THE ASSESSMENT OF MAJOR HAZARDS: THE FACTORS AFFECTING LETHAL TOXICITY ESTIMATES AND THE ASSOCIATED UNCERTAINTIES

R.M.J. Withers and F.P. Lees*

A difficult aspect of the assessment of a toxic gas hazard is the estimation of the lethal toxicity of the gas. The methodology of obtaining toxicity data from experimental work and the factors which enter into the interpretation of these data, and their use in hazard assessment, are outlined. The uncertainties in, and introduced by, the toxicity data are described and proposals are made for mitigating the problem.

Keywords: Major hazards, hazard assessment, toxic gases

INTRODUCTION

One of the most difficult aspects of hazard assessment is the estimation of the injury to people and damage to property from the physical phenomena of fire, explosion and toxic release. In recent years much work has been done on the estimation of the intensity of the physical effect from these phenomena, but less on the relation between the intensity of the effect and the probability of injury.

It is the purpose of this paper to review the derivation of the injury relations for toxic gases, to describe the factors affecting the estimation of the lethal toxicity and the associated uncertainties, and to indicate ways in which this problem may be treated and to some extent mitigated. The discussion is confined to bulk chemicals and to lethal toxicity.

Hazard assessment may be carried out for different purposes and this affects the nature and the accuracy of the toxicity data required. One aim is to estimate the total number of people killed by a release, another to determine the distance at which a given lethality, typically 1-10%, applies. In general, the accuracy of estimation of lethal toxicity is lower at the extremes of mortality than in the middle of the range and hence the second task is more difficult than the first.

The lethal toxicity estimate sought is a realistic rather than a conservative one. This estimate may then be interpreted with any degree of conservatism desired.

Many of the factors discussed in this paper are treated in more detail in a study of the lethal toxicity of chlorine which has been described elsewhere (1,2).

*Department of Chemical Engineering, Loughborough University of Technology, Loughborough, Leicestershire.

LETHAL CONCENTRATION AND LOAD

In general, the injurious effect of the inhalation of a toxic gas is a function of concentration and of time which may be expressed by the relation

$$c^m t^n = \text{constant} \qquad (1)$$

where c is concentration and t time.

If the exposure time is constant, a lethal concentration LC_i may be defined such that for this exposure time C_i is the concentration which is lethal at the i% level. If the exposure time is not constant, but the injurious effect is proportional to the product ct of the concentration and time (m=n=1), and hence to the dosage D, a lethal dosage LD_i may be defined with

$$D = ct \qquad (2)$$

If the injurious effect is proportional to some other function ($m \neq n$), it is necessary to use the concept of a toxic load L and to define a lethal load LL_i with

$$L = ct^n \qquad (3)$$

An alternative toxic load L* may also be defined with

$$L^* = c^m t \qquad (4)$$

This second form of the lethal load, which is also called the dosement, is that most often used in hazard assessment studies. In such studies it is usually necessary to estimate mortality for exposures at a number of different combinations of concentration and time and in this case the lethal load function is usually expressed in the form

$$L^* = \Sigma\ C^m T \qquad (5)$$

where C is concentration (ppm) and T time (min). The lethal load function in the form of equation (5) has been widely used in hazard assessment (3-6).

The relation between the toxic load and the mortality is usually a lognormal distribution and may therefore be plotted on log-probability paper. It may also be expressed as a probit equation (7):

$$Y = k_1 + k_2 \ln L^* \qquad (6)$$

where k_1 and k_2 are constants and Y is the probit.

A more detailed discussion of the form of the toxic load function and of the distribution of this function is given in the work on chlorine (1,2).

TOXIC EFFECTS AND MECHANISMS

Some of the principal toxic materials which are handled in bulk in the chemical industry and the toxic effect which each exerts are listed in Table 1.

All except one of the toxic gases in Table 1 are irritants (8). In this context irritation is a technical term: the effect ranges from mild discomfort to death. An irritant gas attacks the respiratory tract and the lungs. The locus of action depends mainly on the solubility of the gas, the more soluble gases attacking the respiratory tract and the less soluble the lungs. The action of irritant gases has been described by Haggard (9) as follows:

"Ammonia produces intense congestion of the upper respiratory passages and immediate death from laryngeal spasm or edema; on the other hand phosgene and nitrogen peroxide cause little irritation of the upper respiratory tract but induce pneumonia or lung edema through their action upon the lung alveoli; chlorine in its action is intermediary between ammonia on the one hand and phosgene and nitrogen peroxide on the other".

The main action of chlorine is on the lungs. Bromine, which is more soluble than chlorine but less soluble than ammonia, attacks both the respiratory tract and the lungs.

Hydrogen sulphide is an irritant gas but also attacks the nervous system and causes respiratory paralysis. It is oxidised in the blood stream to pharmacologically inert compounds. Hydrogen fluoride is again an irritant gas but also gives rise to fluoride poisoning in the body.

Hydrogen cyanide is the only one of the gases listed which is not an irritant; it causes cyanide poisoning. The most important effect of this is probably the inhibition of cytochrome oxidase, which in turn prevents the utilisation of molecular oxygen by the cells. The cyanide is excreted in the urine.

EXPERIMENTAL DETERMINATION OF TOXICITY

The primary source of information on the lethal toxicity of gases is experimentation on animals, particularly mice. In a typical study groups of mice are exposed to different concentrations of gas for a single exposure period and the mortality is determined over a given period of observation after the exposure is over.

For a particular gas, assuming there are any data, there will typically be between one and half a dozen studies quoted in the literature which appear applicable. There may be one or two in which the exposure period has been varied. There may also be one or two studies with other species such as rats, guinea pigs, rabbits, and, in older work mainly, cats and dogs.

The determination of the lethality of a toxic gas by inhalation experiments with animals is a difficult undertaking and is subject to various sources of error (10-14, 1). In addition to the concentration of the gas (which needs to be standardised), other important variables are the exposure time, the caging conditions, the breed, sex, age and health of the animals, and their behaviour, including their breathing rate. The animals may not die immediately and it is necessary to observe delayed deaths over a period of time, usually ten days, and to record both immediate and delayed deaths. A sufficient number of animals needs to be used to obtain results with a high level of confidence and pathological examinations should be conducted. The toxicity data sought are usually the value of the LC_{50}, i.e. the concentration at which, for a given exposure time, the mortality is 50%, together with suitable values nearer the extremes of mortality such as the LC_{10} and LC_{90}.

STATISTICAL INTERPRETATION OF EXPERIMENTS

The number of animals which can be used in gas toxicity experiments has to be kept as low as possible for obvious reasons and the statistical interpretation of the results is therefore crucial. In an early paper Trevan (15) showed that for a particular dose-mortality determination the confidence level depends both on the number of animals and on the mortality. For a given confidence level it is necessary to use more animals to determine an LC_{10} or LC_{90} than to determine an LC_{50}. Alternatively, and this is the more usual case experimentally, for a given number of animals the confidence in the LC_{10} and LC_{90} values is less than that in the LC_{50}.

Trevan found that the dose-mortality curve (on linear paper) has a characteristic shape with an approximately linear section between 20 and 80% mortality. He showed that for a given number of experimental animals a more accurate result is obtained if most of the experimental points lie in the 20-80% mortality range and if the points are symmetrical about 50% mortality and that the converse is liable to lead to error in the determination of the slope of the linear portion.

A method widely used for determining the lethal toxicity parameters and confidence limits in a study where groups of animals are exposed to different concentrations for a fixed period is that of Litchfield and Wilcoxon (16). The method requires information on the number of animals and the number of concentrations and yields the LC_{50}, the LC_{16} and the LC_{84}, and the confidence limits.

Figure 1 shows the toxic concentration-mortality relation for dogs exposed to chlorine for 30 min using the data of Underhill (17) analysed by the method of Litchfield and Wilcoxon. The confidence interval is least for the LC_{50}, increases for the LC_{10} and LC_{90} and is very wide for the LC_{01} and LC_{99}.

Accounts of the statistical interpretation of experimental work are available in the literature (7,18,19). The literature on low concentration toxicity, such as that on carcinogens and food additives, is also relevant in relation to methodology (20-23).

ESTIMATION OF LETHAL TOXICITY TO ANIMALS

The lethal toxicity estimates required for hazard assessment are essentially the LC_{50}, the slope of the concentration-mortality line, which may be expressed in terms of the ratio LC_{90}/LC_{10}, and the load function, which defines the equivalence between concentration and time.

Usually, if there are any data at all, there will be enough to permit some estimate to be made not only of the LC_{50}, but also of the ratio LC_{90}/LC_{10}, but, equally, the latter estimate will generally be such as to yield much less confidence in the LC_{10} than in the LC_{50}.

Some guidance on the slope of the concentration-mortality line may be obtained by comparison with that for other related gases. Thus there is evidence (1,2) that the ratio LC_{90}/LC_{10} for chlorine is about 4 and it would be appropriate to take this into account in considering the ratio for other gases such as bromine or phosgene. A very low slope (say, much less than 2) implies a very narrow range of lethal concentrations which may be regarded as unlikely.

For some gases there may be a single set of experiments on one species, for others several sets on one species and for others again several sets on different species. In the first case the estimate is straightforward, but it should be borne in mind that where there are several sets of experiments on one species, there may be appreciable differences (say a factor of 2) in the LC_{50} reported by different workers, even though each group quotes relatively narrow confidence limits for its results. Thus for chlorine there is a factor of about 2 in the LC_{50} values reported for mice for 30 min exposure.

In the second case the variability in the LC_{50} determined by different workers may well be found. If it is, it is necessary to decide whether to average the results or to select those which appear of highest quality. Each case must be treated on its merits. The third case, where different species are involved, requires consideration of extrapolation between species, which is discussed below.

In general, the lethal toxicity is a function of concentration and time. Although concentration may sometimes be completely dominant, there tends to be a trade-off between the two, so that at a particular value of the load as defined, say, by equations (3) or (4) there is a given degree of injury.

The experimental data from which to determine the parameters in equations (3) or (4) are often sparse and in weak agreement. Thus for chlorine the index m in equation (4) has been estimated as 2 by the authors (2) and as 2.75 by others (3,5,6). The former estimate is equivalent to n=1/2 in equation (3).

Some guidance on the value of the index may be obtained by comparison with results obtained for other gases. Early German work on war gases, notably that on phosgene described by Flury (24), suggested that for irritant gases equation (2) is applicable. This equation was proposed by Haber (25) and became known as Haber's law. Subsequently Flury (10) and others have warned against the indiscriminate use of this 'law'.

Work by Doe and Milburn (26) gives a value for m of about 1 for some other gases, but for many of the irritant gases a value of about 2. This is also the value obtained in work on ammonia (27), another major irritant gas. A similar value has also been obtained for the non-irritant gas hydrogen cyanide (28,26).

It is often necessary to determine the effect of a series of exposures at different concentrations and in this case equation (4) is normally used in the form of equation (5). The use of the load function in this way appears to be the best which can be done at the present time, but it is rather mechanistic, and it cannot be regarded as a satisfactory approach.

There is need, therefore, for a more fundamental method based on the modelling of the toxic effect, as discussed below.

INHALATION RATES

In applying the results of animal experiments to man it is necessary to make allowance for the effect of inhalation rate. If the base case for comparison between animal and man is that each has the inhalation rate which is normal at rest, there are two separate allowances, or factors, which need to be applied. The first is between the inhalation rate of the

animal at rest and in the experiment, the second between that of man at rest and in the accident condition envisaged in the hazard assessment.

Data on inhalation in animals and man are available (29-35) and some typical values are given in Table 2, Section A. It can be seen that *there are appreciable differences in the inhalation rates as related to* features such as body weight and lung surface area.

Information on the breathing of animals during exposure is recorded in some experiments, although quantitative data appear to be relatively rare. Accounts have been given of the breathing rate during experiments using chlorine for mice (36) and for dogs (17, 37), and Lehmann's pioneering work (38) always included such information.

By contrast, the variation of the inhalation rate of man with different degrees of exercise is well documented (39). Some data on this are given in Table 3.

Even if all this information is available, it is still necessary to take a view as to how it is to be applied. This decision can only be put on a sound basis by the use of some form of toxicokinetic model. Any assumption made in the absence of an explicit model must tend to imply some model which the investigator has in mind but which is unstated.

TOXICOKINETIC MODELS

The unsteady-state modelling of toxic effects is in fact practised by toxicologists, who have developed a number of toxicokinetic (or pharmacokinetic) models (40-46) Although early work in this area was concerned with inhalation of anaesthetic gases (44), the typical model quoted in toxicological texts applies to a toxin or drug which is taken in a single dose rather than inhaled over a period of time.

One of the simplest models is the one-compartment model with finite rate elimination illustrated in Figure 2. For this model the two cases commonly treated are the impulse and the step response, the first corresponding to the instantaneous introduction of a quantity of the chemical and the second to the constant input of the chemical into the body, the prior concentration being zero in both cases. For the first case

$$dX/dt = -k_e X \qquad (7)$$

with

$$X(0) = D_o \qquad (8)$$

where D_o is the dose of the chemical, k_e the elimination constant and X the mass of the chemical in the body. For the second case

$$dX/dt = D - k_e X \qquad (9)$$

where D is the dose rate. The concentration C is given by

$$C = X/V_d \qquad (10)$$

where V_d is the apparent volume of distribution of the chemical in the body. The chemical is distributed between the bloodstream and other body matter, aqueous and non-aqueous, and the total effective capacity

constitutes the apparent volume of distribution. For elimination after instantaneous input of the chemical

$$C = C(0) \exp(-k_e t) \qquad (11)$$

From equation (11) the half-life $t_{0.5}$ of the chemical in the body is $0.693/k_e$. Some typical half-lives of drugs in the body are aspirin 0.3 h, morphine 3 h, quinidine 6 h, diazepam 50 h, phenobarbital 86 h (44).

The model describes the variation of concentration with time of the chemical in the body and is based on the assuumption that the body has a mechanism for the elimination of the chemical. Elimination occurs by metabolism or by secretion. If then a lethal concentration in the body fluids can be specified, this model can be used to describe lethal toxic effects.

Models of this kind may be applicable to certain toxic gases, although no such applications have been found. They do not, however, seem to be applicable as such to the important class of irritant gases, which act directly on the lung surface rather than by accumulation in the body fluids.

A toxicokinetic model for an inhaled gas may be derived by modelling the absorption of gas in the lung into the bloodstream. The difference between the mass inhaled and that exhaled equals the mass transferred across the membrane of the lung and this in turn equals the mass deposed in the body. Then if the chemical enters the main blood stream, its concentration in the blood will be a function of the rate of absorption and of elimination. This situation may be modelled as a single exponential stage with a time constant which is a function of the apparent volume of distribution. The equilibrium backpressure of the chemical at the lung surface will depend on the concentration in the blood. If the chemical is an irritant gas, however, it will attack the respiratory tract and lungs so that these then act as a sink for the chemical. This clearly requires a different model which will characterise the backpressure at the lung surface in a different way.

Some important parameters in models for an irritant gas are the alveolar volume and the inhalation rate, the equilibrium constant of the gas between the alveolar air and the capillary blood, the mass transfer capacity between the alveolar space and the blood, and, if the chemical enters the main blood stream, the apparent volume of distribution. Data on alveolar volume and breathing rate are generally well documented. The equilibrium constant may be obtained from solubility data, but it may be necessary to allow for features such as hydrolysis and to check on reactions with blood constituents. The mass transfer capacity may be obtained from the pulmonary diffusion capacity D_L. Values of D_L are available for oxygen and carbon monoxide and may be obtained for other gases from the fact that D_L is proportional to solubility and inversely proportional to the square root of the molecular weight.

Data on respiratory and blood parameters are available in texts on physiology (29-32) and respiration (33-35). There are also several classic works on respiration deriving from work on lung irritants (47-49). Some data on respiratory parameters for man are given in Table 2, Section B.

The outline of a toxicokinetic model for toxic gases is given by Henderson and Haggard (39). This model is based, however, on the absorption of the

gas into the main blood stream.

Some account has been taken of these aspects in the work on chlorine (2). Thus, for example, it was recognised that if it was assumed that the chlorine is distributed in the main bloodstream, it would be necessary to take into account the effective solubility in water, and in plasma, allowing for the hydrolysis of chlorine (50). However, the evidence is that the chlorine does not enter the main bloodstream in significant concentrations, since if it did, it would presumably attack organs which do not in fact seem to suffer damage. Therefore the alternative model was preferred in which the lungs act as a sink for the chlorine. Then in order to estimate the backpressure of chlorine in the lungs, use was made of experiments by Lehmann (51) on the inhalation (and exhalation) of air contaminated with chlorine. In these experiments it was found that there was no chlorine in the exhaled air. The chlorine concentrations used were relatively low, but they suggest that near total absorption may occur so that the backpressure of chlorine is almost zero. If this is correct, it greatly simplifies the modelling for this case.

INTERPSPECIES EXTRAPOLATION

Extrapolation of results obtained on one particular species to another species is beset with many difficulties, but it is an unavoidable step in the estimation of toxicity. There are available a number of accounts of the principles involved (10,11,46,52,53).

The crucial question is whether or not the toxic effects are the same, or at least sufficiently similar, in the two species, thus providing a basis for extrapolation. Other important features are the relative rates of inhalation and of absorption and the mechanisms and rates of elimination.

In the case of irritant gases the toxic effects in the main laboratory animals and in man appear to be broadly similar in that the gas attacks the respiratory system. It is necessary to consider, however, the locus of action for each gas in each species, bearing in mind the solubility of the gas and the anatomy and respiratory behaviour.

VULNERABLE POPULATIONS

Extrapolation from animals to man is usually done in the first instance for healthy young adults. It may be necessary, however, to allow for vulnerable members of the population.

It is commonly assumed in hazard assessment that a section of the population including young children and old people is particularly vulnerable. In the case of toxic gas hazard, those with respiratory diseases are also included. However, this is an aspect on which very little work has been done. It may well be that for some hazards some of the sections of the population mentioned are not more susceptible.

It may be preferable to derive separate estimates of the lethal toxicity for the regular and vulnerable populations. This makes it possible to allow for differences in the numbers and composition of the exposed population at different times of day.

HAZARD IMPACT MODELS

One of the most difficult problems in hazard assessment and one which is particularly relevant in setting safety distances around hazardous sites is the estimation of the lethality of the gas at low concentrations. As the distance from the hazard source increases, the concentration of the gas decreases, but the number of people exposed increases. The concern for the hazard analyst is that there may still be an appreciable lethality at a distance at which the numbers of people become very large due to the square law increase with distance.

What the overall effect will be can be studied using a hazard impact model (54, 55). Such a model describes the decay of the physical effect with distance, the probability of death due to the physical effect and the number of people affected. It has been shown that if the decay of the physical effect is proportional to $1/r^n$, where r is the radius, the number of people killed may be estimated using the equation

$$N_i = \pi r_{50}^2 \, d_p \phi \qquad (12)$$

with

$$\phi = \exp(2\sigma^2/n^2) \qquad (13)$$

where d_p is the population density, n the decay index, N_i the number of people killed, r_{50} the radius at which the lethality is 50%, σ the spread parameter of the lognormal distribution for lethality, and ϕ a correction factor.

A rough estimate of the number of people killed may be made using equation (12) with $\phi = 1$. In this case the only toxicity value needed is the LC_{50}. This approach has been used in some hazard assessments. The correction factor gives an estimate of the error involved in doing this. The error is a function of σ and n, and more particularly the ratio σ/n.

For a toxic gas release the decay index for the concentration function ct will tend to be of the order 1-2, depending on the type of release and on the model used, but that for the function c^2 will be higher. Thus for the Sutton models for neutral density gas release in neutral stability conditions the decay index for ct is 1.75 for both instantaneous and continuous releases. For σ a value of about 1 appears typical. Thus for chlorine a value of 0.92 has been obtained (2).

These theoretical models tend to indicate that the contribution to the number killed obtained from the product of low lethalities and large numbers exposed at large distances is not likely to be a dominant one.

This appears to accord with historical experience. For all types of major hazard, whether fire, explosion or toxic release, the evidence seems to be that most of the fatalities occur relatively close to the hazard source. The number of fatalities per unit distance may pass through a maximum very close to the source, but then tends to decrease, often fairly sharply.

DISCUSSION

The aim of work on gas toxicity for hazard assessment should be to obtain a lethal toxicity estimate which is realistic rather than conservative and which gives at least the values of the LC_{50}, the LC_{90}/LC_{10} ratio and the

lethal load function L^* together with information on confidence and range of applicability.

If experimental work is carried out, it is desirable that experiments be done not only at several concentrations but also at several exposure times. The concentrations should be such as to allow the LC_{50} and the slope of the concentration-mortality line to be estimated. The exposure times should be such as to allow both the form and the value of the lethal load function to be estimated. *Information on breathing rate and concentration in the* exhaled air is also of great value.

In analysing the experimental data available, each case should be treated on its merits. It may be appropriate to be guided by work judged to be of high quality or particular applicability rather than crude averaging.

There is need to put the estimation of the lethal toxicity of gases on a more fundamental basis. The development of toxicokinetic models appears to be an essential requirement for this. In particular, there is need for a good toxicokinetic model for the main irritant gases. Such a model would give much greater confidence in extrapolation to other exposure times and inhalation rates. It might also help with other problems such as lethalities at low concentrations and to vulnerable populations.

Lethality at low concentrations is likely to remain a problem, but there are two approaches which can mitigate it. One is the careful study of the slope of the concentration-mortality line. The other is study, using hazard impact models, of the relation between the rate of decay with distance of the toxic load and the product of the number of people and of the lethality.

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SYMBOLS USED

c	concentration (various units)
C	concentration in air (min); concentration in body (kg/m^3)
d_p	density of population ($persons/m^2$)
D	dosage (equation (2))(various units); dose rate (equation (9)) (kg/s)
D_L	*pulmonary diffusion capacity (ml/min mm Hg);*
D_o	dose
k_e	elimination constant (s^{-1})
k_1, k_2	constants
L	toxic load ($ppm\ min^n$)
L^*	toxic load (alternative formulation) ($ppm^m\ min$)
m	index
n	index
N_i	total number of people injured
r	radial distance (m)
t	time (various units)
T	time (min)
V_d	apparent volume of distribution (m^3)
X	mass in body (kg)
σ	spread parameter in lognormal distribution
ϕ	correction factor for variance and decay index

Subscript
50 for probability of injury equal to 0.5

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Table 1 Some principal toxic gases and their effects (after Patty (8))

Gas	Toxic effect
Ammonia	Irritant
Bromine	Irritant
Chlorine	Irritant
Hydrogen chloride	Irritant
Hydrogen cyanide	Systemic (cellular respiration)
Hydrogen fluoride	Systemic (fluoride poisoning), irritant
Hydrogen sulphide	Systemic, irritant
Phosgene	Irritant
Sulphur dioxide	Irritant

Table 2 Some principal physiological parameters of animals, including man

A. Animals (after Altman and Dittmer [a] (29))				
	Mouse	Rat	Rabbit	Dog
Bodyweight (kg)	0.023	0.14	3.6	22.8
Lung volume (ml)	0.74	6.3	79	1501
Minute volume (at rest) (ml/min)	24	73	620	2923
Alveolar surface area (m^2)	0.068	0.39	5.9	90
Minute volume/ bodyweight (ml/min kg)	1043	521	172	128
Minute volume/alveolar surface area (ml/min m^2)	353	187	105	32

B. Man (after Mountcastle (30))		page
Bodyweight (kg)	75	1009
Lung volume (ml)	6000	1367
Tidal volume (ml)	500	1382
Alveolar volume (ml)	350	West (33)
Anatomical dead space (ml)	150	West (33)
Breathing rate (at rest)(breaths/min)	12	1382
Minute volume (at rest)(ml/min)	6000	1382
Alveolar surface area (m^2)	70	1387
Pulmonary diffusion capacity for carbon monoxide D_{LCO} (ml/min mm Hg)	61	1391
Mean thickness of alveolar capillary tissue barrier (mm)	1.7	Altman and Dittmer (29)
Volume of lung capillaries (ml)	140	1387
Residence time of blood in lung capillaries (s)	0.75	1387
Volume of blood (ml)	5000	844
Volume of plasma (ml/kg bodyweight)	45	1020
Volume of cell fluid (ml/kg bodyweight)	30	1020

(a) p.1581-1585

Table 3 Inhalation rate for various levels of activity for man (after Henderson and Haggard (39))

Activity	Inhalation rate l/min[a]
Rest in bed, fasting	6
Sitting	7
Standing	8
Walking, 2 mile/h	14
Walking, 4 mile/h	26
Slow run	43
Maximum exertion	65-100

(a) Measured at 0°C and 760 mm Hg

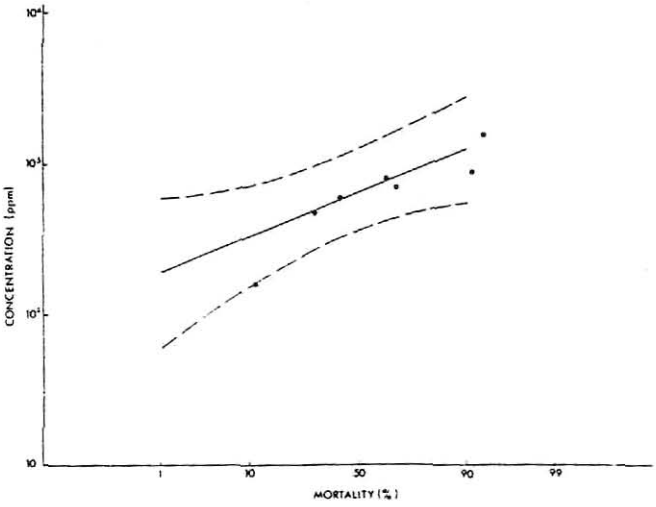

Fig.1 Concentration of chlorine lethal to dogs for 30 min exposure in Und;erhill's work (after Withers and Lees (1)) Dotted lines are 95% confidence limits

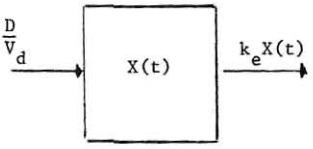

Fig.2 One compartment model of toxic chemical in human body.