Industrial Health 2011, **49**, 133–138

Field Report

Occupational Exposure in Methyl Bromide Manufacturing Workers: 17-year Follow-up Study of Urinary Bromide Ion Concentration for Biological Monitoring

Yuko YAMANO[1]*, Tomoko TOKUTAKE[2], Sumiko ISHIZU[2] and Toshio NAKADATE[1]

[1]Department of Hygiene and Preventive Medicine, Showa University School of Medicine, 1–5–8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan

[2]Department of Hygiene and Public Health, Tokyo Women's Medical University, 8–1 Kawada-cho, Shinjuku-ku, Tokyo 162-8111, Japan

Received September 3, 2009 and accepted May 21, 2010

Abstract: To elucidate the circumstances of their occupational exposure to methyl bromide (MeBr), we conducted a 17-yr study on 124 workers employed by a MeBr manufacturer. Subjects were classified into three groups according to the nature of their work: synthesis group, filling group, and other group. Urinary concentrations of bromide ion (Br^-) were assessed, and data attained via MeBr-health examinations were analyzed. The highest Br^- concentrations were seen in the synthesis group, with a median value of 13.0 μg/mg CRE (2.5–51.8), followed by the filling group, with a concentration of 11.9 μg/mg CRE (3.1–34.8). Both values were significantly higher than the levels noted in the other group ($p<0.001$). Three major opportunities for exposure were identified: during exchange of reaction equipment for maintenance or cleaning, during operations to adjust for weight variations after filling canisters, or when canisters were recycled. Overall, however, the workplace environment concentration remained largely below the administrative control level throughout the study period. Therefore, while this was a relatively well-controlled workplace, exposure opportunities still arose when performing certain tasks, indicating the need for ongoing improvement in workplace procedures and underscoring the importance of biological monitoring.

Key words: Methyl bromide, Occupational exposure, Urinary bromide ion, Biological monitoring, Follow-up study

Introduction

Methyl bromide (MeBr) has been widely used as a fumigant for plant quarantine and as a soil fumigant[1)]. At the 1992 meeting of the signatory states to the Montreal Protocol, however, the compound was designated as an ozone-depleting substance, and its use in soil fumigation was to be fully phased out in advanced countries by 2005, and in developing countries by 2015[2)]. In Japan, production has since shrunk to less than approximately 20% of the peak level[3)]. Given the absence of alternatives, however, its use has been permitted even after phase-out in applications for quarantine treatment, pre-shipment processing, certain essential applications, and emergency treatment[4)], and production is set to continue in the future.

Over the past 17-yr, we have treated 112 cases of MeBr poisoning in 67 events[5)]. By occupation, 41.8% of cases occurred in agricultural workers exposed during soil fumigation, 22.4% in workers engaged in pest eradication when fumigating museums or other institutions,

---

*To whom correspondence should be addressed.
E-mail: yamano@med.showa-u.ac.jp

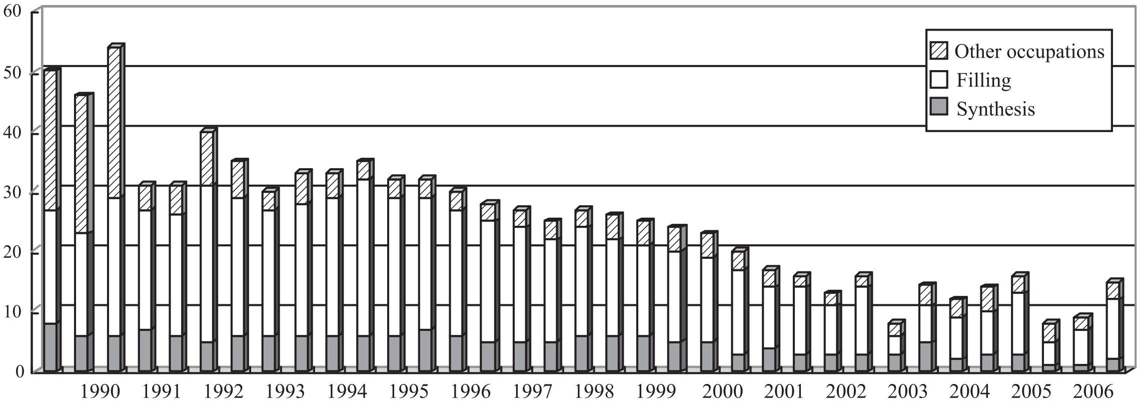

Fig. 1. Number of subjects by type of work.

and 16.4% in workers engaged in MeBr manufacture (including exposed asymptomatic individuals). At present, although the number of incidents in the manufacturing setting has markedly decreased[6], the circumstances under which exposure can occur remain unclear.

Here, we report the results of a 17-yr follow-up study conducted among a group of MeBr manufacturing workers to determine how much actual exposure they received, and if they had been exposed, how the exposure occurred.

Subjects and Methods

Subjects

The present study involved employees at a factory that primarily manufactured MeBr. They had undergone special health examinations for MeBr in accordance with the Ordinance on Prevention of Hazards Due to Specified Chemical Substances[7] (MeBr-health examination). The study was conducted over 17-yr (1989 to 2006) and involved a total of 124 subjects aged 18 to 64-yr. Number of years worked ranged from 0.3 to 16 yr, and the mean number of measurements was 6.0 ± 6.0 (range: 1–31). Changes in the number of subjects at each measurement time-point are shown in Fig. 1.

Analytical methods

Urine and blood samples were collected at MeBr-health examinations conducted biannually, and bromide ion concentrations were measured by headspace gas chromatography (HS-GC)[8]. Serum or urine samples and dimethyl sulfate were placed in a reaction vial, which was then incubated at 85°C for 10 min. After incubation, 1 ml of headspace gas was injected into the GC unit. Urinary bromide ion (Br^-) concentration (μg/mg CRE) was divided by the corresponding individual urinary creatinine concentration to correct for variation in urine dilution. In accordance with the workplace environment measurement standards[9], the concentration of MeBr in the workplace (Measurement A) was determined biannually by analyzing samples obtained at 15 sites within the MeBr synthesis workplace (synthesis workplace) and 11 sites within the gas filling workplace (filling workplace). An atmospheric sample was captured in a tedlar bag, and its FID-GC data were used in analyses.

Statistical analysis

Subjects were divided into three groups according to the nature of their work (synthesis group, filling group, and other group). Br^- concentration by type of work was analyzed using the Kruskal-Wallis method, taking each worker's average concentration as that worker's representative characteristic. Changes in MeBr concentration in the workplace environment over time were analyzed by repeated measures ANOVA with log transformation. SPSS *v*.10.1 statistical software was used, and differences of $p<0.05$ were regarded as significant.

Results

Analysis showed that median urinary Br^- concentration for all three groups over the 17-yr period was approximately 11 μg/mg CRE; however, particularly high values were observed in the synthesis group (Fig. 2). Analysis by work type showed median values of 13.0 μg/mg CRE (2.5–51.8 μg/mg CRE) in the synthesis group, 11.9 μg/mg CRE (3.1–34.8 μg/mg CRE) in the filling group, and 7.2 μg/mg CRE (1.7–14.6 μg/mg CRE) in the other group (Fig. 3). Levels in the synthesis and filling groups were significantly higher than that in the other group ($p<0.01$). Further, with ≥30 μg/mg CRE provisionally defined as "high", based on the range of Br^- levels in the normal range (1.2–27.8 μg/mg CRE[8]), high levels were noted in 16.3% of individuals in the synthesis group and 6.9% in the filling group

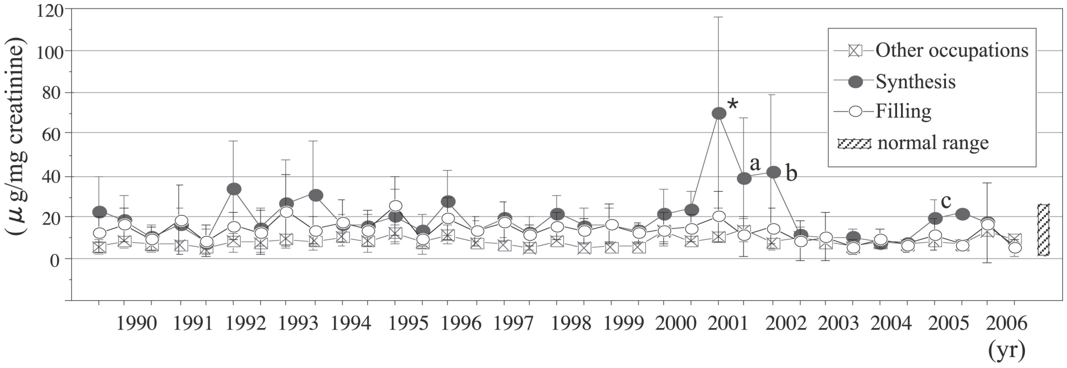

Fig. 2. Change over time in urinary bromide ion concentration by type of work (mean ± SD).
(a) The workplace environment MeBr concentration reached 39.8 ppm when three workers had been replacing activated carbon for decolorizing MeBr. (b) The workplace environment MeBr concentration reached 25.5 ppm, when four workers were cleaning the synthesis reaction tanks. (c) The workplace environment MeBr concentration reached 14.0 ppm when workers inhaled gas leaking from a MeBr canister. (*)The cause of the high concentration is unknown.

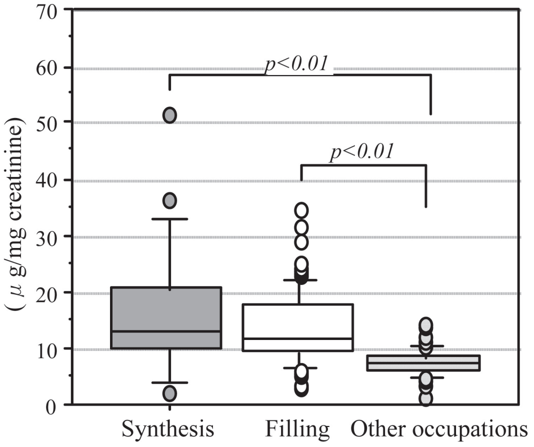

Fig. 3. Box and whisker plot of urinary bromide ion concentration by type of work.
For each box, the middle line represents the median. The box encompasses the 75th through 25th percentiles, and the arrows are at the 90th and 10th percentiles, respectively.

Table 1. Percentages of high levels of urinary bromide ion concentration by control classes

Control class	Synthesis group %	Filling group %
1	11.8%	5.7%
2	22.2%	10.1%
3	38.1%	6.9%
Totals	16.3%	6.9%

(≥30.0 μg/mgCRE)

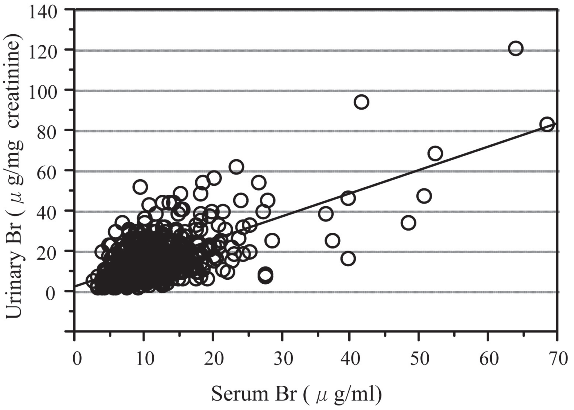

Fig. 4. Relationship between serum and urinary bromide ion concentration.
($y = 1.156x + 2.348$, $R^2 = 0.443$)

(Table 1). In contrast, no high levels were observed in the other group. Further, with regard to control classes, a high percentage of high levels was also noted in control classes 2 and 3, with respective values of 22.2% and 38.1% for the synthesis group and 10.1% and 6.9% for the filling group (Table 1). Serum bromide ion concentration was significantly correlated with urinary concentration ($p<0.01$) (Fig. 4) and showed similar changes in trend.

No remarkable changes in MeBr concentration in the workplace environment were observed over time in any area. Further, no significant differences in MeBr level were noted between the synthesis and filling workplaces (geometric mean: 0.68 and 0.77 ppm respectively; Fig. 5). On calculation by control class, results showed that respective proportions for Classes 1, 2, and 3 were 80%, 10%, and 10% for synthesis workplaces and 65%, 25%, and 10% for filling workplaces.

Discussion

The factory in the present study develops and produces chemicals, protective respiratory equipment, and

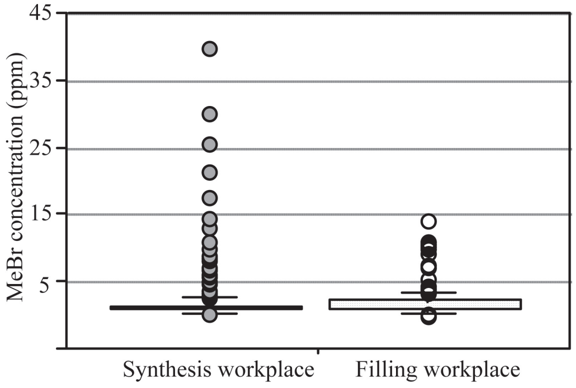

Fig. 5. Box and whisker plot of the workplace environment MeBr concentration is represented classified by workplace type. For each box, the middle line represents the median. The box encompasses the 75th through 25th percentiles, and the arrows are at the 90th and 10th percentiles, respectively.

Fig. 6. Filling a canister with methyl bromide. The hood is lifted and the gas injector is adjusted manually.

fumigants, specializing in the manufacture of MeBr fumigants. In the 1990s, annual production of MeBr at this factory amounted to some 4,000 tons, but volume gradually decreased after MeBr was designated as an ozone-depleting substance in the Montreal Protocol[2)], and production is presently approximately 450 tons. For this reason, the number of subjects targeted for the present study was in constant flux, shrinking during the study period from 50 to 15 (Fig. 1).

Measurement of urinary Br^- concentration over the 17-yr period (Fig. 2) showed that levels remained within the normal range, at approximately 11 μg/mg CRE for all three groups, with no change in work schedule or ventilation. However, high levels were occasionally observed among individuals in the filling and synthesis groups, and comparison across the entire period also revealed that the highest levels in the entire study occurred in the synthesis group, followed by the filling group (Fig. 3). In contrast, no high levels were seen in the other group.

Subjects in the synthesis group were involved in the manufacture of MeBr. Since the reactive process is usually fully closed, exposure to MeBr should theoretically not occur. However, it was found that exposure could occur during maintenance of the reactive system, when piping and tanks are changed out for cleaning or replacement. Further, the route of exposure may have involved not only the inhalation of gas, but also absorption of liquid MeBr through skin. In addition, since bromine, methanol, and sulfur are reacted together and heated during MeBr synthesis, we hypothesized that workers were exposed not only to MeBr, but to bromine itself as well.

Subjects in the group with second-highest levels, the filling group, were mainly involved in filling cylinders or canisters with MeBr gas. While no exposure was found to occur during filling cylinders, we did notice a number of exposure opportunities in filling canisters. Canister filling is usually carried out using an automated filling apparatus in a draft chamber. However, after filling, the canisters are weighed, and if any variation in weight is noted, the piston spring of the MeBr gas injector is adjusted manually (Fig. 6), providing an exposure opportunity. In addition, when MeBr canisters are recycled, they are first cooled in a freezer, and then an opening is made in the canister with a piston, and the MeBr liquid inside is separated from the canister by an un-masked operator, representing yet another exposure opportunity.

No significant differences were noted between the Br^- values in other group and the normal values. The other group' work involves the synthesis of agrichemical intermediates or pharmaceuticals using bromine or other organic solvents, or occupations in which analytical tests are performed for quality control of manufacturing processes or products. Occasionally, however, these subjects assist in synthesis or filling operations and are therefore also subject to health examinations. Given the present results, we concluded practically no opportunities for exposure in these subjects.

For all workplaces, results of measuring administrative areas showed that Class 1 and 2 areas comprised 90% of the total, and throughout the entire study period, most control levels were less than 5 ppm (ACGIH, changed to 1 ppm from April 1, 2009). Thus, the working environment appeared to be largely well maintained. However, over the 17-yr study period, occasion presented itself when the level of exposure exceeded the Administrative Control level, with maximum detected values of 39.8 ppm in the synthesis workplace and 14.0 ppm in the filling workplace.

At the time when the workplace environment MeBr concentration was 39.8 ppm, three workers in the area of the synthesis workplace with this level (Class 3) had been replacing the activated carbon for decolorizing the MeBr, although the workers had been under constantly ventilated conditions. Br^- concentrations at this time were 68.7, 34.2, and 38.4 μg/mg CRE for each of the workers (Fig. 2-a), and serum bromide ion concentrations were appreciably high, at 52.3, 48.3, and 36.2 μg/ml, respectively. At another point, when the detected workplace environment MeBr concentration was 25.5 ppm, four workers were found to be involved in cleaning the synthesis reaction tanks. Br^- concentration in these workers at this time ranged from 22.6–83.4 μg/mg CRE, and serum bromide ion concentration ranged from 20.7–68.5 μg/ml, values higher than normal values or those measured on joining the company (urine:10.1 ± 4.8 μg/mg CRE, serum: 3.7 ± 1.5 μg/ml; Fig. 2-b). In addition, when a level of 14 ppm was detected in the filling workplace, gas leakage from a MeBr canister was noted; however, workers' Br^- concentration remained low in this instance (range: 3.0–22.3 μg/mg CRE; Fig. 2-c). Of further note, no subjective symptoms were reported in any of these instances.

Taking into account the above three examples noted on MeBr health examination, reported MeBr exposure at this factory over the past 17-yr has totaled 10 events involving a total of 32 individuals (unpubished data). Although the average urinary Br^- concentration for these cases was 25.2 ± 18.7 μg/mg CRE (3.0–125.5 μg/mg CRE), admittedly significantly higher than the normal value, many workers appeared unaware of their exposure; further, even if they were aware of exposure, as mentioned above, many experienced no subjective symptoms, which made health care control difficult. A number of instances were noted where exposure was evident after questioning workers who showed elevated levels in Br^- concentration measured at the MeBr-health examinations. These above observations appear to underscore the importance of measuring urinary Br^- concentration during biological monitoring.

With regard to the relationship between poisoning symptoms and Br^- concentration, no correlation was occasionally noted[11, 12]; indeed, some individuals found to have a relatively high Br^- concentration were completely asymptomatic, while others in whom a low concentration was detected still exhibited symptoms[13]. Results from animal studies have shown that lethal and survival dosages are similar[14, 15], and other reports have suggested that symptom onset susceptibility may differ between individuals[16, 17]. Given the findings from the present and previous studies, we conclude that the safety margin for MeBr is narrow, and that poisoning may still occur even with minor differences in exposure dosage.

In the present study, only three workers experienced subjective symptoms: one was working in the filling group when liquid leakage occurred during recycling of a MeBr canister, resulting in burned hands and a Br^- concentration of 56.2 μg/mg CRE; the second was a worker in the synthesis group who came into contact with liquid MeBr when replacing synthesis pipework, sustaining a burn to the head and showing a low Br^- concentration of 11.5 μg/mg CRE; the third was a worker in the filling group who sustained inhalation exposure during removal of MeBr from a canister while not wearing a mask, reporting feeling dizzy and having a Br^- concentration of 39.5 μg/mg CRE. Symptoms of exposure to MeBr can be diverse, ranging from mild symptoms[15, 18] such as headache, nausea, vomiting, or burn wounds, to neurological symptoms[6, 19] such as intention tremors, action myoclonus, and convulsions, and in serious cases, even death[20]. In the factory involved in the present study, however, no serious cases have been reported.

Conculusion

In the present study regarding exposure opportunities at a MeBr manufacturing plant, urinary Br^- concentration results demonstrated that exposure may occur, albeit in minute amounts, even in a relatively well-controlled work environment without subjective symptoms. Further, workers are at risk of high-concentration exposure when performing certain tasks. In the future, measurement of urinary concentrations of bromide ions as biological monitoring combined with comprehensive work environment control and work practice management will likely be necessary to achieve effective health management.

References

1) Ministry of Agriculture, Forestry and Fisheries, and Plant Protection Division, Agricultural Production Bureau (2008) Noyaku Yoran 2008. Japan Plant Protection Association, Tokyo (in Japanese).
2) UNEP (2000) Handbook for the International Treaties for the Protection of Ozone Layer. The Montreal Protocol, 5th Ed., 42–3, UNEP, Nairobi.
3) Ministry of Agriculture, Forestry and Fisheries, and Plant Protection Division, Agricultural Production Bureau (1991–2006) Noyaku Yoran. Japan Plant Protection Association, Tokyo (in Japanese).
4) UNEP (2004) Report of the sixteenth meeting of the parties to the Montreal protocol on substances that deplete the ozone layer, 43–6, UNEP/OzL.Pro., Nairobi.

5) Yamano Y (2008) The measures for health effects caused by chemical substances. Methyl Bromide. Digest of Science of Labour **63**, 222–6 (in Japanese).
6) Yamano Y, Nakadate T (2006) Three occupationally exposed cases of severe methyl bromide poisoning: accident caused by a gas leak during the fumigation of a folklore museum. J Occup Health **48**, 129–33.
7) Ordinance on Prevention of Hazards Due to Specified Chemical Substances (1972) (in Japanese).
8) Yamano Y, Ito I, Nagao N, Ishizu S (1987) A simple determination method of bromide ion in plasma of methyl bromide workers by head space gas chromatography. Sangyo Igaku **29**, 196–201 (in Japanese).
9) Goverment of Japan (2005) Working Environment Measurement Law. Working environment measurement system in Japan (in Japanese).
10) American Conference of Governmental Industrial Hygienists (1999) TLVs and BEIs Threshold limit values for chemical substances and physical agents and biological exposure indices. ACGIH, Cincinnati.
11) Minami M, Hirata Y (1986) Methyl bromide poisoning. Nippon Ika Daigaku Zasshi **53**, 129–36 (in Japanese).
12) Kishi R, Itoh I, Ishizu S, Harabuchi I, Miyake H (1991) Symptoms among workers with long-term exposure to methyl bromide. An epidemiological study. Sangyo Igaku **33**, 241–50.
13) Ishizu S (1989) Human toxicity of methyl bromide. In: Methyl bromide poisoning, Ishizu S (Ed.), 26–98, Japan Fumigation Technology Association, Tokyo (in Japanese).
14) Yamano Y (1991) Experimental study on methyl bromide poisoning in mice. Acute inhalation study and the effect of glutathione as an antidote. Sangyo Igaku **33**, 23–30 (in Japanese).
15) Organisation for Economic Co-operation and Development (OECD) (2001) SIDS Initial Assessment Report for 13th SIAM, November 6–9, Bern.
16) Thier R, Wiebel FA, Bolt HM (1999) Differential substrate behaviours of ethylene oxide and propylene oxide towards human glutathione transferase theta hGSTT1-1. Arch Toxicol **73**, 489–92.
17) World Health Organization (1995) International Programme on chemical safety: methyl bromide. Environmental Health Criteria 166, 1–127, World Health Organization, Geneva.
18) Alexeeff GV, Kilgore WW (1983) Methyl bromide. Residue Rev **88**, 101–53.
19) Uncini A, Basciani M, Di Muzio A, Antonini D, Onofrj M (1990) Methyl bromide myoclonus: an electrophysiological study. Acta Neurol Scand **81**, 159–64.
20) Hine CH (1969) Methyl bromide poisoning. A review of ten cases. J Occup Med **11**, 1–10.