METHYL BROMIDE POISONING

BY

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Seven cases of methyl bromide poisoning which occurred amongst workers engaged on a fumigation project are described. The methods adopted for investigation of the environmental situation are discussed and the measurement of blood bromide levels on random samples of workers is suggested as an index of the effectiveness of equipment and working methods.

Methyl bromide is a highly volatile liquid which disperses rapidly and readily. As a fumigant it ranks amongst the most efficient because of its extremely effective penetrating power and absence of fire or explosion hazard. It is, unfortunately, highly toxic and poisoning occurs readily in circumstances of careless or inadvertent exposure.

Before 1940, only 42 cases of methyl bromide poisoning had been reported, mostly in Germany. Twelve of these had been fatal. With the advent of the second World War and the use of methyl bromide as a fire extinguisher in ships, a further 26 cases were reported in the Royal Navy with eight fatalities (Clarke, Roworth, and Holling, 1945).

Mazel, Bourret, and Roche (1948) reported an astonishing case which occurred in France where a whole family of five were poisoned, the three children being fatally affected. In this case, the family had continued to occupy part of a house while the rest was being treated.

Present Investigation

A large housing scheme, which involved the construction of some 2,700 houses, was undertaken in Queensland some years ago. Much of the timber (a European soft-wood, prone to infestation by the European house-borer, *Hylotruncus bajulus*) was pre-cut and imported from various European countries.

By 1956, it was obvious that the borer was present in the timber of these houses and it was decided to undertake mass fumigation with methyl bromide.

Method of Fumigation.—Several adjoining houses were evacuated and completely covered by heavy-duty polythene sheeting. Methyl bromide was then run in from cylinders to a concentration of 4 lb./

1,000 ft.³. The sheeting was left untouched for 24 hours. At the end of this time the sheets were lifted and all doors and windows were opened. Tenants were allowed to return after the houses had been aired for not less than three days, and negative readings for halides had been obtained at all points with a halide detector.

About 40 men were engaged in the actual fumigation procedures and a total of between eight and 10 houses were completed daily, depending on weather conditions. Altogether, 2,643 houses were fumigated in a period of 16 months, extending from February, 1958 to May, 1959.

Safety Precautions.—These stated that respirators comprising regulation Army type facepieces (as issued in the period 1941 to 1942) with gas canisters effective against methyl bromide were to be used at all times when exposed to gas. The equipment was inspected by the Department of Industrial Medicine and scientists of the Government Chemical Laboratory; canisters stated to be effective against methyl bromide were inspected and tested before fumigation began. These canisters absorbed high concentrations of chloroform vapour (5 lb./1,000 ft.³) for 34 minutes, and were also found to be capable of absorbing methyl bromide at a concentration of 3.5 lb./1,000 ft.³ for 22 minutes.

A circular letter describing the symptoms of exposure was provided and the usual exhortations for care by the operators were made. Exposure to concentrations of the gas was to be cut to a minimum by proper organization, and only to be allowed during the necessary lifting of the sheeting and the opening of doors and windows.

All the cases to be described occurred amongst men exposed to the greatest concentrations of gas, that is, those men who cleared the houses for

TABLE 1
SUMMARY OF CASES

Case No.	Date of Onset	Period in Hospital	Result	Blood Bromide on Admission (mg./100 ml.)	Electroencephalogram
1	30.4.58	10 weeks	Gross disability	40 (Gold chloride)	Two months after admission; alpha rhythm 9 c.p.s. with faster activity. Occasional symmetrical 5-6 c.p.s. activity from all regions
2	29.5.58	10 days	Epilepsy	25 (Gold chloride)	Five months after admission; no abnormality
3	2.6.58	Not admitted	Recovery complete	2.4 (Conway)	—
4	24.7.58	6 weeks	Moderate disability	13.5 (Conway)	Five months after admission; no abnormality
5	25.7.58	6 days	Recovery complete	7.2 (Conway)	—
6	25.7.58	6 days	Slight residual ataxia	17.6 (Conway)	—
7	26.7.58	6 days	Recovery complete	9.6 (Conway)	—

ventilation after fumigation had progressed for the requisite time.

On April 30, 1958, the first case occurred and was admitted to hospital, with serious methyl bromide poisoning. After this incident, a tightening up of all procedures was planned and an army-type discipline was instituted under a safety officer. However, further cases occurred on May 29, July 1, and July 25.

This outbreak of cases of methyl bromide poisoning was investigated by the Division of Industrial Medicine. An alarming feature was the fact that three of the four cases which occurred on July 25 showed severe erythema of the face under the mask, indicating the presence of free methyl bromide in the inspired air.

The efficiency of the canisters was suspected and tests on those supplied revealed that none of them protected against methyl bromide for more than 30 seconds.

The cases are summarized in Table 1.

Case Histories

Case 1.—While at work he started to vomit and noticed he was short-winded. On the way home, two hours later, he noticed twitching of the muscles of the right leg.

On arrival at hospital he evidenced an epilepsy partialis continuans of the right foot, and right ankle clonus was present; plantars were flexor. While being examined he had two major fits and passed into status epilepticus.

For the next seven days he was unconscious, responding to painful stimuli; peripheral stimuli produced epilepsy partialis continuans of the limbs. His generalized convulsions ceased on the third day, after large doses of sod. phenobarbitone intramuscularly and myanesin intravenously.

On discharge from hospital, 10 weeks after admission, he was still grossly ataxic and was experiencing recurrent Jacksonian motor attacks of the right leg, and local myoclonia of the right arm. His signs have remained unchanged until the present time (May, 1960).

Case 2.—Fourteen hours after completing a fumigation he found he could not keep his balance and was admitted to hospital.

Three epileptiform seizures occurred in the next three days. There was gross intention tremor of the right hand and ataxic gait. His signs cleared up over the following six months, though he has subsequently had several grand mal attacks, and, in addition, episodes which are hysterical in nature. No previous history of fits of any kind could be obtained.

Case 3.—He complained of dizziness, nausea, and red eyes but recovered rapidly. The conjunctival irritation was regarded as evidence of minimal exposure.

Case 4.—He inhaled methyl bromide two hours before admission to hospital. On admission he was drowsy and half an hour later he had a generalized fit. The following day he had generalized convulsions when disturbed. He was unconscious for three days. On regaining consciousness he had visual and auditory hallucinations lasting 24 hours. He manifested a gross tremor in the finger-nose test and ataxic heel-knee test, an increased tone in the limbs, increased deep reflexes, and extensor plantar reflexes.

When examined 10 months later, his left pupil reacted sluggishly to light. There was an intention tremor of the left hand; he walked on a wide base; heel-toe walking was unsteady. There were increased deep reflexes in the arms and cogwheel rigidity at the right wrist. He was experiencing myoclonic jerks in the legs at night. He stated that on one occasion while walking along the road, a pipe was dropped near him and he was suddenly and spontaneously thrown to the ground.

Case 5.—While fumigating he noticed dizziness. Next morning, on getting out of bed, he suffered violent shaking, commencing in the left foot, which spread up his leg and was of such force as to throw him backwards.

On examination, he had nystagmus and any movement of the left foot produced an epilepsy partialis continuans which at intervals progressed to a Jacksonian motor attack.

Case 6.—In this case also there was a latent period of 12 to 18 hours after fumigation before unsteadiness in walking and incoordination of the left arm were noticed.

Six months after admission he was slightly unsteady on heel-toe walking.

Two days after admission to hospital he developed a Jacksonian motor attack in his left leg, which spread to involve the left arm.

Case 7.—This case had a latent period of 12 to 14 hours after fumigating. He then complained of dizziness and was unsteady on his feet. There was incoordination of the left arm and ataxia in heel-toe walking.

The Tests

When four cases occurred in one day (24/25 July, 1958) it was realized that the fault could not lie in carelessness unless there had been a complete breakdown in discipline. As it was known that this was not the case, and the men were all cognizant of the severity of poisoning as a result of Case 1, the canisters were suspected and a test was made by using a fully gassed house as source of supply of methyl bromide at 4 lb./1,000 ft.³.

The canisters were connected to a Willson pump adjusted to a flow-rate of 15 litres per minute, though some tests were run at 20-22 litres. The inlet valve was either connected to a pipe passing under the sheet, or the canister itself placed within the canopy. The other end of the canister was led via the pump to a 4-gallon drum with a relatively narrow opening. The tubing was let down to the bottom of the drum and the air supply nozzle of a halide lamp was let down to just within the opening.

Breakdown of a canister was accepted on the first showing of a light green halo on the halide lamp.

Tests were carried out on the same apparatus by human aspiration in lieu of the pump, utilizing the same apparatus but substituting an Erlenmeyer flask for the drum. It was reasoned that, in view of the rapid breakdown, the smaller the volume inhaled, the better it would be for the volunteer.

All canisters were found to break down from 30 seconds to one minute, and to allow 200-500 parts per million to pass after this time. The canisters of all seven cases (including Case 1 whose canister had been retained) showed no protection whatever.

It was concluded, therefore, that all the affected men had been breathing methyl bromide vapour in concentrations up to 4 lb./1,000 ft.³ for short periods during fumigation operations, and this was sufficient to cause severe poisoning in two cases.

The fact that the faces of three men were burnt within the area of face covered by the respirators indicates that the gas must have been coming through the canisters. There did not seem to be any reason to suspect that masks were ill-fitting or that gas could have passed under the edges of the face-pieces.

Method of Estimating Bromide in Body Fluids

Gold Chloride Method is an easy and convenient method for estimating intoxication with metallic bromides or ammonium bromides. It is suitable only for the higher levels from 25 to 200 mg./100 ml.

Fluorescein Test is inaccurate and merely indicates levels above or below 5 mg./100 ml.

Conway's Micro-diffusion Method (Conway, 1950) is the only method suitable for the estimation of blood bromides in methyl bromide poisoning. The tolerances possible with colorimetric methods such as the gold chloride method are not accurate enough for levels below 10 mg./100 ml. Symptoms of poisoning are possible at levels as low as 2.8 mg./100 ml., and severe symptoms at as little as 12 mg./100 ml. The supervision of workers engaged in large scale operations should include blood bromide surveys of random groups at frequent intervals. Blood bromide levels enable an estimate to be made of the efficiency of safety precautions and of safety equipment. The method is accurate enough to define exposure fairly exactly, particularly so when a man presents with symptoms which are not specific. A negative finding will exclude methyl bromide as the cause.

It is, therefore, emphasized that for the purposes of supervision, where levels of blood bromide below 5 mg./100 ml. are to be expected, the micro-diffusion method of Conway is mandatory.

The results of bromide estimations are given in Table 2.

From the experience gained in the situation described it is clear that the presence of bromide in the blood of any worker should indicate the need for a reinspection of equipment, examination of precautions, and a search for the responsible flaw.

In this case, the certainty that strict precautions were being followed led to an examination of the equipment, with the discovery that the canisters offered no protection from the gas. As a result, the total consignment was condemned and a reliable and well-known make substituted. Preliminary tests on these canisters showed full protection for more than an hour at a concentration of 4 lb./1,000 ft.³ After these canisters were used, no man showed the slightest trace of bromide in the blood after working continuously in exposed situations.

Discussion

The mechanism of action of methyl bromide was discussed by Clarke *et al.* (1945) who showed that there is no apparent relationship between methanol and sodium bromide poisoning and methyl bromide poisoning. In summary, amblyopia is never found

TABLE 2
BROMIDE ESTIMATIONS

Case No.	Date	Method	Blood Bromide (mg./100 ml.)	Cerebrospinal Fluid Bromide (mg./100 ml.)	Urine Bromide (mg./100 ml.)
1	30. 4.58	Gold chloride	40	—	—
	1. 5.58	Gold chloride	40	—	—
	1. 5.58	Gold chloride	—	15	—
	2. 5.58	Gold chloride	40	—	—
	5. 5.58	Gold chloride	25	—	—
2	6. 6.58	Gold chloride	nil	—	—
	29. 5.58	Gold chloride	25.0	—	—
	2. 6.58	Conway	12.0	4.5	—
3	6. 6.58	Conway	4.8	—	—
	19. 6.58	Conway	2.4	—	—
	1. 7.58	Conway	2.4	—	—
4	31. 7.58	Conway	1.5	—	—
	10.10.58	Conway	nil	—	—
	25. 7.58	Conway	13.5	—	—
5	28. 7.58	Conway	6.0	8.0	1.6
	6. 8.58	Conway	4.8	—	—
	5. 9.58	Conway	1.5	—	—
6	25. 7.58	Conway	7.2	—	—
	28. 7.58	Conway	7.2	—	7.2
	8. 8.58	Conway	1.0	—	—
7	12. 9.58	Conway	Undetectable	—	—
	26. 7.58	Conway	17.6	—	—
	28. 7.58	Conway	12.0	—	13.6
7	6. 8.58	Conway	8.4	—	—
	26. 7.58	Conway	9.6	—	—
	28. 7.58	Conway	6.4	—	3.0
7	8. 8.58	Conway	1.5	—	—
	31.10.58	Conway	nil	—	—

in methyl bromide poisoning, nor do fits occur in methanol poisoning. Clarke *et al.* (1945) concluded that some unknown decomposition product is the responsible factor, but in our opinion, there is no need to postulate any more complicated chemical action than a direct attachment to intracellular protein moieties.

The medicinal or water soluble bromides (NaBr, KBr, NH₄Br) do not cause toxic symptoms until a blood level of at least 50 mg./100 ml. is reached. In a general way, the symptoms overlap those of methyl bromide poisoning, but complete recovery is the rule in therapeutic overdosage with bromides.

The presumption is that methyl bromide attaches itself to protein molecules as do the heavy metals, and probably attaches itself to the sulphhydryl groups. Its affinity appears to be for the conjugated intracellular proteins which comprise the complex enzyme systems.

The general disturbance of the central nervous system in acute poisoning may be explained on this basis of interference with essential intracellular metabolic processes. The gradation of severity with exposure, and the known possibility of recovery from minimal absorption, may be explained as recovery of partially damaged cells gradually returns to normal levels. Where, however, destruction of any cellular system has been complete, residual damage is permanent.

Methyl bromide has a fairly specific effect on cortical, cerebellar, and basal ganglion structures, and is probably first absorbed in the extracellular

fluid and slowly diffuses into the cells and interferes with their metabolism, affecting the enzyme system which controls intracellular oxidative reactions. In low concentrations, it is irritative and in higher concentrations paralytic; its action thus depends on the concentration of the conjugated methyl bromide complex in the cells.

On this basis, it was decided to use B.A.L. in all cases admitted to hospital, and though Case 1 only had B.A.L. late in the recovery phase, all subsequent cases were treated with B.A.L. as routine. All the seven cases in this series survived.

In all cases there was a latent period between exposure and the onset of neurological symptoms and signs. In the milder cases these took the form of giddiness, epileptic attacks, which in some cases were continuous, and ataxia. In the more severe cases there was unconsciousness, with pyramidal and extra-pyramidal signs. In the severe cases the neurological signs persisted (Cases 1, 2, 4, and 6).

The portions of the central nervous system which were chiefly affected were the cerebral cortex, the basal ganglia (pallidum), the cerebellum, and probably the red nucleus (Dechaume, Bourrat, Schott, and Buffard, 1948).

The time of onset of neurological symptoms varied from two to four hours after exposure. A sweet odour of the breath was noticeable for some days after admission to hospital. Cases 1 and 4 showed a cyanotic tinge in the skin which was present before the onset of any evidence of pulmonary oedema. The early exhibition of B.A.L. in such cases possibly

TABLE 3

BLOOD BROMIDES: RANDOM SAMPLES ON WORKERS USING OLD TYPE CANISTERS UP TO AUGUST 29, 1958

Date	Blood Bromide (mg./100 ml.) (Conway)	Remarks
3.6.58	8	Dizziness, nausea for 48 hrs.; quite well thereafter; blood bromide 3.5 mg./100 ml. (14.6.58); removed from exposure
3.7.58	5.5	Dizziness only; removed from exposure; blood bromide 0.5 mg./100 ml. by Sept. and not detectable in October
10.7.58	3.6	No symptoms
10.7.58	1.2	No symptoms
10.7.58	0.8	No symptoms
10.7.58	0.8	No symptoms
24.7.58	1.2	No symptoms
31.7.58	0.5	No symptoms
14.8.58	1.6	No symptoms
21.8.58	1.2	No symptoms
21.8.58	1.2	No symptoms
29.8.58	0.4	No symptoms
29.8.59	1.8	No symptoms
12.9.58	3.2	Accidental spillage; no symptoms

prevents the condition from becoming irreversible.

Despite the fact that all cases suffered directly in relation to apparent exposure, only the two most severely affected had any pulmonary signs. Case 1 had a marked bronchorrhoea during the first four days after admission and Case 4 had basal crepitations for three days.

Large doses of intramuscular phenobarbitone and intravenous myanesin were required to control the fits in these two cases. Pulmonary oedema was combated by nursing on a rotor bed to facilitate bronchial drainage, with bronchial aspiration at the first stage of moist lungs.

Most of the cases of poisoning with severe neurological signs seem to be dependent on a sudden exposure to large concentrations, following continuous slight exposure. Such cases usually escape pulmonary oedema, though this is not invariable. Irish, Adams, Spencer, and Rowe (1941), suggested that careful animal investigations might lead to improved treatment in man.

Casualties have continued to increase, as the literature demonstrates.

From the end of August, 1958 to May, 1959, when fumigation was completed, a further 82 men were examined. Bromides were not detected in the blood in any of them, as contrasted with Table 3. The new type canisters were introduced on August 29, 1958.

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