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THE ASSESSMENT OF MAJOR HAZARDS: THE LETHAL TOXICITY OF BROMINE

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Summary

Measures for the control of hazardous installations handling toxic materials create a requirement for data on toxicity. In a previous paper the toxicity data for chlorine were reviewed and a model was derived for the lethal toxicity of chlorine to man. Another industrially important toxic gas which is closely related to chlorine is bromine. Information on the toxicity of bromine is mainly to be found in papers which deal with both chlorine and bromine. In this paper the toxicity data for bromine are reviewed and a model is derived for the lethal toxicity of bromine to man. A distinction is made between less vulnerable and more vulnerable populations and between different levels of physical activity. Mortality is expressed in terms of a lethal toxic load which is a function of concentration and time. The concentrations lethal at the 50% level for a 10 min exposure with standard level of activity are estimated as 650, 260 and 546 ppm for the regular, vulnerable and average population, respectively, and those for a 30 min exposure as 375, 150 and 315 ppm, respectively. The probit equation derived for the regular population at the standard level of activity is

$$Y = -9.04 + 0.92 \ln L^*$$

with

$$L^* = \Sigma C^2 T$$

where C is concentration (ppm), L^* toxic load (ppm^2 min), T time (min) and Y the probit. A methodology for the application of the toxicity relationships in hazard assessment is given.

Introduction

There are a number of toxic chemicals which are produced, handled and stored in quantities sufficiently large to constitute serious hazards and control measures require an estimate of their toxicity. In previous papers [1, 2] an estimate was obtained of the lethal toxicity of chlorine. This paper gives an estimate of the lethal toxicity of bromine. The estimate sought is a realistic rather than a conservative one.

Both chlorine and bromine are halogens and act as irritant gases. Industri-

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ally, bromine is an important chemical, though not on the scale of chlorine. For bromine the literature on toxicity is much less substantial than that for chlorine. The few papers available tend to treat the toxicity of bromine by comparison with that for chlorine.

This paper reviews the work done on bromine using animal experiments, the physiology and pathology of poisoning, the toxicity values given in the literature and on the basis of this information presents a model for the lethal toxicity of bromine to man and a methodology for its use in hazard assessment.

Material properties

Properties of bromine are given by Jolles [3].

Experimental work on, and estimates of, acute toxicity

Most of the experimental work on bromine has been done in conjunction with work on chlorine.

Work of Lehmann 1887

The work of Lehmann on chlorine was described in Ref. [1]. One series of experiments which Lehmann [4] conducted on cats, rabbits and guinea pigs involved 11 experiments with chlorine and 6 with bromine. The animals were exposed to concentrations of bromine ranging from 1.3 ppm to 300 ppm for exposure periods of 2 h 30 min to 7 h. All three species developed pulmonary oedema at concentrations of 180 ppm for exposures of 6 h 30 min and at concentrations of 300 ppm for exposure periods of 3 h. For both these conditions the rabbits died within one hour, while the cats and guinea pigs were removed from the experiment, killed immediately and dissected. Lehmann [5] also carried out experiments, considered below, in which he measured the degree of absorption of bromine from air by men.

Lehmann concluded that both qualitatively and quantitatively the effects of bromine are similar to those of chlorine.

Work of Hess 1911

Hess' dissertation [6] on toxicological features of Swiss factory liability insurance law contains two tables which refer to bromine, one on symptoms and one on toxic concentrations. The concentration of bromine given as dangerous for ½—1 h exposure is 40—60 ppm. This is the same value as that given for chlorine.

German work ca. 1914—1918

There was relatively little work done on bromine as a war gas in the First World War. There was reason to think that it was no more toxic than chlorine and it was certainly much more difficult to produce in quantity.

According to Wachtel [7] bromine was used first by the Germans in April 1915. In another passage he states that bromine was used to a very limited extent, particularly in special bombs, partly in conjunction with chlorine to increase the persistence of the latter. No other significant reference to bromine has been found in the writings of other German workers such as Haber, Flury and Muntsch.

British work ca. 1914—1918

The work of British doctors on poison gases during the war involved some work on bromine. In a wartime lecture Hill [8] refers to experiments on animals at a concentration of bromine of 1000 ppm. In a postwar paper [9] he refers to experiments on guinea pigs. Symes [10] describes experiments using bromine on anaesthetised cats.

Russian work ca. 1914—1918

Work on gas toxicity in Russia was carried out at a number of laboratories as described by Chlopin [11]. He gives a table of the toxicity relative to chlorine (taken as unity) of a number of war gases, in which the toxicity of bromine is given as 0.5.

Like Wachtel, Chlopin states that bromine can be used in warfare in special bombs. This statement by Chlopin is quoted by Sartori [12], who in turn is quoted by Wachtel, and may be one source of the latter's comment on bombs.

Work since 1918

In the interwar years a number of books were published on war gases. Two of the principal texts are those of Prentiss [13] and Vedder [14]. Neither deals with bromine.

Schlagbauer and Henschler [15] carried out experiments in which mice in groups of 10 were exposed for 30 min to concentrations of bromine of 111, 140, 200, 236, 252, 268, 290 and 315 ppm. The deaths occurring in the intervals 0—2, 2—4 and 8—10 days after exposure were recorded. In contrast to their work on chlorine, an appreciable fraction of the deaths occurred in the latter period. The LC_{50} values obtained were 196 and 174 ppm for observation periods of 4 and 10 days, respectively. They state that the lethal dose for bromine is 1.5 times that for chlorine.

These authors also report work done at lower bromine concentrations and longer exposure periods. They carried out experiments in which 10 mice were exposed for 3 h to concentrations of bromine of 22 and 40 ppm with an observation period of 10 days. The mortalities of the mice at these two concentrations were 0/10 and 3/10, respectively. For 6 h exposure at these concentrations the mortalities were 7/10 and 8/10, respectively.

Experiments were carried out by Bitron and Aharonson [16] in which mice in groups of 16 were exposed to concentrations of bromine of 240 and 750 ppm for periods of 15—270 and 5—30 min, respectively. The times

of death after exposure were recorded over an interval of 30 days. As with their work on chlorine, most of the deaths were delayed deaths. The LC_{50} values obtained were 240 ppm for 100 min and 750 ppm for 9 min. The LC_{50} values obtained by these various workers are summarised in Table 1.

TABLE 1

Concentration of bromine lethal to mice given by various authors

Author(s)	Concentration lethal to 50% (ppm)	Exposure time (min)
Schlagbauer and Henschler [15]	174	30
Bitron and Aharonson [16]	750	9
	240	100

In both sets of work the mortality is strongly affected by the observation period and in both there are some differences from the work on chlorine. The data of Schlagbauer and Henschler on the effect of concentration are shown in Table 2. Whereas with chlorine these workers observed no deaths after 4 days, with bromine an appreciable number occurred later than this. In the work of Bitron and Aharonson with chlorine most of the deaths were delayed deaths, the mortality—observation time curve running first flat along the axis and then rising sharply at about the fourth day, while with bromine most of the deaths were again delayed deaths, except at the highest mortalities, but in this case the mortality—observation time curve rises quite sharply from the start. The data for both sets of authors for the effect of time of exposure and the proportion of acute deaths are given in Table 3. Acute deaths are taken as those occurring in the first 4 days.

The experimental results also yield information on the slope of the concentration—mortality line and the proportion of acute deaths. For the former the main data available are those of Schlagbauer and Henschler. Here it is necessary to decide whether to use the data for the 4 day or 10 day observation periods. Although in principle it is total mortality and hence the longer observation period which is of interest, the mortalities for the latter are high and it is difficult to extract the required information. It is therefore the 4 day results which have been used. The results obtained for the lethality of different concentrations of bromine for a 4 day observation period as given in Table 2 are plotted in Fig. 1.

For the proportion of acute deaths it is convenient to define an acute death as one which occurs in the first 4 days. This definition differs slightly from that used in the work on chlorine described in Ref. [1], where the observation period was 3 days. For both gases the definition has been chosen to

TABLE 2

Mortality of mice exposed to bromine as a function of concentration given by various authors

A. Unnormalised Concentrations

Author(s)	Concentration (ppm)	Exposure time (min)	Concentration at 30 min (ppm)	Mortality Observation period	
				4 days (%)	10 days (%)
Schlagbauer and Henschler [15]	111	30	111	0	0
	140		140	30	30
	199		199	40	60
	236		236	50	90
	252		252	70	100
	268		268	70	90
	290		290	90	100
	315		315	100	100
Bitron and Aharonson [16]	240	24— 9	215		1
		65—14	353		11
		120—30	480		40
		215—55	642		88
	750	7— 2	362		16
		13— 3	494		42
		24— 5	671		88

B. Normalised Concentrations

Author(s)	Normalised concentration	Mortality[a] (%)
Schlagbauer and Henschler [15]	0.700	30
	0.995	40
	1.18	50
	1.26	70
	1.34	70
	1.45	90
Bitron and Aharonson [16]	0.695	11
	0.945	40
	1.26	88
	0.731	16
	0.998	42
	1.36	88

[a]Observation period 4 days for Schlagbauer and Henschler data and 10 days for Bitron and Aharonson data.

TABLE 3

Mortality of mice exposed to bromine as a function of time of exposure given by various authors

Author(s)	Concentration (ppm)	Exposure time (min)	Mortality Observation period		Proportion of acute deaths
			4 days (%)	10 days (%)	
Schlagbauer and Henschler [15]	111	30	0	0	0
	140		30	30	1.0
	199		40	60	0.67
	236		50	90	0.56
	252		70	100	0.70
	268		70	90	0.78
	290		90	100	0.90
	315		100	100	1.0
Bitron and Aharonson [16]	240	24— 9	0	1	0
		65—14	1	11	0.09
		120—30	15	40	0.38
		215—55	62	88	0.70
	750	5	0	0	0
		7— 2	0	16	0
		13— 3	13	42	0.31
		24— 5	64	88	0.73

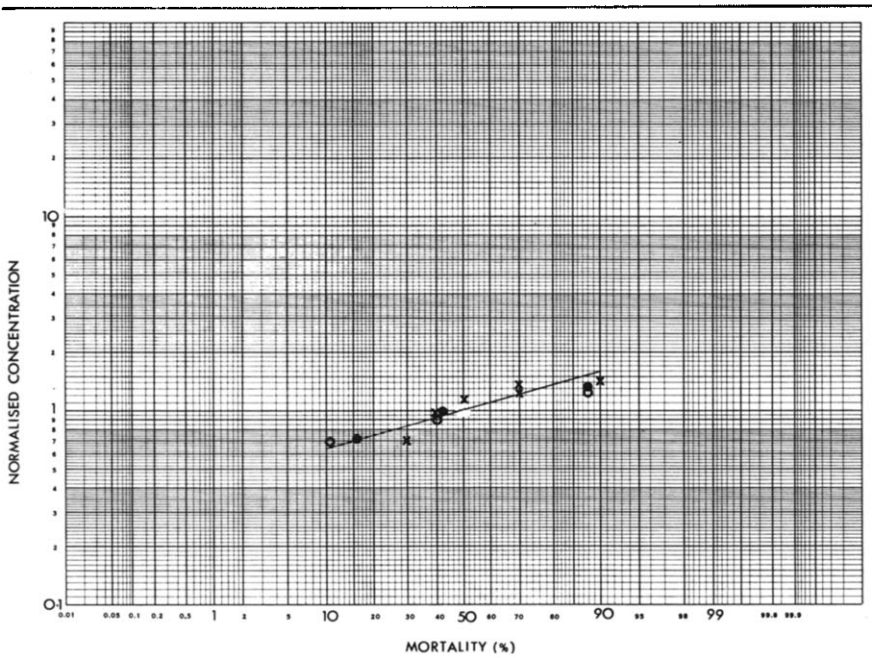
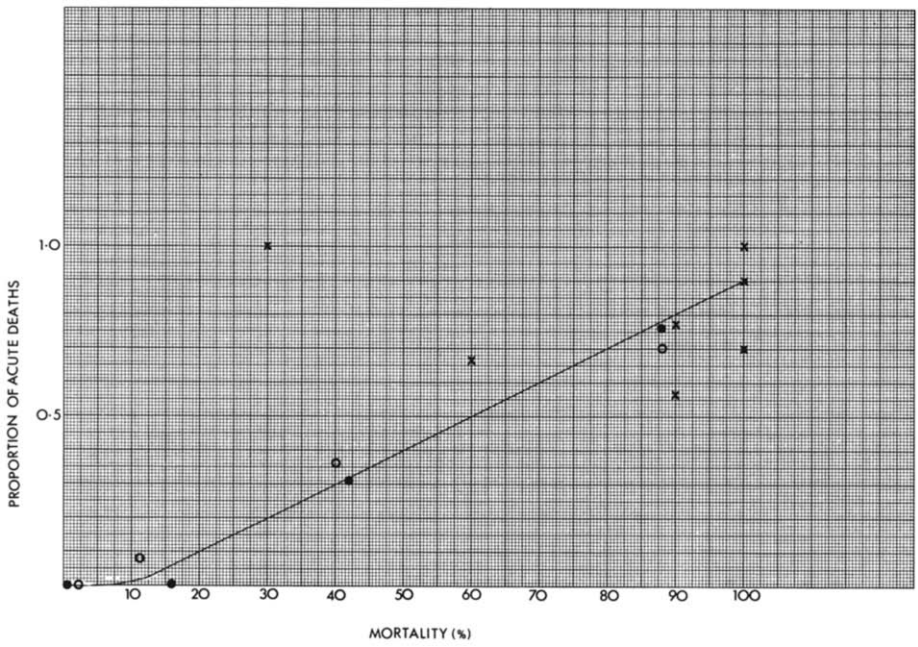
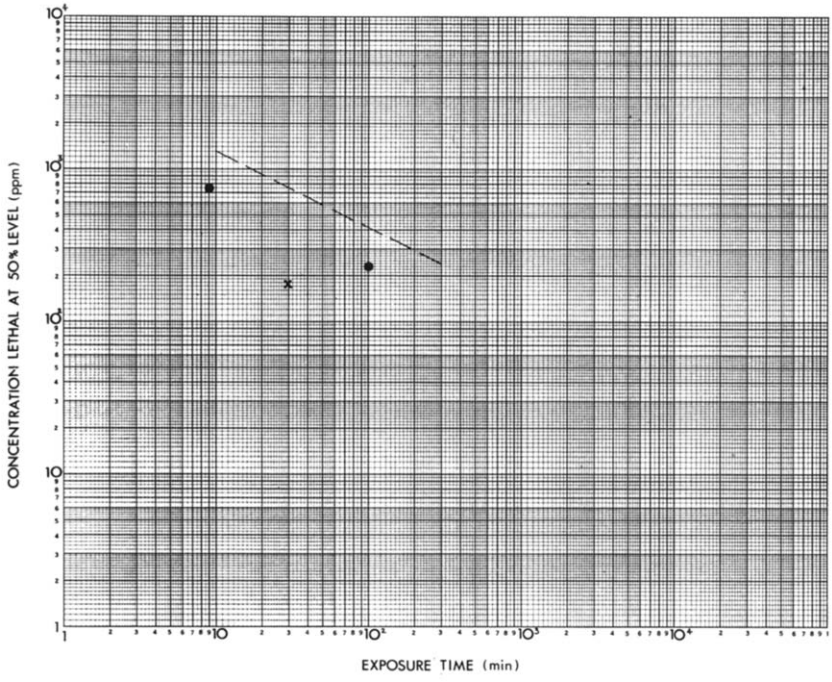


Fig. 1. Concentration of bromine lethal to mice. Data adjusted for exposure period of 30 min and normalised with respect to LC_{50}. ×, Schlagbauer and Henschler [15]; ○, Bitron and Aharonson [16], concentration 240 ppm; ●, Bitron and Aharonson [16], concentration 750 ppm.


PROPORTION OF ACUTE DEATHS
1·0
0·5
10
20
30
40
50
60
70
80
90
100
MORTALITY (%)


CONCENTRATION LETHAL AT 50% LEVEL (ppm)
EXPOSURE TIME (min)

fit the data available. For chlorine the principal data were those of Underhill [17], who drew the dividing line at 3 days. For bromine the data of Schlagbauer and Henschler require the use of a 4 day period. The results obtained by both sets of workers on bromine are given in Table 3 and plotted in Fig. 2.

The three LC_{50} values obtained by these workers are shown plotted in Fig. 3. The dotted line is drawn through an LC_{50} of 750 ppm for a 30 min exposure period and has slope equal to −0.5. The justification for this is given below.

It is also of interest to consider the lowest concentration of bromine at which any death occurred. The lowest concentration used by Bitron and Aharonson was 240 ppm and a single death was recorded by these authors after 15 min exposure. The lowest concentration found to be lethal for a 30 min exposure is Schlagbauer and Henschler's value of 62 ppm.

Experimental work on odour and chronic toxicity

There is a small amount of experimental work on animals at low concentrations.

Early work on odour was carried out by Matt [18]. More recent work is that of Rupp and Henschler [19]. They found that the odour threshold for bromine is 0.01 ppm compared with 0.02—0.05 ppm for chlorine. They propose threshold values (MAK Werte) for chlorine and bromine of 0.5 and 0.1, respectively.

These authors also draw attention to an apparent error in the values for bromine quoted by Flury and Zernik [20] from the work of Matt. They state that Flury and Zernik treated Matt's values expressed as ‰ (parts per thousand) as if they were mg/l and then converted them to ppm so that both sets of values (mg/l and ppm) are incorrect. The values given for chlorine, however, are correct. Further information is given in the footnote in Table 5.

Physiology and pathology of gas poisoning

Accounts of the physiology and pathology of bromine poisoning tend to relate its effects to those of chlorine.

A description of the physiology of gas poisoning by irritant gases such as ammonia, chlorine and phosgene has been given by Haggard [21]. The differences in the action of such gases tend to be due to the physical rather than the chemical properties. In particular, the more soluble the gas the more it tends to attack the upper respiratory passages rather than the lungs. Thus ammonia, which is highly soluble, attacks the inlet airways, while phosgene, which is very insoluble, enters deep into the lungs. Chlorine is intermediate between these two gases. Haggard gives the solubilities by volume in water at 40°C of ammonia, chlorine and phosgene as 444, 1.4 and 'decomposes', respectively, and that of bromine as 9.4. Thus bromine is 7 times more soluble in water than chlorine.

Many of the researchers who have carried out experimental work on animals have discussed the physiology and pathology of bromine poisoning. Lehmann came to the conclusion that both qualitatively and quantitatively chlorine and bromine have similar effects.

The description of the effects of bromine given by Flury and Zernik [20] is broadly similar to that given for chlorine. They state, however, that bromine attacks much more strongly than chlorine the skin and hair and the respiratory tract and stomach lining, i.e. external and internal surfaces.

Hill [8] describes experiments on animals with bromine at concentrations of 1000 ppm. He states that the mucous membrane was killed by the gas and stripped off by the respiratory efforts so that it was drawn down into the bronchi, forming a tree-like cast, thus suffocating the animal. He does not give the animal species, but in a later paper [9] refers to work with bromine on guinea pigs.

Symes [10] describes experiments with bromine on anaesthetised cats. He gives a trend record showing the rapid obstruction of the airways.

Schlagbauer and Henschler [15] found several differences between chlorine and bromine. In the main series of experiments at high, lethal concentrations for chlorine all the deaths occurred in the observation period 0—4 days, whereas for bromine there were some deaths in the observation period 8—10 days. They comment that this result suggests a difference in toxic mechanism. Dissection of the animals showed that recovery of the tissues was much slower with bromine than with chlorine. Further confirmation of this was obtained in a subsidiary series of experiments at low, sublethal concentrations in which it was found that animals suffered loss of weight and that those exposed to bromine were much slower to recover than those exposed to chlorine.

It may be expected, therefore, that asphyxiation due to damage to and blockage of the respiratory tract will be a more serious hazard with bromine than with chlorine.

The effects of bromine on man are discussed below.

Lethal load function

As described in Refs. [1] and [2] the lethal load functions used are

$$L = CT^n \tag{1}$$

where C is concentration (ppm), L is toxic load (ppm min^n), T is time (min) and where usually $n < 1$, and

$$L^* = C^m T \tag{2a}$$

where L^* is an alternative toxic load (ppm^m min) and where usually $m > 1$.

In hazard assessment there are likely to be exposures over a range of concentrations so that the toxic load is strictly the time integral of the concentration function, but this is usually approximated by the summation

$$L^* = \Sigma\, C^m T \qquad (2b)$$

and this approach is used here.

Toxic concentrations given in the literature

Values of the lethal concentration of bromine are quoted in standard texts on toxicology [20, 22—25]. Some values given in leading texts are shown in Table 4.

The lethal concentrations for man quoted by Flury and Zernik [20] are not referenced. The dangerous concentration is attributed to Hess. The values given by Patty appear to derive from Flury and Zernik. He quotes this text explicitly for the lethal concentration to animals and his other data are to be found there also. The NIOSH compilation [24] gives a number of sources as shown in the table. The data given by Sax [25] are the same as in the NIOSH text.

A value of 1000 ppm for the lethal concentration for man which is rapidly fatal for short exposure is quoted in a table by Henderson and Haggard [23, p. 133]. The source of this value is uncertain.

The concentrations of bromine tolerable and intolerable to man are shown in Table 5.

TABLE 4

Lethal concentration of bromine quoted in standard toxicological texts

Text	Effect	Concentration	Exposure time	Source
Flury and Zernik [20]	Lethal concentration for man	3.5 mg/l ca. 550 ppm	Immediate	
	Lethal concentration for man	0.22 mg/l 35 ppm	½—1 h	
	Dangerous concentration for man	0.04—0.06 mg/l 6—9 ppm	½—1 h	Hess[a]
Patty [22]	Lethal concentration for animals	ca. 550 ppm	Immediate	
	Concentration causing some fatalities among rabbits	180 ppm	6½ h	
	Lethal concentration for guinea pigs and rabbits	300 ppm	3 h	
Henderson and Haggard [23]	Lethal concentration	1000 ppm	short exposure	
Tatken and Lewis (NIOSH) [24]	LC_{50} mus (mouse)	750 ppm	9 min	Bitron and Aharonson [16]
	LCLo gpg (guinea pig)	140 ppm	7 h	Lehmann [4]
	LCLo rbt (rabbit)	180 ppm	6.5 h	Anon. [26]
	LCLo hmn (man)	1000 ppm		Deichmann and Gerarde [27]
	LCLo cat	140 ppm	7 h	Lehmann [4]
Sax [25]	as Tatken and Lewis			

[a] Quoted without reference by Flury and Zernik [20]. See also Table 5.

TABLE 5

Concentrations of bromine tolerable and intolerable to man

Author(s)	Effect	Concentration	Exposure time	Source
ACGIH [28]	Threshold Limit Value (TLV)			
	Long term TLV—TWA (8 h)	0.1 ppm[a]		
	Short term TLV—TWA	0.3 ppm		
Kobert [29]	Dangerous concentration	60 ppm	1 h	
Flury and Zernik [20]	Concentration at which work can be continued without interference	0.15—0.3 ppm[b]		Matt [18]
	Concentration at which work becomes impossible	0.6 ppm[c]		Matt [18]
	Concentration tolerable without immediate or later consequences	3.5 ppm	½—1 h	
	Dangerous concentration	6—9 ppm	½—1 h	Hess[d]
Henderson and Haggard [23]	Maximum concentration allowable for prolonged exposure	0.1—0.15 ppm		
	Maximum concentration allowable for short exposure	4 ppm	½—1 h	
	Dangerous concentration for short exposure	40—60 ppm		
Patty [22]	Selected values from Flury and Zernik and from Henderson and Haggard			
Rupp and Henschler [19]	Odour threshold	0.01 ppm		
	Identification threshold[e]	> 1 ppm		

[a]Rupp and Henschler [19] suggest that this value is based on the data of Matt, erroneously converted by Flury and Zernik [20].
[b]Rupp and Henschler state that these values are in error. The correct values are apparently 1—2 ppm.
[c]Rupp and Henschler state that this value is in error. The correct value is apparently 4 ppm.
[d]Quoted without reference by Flury and Zernik [20]. Compare Hess' original values of 40—60 ppm (see text) and Rupp and Henschler's comments.
[e]Identification of bromine given choice between chlorine and bromine.

Analysis of available data

The data available on the lethal toxicity of bromine are relatively sparse. Analysis to determine the effects of species, concentration and time is thus more difficult. The application to man of toxicity results obtained by experi-

mentation on animals is attended by many difficulties and much uncertainty, as discussed in Refs. [1] and [2].

The approach used in evaluating toxicity data must necessarily depend on the type and quality of the data. The approach adopted here is to interpret the information available on bromine by reference to that on chlorine, since the chlorine data are considerably more numerous than those on bromine. It is proposed that the estimate of the lethal toxicity of chlorine to man should be obtained by reference to that for chlorine, which is based primarily on the work of Underhill [17] on dogs.

Effect of time

It is convenient to begin by considering the effect of exposure time. There is one set of data by Bitron and Aharonson [16], in which the LC_{50} was obtained for different combinations of concentration and exposure period. Table 6 shows the results obtained by these investigators for the concentrations of bromine lethal to mice as a function of time, together with the lethal load function CT^n for different values of n. The table shows that the best fit is given by a value for n of 0.5. In their work on chlorine these authors obtained a proportion of acute deaths which appears unusually low. Their results for bromine show mortality rising more rapidly after exposure and thus a larger proportion of acute deaths. Thus for the latter gas the possible objection that the work is atypical is less cogent. Doe and Milburn [30] have also estimated the value for n for bromine as 0.49.

TABLE 6

Concentration of bromine lethal to mice at 50% mortality level as a function of time (Bitron and Aharonson [16])

C (ppm)	T (min)	CT	$CT^{0.4}$	$CT^{0.5}$	$CT^{0.6}$
750	9	6750	1806	2250	2803
240	100	24000	1514	2400	3804

The value of 0.5 for n is the same as that estimated for chlorine and, in unpublished work, for ammonia. Since bromine is broadly intermediate in solubility and irritant action between these two gases, the value of n obtained for bromine accords with that expected. It appears, therefore, that the best estimate of n is 0.5 so that the toxic load is taken as

$$L = CT^{0.5} \tag{3}$$

The range of concentrations and times covered by the data on which eqn. (3) is based is 240—750 ppm and 9—100 min.

Effect of concentration

For the effect of concentration there are two sets of data, those of Schlagbauer and Henschler [15] and Bitron and Aharonson [16].

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 are given in Table 1. Adjusting the values of Bitron and Aharonson to an exposure period of 30 min using eqn. (3) and averaging the two values, the LC_{50} value obtained is 425 ppm, and averaging this again with the value of Schlagbauer and Henschler gives a mean LC_{50} for mice of 300 ppm. This compares with a mean LC_{50} for mice of 256 ppm for chlorine derived in the chlorine paper. However, this value for bromine is heavily weighted by that of Schlagbauer and Henschler, whose value for both chlorine and bromine is much less than that of other workers. These authors in fact make their own comparison of the ratio of the LC_{50}s for bromine and chlorine and, as stated earlier, give a figure of 1.5.

As argued in Ref. [1], the LC_{50} value for mice is almost certainly less than that for larger animals. It is therefore proposed that the LC_{50} value for man be derived from that for chlorine using a bromine/chlorine lethal toxicity ratio of 1.5.

For the slope of the concentration—mortality line the same two sets of data are applicable. For the Schlagbauer and Henschler work the data are for the 4 day observation period, since the mortalities for the 10 day period are very high, whilst for the work of Bitron and Aharonson those used are for a 10 day observation period, which is preferred for this purpose to the very long 30 day period. The work of the latter authors was done at two fixed concentrations of 240 and 750 ppm with variable exposure times and equivalent concentrations for a 30 min exposure period have been calculated using eqn (3). The data from these two sets of workers are shown in Table 2, Section A. For these data the LC_{50}s were estimated using the data within the 10—90% mortality range, those within the preferred 20—80% range being too sparse. The corresponding sets of data normalised with respect to these LC_{50} values are shown in Table 2, Section B, and are plotted in Fig. 1. The line has been fitted using again the points in the 10—90% mortality range. From the slope of this line the ratio LC_{90}/LC_{10} is 2.5. For chlorine the value of the ratio obtained by workers, including Schlagbauer and Henschler who used mice, was about 2, but that obtained by Underhill using dogs was nearly 4 and a value of 4 was proposed for man. It is proposed that a value of 4 should be used for man for bromine also.

Concentrations intolerable to man

Information is available on the effect on man of concentrations of bromine which are not normally lethal. Some data on concentrations which are tolerable and intolerable to man are given in Table 5. At concentrations of about 4 ppm irritation is said to be experienced and normal work to be im-

possible. The dangerous concentration for ½—1 h is given as 40—60 ppm; this is the value of Hess, that of Flury and Zernik evidently being in error, as described earlier, but the degree of danger is ill defined. The data were apparently obtained by observation of the effects of bromine on man. The basis of the data is different, therefore, from those for lethality to man derived from animal experiments. They include the effects of any enhancement of activity which may have occurred.

Concentrations lethal to man

Following the earlier discussion, the concentrations of bromine lethal to man are taken as greater than those for chlorine by a factor of 1.5. The specific applications of this are now considered.

In Ref. [2] the LC_{50} proposed for man was 500 ppm. Applying the bromine/chlorine lethal toxicity ratio of 1.5, the LC_{50} proposed for bromine is 750 ppm. Further, applying the LC_{90}/LC_{10} ratio of 4 proposed above, the LC_{10} and LC_{90} for bromine are 375 and 1500 ppm, respectively.

TABLE 7

Concentration of bromine proposed as lethal to man for an exposure period of 30 min

Concentration (ppm)	Mortality (%)	Toxic load $CT^{0.5}$ (ppm $min^{0.5}$)
A. Regular Population: Base Level of Physical Activity		
375	10	2054
750	50	4108
1500	90	8216
B. Vulnerable Population: Base Level of Physical Activity		
150	10	822
300	50	1644
600	90	3288
C. Regular Population: Standard Level of Physical Activity		
188	10	1027
375	50	2054
750	90	4108
D. Vulnerable Population: Standard Level of Physical Activity		
75	10	411
150	50	822
300	90	1644
E. Average Population: Standard Level of Physical Activity		
120	10	657
315	50	1725
698	90	3823

These values are for the regular population at the base level of activity for a 30 min exposure period. They are shown in Table 7, Section A.

Lethal loads

An estimate of the lethal load LL_{50} at the base level of activity follows directly from the foregoing. The concentration lethal at the 50% level for an exposure period of 30 min has been taken as 750 ppm. Hence

$$LL_{50} = CT^{0.5} = 750 \times 30^{0.5} = 4108 \text{ ppm min}^{0.5} \quad (4)$$

Similarly, the toxic loads lethal at the 10% and 90% levels are 2054 and 8216 ppm $\text{min}^{0.5}$, respectively.

Vulnerable population

The treatment of the vulnerable population is similar to that in Ref. [2]. The total population is assumed to consist of 75% less vulnerable, or regular, and 25% vulnerable population.

For chlorine at the base level of activity a value of 100 ppm was taken as the concentration lethal to 10% of the vulnerable population for an exposure time of 30 min. The slope of the concentration—mortality line was also taken as the same as that for the regular population, which gave for the concentrations lethal at the 50% and 90% levels 200 and 400 ppm, respectively. Applying the bromine/chlorine lethal toxicity ratio of 1.5, this gives for bromine concentrations lethal at the 10%, 50% and 90% levels of 150, 300 and 600 ppm, respectively. These values are shown in Table 7, Section B.

Inhalation rate factor

It was argued in Ref. [2] that as a first approximation it is reasonable to assume that most of the chlorine inhaled is absorbed and that the rate of absorption of the gas is proportional to the inhalation rate. Bromine is some 7 times as soluble as chlorine and the argument applies to it with greater force. This is supported by experiments by Lehmann [5] in which he measured the inlet and outlet concentrations of bromine in bromine-contaminated air breathed by men. The inlet concentration of bromine was 2.9 ppm, the outlet concentration undetectable, the absorption being thus total. The inhalation rate factor approach is therefore used for bromine also.

The inhalation rate factor ψ_1 is defined as the ratio of the inhalation rate at the actual level of activity to that at the base level (6 l/min). This factor is applied directly to the inhaled concentration. For the standard level of activity, $\psi_1 = 2$. The values of the lethal concentration for a 30 min exposure time for both the regular and vulnerable population for the standard level of activity are given in Table 7, Sections C and D, respectively. The values in Sections C and D are obtained by dividing by ψ_1 (= 2) the values in Sections A and B, respectively.

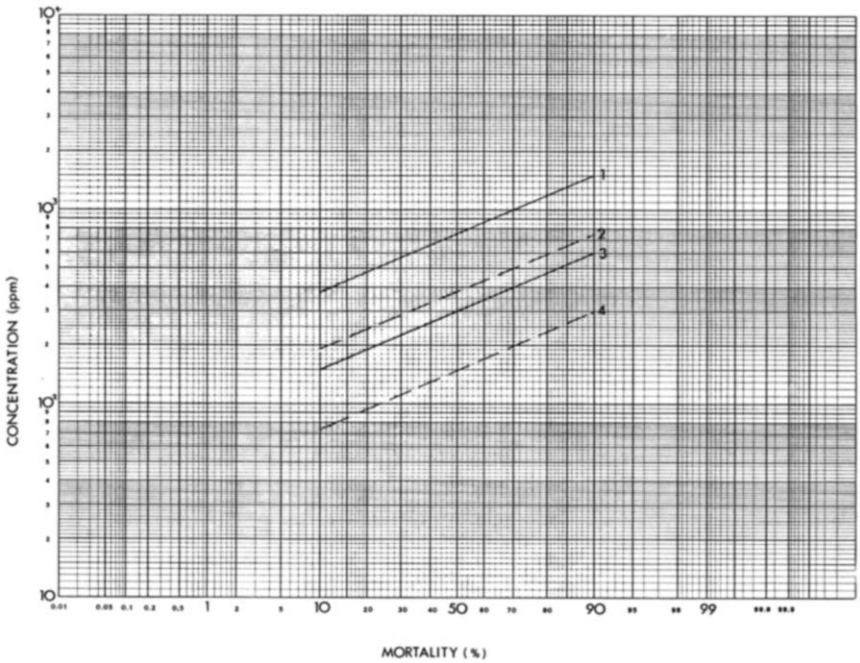


Fig. 4. Concentration of bromine proposed as lethal to man for an exposure period of 30 min. Line 1, regular population, base level of activity; line 2, regular population, standard level; line 3, vulnerable population, base level; line 4, vulnerable population, standard level.

TABLE 8

Concentration of bromine proposed as lethal to man for an exposure period of 10 min

Concentration (ppm)	Mortality (%)	Toxic load $CT^{0.5}$ (ppm $min^{0.5}$)
A. Regular Population: Standard Level of Physical Activity		
325	10	1027
650	50	2054
1300	90	4108
B. Vulnerable Population: Standard Level of Physical Activity		
130	10	411
260	50	822
520	90	1644
C. Average Population: Standard Level of Physical Activity		
208	10	657
546	50	1725
1209	90	3823

Lethal concentrations

The lethal concentrations proposed for both regular and vulnerable populations and for both base and standard levels of activity for a 30 min exposure period are shown in Table 7 and plotted in Fig. 4. From the plot in Fig. 4 it is possible to estimate the lethal concentrations for an average population drawn 75% from the regular and 25% from the vulnerable population. These are shown in Table 7, Section E.

The lethal concentrations proposed for both regular and vulnerable populations for the standard level of physical activity for a 10 min exposure time are shown in Table 8, Sections A and B. These values are derived from those in Table 7, using eqn. (3). The values given in Table 8 are plotted in Fig. 5. Lethal concentrations for the average population are given in Table 8, Section C.

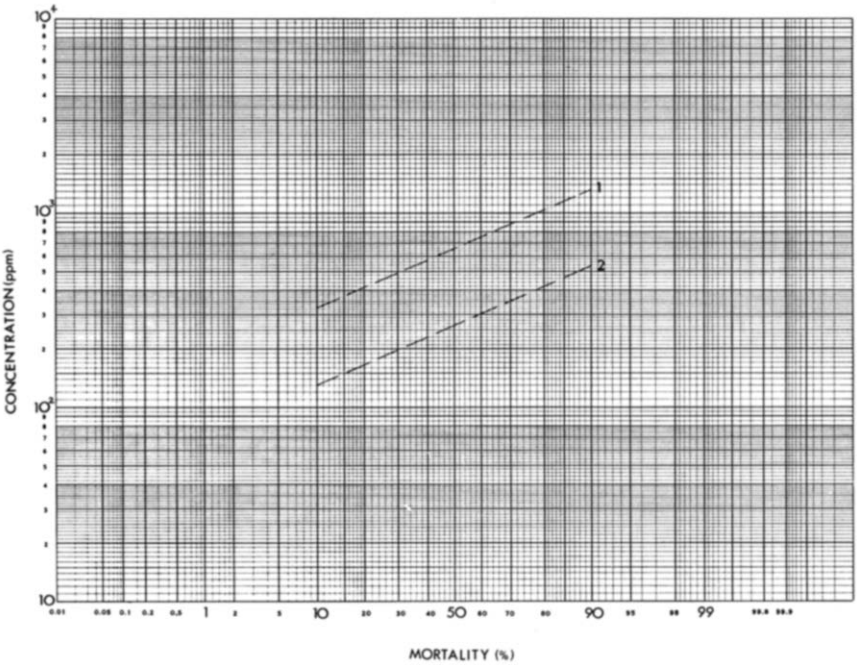


Fig. 5. Concentration of bromine proposed as lethal to man for an exposure period of 10 min. Line 1, regular population, standard level of activity; line 2, vulnerable population, standard level.

Probit equations

The following probit equations may be derived from the data given in Table 7:

Regular population

Base Level of Physical Activity

$$Y = -10.32 + 0.92 \ln \Sigma C^2T \qquad (5)$$

Standard Level of Physical Activity

$$Y = -9.04 + 0.92 \ln \Sigma C^2T \quad (6)$$

Vulnerable population

Base Level of Physical Activity

$$Y = -8.63 + 0.92 \ln \Sigma C^2T \quad (7)$$

Standard Level of Physical Activity

$$Y = -7.36 + 0.92 \ln \Sigma C^2T \quad (8)$$

Very high concentrations

There may be a limiting value of the concentration at which the relation given for the injurious effect of bromine as a function of concentration and of time breaks down so that at this level it is concentration only which matters. This may be somewhat more likely for bromine than for chlorine in so far as asphyxiation due to blockage of the respiratory tract is more probable. Nevertheless, it is expected that as with chlorine any error in the use of the probit equations even at very high concentrations will be small.

Acute death factor

From the work on mice it is possible to derive a relation between the mortality and the proportion, P_a, of acute deaths, or acute death factor, but it was shown in Refs. [1] and [2] that the evidence from war gas casualties is that for man the proportion of acute deaths is much higher than the animal experiments suggest. It is proposed, therefore, that for bromine the acute death factor used be that derived for chlorine from the gas attack data:

$$P_a = 0.8 + 0.2P \quad (9)$$

where P is the overall probability of death and P_a the probability of acute death.

Medical treatment factor

An allowance is made, as in Ref. [2], for the reduction in delayed deaths due to appropriate medical treatment compared with total neglect. This aspect is taken into account by the medical treatment factor ψ_2, which is applied to the estimated potential delayed deaths to determine the proportion which become recoveries.

For chlorine the proposed values of the medical treatment factor were 0.9 and 0.7 for the regular and vulnerable populations, respectively. The evidence is that recovery tends to be fairly rapid and complete from chlorine, but much slower from bromine poisoning, although it is not clear whether this gives more or less scope for medical treatment. In the absence of information to the contrary it is proposed that the same values be used for the medical treatment factor for bromine as for chlorine.

Methodology for hazard assessment

An overall methodology for the estimation of the mortality from an accidental release was given in Ref. [2]. The same methodology is proposed for bromine.

Discussion

A set of values has been derived for the concentration of bromine lethal to man for use in the assessment of major hazards and a methodology has been given for applying these values to obtain an estimate of the mortality. Separate values are given for the regular and vulnerable populations and for different levels of physical activity.

The lethal toxicity of bromine has been considered in relation to that of chlorine and the lethal loads and concentrations are based on the estimate that bromine is 1.5 times less toxic than chlorine. This figure has been not been applied, however, as a blanket value but as far as possible has been justified at each stage.

The use of a toxic load as in eqn. (2b) appears at present to be the only way of applying experimental toxicity data in hazard assessment but, as discussed in Ref. [2], it is a rather mechanistic method and cannot be regarded as entirely satisfactory. It has been shown for example, by Griffiths and Megson [31] and by Ride [32], that the toxic effect is sensitive to concentration intermittency. It is necessary, therefore, to exercise caution in applying equations of this type.

There is need for a toxicokinetic model for irritant gases which would put the interpretation and correlation of the experimental results, and their application to hazard assessment, on a sounder basis. This aspect has been discussed by the authors elsewhere [33].

The various other qualifications and comments on the toxicity estimates derived, which are made in Ref. [2] for chlorine, apply equally to bromine. In addition, it is emphasised that the information available on bromine is much more sparse than for that on chlorine.

Attention is drawn as in Ref. [2] to one set of experiments in which mice were exposed for periods of 3 and 6 hours to concentrations as low as 22 ppm and had high mortalities.

The estimates of bromine toxicity derived in this work are based upon a number of assumptions and are necessarily tentative.

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List of symbols

C concentration of toxic gas (ppm)
L toxic load (ppm min^n)
LC_i concentration lethal at i% level (ppm)
LL_i toxic load lethal at i% level (ppm min^n)
L^* toxic load (alternative formulation) (ppm^m min)
m index
n index
P probability of death
P_a probability of acute death
T time (min)
Y probit
ψ_1 inhalation rate factor
ψ_2 medical treatment factor

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