Methyl Bromide – toxicology review and proposal for BEI (blood)

Clinical effects

Methyl bromide is a colourless gas, used in fumigation because of its insecticidal properties, effective penetrating power, and lack of explosive hazard. Extensive experience suggests that significant adverse effects do not occur at average exposures of 5 parts per million (5 ppm or 0.0005 %) in air over an eight hour period,[1] (provided fluctuations around this value are limited). While it can be highly toxic both to the lungs and internally, particularly to the nervous system, the great majority of reports indicate that higher concentrations than 5ppm are required for such effects, particularly with exposure durations much shorter than 8 hours. On the other hand, isolated reports suggest the possibility of subtle effects with prolonged exposure to levels below 5 ppm,[2] but this is not a commonly held view.

Its "odour threshold" is above 5 ppm.[3] One estimate is 65 mg/m3 (~ 16.5 ppm)[4] though others range from 20 ppm up to 940 ppm.[5] Therefore odour detection is not sufficient to provide adequate warning against potentially toxic levels, so that chloropicrin is often added. However there is some evidence that in certain circumstances it cannot be relied on (see Appendix). Charcoal filters in respirators may also preferentially remove chloropicrin, presenting a risk of loss of warning with prolonged use.[6] The quality of respirator fit is recognized as very important. Methyl bromide is three to four times heavier than air, and can spread efficiently near ground level. Hidden underground pipes have been a source of unforeseen exposure and fatalities.

In milder acute exposures, nausea, vomiting, headache and some confusion are not uncommon. However the clinical picture in acute or acute-on-chronic poisoning is very variable. Fatigue, visual disturbances, nausea and vomiting are frequent, and dizziness (or a "floating" sensation), incoordination, tremors, ataxia, and other neurological effects (including myoclonic contractions)[7] may develop. Higher acute exposures can cause increasing loss of coordination and disturbance of gait, followed by progressive coma and/or convulsions;[8] the latter can be resistant to pharmacological treatments.[9]

Pulmonary symptoms are comparatively slight in mild poisoning. Irritation and burning of the nose, throat, and upper airways can occur. Moderate to severe exposure causes chest pain and breathlessness, which may be secondary to an inflammatory bronchitis, with or without pulmonary oedema, which can be prominent at high exposures. (Unless the concentration is extreme enough to cause rapid narcosis and death from associated respiratory failure, the most striking response to high concentrations is pulmonary congestion and oedema).[10] There may be complicating bronchial pneumonia.

Hepatic and renal[11] effects are occasionally described. The combination of hepatomegaly and encephalopathy may occasionally resemble Reye syndrome.[12]

The onset of (at least some) acute symptoms may be delayed, with latent periods ranging from 2 to at least 48 hours.

Neurological deficits may persist after recovery from the severe acute stage. Long term sequelae also include an organic brain syndrome and neuropsychiatric symptoms, such as anxiety, depression, and inability to concentrate.[13] The "recovery stage" may last for years, with hallucinations, apathy, amnesia, aphasia, and incoordination.[14]

Chronic exposure to relatively low concentrations (below 35 ppm) can result in behavioural and neurological effects, including headache, visual disturbance, general malaise, weakness and ataxia.

There is a small risk of adverse effects from relatively low chronic exposures, even in the absence of any obvious accidental over-exposure incidents. At least two such cases have been described involving cerebello-vestibular and pyramidal tract signs and visual defects, followed by peripheral neuropathy.[15] The latter can result in persistent numbness in the hands and legs, impaired sensation, reduced distal deep tendon reflexes, and muscle weakness. (Given the lack of high exposure accidents or chronic symptoms in one case, other etiologies were suspected and some investigated, but were not identified).[16] The neuropathy is reported as due to axonal degeneration (of the dying-back type, consistent with impairment of axonal transport mechanisms),[17] but with acute poisoning, demyelinisation (possibly secondary) is also described.[18]

Behavioural disturbances and psychometric dysfunction are also described, both with acute poisoning[19] and lesser, more chronic exposures.[20]

No evidence was located to suggest that it has been a cause of motor neuron disease.

The liquid is a strong irritant, and direct splash contact, especially if repetitive, results in a burning or tingling sensation, followed in severe cases by numbness and aching. There may be initial erythema, followed by blistering (vesication) and first or second degree burns, appearing after 2 to 12 hours.[21,22] The blisters may be very large, and burns severe, but they are rarely deep enough to destroy the entire skin layer. Lesser but repetitive exposures can cause a severe itchy dermatitis.[23] The liquid has penetrated through all articles of clothing to cause extensive vesication and superficial burns.

Dermal absorption of liquid sufficient to cause serious systemic effects has been described with heavy skin contact.[24] However in some cases, a contributory effect from inhalation cannot be excluded. In contrast, in one incident involving gaseous exposure, with no apparent opportunity for additional respiratory uptake, the evidence suggested only very limited dermal absorption of this form. (An estimated airborne skin exposure of 10,000 ppm gas for ~ 40 minutes resulted in an average plasma bromide level of 9 mg/L, falling to 6.8 mg/L 12 hours after exposure).[25] It is considered that significant dermal absorption of gas is only likely with extremely high air levels; symptoms are reported at levels > 8000 ppm.

On the other hand, high concentrations of gas (~40 g/m^3 or ~ 10, 000 ppm) has caused local dermal effects, including early erythema followed about eight hours later by

oedema and multiple vesicles, sometimes merging into large bullae.[26] Moist areas and/or those most subject to mechanical trauma were much more affected. Leucocytosis and in some cases moderate fever was noted.

The liquid can cause severe corneal burns but the vapours do not appear to be very painful. (However the commonly used additive, chloropicrin, can cause intense conjunctival irritation).

Toxicity and "dose-response relationships"

Likely mechanisms explaining methyl bromide toxicity include direct cytotoxicity, and methylation of sulfhydryl groups, such as those present in proteins, as these are key determinants of the structure and hence activity of enzymes.

There are inconsistencies between various estimates of the relationship between airborne levels and effect severity. Consequently there is some uncertainty regarding the "dose-response relationship".

However there appears little evidence to suggest that concentrations of 4 to 5 ppm (15 to 19 mg/m^3) even over several hours have caused adverse effects in occupational contexts. On the other hand, exposure for two weeks at levels "generally below 35 ppm" have been associated with toxicity.[27, 28] Effects described were nausea, vomiting, headache, other mild systemic symptoms, and skin lesions.[29]

Severe poisoning with some fatalities have been associated with greenhouse operations, but the concentrations occurring during this application have varied between 30 to 3,000 ppm;[30] and 8,000 ppm over a few hours (or higher levels for shorter times) are considered more typical fatal exposure levels,[31] though even 600 ppm for several hours is considered potentially fatal.[32] An estimated level of 4,500 ppm for one hour caused long-term neurological effects in one case.

Occupational exposures and workplace exposure standards

In many cases of acute or acute-on-chronic poisoning, the severity and duration of exposure have not been known accurately. With greenhouse fumigation, levels may vary from 30 to 3000 ppm, though more typically from 100 to 1200 mg/m^3 (26 to 316 ppm). Measured peak values have been ~ 200 ppm upon initial soil injection, declining to 4 ppm by five days post-treatment,[33] though the specific task of discarding the plastic sheet can also involve peak levels of ~200 ppm. At the application rates used in one study however, tilling the soil could produce levels of ~ 15 ppm as long as nine days after soil treatment.[34] In structural fumigation (after 24 hours aeration) levels encounte
red could range from 80 to 2000 mg/m^3 (21 to 526 ppm). In the date processing and packing industry, levels may be usually less than 50 ppm, but can reach up to 100 to 500 ppm in the packing room during the fumigation of the chamber.[35]

In contrast, the workplace exposure standard (WES) in N.Z. is a level of 5 ppm as an average over 8 hours. Therefore adequate control measures including effective respiratory protective equipment will be required for many situations involving methyl bromide, particularly if exposures are of any duration. (However there are also instances such as in berry farming employing specialised soil injection techniques and associated precautions, where anecdotally, above ground levels are reported to be very low).

The N.Z WES was based on a TLV-TWA of 5 ppm set by the American Conference of Governmental Industrial Hygienists (ACGIH),[36] on the basis that extensive industrial experience had not indicated any adverse human effects at that average level. The major concern at such levels was considered its irritant effects rather than any neurotoxicity or other systemic effects, and it was the presence of irritant symptoms at slightly higher levels that was the major factor in establishing the 5 ppm standard. Recently the ACGIH has revised its TLV downwards; from 5 ppm to 1 ppm.[37] (This was on the basis of mild nasal mucosa irritation in rats exposed for almost 2 ½ years to 3 ppm; however this is of questionable relevance to humans particularly as such irritation proved reversible).

The current NZ WES of 5 ppm (as an average over 8 hours) still represents an airborne exposure considered (on the basis of human experience) not to carry excess risk of systemic toxicity, and for much shorter exposure periods the equivalent "internal"or absorbed dose could only be achieved by substantially higher air levels, which in turn would likely produce warning respiratory irritant symptoms with significant breathing problems (especially if chloropicrin was also present at proportionately elevated levels).

Therefore, with situations involving short-term, one-off exposure, which were too low to cause any symptoms either at the time or within 48 hours or so, it is unlikely that sufficient would be inhaled then absorbed to cause significant adverse effects subsequently, particularly irreversible effects. The same applies to brief, one-off exposures causing only mild irritant symptoms (if chloropicrin is also present); again the overall absorption would be most unlikely to cause systemic effects. If on the other hand exposures were frequent, and not uncommonly were sufficient to cause mild to moderate irritant symptoms, then it is possible enough could be absorbed long term to cause neurological effects. Indeed neurotoxicity has been described occasionally with repetitive exposures even when insufficiently heavy to cause any significant irritant symptoms at the time,[38] and it has been stated that in chronic low dose respiratory exposures, systemic effects may be noted without any pulmonary symptoms.[39] (This however would seem less likely in situations where the highly irritant chloropicrin is also present in the product). The most severe effects however have generally followed high exposures which were accompanied by marked respiratory irritation at the time or shortly afterwards.

Kinetics

Absorption

Absorption from the respiratory tract has been estimated as ~ 50% (at least with relatively low air levels), in one small study.[40] Dermal absorption of liquid is well established.

Distribution

It is rapidly distributed to almost all tissues.

Metabolism

It is partially (up to ~ 50%) metabolised. A major metabolic pathway is hydrolysis to inorganic bromide and methanol. $CH_3Br + H_2O – HBr + CH_3OH$.; and $HBr – H^+ + Br^-$

(Time course animal studies suggest the CNS toxicity is unlikely to be related to either of these metabolites.[41] A lesser amount is metabolised to methylcysteine).

Elimination

A significant proportion (50% or more) is exhaled fairly rapidly in unchanged form. Much of the balance is excreted as inorganic bromide. One quoted estimate of the biological half life of the bromide ion in humans is ten to twelve days.[42] Estimates of the serum half life of bromide, (whether "per se" or when derived from methyl bromide) vary, with values of ~ 5 days, 12 days,[43] and 15 days[44] quoted.

Methyl bromide "versus" inorganic bromides

As a significant proportion of methyl bromide is metabolised to inorganic bromide, it increases blood levels of the latter. However methyl bromide itself is more toxic than inorganic bromide, and its toxic effects do not arise primarily from the inorganic bromide it produces. (Therefore a given blood level of inorganic bromide derived from methyl bromide reflects a greater risk than the same level arising directly from an inorganic bromide compound, though in the former case, the risk is due to methyl bromide itself). It follows therefore that dietary modifications in an attempt to slightly lower serum inorganic bromide levels will not render someone less susceptible to methyl bromide.

Inorganic bromides too can be toxic, including to the nervous system, but higher doses (and higher blood levels) are required for adverse effects. The body distribution and toxicology of the two forms are different.

Sources of bromides

Both inorganic bromides and methyl bromide may be present in various environmental media and commodities. The two forms require different analytical methods to identify. Fumigation of foodstuffs is an important source of both methyl bromide and inorganic bromides (which can be produced from the former). Oceanic biological processes (mainly algal) are a major natural source of methyl bromide emissions. The contribution of natural versus anthropogenic sources (primarily related to soil fumigation) is uncertain.[45]

Dietary intake is usually the major source of bromide in humans. It is beyond the scope of this document to discuss the major contributors. However it is known that methyl bromide fumigated produce is a major source of inorganic bromide, and limits for total bromide have been set, of 400 ppm, 200 ppm, and 50 ppm for spices, nuts, and any other foods including cereals respectively.[46] Sea water is a natural source of bromide compounds, and fish and other sea foods may contain significant levels. A further potential source are bromate (BrO_3^-) compounds, which can be employed as food additives, and in some bread making and beer brewing activities, due largely to their oxidizing properties. However there is only limited evidence of extensive conversion of bromate to bromide in the body.[47] The Food Safety Authority has been approached for further information regarding major dietary sources.

Specific dietary supplements, and in particular certain medications, can contribute very high levels, occasionally resulting in inorganic bromide toxicity.[48, 49] In the latter report the serum bromide level was 19.7 mEq/L (~1574 mg/L). (Routine laboratory methods do not distinguish chloride from bromide ion, so that artifactual elevation of serum chloride can occur. Indeed apparent hyperchloremia and a negative anion gap in the presence of neurological or neuropsychiatric effects should alert one to the possibility of inorganic bromide poisoning, with testing for bromide more specifically).

Normal blood levels and toxic blood levels

Blood levels of inorganic bromide in the general population have been quoted as 1 to 5 mg/L (average ~ 3 mg/L),[50] and (for serum) 3.5 to 5.5 mg/L.[51] However recent data, including from New Zealand as discussed below, suggest normal "background" levels of up to at least 10 mg/L are not unusual. These normal levels are derived largely from dietary sources (sea food is a major source, but other foodstuffs, including those fumigated with methyl bromide can also contribute).

In assessing occupational exposures, it is the inorganic bromide metabolite, not the "intact" methyl bromide, that is measured. (Indeed blood levels of intact methyl bromide after either low level exposure or severe poisoning are not well established, partly due to its very short half life). [52] This is a legitimate approach, given its appreciable metabolism to the inorganic form. However, it is important not to think that a given blood level of inorganic bromide derived from methyl bromide reflects no greater risk than the same blood level obtained directly from inorganic bromide consumption. For example, patients receiving sodium bromide in the past as an anticonvulsant could develop blood levels of at least 75 to 100 mg/L with little apparent effect, but such levels cannot be assumed to be equally safe in methyl bromide workers. Consumption of bromide containing medications or folk remedies should be considered in non-occupationally exposed persons with levels substantially > 10 mg/L.

Inorganic bromide levels have been measured in asymptomatic methyl bromide workers and found to range from 4 to 36 mg/L (average 15 mg/L) in one study[53] and between 0 to 114 mg/L (average 55 mg/L) in another.[54]

On the other hand, the latter authors noted mild euphoria, adversely affecting work practices, at serum levels above 50 ppm (mg/L). The Canterbury Health Laboratory cites blood levels > 50 mg/L as reflecting potentially hazardous levels of exposure. In another report, patients presenting with severe, moderate or mild symptoms had blood levels of 220, 180, and 120 ppm respectively.[55]

A more recent publication[56] notes that the data is inconsistent regarding whether there is a high correlation between blood inorganic bromide levels and severity of methyl bromide poisoning. However some authors have proposed a rough correlation as follows:[57, 58]

400 mg/L or more – severe disability, death in some
250 mg/L – seizures (convulsions), sometimes fatal
176 mg/L – not fatal, but may be incomplete recovery (slight residual ataxia)
135 mg/L – moderate disability may occur
100 mg/L or less – full recovery

However, severe symptoms have been reported in association with blood levels of 120 mg/L, and indeed lower. The blood level was 46.6 mg/L about 48 hours after a high, brief exposure sufficient to cause dizziness, fatigue, nausea, vomiting, chest pain, and breathlessness.[59] Some symptoms are described even at levels as low as 28 mg/L.[60, 61] In a case of suspected chronic neurotoxicity, a blood level of just 24 mg/L was found,[62] but this was taken 3 to 4 days after cessation of exposure, and twenty days after symptom onset. (The effect of delayed analysis is illustrated in nine symptomatic cases, whose levels all exceeded 50 mg/L at 12 hours, while five had levels below 50 mg/L by six days; the lowest being 25 mg/L).[63] There is another report of a patient with symptoms of dizziness at a blood level of 24 mg/L.[64] One report[65] is cited as indicating that symptoms were present despite blood levels apparently being no higher than 32 mg/L in the involved workers.[66] Another report (abstract) noted symptoms, involving conjunctival irritation, headache or nausea, at plasma concentrations ranging (widely) between 17.5 and 321 mg/L.[67] Further, as noted above, a direct association between severity of neurological symptoms is not always found, certainly in acute poisoning incidents.[68]

In 11 fatal cases, blood bromide levels ranged between 40 and 656 mg/L (average 237 mg/L).[69, 70] However it is not clear when these samples were taken in relation to symptoms and it is quite possible (and indeed likely) that the 40 mg/L result underestimated the maximum level that occurred in that case. (Levels are often expressed in terms of mg/dL, not mg/L, requiring distinction. Also 1 mmol/L ~ 80 mg/L).

Normal urine levels and "toxic" urine levels

In one Japanese study, "control" (non-industrially exposed) subjects had an average urinary bromide level of 6.3 mg/L (with an upper 95% confidence limit of 10 mg/L).[71] Another study found a closely similar average level of 6.5 mg/L in "urban" male controls, with an upper 95% confidence limit of about 10 mg/L.[72]

The latter study also looked at 52 workers (24 males, 28 females) engaged in handling methyl bromide. The average urine levels were 13.7 mg/L (SD ~8.3) in the former and 17.2 mg/L (SD ~10.6) in the latter. A correlation was found between the ambient air levels and the urine levels. For those working in an atmospheric concentration of 4 to 5 ppm (just within the current WES-TWA), and without associated symptoms, the average urinary bromide level was 23 ppm (mg/L).[73] The authors concluded that this test could serve as a useful index of exposure, provided the effect of bromine-containing medications was taken into account. They suggested a "standard" of 10 mg/L.

Given the lack of apparent effects at an average level of 23 mg/L, a standard of 10 mg/L may seem unduly conservative; however given the former figure was the mean level, not all workers had urinary concentrations that high, and conceivably could have developed symptoms if they had been exposed sufficiently to increase their levels to 23 mg/L.

Indeed, in a case of suspected chronic neurotoxicity, (associated with a blood level of 24 mg/L at 3 to 4 days post-exposure), the associated urine level was only 19 mg/L.[74] The latter however would likely have been a bit higher if taken during an exposure day.

In the study by Tanaka et al, workers exposed to an average air concentration of 3.8 ppm had average urine levels of 9.0 mg/L, which does not "tally" very closely with the findings of Momotani et al, where only slightly higher exposure (4 to 5 ppm) was associated with average levels of 23 mg/L (ppm). However the results are likely not strictly comparable, in that the durations of exposure were probably different; it appears that in the former study for example, significant exposure occurred only for about two hours daily on average.

In fact, if it is assumed the former was an average over two and the latter over eight hours, the results agree quite closely. Thus in the Tanaka et al study (workers provided with full face-piece respirators), typical exposure duration (to the two fumigation processes presenting the highest risk of exposure) was ~ two hours daily, for six days per week. Personal breathing zone ambient air was collected for about 30 minutes while workers were engaged in this process. Workers exposed to an average concentration of 3.8 ppm over this time had average urine levels of 9.0 mg/L, indicating a difference from the controls (whose mean level was 6.3 mg/L) of 2.7 mg/L. This suggests that every 1 ppm (for two hours) methyl bromide contributes on average about 0.71 mg/L of inorganic bromide in urine, or 2.84 mg/L for an eight hour exposure. . Therefore at the current WES-TWA of 5 ppm, the average occupational contribution would be ~ 14.2 mg/L in urine. Using the average "background" level of 6.3 to 6.5 mg/L, it can therefore be estimated that eight hour exposures at the WES-TWA of 5 ppm would be associated with an average urine level of about 20.5 mg/L. This is close to the figure of 23 mg/L obtained by Momotani et al (for exposures of 4 to 5 ppm of likely longer duration than two hours, and possibly near 8 hours).

Biological Monitoring - proposal for a BEI

Biological monitoring is most justifiable and helpful if there exists an acceptable level or "standard" for the monitored parameter, such as a "biological exposure index" (BEI) or concentration of the chemical (typically in blood or urine), by which to assess the acceptability or otherwise of the results obtained. However there is quite limited data to assist with establishing such a standard, and none has been set by any Agency. Nevertheless, given the concerns, establishment of such a standard is warranted.

One approach is to base the biological exposure standard on the WES; that is, to determine the typical blood or urine level produced when unprotected exposure occurs to 5 ppm (or indeed 1ppm) as an average air level of 8 hours. A second, more direct option is to identify blood and/or urine levels that have been associated with toxic effects, and distinguish these from non-toxic "background" levels, and indeed from levels above background but which have not been associated with toxic effects, then to select a standard somewhere in the latter "above normal but non-toxic" range, if this can be clearly identified, but tending more to the lower end of this range, so providing a larger margin of safety.

Blood

Basing the BEI on blood is a more practical option, given the current availability of a blood test.

Published data suggests levels of 5 to 10 mg/L can be found in non-exposed members of the general population. This is also supported from the findings of Canterbury Health Laboratories (CHL). (Their currently quoted normal range would encompass 10 mg/L;[75] however analysis is generally done on "blank", pooled plasma samples, which will not reflect or detect the levels in an isolated individual having recently had meal(s) of relatively high bromide content).

On the other hand, anecdotally, one Company has found levels of 12 to 15 mg/L in supposedly unexposed staff, and there is the belief that dietary factors, particularly sea food, can result in levels of at least 20 mg/L. Some of the fumigators employed have had levels of at least 30 mg/L. There are also anecdotal reports of apparent inconsistencies, such as levels increasing rather than decreasing after returning from holiday.[76] CHL have generally found that levels in employees of companies they monitor are either within the "normal range" (up to ~ 10 mg/dL), or between about 12 to 22 mg/dL.

It is clear from some of the data presented earlier that levels up to 36 mg/L or even 114 mg/L are often not associated with toxic effects, at least not overt effects. However, on the other hand, as noted above, adverse effects have occasionally been described in

association with levels as low as 28 mg/L[77,78] or 24 mg/L.[79] It has been stated that serum levels should probably not exceed 15 to 30 mg/L.[80, 81]

Most of these "lowest toxic" blood levels have been reported in association with acute or acute-on-chronic exposure incidents of sufficient severity to cause acute symptoms, which provide a warning in themselves. They are also often not an exact index of what the peak blood bromide levels would have been at the time, having being taken 3 or 4 days or more after cessation of exposure. As such, they are not a reliable guide to the minimum levels of exposure which, despite not causing acute symptoms, could present a risk of subtle but significant subclinical effects, such as impairment of neurocognitive function, in the long term.

One of the most useful studies is that by De Haro et al, as no acute over-exposure incident occurred. However even in that case, involving a blood level of 24 mg/L, clear symptoms had developed prior to the blood test, which was not taken until about 3 days post-exposure, and hence would have been higher at the time of symptom onset.

The most relevant data is the blood concentrations associated with routine chronic levels of exposure that give no warning of risk but nevertheless do have risk. The main value of a blood BEI is to provide warning of potentially hazardous levels of exposure even in the absence of symptoms, which could present risk if persisting long term. In that respect, the most relevant study is arguably that by Verbeck et al. They noted blood levels of between 4 and 23 ppm in a group of 33 men engaged in greenhouse soil disinfection.[82] There was not a strong correlation between blood level and number of symptoms reported on questionnaire, or presence of neurological signs. (Slight signs, which "theoretically could have been caused by methyl bromide" were found in five subjects; these were hyporeflexia (two cases), myoclonia, ataxia and nystagmus). The authors considered the findings provisional, requiring further confirmation, as they had not been reported earlier in apparently healthy workers (though in this study two of the 33 workers did not indicate on questionnaire that they felt healthy). Further, ten subjects had a "slightly disturbed" electroencephalogram. There was some degree of concentration - response relationship, in that this applied to 60% (6 in 10) of those with blood levels of 12 mg/L or above, but "only" 17% (4 in 23) of those with levels below 12 mg/L. (They calculated that at blood levels of 12 to 23 ppm, the risk of having an abnormal EEG is 3 ½ times greater than that for those with levels less than 12 mg/L). However, there may be subtle EEG effects even at levels less than 12 mg/L, because the same observer using the same methods found an EEG disturbance prevalence of only 10% in a healthy non-exposed population. The authors suggested more extensive longitudinal studies employing blood monitoring should be conducted to better clarify the relationship between blood levels and effects, including potentially relevant subclinical abnormalities.

One might conclude from this study that the BEI should be somewhere between 10 and 23 mg/L, (even though a large percentage of workers with these levels are likely to be asymptomatic). However, the findings of this study, as noted by the authors, were "provisional". Taken at face value, their data suggest a standard of 12 mg/L could be appropriate.

However a value of only 12 mg/L could barely discriminate between exposed and non-exposed cases, unless extensive longitudinal data including a "baseline" on the individual was available. There is some anecdotal (NZ) evidence to suggest that fluctuations in the type of dietary intake might also result in levels sporadically reaching up to ~20 mg/L in workers despite extremely little methyl bromide exposure. Further, while health issues are the paramount concern, establishment of workplace standards such as TLV's and BEI's has historically always also involved considerations of the technical and economic feasibility of achieving the proposed standard.

In that regard, it appears that currently in New Zealand, despite apparent care in matters of occupational hygiene, levels within 12 mg/L (representing only a very minor level of exposure above background) are not consistently achieved, and indeed 20 mg/L is exceeded in a significant proportion of cases. Therefore it may be unrealistic to set a BEI value much lower than 20 mg/L in blood in the first instance.

There is clearly a "grey zone" between 10 and 20 mg/L, in terms of where the ideal standard should lie, and 15 mg/L or even 12 mg/L may be the desirable target to aim for. However more consideration of the practicalities is required before setting a standard below 20 mg/L. This could be revised downward in future if harder evidence became available to suggest significant effects can occur at blood levels below 20 mg/L

For example, there is one study which suggests that certain symptoms and subtle neuropsychological effects may occur at average levels below the WES-TWA of 5 ppm. Structural fumigators were exposed for up to 1 ½ hours daily to levels up to 2.2 ppm, and soil fumigators to ~ 2.3 ppm for typically 8 hours daily. In those exposed to methyl bromide predominantly (as opposed to mainly sulfuryl fluoride or both) for at least a year, deficits relative to controls were found in a number of neurobehavioural tests.[83] There was also an increased prevalence of various symptoms, and signs such as increased tremor, unsteadiness on simple tests of balance and position sense, and poorer grip strength on dynamometer tests. These findings raise the question of whether the WES should be lowered, and also (in parallel) the blood BEI set at lower than 20 mg/L.

The authors discussed the possibility of biases in this study, but considered they were unlikely to entirely explain the observed differences noted. However the exposure levels were not fully characterised, and some of the (licensed) fumigators (who did worse on a number of the tests) may have also been exposed to (unrecorded) higher levels at times. There was also the question of whether higher levels, that may have existed in the past, could have contributed to the observed effects. The authors noted the desirability of a repeat study along the same lines. If such a study were to replicate the findings, more confidence could be placed in the results.

If a downward revision of the BEI was to occur in future, there would be an even greater need to ensure appropriate dietary restrictions (possibly including low sea food intakes) for a few days at least prior to testing, to prevent "confounding" from high bromide levels via this route.

The preferability of a more specific marker for methyl bromide has been recognized, partly because of the various sources of inorganic bromide. More sensitive measures of early effect would also be ideal.

Fortnightly blood tests, currently being taken in some cases, are unnecessarily frequent, certainly in those established workers who have levels typically under 20 mg/L. Less frequent tests could be supplemented by post-incident testing if relevant. The precise timing of the blood test in relation to regular exposure should not have a major influence on the result, because while methyl bromide itself "disappears" rapidly, the fraction converted to bromide is excreted in urine quite slowly, with a half life of ~12-15 days.

(It should be noted however that while the typical plasma half life for methyl bromide may be 12 to 15 days, the absolute (as opposed to fractional) rate of fall is not constant over this period. Absolute falls are higher earlier on when blood levels are higher. For example, while levels may fall only by one half over 12 days, over the first quarter of that period (3 days), the concentration will fall by substantially more than one eighth).

Urine

It has been stated that there is not necessarily a close correlation between urine bromide levels and presence of symptoms.[84] However Momotani et al found those working in an atmospheric concentration of 4 to 5 ppm (just within the current WES-TWA), and without associated symptoms, had an average urinary bromide level of 23 ppm (mg/L).[85] They actually proposed a urinary BEI of 10 mg/L,[86] which seems unduly conservative. However the 23 ppm in urine was an average level, so not all workers had urinary concentrations that high, and conceivably some could have developed symptoms if they had been exposed sufficiently to increase their levels to 23 mg/L. On the other hand, Tanaka et al found non-industrially exposed subjects had an average urinary bromide level of 6.3 mg/L (with an upper 95% confidence limit of 10 mg/L).[87] Therefore, a standard of 10 mg/L would barely differentiate between occupational exposure and other sources of bromide.

In one case of suspected chronic neurotoxicity, (associated with a blood level of 24 mg/L at 3 to 4 days post-exposure), the associated urine level was only 19 mg/L.[88] It is very likely that this would have been somewhat higher if taken on a day when exposure was still occurring. However despite this, given the above finding, it would seem sensible to set a urinary BEI below 19 mg/L, if not as low as 10 mg/L. A guideline value of 15 mg/L is proposed, should this form of biological monitoring be adopted in the future.

Recommendations

A provisional BEI of 20 mg/L in blood is proposed. Consider revising downwards to 15 mg/L should further supportive evidence become available. A guideline value of 15 mg/L in urine is proposed, should this form of biological monitoring be adopted in the future.

Appendix – the effects of chloropicrin

Chloropicrin (CCl_3NO_2, also known as trichloronitromethane) is a colourless oily liquid. It is a severe irritant of the eyes, mucous membranes, skin and lungs. Lacrimation and conjunctival inflammation have been reported to occur at concentrations of 0.3 to 0.4 ppm,[89] in 3 to 30 seconds,[90] depending on individual sensitivity. It also has a strong odour, generally detectable at around 0.78 to 1.1 ppm.[91, 92] These properties of eye irritation and odour, but particularly the former, provide an early warning of exposure, even to very low levels. The lowest concentration of chloropicrin at which symptoms appear to occur is around 0.3 ppm, and indeed the workplace exposure standard has been set at 0.1 ppm, to prevent eye irritation and the potential for pulmonary changes.[93]

It is said that 15 ppm for about 4 seconds results in respiratory tract injury.[94] However it appears lower levels are also hazardous. For example, levels as low as 1.3 ppm may cause respiratory irritation, and in the U.S, the National Institute of Occupational Safety and Health (NIOSH) has set an "immediately dangerous to life and health" (IDLH) level of 2 ppm, based in part on a 1931 reference, which states "a few seconds exposure to 4 ppm renders a man unfit for action". One report suggests chloropicrin intoxication generally occurs in 3 phases; firstly "irritation", followed by a latent period (mean 2 to 5 hours), then a third stage involving pulmonary oedema.[95]

Of course, the warning ability conferred by addition of chloropicrin to methyl bromide will depend on the amount added and the respective concentrations of the two gases in the mixture. The proportion of chloropicrin versus methyl bromide may be as high as 70% versus 30% (and ratios of 1 to 1 or 1 to 2 are not uncommon), but can also be as low as 2% versus 98%.[96] Given lacrimation occurs at about 0.4 ppm chloropicrin, its warning of the presence of methyl bromide at the WES-TWA of 5 ppm should occur with chloropicrin at proportions of ~ 8% or more in the mixture, if there was complete "admixture" of the gases. Others suggest 0.6 ppm provides a more reliable warning due to eye irritation, in which case ~12% would be a more desirable proportion for chloropicrin. However such perfect mixing may not always be the case, and indeed there is evidence that in some applications, chloropicrin disappears more rapidly than methyl bromide.[97] In post-harvesting fumigation, 100% methyl bromide may be used.

Michael Beasley
March, 2005.

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