THE TOXICITY OF METHALLYL CHLORIDE AND METHYL BROMIDE TOWARDS WHITE RATS

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(With 1 Figure in the Text)

INTRODUCTION

Gaseous insecticides, such as methyl bromide and methallyl chloride, are being used on an increasing scale against insects attacking stored products such as grain, tobacco, etc. Their use involves two possible dangers. In the first place, the worker may be poisoned either during the actual gassing operation or during the preparatory period. Secondly, there is the possible danger to consumers through the absorption of these fumigants into the stored product.

The use of methyl bromide as a gaseous insecticide has increased enormously of late, probably because it is commercially available, since it is the active ingredient of certain types of fire extinguishers and is non-explosive. But it is recognized that special precautions are necessary when handling methyl bromide, since it is practically odourless even at very high concentrations. Some authorities recommend that it should be mixed with a lachrymatory substance.

Methallyl chloride, on the other hand, is a relatively new product and not as yet so widely known and appreciated as methyl bromide for use as a gaseous insecticide. While it is not so volatile as methyl bromide, it has a very pronounced odour even at concentrations well below the lethal limit of toxicity. Indeed it is physically impossible without very great distress to work in an atmosphere containing the amount of methallyl chloride known to be lethal to warm-blooded animals.

The purpose of these studies was to determine the relative toxicity of methyl bromide and methallyl chloride to warm-blooded animals. A further study is in progress to determine whether these substances are absorbed by grain, and if so, to what extent and for how long.

Previous extensive experiments carried out in our laboratories showed that the continued exposure of rats to a given concentration of methallyl chloride was more dangerous than was a series of intermittent exposures comprising the same total time. It was found, for example, that continuous exposure for 24 hr. to air containing 2 g. of methallyl chloride per cu.m. resulted in a 50 % kill of rats, whereas no deaths occurred among rats exposed to the same concentration of methallyl chloride for 2 hr. per day for 12 successive days. For this reason, and because it corresponds more closely to commercial practice, intermittent exposure for short periods has been adopted in these studies in preference to continuous exposure for the same length of time.

The results of these studies have given a clear indication of the possible dangers from the use and handling of these products, where poisoning of man is most likely to occur by the cumulative effect of inhaling small amounts at successive intervals of time.

MATERIALS, METHODS AND EXPERIMENTS

The experiments were carried out with the white rat (*Rattus norvegicus albinus*).

The animals were fed with food of the following composition:

	%
Ground wheat	60
Skimmed milk powder	30
Fat	8·5
Cod-liver oil	1·35
Salt mixture	0·15

Endive or lettuce leaves were given once a week

When not undergoing treatment the rats were kept in a room with continuous ventilation and at a temperature between 22 and 24° C.

It was found that the small unavoidable differences in the initial weight and the growth rate of the individual rats were of no importance as regards their reaction towards methallyl chloride and methyl bromide.

Two series of experiments were carried out, each occupying 5 weeks. Each week the rats were gassed for 1 hr. on Mondays, Wednesdays and Fridays.

The first series comprised:

(1) Methallyl chloride gassings at concentrations of 2, 4 and 8 g. per cu.m. of air.
(2) Methyl bromide gassings at the same concentrations.
(3) Treatment of control rats with a constant current of air without toxicant.

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The rats used in these experiments were 2½ months old.

The second series comprised:

(1) Methallyl chloride gassings at concentrations of 12, 16 and 20 g. per cu.m. of air.

(2) Methyl bromide gassings at the same concentrations.

(3) Treatment of control rats with a constant current of air without toxicant.

The rats used in these experiments were 5 months old.

Thus, only the concentration of toxicant was varied; the other factors influencing the toxic effect being kept constant.

The experiments were carried out in an apparatus which provided a continuous flow of air plus toxicant. During gassing, the rats were kept in a closed chamber, provided with inlet and outlet tubes, through which the mixture of air and the gaseous toxicant were passed at a constant rate. This chamber contained a wire cage, divided into four parts by wire gauze partitions, so that while being gassed the animals could not come into contact with each other and the air and gas could circulate freely.

The rate of air supply was kept as constant as possible. After being purified by passing through vessels with carbon and cotton-wool the air passed a water-filled manostat and a flow meter and finally reached the fumigation chamber.

The supply of methallyl chloride was effected by evaporating the substance by means of a predried nitrogen current bubbling through the liquid.

The supply of methyl bromide was effected by opening the cock of the gas cylinder, in which liquid methyl bromide (boiling-point 4·6° C.) was kept under pressure.

After evaporation the toxicants were fed into the air-feed line before its entrance to the two fumigation chambers, so that the test animals were exposed to mixtures of air and methallyl chloride or methyl bromide.

The supply of air plus toxicant was regulated by means of a water-filled manostat in the case of air and methallyl chloride, and a needle valve in the case of methyl bromide.

The exact quantity of methallyl chloride or methyl bromide applied at each fumigation was determined by weighing the vessels containing these substances before and after gassing.

All gassings were made at a temperature of 20° C. The toxic effect of the gases used will be evaluated by the number of gassings at a given concentration necessary to obtain a given percentage of kill. In addition, data will be presented on the influence of the gassings upon changes in the weight of the test animals.

RESULTS

Data giving the effect of concentration and number of successive treatments with methyl bromide and methallyl chloride on the mortality of rats are given in Table 1. It is shown that no animals died even

Table 1. *Relation between percentage of kill and concentration of methallyl chloride and methyl bromide at which the animals have been gassed*

No. of test animals	Concentration (g./cu.m.)	No. of gassings	Percentage kill: Methallyl chloride	Percentage kill: Methyl bromide
6	2	15	0	0
6	4	15	0	0
6	8	5	0	0
		6	0	100
		15	0	—
8	12	1	0	25
		2	0	75
		3	0	100
		15	0	—
		16	0	—
8	16	1	0	100
		8	0	—
		9	12·5	—
		15	12·5	—
		16	12·5	—
8	20	1	0	100
		4	0	—
		5	12·5	—
		13	12·5	—
		14	25	—
		15	37·5	—
		16	50	—
13	0	—	0	

after being exposed for sixteen successive 1-hourly periods spread over 36 days to air containing 12 g. of methallyl chloride per cu.m. In contrast, all the rats died almost simultaneously after the sixth exposure to methyl bromide at only 8 g. per cu.m. of air. Furthermore, even one exposure to methyl bromide at 12 g. per cu.m. of air resulted in some rats dying, and they all died after the third exposure to methyl bromide at this concentration. Further tests showed that all the rats died after one exposure to methyl bromide at concentrations of 16 and 20 g. per cu.m. of air, whereas none died after eight exposures to methallyl chloride at 16 g., or after four exposures to methallyl chloride at 20 g. per cu.m. of air. Furthermore, only 16·5 % of the rats died after sixteen exposures to methallyl chloride at 16 g. and only 50 % died after sixteen exposures at a concentration of 20 g. per cu.m. of air. None of the untreated rats died during these experiments.

Summarizing the data, it is shown that 1 hour's exposure to methyl bromide at concentrations of 12,

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16 and 20 g. per cu.m. of air is far more fatal to rats than are sixteen successive 1-hourly exposures to methallyl chloride at the same concentration. It is concluded that methyl bromide is much more toxic to rats—and presumably to other warm-blooded animals as well—than is methallyl chloride.

EFFECT UPON SUBSEQUENT GROWTH AND DEVELOPMENT

The effect of the several treatments upon those rats which survived was studied during the period immediately following the cessation of treatment. The results are given in Tables 2 and 3, and Fig. 1. It is shown that the subsequent growth and development of treated rats was not adversely affected by fifteen successive exposures to methallyl chloride at 8 g. or to methyl bromide at 4 g. per cu.m. of air. With increasing concentrations of methallyl chloride up to 20 g. per cu.m. of air there was an increasing detrimental effect upon subsequent increase in body weight. Thus, whereas untreated rats gained about 8 % in body weight over the test period, rats exposed for fifteen times to methallyl chloride at 12 g. per cu.m. showed an average gain of only 1 %. Rats

Table 2. *Showing the percentage change in body weight of rats over a 35-day period during which they were gassed with various concentrations of methallyl chloride for fifteen 1-hourly periods three times a week*

Concentration (g./cu.m.)			
0 (control)	12	16	20
2	−4·5	−15·5	−11·5
4	−1·5	−10	−8·5
8	−1·5	−9	−7
8	1	−4·5	−5
8·5	2·5	−3	−5·5
11·5	3·5	−1·5	—
13	3·5	2·5	—
—	5·5	(1 killed)	(3 killed)

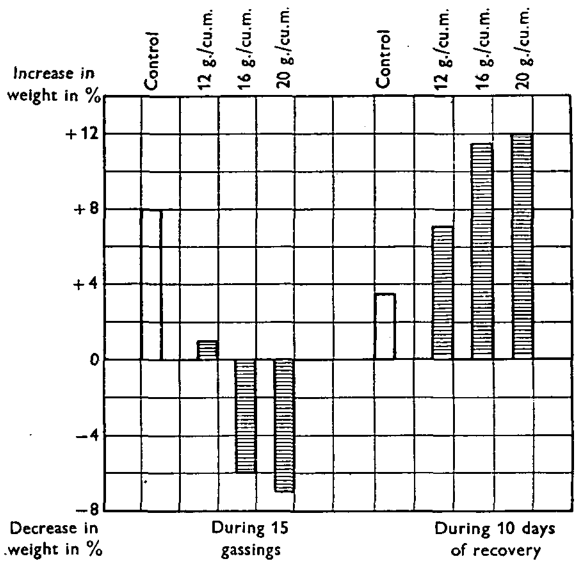

Fig. 1. Influence of the concentration of methallyl chloride applied on the average changes in weight during and after gassings.

exposed to higher concentrations (e.g. 12 and 16 g. per cu.m.) actually lost from 6 to 7 % body weight. It should be remembered that some of the rats died as the result of exposure to these higher concentrations, and that the above data were obtained upon those which survived.

Methyl bromide, on the other hand, had a much more pronounced effect both upon mortality and subsequent growth and development. One hour's exposure to methyl bromide at 8 g. per cu.m. of air resulted in a decrease in body weight. With increasing concentrations of methyl bromide the loss of body weight fell more sharply than with increasing concentrations of methallyl chloride. It should be remembered that all the rats died after three exposures to methyl bromide at 12 g. per cu.m. of air and one exposure at 16 or 20 g.

Table 3. *Showing the effect upon body weight of rats after one and two gassings of 1 hr. each with methallyl chloride and methyl bromide at 12 g. per cu.m. of air*

Changes in weight in percentages after treatment during					
2 days (1 gassing)			5 days (2 gassings)		
Control	Methallyl chloride	Methyl bromide	Control	Methallyl chloride	Methyl bromide
−1	−7·5	−7·5	0	−4·5	−16·5
0·6	−4·5	−7	0·35	−2·7	−10
1	−2·5	−6·5	0·35	−2·5	−6·5
1·4	−1·5	−6	2·5	−1·8	—
1·8	−1·4	−4	2·8	−1·7	—
3	−1·3	−3·5	6	−0·7	—
—	−0·9	—	—	−0·4	—
—	0	(2 killed)	—	0	(5 killed)

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It is clear, therefore, that not only has methyl bromide a much greater residual effect upon growth and development than methallyl chloride at low concentrations, but that it has a much steeper dosage response curve (see Table 4).

It was found during the period when the rats were undergoing successive exposures to methallyl chloride that growth was inhibited. Some of the rats actually lost weight during this period. However, during the period following the cessation of treatment these same rats showed an increased growth rate as compared with controls. This rapid growth rate was sufficient to compensate for any loss or failure to increase in weight during treatment, so that within a few weeks there was no difference in weight between the treated and untreated animals. whereas all the rats survived eight successive exposures to methallyl chloride at the same concentration.

It remains to discuss the relative merits of these materials as fumigants for insects infesting stored products such as grain. In this connexion it must be mentioned that previous work carried out in our laboratory shows that for *Calandra granaria* (1 month old) the minimum lethal concentrations were as follows:

8 g. per cu.m. of air for 20 hr. continuous fumigation with methallyl chloride;

2 g. per cu.m. of air for 20 hr. continuous fumigation with methyl bromide.

Thus the latter is four times as effective as the former and in practice it is necessary to use methallyl

Table 4. *Showing the change in body weight of rats gassed for 1 hr. three times a week with increasing concentrations of methallyl chloride and methyl bromide*

	Changes in weight in percentages after treatment during					
	11 days (5 gassings)		14 days (6 gassings)		2 days (1 gassing)	
Concentration (g./cu.m.) ...	4	8	4	8	12	16
Methallyl chloride	6·5	6·5	8	8·5	−7·5	−2·4
	13·5	17	14	19	−4·5	−2·1
	17·5	23	21·5	28	−2·5	−2·1
	—	—	—	—	−1·5	−2
	—	—	—	—	−1·4	−1·9
	—	—	—	—	−1·3	−1·9
	—	—	—	—	−0·9	−1·9
	—	—	—	—	0	−1·4
Methyl bromide	16·5	−2·5	20	—	−7·5	—
	20	8	22	—	−7	—
	25	9	28	—	−6·5	—
	—	—	—	(3 killed)	−6	—
	—	—	—	—	−4	—
	—	—	—	—	−3·5	—
	—	—	—	—	(2 killed)	(8 killed)

The detrimental influence upon body weight, as well as the subsequent recovery effect is dependent upon the concentration of methallyl chloride to which the animals were exposed. By raising the concentration from 12 to 16 g. per cu.m. of air the toxic effect and recovery rate are greater than occur when the concentration is raised from 16 to 20 g. per cu.m. of air (see Fig. 1). At the low concentrations of 2, 4 and 8 g. per cu.m. of air there is no inhibiting effect upon growth and no subsequent stimulation.

DISCUSSION

The data obtained during this investigation show conclusively that methyl bromide is much more toxic towards rats than is methallyl chloride at the same concentration. Indeed, it has been shown that 1 hour's exposure to methyl bromide at a concentration of 16 g. per cu.m. of air resulted in 100% kill, chloride at four times the concentration of methyl bromide. Thus, if the danger of poisoning should consist only in inhaling the fumigants at the concentrations developed inside grain silos, warehouses, etc., then the lower toxicity of methallyl chloride would not necessarily make it preferable to methyl bromide.

It is known, however, from a study of the literature (Michaux *et al.* 1944–5; von Oettingen, 1946) that only a minority of the cases of poisoning by methyl bromide are caused by accidents during fumigation practice. The risk is confined largely to the chemical processes of manufacture and manipulation, e.g. filling of cylinders, leakages in store houses, etc., which are all independent of the fumigation concentration. In this connexion methallyl chloride has the advantage over methyl bromide, since owing to its characteristic smell its presence

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can be detected even at very low, harmless concentrations. Furthermore, it is physically impossible without the utmost discomfort, which no normal person will tolerate, to inhale methallyl chloride at the concentration necessary to provide adequate fumigation effects. In contrast, methyl bromide is almost odourless even at lethal concentrations. In this connexion it must be mentioned that concentrations of 1 g. of methyl bromide per cu.m. of air must be considered as dangerous to man (Florentin, 1944).

Arguing on the assumption that humans will respond to methallyl chloride and methyl bromide in the same way as rats, the former would have a further distinct advantage in that subjects accidentally exposed to a high concentration for a short time are much more likely to recover than would be the case with exposure to methyl bromide.

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