms of the integral time scale of χ using Eq. (29). This completes the formulation for toxic load model 2.

2.3 Toxic load model 3

The toxic load model 3 is a simple variant of toxic load model 2, and is the toxicity model that has been implemented in HPAC [30]. In this formulation of the toxic load for a fluctuating concentration, the exposure time factor t_e in Eq. (30) [viz., the factor that is raised to the power $(1-n)$] is replaced by an effective exposure time $t_{e,\text{eff}}$ which is defined as follows:

$$t_{e,\text{eff}} \equiv \frac{\left(\int_0^{t_e} \langle \chi_\tau(t) \rangle \, dt \right)^2}{\int_0^{t_e} \langle \chi_\tau^2(t) \rangle \, dt}, \tag{38}$$

which by substitution of t_e^{1-n} by $t_{e,\text{eff}}^{1-n}$ in Eq. (30) leads to a toxic load definition given by

$$L = \left(\int_0^{t_e} \chi_\tau(t)\, dt \right)^n t_{e,\text{eff}}^{1-n} \equiv D_\tau^n(t_e) t_{e,\text{eff}}^{1-n} = D_\tau^n(t_e) \times \left(\frac{\left(\int_0^{t_e} \langle \chi_\tau(t) \rangle\, dt \right)^2}{\int_0^{t_e} \langle \chi_\tau^2(t) \rangle\, dt} \right)^{1-n}. \tag{39}$$

Note that for a *constant* concentration χ, the effective exposure time $t_{e,\text{eff}}$ reduces exactly to the exposure time t_e. For this case, the toxic load definition given by Eq. (30) is identical to that given by Eq. (39). Finally, the toxic load ratio corresponding to Eq. (39) is given by

$$LR = \frac{\left(\int_0^{t_e} \chi_\tau(t)\, dt \right)^n t_{e,\text{eff}}^{1-n}}{\int_0^{t_e} C^n(t)\, dt}. \tag{40}$$

It should be noted that Sykes [30] normalizes the effective exposure time defined by Eq. (38) by a reference (generally arbitrary, but constant) time scale t_r (viz., $t_{e,\text{eff}}/t_r$) and then replaces the exposure time factor t_e in Eq. (30) by the normalized (dimensionless) effective exposure time to define a so-called "toxic dosage" L_D. In other words, $L_D = L/t_r^{1-n}$. However, owing to the fact that t_r is a constant, the statistical properties of the "toxic dosage" are identical to those of the toxic load defined by Eq. (39), apart from the presence of constant scaling factors depending on t_r. It is important to note that if the "toxic dosage" is used rather than the toxic load in the probit relationship of Eq. (1) to assess the probability of effect (death or injury), the constant k_1 needs to be replaced by $k_1 + k_2 \log(t_r^{1-n})$. This transformation of the probit relationship ensures that the probability of effect is independent of the (arbitrary) choice of the reference time scale t_r in the "toxic dosage" definition, as it should be.

For a continuous source emitting at a steady rate into a stationary atmosphere, the toxic load and toxic load ratio given by Eqs. (39) and (40), respectively, simplify as follows (again, recalling that $\langle D_\tau(t_e) \rangle = C t_e$, that $\langle \chi_\tau \rangle = C$, and that all statistical quantities in this case are independent of time):

$$L = D_\tau^n(t_e) \times \left(t_e \frac{C^2}{\langle \chi_\tau^2 \rangle} \right)^{1-n}, \tag{41}$$

and

$$LR = \frac{D_\tau^n(t_e)}{\langle D_\tau(t_e) \rangle^n} \left(\frac{C^2}{\langle \chi_\tau^2 \rangle} \right)^{1-n}. \tag{42}$$

As in the case of toxic load model 2, it is noted that the statistical characteristics of L and LR in Eqs. (41) and (42) depend only on the statistical characteristics of the random variable $D_\tau(t_e)$. The ensemble-averaged toxic load and toxic load ratio for model 3 are derived *mutatis mutandis* as the comparable statistic for model 2. As a consequence, only the final results of the derivation of these two statistical quantities for L and LR are summarized below.

The ensemble-averaged toxic load ratio for model 3 is given by

$$\langle LR \rangle = \left\langle \left(\frac{D_\tau(t_e)}{\langle D_\tau(t_e) \rangle} \right)^n \right\rangle \left\langle \left(\frac{\chi_\tau}{C} \right)^2 \right\rangle^{n-1}. \tag{43}$$

On comparison of Eq. (43) with Eq. (32), it is seen that $\langle LR \rangle$ for model 3 differs from that for model 2 by the presence of a factor that can be identified as the normalized mean-square effective concentration raised to the power $(n-1)$. Given Eq. (43), the ensemble-averaged toxic load can be computed easily from $\langle L \rangle = \langle LR \rangle \times \langle D_\tau(t_e) \rangle^n t_e^{1-n}$.

The variance of the toxic load ratio for model 3 has the following form:

$$\sigma_{LR}^2(t_e) = \left(\left\langle \left(\frac{D_\tau(t_e)}{\langle D_\tau(t_e) \rangle} \right)^{2n} \right\rangle - \left\langle \left(\frac{D_\tau(t_e)}{\langle D_\tau(t_e) \rangle} \right)^{n} \right\rangle^2 \right) \cdot \left\langle \left(\frac{\chi_\tau}{C} \right)^2 \right\rangle^{2(n-1)}, \qquad (44)$$

which differs from the toxic load ratio variance for model 2 [cf. Eq. (34)] through a factor that is seen to be the normalized mean-square effective concentration raised to the power $2(n-1)$. From this result, the toxic load variance for model 3 can be obtained easily from $\sigma_L^2(t_e) = \sigma_{LR}^2(t_e) \times \langle D_\tau(t_e) \rangle^{2n} t_e^{2(1-n)}$. This completes the formulation of the toxic load model 3.

3 Probability distribution for concentration

The determination of the two lowest-order moments of the toxic load for models 1, 2, and 3 described above requires one to provide an estimate for an arbitrary moment of the effective concentration χ_τ (for model 1) and of the effective dosage $D_\tau(t_e)$ (for models 2 and 3). The only information that is assumed *a priori* to be available for the estimation of these moments are the first two moments of the exposure concentration χ (i.e., the mean and variance) and the integral time scale T_χ of concentration fluctuations (which can be obtained from a modern atmospheric dispersion model). Obviously, with this limited input information, this requires that we formulate a simple concentration probability density function (PDF) that can be used to predict an arbitrary moment of the concentration given information on only the two lowest-order moments of concentration; namely, the mean concentration (first-order moment) and the mean-square concentration or concentration variance (second-order moment). In other words, we require a simple concentration PDF form that can be specified with no more than two parameters, and yet is capable of modeling the distribution of cloud or plume concentration fluctuations over a wide range of atmospheric conditions (various diabatic conditions) and terrain types (level, unobstructed terrain, urban terrain, etc.).

An analysis of an extensive set of plume concentration fluctuation data obtained from field trials and from water-channel experiments by Yee and Chan [31] and Yee [32] demonstrated the collapse of the higher-order normalized concentration moments (higher than second-order and up to eighth-order) on the second-order normalized concentration moment onto a series of "universal" curves. This remarkable collapse suggests that the concentration PDF of plumes dispersing in either a built-up or open-terrain environment can be described adequately by at most two parameters [namely, a location parameter which can be chosen to be the mean concentration and a scale parameter which can be chosen to be the concentration standard deviation (square root of the concentration variance)]. A number of two-parameter models for the concentration PDF have been proposed. The lognormal

distribution for concentration was proposed by Csanady [33]. The exponential distribution was advocated by Barry [34]. The clipped-normal distribution was proposed by Lewellen and Sykes [35] through application of the principle of maximum entropy. Yee and Chan [31] proposed a clipped-gamma distribution for the concentration PDF and demonstrated that this distribution provided excellent agreement with the observed higher-order concentration moment relationships for plume dispersion over open terrain. Later, Yee [32] showed that the clipped-gamma distribution can adequately model (predict) the higher-order normalized concentration moments for dispersion in an urban (built-up) terrain.

In this report, we will use the clipped-normal distribution for the concentration PDF. The motivation for this choice resides in the fact that this concentration PDF is used in the HPAC software. The clipped-normal PDF for concentration has the following functional form:

$$f(\chi) = \frac{1}{\sqrt{2\pi}\sigma_c} \exp\left(-\frac{1}{2}\left(\frac{\chi - \mu_c}{\sigma_c}\right)^2\right) + (1-\gamma)\delta(\chi), \tag{45}$$

where

$$\gamma = \gamma(\mu_c, \sigma_c) \equiv \frac{1}{2}\left(1 + \operatorname{erf}\left(\frac{\mu_c}{\sqrt{2}\sigma_c}\right)\right). \tag{46}$$

Here, $\delta(x)$ denotes the Dirac delta function, γ is the intermittency function (probability that the concentration χ is nonzero), and μ_c and σ_c are the location and scale parameters of the clipped-normal distribution, respectively. We now derive some properties of the clipped-normal distribution which will allow us to use it to predict an arbitrary moment of the concentration, when given only the mean concentration C and concentration variance σ_χ^2.

Firstly, we would like to determine the mapping from (C, σ_χ^2) to (μ_c, σ_c), and vice-versa for the clipped-normal distribution. Towards this objective, using the method of moments it is straightforward to show that the model concentration PDF parameters μ_c and σ_c can be obtained by solving the following system of transcendental equations:

$$\left\langle \left(\frac{\chi}{C}\right)^2 \right\rangle = \frac{\dfrac{\phi}{2\sqrt{\pi}}\exp(-\phi^2) + (\phi^2 + 1/2)\gamma}{\left(\dfrac{1}{2\sqrt{\pi}}\exp(-\phi^2) + \phi\gamma\right)^2}, \tag{47}$$

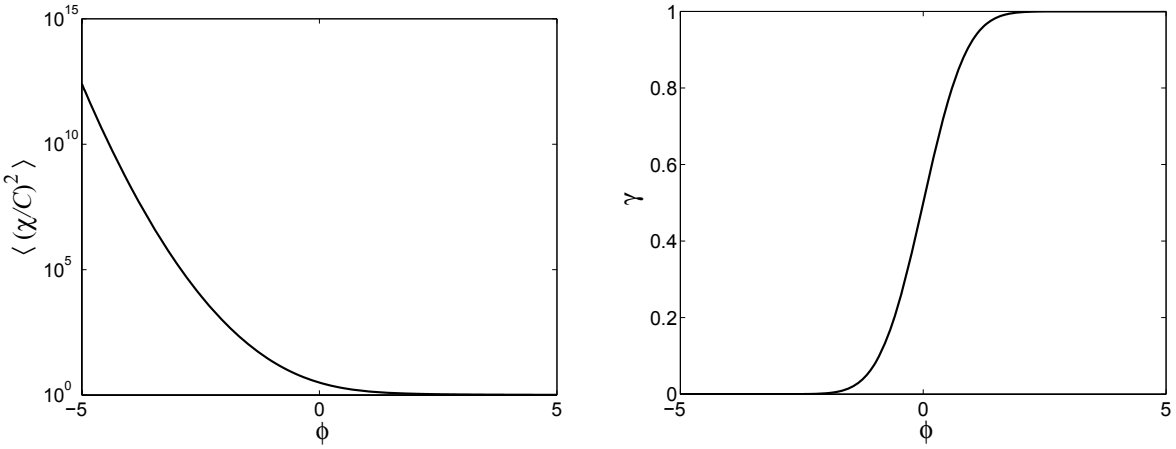
$$\gamma = \frac{1}{2}\big(1 + \operatorname{erf}(\phi)\big), \tag{48}$$

and

$$\frac{1}{\sqrt{2}\sigma_c} = \frac{1}{2\sqrt{\pi}}\exp(-\phi^2) + \phi\gamma, \tag{49}$$

where $\phi \equiv \mu_c/(\sqrt{2}\sigma_c)$. For a specified value of the normalized mean-square concentration $\langle(\chi/C)^2\rangle \equiv \sigma_\chi^2/C^2 + 1$, [3] Eqs. (47) and (48) are solved for ϕ, the value of ϕ is substituted in Eq. (49) to obtain σ_c and, finally, this value of σ_c is used in the definition of ϕ to determine

3. Note that $i \equiv \sigma_\chi/C$ is the fluctuation intensity of the exposure concentration and provides a quantitative measure of the *degree* of fluctuations in the exposure concentration. Typically, point exposure



(a) ϕ vs $\langle(\chi/C)^2\rangle$ (b) ϕ vs γ

Figure 4: *Dependence of (a) the normalized mean-squared concentration $\langle(\chi/C)^2\rangle$ and (b) the intermittency factor γ on the parameter $\phi \equiv \mu_c/(\sqrt{2}\sigma_c)$.*

μ_c. The variation of $\langle(\chi/C)^2\rangle$ and γ as a function of ϕ as given by Eqs. (47) and (48) is displayed in Figure 4.

Once the normalized parameter $\phi \equiv \mu_c/(\sqrt{2}\sigma_c)$ has been determined given the normalized second-order concentration moment $\langle(\chi/C)^2\rangle$, an arbitrary normalized concentration moment $\langle(\chi/C)^n\rangle$ can be predicted by substituting the clipped-normal distribution [cf. Eq. (45)] into the definition of the moment of a distribution and evaluating the resulting integral:

$$\begin{aligned}\langle(\chi/C)^n\rangle &= \frac{1}{C^n}\int_0^\infty \chi'^n f(\chi')\,d\chi' \\ &= \frac{\Gamma(n+1)}{2}\cdot\frac{\mathrm{i^n erfc}(-\phi)}{\left(\frac{1}{2\sqrt{\pi}}\exp(-\phi^2)+\phi\gamma\right)^n},\end{aligned} \tag{50}$$

where $\Gamma(x)$ denotes the gamma function and $\mathrm{i^n erfc}(x)$ denotes the repeated integrals of the error function complement (whose generalization, or analytic continuation, to non-integer values of n can be accomplished using procedures of the fractional calculus [36]). Note that the normalized concentration moment depends only on the parameter $\phi \equiv \mu_c/(\sqrt{2}\sigma_c)$, rather than on μ_c and σ_c separately.

To evaluate $\mathrm{i^n erfc}(\phi)$ in Eq. (50), we use the relationship of this function to the confluent hypergeometric function (or, the Kummer function) $M(a,b,z)$ [37] (see item 7.2.12, page

concentration measurements from a plume dispersing in the turbulent atmosphere display considerable deviation (or, inherent variability) from the ensemble mean concentration C, with the result that typically the standard deviation of concentration is comparable to the mean concentration (viz., $i \sim \mathcal{O}(1)$).

300):

$$\mathrm{i^n erfc}(\phi) = \exp(-\phi^2)\left[\frac{1}{2^n\Gamma\left(\frac{n}{2}+1\right)}M\left(\frac{n+1}{2},\frac{1}{2},\phi^2\right) - \frac{\phi}{2^{n-1}\Gamma\left(\frac{n+1}{2}\right)}M\left(\frac{n}{2}+1,\frac{3}{2},\phi^2\right)\right]. \quad (51)$$

The numerical evaluation of the confluent hypergeometric function, especially for arguments of large magnitude, is fraught with difficulties on a finite precision computer. In many cases, even double precision is not sufficient to secure a numerical evaluation of $M(a,b,z)$ that is sufficiently accurate. In this report, we use a numerical evaluator for $M(a,b,z)$ that utilizes a direct summation of Kummer's series, but implemented using extended precision subroutines using large integer arrays to accumulate a single numerator and a single denominator in a single division to determine the numerical value of $M(a,b,z)$. This numerical evaluator for $M(a,b,z)$ is described by Nardin et al. [38] and a Fortran routine CONHYP is available that implements this algorithm [39]. Unfortunately, using Eqs. (50) and (51) with CONHYP to evaluate the n-th normalized concentration moment did not eliminate entirely computer overflow errors for certain values of n and ϕ.

To circumvent the problem of computer overflow errors, we applied Kummer's first formula [37] to extract a factor of $\exp(\phi^2)$ from each of the two terms containing $M(a,b,z)$ in Eq. (51). Note that this exponential then 'cancels' the factor $\exp(-\phi^2)$ in Eq. (51). This procedure leads to the following representation of $\mathrm{i^n erfc}(\phi)$ in terms of the confluent hypergeometric function:

$$\mathrm{i^n erfc}(\phi) = \frac{1}{2^n\Gamma\left(\frac{n}{2}+1\right)}M\left(-\frac{n}{2},\frac{1}{2},-\phi^2\right) - \frac{\phi}{2^{n-1}\Gamma\left(\frac{n+1}{2}\right)}M\left(\frac{1}{2}-\frac{n}{2},\frac{3}{2},-\phi^2\right). \quad (52)$$

The use of Eq. (52) in conjunction with Eq. (50) allows the n-th normalized concentration moment to be computed reliably and accurately without the problem of computer overflow errors.

In addition to the normalized moments of the exposure concentration χ, the toxic load model 1 requires also the normalized moments of the effective concentration χ_τ. It is assumed that the fluctuations of the effective concentration can also be characterized using a clipped-normal distribution. The normalized moments of the effective concentration can be obtained by using Eqs. (17) and (18) to determine the concentration variance of χ_τ in terms of the concentration variance of χ (which is assumed to be known *a priori*), and then using this information in conjunction with Eqs. (47), (48) and (49) to calculate the corresponding value of ϕ for the clipped-normal distribution associated with the effective concentration. Once this value of ϕ is determined, the n-th order concentration moment of χ_τ can be calculated using Eqs. (50) and (52).

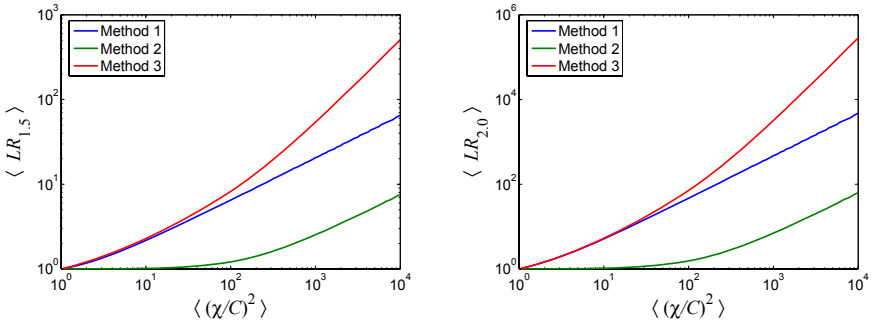
In a similar manner, the toxic load models 2 and 3 require a knowledge of the n-order moments of the effective dosage D_τ. Again, it is implicitly assumed that this random variable can be characterized using a clipped-normal distribution. The effective dosage variance can be expressed in terms of the statistical characteristics of the exposure concentration χ (assumed to be known *a priori*) using Eqs. (36) and (37), and this information can be used to determine the value of ϕ of the associated clipped-normal distribution. Given this value of ϕ for the clipped-normal distribution associated with D_τ, the normalized effective dosage moments required for toxic load models 2 and 3 can be calculated using Eqs. (50) and (52).

4 Comparison of toxic load models

In this section, we compare predictions of the toxic load ratio ensemble average and standard deviation (square root of the variance) for the three models described in Section 2. This is a useful comparison owing to the fact that the toxic load ratio is a dimensionless quantity and can be interpreted as the enhancement in the toxicity arising from the nonlinear effects of random concentration fluctuations with reference to the mean concentration toxic load (viz., the toxic load that would result if the ensemble mean concentration was used for its determination, ignoring as such the effects of the fluctuations in concentration about the mean). All the results shown in this section correspond to an exposure to a continuous source emitting at a constant rate into a stationary atmosphere.

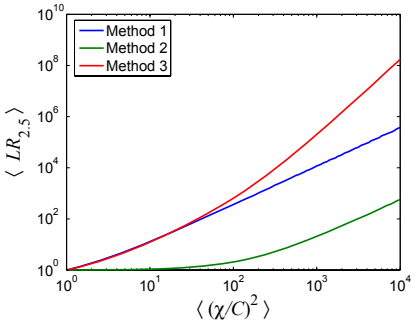
To this purpose, the ensemble-averaged toxic load ratio $\langle LR_n \rangle$ for various values of n was computed as a function of the normalized exposure mean-square concentration $\langle (\chi/C)^2 \rangle$ with values in the range $1 < \langle (\chi/C)^2 \rangle < 10,000$ for the three different toxic load models. Typical results for $\langle LR_n \rangle$ for the three methods for four values of n (namely, $n = 1.5$, 2.0, 2.5, and 3.0) are displayed in Figure 5. These results correspond to an integral time scale for the exposure concentration of either $T_\chi = 1$ s or 10 s, for an uptake time constant of $\tau = 3$ s (corresponding roughly to the characteristic time associated with the breathing rate for a human) and an exposure time of $t_e = 300$ s. Figure 6 shows the comparable results for $\langle LR_n \rangle$ for an exposure time of $t_e = 600$ s, with all other parameter values remaining the same as the corresponding result in Figure 5.

A comparison of Figures 5 and 6 shows (as expected) that for all three toxic load models, $\langle LR_n \rangle \to 1^+$ as $\langle (\chi/C)^2 \rangle \to 1^+$, implying no fluctuations in the exposure concentration or, equivalently, the exposure concentration is a constant. As indicated earlier, for a constant exposure concentration, all three toxic load models give exactly the same prediction. Moreover, an examination of Figure 5 shows that the values of the ensemble mean toxic load ratio are comparable (approximately or better) for toxic load models 1 and 3 over the range $1 < \langle (\chi/C)^2 \rangle \lesssim 40$ for $t_e = 300$ s and $T_\chi = 1$ s. The range of $\langle (\chi/C)^2 \rangle$ over which values of $\langle LR_n \rangle$ are comparable for toxic load models 1 and 3 is reduced as the integral time scale of the exposure concentration is increased from $T_\chi = 1$ s to $T_\chi = 10$ s [cf. Figures 5 and 6, panels (a)–(d) with panels (e)–(h), respectively].

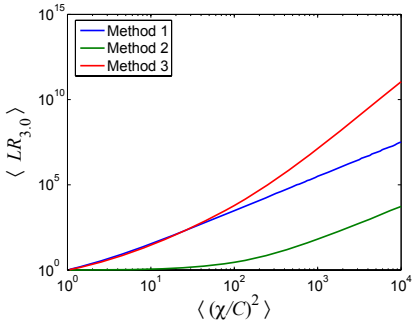


(a) $n = 1.5$, $T_\chi = 1$ s

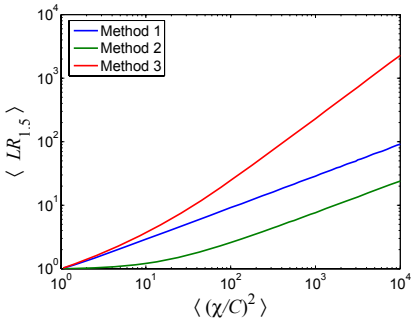
(b) $n = 2.0$, $T_\chi = 1$ s



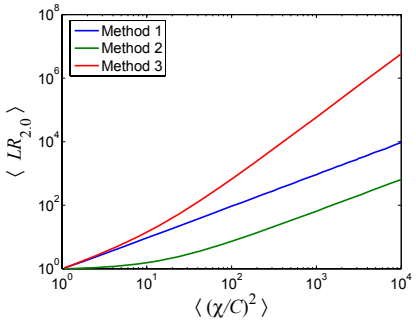
(c) $n = 2.5$, $T_\chi = 1$ s



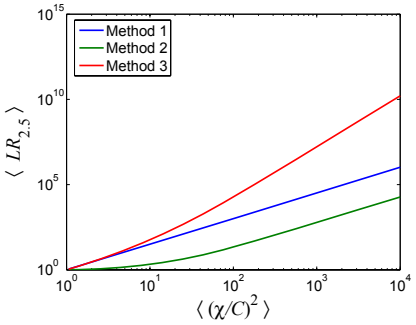
(d) $n = 3.0$, $T_\chi = 1$ s



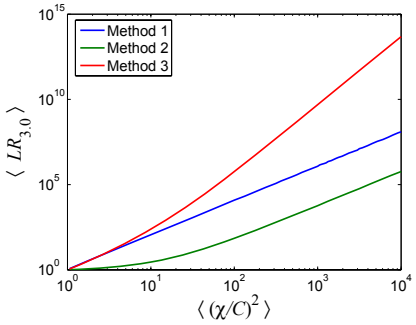
(e) $n = 1.5$, $T_\chi = 10$ s



(f) $n = 2.0$, $T_\chi = 10$ s

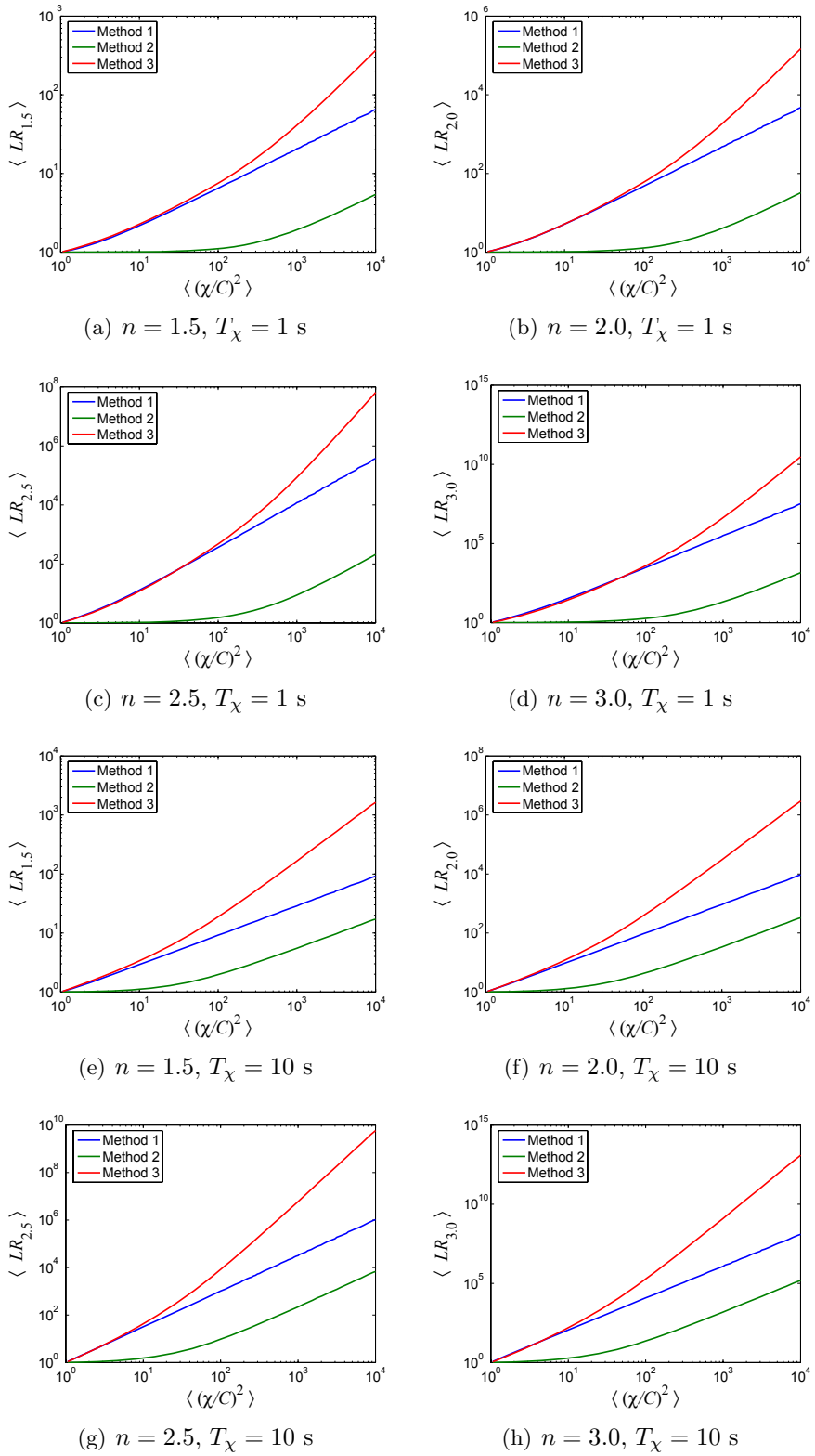


(g) $n = 2.5$, $T_\chi = 10$ s



(h) $n = 3.0$, $T_\chi = 10$ s

Figure 5: *Toxic load ratio ensemble average* $\langle LR_n \rangle$ *as a function of* $\langle (\chi/C)^2 \rangle$ *for toxic load models (methods) 1 (blue curve), 2 (green curve), and 3 (red curve) with* $\tau = 3$ *s,* $t_e = 300$ *s for (a)* $n = 1.5$*, (b)* $n = 2.0$*, (c)* $n = 2.5$*, (d)* $n = 3.0$ *and* $T_\chi = 1$ *s; and, for (e)* $n = 1.5$*, (f)* $n = 2.0$*, (g)* $n = 2.5$*, (h)* $n = 3.0$ *and* $T_\chi = 10$ *s.*



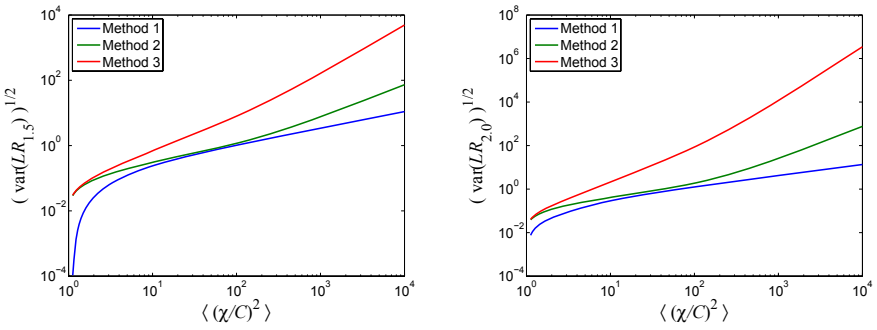
(a) $n = 1.5$, $T_\chi = 1$ s (b) $n = 2.0$, $T_\chi = 1$ s

(c) $n = 2.5$, $T_\chi = 1$ s (d) $n = 3.0$, $T_\chi = 1$ s

(e) $n = 1.5$, $T_\chi = 10$ s (f) $n = 2.0$, $T_\chi = 10$ s

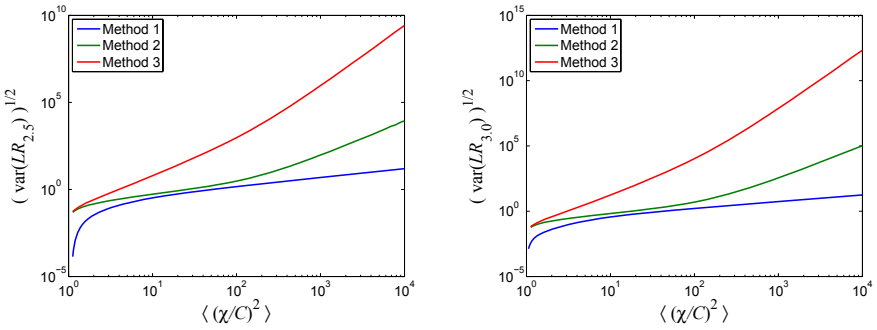
(g) $n = 2.5$, $T_\chi = 10$ s (h) $n = 3.0$, $T_\chi = 10$ s

Figure 6: *Toxic load ratio ensemble average* $\langle LR_n \rangle$ *as a function of* $\langle (\chi/C)^2 \rangle$ *for toxic load models (methods) 1 (blue curve), 2 (green curve), and 3 (red curve) with* $\tau = 3$ *s,* $t_e = 600$ *s for (a)* $n = 1.5$*, (b)* $n = 2.0$*, (c)* $n = 2.5$*, (d)* $n = 3.0$ *and* $T_\chi = 1$ *s; and, for (e)* $n = 1.5$*, (f)* $n = 2.0$*, (g)* $n = 2.5$*, (h)* $n = 3.0$ *and* $T_\chi = 10$ *s.*



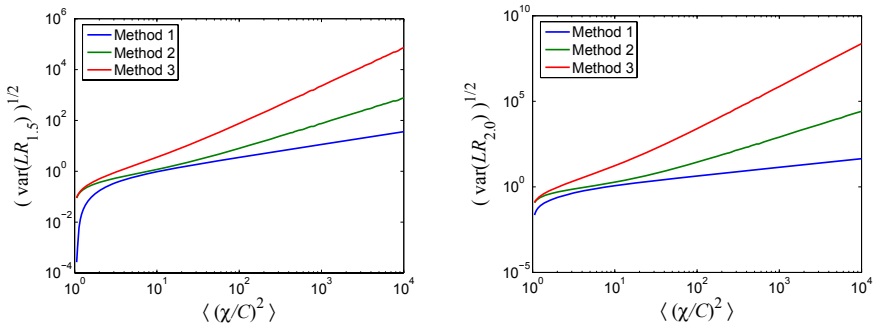
(a) $n = 1.5$, $T_\chi = 1$ s

(b) $n = 2.0$, $T_\chi = 1$ s



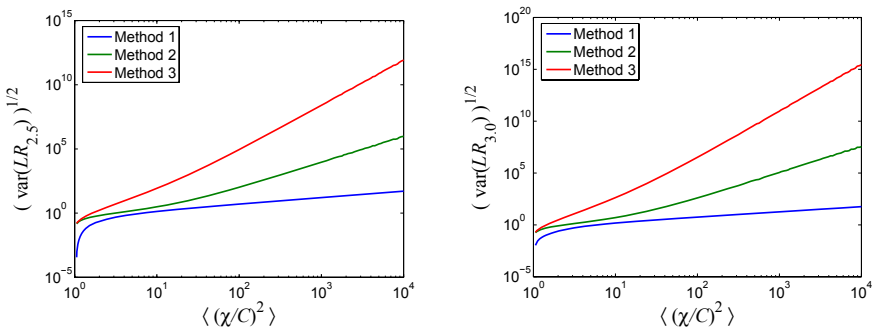
(c) $n = 2.5$, $T_\chi = 1$ s

(d) $n = 3.0$, $T_\chi = 1$ s



(e) $n = 1.5$, $T_\chi = 10$ s

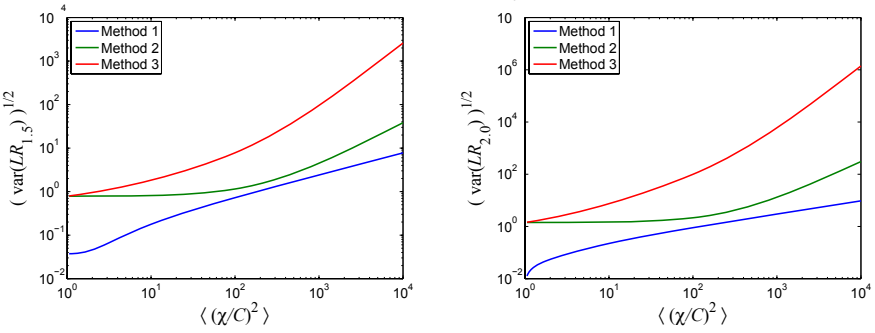
(f) $n = 2.0$, $T_\chi = 10$ s



(g) $n = 2.5$, $T_\chi = 10$ s

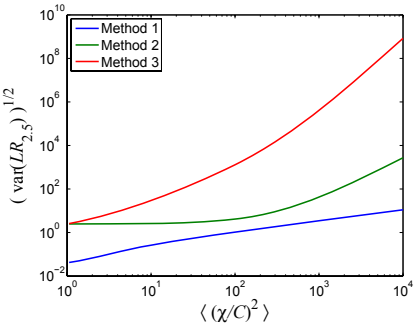
(h) $n = 3.0$, $T_\chi = 10$ s

Figure 7: *Toxic load ratio standard deviation* $\sigma_{LR} \equiv (\mathrm{var}(LR_n))^{1/2}$ *as a function of* $\langle(\chi/C)^2\rangle$ *for toxic load models (methods) 1 (blue curve), 2 (green curve), and 3 (red curve) with* $\tau = 3$ *s,* $t_e = 300$ *s for (a)* $n = 1.5$*, (b)* $n = 2.0$*, (c)* $n = 2.5$*, (d)* $n = 3.0$ *and* $T_\chi = 1$ *s; and, for (e)* $n = 1.5$*, (f)* $n = 2.0$*, (g)* $n = 2.5$*, (h)* $n = 3.0$ *and* $T_\chi = 10$ *s.*

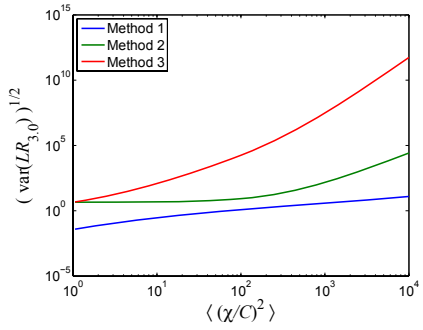


(a) $n = 1.5$, $T_\chi = 1$ s

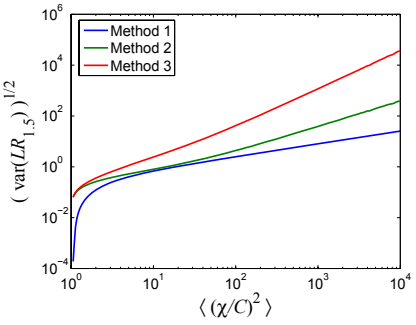
(b) $n = 2.0$, $T_\chi = 1$ s



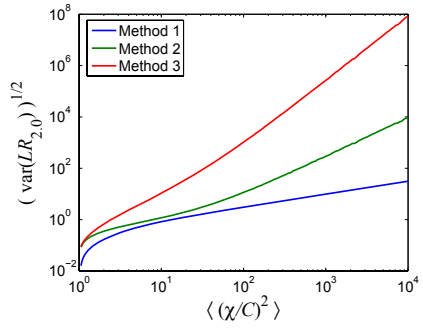
(c) $n = 2.5$, $T_\chi = 1$ s



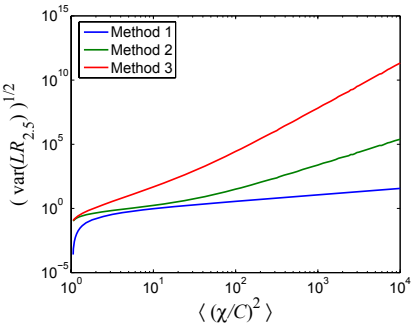
(d) $n = 3.0$, $T_\chi = 1$ s



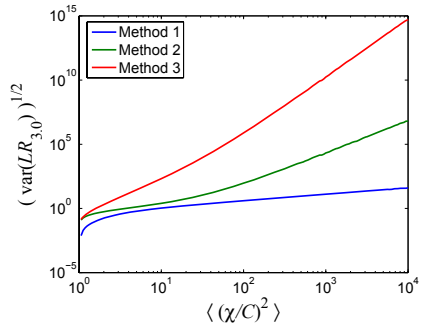
(e) $n = 1.5$, $T_\chi = 10$ s



(f) $n = 2.0$, $T_\chi = 10$ s



(g) $n = 2.5$, $T_\chi = 10$ s



(h) $n = 3.0$, $T_\chi = 10$ s

Figure 8: *Toxic load ratio standard deviation* $\sigma_{LR} \equiv (\mathrm{var}(LR_n))^{1/2}$ *as a function of* $\langle(\chi/C)^2\rangle$ *for toxic load models (methods) 1 (blue curve), 2 (green curve), and 3 (red curve) with* $\tau = 3$ *s,* $t_e = 600$ *s for (a)* $n = 1.5$*, (b)* $n = 2.0$*, (c)* $n = 2.5$*, (d)* $n = 3.0$ *and* $T_\chi = 1$ *s; and, for (e)* $n = 1.5$*, (f)* $n = 2.0$*, (g)* $n = 2.5$*, (h)* $n = 3.0$ *and* $T_\chi = 10$ *s.*

An examination of Figures 5 and 6 shows that as the exposure time t_e increases from 300 s to 600 s, the range of values of $\langle(\chi/C)^2\rangle$ over which the ensemble-averaged toxic load ratio is roughly the same for toxic load models 1 and 3 increases. A comparison of the three toxic load models shows that predictions of $\langle LR_n\rangle$ are smallest for model 2 and largest for model 3, with the predictions of $\langle LR_n\rangle$ obtained from model 1 lying somewhere between those provided by models 2 and 3. It is interesting to note that $\langle LR_n\rangle$ is only slightly larger than unity for toxic load model 2 (implying that concentration fluctuations are not important for the toxic response) over a wide range of values of $\langle(\chi/C)^2\rangle$ for $T_\chi = 1$ s and that this range decreases as T_χ increases from 1 s to 10 s. Furthermore, beyond the range of values of $\langle(\chi/C)^2\rangle$ over which $\langle LR_n\rangle$ is approximately unity for the toxic load model 2, the rate of increase in $\langle LR_n\rangle$ for this model as a function of $\langle(\chi/C)^2\rangle$ is approximately the same as that for toxic load model 1.

The difference in predictions of $\langle LR_n\rangle$ obtained from models 2 and 3 lies in the presence of the factor $\langle(\chi_\tau/C)^2\rangle^{n-1}$ in model 3 [see Eq. (43)]. This factor can be interpreted as the normalized mean-square effective concentration (raised to the power $n-1$), and the discrepancy between $\langle LR_n\rangle$ predictions for models 2 and 3 will increase as $\langle(\chi/C)^2\rangle$ increases and/or as n increases. As a result of this factor and owing to the fact that $\langle(\chi_\tau/C)^2\rangle \geq 1$, it follows from this that the ensemble-averaged toxic load ratio for model 3 must be greater than or equal to that for model 2 (and, in particular, the value $\langle LR_n\rangle$ is equal for models 2 and 3 if and only if $\langle(\chi_\tau/C)^2\rangle = 1$). Furthermore, of the three models, the toxic load model 3 exhibits the most rapid rate of increase of $\langle LR_n\rangle$ with increasing $\langle(\chi/C)^2\rangle$. Unlike toxic load models 1 and 2, it is seen that for toxic load model 3 the $\langle LR_n\rangle$ versus $\langle(\chi/C)^2\rangle$ relationship exhibits an increasing slope as $\langle(\chi/C)^2\rangle$ is increased (at the upper end of the range of values in the normalized mean-square concentration considered in this study).

Figures 7 and 8 exhibit predictions for the toxic load ratio standard deviation σ_L for the three toxic load models as a function of the normalized mean-square exposure concentration $\langle(\chi/C)^2\rangle$ for the same combination of parameters as shown, respectively, in Figures 5 and 6 for the ensemble-averaged toxic load ratio $\langle LR_n\rangle$. The predictions for σ_L for all three models must approach zero as $\langle(\chi/C)^2\rangle \rightarrow 1^+$ (or, equivalently, as the exposure concentration variance approaches zero implying no concentration fluctuations). A perusal of Figures 7 and 8 shows that the rate of convergence of σ_L towards zero as $\langle(\chi/C)^2\rangle \rightarrow 1^+$ differs among the three toxic load models. It is evident that σ_L for toxic load model 1 exhibits the most rapid approach towards zero as $\langle(\chi/C)^2\rangle \rightarrow 1^+$.

It is seen that predictions of the toxic load ratio standard deviation provided by model 1 have the smallest values over the entire range of $\langle(\chi/C)^2\rangle$. The predictions of σ_L for toxic load model 2 are larger than those for model 1, and those for model 3 exceed those for model 2. Again, as for the ensemble-averaged toxic load ratio $\langle LR_n\rangle$, the values of σ_L for model 3 are generally greater than those of model 2 owing the presence of the factor $\langle(\chi_\tau/C)^2\rangle^{n-1}$ in model 3 [see Eq. (44)]. The presence of this factor leads to predictions of very large values for σ_L at large values of the normalized mean-square exposure concentration and/or large values of the toxic load exponent n. These very large values for σ_L seem to be excessive, given the fact that the results correspond to relatively long sampling times (exposure times) of 300 or 600 s.

5 An approximation for the average toxic load ratio

The statistics (ensemble mean and variance) of the toxic load ratio and toxic load were determined under the assumption that the clipped-normal distribution (see Section 3) provided a good model for the probability density function of natural (random) concentration fluctuations. However, the arbitrary moments of the clipped-normal distribution are difficult to compute, and require the accurate numerical evaluation of a confluent hypergeometric function $M(a, b, z)$ (which in and of itself is a difficult task to accomplish).

However, if only the ensemble-averaged toxic load ratio (or, toxic load) is required, then this first-order statistic of the toxic load can be approximated as follows. Yee [27], [40] showed that the lower-order moments (up to about order four) of the intermittent exponential distribution provide a very good approximation for the lower-order moments of the clipped-normal distribution. To this end, the intermittent exponential PDF is a two-parameter PDF that has the following form [34]:

$$f(\chi) = \frac{\gamma^2}{C} \exp\left(-\frac{\gamma\chi}{C}\right) + (1-\gamma)\delta(\chi), \tag{53}$$

where the intermittency factor γ is related to the normalized second-order concentration moment as

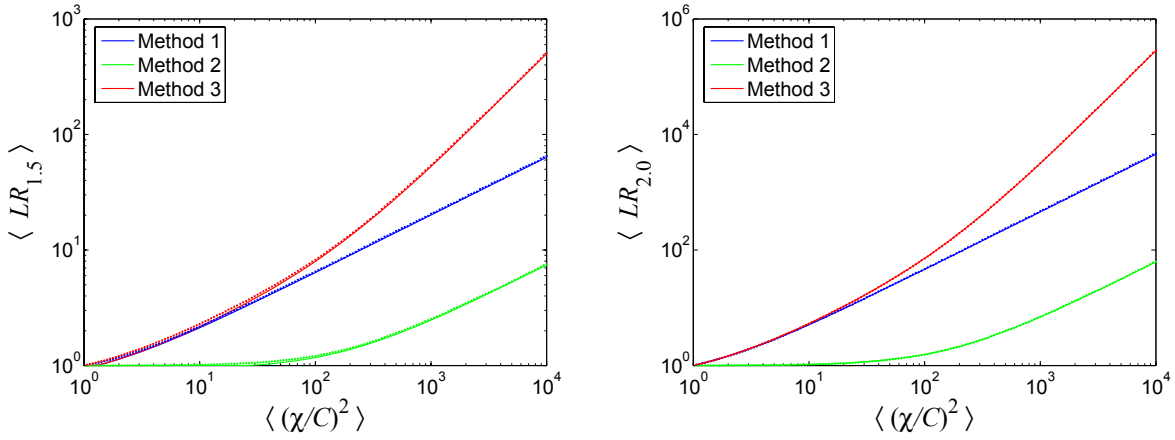
$$\gamma = \frac{2}{\langle(\chi/C)^2\rangle}. \tag{54}$$

This distribution has a very simple functional form and, in consequence, it is possible to determine explicitly the relationship between the higher-order concentration moments and the second-order concentration moment for this distribution. More specifically, it can be shown easily that

$$\left\langle \left(\frac{\chi}{C}\right)^n \right\rangle = \frac{\Gamma(n+1)}{2^{n-1}} \left\langle \left(\frac{\chi}{C}\right)^2 \right\rangle^{n-1}. \tag{55}$$

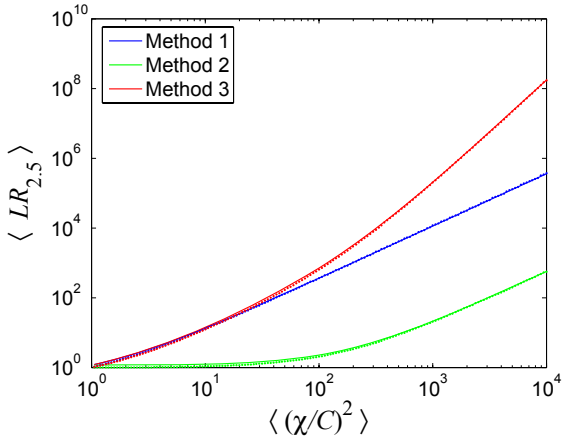
Strictly speaking, the relationship given by Eq. (55) for the exponential distribution is only valid for $\langle(\chi/C)^2\rangle \geq 2$. The lower bound here arises owing to the fact that $\gamma = 1$ exactly at $\langle(\chi/C)^2\rangle = 2$ [cf. Eq. (54)]. However, for the purposes of the approximation of the ensemble-averaged toxic load ratio (or toxic load), Eq. (55) will be applied even for values of $\langle(\chi/C)^2\rangle < 2$. In the latter case, $\langle LR_n\rangle$ will be taken simply as the greater of unity or the value of $\langle LR_n\rangle$ evaluated using the exponential distribution.

Figure 9 compares the ensemble-averaged toxic load ratio with $n = 1.5$, 2, 2.5, and 3 for toxic load models 1, 2, and 3 using both the clipped-normal (solid lines) and intermittent exponential (dotted lines) to predict either the higher-order effective concentration or dosage moments. A comparison here readily shows that the simpler intermittent exponential distribution provides a very good approximation for the ensemble-averaged toxic load ratio over the range of normalized mean-square exposure concentrations exhibited in Figure 9 as compared to that determined using the more sophisticated clipped-normal distribution. Generally, it is seen that the approximation improves for larger values of $\langle(\chi/C)^2\rangle$, but even at the smaller values for $\langle(\chi/C)^2\rangle$ the toxic load ratio ensemble average predicted using the clipped-normal and exponential distributions are virtually indistinguishable.

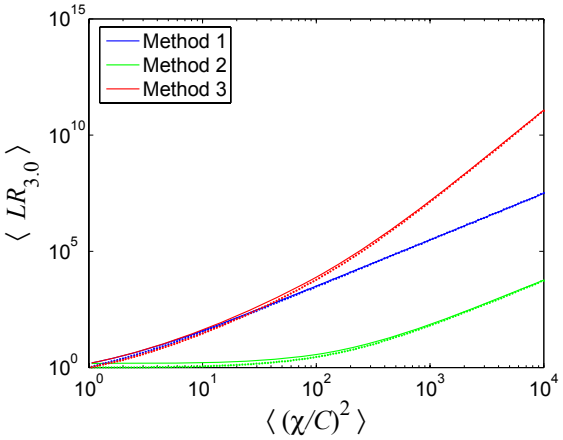


(a) $n = 1.5$, $T_\chi = 1$ s

(b) $n = 2.0$, $T_\chi = 1$ s



(c) $n = 2.5$, $T_\chi = 1$ s



(d) $n = 3.0$, $T_\chi = 1$ s

Figure 9: *Toxic load ratio ensemble average $\langle LR_n \rangle$ as a function of $\langle (\chi/C)^2 \rangle$ for toxic load models (methods) 1 (blue curve), 2 (green curve), and 3 (red curve) with $\tau = 3$ s, $t_e = 300$ s for (a) $n = 1.5$, (b) $n = 2.0$, (c) $n = 2.5$, (d) $n = 3.0$ and $T_\chi = 1$ s. The results are shown using both the clipped-normal (solid lines) and intermittent exponential (dotted lines) distributions to estimate the higher-order concentration or dosage moments required for toxic load models 1, 2, or 3.*

6 A proposed toxicity experiment

In Section 4, it was explicitly demonstrated that for a random fluctuating concentration (which can be only characterized statistically), the toxic load ratio ensemble average and standard deviation predicted using models 1, 2 and 3 differ. To determine which, if any, of these three models for the toxic load provides an adequate prediction of toxicity arising from an exposure to a naturally (random) fluctuating concentration will require experimental data. Ideally, these experiments should involve exposure of various animal species to the

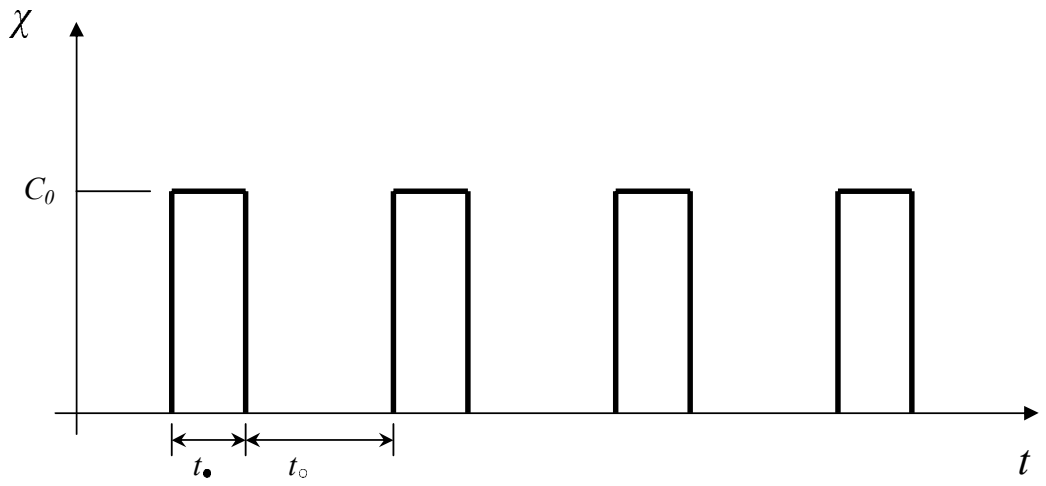


Figure 10: *An idealized fluctuating concentration pattern $\chi(t)$ consisting of a series concentration pulses of amplitude C_0 with a duration of $t_\bullet$ (on time for pulse) separated by a duration of $t_\circ$ (off time for pulse) in which the concentration is zero.*

naturally fluctuating plume concentrations of various toxic gases. Unfortunately, these types of experiments have never been conducted owing to the difficulty in their implementation. In fact, the only experimental data available for validation of acute toxicity models involve exposing laboratory animals to constant concentrations C for a given fixed exposure time t_e.

Given the difficulty of exposing laboratory animals in toxicity experiments to naturally (random) fluctuating concentrations such as those observed in a dispersing plume of a toxic gas in the atmosphere, it would be useful as a first step to consider a toxicity experiment involving the exposure of various laboratory animal species to a simple *deterministic* time varying (or, fluctuating) concentration pattern $\chi(t)$ such as that shown in Figure 10. Here, $\chi(t)$ consists of a series of rectangular concentration pulses of constant amplitude C_0 with a duration of $t_\bullet$ (on time for pulse). Each pulse is separated from the next pulse by a gap of zero concentration with a duration of $t_\circ$ (off time for pulse). For the proposed toxicity experiments involving exposure of animals to the series of concentration pulses, it is assumed that the uptake rate constant τ is significantly smaller than both $t_\bullet$ and $t_\circ$ (viz., $\tau \ll t_\bullet$, $t_\circ$) so the effects of time averaging of the exposure concentration χ to give the effective concentration χ_τ is negligible. In other words, to a very good approximation $\chi_\tau \approx \chi$.

Owing to the fact that the fluctuating concentration pattern shown in Figure 10 is deterministic, the prediction of the toxic load ratio variance σ^2_{LR} provided by the three models is zero. This is as it should be because the fluctuating concentration pattern does not vary from realization to realization (i.e., the concentration pattern is exactly fixed and the same for each realization). We can predict the toxic load ratio ensemble average for the three models for the concentration pattern displayed in Figure 10 as follows. Because the concentration pattern here is deterministic, the ensemble-averaged toxic load ratio is also identical to the instantaneous exposure toxic load ratio.

The ensemble-averaged toxic load ratio for model 1 for the concentration pattern of Figure 10 can be determined directly by application of Eq. (8). Firstly, note that for this concentration pattern, the mean concentration C is given by

$$C = \frac{t_\bullet}{t_\bullet + t_\circ} C_0 \equiv \gamma C_0, \tag{56}$$

where the intermittency factor has been identified as $\gamma \equiv t_\bullet/(t_\bullet + t_\circ)$. Similarly, the n-th concentration moment is $\langle \chi^n \rangle \approx \langle \chi_\tau^n \rangle = \gamma C_0^n$. Inserting this result in Eq. (8) gives

$$\langle LR_n \rangle = \frac{\gamma C_0^n}{(\gamma C_0)^n} = \frac{1}{\gamma^{n-1}} \tag{57}$$

for model 1.

The ensemble-averaged toxic load ratio for model 2 for a concentration pattern consisting of a series of rectangular pulses can be obtained from Eq. (32). Again, recalling that $\chi_\tau \approx \chi$, that $\langle D_\tau \rangle = D_\tau = C t_e = \gamma C_0 t_e$ and that $\langle D_\tau^n \rangle = D_\tau^n = (\gamma C_0 t_e)^n$, it follows immediately that

$$\langle LR_n \rangle = \frac{\langle D_\tau^n \rangle}{\langle D_\tau \rangle^n} = 1 \tag{58}$$

for model 2. Hence, it is seen that for the "average concentration model", the prediction is that the concentration pattern of Figure 10 does not result in an enhancement in the toxicity with respect to the toxic load determined using the mean concentration C.

Finally, the ensemble-averaged toxic load ratio for model 3 can be determined for the series of concentration pulses using Eq. (43). To this purpose, note that $\langle \chi_\tau^2 \rangle \approx \langle \chi^2 \rangle = \gamma C_0^2$, so

$$\langle LR_n \rangle = \frac{\langle D_\tau^n \rangle}{\langle D_\tau \rangle^n} \left(\frac{\langle \chi_\tau^2 \rangle}{C^2} \right)^{n-1} = \left(\frac{\gamma C_0^2}{(\gamma C_0)^2} \right)^{n-1} = \frac{1}{\gamma^{n-1}}, \tag{59}$$

for model 3. A comparison of Eqs. (57) and (59) shows that models 1 and 3 give exactly the same prediction for the enhancement in toxicity relative to the mean concentration toxic load for the series of concentration pulses. Furthermore, this prediction differs from that provided by model 2 for the ensemble-averaged toxic load ratio given by Eq. (58). Models 1 and 3 predict that the enhancement of toxicity varies inversely with the intermittency factor for the concentration pulses raised to the power $(n-1)$. Model 2, in stark contrast, predicts no such toxicity enhancement for the concentration pulses (viz., the toxic load ratio for this model is independent of the intermittency and, hence, of the degree of fluctuations in the series of concentration pulses).

The toxicity experiment proposed herein would allow one to determine whether the toxic load model 2 is to be preferred with respect to toxic load models 1 and 3. The experiments cannot be used to distinguish between the predictive capabilities of toxic load models 1 and 3 because for the concentration pulse pattern, these two models give exactly the same predictions for the ensemble-averaged toxic load ratio. Experiments involving more complex concentration patterns (or, perhaps random concentration patterns) where the predictions of the ensemble-averaged toxic load ratios for models 1 and 3 differ would be required to

properly assess the prediction efficacies of these two models. Finally, it should perhaps be noted that the prediction of model 2 appears to contradict the experimental results summarized in [10]. However, the results of the toxicity experiments purportedly conducted by the Japanese military toxicologists during the Second World War have never been replicated by other investigators (to the author's best knowledge) and, as a consequence, model 2 cannot be rejected outright.

7 Conclusions

The information that is used to formulate acute toxicity models based on the toxic load has been obtained from various experiments involving exposing laboratory animals to *constant* concentrations of a toxic gas for a fixed exposure time. Unfortunately, the stirring and mixing behaviour of a turbulent plume or cloud dispersing in the atmosphere implies that exposure concentrations will exhibit natural (random) fluctuations over a wide range of space and time scales and, indeed, these fluctuations in concentration (particularly for small discrete sources) will be comparable with or larger than the mean concentration. This may have significant consequences for the toxicity of many gases which do not depend linearly on the concentration and exposure time, so that the toxic response cannot be assessed properly from a knowledge of the mean concentration alone. In consequence, there have been various attempts to generalize the toxic load model for constant concentrations in order to deal with the toxicity of fluctuating concentrations.

In this report, we consider three different models for the toxic load and toxic load ratio for random fluctuating concentrations. A prediction of the statistical characteristics of the toxic load (or, toxic load ratio) using first principles would be dependent on an infinite amount of statistical information about the fine-scale structure of the concentration fluctuations. Naturally, in general, for natural (random) concentration fluctuations arising from dispersion of a toxic gas in the atmosphere, the infinite amount of information can never be ascertained in practice. Despite this insuperable difficulty, progress can be made. To this purpose, it is shown how some statistical characteristics of the toxic load and toxic load ratio (and, more specifically, the ensemble average and variance) can be predicted given only very limited information on the statistical properties of the fluctuating exposure concentration χ (namely, the mean concentration, the concentration variance, and the integral time scale of concentration fluctuations).

The explicit dependence of the ensemble average and variance of $\langle L \rangle$ and $\langle LR \rangle$ on the uptake time constant τ, the exposure time t_e, the integral time scale of concentration fluctuations T_χ, the toxic load exponent n, and various moments of the exposure concentration or dosage for three different models have been determined. These relationships have been used in conjunction with a specific model for the probability density function of the concentration or dosage (namely, the clipped-normal distribution) in order to provide specific predictions for the mean and variance of the toxic load and toxic load ratio for the three models.

It has been demonstrated that the three models for toxic load and toxic load variance provide distinct (different) predictions, although each of these models provides exactly the

same prediction for a constant concentration exposure (viz., these three models are mathematically equivalent for a constant concentration). The predictions have been undertaken for a large number of combinations of n, τ, t_e, T_χ and $\langle(\chi/C)^2\rangle$. There are no experimental data that currently exists which can be used to assess the predictive accuracy of the three toxic load models for (random) fluctuating concentrations. As a preliminary attempt to resolve this deficiency, a toxicity experiment involving the exposure of laboratory animals to a simple fluctuating concentration consisting of a series of rectangular concentration pulses has been proposed. Predictions of the three toxic load models for this simple fluctuating concentration pattern has been provided and the undertaking of the proposed toxicity experiment would allow one to determine whether the predictions provided by either models 1 and 3 or model 2 is in better conformance with the observed results. The use of a simple concentration pattern consisting of concentration pulses of constant duration does not allow one to distinguish between the prediction efficacy of toxic load models 1 and 3. To do this would require the design of an experiment involving exposures of animals to more complex (albeit random) concentration fluctuations than that provided by a deterministic series of regularly spaced concentration pulses of fixed amplitude.

In addition to conducting experimental studies involving exposures of animals to more complex concentration patterns, it is conceivable that the application of physiologically-based toxicokinetic/toxicodynamics modeling may provide additional insights into the "correct" avenue to proceed vis-à-vis the generalization of the toxic load model for naturally fluctuating concentration exposures. Furthermore, it is conceivable that advances in systems pathobiology that involves the holistic integration of genetic, genomic, biochemical, cellular, physiological, and clinical data to create a network that can be used to model predictively the effect and fate of chemical agent ingestion in the body may add significantly to these insights. What we lack currently is a rigorous scientific theory that provides a *good* explanation as to if, how and why the presence of naturally occurring concentration fluctuations enhances the effects of a toxic gas on exposed personnel. By good explanation here, we are referring to a search for an explanation that has reach (viz., an explanation that explains more and solves problems beyond those that it was created for).

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The toxic load model is widely used in hazard assessment involving the release of toxic gases into the atmosphere. The underlying basis of this model consists of laboratory experiments in which various animal species are exposed to constant concentrations of a toxic gas for a fixed exposure duration. However, natural variability (fluctuations in the concentration of a toxic gas at a point in a plume dispersing in the atmosphere is a ubiquitous feature that must be properly incorporated into the toxic load model for noxious gases which do not vary linearly with the concentration and exposure time. Towards this purpose, the statistical characteristics of the toxic load (or, equivalently, the toxic load ratio) have been explicitly derived from the statistical properties of the exposure concentration on which it depends for three different models. In particular, the ensemble average and variance of the toxic load (and the related toxic load ratio) have been determined assuming that the probability density function of either the exposure concentration or dosage is well characterised using a clipped-normal distribution.

Although these three models give the same predictions of the toxic load for constant concentration exposures, it is shown that predictions of the statistical characteristics (ensemble average and variance) of the toxic load ratio appropriate for a naturally fluctuating concentration exposure differ for the three models over a wide range of combinations of parameters on which the models depend (e.g., uptake time constant, exposure time, integral time scale of concentration fluctuations, and higher-order moments of exposure concentration or dosage). Owing to the fact that there is no experimental data that can be used to assess the prediction efficacy of these three toxic load models for a random fluctuatin concentration, a simple toxicity experiment is proposed involving a series of constant concentration pulses. An analysis of this proposed experiment with reference to the three toxic load models is provided.

Le modèle de charge toxique est largement utilisé pour l'évaluation des risques posés par le rejet de gaz toxiques dans l'atmosphère. La base sous-jacente de ce modèle est constituée d'expériences en laboratoire au cours desquelles diverses espèces animales sont exposées à des concentrations constantes d'un gaz toxique pendant une durée fixe. Toutefois, la variabilité naturelle (fluctuation) de la concentration d'un gaz toxique à un point donné d'un panache se dispersant dans l'atmosphère est une caractéristique ubiquiste qui doit être correctement incorporée dans le modèle de charge toxique pour des gaz nocifs qui ne varient pas linéairement avec la concentration et la durée d'exposition. À cette fin, les caractéristiques statistiques de la charge toxique (ou, de manière équivalente, le rapport de charge toxique) ont été dérivées explicitement des propriétés statistiques de la concentration d'exposition, dont elles dépendent pour trois modèles différents. En particulier, la moyenne d'ensemble et la variance de la charge toxique (et le rapport de charge toxique relié) ont été déterminées en assumant que la fonction de densité de la concentration d'exposition ou du dosage est bien caractérisée au moyen d'une loi normale partielle.

Bien que ces trois modèles conduisent aux mêmes prédictions de la charge toxique pour des expositions à concentration constante, nous avons montré que les prédictions des caractéristiques statistiques (moyenne d'ensemble et variance) du rapport de la charge toxique appropriée pour une exposition à une concentration fluctuant naturellement diffèrent pour les trois modèles sur une large gamme de combinaisons de paramètres desquelles le modèle dépend (p. ex. constante de la durée d'absorption, durée de l'exposition, échelle de temps intégrée des fluctuations de la concentration et moments d'ordre supérieur de la concentration ou du dosage d'exposition. Étant donné que nous ne disposons d'aucune donnée expérimentale pouvant être utilisée pour évaluer l'efficacité de prédiction de ces trois modèles de charge toxique pour une concentration fluctuant aléatoirement, nous proposons une simple expérience de toxicité mettant en jeu une série d'impulsions de concentration constantes. Une analyse d'une telle expérience proposée avec référence aux trois modèles de charge toxique est fournie.

14. KEYWORDS, DESCRIPTORS or IDENTIFIERS

concentration fluctuation
concentration probability distribution
hazard assessment
plume dispersion
toxic load

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