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THE APPLICATION OF BOX MODELS IN THE ANALYSIS OF TOXIC HAZARDS BY USING THE PROBIT DOSE–RESPONSE RELATIONSHIP

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Summary

Quantification of the risk from industrial major hazard sites often requires knowledge of the dispersion of toxic gas arising from accidental releases and knowledge of the effects of gas concentrations on the population exposed. The development in recent years of Box models of dense gas dispersion has made it possible to predict the bulk behaviour of a cloud of hazardous gas released in a major industrial accident. Similarly, Probit analysis has advanced our ability to predict mortality rate as a function of received dose. This paper combines both techniques in a theoretical study of the statistical properties of the number of people killed in a site in an industrial plant as the result of a toxic spill. The effect on the percentage mortality rate of ignoring the between-spill variability is illustrated with reference to a hypothetical spill of 20 tonnes of chlorine. The paper also contains a discussion of the distribution of the Probit parameters evaluated over a range of commonly occurring volatile industrial compounds, and closed with some recommendations whose purpose is to improve the reliability of quantitative risk assessment of toxic spills.

1. Introduction

Quantification of the risk from industrial major hazard sites often requires knowledge of the dispersion of toxic gas arising from accidental releases and knowledge of the effects of gas concentrations on the population exposed. The increasing interest shown in recent years in the development of simple mathematical models ('Box' models) of the dispersion of denser-than-air clouds — see, for example, [1] for a general account — has gone a long way towards increasing our ability to predict the behaviour of clouds of hazardous gas released to the atmosphere as the result of a major industrial accident. Progress in the development of such models has brought with it the need to look into the question of how such models may best be used in predicting the statistical properties of the number of people killed at a site as the result of such a release. This paper describes a preliminary attempt to answer this question.

For acutely toxic gases such as chlorine, ammonia and sulphur dioxide the

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connecting link between cause and effect — the so-called 'dose–response' relationship — is already reasonably well researched, at least for animals [2]. The type of effect considered is that of death to a person exposed to the release. It should be noted that other types of effect (serious injury, etc.) could be handled within the same formalism, and other types of cause (radiation, blast, etc.) could also be considered by suitably redefining the dose–response relationship.

Section 2 describes a simple probabilistic model governing the number of people killed at a given site as the result of a toxic spill, taking due account of between-spill variation in dose received. Section 3 describes an attempt to quantify the effect of ignoring the between-spill variability in the dose received when calculating the probability of death. Section 4 contains the results of some calculations in which a new parameterization of the Probit model was fitted to a collection of dose–response data sets mentioned in [3] while the implications of this work for the use of Box models in hazard assessment are discussed in Section 5.

2. Statistical analysis of toxic spills

We envisage a cloud of toxic gas dispersing over an industrial plant as the result of an accidental spillage, and set up a simple statistical model for the number of people killed at a given location in the plant as a consequence of the spill. In any one instance of the spill, the toxic dose received at a given location will be a function, amongst other things, of the time-varying concentration at that location. In a future replication of the spill, the dose received at the location in question will be different from its previous value as a result of the turbulent nature of the diffusion process. The extent of the between-spill variability will depend on those physical parameters which are held fixed from spill to spill and those which are allowed to vary. In all cases, the magnitude of the variability will be measured by the standard deviation of the ensemble of spills considered.

In this model the following assumptions are made:

(i) that there are N people at risk at the location in question, each one of whom receives a dose $D = \int C^n dt$, where C is the instantaneous concentration of the toxic gas, n is an exponent characteristic of the gas, and the integration is over the duration of the exposure;

(ii) that, on the basis of the results quoted in [4], over successive realisations of the spill the dose D is Lognormally distributed in the sense that the (natural) logarithm of the dose, $\ln D$, has a mean value of $\ln \bar{D}$ and a variance of $\sigma^2 (\ln D)$:

$$\ln D \sim N(\ln \bar{D}, \sigma^2 (\ln D)); \tag{1}$$

(iii) that the probability, θ, that an individual taken at random from the pop-

ulation at risk will be killed as a result of the dose received during the spill is given by a dose–response relationship of the form $\theta=\theta(D)$, and

(iv) that the dose–response relationship may be approximated by the Probit (*Pro*bability un*it*) model

$$\theta(D)=\Phi(K\ln(D/D_{50})=\Phi(\delta), \tag{2}$$

where Φ is the standard cumulative Normal distribution function and $\delta=K\ln(D/D_{50})$ is the standardised log-dose, in which D_{50} is the median fatal dose and K is a scaling parameter proportional to the slope of the curve θ against ln D when $D=D_{50}$.

It is perhaps worth remarking, in connection with assumption (ii) above, that the analysis reported in [4] was carried out by using unaveraged concentration records. Mylne [5] shows that the initial application of a running average to a concentration record leads to a reduction in the calculated dose for that record. It follows that at the level of the ensemble an increase in averaging time would lead to a reduction in $\sigma(\ln D)$.

The form adopted above for the dose–response relationship may be reduced to the more familiar (but less informative) version of the Probit model by noting that if $\theta=\Phi(K\ln(D/D_{50})$ and $D=C^n t$, then

$$\Phi^{-1}(\theta)=K\ln(D/D_{50})=-K\ln D_{50}+K\ln C^n t, \tag{3}$$

from which it follows in the usual Probit notation that

$$Y=\Phi^{-1}(\theta)+5=A+B\ln C^n t, \tag{4}$$

where $A=(5-K\ln D_{50})$ and $B=K$.

Assumption (iii) above enables us to write down the mean and variance of the number v of people killed in any one realisation of the spill by reference to the properties of the Binomial distribution. The mean of the number of people killed as the result of receiving a dose D – the 'conditional' mean – is given by the expression

$$\mu(v|D)=N\theta(D) \tag{5}$$

respectively. In a subsequent realisation of the spill, of course, the dose received will be different, though by (ii) above all doses are drawn from a suitable Lognormal distribution. The problem is then to determine the marginal mean of the number of people killed, i.e. the mean making due allowance for the between-spill Lognormal variation in the dose.

In terms of the dose D, the marginal mean is given by

$$\mu(v)=E_D[\mu(v|D)], \tag{6}$$

where the expectation operator $E_D[.]$ denotes integration with respect to variation in D. Thus

$$\mu(v) = \int \mu(v|D)p(D)\mathrm{d}D = N\int \Phi(K\ln(D/D_{50})p(D)\mathrm{d}D, \tag{7}$$

by using eqns. (2) and (5), where $p(D)$ is the probability density function of D, which follows immediately from the Lognormality of D as in eqn. (1).

Equation (7) enables us to define the marginal mean in terms of an effective dose D^*, by means of the expression

$$\mu(v) = N\Phi(K\ln(D^*/D_{50})) \tag{8}$$

Thus, the effective dose D^* is the dose that gives rise to the same mean number of deaths as would be found by averaging the number of deaths observed in successive realisation of the spill in which the dose D is allowed to vary in the Lognormal manner of eqn. (1), rather than being held fixed a in the discussion of the conditional statistics.

The above development can also be carried through in terms of the standardised log-dose δ defined, from eqn. (2), as

$$\delta = K\ln(D/D_{50}) \tag{9}$$

For the purpose of a general discussion such as this, it is more useful to work in terms of δ than D, because the introduction of the parameters K and D_{50} into eqn. (9) has the effect of compensating for the specific characteristics of a given toxic gas and the argument thus becomes quite general. Lognormality in D then becomes Normality in δ, and we can write

$$\delta \sim N(\bar{\delta}, \sigma^2(\delta)), \tag{10}$$

where $\bar{\delta} = \ln(\bar{D}/D_{50})$ and $\sigma^2(\delta) = K^2\,\sigma^2(\ln D)$.

Analogously with eqn. (8), the effective standardised log-dose δ^* is then defined implicitly by the expression

$$\mu(v) = N\Phi(\delta^*) = N\int \Phi(\delta)p(\delta)\mathrm{d}\delta, \tag{11}$$

where δ^* is the standardised log-dose that gives rise to the same mean number of deaths as would be found by averaging the number of deaths observed in successive realisations of the spill in which the standardised log-dose is allowed to vary in the Normal manner of eqn. (10).

The difference $\delta^* - \bar{\delta}$ is, in effect, the correction that should be applied to the ideal Box model prediction $\bar{\delta}$ in order to allow for the effect of between-spill variations in δ. This is illustrated in Fig. 1. In practice, of course, a Box model would contain systematic error, and would produce a prediction $\delta_m \pm \bar{\delta}$. In view of the preceding discussion, it seems reasonable to regard a Box model as acceptable if it produces predictions such that the discrepancy between δ_m and $\bar{\delta}$ is comparable to that between δ^* and $\bar{\delta}$.

3. Statistical analysis of dose variability

The effect of the difference between δ^* and $\bar{\delta}$ on the probability of death at

the site in question may perhaps best be studied by reference to a tabulation of the difference $\Phi(\delta^*) - \Phi(\bar{\delta})$ for a range of values of $\bar{\delta}$ and $\sigma(\delta)$, where, from eqn. (2), $\Phi(\bar{\delta})$ is the probability of death obtained by substituting the Box model prediction $\bar{\delta}$ in the dose–response relationship, and $\Phi(\delta^*)$ is the probability of death by using the corrected log-dose δ^*. δ^* may be calculated by selecting values of δ from the normal distribution shown in Fig. 1 and calculating the probability of death ($\Phi(\delta)$, eqn. 2) for each choice. The mean of these probabilities of death is used to back-calculate an equivalent dose δ^*.

Table 1 shows the results of such a calculation for the range $-3 \leq \bar{\delta} \leq 3$ and $0 \leq \sigma(\delta) \leq 5$. These ranges were chosen to cover all the values of $\bar{\delta}$ and $\sigma(\delta)$ that might be expected to occur in practice. Thus the limits $\bar{\delta}=3$ and $\bar{\delta}=-3$ correspond, respectively, to doses where there is a chance of approximately 1000-to-1 of being killed or of not being killed. The value $\sigma(\delta)=0$ corresponds, of course, to the deterministic case; while $\sigma(\delta)=1$ corresponds to what might be expected in the body of the cloud, and $\sigma(\delta) \gg 1$ to values at the edge of the cloud [4].

The main conclusions to emerge are:

(i) that the use of $\bar{\delta}$ instead of δ^* will lead to an overestimate of the marginal mean of the number of people killed, $\mu(n)$, when $\bar{D} > D_{50}$, and, conversely, to an underestimate when $D < D_{50}$,

(ii) that the extent of the mis-estimation is less than 10% in absolute terms if $\sigma(\delta) < 1$, whatever the dose; and

(iii) that for $\sigma(\delta) > 1$ the discrepancy becomes progressively more serious as $\sigma(\delta)$ increases, a value of $\sim 30\%$ being reached when $\sigma(\delta) = 5$.

An illustrative calculation of the discrepancy between $\Phi(\delta^*)$ and $\Phi(\bar{\delta})$ re-

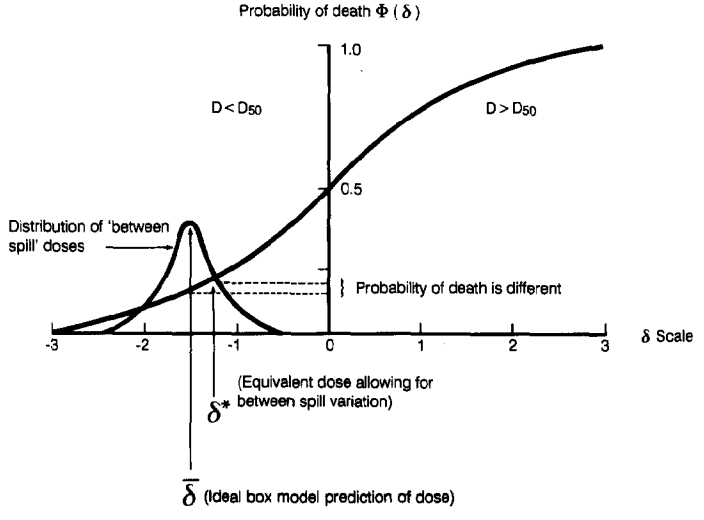

Fig. 1. An illustration of the smoothing operation required to compensate for between-spill variability on dose levels.

TABLE 1

Between-spill variation
$\Phi(\delta^* - \Phi(\delta)$ for a range of values of $\bar{\delta}$ and $\sigma(\delta)$

$\sigma(\delta)$	$\bar{\delta}$						
	−3	−2	−1	0	1	2	3
0	0	0	0	0	0	0	0
0.2	0	0	0	0	0	0	0
0.5	0	0.02	0.03	0	−0.03	−0.02	0
1	0.02	0.06	0.08	0	−0.08	−0.06	−0.02
2	0.09	0.17	0.17	0	−0.17	−0.17	−0.09
5	0.29	0.28	0.20	0	−0.20	−0.28	−0.29

quires knowledge of the Probit parameters of the substance of interest, and so must be deferred to the end of the following section, in which Probit parameters are given for a range of commonly occurring toxic agents.

4. Dose–response analysis

The previous two sections have been concerned with analysing the statistical aspects of the stochastic process governing the number of people killed at a site in an industrial plant as the result of a toxic spill. The process itself was assumed to be a Binomial point process in which the probability of death, Φ, was given as a function of the standardised log-dose $\delta = K \ln D/D_{50}$ by means of the Probit law, $\theta = \Phi(\delta)$. The Probit law thus contains two parameters explicitly, D_{50} for location and K for scale, and one parameter implictly, the exponent n in the relationship $D = \int C^n dt$, giving the received dose a a function of concentration, C.

Specific values for these three parameters were not needed in the investigation described above, which only required an estimate of the useful ranges of $\bar{\delta}$ and $\sigma(\delta)$. In practice, however, specific values of these parameters would be needed, and in view of this the model of eqn. (2) which is equivalent to the Probit model was fitted to the dose–response data sets described in [2] in which concentration is given in mg/m^3 and time in minutes using the method of Maximum Likelihood [3]. The estimated values of the parameters K, n and $\ln D_{50}$, together with their respective standard errors, are given in Table 2 for the local irritant (LI) group and in Table 3 for the systemically acting (SA) group. The transformations from K, n and $\ln D_{50}$ to the more familiar Probit coefficients are given following eqn. (4). It should be noted that 5 of the substances mentioned in [2] have been omitted from these tables because some of the standard errors involved were greater than 30% of the quantity estimated.

It is worth remarking that the values obtained for $\ln D_{50}$ were very stable

TABLE 2

Local irritant group; values of K, n and ln D_{50} (values in parentheses are standard errors)

Substance	K	n	ln D_{50}
Ammonia	1.80	2.02	23.0
NH_3	(0.20)	(0.16)	(1.5)
Hydrogen chloride	0.75	1.02	11.9
HCl	(0.14)	(0.08)	(0.8)
Chlorine	1.00	3.49	25.8
Cl_2	(0.14)	(0.28)	(1.8)
Perfluoroisobutylene	1.72	1.22	8.4
iso-C_4F_8	(0.15)	(0.04)	(0.3)
Crotonaldehyde	1.49	1.16	12.0
	(0.13)	(0.05)	(0.4)
Ethylene	0.72	1.06	10.5
imine	(0.16)	(0.13)	(0.9)
Bromine	1.26	2.16	20.6
Br_2	(0.09)	(0.08)	(0.7)
Dibutylhexamethylene-	0.84	0.90	11.7
diamine	(0.19)	(0.17)	(1.7)

TABLE 3

Systematically Acting (SA) group; values of K, n and ln D_{50} (values in parentheses are standard errors)

Substance	K	n	ln D_{50}
Methyl t-butylether	1.78	1.95	14.7
(MTBE)	(0.11)	(0.31)	(2.0)
Methylene chlorobromine	1.80	1.65	23.1
(CH_2ClBr)	(0.13)	(0.10)	(1.2)
Ethylene chlorobromine	2.68	1.20	16.4
(CH_2H4Cl_2)	(0.07)	(0.03)	(0.3)
Ethylene dibromide	2.28	1.15	13.8
($C_2H_4Br_2$)	(0.08)	(0.03)	(0.2)
Tetrachloro-ethylene	1.39	2.00	26.5
(C_2Cl_4)	(0.10)	(0.18)	(2.0)
Trichloro-ethylene	0.80	0.82	14.4
(C_2HCl_3)	(0.18)	(0.25)	(2.8)
Carbon Tetrachloride	1.04	2.86	36.6
CCl_4	(0.13)	(0.32)	(3.6)
Acrylonitrile	2.20	0.99	12.1
CH_2CHCN	(0.10)	(0.04)	(0.3)

with respect to variation in the probability model used to describe the dose-response relationship. Although only the results for the Probit model have been reported, parallel calculations were carried out for three additional prob-

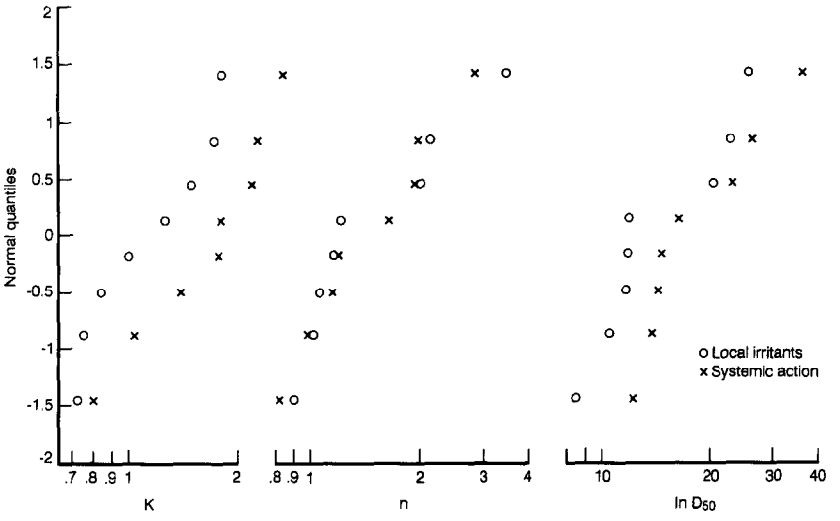

Fig. 2. A composite Normal probability plot for K, n and ln D_{50}.

ability models — the Logistic [3], the Extreme-value [3] and the Binit (*Binary unit*) [6]. It was found that overall the best fits were obtained using the Probit and Binit models, with the edge being slightly in favour of the Binit model. However, as the Binit model is essentially a two-parameter model which does not lend itself to the theoretical development of Section 2, it was discarded in favour of the Probit model which is, in any case, widely used in this and in related fields.

The values of K, n and D_{50} are shown plotted in Lognormal probability form in Fig. 2, as described in [7]. In the figure the vertical axis labelled 'Normal Quantities' is a scale of quantiles of the standard Normal cumulative distribution function $\Phi(.)$. Scatterplots of K against n, K against ln D_{50} and n against ln D_{50} are shown in Fig. 3. In each case data from the LI group were plotted with circles and data from the SA group with crosses.

Inspection of Fig. 2 shows:

(i) that, considering the sparseness of the data, a Lognormal probability model fits the distributions of K, n and ln D_{50} reasonably well;

(ii) that there is evidence of a systematic difference between the distribution of K in the LI group and its distribution in the SA group;

(iii) that there is evidence of a similar but less pronounced difference in the distributions of ln D_{50}; and

(iv) that for n there is no evidence of a group-specific effect.

Figure 3, indicates that a quite strong positive correlation exists between n and ln D_{50}. Pooling the LI and SA groups together enables a reasonably accurate calculation to be made of the correlation coefficient in the three cases: the

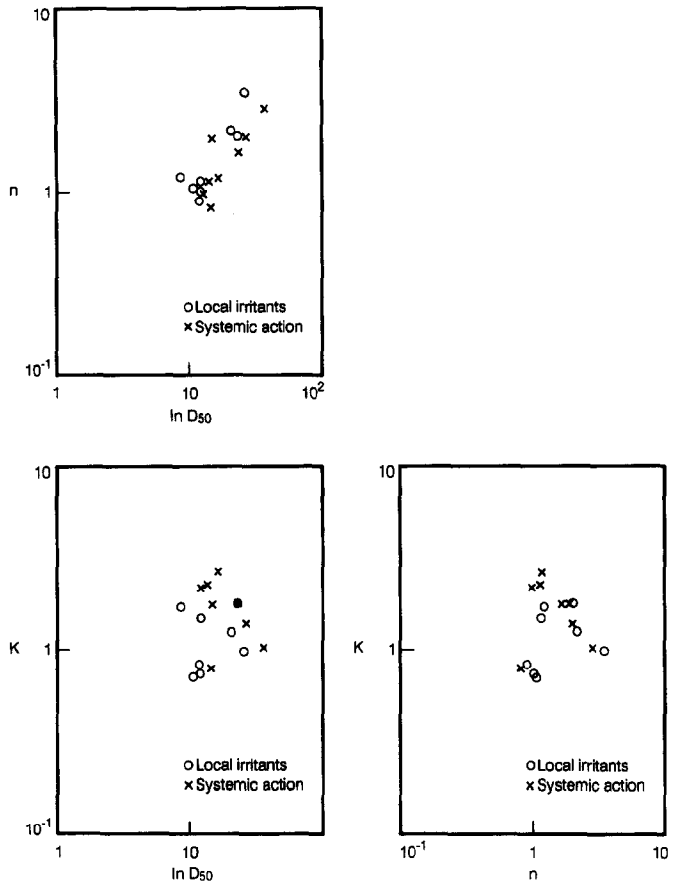

Fig. 3. A display of three pairwise scatter-plots of K, n and ln D_{50}.

TABLE 4

Correlation coefficients (values in parentheses are standard errors)

K with n	K with ln D_{50}	n with ln D_{50}
0.07	0.03	0.81
(0.27)	(0.23)	(0.08)

values obtained are shown in Table 4, together with their standard errors in parentheses. It will be seen, as expected, that K is effectively uncorrelated with n and ln D_{50}, while the correlation between n and ln D_{50} is roughly 0.8.

5. Discussion

Section 2 has shown by means of a simple probabilistic model for the number of people killed at a given location as a result of a toxic spill that the probability of death for a person chosen at random — as determined from the Box model prediction of the dose received used in conjunction with the dose–response relationship — should be corrected to take into account the effect of between-spill variability in the dose received.

Section 3 has described an attempt to quantify the effect of ignoring the between-spill variability in the dose received at the location when calculating the probability of death. It was found that the error in the calculated probability of death could be as large as 0.3.

The calculations in Section 4 were carried out using two groups of 8 dose–response datasets, one covering locally irritant toxins and the other systemic action toxins. Each dataset was fitted with a Probit law, giving 16 sets of values for the three Probit law parameters K, n and $\ln D_{50}$.

To illustrate the use of the work described above it is helpful to consider a specific example. For this purpose a release of 20 tonne of chlorine in neutrally stable weather with a windspeed of 3 ms^{-1} was considered. The dispersion calculation was carried out using the computer code DENZ [8], while the toxicity parameters used were taken from Table 2 and the values for $\Phi(\delta^*) - \Phi(\bar{\delta})$ from Table 1.

The results obtained are summarised in Table 5, and refer to a down-wind distance of 1000 m from the point of the spill. Cross-wind distances are given which correspond to the approximate levels of fatalities given in the table. Values for $\sigma(\delta)$ have been chosen as representative of those expected at different positions in the cloud [4]. The final column shows the error in the percentage fatality rate resulting from ignoring the between spill variation. The effect would be most important when a population is at the edge of a concentrated release of toxic material, and is consistent with the findings of Griffiths and Harper [9].

It should be noted that in assessing the toxicity of a substance its K-value is just as important as its D_{50} value, since two substances with the same exponent n and the same median dose D_{50} will give rise to quite different probabilities of death at extreme dose levels, as inspection of eqn. (2) shows. Also note that the linearity of eqn. (4) in $\ln C$ and $\ln t$ shows that the concept of one substance being more toxic than the other is only valid for a range of values of C and t which are likely to occur in practice. The $\ln C - \ln t$ plane will always be divided by a characteristic straight line such that for values of $\ln C$ and $\ln t$ on one side of the line, the first substance will be more toxic than the second while on the other side of the line the opposite is true.

TABLE 5

The effect of ignoring the between-spill variability on the percentage mortality rate from a 20-tonne release of chlorine[1,2]

Crosswind distance (m)	$\Phi(\delta)$ (×100)	δ	Y	$\ln C^n t$	σ	$\Phi(\delta^*) - \Phi(\delta)$ (×100)
52	100	3	8	28.80	0.5	0
215	85	1.04	6.04	26.84	1	−8
235	70	0.52	5.52	26.32	1.2	−4
287	20	−0.84	4.16	24.96	2	17

[1]Toxicity: $K=1$, $n=3.49$, $\ln D_{50}=25.8$.
[2]Values in the table relate to 1000 m downwind from a 20-tonne chlorine release. Source term allowed 400 te of air to be entrained. Cloud radius at 1000 m = 417 m, defined as 10% of the centre-line concentration. Weather considered: Pasquill stability D, wind speed 3 ms^{-1}.

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