Health Consultation

Exposure to Methyl Bromide as a Result of Fumigation at ADM Milling Company

ADM/IFC METHYL BROMIDE EXPOSURE
MINNEAPOLIS, HENNEPIN COUNTY, MINNESOTA

MARCH 11, 1999

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry
Division of Health Assessment and Consultation
Atlanta, Georgia 30333
Health Consultation: A Note of Explanation

An ATSDR health consultation is a verbal or written response from ATSDR to a specific request for information about health risks related to a specific site, a chemical release, or the presence of hazardous material. In order to prevent or mitigate exposures, a consultation may lead to specific actions, such as restricting use of or replacing water supplies; intensifying environmental sampling; restricting site access; or removing the contaminated material.

In addition, consultations may recommend additional public health actions, such as conducting health surveillance activities to evaluate exposure or trends in adverse health outcomes; conducting biological indicators of exposure studies to assess exposure; and providing health education for health care providers and community members. This concludes the health consultation process for this site, unless additional information is obtained by ATSDR which, in the Agency's opinion, indicates a need to revise or append the conclusions previously issued.

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Health Consultation

Exposure to Methyl Bromide

as a result of fumigation at

ADM Milling Company

City of Minneapolis, Hennepin County, Minnesota

March 1999

Prepared By:

The Minnesota Department of Health
in Cooperative Agreement with the
Agency for Toxic Substances and Disease Registry
FOREWORD

This document summarizes potential public health concerns associated with the use of the fumigant methyl bromide in a flour mill in Minneapolis, Minnesota. This document is based on a formal site evaluation prepared by the Minnesota Department of Health (MDH). A number of steps are necessary to do such an evaluation, and include the following:

! Evaluating exposure: MDH scientists begin by reviewing available information about environmental conditions at the site. The first task is to find out how much contamination is present, where it is found on the site, and how people might be exposed to it. Usually, MDH does not collect its own environmental sampling data. We rely on information provided by the Minnesota Department of Agriculture (MDA), U.S. Environmental Protection Agency (EPA), and other government agencies, businesses, and the general public.

! Evaluating health effects: If there is evidence that people are being exposed—or could be exposed—to hazardous substances, MDH scientists will take steps to determine whether that exposure could be harmful to human health. The report focuses on public health—the health impact on the community as a whole—and is based on existing scientific information.

! Developing recommendations: In the evaluation report, MDH outlines its conclusions regarding any potential health threat posed by a site, and offers recommendations for reducing or eliminating human exposure to contaminants. The role of MDH in dealing with hazardous waste sites is primarily advisory. For that reason, the evaluation report will typically recommend actions to be taken by other agencies—including EPA, MDA, and MPCA. However, if there is an immediate health threat, MDH will issue a public health advisory warning people of the danger and will work to resolve the problem.

! Soliciting community input: The evaluation process is interactive and ongoing. Typically, MDH begins by soliciting and evaluating information from various government agencies, the organizations responsible for cleaning up the site, and the community surrounding the site. Any conclusions about the site are shared with the groups and organizations that provided the information. Once an evaluation report has been prepared, MDH seeks feedback from the public. If you have questions or comments about this report, we encourage you to contact us.

Please write to: Community Relations Coordinator
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OR call us at: (651) 201-4897 or 1-800-657-3908
(toll free call—press "4" on your touch tone phone)
The Minnesota Department of Health (MDH) prepared this document in response to multiple requests from private citizens, the City of Minneapolis, and the Minnesota Department of Agriculture (MDA) for information about the health effects of methyl bromide and its potential to be a public health hazard during application in an urban area by licensed fumigators. This document includes: a site description and a review of the incident; a review of physical characteristics of methyl bromide and exposure levels which are associated with health concern; a review of other incidents involving acute methyl bromide intoxication; an analysis of the potential for future incidents involving acute exposure to methyl bromide; a review of general tactics which may be employed to minimize the risk of future incidents; and recommendations that MDH believes should be considered by applicators and regulatory agencies when planning future applications of methyl bromide. In response to requests by medical practitioners for information about methyl bromide toxicity and potential biomarkers of exposure, an appendix containing technical information has been included in this document.

Methyl bromide has the potential to deplete atmospheric ozone; while ozone depletion has public health relevance this health consultation will not include a discussion of ozone depletion or related issues. Furthermore, potential health effects to applicators of low level or chronic occupational exposure to methyl bromide are not discussed in this health consultation.

Introduction

Incident review

On the morning of August 24, 1997 at 9:08 A. M. Santos Fernandez was found dead in his warehouse studio at 302 SE. 2nd St. in Minneapolis, Minnesota (MDH, 1997; see attached Death Certificate). A cat was also found dead at the scene (MDH, 1997). The cause of death was determined to be methyl bromide poisoning (MDH, 1997). Methyl bromide, a fumigant, was being used at the time of the accident to control pests at the Archer Daniels Midland Milling Co. (ADM) mill at 335 SE. Main St., about 160 feet south-southwest of the warehouse (O'Connor, 1997; MDH, 1997; Gramm, 1998; Read, 1998). It has been reported that between five and nine of the first individuals on the scene (family, friends, police, and firefighters) may have also suffered symptoms consistent with methyl bromide poisoning (O'Connor, 1997; Taylor, 1998; Niebeling, 1997; Gramm, 1998).

Investigation of this incident is continuing with the possibility of criminal charges and / or civil charges being brought against the owners of the mill and the fumigators, Industrial Fumigant Co. (IFC) (O'Connor, 1997; Taylor, 1998; Gramm, 1998; Read, 1998). Due to the potential for legal action involving this incident, some information about the event is not available to MDH or the public at-large at this time. In addition to newspaper reports of the incident, information for this health consultation was obtained from papers and reports on the toxicity of methyl bromide, as well as information available from the Environmental Protection Agency (EPA) and MDA on regulations restricting the use of methyl bromide and methods used to apply the fumigant.

MDH was contacted in November 1997 and again in December 1997 by doctors for individuals who were possibly exposed to methyl bromide in the warehouse. MDH staff was able to provide
some information about the potential use of biomarkers to show probable exposure to methyl bromide; however, while some references were provided to the physicians no written report was available for their use. MDH was contacted in February 1998 by a MDA investigator who also requested information about potential biomarkers of methyl bromide exposure. In June 1998, following conversations with City of Minneapolis Environmental staff, MDH faxed the City a statement of concerns on the use of methyl bromide in Minneapolis. This health consultation contains a detailed response to questions which have been directed to MDH over the last year concerning methyl bromide toxicity and use. Technical information is contained in the attached Appendix I.

**Site description**
The mill and warehouse are the two major structures on the west-northwest end of a block in Southeast Minneapolis (See Figure 1). An underground pipe tunnel connects the two buildings. The facility is located on the edge of the Marcy-Holmes neighborhood. Across the street from the mill and warehouse to the west-northwest (in a renovated industrial building) is a retail shopping area (Saint Anthony Main); to the south-southwest is a street with low traffic-volume, a park, and the Mississippi River; to the east-southeast are more mills and grain elevators; and to the north-northeast is a business and parking lot, with a residential area of apartments and single-family houses beyond the business.

Prior to fumigation of the mill, IFC employees spent 2 weeks sealing up the building (O'Connor, 1997). This included sealing of the pipe tunnel, reportedly with plastic (O'Connor, 1997). The amount of fumigant used, method of application, and other information about this specific event are not available to MDH at this time due to the possibility of legal actions. Methyl bromide is applied by sealing up a facility, evacuating the building, releasing methyl bromide (11 to 97 kilograms per 1000 cubic meters (kg / 1000 m³)) from pressurized canisters in predetermined areas of a building, waiting for a predetermined length of time (10 - 72 hours) for the fumigant to penetrate stores within the building and eradicate pests, and then venting the building until concentrations of the fumigant fall below 5 parts per million (ppm) before reoccupying (Great Lakes, 1994). One ppm methyl bromide is equal to 3.95 milligrams per cubic meter (mg / m³). Therefore according to label instructions, the building should remain vacant at least until methyl bromide concentrations fall below 19.75 mg / m³.

According to published reports of the incident (O'Connor, 1997), fumigation with methyl bromide had previously occurred in the mill 8 times in 1991, 3 times in 1992, 3 times in 1993, 3 times in 1994, 2 times in 1995, 3 times in 1996, and once in 1997. Use of the fumigant within the city of Minneapolis requires notification of the Minneapolis Fire Department. The Fire Department was, reportedly, unable to verify that notification had taken place prior to the August 23 - 24, 1997 incident (O'Connor, 1997).

**Methyl bromide physical characteristics**
Methyl bromide, also called bromomethane, is a very toxic fumigant which is a gas at normal temperatures and pressures (boiling point 3.6°C). It is heavier than air with a relative gas
density of 3.36. Its boiling point makes it appealing as a refrigerant and its gas density makes methyl bromide useful in fire extinguishers. These uses were discontinued during the 1950's. Another use was as an anesthetic in the late 1800's. Methyl bromide (sold under various trade names including Meth-O-Gas, Brom-O-Gas, Terr-O-Gas, Celfume, Kayafume, Brom-O-Sol, and Terr-O-Cide) is registered for use to control insects and pests in grain storage facilities and sealed residences (tented houses); as a preplant soil fumigant, applied with chloropicrin (odor agent) to control nematodes, weed seeds and fungi (tarp covered soil); as a treatment for strawberries, cherries, oranges, peaches and other crops prior to shipping (in enclosed control structures); as a compost disinfectant for mushroom farming; and as a fumigant of books and archives. Although methyl bromide has been considered the most effective fumigant in use, it was scheduled for phaseout by 2001 due to its ozone depleting potential. Phaseout has been pushed back by the EPA and is now scheduled to be completed in 2005 (EPA, 1998).

Methyl bromide, with an odor threshold of 80 mg / m$^3$ (ATSDR, 1992), is odorless at levels of health concern but may smell like chloroform at dangerous concentrations. With an octanol-water coefficient of 15 it is implied that methyl bromide is soluble in plastics and other synthetic materials. DuPont publishes the actual breakthrough time of methyl bromide through Tychem 10,000™ (chemical splash protection material) to be immediate (DuPont, 1998). This does not mean that large amounts of methyl bromide will pass through organic materials under normal conditions. However, it does raise the possibility that under pressure a quantity of methyl bromide may pass from a sealed area into an adjacent room or enclosure. It is possible that under some conditions, including a high air pressure differential and use of a thin sealing material which is relatively porous to methyl bromide, that significant quantities of methyl bromide could escape sealed areas.

Methyl bromide does not degrade significantly in air. However, since it is a strong alkylating agent it will methylate many proteins and organic macromolecules. Use of methyl bromide must be well controlled because it is considered to be toxic to all living things.

**Toxic levels of methyl bromide**

Methyl bromide has deleterious effects on individuals exposed by inhalation or by dermal exposure. Generally, inhalation exposures are associated with the most serious outcomes including death or permanent damage to the nervous system; dermal exposures cause irritation, or severe lesions and scarring depending on the type, concentration, and duration of exposure (see Alexeef & Kilgore, 1983; ATSDR, 1992; Hezemans-Boer et al., 1988; Zwaveling et al., 1987 for information on dermal exposures). Incidents where severe dermal exposures are not accompanied by inhalation of methyl bromide have usually occurred with exposure to liquid from fire extinguishers or when applicators using respirators failed to wear proper clothing.

The EPA has an inhalation reference concentration (RfC) for methyl bromide of 0.005 mg / m$^3$ (EPA IRIS, 1998). Exposure to this concentration over a lifetime is considered to be without appreciable risk of non-carcinogenic adverse effects. This reference concentration is not applicable for instances of acute exposure. The RfC is useful for assessing risks to soil or
structural fumigators (Anger et al., 1986; De Haro et al., 1997; Kishi et al., 1991), or to the
general public near locations where methyl bromide is manufactured or near facilities where
produce is regularly fumigated.

Concentrations in air of 4,700 mg / m³ or greater may be lethal (Alexeef & Kilgore, 1983) and
990 mg / m³ is considered immediately dangerous to human life or health (IDLH) (NIOSH,
1994). The Occupational Safety and Health Administration (OSHA) ceiling concentration for
methyl bromide, which must not be exceeded during any part of the workday, is 79 mg / m³
(NIOSH, 1994).

California has developed a draft Acute (1 hour) Reference Exposure Level (REL) for methyl
bromide of 3.9 mg / m³ which is believed to be protective of the general public (CA EPA, 1998).
MDH has not yet established exposure criteria for methyl bromide which is protective of the
general public. However, we believe that this California standard may be reasonable. The
California Environmental Protection Agency notes that the toxicological endpoint for acute
methyl bromide intoxication is severe. Furthermore, California has developed a draft acute
exposure level protective against life-threatening effects of 10.5 mg / m³ (CA EPA, 1998).

Symptoms of exposure to methyl bromide are not immediately obvious, but may begin to appear
one to two hours following the initial exposure. Early symptoms often include headache,
dizziness, nausea, vomiting, tremor, and ataxia which may be followed in severe cases by
convulsions, pulmonary edema, central nervous system depression, and respiratory distress.
Permanent neurological damage often appears 4 to 12 hours following acute exposures.

Methyl bromide is rapidly taken up by blood upon inhalation. Due to the rapid metabolism of
methyl bromide, it is not found in the blood of exposed individuals. Therefore, total blood
bromide levels are measured in cases of suspected exposures. Typical whole blood bromide
concentrations in unexposed individuals range from 0.35 - 0.55 mg / deciliter (dL) (van Leeuwen
& Sangster, 1987). The regulated tolerance limit for blood bromide in France is 0.35 mg / dL
(De Haro et al., 1997). Neurological symptoms have been reported in people with 2.8 mg / dL or
greater bromide in blood following acute exposure to methyl bromide, including lethal results in
individuals with 8 - 9 mg / dL (Zatuchni & Hong, 1981).

Serum bromide levels in the general population are typically below 1.5 mg / dL (ATSDR, 1992;
Cuenca et al., 1988). In contrast, individuals exposed to lethal concentrations of methyl bromide
have been found to have 4 - 58.3 mg / dL total bromide concentrations in blood serum
(Marraccini et al., 1983). Similar or slightly lower serum bromide levels (1.75 - 32.1 mg / dL)
have been measured in cases where exposures are sublethal (Marraccini et al., 1983). Bishop et
al. (1992) found 12 mg / dL bromide in blood serum following inhalation of methyl bromide to
be associated with leg weakness, epileptic seizures, vision, hearing and balance impairment.

In instances where methyl bromide is applied to living quarters or workplaces there is a potential
for methyl bromide to react with sulfhydryl groups in foam rubber, rug backings, feathers pillows
and other products releasing mercaptans (Reidy et al., 1994). Mercaptans are irritants which have been associated with dermal irritation, headaches, fatigue, and gastrointestinal symptoms. Therefore, adverse symptoms experienced following methyl bromide use need not be limited to a direct exposure to methyl bromide.

**Human Exposure to Bromide**
Bromine is found, in the form of bromide, in all animals. Background bromide levels measured in humans appear to be the result of uptake from bromide containing foods. Numerous studies have looked at dietary uptake of bromide and found average daily intake to be between 7.5 and 27.9 mg / day (de Vos et al., 1984; Duggan & Corneliussen, 1972; Duggan & Lipscomb, 1969; Duggan & Weatherwax, 1967; Cummings, 1965). The average concentration of bromide in the analyzed diets was 3.2 - 12.7 mg / kg (de Vos et al., 1984; Duggan & Weatherwax, 1967; Cummings, 1965; Duggan & Lipscomb, 1969). While there is mention in scientific literature of fish potentially containing high levels of bromide, we have been unable to locate any primary citations on data describing this reported phenomena. On the other hand three large studies (cited above) of trace element and pesticide concentrations in food determined that fish in average diets contains very little bromide, and that the majority of bromide uptake comes from grains and cereal.

While typical whole blood bromide levels in the general population range from 0.35 - 0.55 mg / dL (see above), levels of 23 mg / dL over 36 hours, are not associated with known effects in humans (Haerer et al., 1964), and concentrations of 75 - 150 mg / dL have been attained in some treatments of epilepsy; however, these high concentrations may be accompanied by some health effects (Woodbury, 1972). Since there is no direct correlation between total blood bromide and toxicity of bromide from different sources, it is believed that bromide is not the toxic metabolite of methyl bromide. Blood bromide apparently is a breakdown product of limited consequence which, given typical low levels in most of the general population, can be used as a marker of methyl bromide exposure (see below).

**Biomarkers of Exposure**
As discussed above, typical whole blood bromine concentrations in the general population are between 0.35 - 0.55 mg / dL. Individuals exposed to lethal concentrations of methyl bromide have been shown to have whole blood bromine concentrations from 4 to 66 mg / dL, and individuals who have ingested bromine from other sources have maintained much higher levels of blood bromide with little or no effect (Haerer et al., 1964; Woodbury, 1972). Therefore, without supplementary information, the use of blood bromide as a biomarker for methyl bromide exposure may be problematic. However, it may be possible to infer that high levels of bromide in blood are from methyl bromide if there has been a known or potential exposure, there are no other known sources of bromide, and if the exposed individual demonstrates symptoms which are consistent with methyl bromide intoxication. Further confirmatory information may include blood bromide levels following a single-dose / first order excretion model and decreases at a rate which conforms to bromide’s expected half-life. The half-life of bromide in blood is between 10 and 16 days (Soremark, 1960; Ohmori & Hirata, 1982).
Bromide concentrations have been measured in the hair of individuals exposed to methyl bromide, as well as individuals ingesting bromide supplements. It appears that hair bromide may, like blood bromide, be a measure which correlates with total bromide exposure, not just methyl bromide exposure. Additionally though, hair measurements may be affected by non-internal sources including exposure to bromide containing dust, hair care products, or even external exposure to methyl bromide. Even though problems of source identification exist, hair concentrations of bromide have been shown to be elevated in methyl bromide workers (Ohmori & Hirata, 1982) and to increase in individuals following ingestion of bromide containing tablets (Cross & Smith, 1978).

Ohmori and Hirata (1982) found that occupational exposure to low concentrations of methyl bromide did not significantly correlate with serum total bromine concentrations. This may be due to the relatively low direct exposure via inhalation in the exposed sample population or the small difference in blood bromine levels between exposed individuals and non-exposed individuals. Furthermore, there may be some, as yet undetermined link between conjugator status (see Appendix I) and blood bromide levels or half-life. However, exposure did result in a significant increase in hair total bromine concentration.

Cross and Smith (1978) analyzed total bromine from a single individual in 1 centimeter (cm) sections of hair making up about a year’s growth. During the time the hair was growing the subject ingested 85 mg bromine (in the form of 250 mg carbromal; 5 mg carbromal / kg body weight) at four months and 218 mg bromine (640 mg carbromal) after 10 months. A significant increase in hair bromine was noted following both ingestion points. While population differences in blood bromine are normally distributed, hair bromine shows non-normal distribution suggesting that some individuals are absorbing bromine in hair directly from an external source (Cross & Smith, 1978). Some hair care treatments contain bromine and these products are a likely source of an occasional high hair bromine concentration found in the general population.

The Cross and Smith study is interesting because it demonstrates the potential for hair bromine to record a history of internal bromide exposure. Clearly, low exposures, multiple exposures, and high external exposures to bromine could confound interpretation of hair analysis. However, hair bromine analysis may still be useful in identifying a suspected exposure to methyl bromide.

Some recent studies have demonstrated the potential for utilizing adducts as biomarkers of exposure to methyl bromide and other alkylating agents. Bailey et al. (1981) demonstrated a linear relationship between exposure of rats to methyl methanesulfonate, an alkylating compound, and the formation of S-methyl cysteine hemoglobin adducts. In contrast, dimethylnitrosamine, a precursor of an alkylating agent, does not cause the formation of S-methyl cysteine hemoglobin adducts at low concentrations (below 10 mg / kg in rats).

In humans, as discussed Appendix I, GST T1 conjugator status can have a large effect on adduct formation (in vivo) (Garnier et al., 1996), sister chromatid exchange (in vitro) (Hallier et al., 1993), and the formation of glutathione conjugation products (in vitro, dichloromethane) (Hallier
et al., 1994). Garnier et al. demonstrated that in one incident, while accidental human exposures to methyl bromide were thought to be similar, the individual who was a conjugator had significantly fewer S-methyl cysteine hemoglobin adducts in blood than the non-conjugator. However, both individuals showed elevated levels of the adducts. Iwasaki, et al. (1989) demonstrated that, given the apparently low variability on S-methyl cysteine hemoglobin adduct formation in control populations, even small exposures to methyl bromide can be seen using this biomarker (see Appendix I). The actual level of exposures of individuals in the Iwasaki et al. study were not reported; however, job classifications were compared with blood analyses results and were consistent with exposures inferred from quantification of adduct formation.

If an individual who is a GST T1 conjugator is exposed to methyl bromide it is likely that the formation of S-methyl cysteine hemoglobin adducts could be limited to a fraction of the amount of adducts found in a similarly exposed non-conjugator. This may limit the utility of this assay when performing a dose reconstruction of exposed individuals. However, exposure of non-conjugators as well as conjugators to methyl bromide should significantly increase the concentration of hemoglobin adducts found when compared with the general population and directly implies exposure to an alkylating compound such as methyl bromide. A further advantage to the use of hemoglobin S-methyl cysteine adduct concentration as a biomarker for methyl bromide is that this biomarker remains in the blood of the exposed individual for an extended period ($t_{1/2} = 60$ days).

**Other Methyl bromide incidents**

Over 900 people have been lethally poisoned by methyl bromide since the late 1800's. Serious accidents in the last 40 years have been primarily related to field or greenhouse fumigation of soil (Bishop, 1992; Hustinx et al., 1993; Herzstein & Cullen, 1990; Goldman et al., 1987), residential fumigations (Fuortes, 1992; Reidy et al., 1994), grain and commodity fumigation (Deschamps & Turpin, 1996; Zatuchni & Hong, 1981; Uncini et al., 1990; Collins, 1965). There are also occasional reports of poisoning from old fire extinguishers (Behrens & Dukes, 1986; Squier et al., 1992). Historically, methyl bromide has been used in urban areas to fumigate houses and grain mills or elevators. Typically, houses undergoing fumigation in warm climates (not Minnesota) are clearly visible because they are covered by large tents to allow complete internal and external fumigation of the structure, as well as better treatment control by the applicator. The maximum concentration in a tented house can be from 12,000 - 50,000 mg / m$^3$ (Langård et al., 1996; Marraccini et al., 1983). Entry into tented houses without correct respiratory protection has led to numerous deaths of individuals attempting to gain unauthorized entry into the residences (O'Neal, 1987; Marraccini et al., 1983).

Other incidents, similar to the 1997 incident in Minneapolis, have occurred when methyl bromide has migrated from fumigated houses to other nearby houses via sewer pipes, causing death and / or injury to residents. In an incident in Norway (Langård et al., 1996) the houses were separated by 20 - 25 meters. The fumigated house was situated about 7 meters above the house where the incidental exposure occurred. Bromide levels in whole blood were found to be 17 mg / dL in the infant that died and 11 and 13 mg / dL in two affected adults about 39 hours after exposure. Sewer lines had been cleaned the day of the accident clearing out water traps and
allowing gas, especially gas which is heavier than air, to flow from one house to the other. During a reconstruction of the accident with SF₆ (1.5 times heavier than air), it was demonstrated that it was likely that methyl bromide leaked from the fumigated house into the house of the affected family. In this incident the movement of methyl bromide from the house where it was applied, to the house where an infant died, may have been assisted by the elevation difference between the two houses.

MDH and MDA are unaware of any human exposure events in the state of Minnesota involving methyl bromide other than the event on August 23, 1997. However, symptoms are not easily recognizable and can often be confused by the medical community, or by the patients themselves, with symptoms of influenza or psychosis (Zatuchni & Hong, 1981). A newspaper report (O'Connor, 1997) reviewed evidence that another individual may have been exposed on August 17, 1996 to methyl bromide in the same warehouse, next to the ADM mill, where Mr. Fernandez was exposed. Symptoms included vertigo and ataxia. Severe symptoms lasted a couple of weeks, and more minor symptoms lasted about a year.

Potential for further incidents
According to EPA Toxic Release Inventory (TRI) data, 4 companies in Minnesota have used large amounts of methyl bromide during the period from 1987 through 1996. Bay State Milling, Winona, reported using methyl bromide only in 1990. The company apparently discharged 12,015 pounds during that year. ADM reportedly used a total of 127,068 pounds (15,883 pounds per year, average) from 1989 through 1996. Conagra Flour Milling Co., Hastings, reported using 101,204 pounds (20,240 pounds per year, average) of methyl bromide from 1992 through 1996. Primo Piatto, Inc., Plymouth, has also reported using 71,283 pounds (10,183 pounds per year, average) of methyl bromide from 1990 through 1996.

Often fumigation accidents with methyl bromide occur during the venting stage of the operation. Applicators walk through the building opening outside doors and windows and removing seals from vents and other openings to unfumigated areas. Venting of fumigated buildings allows methyl bromide to mix with air outside of the building, dissipating toxic concentrations inside the building. During the venting process methyl bromide concentrations are somewhat reduced from the high levels during the initial application. Accidents have occurred to applicators who have failed to adequately protect themselves from the decreased but still potent concentrations remaining in the building.

A study was conducted by Bond and Dumas (1987) during the fumigation of three flour mills. Maximum methyl bromide concentrations measured in the mills were 23,000 mg / m³, 23,000 mg / m³, and 37,000 mg / m³ in mills 1, 2, and 3, respectively. Within 5 hours of the initial treatment, concentrations of methyl bromide inside the mills declined significantly in all three mills making it necessary to supplement the initial charges. The total amount of methyl bromide applied to each mill divided by the mill area was 21,000 mg / m³; 45,000 mg / m³; and 48,000 mg / m³ for mills 1, 2, and 3, respectively. Concentrations just prior to final aeration (at 15 hour in mills 1 and 3, and at 20 hours in mill 2) were measured at about 5,000 mg / m³, 1,000 mg / m³, and 1,000 mg / m³ in mills 1, 2, and 3, respectively. During venting, 2 stations were used to record methyl bromide concentrations in outdoor air downwind from each mill. These sampling
sites were different distances from each mill, but ranged from 14 meters to 75 meters from the mills. The maximum concentration measured at these sites was 110 mg / m³ at 25 meters from the exhaust point of mill 2. These data show that it is possible to exceed the OSHA ceiling concentration of 79 mg / m³ in an outdoor area near a venting fumigated mill. Furthermore, measured methyl bromide concentrations at a point 14 meters from mill 2 remained above the California REL of 3.9 mg / m³, as well as the California draft acute exposure level protective against life-threatening effects of 10.5 mg / m³, for at least 90 minutes following venting (all 5 measurements taken were greater than 24 mg / m³).

MDH is unaware of any published data on methyl bromide concentrations near a mill during fumigation, but is concerned that these concentrations may also be significant in certain, specific locations. Bond and Dumas (1987) showed that methyl bromide concentrations inside the three mills investigated decreased from 23,000 to 5,000 mg / m³, 23,000 to 1,000 mg / m³, and 37,000 to 1,000 mg / m³ during fumigation of Mills 1, 2, and 3, respectively. The overall loss of methyl bromide was even greater if the applied nominal mass is assumed to be correct. Early dissipation rates, calculated from measured concentrations in Mills 1, 2, and 3 were about 13 kg / hr, 90 kg / hr, and 20 kg / hr, respectively. The decrease in methyl bromide concentrations in the sealed mills represents potential loss of fumigant via two pathways: fugitive emissions from the mill, and decomposition or sorption of methyl bromide. The greatest portion of the sorbed / decomposed fraction alkylates proteins, primarily sulphhydryl containing proteins, in flour and other organic materials in the mills (Lewis & Eccleston, 1946; Winteringham & Harrison, 1946). It is not possible to evaluate the relative dissipation of methyl bromide by each route given the available data. However, it is probable, as noted by the authors, that a significant portion of the loss, especially from Mills 2 and 3, was due to leakage (Bond & Dumas, 1987). Similarly, Langård et al. (1996) noted that the rapid decrease in methyl bromide concentration inside of a fumigated house was assumed by the applicator to be the result of unexpected leakage. As noted above, the leakage was through a sewer and resulted in the death of an infant.

Methyl bromide is a very effective fumigant which can potentially be used with minimal risk to the applicators or the general public. Limiting risk requires full knowledge of the particular characteristics of the specific application site. This includes knowledge of pipes or tunnels connecting the fumigated building to other buildings and of normal air movement in the area of the facility and venting areas, as well as air movement around air intakes of adjacent buildings. All potential factors in the area of the site which might increase risk during fumigation need to be investigated (e.g. utility or construction work; proximity to a daycare center). Notification of public works and emergency response employees, as well as individuals working or living near the fumigated facility is important. Furthermore, ambient concentrations adjacent to the structure should be monitored throughout the fumigation and venting. If proper precautions are taken, including those mentioned above, and methyl bromide is applied by educated and experienced fumigators, risk of an accident should be minimal. Unfortunately though, if an accidental exposure to methyl bromide causes symptoms in an exposed individual, the health effects are likely to be severe.
By 2005 the use of methyl bromide in the United States is scheduled to be phased out. Replacement fumigants are expected to have some potential for public health concern. Without knowing what pesticides will be used it is not possible for MDH to compare the relative risk to public health. Risks that may need to be investigated which are typically not of concern with methyl bromide and have not been discussed in this health consultation include: the amount of residue reaching and remaining in the final food product; chronic effects and latent effects of exposure to the pesticide and residue; and bioaccumulation of the replacement fumigant. Health risks are reviewed by the EPA prior to registration of pesticides. This does not preclude individual states from adding additional regulations to govern specific pesticide use. The US Food and Drug Administration (FDA) generally enforces tolerances associated with pesticides to be used on foodstuffs.

Procedures to minimize risk
MDH has reviewed available information on the death of Mr. Fernandez and literature detailing numerous other accidents involving methyl bromide use, and concludes that great care must be used to eliminate human exposure to this fumigant. Furthermore, MDH concludes that stringent measures may be necessary to insure public safety during fumigation with methyl bromide in an urban area. Among the methods which may be employed to limit exposure are:

- Notification of community residents, businesses, and employees.
- Evacuation of nearby residences and businesses
- Environmental monitoring throughout event and venting
- Controlled access and patrol of areas, outdoors and indoors, which are adjacent to the facility
- Addition of an odorizing agent to the fumigant

An odorant (and pesticide), chloropicrin, has been used in some applications of methyl bromide (Marraccini et al., 1983; Alexeef & Kilgore, 1983). However, regulations limit the use of chloropicrin, and possibly other odorants, in the fumigation of certain food products. Therefore, it may not be possible use chloropicrin in facilities such as ADM when they contain grain or flour. Furthermore, there are other potential problems which may be associated with the use of chloropicrin or other odorants. While odorants have extremely irritating odors, the odor itself is often not enough to deter individuals from entering fumigated buildings. Without knowledge of an on-going methyl bromide fumigation and the potentially serious health effects which may accompany exposure, a pungent smell may not cause individuals to evacuate an area (Marraccini et al., 1983). Also, applicators should be aware that while exposure areas for chloropicrin and methyl bromide should be similar, they will not be identical due to different physical characteristics of the two fumigants. Chloropicrin has a vapor pressure which is about 1/75th of methyl bromide’s at 20°C (Alexeef & Kilgore, 1983). Therefore, under ideal conditions with a 2% chloropicrin mixture, the methyl bromide concentration will be about 450 mg / m³ when chloropicrin is detected. Exposure to this concentration of methyl bromide is of concern to MDH.

Treatments
This section is not intended to provide a review of the success or failure of clinical treatments for methyl bromide exposure, but as a limited review of potential references for clinical practitioners. In addition to reported treatment for clinical symptoms associated with exposure, doctors attempted to limit the assumed, affected mechanism of methyl bromide toxicity in some reports reviewed by MDH. None of the treatments conclusively demonstrated a benefit to the patient. British Anti-Lewisite (BAL) (O'Neal, 1987), a sulfhydryl containing chelator, and acetylcysteine (Zatuchni & Hong, 1981), a glutathione precursor, have been administered in some cases, and hemodialysis (Moosa et al., 1994) and hemofiltration (Deschamps & Turpin, 1996; Garnier et al., 1996) have also been attempted. The use of BAL and glutathione (or glutathione precursors) have been recommended by other investigators (Behrens & Dukes, 1986; Collins, 1965; Zatuchni & Hong, 1981). It must be noted, again, that if methyl bromide toxicity is a result of the toxicity of S-methyl glutathione metabolic products, the use of glutathione or glutathione precursors to treat exposed individuals may be counter-productive (Garnier et al., 1996).

See Appendix I for further information about proposed mechanisms of toxicity of methyl bromide.

Conclusions
The Minneapolis Medical Examiner determined that an individual was killed by methyl bromide in August 1997 in Minneapolis, as a result of fumigation of a flour mill adjacent to the studio where the deceased worked. A cat was also killed.

The exact mechanism of methyl bromide toxicity is not known, but it appears to be related to the ability of methyl bromide to alkylate proteins and not due to its ability to form nucleic acid adducts. Methyl bromide has not been shown to be a human carcinogen.

Methyl bromide is not found in the blood of individuals exposed to methyl bromide, but bromide blood levels have been shown to be elevated. Other exposures to non-toxic forms of bromide may also raise the level of bromide found in blood. Therefore, elevated levels of bromide in blood cannot alone demonstrate an exposure to methyl bromide.

Methyl bromide has been shown to form adducts with human sulfhydryl containing proteins including glutathione, hemoglobin, and albumin. Glutathione adduct formation is assisted by a glutathione-S-transferase which has been shown to be absent in a significant portion of the population. While the presence of a GST appears to limit the formation of hemoglobin and albumin adducts, these adducts are potentially useful biomarkers for exposure to alkylating agents including methyl bromide.

Bromine content in hair has also been shown to demonstrate a dependence on ingested bromine. Hair analysis may be complicated by factors including external exposure to bromine containing products.
Methyl bromide is a very effective fumigant which is also very toxic to humans. Exposure of individuals to dangerous levels of methyl bromide outside of a facility being fumigated could occur during the fumigation, or during venting of the facility. Any unplanned exposure to methyl bromide could have serious health consequences. Therefore, if methyl bromide is to be used in an urban area, its use must be well planned, controlled, and monitored.

Use of methyl bromide is due to be phased out by 2005 due to its ozone depletion potential. MDH is concerned that acute, chronic, or latent effects of replacement fumigants on public health may not be fully understood. Furthermore, in contrast to methyl bromide, replacement fumigants may leave significant residues in food products.

Recommendations
MDH conducts health assessments and recommends procedures to minimize public health risks. A major purpose of MDH recommendations is to inform state and local regulatory and decision-making agencies.

If methyl bromide is to be used to fumigate facilities in urban areas, MDH recommends:

! Notification of city, county, and state officials, including public works, health, and emergency personnel.

! Notification of the community, including residences and businesses.

! Labels already require the evacuation of areas maintaining a common wall with the area of application. MDH is concerned that there are other circumstances when evacuation may be prudent. For example, pesticide may leak into unknown areas. If this occurs, monitored methyl bromide concentrations inside the fumigated area may then decrease well below modeled, projected concentrations. This, or some similar warning, could serve as an additional criteria for evacuation of nearby residences and businesses.

! Environmental monitoring throughout fumigation and venting process.

! Controlled access and patrol of areas, outdoors and indoors, which are adjacent to the facility.

! If possible, an odorant should be used in conjunction with methyl bromide. MDH understands that certain odorants may not be registered for use under conditions found in grain elevators. Furthermore as discussed above, MDH recognizes that the physical characteristics of an odorant will not be the same as methyl bromide. Therefore, an odorant will not behave identically to methyl bromide during fumigation. Under certain conditions MDH believes that odor can serve as an effective warning to immediately evacuate an area previously presumed to be safe either during application or during venting. Use of an odorant should be in addition to air monitoring, not as a substitute for
air monitoring. If the air flow and dissipation characteristics at a site are not completely understood, an odorant could mean the difference between minimal and severe health risk to an exposed individual.

MDH recommends that before other fumigants are used as replacements for methyl bromide, potential health risks associated with these fumigants be reviewed and appropriate procedures be developed to minimize exposures and risks.

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Appendix I - Technical report

Toxicology of Methyl Bromide
The direct cause of methyl bromide acute toxicity is not known. Early research suggested that the toxicity of methyl bromide is due to the destruction of essential, but unknown, enzyme functions (Lewis, 1948; Collins, 1965; Alexeef & Kilgore, 1983). Methyl bromide is a potent alkylating agent (Alexeef & Kilgore, 1983; Goergens et al., 1994) and a mutagen (Djalali-Bezhad et al., 1981; Goergens et al., 1994). Its is unknown whether methyl bromide is a human carcinogen (IARC, 1987; IARC, 1986). Alkalyating agents can form adducts with DNA and proteins, potentially leading to genetic modification or loss of protein function (Farmer, 1995; Goergens et al., 1994; Djalali-Behzad et al., 1981). Furthermore, methyl bromide has been identified as a causative agent of sister chromatid exchange (Hallier et al., 1993; Goergens et al., 1994), a potential mechanism of cytogenetic toxicity which can be used to assess the mutagenic potential of compounds. Even though in vitro data appear to demonstrate the potential of methyl bromide to cause cancer, human data does not appear to support this hypothesis. While lung and liver tumor incidence was not elevated in a study of individuals occupationally exposed to a similar compound, dichloromethane (Hearne et al., 1987), a slight elevation in pancreatic cancer (8 observed, 3.1 expected) was noted in the same exposed population (Mirer et al., 1988). However, there does not appear to be a workable mechanistic model which can explain this association at this time.

Metabolism of methyl bromide: effects of a genetic polymorphism
The metabolic pathway by which methyl bromide is broken down is believed to be the same as that used to breakdown other monohalomethanes, including methyl iodide and methyl chloride, as well as dichloromethane (methylene chloride) and ethylene oxide (Hallier et al., 1993). Initially monohalomethanes bind to glutathione releasing a halogen ion. The resulting S-methyl glutathione is then metabolized by peptidases to S-methyl cysteine. Products of this pathway have been shown to include formaldehyde, methanethiol and hydrogen sulfide (Kornburst & Bus, 1983).

While the formation of S-methyl glutathione can proceed slowly without enzymatic assistance, glutathione-S-transferases (GSTs) are responsible for a more rapid conjugation with glutathione (Johnson, 1966; Habig et al., 1974; Schroder et al., 1992). Humans and laboratory animals appear to have different GSTs (Green et al., 1988; Davenport et al., 1992; Hallier et al., 1994). In rats (and mice), the GST responsible for conjugating glutathione with methyl bromide (GST 5-5) is not present in blood (investigated in lung and liver), whereas in humans, enzymatically assisted conjugation (GST T1-1) has been demonstrated in erythrocytes but is not found to be significant in lung and liver tissue. The implications of this species difference on using an animal model for methyl bromide toxicity or carcinogenic potential is not fully understood at this time.

The existence of a genetic polymorphism in the expression of GST T1-1 in human erythrocytes has been demonstrated (Hallier et al., 1993; Hallier et al., 1994; Nelson et al., 1995; Garnier et al., 1996). Individuals with GSST T1-1 in their blood are conjugators, while those without an active
enzyme are called non-conjugators. Non-conjugators make up different proportions of sampled populations: 64.6% Chinese, 60.2% Koreans, 21.8% African-Americans, 20.4% Caucasian-Americans, and 9.7% Mexican-Americans (Nelson et al., 1995). Erythrocytes from conjugators exposed to dichloromethane \textit{in vitro} have been shown to produce greater amounts of formaldehyde (an end-product of the GST/glutathione metabolic pathway) than non-conjugator blood cells (Hallier et al., 1994). In contrast, the occurrence of sister chromatid exchange in cells from conjugators exposed to dichloromethane, methyl bromide, and ethylene oxide is reduced (Hallier et al., 1993). These data suggest that the GST/glutathione pathway increases the availability of toxic metabolic products and decreases the occurrence of genetic damage in methyl bromide exposed cells. Furthermore it has been demonstrated that a functioning GST decreases the formation of other adducts which arise from exposure to alkylating agents (Garnier et al., 1996).

Exposure of tissue to alkylating compounds has been shown to cause the formation of many types of adducts (Bailey et al., 1987; Muller et al., 1994; Djalali-Behzad et al., 1981). In particular, the concentration of hemoglobin and albumin adducts have been shown to increase (Goergens et al., 1994; Muller et al., 1994). Furthermore, the increase seen upon exposure to monohalomethanes is highest in cells from individuals lacking GSST T1-1 (Garnier et al., 1996). Human hemoglobin adducts have half-lives around 2 months and the half-lives of albumin adducts are about 7 - 10 days. Both half-lives are equivalent to that of their non-altered counterparts, implying that their formation is not reversible and that the adducts formed are not selectively removed from the body. S-methyl hemoglobin adducts occur in the general population at a rate of about 15 - 16 nanomole per gram (nmol/g) globin (Bailey et al., 1981; Goergens et al., 1994). Iwasaki et al. (1989) reported 5 - 10 nmol / g globin for unexposed workers in an occupational study.

\textbf{Human evidence: conjugator status impacts methyl bromide toxicity}

Garnier et al. (1996) reported a case which may provide important information about the mechanism of toxicity of methyl bromide. Two individuals were treated in a poison center for 45 minute exposure, through improper breathing equipment, to methyl bromide at an initial concentration of 17,000 mg/m$^3$ (4,300 ppm). Exposure took place during the opening of windows and sealed doors following the fumigation of a mill. Within minutes following completion of the task both workers developed symptoms of nausea, vomiting, headache, and dizziness. Within 2 hours of the onset of symptoms the first patient suffered severe myoclonic seizures. Upon admission the patient’s plasma bromide was 15.6 mg/dL. On the second day, following hemofiltration, bromide levels were found to be normal (0.35 - 0.55 mg/dL). Subsequently this patient required mechanical ventilation until the 22$^{nd}$ day and remained in intensive care until the 52$^{nd}$ day following exposure. One year following the accident the patient continued to suffer from ataxia and debilitating action/intention myoclonus, bilateral cortical deafness, and mental deterioration.

The second patient never developed seizures or myoclonus and suffered mild symptoms for only two days. Serum bromide was measured on the second day in this patient at 4.66 mg/dL. Further investigation showed that the first patient was a GST conjugator, while the second patient
lacked the conjugating enzyme. Data showed that the conjugator had fewer adducts formed with both hemoglobin and albumin than did the non-conjugator (31 and 69 % respectively). Adduct status in the two patients was about 2 times and 5 times normal for the conjugator and non-conjugator, respectively. While Garnier et al. presumed equivalent exposures, it must be noted that other investigators reporting on the same incident (Deschamps & Turpin, 1996) cite possible variables which may have resulted in the two fumigators receiving different exposures.

Potential mechanisms of methyl bromide toxicity
Since conjugators of GST appear have much more severe symptoms than non-conjugators, as well as (apparently) fewer affected blood proteins, the mechanism of methyl bromide toxicity is probably not due to its direct effect on (unidentified) enzymes or other proteins in the brain or nervous system. In fact, the glutathione metabolic pathway itself may be responsible for the severe neurotoxic effects of methyl bromide. Two alternative hypotheses have been advanced which could account for these data: the products of the S-methyl cysteine conjugation of glutathione are responsible for the neurotoxicity of methyl bromide; or, the rapid conjugation of glutathione in individual cells leave some cells in the brain depleted of glutathione stores, and therefore, subject to oxidative stress.

I. Metabolic product toxicity
If metabolic products of monohalomethane S-methyl cysteine conjugation of glutathione, such as formaldehyde, methanethiol, or hydrogen sulfide are responsible for neurotoxicity then treatment of exposed patients with glutathione precursors, such as N-acetylcysteine, could have a detrimental effect on patient outcome (Garnier et al., 1996). Increased amounts of glutathione could increase the substrate availability and thereby increase the toxic product formation. Animal and cell culture experiments have not demonstrated this relationship. Nishimura et al. (1980) recorded decreased methyl bromide toxicity to human HeLa cells upon simultaneous treatment with glutathione. The use of a 3 day exposure in this study may make interpretation of these data problematic. It has been reported (Garnier et al., 1996) that glutathione, cysteine, N-acetylcysteine, and methionine have been shown to be protective of mice, rats, and rabbits if treated prior to methyl bromide exposure. On the other hand, evidence from a mice study is not consistent with these results. Depletion of glutathione has been shown to decrease the toxicity of methyl chloride in mice (Chellman et al., 1986). It must be emphasized that GST T1-1 has not been found in any laboratory animal, and that the only GST’s which have been found to potentiate methyl bromide - glutathione conjugation in animals have been found in hard tissue, not in blood. Furthermore, exogenous and endogenous compounds as well as sex, animal health, stress, or nutritional status may affect GST activity (Davenport et al., 1992).

II. Glutathione depletion
If glutathione stores in regions of the brain are depleted following exposure to methyl bromide, individual cells may not be able to function properly or protect themselves from reactive compounds created during normal cellular activity. Glutathione performs many functions in cells, including maintenance of other sulfhydryl enzymes in the reduced state, as a glutathione peroxidase co-factor, and as a scavenger of toxic enzyme products (typ. cytochrome P450s). The
rapid depletion of glutathione in localized regions of the brain may cause damage to individual
cells. Necrosis or apoptotic mechanisms may be triggered leading to the death of these cells and
the loss of nervous system function.

Analyses of blood from individuals with an expressed GSST T1 have demonstrated a decreased
incidence of sister chromatid exchange (in vitro) (Hallier et al., 1993) and a decrease in adduct
formation (in vivo) (Garnier et al., 1996) upon exposure to methyl bromide. Garnier et al. (1996)
observed that individuals who are conjugators appear to be more likely to incur neurotoxic effects
from acute methyl bromide exposures than non-conjugators. Bonnefoi et al. (1991) have
demonstrated that the rapid depletion of glutathione in the brain by monohalomethanes, especially
in glial cells, may result in damage to specific areas of the brain. They have further shown that
while cytosolic glutathione depletion may be directly caused by monohalomethanes (methyl
iodide was used in their experiments), monohalomethanes apparently cause an alteration in
mitochondrial function which does not cause the formation of glutathione adducts in
mitochondria, but indirectly causes glutathione depletion within mitochondria (Bonnefoi, 1992).

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CERTIFICATION

This Health Consultation for the ADM Milling Company site Methyl Bromide Exposure was prepared by the Minnesota Department of Health under a cooperative agreement with the Agency for Toxic Substances and Disease Registry (ATSDR). It is in accordance with approved methodology and procedures existing at the time the Health Consultation was initiated.

[Signature]

Technical Project Officer
Superfund Site Assessment Branch (SSAB)
Division of Health Assessment and Consultation (DHAC)

The Division of Health Assessment and Consultation (DHAC), ATSDR, has reviewed this Health Consultation and concurs with its findings.

[Signature]

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Figure 1
ADM Mill and Warehouse
Southeast Minneapolis, MN