Journal of Hazardous Materials 167 (2009) 351–356

Contents lists available at ScienceDirect

Journal of Hazardous Materials

journal homepage: www.elsevier.com/locate/jhazmat

A model for the toxic dose under time-varying concentration

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ARTICLE INFO

Article history:
Received 15 April 2008
Received in revised form 27 October 2008
Accepted 31 December 2008
Available online 13 January 2009

Keywords:
Toxic load
Effective dose
Time-varying concentration
Shielding factor

ABSTRACT

The concept of dose-load is used widely in risk assessment literature. This concept is based on animal experiments in which the animals were exposed to *constant concentration* during a set period of time. However, in most accident scenarios, people are exposed to time varying concentration of the toxic materials. The extension of the dose-load concept to such conditions is not straightforward. The assumption that the dose-load is additive leads to a paradox. We suggest a different approach for extending the experimental results for time-varying concentration. We introduce the concept of the effective dose, which considers physiological recovery processes. It is found that in many cases, especially those which include intermittent time series of the concentration, the number of casualties is reduced when considering the recovery process. It is also shown that by using the effective dose concept we can resolve the apparent paradox in the dose-load concept for intermittent concentration time series.

We demonstrate the importance of buildings as shelter against toxic gases especially for an instantaneous release, a fact that should be considered in hazard evaluation.

1. Introduction

On the basis of animal experiments, it was found that the effect due to exposure to a toxic gas depends nonlinearly upon concentration and duration for exposure periods greater than a few minutes. Busvine [2] suggested an exponential dependence on the concentration. According to his analysis the casualty fraction depends on $L = C^n t$, where C is the concentration and t is the exposure time. L is defined as the toxic dose-load. The exponent n was determined by analyzing the experimental data using the probit method (see [4]). Ten-Berge [9] determined the parameter n for many toxic gases. He found that the value for industrial gases is 2–3. The concept of the dose-load is used widely in hazard evaluation. In most of the realistic accident scenarios, concentration time series includes numerious fluctuations and even intermittent periods. Such fluctuations were measured in wind tunnel modeling (see, for example [10–12]). Although all of the animal experiments were performed for constant concentration, the concept of dose-load was used for cases of time-varying concentration (see, for example [9,5]). Several works deal with time-varying concentration using idealized functions (see, for example [7]). Ride [6] suggested that the response to the time-varying concentration should take into account filtering rapid concentration fluctuations and uptake time. A detailed model which considers these effects was suggested by Hilderman et al. [8]. In this work the authors suggest a set of differential equations which relate the dose-load to the effective toxicity. Their model requires parameters in addition to the exponent n in order to determine the fraction of casualties, for example: take-up time and recovery time, but in general, these parameters are not available.

A different analysis for the experimental data was performed by Johnson et al. [3]. They found that the fraction of casualties depends on Dt^m ($m < 0$) for exposure time greater than a few minutes, where $D = Ct$ is the accumulated dose, t is the exposure time and m an experimental exponent.

In this work we will show that the toxic dose-load approach and the time-dependent dose approach are equivalent for exposures to constant concentrations. We derive the relation between m and n (the time exponent and concentration exponent respectively). Johnson's result that the casualty fraction decreases with exposure time although the accumulated dose is constant is attributed to the fact that for long exposure time physiological recovery processes take place. Due to these processes the dose that determines the casualties fraction differs from the accumulated dose. We define this dose as the effective dose. We define a recovery function and evaluate it using probit analysis for the experimental data. We use the recovery function to calculate the effective dose for exposures to time-varying concentrations. The formula we derive depends only on the exponent n and does not involve unknown parameters. Examples are shown for different time-varying series of the concentration. We also use this model to calculate the shielding factor of a building to exposures to instantaneous and continuous sources.

In Section 2 we introduce the concept of the dose-load. In Section 3 we define the concept of effective dose, derive the relation

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doi:10.1016/j.jhazmat.2008.12.132

Nomenclature

L	toxic dose-load ($(mg/m^3)^n$ min)
D	accumulated dosage (mg min/m^3)
D_{eff}	effective dosage (mg min/m^3)
D_{tox}	toxic dosage (mg min/m^3)
$F_R(t)$	recovery function
Pr	probit
Fr	casualties fraction
S	shielding factor

between the effective dose and the dose-load and evaluate the recovery function from the experimental results. In Section 4 we present the difference between the traditional extension of the dose-load to time-varying concentration and the extension of the effective dose concept for these conditions. An application for calculating the building shielding factor is presented in Section 5.

2. The dose-load concept

The probit, Pr, was introduced by Bliss [1] in order to linearize the commulative normal distribution. The fraction of the population, F, affected by the toxic gas is

$$F = 0.5\left[\mathrm{erf}\left(\frac{Pr-5}{\sqrt{2}}\right)+1\right] \tag{1}$$

In this formula the probit is defined arbitrarily as 5 for the median, i.e., 50% of the population responding to the exposure.

In the various animal experiments it was found that for exposure time greater than critical time, t_0, of the order of few minutes, the probit, Pr, is a linear function of the logarithm of the concentration, C, and the logarithm of the exposure duration time, t:

$$Pr = a_0 + a_1 \ln C + a_2 \ln t \tag{2}$$

This linear dependence can be written in the form:

$$Pr = a_0 + a_2\left(\frac{a_1}{a_2}\ln C + \ln t\right) = a_0 + a_2 \ln(C^n t), \qquad n = \frac{a_1}{a_2} \tag{3}$$

The dose-load is defined as

$$L = C^n t \tag{4}$$

In terms of the dose-load the probit can be written in the form:

$$Pr = a_0 + a_2 \ln L \tag{5}$$

All animal experiments on which Eq. (5) is based were performed with constant concentration during different time periods. Ten-Berge [9] extended this equation to time-varying concentrations, i.e., Eq. (5) holds also for

$$L = \int_0^t C^n(t')\,dt' \tag{6}$$

This extension was done arbitrarily and without any justification. However the concept of the dose-load is widely used in hazard evaluation. In this work we would like to suggest an alternative approach for extending the probit dependence on the concentration and time to time-varying concentrations. We define the effective dose concept and show that it can explain several paradoxes in the dose-load concept.

3. The effective dose concept

We rewrite Eq. (2) in the form

$$Pr = a_0 + a_1\left(\ln C + \frac{a_2}{a_1}\ln t\right) = a_0 + a_1 \ln(Ct^{1/n}) \tag{7}$$

The accumulated dose under exposure to constant concentration during a period t is $D = Ct$. Define $\tilde{a}_0$ by

$$\tilde{a}_0 = a_0 + a_1 \ln(t_0^{1/n-1}) \tag{8}$$

with t_0 the critical time.

The probit can then be expressed as

$$Pr = \tilde{a}_0 + a_1 \ln\left[D\left(\frac{t}{t_0}\right)^{1/n-1}\right] \tag{9}$$

We define the effective dose as

$$D_{eff} = D\left(\frac{t}{t_0}\right)^{1/n-1} \tag{10}$$

Using the effective-dose concept the probit can be written as

$$Pr = \tilde{a}_0 + a_1 \ln(D_{eff}) \tag{11}$$

As the exposure time tends to the critical time t_0, the effective dose presentation of the probit (Eq. (11)) tends to the familiar linear dependance of the probit on the dosage. The two ways of presenting the probit (Eqs. (5) and (11)) are equivalent as long as there is exposure to constant concentration.

In order to extend the concept of the effective dose to exposures under time-varying concentrations we should first understand this concept. From Eq. (10) we deduce that the effective dose, D_{eff}, is smaller than the actual dose, D ($n \geq 1$). We can explain this behaviour by the existence of a recovery process; the toxicity of absorbed material diminishes with time due to recovery processes of the body. The time scale of this recovery process is greater than t_0 and that is the reason why for exposure time smaller than t_0, the probit depends on the dose.

The fraction of the population affected is a function of the dose remaining after recovery: D_{eff}. Denote by $F_R(t)$ the recovery function. The extension of the effective dose concept to time varying concentrations is straightforward:

$$D_{eff} = \int_0^t C(t')F_R(t-t')\,dt' \tag{12}$$

Using this equation we can eliminate $F_R(t)$ from the known time dependency of the effective dose in the case of exposure to constant concentration (Eq. (10)). From Eqs. (10) and (12) it follows that in this case:

$$D_{eff} = C\int_0^t F_R(t-t')\,dt' = Ct\left(\frac{t}{t_0}\right)^{1/n-1} \tag{13}$$

Therefore

$$F_R(t) = \frac{d}{dt}\left[t\left(\frac{t}{t_0}\right)^{1/n-1}\right] = \frac{1}{n}\left(\frac{t}{t_0}\right)^{1/n-1} \tag{14}$$

From Eqs. (12) and (14) it follows:

$$D_{eff} = \int_0^t C(t')\frac{1}{n}\left(\frac{t-t'}{t_0}\right)^{1/n-1} dt' \tag{15}$$

D, the accumulated dosage, is a nondecreasing function of time, while the time dependency of the effective dosage is not necessarily monotonic and depends on the exposure. The reason is the competition between the rate of intake of the toxic material to the body and the rate of its removal. If the recovery process is faster than the rate of accumulation the effective dose will decrease with time. As an example we calculate the effective dose for exposure to constant concentration C_0 during time T_0. With Eq. (15) the effective

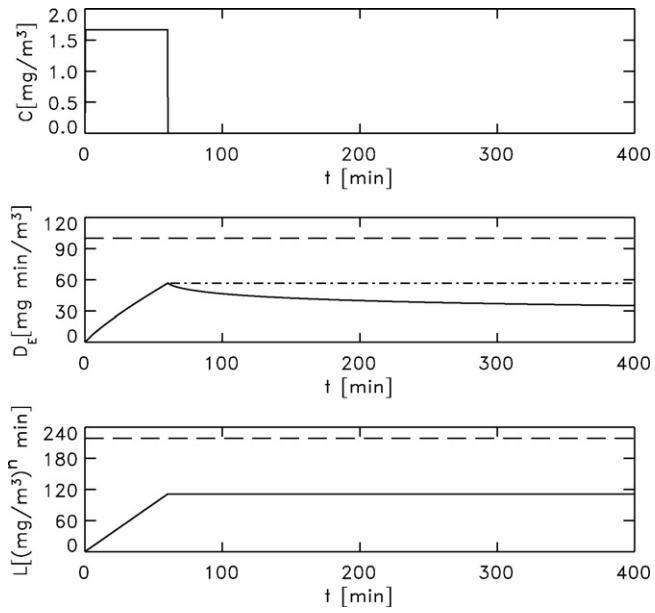

Fig. 1. The effective dose, toxic dose and dose-load for exposure to constant concentration during 1 h. The accumulated dose is 100 mg min/m^3 ($n = 1.2$). Top: the concentration; middle: the effective dose, line; and the toxic dose, dash-dot line; bottom: the dose-load. Dashed line indicates the critical value.

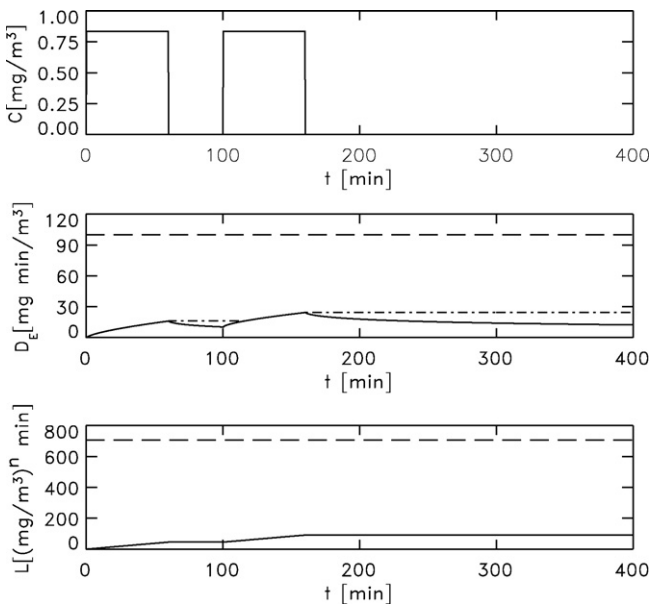

Fig. 2. The effective dose, toxic dose and dose-load of exposure to two pulses of constant concentration 40 min apart. The duration of each pulse is 1 h. The accumulated dose is 100 mg min/m^3 ($n = 1.5$). Top: the concentration; middle: the effective dose, line; and the toxic dose, dash-dot line; bottom: the dose-load. Dashed line indicates the critical value.

dose in this case is

$$D_{\text{eff}}(t) = \begin{cases} C_0 t \left(\dfrac{t}{t_o}\right)^{1/n-1} & t \le T_0 \\ C_0 T_0 \dfrac{(t/t_0)^{1/n} - ((t-T_0)/t_0)^{1/n}}{T_0/t_0} & t > T_0 \end{cases} \tag{16}$$

This behaviour is presented in Fig. 1 for $n = 1.2$, $t_0 = 2$ min and $T_0 = 60$ min. The fraction of the population affected during the period $[0, t]$, $t > T_0$ depends on the maximum of the effective dose in this period. Define the toxic dose D_{tox} as the maximum of the effective dose:

$$D_{\text{tox}} = \max_t(D_{\text{eff}}(t)) \tag{17}$$

The probit is a linear function of the logarithm of D_{tox}:

$$Pr = \tilde{a}_0 + a_1 \ln D_{\text{tox}} \tag{18}$$

4. The effective dose concept versus the toxic dose-load concept

The two ways of presenting the probit (Eqs. (5) and (11)) are equivalent as long as the exposure is to constant concentration. It follows from these equations that if D_0 is the value of the effective dose causing a given fraction of responses, then the value of the dose-load required to achieve the same fraction, R_0 is

$$R_0 = D_0^n t_0^{1-1/n} \tag{19}$$

However, in case of exposure to time-varying concentration there is a difference between the two cases. The following example demonstrates this difference. Assume that the exposure is to two successive pulses of concentration, C_0 each of them of length τ seperated by an interval T (see Fig. 2). The dose-load in this case is

$$L = 2C_0^n \tau \tag{20}$$

and does not depend on T. This behaviour leads to a paradox. If the time dependency of the affected fraction is attributed to recovery processes, then we expect dependency on the interval between the two pulses.

The toxic dose is the maximum of the effective dose which is obtained at $t = 2\tau + T$ (see Fig. 2). This value is

$$\begin{aligned} D_{\text{tox}} &= \max_t[D_{\text{eff}}(2\tau + T)] = C_0 \int_0^{\tau} F_R(2\tau + T - t')\,dt' \\ &\quad + C_0 \int_{T+\tau}^{T+2\tau} F_R(2\tau + T - t')\,dt' \\ &= C_0 t_0 \left[\left(\frac{2\tau + T}{t_0}\right)^{1/n} - \left(\frac{\tau + T}{t_0}\right)^{1/n} + \left(\frac{\tau}{t_0}\right)^{1/n}\right] \end{aligned} \tag{21}$$

For two adjoining pulses, i.e., $T = 0$, the toxic dose is the same as one pulse of length 2τ:

$$D_{\text{tox}} = C_0 2\tau \left(\frac{2\tau}{t_0}\right)^{1/n-1} \tag{22}$$

When the two pulses are far apart ($T = \infty$) the contribution to the probit is only from the second pulse:

$$D_{\text{tox}} = C_0 \tau \left(\frac{\tau}{t_0}\right)^{1/n-1} \tag{23}$$

An example is shown in Figs. 2 and 3, the exposure is in two periods of 1 h each. The total dose is 100 mg min/ m^3. The assumed exponent factor of the material is $n = 1.5$. In the first example (Fig. 2) the two pulses are 40 min apart. After the exposure the toxic dose is less than the total dose by a factor of 4. When the two pulses are 240 min apart (Fig. 3), the ratio between the toxic dose and the total dose is a factor of 10. The dose load is the same in the two cases.

5. Examples: shielding factor of buildings

In this section, we use the concept of the toxic dose to calculate the efficiency of protective measures. We define the shielding factor, S, as the ratio between the toxic dose with the protective measure to the toxic dose without it. The shielding factor can be used to estimate the fraction of population not affected due to the protective measure. Using Eq. (18) we can see that in the presence of protective measures with shielding factor S, the probit, Pr, decreases by $\ln S$.

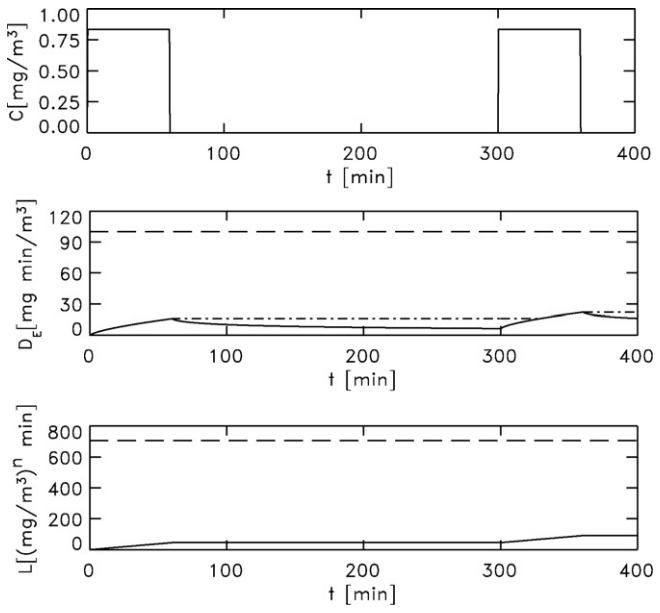

Fig. 3. The effective dose, toxic dose and dose-load of exposure to two pulses of constant concentration 240 min apart. The duration of each pulse is 1 h. The accumulated dose is 100 mg min/m^3 ($n = 1.5$). Top: the concentration; middle: the effective dose, line; and the toxic dose, dash-dot line; bottom: the dose-load. Dashed line indicates the critical value.

For example, for $a_1 = 1$, if at $Pr = 5$ we expect 50% effect without the protective measure, than in presence of a protective measure with shielding factor $S = 0.4$, the fraction is reduced to 17% ($Pr = 4.08$). Fig. 4 presents the fraction of affected population in presence of various shielding factors for two cases: unprotected dose of LD_{50} and unprotected dose of LD_{10} (dashed line).

Masks or filters reduce the affected fraction by reducing the concentration and not the exposure time. Therefore the shielding factor of masks equals the ratio of the concentration inside and outside the masks. Buildings, on the other hand, change the exposure time. If the population stays inside buildings they are exposed to concentration $C_{\text{in}}(t)$ which depends on the ventilation rate. With T_E the typical ventilation time, the equation describing the concentration inside the building is

$$\frac{dC_{\text{in}}}{dt} = -\frac{1}{T_E}C_{\text{in}}(t) + \frac{1}{T_E}C_{\text{out}}(t) \tag{24}$$

C_{out} is the concentration outside the building. The solution to this equation is

$$C_{\text{in}}(t) = \frac{e^{-t/T_E}}{T_E}\int_0^t C_{\text{out}}(t')e^{t'/T_E}dt' \tag{25}$$

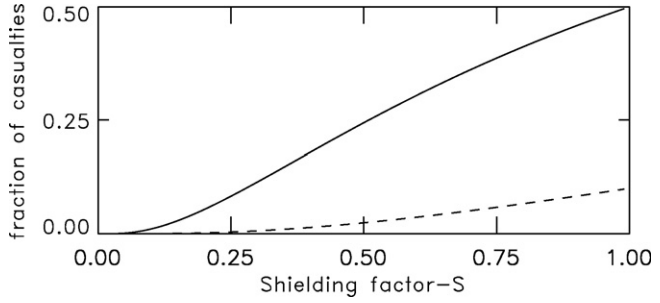

Fig. 4. The affected fraction as a function of the shielding factor for LD_{50} and LD_{10}. Line: LD_{50}; dashed line: LD_{10}.

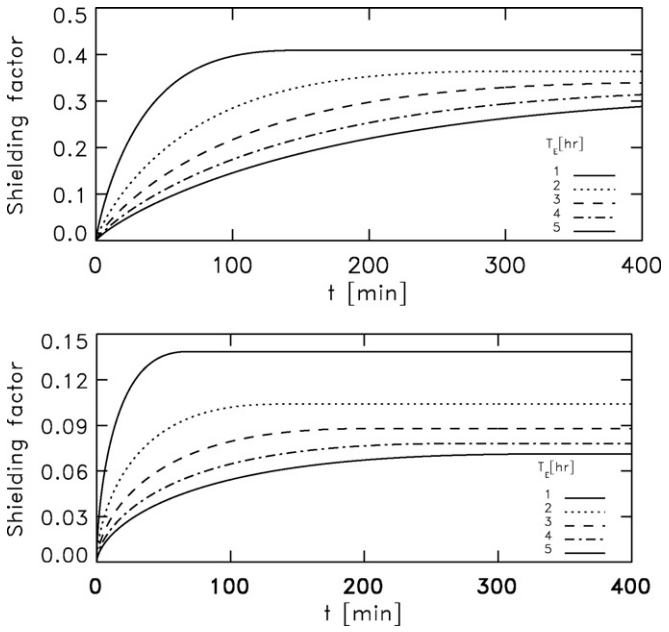

Fig. 5. Shielding factor of building for an instantaneous release. Different curves are for different ventilation rates of the building. Top: $n = 1.2$; bottom: $n = 1.7$.

The effective dose outside the building is

$$D_{\text{eff}}^{\text{out}} = \int_0^t C_{\text{out}}(t')F_R(t-t')\,dt' \tag{26}$$

where $F_R(t)$ is the recovery function given by Eq. (14). The effective dose inside the building is

$$D_{\text{eff}}^{\text{in}} = \int_0^t C_{\text{in}}(t')F_R(t-t')\,dt' \tag{27}$$

where C_{in} is given by Eq. (25). The shielding factor, S, is the ratio between the toxic dose inside the building to that outside the building:

$$S = \frac{\max_t D_{\text{eff}}^{\text{in}}}{\max_t D_{\text{eff}}^{\text{out}}} \tag{28}$$

5.1. Shielding factor of buildings in case of an instantaneous release

In case of an instantanous release, the exposure time is usually of the order of few minutes (t_0), therefore the toxic dose is equal to the dose acumulated during the cloud passage, D_{out}. We can approximate the integral in Eq. (25) by D_{out}, so that C_{in} decays exponentially:

$$C_{\text{in}}(t) = \frac{D_{\text{out}}}{T_E}e^{-t/T_E} \tag{29}$$

Using Eq. (11) with the expression (29) for the concentration inside the building, we can calculate the shielding factor, S, of the building for exposure to an instantaneous release:

$$S = \max_t \int_0^t \frac{1}{T_E}e^{-t'/T_E}F_R(t-t')\,dt' \tag{30}$$

In Fig. 5 (top) we present the shielding factor as a function of time for a material with $n = 1.2$ and buildings with several ventilation rates. As expected the smaller the ventilation time, the larger the building shielding (i.e., the smaller the shielding factor). A similar result is presented in Fig. 5(bottom) for $n = 1.7$. In this case the shielding factor is almost 0.1 for all ventilation times. It follows that

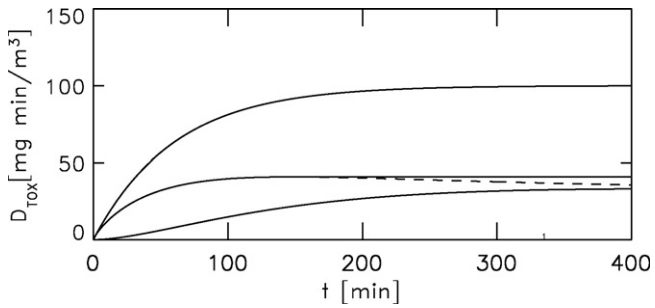

Fig. 6. The effective dose and toxic dose of an exponentially decaying continuous source $(100/60)e^{-t/60}$ ($n = 1.2$). The ventilation time of the building is 2 h. Lower curve: inside toxic dose; middle curve: outdoor effective dose and toxic dose (dashed); upper curve: the commulative dose.

buildings are very efficient in providing protection against instantaneous sources, especially if people know to leave the building after the cloud passes.

5.2. Shielding factor of buildings in case of a continuous source

The toxic dose outside the building, $D_{\text{tox}}^{\text{out}}$ of a continuous source, C_{out}, is given by (see (15))

$$\max_t(D_{\text{eff}}(t)) = \max_t\left(\int_0^t C_{\text{out}}(t')\frac{1}{n}\left(\frac{t-t'}{t_0}\right)^{1/n-1}\right)\mathrm{d}t' \tag{31}$$

Due to the recovery process, $D_{\text{tox}}^{\text{out}}$ is less than the actual dose D_{out}:

$$D_{\text{out}} = \int_0^t C_{\text{out}}(t')\,\mathrm{d}t' \tag{32}$$

When a person is inside the building, another reduction in the toxic dose is obtained. The effective dose inside the building, D_{in}, is given by

$$D_{\text{in}}(t) = \int_0^t C_{\text{in}}(t')F_R(t-t')\,\mathrm{d}t' \tag{33}$$

Using the expression for the concentration inside the building (Eq. (25)), the effective dose can be expressed in terms of the outdoor concentration, C_{out}:

$$D_{\text{in}}(t) = \int_0^t F_R(t-t')\frac{\mathrm{e}^{-t'/T_E}}{T_E}\int_0^{t'} C_{\text{out}}(t'')\mathrm{e}^{t''/T_E}\,\mathrm{d}t''\,\mathrm{d}t' \tag{34}$$

For an exponential decaying source of the form $(C_0/T_C)\mathrm{e}^{-t/T_C}$ this equation can be rewritten in the form:

$$D_{\text{in}}(t) = \int_0^t F_R(t-t')\begin{cases}\dfrac{C_0}{T_C T_E}\mathrm{d}t' & T_C = T_E\\ \dfrac{C_0}{T_C - T_E}(\mathrm{e}^{-t'/T_C} - \mathrm{e}^{-t'/T_E})\,\mathrm{d}t' & T_C \neq T_E\end{cases} \tag{35}$$

In Fig. 6 we present the effective doses outside and inside the building for an exponentially decaying source with a decay time of 1 h. The ventilation time of the building is 2 h. The toxic load exponent, n, is 1.5. The outside effective dose in this case is an increasing function of time and therefore equals the toxic dose. The inside effective dose decreases after 2 h. The toxic dose is constant after that time (dashed line). The upper curve is the accumulated dose. Fig. 7 presents the shielding factor of building for exponential decaying continuous source ($(100./60)\mathrm{e}^{-t/60}$) and different ventilation times. The shielding factor for materials with $n = 1.2$ (Fig. 7 top) is of the order 0.6–0.9 for the different ventilation times. For materials with $n = 1.7$ (Fig. 7 bottom) is of the order 0.4–0.6.

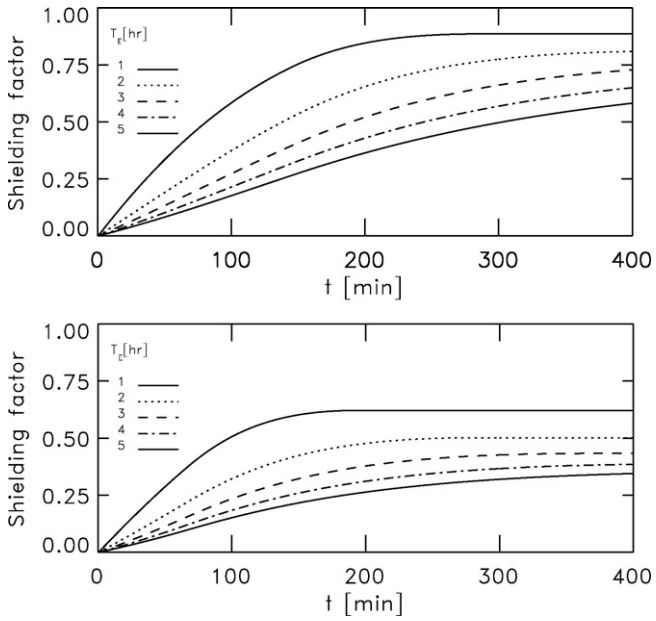

Fig. 7. Shielding factor of building for exponential decaying continuous release. Different curves are for different ventilation rates of the building. The source decay time is 1 h. Top: $n = 1.2$; bottom: $n = 1.7$.

5.3. Example

In order to illustrate the importance of the recovery process, we use the example of Chan [14]. In this example a simulation of a 4-h Cl_2 release near downtown Albuquerque is presented. In Fig. 8 (top) the calculated in-door concentration profile of a typical dwelling 10 km downwind of the release point is presented. The calculated accumulated dose (dot-dashed) and effective dose (line) are presented in the bottom figure. The effective dose was calculated for $n = 1.3$ (see [15]). In this example the exposure for 4 h was reduced by a factor of 2.8 due to the recovery process.

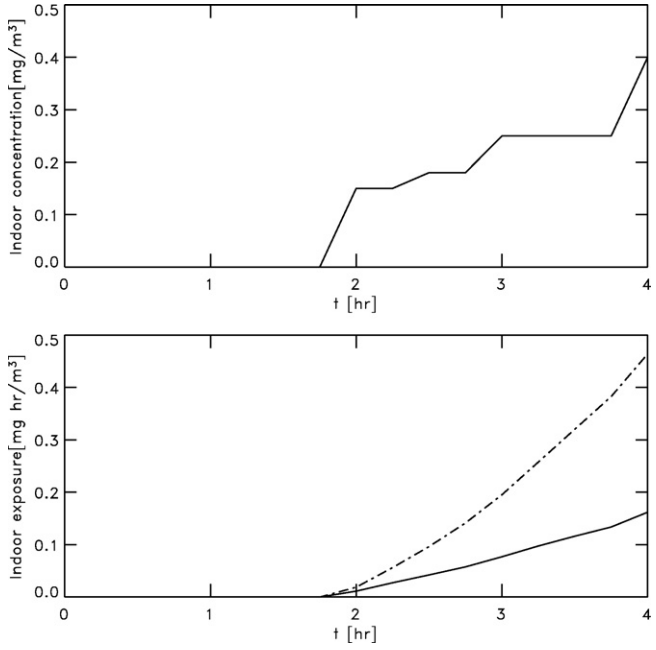

Fig. 8. Example: Cl_2 release within a the city. Top: indoor concentration profile 10 km downwind to the source. Bottom: exposure—accumulated dose (dot-dashed), effective dose (line).

6. Summary

In most accidental releases of toxic gas, the concentration at a given location varies with time and its time series includes intermittent periods. This variation is attributed to the release conditions, and to the specific locations (urban canopy, indoor, etc.). Since for most toxic materials there is a physiological recovery process, it is important to include it in the risk assessment estimations.

In this work we suggest a simple model to calculate the toxic dose for exposure to time-varying concentration. The model is based on the experimental observation that for a given accumulated dose, the fraction of affected population decreases with increasing exposure time. Assuming that this behaviour is attributed to physiological recovery process, we derive the recovery function from the experimental results. Using this recovery function we calculate the toxic dose for a general time series of the concentration. In most cases the model predicts fewer affected individuals than that predicted by the traditional dose-load concept. The model is important for continuous sources, or for exposure to an instantaneous release when people are within the urban canopy or sheltered by buildings. Shielding factors of buildings are calculated, both for instantaneous and continuous releases.

It should be emphasised that the experimental results on which the models' parameters are based, are from animal experiments, and the reliability of the extrapolation to humans is questionable unless supported by human exposure data. However, these parameters are in use in hazard estimation tables (see for example [13]). In addition, the effective dose is influenced by human pharmacokinetic variability, a factor which is not included in this model. It is recommended for future research that the conection between animal and human parameter, be better established, either by experimental data or by pharmacokinetic models.

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