Journal of Hazardous Materials, 12 (1985) 231—282
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

THE ASSESSMENT OF MAJOR HAZARDS: THE LETHAL TOXICITY OF CHLORINE

PART 1, REVIEW OF INFORMATION ON TOXICITY

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(Received November 30, 1984; accepted in revised form June 6, 1985)

Summary

Measures for the control of hazardous installations include the assessment of the hazard and the setting of separation distances between the installation and the public. For installations handling toxic materials this creates a requirement for data on toxicity. One of the toxic materials handled industrially in large quantities is chlorine. There is a considerable literature on chlorine which yields a number of different values for the toxicity to animals and man, often of obscure origin. The literature is reviewed and the information evaluated. The results of this evaluation are used in a complementary paper to derive a model of the lethal toxicity of chlorine to man.

Introduction

Chlorine is one of the principal toxic chemicals which are produced and stored in large quantities, and chlorine plants and storages constitute an appreciable proportion of notifiable hazardous installations. Measures for the control of such installations include the assessment of the hazard and the setting of separation distances between the installation and the public. These measures give rise to the need to make an estimate of the lethal toxicity of chlorine.

There are in the literature a number of estimates of chlorine toxicity which vary widely. Individual estimates are not well supported by critical review of alternative values and choice of a particular value tends to be arbitrary. It is the purpose of this paper to evaluate the data available, to attempt some degree of reconciliation and to provide a basis for the estimation of the lethal toxicity to man. It is in the nature of the problem that it is very difficult to establish such an estimate beyond doubt. All that can be attempted is to derive a most likely value and to buttress its credibility.

The paper reviews the work done on chlorine using animal experiments, the physiology and pathology of poisoning, the statistics of animal experimentation, the lethal toxic load function, the toxicity values given in the

0304-3894/85/$03.30

literature and those used in hazard assessments, and attempts to evaluate this information as a basis for deriving a model of lethal toxicity to man. This model is described in a second, complementary paper [1].

Material properties

Properties of chlorine are given by de Nora and Gallone [2] and Sconce [3] and in the Chemical Industries Association code [4].

Lethal concentration, dosage and load

In general, the injurious effect of the inhalation of a toxic gas is a function both of concentration and of time and within certain limits there is a trade-off between these two factors so that for a given degree of injury

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

where c is the concentration and t the exposure time. Equation (1) may not apply at the very high concentrations which give immediate acute effects.

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 ($m = n$), and hence to the dosage D, a lethal dosage LD_i may be defined with

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

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

$$L = f(c, t) \quad (3)$$

Thus the LC_{50}, LD_{50} and LL_{50} are, respectively, the lethal concentration, the lethal dosage and the lethal load for 50% mortality.

Experimental work on, and estimates of, acute toxicity

There is a considerable amount of information available on chlorine toxicity. The first text to treat chlorine toxicology found in the literature is that of Eulenberg [5].

Work of Lehmann 1887—1899

Work on the toxicity of chlorine and other industrial gases was carried out during the period 1887—1899 by Professor Lehmann at Wurzburg. Lehmann's main interest was the effect on factory workers of repeated exposure to toxic gas. Most of the well known industrial gases were investigated by animal experiments, often supplemented by experiments involving himself and his coworkers.

The experimental animals used by Lehmann were cats, rabbits, guinea pigs and dogs. The experimental technique and apparatus were carefully designed, but the number of animals used was too small to give statistically significant results. Nevertheless, the experiments were sufficient for Lehmann to take a view on the hazards to animal life and his work has been widely quoted.

Lehmann wrote a series of papers [6—10] giving an account of his work. In one he describes his apparatus. In another he describes experiments in which his method was to expose single or small groups of cats, rabbits and guinea pigs to the toxic gas in a gas chamber, to observe their reactions and symptoms and subsequently to dissect the animals. In another he describes experiments on single dogs. Here his method was to observe the effect upon a single animal of increasing the exposure time at a constant concentration, both with continuous exposure and with exposure at intervals. The experiments were then repeated at successively increased concentrations. Sometimes a survivor from an earlier series was used at one of the higher concentrations. At the lower concentrations very long exposure times would be involved and there were relatively few observations made in the range 0—30 minutes.

Lehmann established that the effect of exposure time was not always proportional or even progressive. For example, after a while at chlorine concentrations of 30—40 ppm, daily doses of 4—6 hours were tolerated for periods of up to 8 days by some animals with no apparent harm. The dogs learnt to lie quietly in their chamber with the head between the paws. Cats were observed to be less tolerant than dogs.

In a later paper Lehmann revealed that he had found that there was appreciable absorption of chlorine both by the apparatus and by the fur and skin of the animals used. In experiments with a continuous gas flow and with a concentration of 0.2 mg/l (69 ppm) some 4/5—5/6 of the chlorine was absorbed and only a small part was taken up by the lungs. A further paper describes work to determine whether animals become accustomed to chlorine at low concentrations. It was found that they do.

The work of Lehmann provides a cautionary tale of two apparently similar dogs which were both subjected to the same treatment with hydrogen sulphide. One dog became very ill after one hour and died 9 hours later, the other came out of his chamber after 5 hours exposure apparently little the worse.

Work of Hess

The work of Hess is much quoted, particularly by Flury and Zernik [11], who frequently refer both to Hess and to "Lehmann—Hess". The only publication by Hess which has been found is a dissertation [12] on toxicological features of Swiss factory liability insurance law. This contains two tables, one on symptoms and one on toxic concentrations for a number of gases, including chlorine, but gives no references for the source of the data

quoted. The concentration of chlorine given as dangerous for a 1/2—1 h exposure is 40—60 ppm.

First World War 1914—1918

Chlorine was used by both sides in the First World War as a war gas [13—15]. It was first used by the Germans, apparently in shells, on the Russian front early in 1915, but the first large gas cloud attack was by the Germans against the French at Ypres on April 22, 1915. The British made a gas cloud attack at Loos on September 25, 1915. On October 19, 1915 the Germans made a gas cloud attack on the French at Fort Pompelle near Reims using a chlorine—phosgene mixture and thereafter made little use of chlorine alone. The period of the war during which chlorine alone was used as a war gas was therefore relatively short. The use of chlorine in warfare gave rise, however, to a considerable amount of work on the toxicity of chlorine.

German work ca. 1914—1918

Extensive experimental work on the toxicity of war gases was carried out during the First World War at the Kaiser Wilhelm Institute under Professor Haber [16] as Head of the Chemical Section of the War Ministry. Haber's work was directed towards the determination of the toxicity to man of proposed war gases. The principal gases investigated were chlorine, phosgene and mustard gas, but work was also done on a wide range of other gases. A related object of the work was to demonstrate to a sceptical military the effectiveness of these gases as battlefield weapons. The main experimental animals used in Haber's work were cats, though some work was done on other animals, including rodents, dogs and monkeys.

Other workers in the field at this period include Flury [11], Muntsch [17] and Wachtel [18].

The experimental methods used in Haber's work have been described by Wachtel. He lays emphasis on the difficulties of obtaining accurate results and in particular on the importance of the gassing chamber used:

"Most of the older determinations were made with inadequate apparatus, such as glass bells of far too small dimensions. Under such conditions, the absorption of the gas mixture on the walls of the bell and on the fur of the animals is so important that the figures obtained are not only 10- but even 100- or 1,000-fold wrong. What is even worse, is the fact that only recently did research workers themselves realise the enormous extent of this source of error."

Wachtel states that it was concluded that experiments in glass bells were useless, that for smaller animals such as mice, rats or guinea pigs the chamber size should be at least 1 m^3 and that for larger animals provisional results could be obtained in a 1 m^3 chamber, but for accurate work a 10—40 m^3 chamber is necessary. However, it appears later in his account that he may here be referring to experiments in which the toxic substance is sprayed into

the chamber at the start, as opposed to those in which there is a continuous flow. He goes on to say that for long exposures a small chamber may be satisfactory and that for short exposures the merits of a small chamber with continuous flow and of a large chamber with stable atmosphere depend on the particular case.

Wachtel also comments on the suitability of different animal species for such work. He states that rodents such as mice, rats and guinea pigs are unreliable as a source of data on toxicity to man of the gases studied. One factor is their protective respiratory reflexes. Another is the variable susceptibility to poisons, depending on the food they get. He does consider, however, that cats, dogs and monkeys provide useful data. Cats are more sensitive to poisons than man. As a rough approximation he gives the toxicity figure for cats as half that for man. He states, however, that there is wide variability between cats, depending on breed, age, food and domestication. In particular, he discusses the difference between domesticated and undomesticated cats. He says that a cat is strongly affected by what he calls "psychic" influences. An undomesticated cat may well die in captivity within about a month even if it is fed properly and subjected to no experiments.

Wachtel considers that dogs are less sensitive than cats, although again there is wide variability due to breed, size, age and food. He states that the toxicity figures for dogs are higher than those for man or, in some cases, about equal, but gives no basis for this assertion. The toxicity figures for monkeys are about the same as those for dogs. In this respect, therefore, monkeys offer little advantage over dogs as experimental animals. They are, however, instructive to observe, because they express symptoms more vividly than other animals.

Haber carried out investigations on animals at various concentrations and exposure times and found that the same toxic effect was obtained at the same value of the mortality product ct

$$ct = \text{constant} \tag{4}$$

where c is concentration (mg/m^3) and t is time (min). The values of the mortality product, or lethal index, quoted by Haber [16] for chlorine and phosgene are given in Table 1, Section A.

Discussions of the lethal index have been given by other workers such as Flury [12, 19, 20] and Wachtel [18] and from these accounts it appears probable that the formulation of this index was based originally on the results obtained for phosgene. Flury in particular discusses the lethal index in this context. In contrast to phosgene, no detailed information has been found for Haber's work on chlorine and the range of concentrations on which his mortality product is based is not known.

None of the accounts seen gives a precise definition of the lethal index in respect of the degree of lethality. It is necessary, therefore, to try to infer its meaning. This task is made more difficult by the apparently inconsistent values of the index given by other workers. Table 1, Section A, also gives

TABLE 1

Values of the lethal index for cats exposed to chlorine and phosgene given by various German authors

A. Author	Lethal index	
	Chlorine ((mg/m³) min)	Phosgene ((mg/m³) min)
Haber [16]	7,500	450
Wachtel [18]	3,000	900
Muntsch [17]	7,500	900
B. Author		
Hess[a]:	Lethal concentration for chlorine = 0.1—0.15 mg/l for 1/2—1 h Equivalent lethal index (maximum range) = 3,000—9,000 (mg/m³) min	

[a]Quoted without reference by Flury and Zernik [11].

values of the lethal index quoted by Wachtel and by Muntsch. Section B of the table gives the values which may be inferred from data ascribed to Hess by Flury and Zernik.

A clue to the interpretation of the lethal index in Table 1 is given by Flury and Zernik [21], who state that the index has frequently been misinterpreted:

"There are some quite erroneous views on the mortality product for phosgene, which is almost universally given as 450, for man also. In the classic work of Laqueur and Magnus [22], in which this figure, obtained by Flury, is first quoted, it is expressly stated that it refers to the smallest lethal dose, and it applies to cats which are particularly sensitive to phosgene. The modern view is that such minimum values are of much less practical use in assessing the toxicity of a substance than the highest *ct* value at which an experimental animal survives. As large series of experiments show, toxicity values of gases and vapours fall within certain limits about a mean point. For phosgene this mean mortality product *ct* for cats is not 450 but 900."

These comments are taken to mean that phosgene has a lethal index LI_{50} for cats of 900 and perhaps an LI_{10} of 450. This interpretation is discussed further below.

The work done by the Germans on the toxicity of phosgene was extensive and seems to have influenced their thinking on toxicity generally. They first used it on the battlefield against the French in October 1915 and had presumably done experiments before this. Experimentation on phosgene was still continuing in 1917. Data on the toxicity of phosgene for cats has been given by Flury [19] in tabular and in graphical form, the graph being reproduced by Flury and Zernik [11]. These data are shown in Table 2 and in Fig. 1. The triangles represent individual survivals and the closed circles

TABLE 2

Concentration of phosgene lethal to cats in German work during the First World War (after Flury [19])

Concentration, c (mg/m^3)	Exposure time, t (min)	Mortality product, ct ((mg/m^3) min)	Outcome
5	60	300	survived
5	120	600	survived, but ill
10	15	150	slightly ill
11	30	330	death after 2 days
12.5	60	750	death after 1 day
10	120	1,200	death after 1 day
20	25	500	survived (ill)
25	15	375	survived (ill)
25	30	750	death after 1 day
25	60	1,500	death after 1 day
50	7.5	375	survived
45	15	675	death after 1 day
45	30	1,350	death after 1 day
75	5	375	survived
100	5	500	death after 1 day
150	15	2,250	death after 1 day
500	0.5	250	survived
500	1	500	survived
500	2	1,000	ill, death after 9 days
500	3	1,500	death after 1 day

individual deaths. The curve drawn separates the two sets of points and corresponds apparently to a mortality product of about 450. It seems probable that the original lethal index for phosgene for cats was based on this curve. It is suggested, however, that the value of the lethal index was later reassessed, probably by Flury, and that it was revised to 900. If so, this may well have been done after Haber had made public his value.

Turning to the question of the interpretation of the lethal index for chlorine, it is suggested that the same arguments should be applied and that the value of the lethal index of 7,500 for cats quoted by Haber should be interpreted as the LI_{10}, the value of 3,000 quoted by Wachtel being probably an earlier value of this index. If the ratio of the LI_{50} to the LI_{10} is assumed to be the same as that for phosgene, namely 2, this would give a value of 15,000 for the LI_{50} for cats. Again this interpretation is discussed further below.

German military writers such as Hanslian [13] refer to the lethal index and give Haber's values for chlorine and phosgene.

British work ca. 1914—1918

British work on war gases was a response to the German attack and involved a number of eminent scientists, including Sir William Ramsey and

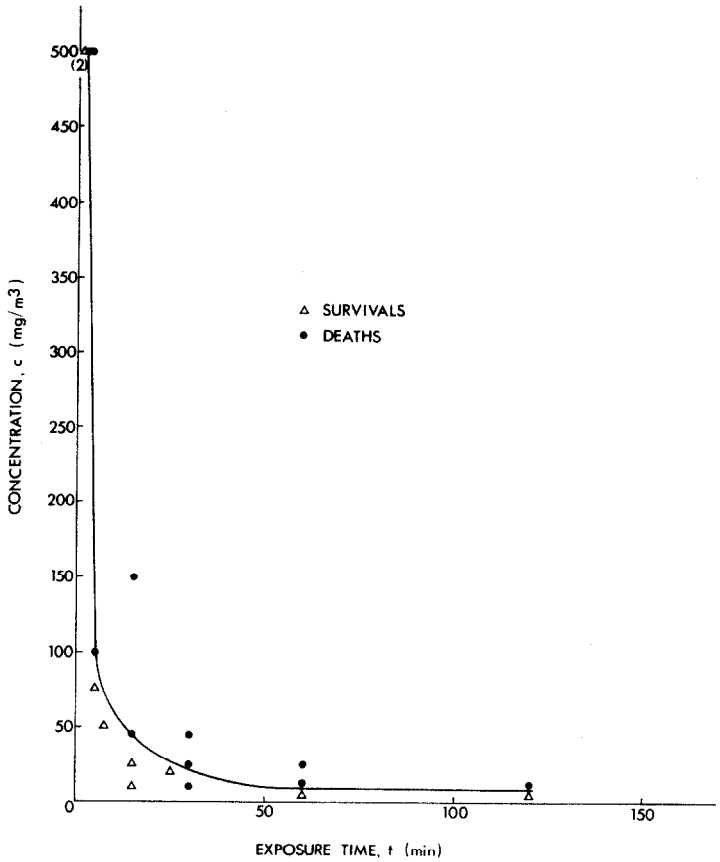

Fig. 1. Concentration of phosgene lethal to cats in German work during First World War (after Flury [19]).

J.S. Haldane. Experimental investigations of gas poisoning were carried out and doctors who had treated or investigated gas casualties published their findings. Early in 1916 an experimental station was established at Porton [23] under Lt-Colonel Crossley with a team of physiologists and pathologists led by Barcroft. A series of investigations of various aspects of gas poisoning, including some toxicity work, was carried out by the Chemical Warfare Medical Committee of the Medical Research Council [24]. This work is discussed further below.

A paper describing experimental work on chlorine gas poisoning was published by Sir E. Schafer [25] as early as August 1915. He describes work on the gassing of rabbits, cats and dogs, but the work was directed towards the elucidation of the physiology of poisoning rather than to the estimation of toxic concentrations and the concentrations of chlorine used were high, of the order of 0.5—1.0% (5,000—10,000 ppm). Chlorine toxicity was the subject of a lecture published in December 1915 by Hill [26, 27], who

states that a concentration of 100 ppm is intolerable. In a further postwar lecture [28] mainly concerned with the physiology of gas poisoning Hill states that cats exposed to concentrations of chlorine of 1 part in 700—2,500 (400—1,430 ppm) may die in less than 15 min. Chlorine gas poisoning is also discussed in two postwar accounts by Herringham [29—31], but he does not quote toxicity figures. In work for the Medical Research Council Gunn [32] carried out experiments on possible bronchial spasm at high chlorine concentrations in which anaesthetised rabbits were exposed to concentrations of 200—1,000 ppm, but no mortality data are given.

There has, therefore, been found no toxicity data on chlorine comparable to the German work. The nearest approach is the figures given in the Manual of Treatment of Gas Casualties [33]. This is quoted by Muntsch, who states that the manual gives lethal concentrations of 1.45 mg/l (500 ppm) for 2 min and 0.29 mg/l (100 ppm) for 10 min and that these figures correspond to a lethal index of about 3,000 mg/m^3 min.

French work ca. 1914—1918

French work on gas toxicity was apparently done mainly in individual laboratories but under the direction of the War Ministry [34—37]. It is not clear what data on chlorine toxicity, if any, this work yielded. Meyer [37] gives a value of the lethal index (indice de mortalité) for chlorine as 7,500, which he ascribes to Flury and to Julius Meyer.

Russian work ca. 1914—1918

Work on the toxicity of war gases in Russia was carried out in St Petersburg in a number of laboratories [38, 39]. In particular, work on gas protection was done at the Heleneninstitute under Professor Chlopin [39]. The Russians appear to have done experimental work on gas toxicity. Chlopin gives a table of relative toxicities which are apparently derived from this work. These toxicities are given relative to chlorine as unity.

An important single item of data given by Chlopin is his statement that, according to observations by Slowzow, horses die in 35—40 min at a chlorine concentration of 1:1,000 (1,000 ppm).

American work ca. 1918

American work on war gases started after the U.S. entered the war in 1917 [40, 41]. Initially it was centred on the Bureau of Mines under Manning, assisted by Burrell. The organisation grew rapidly and a chemical branch was established at the American University, Washington, and the medical division at Yale University. With transfer to the War Department the Medical Division at Yale came under Colonel Lyster with sections on physiology, pathology and pathological chemistry under Henderson, Winternitz and Underhill, respectively. Some U.S. personnel were seconded to Porton. Work ended rather abruptly, however, when war was over. The period of activity was therefore relatively short and came after the introduc-

TABLE 3

Concentration of chlorine lethal to dogs in Underhill's work [41]. Exposure time 30 min

	Concentration[a]						
(mg/l) (ppm)	0.16—0.80 50—250	1.27—1.58 400—500	1.58—1.90 500—600	1.90—2.22 600—700	2.22—2.53 700—800	2.53—2.85 800—900	2.85—6.34 900—2000
Deaths within 3 days	0	1	2	9	9	20	13
Delayed deaths	1	4	2	5	2	1	0
Total deaths	1	5	4	14	11	21	13
Total no of animals	9	17	10	21	18	23	14
Overall mortality (%)	11	29	40	67	61	91	93

[a]The conversion of concentrations from mg/l to ppm by Underhill in this table corresponds to a temperature of 0°C. Henceforth in this paper these concentration values in ppm have been recalculated to a temperature base of 25°C.

tion of war gases more lethal than chlorine. A plant for the manufacture of chemical weapons was built at Edgewood Arsenal.

The work of Underhill [41] at Yale was directed towards the determination of the toxicity to man of gases actually used in the war. The gases investigated were chlorine, phosgene and chlorpicrin.

The experimental animals used in Underhill's work were dogs. For chlorine he used some 112 animals in 7 groups ranging in size from 9 to 23, which is just about sufficient for statistically meaningful results. For phosgene and chlorpicrin he used 327 and 219 dogs, respectively. The experimental method used in Underhill's work was to gas the animals singly in a gas chamber with a continuous gas flow. He experienced some difficulty in maintaining steady flows of gas. All Underhill's work was done using exposure periods of 30 min.

The results obtained by Underhill for the lethality of different concentrations of chlorine to dogs are shown in Table 3. Attention is drawn to the note in the table concerning the units of concentration. The data are plotted in Fig. 2. They have been analysed using the method of Litchfield and Wilcoxon [42]. The line through the points and the 95% confidence limits are shown in the figure. The LC_{50} obtained is 650 ppm. The use of the

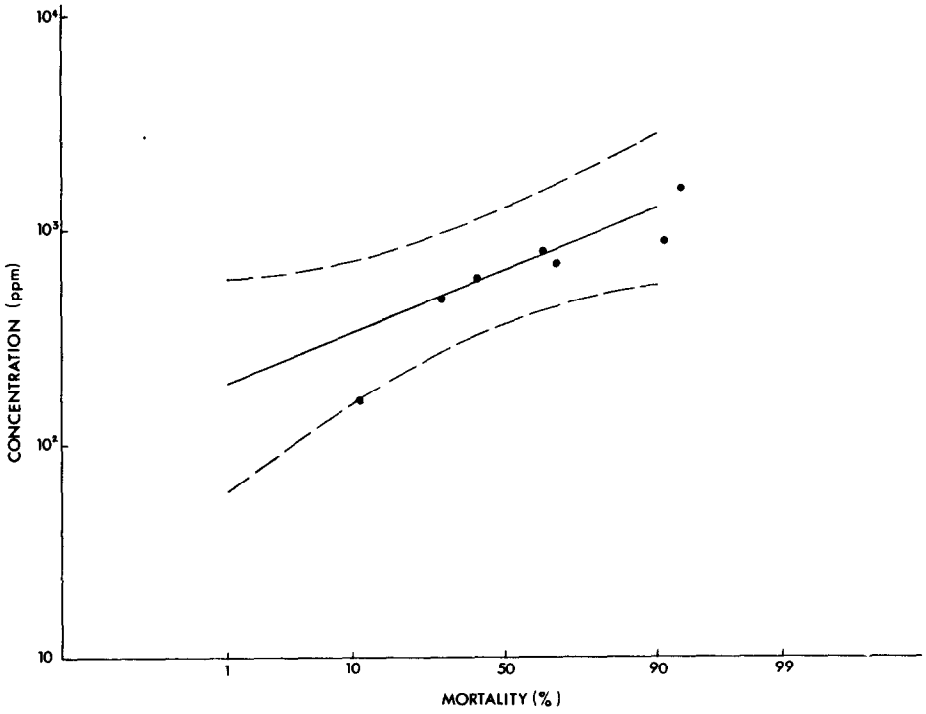

Fig. 2. Concentration of chlorine lethal to dogs in Underhill's work [41]. Exposure time 30 min. Dotted lines are 95% confidence limits.

Litchfield and Wilcoxon method and the interpretation of Underhill's data are discussed below.

Another potentially significant feature in this work is the proportion of acute, early deaths, occurring within three days. Figure 3(a) shows the proportion ψ of acute deaths as a function of the concentration and Fig. 3(b) as a function of the mortality.

The pathological work on Underhill's dogs has been described by Winternitz et al. [43]. Other pathological work on dogs is described by Barbour et al. [44, 45] and Hjort and Taylor [46].

Values of the concentrations of chlorine lethal to man given by various

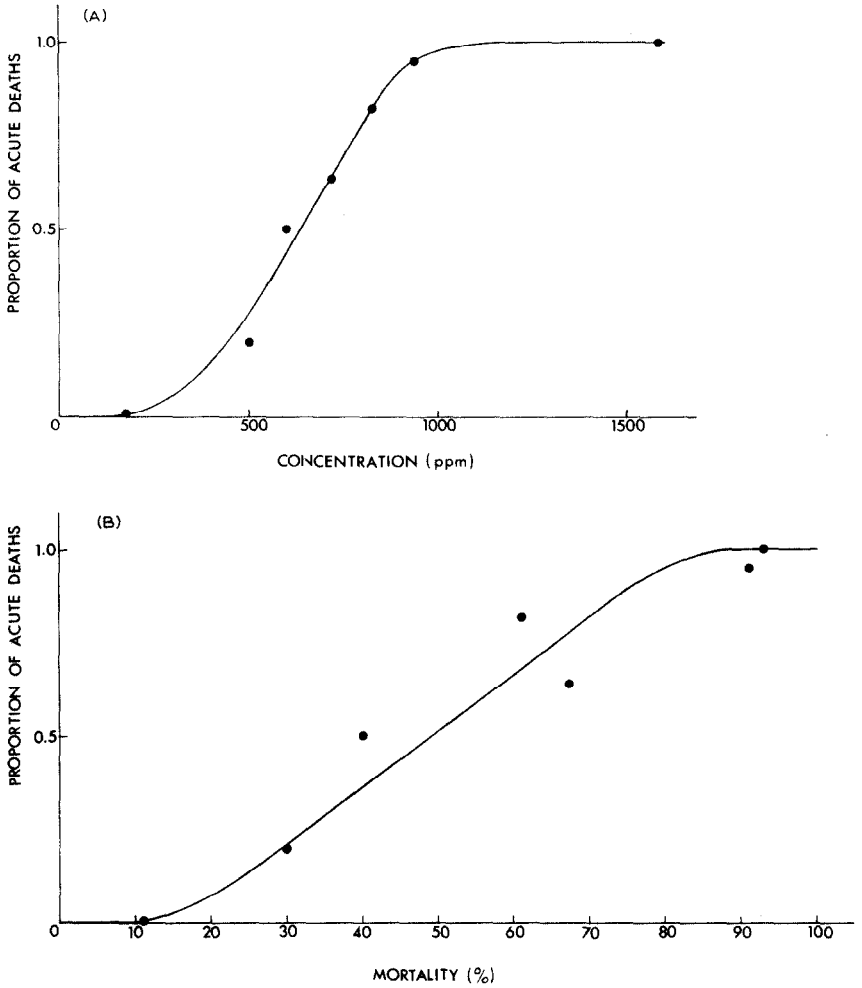

Fig. 3. Proportion of acute deaths by chlorine poisoning of dogs in Underhill's work [41]. Exposure time 30 min. (a) Proportion of acute deaths as a function of concentration. (b) Proportion of acute deaths as a function of mortality.

American military authors writing between the wars are shown in Table 4. Prentiss [15] also quotes values of the lethal index determined by American workers. The lethal indices for phosgene and for chlorine are given as 5,000 and 56,000, respectively. For chlorine this is equivalent to a lethal concentration of 5.6 mg/l (1,932 ppm) for a 10 min exposure time and is therefore consistent with his other data shown in Table 4.

TABLE 4

Concentration of chlorine lethal to man given by various American authors

Author(s)	Lethal concentration (mg/l)	Exposure time (min)	Reference
Prentiss [15]	2.9	30	p.66
	2.53	30	p.150
	5.6	10	p.150
Vedder [47]	3	30	p.83
Fries and West [48]	3.5	30	p.116

If the lethal concentrations for man at 30 min quoted by these military writers are compared with those obtained for dogs by Underhill given in Table 3, it appears that what is being quoted is Underhill's results for the sixth group in which the chlorine concentrations lay in the range 2.53—2.85 mg/l (873—983 ppm) and the mortality was 91%. Thus the American lethal index seems to correspond to an LD_{90}.

The German lethal index for chlorine of 7,500 is quoted by Prentiss. He describes it as a minimum value, but does not expand on this. He acknowledges the need to explain the difference between the American and German indices, but he does this in terms of the experimental animals, i.e. dogs versus cats, rather than in terms of the definition of the index.

A review of American experience with poison gas has been given by Gerchik [49].

Reconciliation of German and American work

The results obtained in the German and American work just described can be reconciled if a hypothesis is made concerning the probable ratio of the lethal concentrations for different mortalities and the relative susceptibility of dogs and cats.

In an account of American views on some aspects of the use of irritant gases in gas warfare based on work done up to 1948 Gerard [50] states that the ratio of the concentration required for 90% mortality to that for 10% mortality tends to lie in the range 5—10. The ratio in Underhill's work

on dogs for chlorine, and also for phosgene, is about 5. As far as relative susceptibility is concerned, there is the comment by Wachtel that cats are more susceptible than dogs.

The hypothesis made is that the lethal indices for dogs and cats for phosgene and chlorine in the German and American work are as shown in Table 5. The starting points for both gases are the LI_{10} values for cats. Application of appropriate ratios then yields the other values. The LI_{90} values for dogs are then equal to the values of the lethal index quoted by Prentiss for the American work. The ratios which have been assumed in order to obtain the values in Table 5 are:

$LI_{50}/LI_{10} = 2$ for cats for both gases

$LI_{90}/LI_{50} = 2$ for cats for both gases

$LI_{50\ (dogs)}/LI_{50\ (cats)} = 2.8$ for phosgene
$= 1.9$ for chlorine

On the basis of the arguments just given these ratios seem to be of the right order.

TABLE 5

Actual and postulated values of the lethal index for cats and dogs exposed to chlorine and phosgene in German and American work

	LI_{10}	LI_{50}	LI_{90}
Phosgene			
Cats	450	900	1,800
Dogs			5,000
Chlorine			
Cats	7,500	15,000	30,000
Dogs			56,000

Work since 1918

Work on war gases was done by the various combattants in the Second World War, but there appears to be relatively little published material on this. There are, however, some general accounts of American work [51—53]. A review of American work on irritant gases is given by Gerard [50], as mentioned above.

No references have been found on experimental work on larger animals since the end of the First World War, but experiments on rodents have been carried out by several investigators. A number of workers have carried out experiments on animals at concentrations of chlorine high enough to be lethal.

The difficulties which can occur in such experiments have already been mentioned in relation to the early German work. Further illustration is

provided by the work of Barrow and Dodd [54], who found that chlorine reacted with ammonia from animal urine and faeces. Other experimental difficulties are referred to below.

The experimental work is first described with minimal comment and then reviewed critically. Zeehuisen [55] carried out experiments in which guinea pigs and white rats were exposed to chlorine for periods of 15—30 min. No animals died after a 30-min exposure to a concentration of 1:300 (3,300 ppm) but they did die when this concentration was increased to between 1:300 and 1:125 (3,330 and 8,000 ppm).

Weedon et al. [56] carried out experiments in which mice and rats, in groups of 4 and 8, respectively, were exposed to concentrations of chlorine of 16, 63, 250 and 1,000 ppm for periods of 1, 4, 15, 60, 240 and 960 min until they died, or for a maximum period of 960 min. The three latter concentrations corresponded to the LC_{50} for mice at exposure periods of >960, 440 and 28 min, respectively, and to that for rats at exposure periods of >960, 440 and 53 min, respectively. Data on the concentrations of chlorine lethal to mice and rats are given in an earlier paper by McCallan and Setterstrom [57]. Their data are similar, but not identical, to those of Weedon et al.

Work on the toxicity of chlorine to mice was carried out during the Second World War by the U.S. military. Lipton and Rotariu [58], in a report by Geiling and McLean, describe experiments in which mice in groups of 20 were exposed to concentrations of chlorine ranging from 310 to 2,357 ppm for a period of 10 min with an observation period of 10 days. The LC_{50} obtained was 628 ppm.

Work on the toxicity of chlorine to mice was carried out at Edgewood Arsenal by Silver and McGrath [59] and by Silver et al. [60]. Silver and McGrath carried out experiments on 49 groups of mice, 45 groups of 20 and 4 groups of 40, in two series. In the first series certain sources of error became apparent. There was a deficiency in the gas analysis, the chlorine reacted with the chamber wall and the normal mortality of the mice used over a 10 day period was variable. In the second series the error from these sources was much reduced. In particular, the quality control on the mice used was improved. In the two series of experiments mice were exposed to concentrations of chlorine in the range 252—1,139 ppm for 10 min with a 10 day observation period. In the first series the LC_{50} was 524 ppm and in the second series 597 ppm. Most of the deaths occurred in the first 24 hours.

Silver et al. carried out further experiments on 15 groups of 20 mice. Again they used a 10 min exposure time and a 10 day observation period. In this third series the concentrations of chlorine were in the range 379—890 ppm and the LC_{50} was 676 ppm. Out of 154 deaths, one was due to mild oedema and congestion and two to pneumonia; the rest were due to severe oedema. Most of the deaths occurred within the first 24 hours. These authors also quote work by the University of Chicago Laboratory on mice of the same strain. The LC_{50} obtained by this laboratory was 628 for

an exposure period of 10 min, which is the same value as that of Lipton and Rotariu [58].

Experiments designed to provide information on pulmonary disease were conducted by Bell and Elmes [61, 62]. Most of their work does not yield results useful in the present study except for one set of experiments in which a lethal concentration was determined for a 30 h exposure. This exposure was, however, intermittent at a rate of 3 h/day.

Schlagbauer and Henschler [63] carried out experiments in which mice in groups of 10 were exposed for 30 min to concentrations of chlorine of 55, 62, 69, 110, 125, 132, 145, 160 and 179 ppm. The deaths occurring in the intervals 0—2 and 2—4 days after exposure were recorded. There were no deaths later than 4 days after exposure. The LC_{50} obtained was 127 ppm.

These authors also report work done at lower chlorine concentrations and longer exposure periods. They carried out experiments in which 10 mice were exposed for 3 hours to concentrations of chlorine of 10 and 22 ppm with an observation period of 4 days. The mortality of the mice at these two concentrations was 8/10 and 10/10, respectively.

Faure et al. [64] reported experiments in which guinea pigs were exposed to chlorine but give no data on mortality.

A survey of the toxicity of chemicals which are transported in the U.S. has been given by Back et al. [65]. This is essentially a literature survey, but it does report some original experimental work done under contract for a limited number of chemicals, including chlorine. In this contract work experiments were carried out in which mice and rats were exposed to chlorine for a period of 1 hour. The LC_{50} values obtained were 137 ppm for mice and 293 ppm for rats. The work was sponsored by the Aerospace Medical Research Laboratory at Wright Patterson Air Force base.

Vernot et al. [66] reported experiments on the toxicity of a number of chemicals, including chlorine. Experiments were carried out in which mice and rats were exposed for a period of 1 hour and LC_{50} values of 137 ppm were obtained with a range of 119—159 for mice and 293 ppm with a range of 260—323 ppm for rats. This work is apparently the same as that reported by Back et al. [65], having the same sponsor and a common co-author (MacEwen). The contract was with the University of California, Irvine.

Barrow and Smith [67] carried out experiments in which rabbits in four groups of 4 were exposed to concentrations of chlorine of 50, 100 and 200 ppm for a period of 30 min. One animal from each group was sacrificed for examination at 30 min, 3 days, 14 days and 60 days after exposure. No mention is made of mortality in these experiments. In preliminary experiments, however, rabbits exposed to 1,000 and 500 ppm died after 30 min and 2 days, respectively, while those exposed to 250 ppm survived.

Barrow et al. [68] carried out experiments concerned with sensory irritation in which mice were exposed to concentrations of chlorine varying between 0.7 and 38 ppm for a period of 10 min. It is not stated that any of the animals died.

Experiments were carried out by Bitron and Aharonson [69] in which mice in groups of 16 were exposed to concentrations of chlorine of 170 and 290 ppm for periods of 15—160 min and 5—30 min, respectively. The times of death after exposure were recorded over an interval of 30 days. The LC_{50} values obtained were 170 ppm and 290 ppm for exposures of 55 and 11 min, respectively.

Alarie [70] carried out experiments in which mice in groups of 4 were exposed to chlorine for a period of 10 min with a 3 hour observation period. The LC_{50} obtained was 302 ppm.

The LC_{50} values obtained by these various authors are summarised in Table 6. Three sets of more detailed data are given in Table 7 and data on the proportion of acute deaths in Table 8.

Zeehuisen's results appear to give anomalously high lethal concentrations

TABLE 6

Concentrations of chlorine lethal to rodents given by various authors

Author(s)	Species	Concentration lethal to 50% (ppm)	Exposure time (min)
Zeehuisen (1922) [55]	Guinea pigs, white rats	>3,330	30
Weedon et al. (1940) [56]	Mice	1,000	28
		250	440
		63	>960
	Rats	1,000	53
		250	440
		63	>960
Lipton and Rotariu (1941) [58]	Mice	628	10
Silver et al. (1942) [59, 60]	Mice	618[a]	10
Bell and Elmes (1965) [61, 62]	Mice	117[b]	1,800
Schlagbauer and Henschler (1967) [63]	Mice	127	30
Back et al. (1972) [65]	Mice	137[c]	60
	Rats	293[c]	60
Bitron and Aharonson (1978) [68]	Mice	290[d]	11
		170	55
Alarie (1980) [70]	Mice	302	10

[a] Value obtained by averaging values of 524 and 597 ppm [59] and then averaging again with value of 676 ppm [60].
[b] Exposure of 30 h limited to 3 h/day.
[c] These values are also given by Vernot et al. [66] — see text.
[d] These values are for 30 day observation period — see text.

TABLE 7

Mortality of animals exposed to chlorine as a function of concentration given by various authors

Author(s)	Species	Exposure time (min)	Concentration (ppm)	Mortality (%)
Underhill [41]	Dogs	30	164[a]	11
			491	30
			600	40
			710	67
			819	61
			928	91
			1,583	93
Silver et al. [59, 60]	Mice	10	380	10
			549	45
			549	25
			583	5
			631	40
			638	45
			690	15
			707	60
			711	55
			745	70
			794	75
			842	40
Schlagbauer and Henschler [63]	Mice	30	62	10
			69	10
			110	30
			125	30
			132	60
			143	60
			160	80

[a]Converted from 0°C to 25°C.

and are not considered further. The lethal concentrations are high also in the work of Weedon et al., but this is readily explained by the fact that an unusual protocol was used in which the concentrations were such that some animals died during the experiment itself, but the exposure period recorded was the full duration of the experiment.

The lethal concentrations are lower in the work of Lipton and Rotariu, Silver et al., Schlagbauer and Henschler, Back et al. (and Vernot et al.) and Bitron and Aharonson, in which the animals were withdrawn after a defined exposure. In the first two sets of work, where the exposure period was 10 min, most of the deaths occurred within the first day. In Schlagbauer and Henschler's work likewise almost all the deaths took place in the interval 0—2 days after exposure. The only deaths in the interval 2—4 days were

TABLE 8

Mortality of mice exposed to chlorine as a function of time after exposure (Lipton and Rotariu [70]). Chlorine concentrations 338—2,574 ppm, exposure time 10 min

Time after exposure (days)	Deaths	Mortality (%)
0	126	85
1	7	4.7
2	1	0.7
3	1	0.7
4	3	2.1
5	1	0.7
6	0	0
7	0	0
8	2	1.4
9	3	2.1
10	4	2.8
Total	148	100

at a concentration of 132 ppm, for which 2 of the 6 deaths were in this interval. In Bitron and Aharonson's work, on the other hand, most of the deaths were delayed deaths, the mortality being only 10% or less during the day of exposure and most of the deaths occurring in the interval 5—7 days after exposure.

The LC_{50} values obtained by these workers are also shown graphically in Fig. 4. The dotted line is drawn through the point for Underhill's dogs and with a slope equal to —0.5. The justification for this is given later.

It is also of interest to consider the lowest concentration of chlorine at which any death occurred. In the work of Weedon et al. there were no deaths for mice or rats exposed to 63 ppm for the full period of 960 min, but at 250 ppm the first deaths occurred after 400 min. Silver and McGrath had two deaths at their lowest concentration of 252 ppm and Silver et al. two at their lowest concentration of 379 ppm, the exposure period in both sets of work being 10 min. Schlagbauer and Henschler had a single death at a concentration of 62 ppm for 30 min exposure. The lowest concentration used by Bitron and Aharonson was 170 ppm and a single death was recorded by these workers after a 20 min exposure. Bell and Elmes obtained deaths at a concentration of 40 ppm with exposures of 30 h with a maximum exposure period of 3 h/day. Disregarding this latter work as involving an unusual and atypical type of exposure, the lowest concentration found to be lethal for a 30 min exposure is Schlagbauer and Henschler's value of 62 ppm.

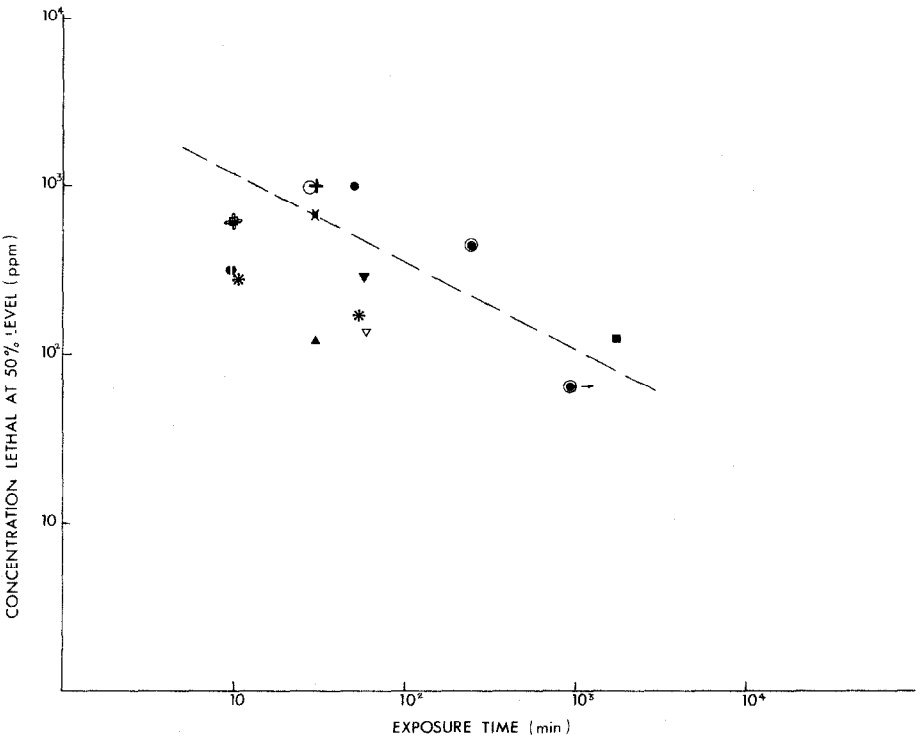

Fig. 4. Concentration of chlorine lethal to various animal species at 50% level. Dotted line has slope equal to —0.5. ○: Weedon et al. [56] — mice; ⌖: Lipton and Rotariu [58] — mice; □: Silver et al. [59, 60] — mice; ▲: Schlagbauer and Henschler [63] — mice; ▽: Back et al. [65] — mice; ✳: Bitron and Aharonson [69] — mice; ◈: Alarie [70] — mice; ●: Weedon et al. [56] — rats; ■: Bell and Elmes [61] — rats; ▼: Back et al. [65] — rats; ×: Underhill [41] — dogs; +: Chlopin [39] — horses (fatal concentration, not necessarily LC_{50}).

Experimental work on odour and chronic toxicity

There is also a large amount of experimental work on animals at low chlorine concentrations, which, although of only marginal relevance to acute toxicity, merits brief mention.

Early work on odour was carried out by Matt [71]. More recent work is that of Beck [72] and Rupp and Henschler [73]. Odour is discussed in detail in a review by a World Health Organisation (WHO) working party [74].

The work on low concentrations and long term effects is also quite extensive. In addition to that already mentioned, it includes the work of Skljanskaja and Rappoport [75], Arloing et al. [76] and Barrow et al. [77, 78]. This work is also discussed by the WHO working party.

Physiology and pathology of gas poisoning

The physiology and pathology of chlorine gas poisoning have been studied by a number of workers, including many of those already mentioned. Many of those who have done experimental work on animals have discussed this aspect. The papers by Lehmann [6—10] give a wide-ranging discussion of the topic. Accounts by German workers around the time of the First World War include those of Flury and Zernik [11] and Wachtel [18], by British workers those of Hill [26, 28] and by American workers those of Underhill [41] and Winternitz et al. [43]. The overall picture which emerges is that while chlorine attacks the whole of the respiratory system, the cause of death is lung oedema. On the other hand, in their work on mice Schlagbauer and Henschler [63] found that bronchial spasm also is a partial or principal cause of death where death occurs within 24—48 hours.

In this area, however, there is a large amount of information which is directly applicable to man. There are a number of accounts by British doctors who dealt with chlorine gas casualties during the war. The early papers by Schafer [25] and Hill [26] have already been mentioned, as have the post-war surveys by Hill [28] and Herringham [29, 30]. Descriptions of and correspondence on gas attacks and casualties [79—95] figure prominently in the medical journals, particularly in 1915. The accounts by Bradford and Elliott [96] and Black et al. [97] are especially valuable.

The Chemical Warfare Committee of the Medical Research Council [24] did extensive work, including that of Gunn [32] on the action of chlorine on the respiratory system, Haldane [98] on the administration of oxygen, Haldane, Meakins and Priestley [99, 100] on breathing, Edkins and Tweedy [101] on lung changes, Barcroft [102, 103] on blood, Hunt and Price Jones [104] and Haldane, Meakins and Priestley [105, 106] on the long term effects. Some later publications by these authors are those of Haldane and Priestley [107] on respiration and Barcroft [108] on the respiratory function of the blood. Other publications include the Manual of Treatment of Gas Casualties [33] already mentioned and a study of the pathology of gas poisoning [109]. The official military account is given in *Diseases of the War* [23].

The extensive American work at this time is described by Underhill [41] and Winternitz et al. [43], while the official military account is given by Ireland [110]. Additional information is given by Henderson and Haggard [111, 112]. Further accounts are given by other military authors such as Prentiss [15] and Vedder [47]. The work of Drinker [113] on pulmonary oedema is also relevant in this connection.

There are also available accounts of accidental chlorine releases, a large proportion of which are by doctors who treated those who were gassed. Accounts [114—124] of some of the principal accidental releases are listed in Table 9. There are a number of further accounts [125—152] of pathology and of industrial and domestic exposures, including long term, low concentration industrial exposures.

TABLE 9

Accounts of some principal accidental releases

Date	Location	Reference
1934	Tilsit	Freitag [114]
1940	Mjondalen	Freitag [114] Romcke and Evensen [115]
1944	Brooklyn	Chasis et al. [116]
ca. 1945	Submarine	Tatarelli [117]
1952	Walsum	Baader [118]
1961	La Barre[a]	Joyner and Durel [119] Weill et al. [120] Segaloff [121]
	Cleveland	Adelson and Kaufmann [122] Kaufmann and Burkons [123] Chester et al. [124]

[a] Also referred to as Morganza.

Investigations of the long term effects of gas warfare exposure are described by Meakins and Priestley [106], Vedder [47], Gilchrist and Matz [153] and Penington [154] and of those of accidental exposure by Chasis et al. [116], Weill et al. [120], Kaufmann and Burkons [123], Kowitz et al. [141] and Colardyn et al. [152]. The response of large animals such as horses in gas warfare has been described by Richters [155—157], Bressou [158] and Chlopin [39]. A revised view on American military work up to 1948 is given by Gerard [50].

Chlorine is a strong oxidising agent. A number of different explanations have been given of the way in which it causes damage. An early suggestion was that its effect is through the formation of hydrochloric acid. Another early suggestion was that it gives rise to nascent oxygen [111]. More recent suggestions are the action of hypochlorous acid and of chlorine itself [68, 159].

Chlorine is an irritant gas and the most serious effect of acute chlorine poisoning is damage to the respiratory system. Another important irritant gas which was also used as a war gas is phosgene and many discussions of gas poisoning treat the two gases together, although there are differences. The symptoms of chlorine poisoning are irritation of the nose, throat and eyes with cough and tears at a concentration of about 15 ppm, restriction of breathing and chest pain at about 30 ppm and development of pulmonary oedema from about 50 ppm. Other symptoms are described in some of the accounts given below. Additional information is given in Table 12 below.

The action of irritant gases on the respiratory tract is described by Haggard [111] 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."

Oedema (edema) is an accumulation of fluid in the tissue spaces.

In the present context it is severe acute poisoning which is of primary interest. Herringham [30] states:

"The whole course of events, and the various degrees of severity, are all due to but one cause, the want of oxygen in the blood due to the wall of oedema interposed between the air and the blood vessels."

An extensive discussion of chlorine poisoning is given in *Diseases of the War* [23] and the following extracts give an overview of the principal aspects. The threat to life is due almost entirely to pulmonary oedema and other effects are relatively unimportant, but later infection can also be dangerous:

"The respiratory organs, eyes and skin, bore the brunt of the attack. Yet even if one recognises this, one must be prepared for serious effects which are secondary to these primary lesions. Severe though temporary shortage of oxygen, resulting from acute pulmonary oedema or interference with the oxygen-carrying power of the blood, may exercise lasting effects on the heart, the central nervous system, or other organs in the body, while secondary bacterial infection may delay recovery or even be the prelude to a fatal termination." [23, p.257]

"The points where the gases classed as acute lung irritants exercise their most pronounced effect are the alveoli of the lungs and the smaller bronchial tubes, and the great danger to be feared, which is common to them all, is the onset of acute pulmonary oedema. It is in the main this oedema which, in the acute stage of poisoning, threatens the life of the subject, for if abundant it causes death by asphyxiation, the patient being in fact drowned by his own exudation."

"The rate of onset and the degree of oedema are dependent on the particular gas and on its concentration, and, though in some cases to a less degree, on the duration of exposure." [23, p.362]

"It is clear from the accounts just given that the major damage caused by the acute lung irritants is confined to the respiratory system and that lesions elsewhere in the body have no very distinctive character." [23, p.374]

"Any pathological changes found in organs of the body other than the lungs are really attributable to changes resulting secondarily from the gross damage in the respiratory apparatus, and from the consequent asphyxia, and that the direct effects of the gas are limited to the lungs and bronchial tubes." [23, p.375]

"The outstanding changes in the lungs are the gross exudation of fluid into the alveoli, inflammatory and necrotic changes in the mucous membrane of the bronchial tubes, acute emphysema, and capillary thrombosis or obstruction of capillaries by strands of fibrin." [23, p.376]

The effect of the oedema is to cause a reduction in the supply of oxygen to the blood:

"These gross changes in the lungs are responsible for serious interference with the gaseous exchange between blood and air, and the indications of asphyxia were obvious in all severe cases of poisoning by the acute lung irritant gases. The cases fell into two categories; the one was characterised by intense florid and deep cyanosis, with vascular congestion and engorgement of the veins, the other exhibited no venous engorgement but pallor akin to that seen in collapse, with grey or lilac-coloured lips and tongue. Both classes had the common feature that the colour of the blood indicated a grave deficiency of oxygen." [23, p.377]

There is also an increase in the concentration of carbon dioxide in the blood:

"The precise functional effects caused by the interference with the gaseous exchange in cases of poisoning by the acute lung irritants will depend largely upon whether or not the shortage of oxygen is accompanied by the damming back of carbon dioxide in the body, though it is in all cases the former which constituted the real danger." [23, p. 380]

The symptoms tended to follow a common pattern:

"All the men gave a similar description of what they felt as the greenish-yellow fumes enveloped them. Immediate choking, coughing, gasping for breath and inability to speak proved the irritation and spasm of the respiratory tract. In many the eyes smarted and ran with water. Retching was at once experienced by some, but many did not vomit until an hour or two later. There was severe pain behind the sternum, which soon radiated outward on each side into the chest and added greater suffering to the distressed breathing. The throat burned and the dry mouth produced an intense sensation of thirst."

"Very soon the developing pulmonary oedema led to the phenomenon of oxygen shortage, with headache, a sense of weakness in the legs, and such lassitude that the men dropped prone upon the ground, the spasmodic violence of their respiratory efforts being then largely quietened. In this posture they lay in still greater danger, since the heavy gas clung in more poisonous concentration in the trench bottoms and recesses of the ground . . . "

"Milder cases in areas where the concentration of chlorine in the air was relatively low, suffered chiefly from lassitude and a great sense of fatigue, which rendered them useless for fighting . . . " [23, p.383]

"Most of the men were in a choking condition, making agonising efforts to breathe, clutching at their throats and tearing open their clothes. At one moment they propped themselves up to gasp, at another they fell back exhausted by their struggle. The skin was cold. There was marked cyanosis, especially of the lips and ears, and in a few cases a light yellowish frothy discharge was escaping from the mouth and nose. Some, especially the older men, were in a state of collapse; their faces and hands were of a leaden hue, their heads fallen forward on their chests. The majority of such cases did not rally. All,

except those moribund or collapsed, were fully conscious and fighting for life. Fourteen men died out of the first batch of seventeen taken off the motor ambulances." [23, p.384]

The complete arrestation of breathing due to spasm was not observed and is not regarded as a significant factor:

"The question has often been discussed as to whether a man might be killed by immediate asphyxiation on the field through such a spasmodic closure of his larynx and bronchi that respiration was completely arrested. Sudden shock and collapse from extreme sensory irritation has been noted in animals immediately upon exposure to chloropicrin; and it might be that this factor would also play its part in determining early death upon the field. But no proof was ever obtained that a man has thus been choked to death on the field. . . . If it ever did happen, it was of little practical importance. No medical officer in the trenches ever had the chance of attempting to treat such a case." [23, p.391]

Pulmonary oedema and its effects are therefore the important factors:

"A rapid development of pulmonary oedema, interfering with gaseous respiration and also with the circulation itself, was probably always the actual cause of death." [23, p.392]

"It is thought that the entire action of pulmonary irritants is exercised solely upon the surface layers of the body with which the gases come into immediate contact, the early circulatory failure being caused only by the influence of pulmonary oedema upon gaseous respiration and blood-flow and by 'shock'." [23, p.398]

A similar picture emerges from the accounts of their work given by Underhill [41] and Winternitz et al. [43]. Acute death is associated with oedema and blood changes. Underhill attributes the effects of oedema not so much to the blockage of oxygen transfer in the lung as to the decrease of the fluid content of the blood and consequent increase in the solids content and the viscosity and reduction of the oxygen-carrying capacity.

The possibility of the sudden arrest of respiration by bronchial spasm at high chlorine concentrations was investigated by Gunn [32] in the experiments on anaesthetised rabbits described earlier. He found that there was an initial constriction, but that breathing continued. There was then a gradual increase in constriction, which he attributed to the onset of oedema. His paper gives trend records which show clearly the effect of the initial exposure on the animal's breathing. His work appears to confirm that sudden cessation of breathing is an improbable cause of death at least for concentrations up to 1,000 ppm.

Physical exertion following gassing can be dangerous even for men apparently unaffected:

"When the tension of a gas attack had passed away, it sometimes happened that, among those who had been exposed to the irritant vapour but had not reported sick, a man

would stop working, complain that he felt done in, and die in a few minutes. Others might survive for an hour or two after a similarly sudden collapse. Their deaths were at first thought to have been caused by heart failure due to a direct intoxication by the gas. Autopsies, though not made in the dramatic cases of abrupt death, always proved the existence of advanced pulmonary oedema, the condition being really identical with that of 'grey' collapse as seen after the ordinary acute onset." [23, p.399]

Vedder [47] gives an explanation of the reasons for sudden death following physical exertion:

"Sudden death following exercise or struggling has often been observed in soldiers in the field and in experimental animals. The cause of these sudden deaths is readily demonstrated. In a normal animal when the corpuscles are saturated with oxygen, the oxygen in the arterial blood fluctuates between 94 and 98 per cent. The oxygen percentage in the venous blood is generally about half that of the arterial blood. Barcroft found, after gassing a goat at a moderate concentration, that the oxygen percentage in the arterial blood dropped to about 80 per cent. This may cause headache, impaired vision and inability to work, but is by no means dangerous to life. However, when the same goat struggled, the arterial oxygen dropped abruptly to 44 per cent. This is caused by the greatly increased consumption of oxygen by the tissues following exercise. Such a high degree of anoxemia affects at once both the cardiac and respiratory centers of the brain." [47, p.104]

The effect of exertion after exposure appears, however, to have been observed mainly with phosgene and the quotation just given probably refers to this gas.

In his review in 1948 Gerard [50] states that much of the theory and practice of the earlier war has been disproved or supplanted, but his detailed comments do not appear to require any major modification of the picture given above. He does state, however, that in the context of handling casualties absolute rest after gassing is not as essential as previously held.

There has been some expression of doubt about the prevalence of pulmonary oedema among those who have treated people gassed by chlorine in industrial accidents. Thus Jones [135] states that in the period 1932—1948 he and his colleagues dealt with 820 such cases of which 9 were severe, but that even in these cases neither pulmonary oedema nor pneumonia ensued, although he indicates awareness of pneumonia in other cases. He suggests that cases of these reported during the First World War may have been caused by mixtures of chlorine and phosgene. It seems more probable that in these cases the gassing was not as severe as in the war gas cases described above. Industrial gassing is also discussed by Haggard [111], who states:

"Even an exposure insufficient to induce the acute symptoms of lung irritation may lead to the development of pneumonia and under industrial conditions the infections thus produced constitute a greater cause of death than primary pulmonary oedema."

It is of interest that in the chlorine release at Mjondalen described by Romcke and Evensen [115] a woman who ran several hundred metres through the gas cloud was diagnosed as having pulmonary oedema.

Although the descriptions quoted of the effects of irritant gases are undoubtedly strongly influenced by experience with phosgene, the account of Black et al. [97], who treated 685 cases of poisoning from chlorine between May 2 and May 7, 1915, before phosgene had been used, shows clearly that the acute deaths involved pulmonary oedema. This was confirmed by 10 post-mortems carried out by these doctors.

If acute death does not occur, there is still the danger of delayed death. The cause of delayed death is described variously as bronchitis, bronchial pneumonia or pneumonia. Black et al. state that the acute stage passes off in about 36 hours, that there is then a quiet stage of some 12 hours and that the bronchial infection is then liable to develop. Underhill [41] found that the dogs which survived gassing were liable to die of pneumonia and set three days after gassing as the dividing line between acute and delayed deaths. Acute and delayed deaths were also observed in the experimental work on rodents described earlier.

The mortality from chlorine gassing may be reduced by appropriate medical treatment. It is not clear how much can be done to increase the chances of survival of acute cases, but for the delayed cases the prospects appear much better. There are descriptions of the treatment given and of its effects in many of the accounts already quoted.

The long term effects of chlorine gassing are also important. Broadly speaking, both the statistical and clinical evidence suggest that these effects are not great. Weill et al. [120] studied 12 people who were severely gassed in an accidental chlorine release near La Barre (also referred to as Morganza) in 1961. All had pulmonary oedema when examined just after the accident but when examined at 3 and 7 years after the event showed little long term damage. The findings of these authors are summarised by Eisenberg et al. [160] as follows:

"They say that their data for subjects seven years after an accidental exposure to chlorine 'are consistent with the prevailing view that significant permanent lung damage does not result from acute exposure to chlorine gas'. Reports referenced in their paper support this finding: for example, 'no evidence that chlorine intoxication produced residual pulmonary disease' in the 33 most severely affected victims of a major accident; a large survey of industrial exposures did not find 'any evidence of permanent damage to the respiratory tract'; another study including war casualties found that 'permanent pulmonary injury was rare.' "

Another important aspect of the physiology of chlorine exposure is the degree of tolerance of people exposed. It has usually been considered that chlorine is sufficiently irritant that a person exposed will seek to escape at a concentration level well below that at which he would suffer permanent harm. However, some recent work [161—166] indicates that some people

may voluntarily expose themselves to concentrations which do prove harmful.

Most of the information available on the physiology of chlorine poisoning is for less vulnerable people such as troops and industrial workers. There is little on more vulnerable members of the population.

If the physiology of poisoning is sufficiently well understood and depends on a mass balance of the toxin in the body fluids, an attempt may be made to model this balance. Accounts of such toxicokinetic modelling are given by Henderson and Haggard [112], Tuey [167] and the World Health Organisation [168]. The main action of the irritant gases, however, is damage to the tissues and such modelling appears therefore less applicable to these gases. No application of toxicokinetics to chlorine has been found.

Statistics of animal experiments

The degree of confidence which can be placed in toxicity values obtained by experiments on animals depends to some extent on the size of the sample used so that in this respect it is desirable to conduct experiments with relatively large numbers of animals. On the other hand humanitarian and economic considerations require that the number be restricted. The final choice is usually a compromise.

The statistical interpretation of animal experiments was discussed by Trevan [169] in a paper to the Royal Society in 1927. He applied the binomial expansion

$$(p + q)^N = 1 \qquad (5)$$

TABLE 10

Expected numbers of deaths in groups of experimental animals (after Trevan [169]). Confidence level 95%

Mortality	N	σ	$z\sigma$	Np	Range
50%	10	1.581	3.099	5	2—8
	20	2.236	4.383	10	6—14
	30	2.739	5.368	15	10—20
	40	3.162	6.198	20	14—26
	50	3.536	6.931	25	18—32
	60	3.873	7.591	30	22—38
	70	4.183	8.199	35	27—43
	80	4.472	8.765	40	31—49
	100	5.000	9.800	50	40—60
25%	30	2.372	4.649	7.5	3—12
	100	4.330	8.487	25	17—33
10%	30	1.643	3.220	3	0—6
	100	3.000	5.880	10	4—16

where p and q are the probabilities of death and survival, respectively, and N is the number of animals in the experiment. Then

mean = Np

standard deviation $\sigma = \sqrt{pqN}$

confidence limits = $Np \pm z\sigma$

where z is the number of standard deviations corresponding to the confidence level. Using this approach Trevan showed that for experiments at the 50% mortality level the number of animals which would be expected to die would be in the range 7—23 for a sample of 30 animals and in the range 34—66 for a sample of 120 at the 99.73% (3 s.d.s.) confidence level.

Applying Trevan's method but using a 95% confidence level, the results given in Table 10 and Fig. 5 are obtained. It can be seen that for experiments with small numbers of animals the confidence limits for 50% mortality are wide and that for other mortalities such as 25% (or 75%) and 10% (or 90%) they are even wider.

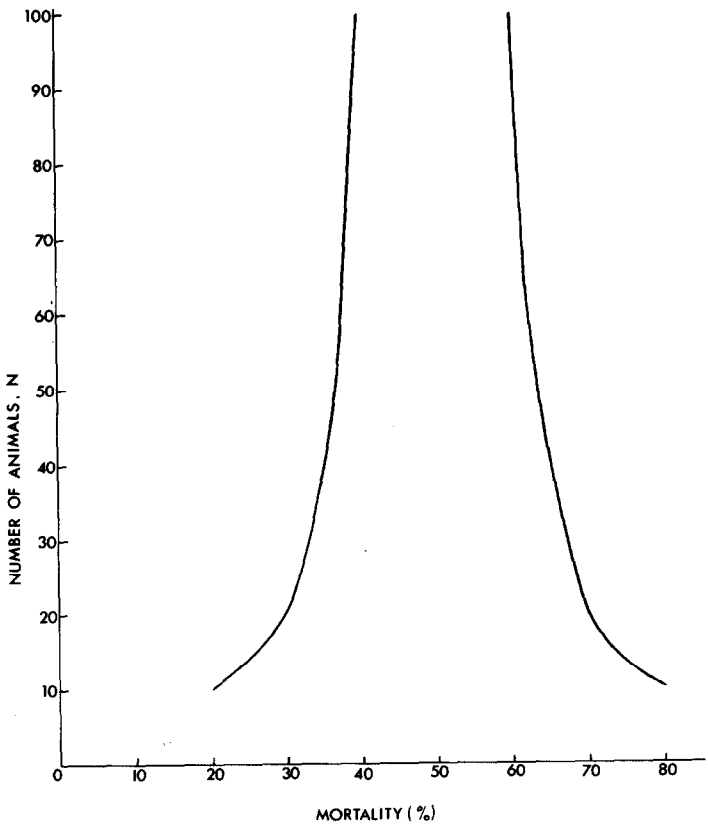

Fig. 5. Expected numbers of deaths in groups of experimental animals (after Trevan [169]).

A statistical method which appears to be widely used by toxicologists in the evaluation of dose—effect experiments is that of Litchfield and Wilcoxon [42]. This method is used in this paper also. Accounts of the statistics of experimentation in toxicology are given by Bliss [170—173].

Lethal load function

One of the first and best known relationships for the injurious effect of the inhalation of toxic gas in terms of concentration and time is Haber's product law [16] given in eqn. (4) above. Haber's early work was on chlorine and phosgene and the derivation of the product law appears to have been influenced by the work on phosgene particularly. Later workers, including Haber's collaborators, have warned against the indiscriminate use of Haber's product law.

More extensive work by toxicologists tends rather to support a relationship of the form

$$ct^n = \text{constant} \tag{6}$$

where usually $n < 1$.

Thus, for example, Doe and Milburn [174] have found that for 32 out of 34 compounds investigated eqn. (6) is applicable, and that for 18 of these n lies between 0.8 and 1.33 and for another 14 between 0.40 and 0.60. The first group includes epichlorhydrin (n = 1.0), ethylene oxide (n = 1.0) and hydrogen chloride (n = 1.1), and the second group bromine (n = 0.49), carbon monoxide (n = 0.50), carbon disulphide (n = 0.52), fluorine (n = 0.53), hydrogen cyanide (n = 0.58), hydrogen fluoride (n = 0.47) and sulphur dioxide (n = 0.46).

Data obtained from animal experiments for chlorine fit eqn. (6) with the index n of the order of 0.5, as described below.

Risk analysts, however, tend to use an alternative form of eqn. (6) which is more readily integrated for concentrations varying over a period of time:

$$c^m t = \text{constant (say } a) \tag{7a}$$

where usually $m > 1$. Thus, for example, this form has been used for chlorine by Eisenberg et al. [160] and by subsequent workers. Equation (7a) is equivalent, however, to the relation

$$ct^{1/m} = a^{1/m} \tag{7b}$$

or, in other words, to eqn. (6) with $n = 1/m$.

These relationships may be expressed in terms of toxic load, which has been widely used in risk analyses such as the Rijnmond Report [175]. Equations (7a) and (7b) give two alternative expressions for toxic load:

$$L = ct^n \tag{8a}$$

and

$$L^* = c^m t \tag{8b}$$

with $m = 1/n$, and the relationship between them is

$$L^* = L^{1/n} \tag{8c}$$

The toxic load given in eqn. (8b) is sometimes called the "dosement".

It is found that the relationship between the factor which causes injury and the proportion of people suffering a defined degree of injury usually follows a lognormal distribution:

$$F = \frac{1}{(2\pi)^{1/2}\sigma} \int_0^{\infty} \frac{1}{x} \exp[-(\ln x - m^*)^2/2\sigma^2]\,dx \tag{9}$$

where F is the distribution function, x the causative factor, m^* the location parameter and σ the spread (σ^2 = variance). This distribution appears to apply not only to injury by toxic gases but to other forms of injury also. In the present case the causative, or injury, factor x is the toxic load. Since the logarithm of the toxic load is involved, it makes no difference which of the two definitions of toxic load, eqn. (8a) or eqn. (8b), is used.

Alternatively, the causative factor—response relation may be expressed as a probit equation:

$$Y = k_1 + k_2 \ln x \tag{10}$$

where Y is the probit. The lognormal distribution and the probit equation are related in the following way:

$$k_1 = (5 - m^*/\sigma) \tag{11a}$$

$$k_2 = 1/\sigma \tag{11b}$$

A more detailed account of probit equations is given by Finney [176].

Acute and delayed deaths

Another important feature is the proportion of acute and delayed deaths. Following Underhill [41], an acute death is defined here as a death occurring within the first three days after exposure.

The animal experiments yield some information on this aspect, but the data do not all point in the same direction. In Underhill's work on dogs there is a broad proportionality between the overall mortality and the proportion of acute deaths. In the work of Silver et al. [59, 60] and Schlagbauer and Henschler [63] on mice the proportion of acute deaths is very high over the whole range of mortalities, while in that of Bitron and Aharonson, also on mice, the proportion of acute deaths is very low over the whole range of mortalities. As stated above, however, Bitron and Aharonson's results are unusual.

Further data on dogs gassed by chlorine are given by Ireland [110]. These show that overall in the American experimental work some 270 dogs died, of which 205 or 76% were acute deaths.

There is also available another source of information in the form of data from gas warfare. On May 1, 1915 there was a chlorine gas cloud attack against the British at Hill 60 in the Ypres salient [14, 23]. The men stood firm and took heavy casualties. 90 men died in the field and of the 207 men admitted to the field ambulances another 58 subsequently died.

This evidence is supplemented by that of Black et al. [97] who treated 685 gas casualties at a casualty clearing station (CCS) between May 2 and May 7, 1915. They state that some 120 were severe cases which seemed in imminent danger of death. In fact 33 died as follows:

On day of admission:	16
On first day after admission:	13
On second day after admission:	2
On third day after admission:	1
On fourth day after admission:	1

Of these 29 died within 36 hours of admission and only 4 in the three subsequent days. None of the cases was kept at the CCS beyond the fifth day.

It seems probable that in this latter case some of the casualties developed bronchitis/pneumonia. If it is assumed that, say, another 4 died later, this gives approximate proportions of acute and delayed deaths of 90 and 10%, respectively, for those cases actually admitted to the CCS. If the same proportions are applied to the casualties admitted to the field ambulances in the Hill 60 attack, this gives the number of delayed deaths as 6 (0.1×58) at the CCS, which corresponds to 4% ($6/(90 + 58)$) of the total deaths. The total number of men exposed to the gas is estimated as 400 and the overall mortality is therefore 37%.

These gas attack data show that for man the proportion of acute deaths is much higher than that which would be predicted from Underhill's data. Thus in the Hill 60 attack his data as given in Fig. 3(b) would indicate for an overall mortality of 37% a proportion of acute deaths of 32%, whereas the proportion of deaths on the field alone was 61%. It seems probable, therefore, that for man the probability of acute death increases from about 80% at very low mortalities to nearly 100% at very high mortalities.

Toxic concentrations given in the literature

Values of the lethal concentration of chlorine are quoted in standard texts on toxicology [177—187]. Some values given in leading texts are shown in Table 11.

The lethal concentration for man immediately on exposure quoted by Flury and Zernik [11] is not referenced. The other two concentrations are attributed to Hess. The values given by Patty [182] appear to derive from Flury and Zernik. He quotes this text explicitly for the dangerous concentration for man and his other data are to be found there also, although there is some doubt about the reference to lethal concentration for large

TABLE 11

Lethal concentration of chlorine quoted in standard toxicology texts

Text	Effect	Concentration	Exposure time	Source
Flury and Zernik [11]	Lethal concentration for man	2.5 mg/l 900 ppm	immediate	
	Lethal concentration for man	0.1—0.15 mg/l 35—50 ppm	1/2—1 h	Hess[a]
	Dangerous concentration for man	0.04—0.06 mg/l 14—21 ppm	1/2—1 h	Hess[a]
	Lethal concentration for man	1,000 ppm	short exposure	Kobert [177]
	Dangerous concentration for man	40—60 ppm	short exposure	Kobert [177]
Patty [182]	Lethal concentration for large animals	1,000 ppm	after brief exposure	Flury and Zernik [11]
	Concentration which may be lethal to cats	300 ppm	60 min	
	Concentration which is rarely lethal to dogs	650 ppm	30 min	
	Concentration which is never lethal to cats	280 ppm	30 min	
	Dangerous concentration for man	14—21 ppm	1/2—1 h	
Tatken and Lewis (NIOSH) [185]	LCL_0 mam[b]	500 ppm	5 min	Flury [20]
	LC_{50} mus (mouse)	137 ppm	1 h	Back et al. [65]
	LC_{50} rat	293 ppm	1 h	Back et al. [65]
	LCL_0 gpg (guinea pig)	330 ppm	7 h	Lehmann [6]
	LCL_0 cat	660 ppm	4 h	Lehmann [6]
	LCL_0 dog	800[c] ppm	30 min	Barbour [44]
	LCL_0 hmn (man)	873 ppm	30 min	Prentiss [15]
Sax [186]	As Tatken and Lewis [185]			
Henderson and Haggard [112]	Lethal concentration	1,000 ppm	short exposure	
Matheson [181]	Lethal concentration	1,000 ppm	after a few breaths	
Stahl [187]	Dangerous concentration	20 ppm	30 min	

[a] Quoted without reference by Flury and Zernik [11].
[b] Lowest lethal concentration recorded.
[c] A death was recorded in the concentration range 50—250 ppm (his values) at a 30 min exposure in Underhill's work [41].

TABLE 12

Concentrations of chlorine tolerable and intolerable to man

Author(s)	Effect	Concentration (ppm)	Exposure time	Source
Rupp and Henschler [73]	Odour threshold	0.02—0.05		
ACGIH [188]	Threshold Limit Value (TLV)	1		
Kobert [177]	Minimum concentration to detect odour	3.5		
	Concentration which causes immediate irritation	14		
	Concentration which causes coughing	28		
	Dangerous concentration	40	1 h	
Flury and Zernik [11]	Concentration tolerable without immediate or later consequences	3.5	1/2—1 h	Lehmann—Hess[a]
	Concentration at which work can be continued without interference	1—2		Matt [71]
	Concentration at which work becomes impossible	4		Matt [71]
	Dangerous concentration	14—21	1/2—1 h	Lehmann—Hess[a]
Henderson and Haggard [112]	Maximum concentration allowable for physical exertion	0.35—1		
	Minimum concentration to detect odour	3.5		
	Maximum concentration allowable for short exposure	4	1/2—1 h	
	Dangerous concentration for short exposure	40—60		
Vedder [47]	Concentration which incapacitates man (crying, coughing) in a few seconds	100		
Wachtel [18]	Concentration which causes severe irritation	3		
	Concentration which causes loss of fighting capacity	47		
Patty [182]	Concentration which causes irritation	3—6		
	Intolerable concentration	100	1 min	

[a] Quoted without reference by Flury and Zernik [11].

animals. The NIOSH compilation [185] gives a number of sources, as shown in the table. One of the principal references is the report by Back et al. [65] which, as stated earlier, contains both literature references and report of original experimental work. The data given by Sax [186] appear to be the same as those given in the previous NIOSH compilation.

A value of 1,000 ppm for the lethal concentration for man, which is rapidly fatal for short exposure, is quoted in a table by Henderson and Haggard [112, p.132]. This appears to derive from a U.S. Bureau of Mines report by Fieldner et al. [189] which, under a table heading of "Kills most animals in a very short time", has the entry of 1,000 ppm for chlorine, but the source of this value is uncertain.

Concentrations of chlorine tolerable and intolerable to man given in the literature are shown in Table 12.

Probit equations given in the literature

The following probit equations for chlorine have been given in the literature.

Eisenberg et al. [160], in a report to the U.S. Coast Guard, have given the following equation for the lethality of chlorine

$$Y = -17.1 + 1.69 \ln \Sigma C^{2.75} T \quad (12)$$

and the following equation for non-lethal injury, i.e. hospitalisation, from chlorine:

$$Y = -2.40 + 2.90 \ln C \quad (13)$$

where C is the concentration (ppm) and T the time (min). These and other probit equations given by these authors have been summarised by Lees [190].

Equation (12) of Eisenberg et al. gives an LL_{50} for 30 min of some 35 ppm. It is apparently derived from a graph consisting of an arbitrary concentration scale versus a percentage mortality scale on which various sets of experimental results for animals are plotted as straight lines. The LL_{50} points on these lines are for dogs 70, for rats 3.5 and 1.4, for mice 20, 15, 3.5 and 0.7, composite for all animals 1 and for man 0.25. It is not clear what is the justification for this low value for man, but the choice appears to be a conservative one.

The values derived by Eisenberg et al. are apparently based on the literature. The references quoted are Vedder [47], Weedon et al. [56], Silver et al. [59, 60], Chasis et al. [116], Joyner and Durel [119], Kowitz et al. [141], C.G. Kramer [142], Weill et al. [120], Zielhuis [191], the National Academy of Science — National Research Council [192] together with private communications from C.G. Kramer and R.M. Wands.

In a further report to the U.S. Coast Guard, Perry and Articola [193]

give revisions of the Eisenberg equations. Their equation for the lethality of chlorine is

$$Y = -36.45 + 3.13 \ln \Sigma C^{2.64} T \quad (14)$$

and that for chlorine injury is again eqn. (13).

The industrial comment on the Rijnmond Report [175] proposes the equation

$$Y = -11.4 + 0.82 \ln \Sigma C^{2.75} T \quad (15)$$

This equation is also recommended by Harris and Moses [194]. Ten Berge and van Heemst [195] propose the equation (in the units used here)

$$Y = -5.04 + 0.5 \ln \Sigma C^{2.75} T \quad (16)$$

Harris and Moses effectively argue that there is no justification for taking a low value of the ratio of the lethal load for man to that for animals, or

TABLE 13

Probit equations for chlorine given in the literature

		Lethal concentration for 30 min exposure period		
		LC_{10} (ppm)	LC_{50} (ppm)	LC_{90} (ppm)
A. Equations for fatality				
Eisenberg et al. [160]	$Y = -17.1 + 1.69 \ln \Sigma C^{2.75} T$	26	34	44
Perry and Articola [193]	$Y = -36.45 + 3.13 \ln \Sigma C^{2.64} T$	36	42	49
Rijnmond Report Industrial Comment, Harris and Moses [175, 194]	$Y = -11.4 + 0.82 \ln \Sigma C^{2.75} T$	237	418	738
ten Berge and van Heemst[a] [195]	$Y = -5.04 + 0.5 \ln \Sigma C^{2.75} T$	170	430	1,093
B. Equations for injury				
Eisenberg et al. [160], Perry and Articola [193]	$Y = -2.40 + 2.90 \ln C$			

[a] Original equation

$Y = -6.5 + 0.5 \ln \Sigma C^{2.75} T$

where C is concentration (mg/m^3) and T time (min).

for assuming a very narrow spread of responses, and set the parameters in eqn. (15) accordingly. Ten Berge and van Heemst apparently derive their parameters from the work of Bitron and Aharonson [69] on mice, together with information on concentrations causing irritation in man.

The probit equations given in the literature for the toxicity of chlorine are summarised in Table 13.

Values of toxicity used in hazard assessments

Some values of the lethal concentration or dosage of chlorine used in a number of hazard assessments are given in Table 14. Most of the assessments listed in Table 14 use a value of the lethal concentration equivalent to 35 ppm for 30 min. The much higher value of 430 ppm, given in the earlier NIOSH compilation and used by Meslin [203], is an exception. It was considered, however, by the authors of the Rijnmond study [175] that the value of 35 ppm which they were requested by their clients to use overestimates the toxicity. A risk evaluation of the chlorine industry has also been

TABLE 14

Values of lethal concentration of chlorine used in various hazard assessments

Author(s)	Effect	Concentration	Exposure time	Source
Howerton (1969) [196, 197]	Dangerous concentration[a]	35 ppm	not defined	
Dicken (1974) [198, 199]	Fatal concentration[a]	90 ppm[b]	10 min	
		70 ppm	30 min	
		40 ppm	100 min	
	Dangerous concentration[a]	30 ppm	10 min	
		15 ppm	100 min	
Simmons et al. (1974) [200, 201]	LD_{50}	1000 ppm min (say 35 ppm for 30 min)		Chlorine Institute
Eisenberg et al. (1975) [160]	Lethal concentration LC_{50}	35 ppm	30 min	Self
Solomon et al. (1976) [202]	LD_{50}	40—60 ppm	30—60 min	
Meslin (1981) [203]	Lethal dose	430 ppm	30 min	NIOSH
Rijnmond Public Authority (1982) [175]	Lethal concentration LC_{50}	35 ppm	30 min	Eisenberg et al. [160]

[a] Concentration not further defined.
[b] Approximate values read from graph.

done by Helmeste and Phillips [204], but they worked in terms of lost man-days rather than fatalities.

Reviews of toxicity

There are a number of reviews of chlorine toxicity, some of which have already been mentioned. They include those of Flury and Zernik [11], the National Academy of Sciences — National Research Council [192, 205], Eisenberg et al. [160], the World Health Organisation (WHO) [74] and the Major Hazards Assessment Panel (MHAP) working party [206].

The WHO review summarises a number of individual papers on acute effects in animal experiments and on long term effects from gas warfare, industrial exposure and accidental releases.

The MHAP report, which, like the present paper, is concerned with chlorine toxicity in relation to major hazards, gives a critical survey of the literature data and the animal experiments and summarises the main papers on the latter. The values of the toxicity of chlorine to man quoted in the literature, including the value given by Eisenberg et al., are held not to be well founded.

The report discusses the applicability of work on animals to man. For mice and rats the volume of air breathed per unit of body weight is some ten times that for man. On the other hand man tends to react to the gas by increased activity whereas rodents tend to become passive. Also rodents have to breath through the nose so that some removal of soluble gas may occur in the nasal passages. It is concluded that broadly these effects are likely to cancel and that the susceptibility of rodents and man to the lethal effects of chlorine is similar.

It is concluded in the report that the animal data point to an LC_{50} for healthy people in the absence of medical treatment of around 400 ppm for a 30 min exposure period and, over a limited range, to a lethal load relation of the form $ct^{1/2}$ = constant. The report also notes that no fatalities have been found for 30 min exposure of any animal species at or below 50 ppm. It does not attempt to quantify further the lethal effects of chlorine.

Analysis of available data

The data available on the lethal toxicity of chlorine are for different animal species over a range of concentrations and exposure periods. They may therefore be analysed to determine the effect of species, concentration and time.

Effect of time

It is convenient to begin by considering the effect of exposure time. Unfortunately most workers have limited their investigations to a single exposure period. It would be possible to combine the results from different

workers using different exposure periods as shown in Table 6 and Fig. 4, but in view of the wide scatter this does not seem appropriate. There are, however, three pairs of results by the same workers, two by Weedon et al. [56] and one by Bitron and Aharonson [69], in which the concentration was held constant and the exposure period was varied. Table 15 shows the results obtained by these investigators for the concentration of chlorine lethal to rodents as a function of time together with the lethal load function CT^n for different values of n. The table shows that of the three pairs of data, the best fit is given by values of n of 0.5, 0.6 and 0.4, respectively.

Neither set of results is free from objections. As described above, Weedon et al. utilised an unusual protocol, while in Bitron and Aharonson's work there was an unusually low proportion of acute deaths. However, these are the only data available by which to assess the effect of time. There seems to be no good reason to prefer one set of data to the other. It appears therefore that the best estimate of n is 0.5 so that the toxic load is taken as

$$L = CT^{0.5} \tag{17}$$

The range of concentrations and times covered by the data on which eqn. (17) is based is 170—1,000 ppm and 11—440 min.

TABLE 15

Concentration of chlorine lethal to rodents at 50% level as a function of time

Author(s)	Species	C (ppm)	T (min)	CT	$CT^{0.4}$	$CT^{0.5}$	$CT^{0.6}$
Weedon et al. [56]	Mice	1,000	28	28,000	3,792	5,292	7,384
		250	440	110,000	2,853	5,244	9,639
	Rats	1,000	53	53,000	4,895	7,280	10,828
		250	440	110,000	2,853	5,244	9,639
Bitron and Aharonson [69]	Mice	290	11	3,190	757	962	1,222
		170	55	9,350	844	1,261	1,882

Effect of concentration

For the effect of concentration there are rather more data, since several workers have done experiments at more than one concentration. Even so the number of investigations which cover a wide range of concentrations is small. One of the principal studies is that of Underhill [41].

Underhill's data have been analysed by the authors utilising the method of Litchfield and Wilcoxon [42], as mentioned above. In this method concentration is plotted against mortality on log-probability paper, a line is drawn through the data and the LC_{50} and slope of the line are read off. The LC_{16} and LC_{84} are also read off and the 95% confidence limits on the LC_{50} and the slope are calculated. The latter can then be used to estimate

the confidence limits on the other LC values. The results obtained depend, however, on the way in which the line is drawn through the data. Litchfield and Wilcoxon suggest that the line be drawn by eye. An alternative approach is to use a least squares fit. In either case it is necessary to decide whether the points at very low and high mortalities are to be weighted equally with points nearer the centre of the mortality range. Since there is much less confidence in the values for the low and high mortality points, as evidenced for example by Trevan's work, the approach adopted here has been to draw a line which is based on the least squares fit over the mortality range 20—80%. The effect of doing this is that for Underhill's data there is significant heterogeneity in the points, this being due to the effect of the point at 11% mortality, which is a single death, and that the confidence limits are comparatively wide. The original data, the line through the points constructed as just described, and the 95% confidence limits are shown in Fig. 2. The LC_{10}, LC_{50} and LC_{90} are 334, 650 and 1,266 ppm, respectively. For comparison, the line through the data has also been calculated using all the points over the whole mortality range 11—93%. This gives the LC_{10}, LC_{50} and LC_{90} as 189, 495 and 1,350 ppm, respectively. The confidence limits are appreciably narrower. The use of the mortality range 20—80% for the calculation of the line is preferred, however, and it is this which is used henceforth. The range of concentrations covered by Underhill's data is 164—1,583 ppm.

The two main parameters which define the effect of concentration are the LC_{50} and the slope of the concentration—mortality line. The LC_{50} values for the animal experiments were given in Table 6. As stated above, the values obtained by Zeehuisen [55] and Weedon et al. [56] appear anomalously high and those of Bell and Elmes [61, 62] inapplicable. Omitting these values and adjusting to a common exposure period of 30 min using eqn. (17), the LC_{50} values obtained for mice, rats and dogs are 256, 414 and 650 ppm, respectively.

For the slope of the concentration—mortality line there are three sets of data which are sufficiently complete to use, those of Underhill [41], Silver et al. [60] and Schlagbauer and Henschler [63]. The analysis of Underhill's data has just been described. The other two sets of data, which are given in Table 7, have been analysed in the same way, again using the mortality range 20—80% to calculate the line through the points and thus to obtain a new estimate of the LC_{50}. The three data sets have then been put on a comparable, normalised basis by dividing the concentration values in each set by the LC_{50} for that set. These normalised data are given in Table 16 and are plotted in Fig. 6.

Application to man

The application of toxicity results obtained by experimentation on animals to man is notoriously attended by many difficulties and much uncertainty. A rule of thumb often used by toxicologists is that if consistent

TABLE 16

Mortality of animals exposed to chlorine adjusted to exposure period of 30 min and normalised with respect to LC_{50}

Author(s)	Species	LC_{50} (ppm)	Concentration (ppm)	Normalised concentration	Mortality (%)
Underhill [41]	Dogs	650	164[a]	0.25	11
			491	0.76	29
			600	0.92	40
			710	1.09	67
			819	1.26	61
			928	1.43	91
			1,583	2.44	93
Silver et al. [59, 60]	Mice	388	219[b]	0.56	10
			317	0.82	45
			317	0.82	25
			337	0.87	5
			364	0.94	40
			368	0.95	45
			398	1.03	15
			408	1.05	60
			410	1.06	55
			430	1.11	70
			458	1.18	75
			486	1.25	40
Schlagbauer and Henschler [63]	Mice	131	62	0.47	10
			69	0.53	10
			110	0.84	30
			125	0.95	30
			132	1.01	60
			143	1.09	60
			160	1.22	80

[a] Converted from 0°C to 25°C.
[b] Converted from original data for 10 min exposure period.

results can be obtained from three animal species, there is reasonable prospect that they will be broadly applicable to man. In the case of chlorine there is a considerable amount of data on smaller animals, particularly mice, rats, cats and dogs, but also rabbits and guinea pigs, and some data on larger animals, including monkeys and horses. In interpreting the data it is prudent to bear in mind the differences in the way in which the various species react to gassing. Dogs tend to be rather passive, whereas cats and monkeys are more active and appear generally more sensitive.

The approach used in evaluating toxicity data must necessarily depend on the type and quality of the data. One approach is to use average values

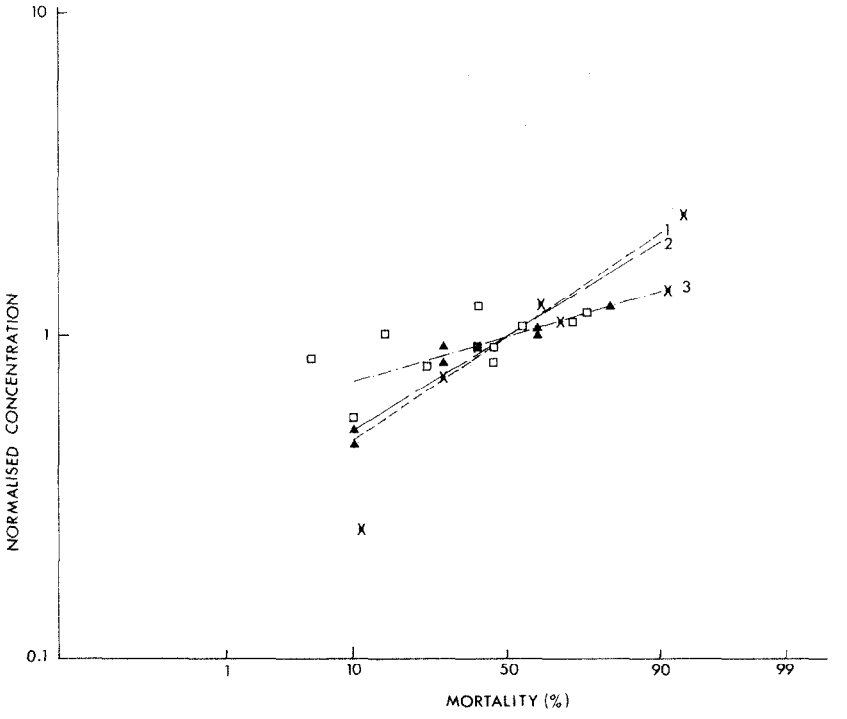

Fig. 6. Concentration of chlorine lethal to various animal species. Data adjusted for exposure period of 30 min and normalised with respect to LC_{50}. □: Silver et al. [60] — mice (line 1); ×: Underhill [41] — dogs (line 2); ▲: Schlagbauer and Henschler [63] — mice (line 3).

derived from different workers and different species. Another is to use selected data from that work which is judged most applicable. In the present case it is the latter approach which is used.

It is proposed that the estimate of the lethal toxicity of chlorine to man should be based primarily on the results of Underhill [41] for dogs. There are several reasons for this choice. The first is the physiological similarities between dogs and men. This was a main reason for the choice of dogs in the American work as described by Ireland [110]:

"In these experiments the dog was the experimental animal of choice . . . The reason for using the dog is that, in the study of respiratory irritant gases, to which the majority of war gases belong, this animal has certain well-recognised advantages: (1) The lungs and other organs are sufficiently large to make gross examination easy. (2) Anatomically the respiratory tract resembles closely that of man. (3) The conditions of pulmonary infection and the reaction of the lungs to bacterial and other injuries are much the same as in human beings."

Another reason is the variation of the LC_{50} with the size of the species. As stated above, the LC_{50} values at 30 min obtained for mice, rats and dogs

are 256, 414 and 650 ppm, respectively. A third reason is the apparent consensus among workers on war gas toxicity that dogs and men have approximately the same susceptibility to chlorine.

The slope of the concentration—mortality line is also relevant. As stated above, there is some evidence that the ratio LC_{90}/LC_{10} for irritant gases is at least 4—5. For lines fitted using data in the mortality range 20—80% the ratios are 3.8 and 4.4 in the work of Underhill [41] and of Silver et al. [59, 60], respectively, but only 1.9 in that of Schlagbauer and Henschler [63]. For comparison, using the whole mortality range, the ratios are 7, 3.3 and 3.5, respectively. The slope is therefore sensitive to the mortality range used, but again a slope based on the range 20—80% is preferred.

Underhill's experiments are the only work available on a larger animal, but they were well planned and executed and are statistically convincing. His work on phosgene is also of high quality. The work of Underhill on dogs does not give information on the effect of exposure time, however, and for this results from work on mice and rats have been used, as described above. It is proposed, therefore, that Underhill's work be used as the basis for estimation of the lethal toxicity of chlorine to man, but this proposal needs to be seen in context and to be qualified. The results apply only over a limited range of concentration and exposure time and only to a base level of very low physical activity.

Acute deaths

For similar reasons Underhill's work [41] is also regarded as the best guide to the estimation of the proportion of acute deaths. As it happens, however, the proportion in his work also lies between the extremes obtained by Bitron and Aharonson [69] and by Schlagbauer and Henschler [63], who had very low and very high acute mortalities, respectively. In addition, his results also appear to be broadly in line with the experience of Black et al. [97] with war gas casualties. What Underhill's work shows is that there is probably a relation between the overall mortality and the proportion of acute deaths, but that even at low mortalities the proportion of acute deaths tends to be high. A reasonable estimate would seem to be that the proportion of acute deaths rises from about 80% at low overall mortalities to 100% at 100% mortality.

Discussion

The estimate sought for the lethal toxicity of chlorine to man is a realistic rather than a conservative one.

In evaluating toxicity data there is often a choice between averaging results from various workers and selecting results on the basis of their quality and applicability. In the present case it is the latter approach which has been used.

The toxicity estimate for man is based on the work of Underhill [41] on

dogs in respect of the LC_{50} and the slope of the concentration—mortality line at 30 min and the proportion of acute deaths. This work does not, however, yield information on the effect of exposure time and for this use has been made of data on rodents from other workers.

Underhill's work applies only where the response is a passive one and the level of physical activity is very low. If there is a higher level of activity, the LC_{50} may be correspondingly reduced. Thus the value applicable to people in an accidental gas release may be less.

Attention is drawn to two other points mentioned earlier. One is that in one set of experiments [63] mice exposed for the relatively long period of 3 hours had a high mortality even at concentrations of chlorine as low as 10 ppm. This result has not been found by other workers and appears to lack a satisfactory explanation. The other is there is evidence [47] that if an animal exhibits extreme exertion while exposed to chlorine it may die from oxygen deficiency in the blood.

The application of these results to the derivation of a model of the lethal toxicity of chlorine to man is described in the second paper [1].

Acknowledgments

The authors wish to acknowledge the support of the Science and Engineering Research Council and the value of discussions with Dr D. Gall,Head of the Toxicology Section, Chemical Defence Establishment, Porton Down, and with Dr. J.E. Doe, Toxicology Laboratories, ICI plc, Alderley Edge. One of them (R.M.J.W.) wishes also to acknowledge the value of discussions with colleagues on the Major Hazards Assessment Panel, Toxic Hazards Group.

List of symbols

a	constant
c	concentration of toxic gas (various units — see text)
C	concentration of toxic gas (ppm)
D	dosage of toxic gas (various units)
F	probability of injury or death (distribution function of injury distribution)
k_1, k_2	constants
L	toxic load (ppm min^n)
LC_i	concentration lethal at i% level (various units)
LD_i	dosage lethal at i% level (various units)
LI_i	lethal index for lethality at i% level ((mg/m^3) min)
LL_i	toxic load for lethality at i% level (various units)
L^*	toxic load (alternative formulation) or dosement (ppm^m min)
m	index
m^*	location parameter of lognormal distribution
n	index

N	number of animals in experiment
p	probability of death
P	probability of injury or death
q	probability of survival
t	exposure time (various units — see text)
T	exposure time (min)
x	causative factor in injury distribution
Y	probit
z	number of standard deviations
σ^2	variance (σ = standard deviation of normal distribution, spread parameter of lognormal distribution)
ψ	acute deaths factor

Conversion of units

The units of concentration used for preference in this paper are ppm. Where other authors have quoted other units without also quoting ppm values, conversion to ppm values has been done at 25°C [189]. Also the concentrations in the work of Underhill [41], which are given in Table 3 in both mg/l and ppm at 0°C, have been recalculated to ppm at 25°C.

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Further references are given in 11, 13, 15, 17, 23, 42, 46, 74, 191, 205 and 206 above. Some of the references in 74 are incorrect.