

METHYL BROMIDE

RISK CHARACTERIZATION DOCUMENT

Volume I

INHALATION EXPOSURE

Medical Toxicology, Worker Health and Safety, and
Environmental Monitoring and Pest Management Branches
Department of Pesticide Regulation
California Environmental Protection Agency

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CONTRIBUTORS

Principle Author: Lori O. Lim, Ph.D., D.A.B.T.
Medical Toxicology Branch

Toxicology Data Review: Stephen J. Rinkus, Ph.D.
Medical Toxicology Branch

Worker and Residential Exposures:

Thomas Thongsinthusak, Ph.D.
David Haskell *
Worker Health and Safety Branch
* *Currently with Registration Branch*

Terrell Barry, Ph.D.
Bruce Johnson, Ph.D.
Pam Wofford, M.S.,
Randy Segawa
Environmental Monitoring Branch

Reviewers: Joyce F. Gee, Ph.D.
Peter Leung, Ph.D., D.A.B.T.
Keith Pfeifer, Ph.D., D.A.B.T.
Jay Schreider, Ph.D.
Medical Toxicology Branch

Gary Patterson, Ph.D.
Chief, Medical Toxicology Branch

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FOREWORD

The Risk Characterization Document for Methyl Bromide is consists of three volumes. These volumes addresses the risk of human exposure to methyl bromide from inhalation (Volume I), oral (Volume II), or both routes (Volume III) of exposure. The introduction and toxicology in Volume I are applicable to Volumes II and III. These latter two volumes are currently being prepared. A document flow chart is provided on page vi. The risk from methyl bromide exposure is expressed as a margin of exposure which involves the consideration of both the toxicology and the human exposure levels under various scenarios. The calculated margins of exposures are used by the risk management to determine if mitigation measures are needed to modify the existing uses. For methyl bromide, the benchmark is a margin of exposure of 100; that is the human exposure should be 100-fold lower than the dose which did not cause any effect in experimental animals. Risk mitigation may be needed for any exposure with a MOE of less than 100. Reference concentrations are also provided in these documents and they are estimates of exposure levels to the human population that are likely to be without an appreciable risk. They are based on the toxicology and incorporated factors to account for uncertainty in the data. For methyl bromide, one such reference concentration is 210 ppb which has been used to develop the DPR permit conditions and regulations for acute inhalation exposure to methyl bromide.

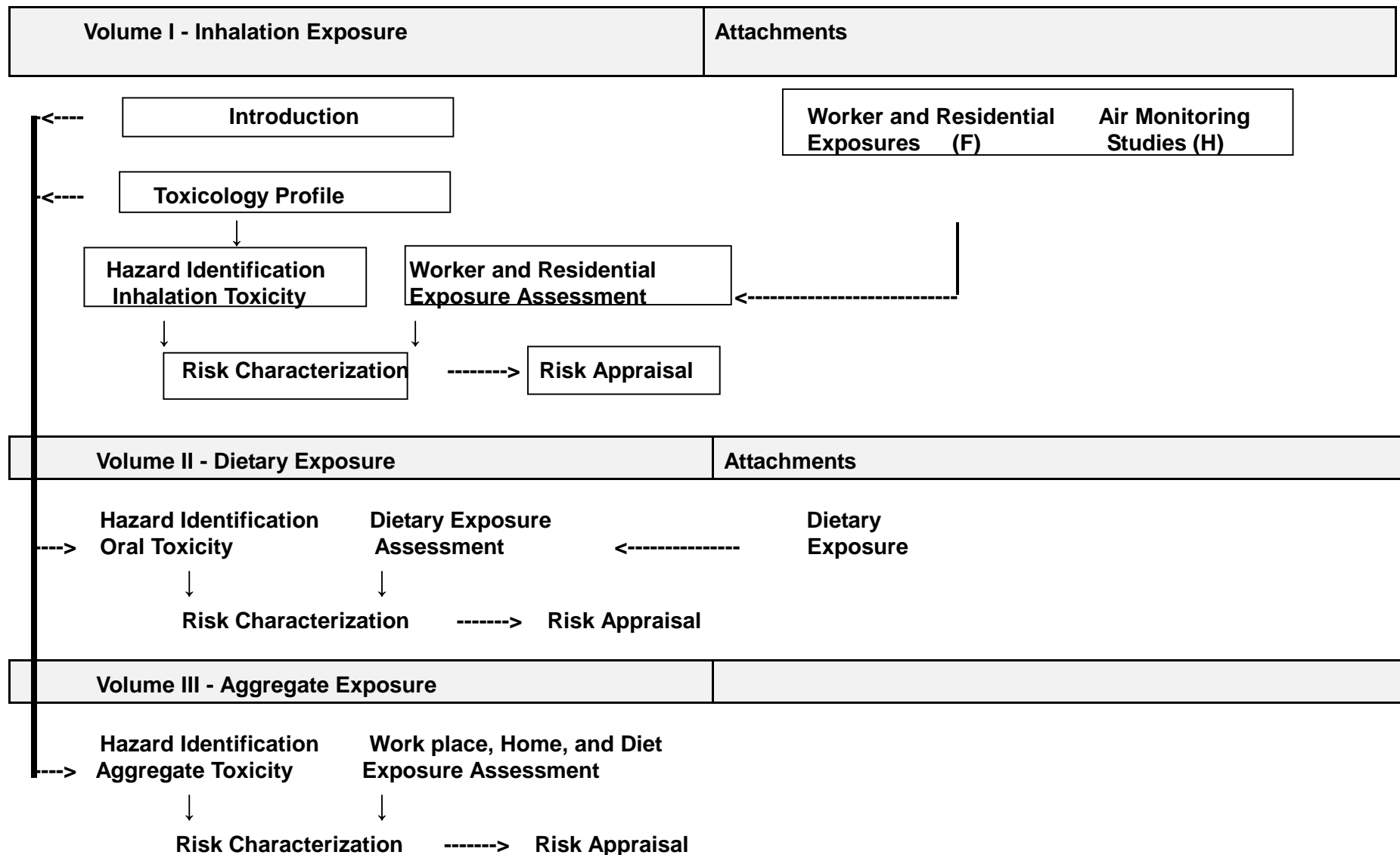
This Volume I on inhalation exposure supercedes previous documents on this subject. The DPR 1992 Preliminary Risk Assessment addressed only the acute and subchronic inhalation toxicity of methyl bromide (Attachment A). The toxicology data were limited in a document prepared for the Proposition 65 Developmental and Reproductive Toxicant Identification Committee (Attachment B). A 1998 preliminary draft of the Toxicology Profile and Hazard Identification sections was reviewed by the U.S. Environmental Protection Agency and Dr. Gerald Last, Professor at the University of California at Davis. A March 1999 draft was reviewed by the Office of Environmental Health Hazard Assessment (California Environmental Protection Agency) and the U.S. Environmental Protection Agency. Based on comments from these reviews, a draft of the risk characterization document for inhalation exposure was completed in October 1999 (DPR, 1999; refer to as "draft RCD/1999" in this Volume) and was made available to the public and was reviewed by the National Research Council Methyl Bromide Subcommittee in 1999-2000, under the mandate of Senate Bill 1320¹.

This document is a revision of the October 1999 draft and incorporated NRC comments as well as other needed changes to reflect current information. Overall, the major change was in the exposure assessment while there was no change in the critical endpoints or No-Observed-Effects Levels for risk characterization. A summary of the changes and the associated sections in the document is presented in the following table.

¹ SB1320 mandate for external peer review of the scientific portions of rules establishing a regulatory level, standard, or other requirement for the protection of public health and the environment.

Section	Revisions to the draft RCD/1999
FOREWORD	A new section was added to give background information and changes made since the draft RCD/1999 and a document organization chart.
I. TECHNICAL SUMMARY	Revised to reflect changes in the main text.
II. INTRODUCTION	II.B.- Updated regulatory information. II.C. and II.D.- Updated use information.
III. TOXICOLOGY	No change in the endpoints or NOELs.
IV. RISK CHARACTERIZATION	IV.A.1.- No change in the critical endpoints or critical NOELs. IV.A.2.d. - Added discussion on the oncogenicity. IV.B. - The worker exposure estimates were revised to reflect only work conditions allowed under the current DPR permit conditions/regulations. In addition, an upper bound level of 210 ppb, rather than the highest measured value, was used for acute worker exposure. The residential exposure section was also revised to include ambient monitoring results and estimates of exposure based on modeling and distributional analysis of buffer zone air concentrations. IV.C.- Margins of exposures were recalculated based on revised exposure values.
V. RISK APPRAISAL	V.A. and B.- No change in these sections V.C.- Revised discussion on the uncertainties in the worker and residential exposure data. V.D.2. - Added discussion on polymorphism.
VI. CONCLUSIONS	Revised to reflect changes in the main text.

DOCUMENT ORGANIZATION



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I. TECHNICAL SUMMARY

I.A. INTRODUCTION

In 1992, the Department of Pesticide Regulation (DPR) conducted a Preliminary Risk Assessment on methyl bromide to address acute inhalation exposures of residents reentering fumigated home. The risk assessment concluded that the reentry level of 5 ppm for residents posed a health hazard and an emergency regulation was promulgated to decrease the exposure. Subsequently, permit conditions were developed to reduce the acute exposure of workers and the residents living near fumigated fields and fumigation chambers. In 1999, a draft of the risk characterization for inhalation of methyl bromide was completed. This draft was reviewed by the National Research Council. This Volume I of the Risk Characterization Document is a revision of the 1999 draft.

I.A.1. Chemical Identification

Methyl bromide is a gaseous fumigant that kills insects, rodents, nematodes, weeds, and organisms that cause plant diseases. Since methyl bromide is released into the air during and after its use, there is a potential for exposure by the workers as well the general population living near the use sites. Methyl bromide is a restricted use pesticide for structural, soil, and commodity fumigations. In 2001, 54 products containing methyl bromide were registered in California. From 1996-1999, 11-16 million pounds were used each year in California.

The primary route of human exposure to methyl bromide is inhalation. Exposure may occur from accidental spills, drift, leakage, or residual levels of methyl bromide released after treatment. Signs and symptoms of inhalation exposure depend on the concentration and exposure duration. Early symptoms of acute exposure to lethal concentrations include: malaise, headache, visual disturbances, nausea, and vomiting. Later symptoms include delirium, convulsions, and respiratory failure or cardiovascular collapse leading to death. Nonlethal exposures result in neurological effects similar to the early symptoms for fatal exposure. These symptoms may persist after exposure, depending on the severity of the effects. Exposure of skin to methyl bromide results in vesication and swelling of the skin. The general population may also be exposed to methyl bromide-treated foods.

Since methyl bromide is acutely toxic, chloropicrin has been added to some methyl bromide formulations as a warning agent. However, there may not be a correlation between methyl bromide concentration in the air and the extent of the irritation induced by chloropicrin due to the differences in physical and chemical properties between these compounds. Also, chloropicrin itself is acutely toxic. With its increased use as a replacement for methyl bromide, there are increased concerns regarding the health effects from chloropicrin exposure.

I.A.2. Regulatory History

The Federal agencies have established regulatory levels for the uses of methyl bromide. For food uses, the U.S. Environmental Protection Agency (U.S. EPA) established tolerances based on inorganic bromide with the assumption that methyl bromide is completely degraded. The U.S. EPA oral chronic reference dose (RfD) is 0.0014 mg/kg/day. In the drinking water, the one-day, ten-day, and longer-term health advisories are 0.1 mg/L for children. The longer-term health advisory is 0.5 mg/L for an adult. The lifetime health advisory is 0.01 mg/L.

For methyl bromide in the air, the U.S. EPA inhalation reference concentration (RfC) is 5×10^{-3} mg/m³. The Agency for Toxic Substances and Diseases Registry minimum risk levels (MRLs) are 50 ppb, 50 ppb, and 5 ppb for acute, intermediate, and chronic exposure scenarios, respectively. For occupational exposure, the federal Occupational Safety and Health Administration permissible exposure limit (PEL) is 20 ppm while California established a lower limit of 5 ppm and a ceiling of 20 ppm. The reentry level is 1 ppm for structural fumigation within the wall voids. Methyl bromide is a Class I ozone depleter and its use is regulated by the U.S. Clean Air Act and the United Nations Montreal Protocol.

In California, the use of methyl bromide is continually being evaluated as regulations/permit conditions are modified to limit exposures. Additional exposure data are being developed in 2001-2002 to determine seasonal (subchronic) exposures. The need for the permit conditions was initially based on the Preliminary Risk Assessment conducted in 1992 to address potential health hazard associated with acute exposures after structural fumigation (Attachment A). In 1993, methyl bromide, as a structural fumigant, was administratively listed as a developmental toxicant by the Office of Environmental Health Hazard Assessment of the California Environmental Protection Agency under Proposition 65 via the provision for listing due to the federal label warning requirement. However, the Proposition 65 Developmental and Reproductive Toxicity Identification Committee decided not to expand the listing to all uses of methyl bromide because results from laboratory animals did not "clearly" show that methyl bromide was a developmental toxicant.

I.A.3. Environmental Fate

Methyl bromide is degraded in the environment. The rate of hydrolysis was enhanced by elevated temperature, ultraviolet irradiation, aerobic conditions, and high organic matter in the soil. Once applied to the soil, methyl bromide volatilized into the air or adsorbed onto soil particles. Because of degradation, methyl bromide residues were not detected in the groundwater or commodities grown on fumigated soil. Residues were found in treated commodities after post-harvest fumigation.

I.B. TOXICOLOGY PROFILE

I.B.1. Pharmacokinetics

Pharmacokinetic studies showed that after inhalation, intraperitoneal, and oral administrations, methyl bromide was rapidly absorbed and radioactivity (¹⁴C) was distributed to all tissues. With inhalation exposure, the percentages of the administered doses absorbed were similar in several species; they were 48% in the rat, 40% in the dog, and 52 to 55% in human. In the rat, the highest levels in the tissues, principally in the lungs, were reached immediately after exposure. With oral and intraperitoneal administration to rats, more than 90% of the dose was absorbed, with the highest radioactivity levels measured in the liver, kidneys, and testes. Methyl bromide was extensively biotransformed into unidentified products and carbon dioxide. In the rat, within 1 hour after inhalation exposure, less than 10% of the radioactivity in the tissues was intact methyl bromide. In humans, both methyl bromide and inorganic bromide were detected in the tissues 5 hours after a lethal dose exposure. The primary routes of excretion were the exhaled air for inhalation and intraperitoneal exposures, and the urine for oral exposure. Carbon

dioxide accounted for almost 50% (inhalation and intraperitoneal routes), and 30% (oral route) of the radioactivity in the exhaled air. After oral administration, biliary metabolites of methyl bromide were reabsorbed from the gut.

I.B.2. Acute Toxicity

Methyl bromide is a Toxicity Category I compound because of its acute inhalation toxicity. Severe irritation to eyes, skin, and mucous membranes occur after acute exposure; therefore, acute oral, ocular and dermal studies are not required for registration. Neurotoxicity has been observed in humans and laboratory animals after inhalation exposure to methyl bromide. The severity of the effects depended on the dose and duration of exposure. In humans exposed to high concentrations, neurological effects included ataxia, convulsion, and tremors. The nonlethal effects observed in laboratory animals included changes in brain catecholamines and tyrosine hydroxylase activity, tissue degeneration (nasal, brain, and adrenal glands), and neurotoxicity (ataxia and paralysis). Signs of oral toxicity in the dog included prostration, increased heart rates, lesions in multiple organs including the stomach and brain, hypoactivity, hypothermia, and death. Human dermal exposure resulted in skin lesions.

I.B.3. Subchronic Toxicity

Subchronic inhalation exposure of laboratory animals to methyl bromide resulted in altered brain catecholamine levels, decreased brain tyrosine hydroxylase activity, neurotoxicity, tissue degeneration (brain, nasal cavity, heart, testes, adrenal glands, thymus, spleen, and kidneys), and death. Based on overt signs of neurotoxicity, the dog, rabbit, and monkey were more sensitive to methyl bromide than other species (rat, mouse, and guinea pig). The primary finding after repeated oral exposure by gavage in the rat was hyperplasia of the forestomach. A decrease in body weight gain and food consumption was observed in rats given micro-encapsulated methyl bromide mixed in the feed.

I.B.4. Chronic Toxicity

The nasal cavity, brain, and heart were major target organs in rodents after chronic inhalation exposure to methyl bromide. Olfactory epithelial damage (hyperplasia, metaplasia, and necrosis) and myocardial degeneration were observed in rats and mice. Cerebellar and cerebral degenerations were detected in mice while reduced brain weight was observed in rats. When rats were exposed to methyl bromide in microcapsules mixed in the feed, the primary effect was body weight reduction. Possible treatment-related lesions were found in the spleen, liver, pancreas, and lungs. In male dogs given methyl bromide-fumigated feed, decreased hematocrit and hemoglobin levels were observed.

I.B.5. Genotoxicity

Methyl bromide was genotoxic in several *in vitro* and *in vivo* assays. It was a base-pair substitution mutagen in the *Salmonella* assays. It was a direct-acting mutagen since a liver S-9 fraction was not required for mutagenicity. It caused micronuclei formation in female mice and an increased frequency of sister chromatid exchanges in CHO cells and in mouse bone marrow cells *in vivo*. It did not induce unscheduled DNA synthesis in rat hepatocytes or cause sperm abnormalities in mice. DNA alkylation was detected in both rats and mice after *in vivo*

exposure by oral, intraperitoneal, or inhalation routes while DNA damage was found in the germ cells of rats after inhalation exposure. There was some evidence of genotoxicity in workers exposed to methyl bromide. Elevated levels of sister chromatid exchanges in lymphocytes and S-methylcysteine adducts in the blood were measured in soil fumigators. An increased frequency of hypoxanthine-guanine phosphoribosyl transferase gene (*hprt*) mutations in the lymphocytes and an increased incidence of micronuclei in oropharyngeal cells were observed in structural fumigators.

I.B.6. Reproductive Toxicity

In a 2-generation reproductive toxicity study in rats by inhalation, methyl bromide reduced the fertility rate of the F₁ parents during the second mating trial. While the body weights of the treated pups at birth showed varied responses, their body weights were significantly lowered during lactation. Brain weight and cerebral cortex width were reduced in the F₁ parents.

I.B.7. Developmental Toxicity

Methyl bromide caused developmental effects in both rats and rabbits after inhalation exposure. The findings in the fetuses included delayed skull ossification in rats and fused sternebrae, gall bladder agenesis, and other effects in rabbits. Methyl bromide did not cause any significant developmental effects in rats and rabbits after oral exposure.

I.C. RISK ASSESSMENT FOR INHALATION EXPOSURE

I.C.1. Hazard Identification for Inhalation Exposure

The evaluation of risks from exposure to methyl bromide followed the four steps of risk assessment: hazard identification, dose-response assessment, exposure evaluation, and risk characterization. In the hazard identification and dose-response assessment, a comprehensive review of the toxicology database from studies submitted by the registrant and published articles was conducted. From this review, the toxicity and the estimates of how much methyl bromide that could potentially cause an adverse effect as well as no-effect levels are identified for each study. Since human case reports did not provide sufficient details to derive the critical no-observed-effect levels (NOELs), results from experimental animal studies were used assuming that the effects observed in the animals would also be observed in humans. The NOELs were expressed as human equivalents (adult or child) to correct for the difference in respiration rates between humans and experimental animals. The studies with most relevant findings for risk assessment were then selected and the associated NOELs were expressed as critical NOELs to be used in the calculation of the margin of exposure (MOE) in the risk characterization step of the process. For methyl bromide, critical NOELs were determined for acute (one-time exposure), short-term (1-2 weeks), subchronic (7-13 weeks, seasonal), and chronic (a year or more) exposures. The National Research Council scientists (NRC) in their review of the draft RCD/1999 agreed with DPR selection of critical endpoints and NOELs for risk characterization.

For acute exposure, neurotoxicity is the primary effect of concern and has been observed in both experimental animals and humans. The clinical signs observed include: decreased activity, ataxia, paralysis, convulsion, and tremors. Of the laboratory animals studied, there was a species sensitivity to the neurotoxicity of methyl bromide after short-term exposure. Based on

the comparisons of the lowest-observed-effect level (LOEL) for neurotoxicity, the dog and rabbit showed greater sensitivity than the guinea pig, mouse and rat. For example, dogs exposed to 156 ppm (human equivalent level of 68 ppm) showed severe neurological effects in 2 to 7 days of exposure while rats exposed to the same concentration in terms of human equivalent level (65 ppm; 70 ppm actual air concentration) for the same exposure duration did not show any neurotoxicity. In pregnant animals, the rabbit was more sensitive to methyl bromide than the rat. For pregnant rabbits, severe neurotoxicity was observed at the LOEL of 70 ppm (Sikov *et al.*, 1981; Breslin *et al.*, 1990) while no neurotoxicity was reported in the pregnant rats at the same level (Sikov *et al.*, 1981).

The selection of results from the most sensitive species, in this case the dog, is consistent with the U.S. EPA Neurotoxicity Risk Assessment guidelines (U.S. EPA, 1998a). The critical NOEL was 103 ppm from short-term inhalation studies in the dog (Newton, 1994a and b). At this dose of 103 ppm, no effects were observed until the 8th day of exposure. Although the dog inhalation toxicity studies were not designed to be a neurotoxicity study as defined by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guideline, they were conducted under Good Laboratory Practices and DPR considered the results valid for hazard identification. These same data were used by the Methyl Bromide Industry Panel (MBIP) to support their position that a chronic inhalation toxicity study in the dog should not be required (CMA, 1994).

The selection of the 103 ppm dose as the acute NOEL considered three major factors: subjectiveness of the observations, severity of the neurotoxicity at higher concentrations, and possibility of delayed neurotoxicity. The finding of no effect at 103 ppm in the dogs was based on gross observations. Neurotoxicity may have been present but not detected unless more refined methods such as the Functional Observation Battery were used. Therefore it is possible that the actual NOEL may be lower than 103 ppm. Furthermore, severe neurotoxicity was observed at higher doses (1.5 times the NOEL) with a few additional days of exposure. At 156 ppm, one of two dogs showed lacrimation (tearing) on the first day. This finding by itself may arguably be considered less significant with respect to adversity. However, there were only two dogs in this group. With 2-3 days of additional exposure, there was significant toxicity as both dogs showed difficulty breathing and decreased activity. In another study, all dogs (8 in the group) exposed to 158 ppm showed decreased activity before the end of the second exposure day. With 5 additional days of exposure, all showed severe neurotoxicity and brain lesions. The selection of 103 ppm as the acute NOEL also addresses, indirectly, the possibility of delayed neurotoxicity which has been reported in humans after accidental poisonings. Since no effects were observed in the dogs at 103 ppm for 7 days of continuous exposure, it is unlikely that there would be delayed neurotoxicity within one week after a single exposure to the same level. The human equivalent NOEL (25 ppm) from the dog study was two-fold or less than those for the acute effects observed in the rats and guinea pigs.

Another endpoint DPR considered for acute exposure risk assessment is the developmental toxicity observed in experimental animals after methyl bromide exposure. In a developmental toxicity study, the pregnant animals were exposed continuously to methyl bromide during a specified period of gestation (when organ formation occurs). Any adverse effect observed in the fetus is considered an acute effect under the current assumption that only a single exposure at a critical time is necessary for the induction of developmental adverse effects according to the U.S. Environmental Protection Agency Guidelines for Developmental Toxicity Risk Assessment. Since this endpoint is the result of exposure during pregnancy, it is

only used for the assessment of exposure by women of childbearing age in the work force and the general population.

The critical NOEL for developmental toxicity was 40 ppm from a study with rabbits (Breslin *et al.*, 1990). The result from this study was the basis for the emergency regulation and permit conditions currently used in California. U.S. EPA also considered these endpoints of concern and has used the same study in a Section 18 evaluation on the use of methyl bromide on imported fruits at ports of entry. In this rabbit developmental toxicity study, fetuses exposed to 80 ppm *in utero* showed gall bladder agenesis (no gall bladders), fused sternebrae (early fusion of the sternebrae), and lowered body weights. The missing gallbladder finding was seen in Part I of the experiment, which by itself is a complete study and fulfilled FIFRA guidelines for an acceptable study. The investigator was concerned with the finding as it was rarely observed in the negative-control litters in the conducting laboratory as well as in other laboratories using the same rabbit strain. When the experiment (Part II) was repeated three months later, missing gall bladders were again observed in fetuses exposed to methyl bromide *in utero*. The fused sternebrae found in Part I was not confirmed since a skeletal examination was not performed in Part II.

The developmental toxicity effects observed in fetuses should not be discounted because of maternal toxicity (body weight changes and neurotoxicity) reported at the same dose level. Consideration must be given to when the effects were observed. First, the decrease in the body weight gain of the 80 ppm group does was not a consistent finding. Statistically significant decreases were reported for gestation days 13-16 in Part I and gestation days 7-20 and 10-13 periods in Part II. The reduced weight gain in the does of Part II occurred concomitantly with a reduction in the mean fetal body weight. Second, there was no significant difference in the strictly maternal parameter calculated as the terminal body weight minus gravid uterine weight. Third, body weight changes in pregnant rabbits are known to be more variable than in rodents. As a result, body weight changes often do not carry as much support as an indicator for maternal toxicity as for rodents as discussed in the U.S. EPA Developmental Toxicity Risk Assessment guidelines. Fourth, maternal neurotoxicity was characterized by clinical signs, including: lethargy, head tilt, slight ataxia and slight lateral recumbency. These signs were observed in only 3 of 43 does (7%) dosed at 80 ppm, and they did not appear until gestation days 19-20 (the last days of the 13-day exposure period). Based on the description and comparison with observations reported in other studies, DPR does not consider these signs as indicators of excessive toxicity.

Furthermore, the failure of gall bladders to form in some fetuses was independent of maternal neurotoxicity. In Part I, 6 of the fetuses with missing gallbladders were from 3 does without neurotoxicity while the remaining 7 affected fetuses were from 2 does with neurotoxicity. In Part II, none of the does showed neurotoxicity while 4 fetuses (from 4 does) had missing gallbladders. In addition, the development of the gall bladder in rabbits can be considered an acute event since it takes place in one to two days after its onset on gestation day 11.5 (Hoar and Monie, 1981). The maternal neurotoxicity reported on gestation days 19-20 would have occurred too late to have been a factor in the agenesis of the gall bladder.

Similar findings have not been reported in the rat developmental toxicity studies. While it is worth noting that rats do not have gall bladders, the absence of these findings in another species should not negate their significance as indicators of the potential for methyl bromide to

cause developmental toxicity in humans. Species specificity in developmental effects has been demonstrated for some chemicals. Developmental toxicity testing under FIFRA guidelines requires two species to be tested, a rodent and a non-rodent species, typically the rabbit, for identifying species susceptibility. The need to test non-rodent species arose from the findings of thalidomide where it was demonstrated that this human teratogen did not exhibit significant teratological effects in rats but caused at least some significant effects in rabbits (Schardein, 1985). As stated in the U.S. EPA Developmental Toxicity Risk Assessment guidelines, developmental effects may not be evident in more than one species. The findings from the most sensitive species are appropriate to use to estimate human risk.

The significance of the developmental toxicity findings was discussed in a 1994 Proposition 65 meeting to determine whether methyl bromide should be listed for all uses. The emergency regulation in 1992 resulted in methyl bromide being listed as a chemical known to the State of California to be a reproductive toxicant. The Developmental and Reproductive Toxicity Identification (DART) Committee was presented with results from animal developmental toxicity (absence of gall bladders and fused sternebrae) and reproductive toxicity (decreased pup body weight) studies. After much discussion, the Committee voted not to expand the listing of methyl bromide from structural fumigation to all uses because there was not enough evidence to support the "clearly shown" criteria as mandated by the Proposition. However, the members expressed several concerns: the need for more experimental studies to clarify the findings, potential for exposure to methyl bromide via the milk during lactation, and the lack of information on human exposure especially during pregnancy.

After this meeting, DPR received additional data to support the consideration of reproductive or developmental toxicity as a pertinent endpoint for risk assessment and regulatory actions. First, supplemental data on the rat reproductive toxicity study showed that methyl bromide caused a reduction in the width of a certain part of the brain (cerebral cortex) in the F₁ adults exposed to methyl bromide *in utero* (American Biogenics Corp., 1986). Second, a study received by DPR in 1998 showed that methyl bromide caused a breakage of DNA in the testicular cells isolated from rats after inhalation exposure (Bentley, 1994). It is not known whether the effect was due to methyl bromide or a metabolite.

DPR also considered studies which showed that methyl bromide caused biochemical changes in the brain which may be associated with neurotoxicity. In the rat, acute exposure to methyl bromide has been shown to alter catecholamine (chemicals involved in the transmission of brain signals) levels and tyrosine hydroxylase (an enzyme involved catecholamine formation) activity in the brain. However, an extensive review of the published articles on this subject by DPR showed inconsistencies in the findings; thus, they were considered not appropriate for use in the determination of regulatory levels. The results of one of these study were used by the Agency for Toxic Substances and Diseases Registry of the Public Health Service to derive a minimum risk level as a screening tool for regulatory agencies to determine the need for regulation. As such, the study review did not critically analyze the results. This minimum risk level has not been adopted as an action level by any regulatory agency.

Therefore, two acute NOELs were selected to address the different human sub-populations. The NOEL of 40 ppm for developmental toxicity in the rabbit was most appropriate for workers and residents since women of child bearing age are in both groups. For children, the NOEL was 103 ppm for neurotoxicity in the dog. When these NOELs are converted to

human equivalent NOELs taking into consideration of duration of exposure and the differences in the respiration rates between species, and between adults and children, the human equivalents were 21 ppm and 25 ppm, respectively, for developmental toxicity and neurotoxicity. The use of the lower human equivalent NOEL of 21 ppm compared to 25 ppm to address occupational and residential exposures would protect children from the effects of methyl bromide.

For short-term and subchronic exposures, neurotoxicity was also selected as the endpoint for the determination of the critical NOELs and was based on the same considerations as discussed for acute exposure. For short-term (1week) exposure, a NOEL was established to address the potential exposure of residents returning to fumigated homes, living near fumigated fields, and workers. The critical NOEL was 20 ppm based on neurotoxicity (convulsion, paresis) in the rabbit after exposure to 70 ppm for 1 week (Sikov *et al.*, 1981). Three of 26 does died after 9 to 10 days of exposure.

For subchronic exposures of longer duration (90 days, seasonal), the critical NOEL was an estimated NOEL (ENEL) of 0.5 ppm based on a lowest-observed-adverse-effect level (LOAEL) of 5 ppm for decreased responsiveness in two of eight dogs during a neurological examination after 6 weeks of exposure (30 exposure days) and a default factor of 10 for the calculation of a NOEL from a LOAEL (Newton, 1994b). While the duration is shorter than the 13-week generally considered for subchronic exposure, it was chosen because of the endpoint (neurotoxicity) and species sensitivity (the dog is a more sensitive species than the rat to methyl bromide) considerations. It is possible that the NOEL may be lower if the dogs were exposed to methyl bromide for 13 weeks.

This ENEL was lower than the NOEL (3 ppm) for lowered body weights of rat pups from dams exposed to methyl bromide before mating and during part of the pregnancy in the reproductive toxicity study (American Biogenics Corp., 1986). Another study also showed a NOEL (estimated) of 3 ppm based on a dose-related decrease in brain weight at 30 ppm and higher concentrations in the female rats (Norris *et al.*, 1993 a and b). The brain weight was also significantly decreased in the 140 ppm male rats. This effect on the brain weight was considered biologically significant since the brain is a target organ of methyl bromide. The absence of neurotoxicity by Functional Observational Battery testing at the same dose (30 ppm) does not diminish the importance of the brain weight finding since the causes of the two effects are not necessarily related.

For chronic inhalation exposure, all chronic studies conducted with rodents (rats and mice), reproductive toxicity study, and subchronic dog inhalation toxicity study were considered in the determination of the chronic critical NOEL. After chronic inhalation exposure, tissue damage was noted in the nasal cavity, brain, and heart of rodents. The critical NOEL was an ENEL of 0.3 ppm based on a LOAEL of 3 ppm for the induction of an increase in the number of cells (hyperplasia) and change in cell type and function (degeneration) in the nasal cavity of rats after 24-29 months of exposure and a default factor of 10 for the calculation of a NOEL from a LOAEL (Reuzel *et al.*, 1987 and 1991). While the exposure duration was considered a life-time for the rodents, the actual duration in the standard chronic toxicity studies is two years. Since humans may be exposed to methyl bromide on a yearly basis, not just one or two years in the lifetime, the NOEL from the chronic toxicity study after two years of exposure was, therefore, appropriate for use. This NOEL may underestimate the risk of repeated yearly exposure as

there is evidence of cumulative toxicity, in particular, neurotoxicity. The LOEL (3 ppm) from this 29-month study for nasal olfactory epithelial damage (Reuzel *et al.*, 1987 and 1991) is further supported by the LOEL of 4 ppm from a 24-month study for lesions at the same site (Gotoh *et al.*, 1994). The U.S. EPA also used the same LOAEL from this study in the determination of the chronic reference dose (RfC).

The significance of the finding in the nasal cavity is that it showed methyl bromide not only injured the cells but also changed the normal function of the cells in the nasal cavity. Such damage may result in the loss of the animal's sense of smell. Tissue damage in other organs occurred at higher concentrations. With acute exposure to 200 ppm, the damage to the rat olfactory epithelium included epithelial disruption, fragmentation, and exfoliation (Hurt *et al.*, 1988). Repair of the epithelium included replacement by a squamous epithelium, loss of sensory cells, and respiratory metaplasia (conversion of the olfactory epithelium to a ciliated respiratory type). In other short-term studies, the damage to the nasal epithelium was described as necrosis and degeneration (Eustis *et al.*, 1988) and dysplasia (NTP, 1992; Eustis, 1992). In the chronic inhalation toxicity study, nasal olfactory epithelial hyperplasia and degeneration were observed in the rat (Reuzel *et al.*, 1987 and 1991).

While the effect on the nasal cavity may generally be considered a finding confined to the rat due to anatomical considerations, it is not the case with methyl bromide. Dogs exposed to 156 ppm methyl bromide for only 6 days showed moderate to moderately severe olfactory degeneration (Newton, 1994b). In addition, the rodent studies are the only available studies to evaluate the chronic toxicity. The requirement for a non-rodent (dog) study was waived by DPR based on the evaluation of short-term studies in the dog which showed that a chronic study would have to be conducted at relatively low dose levels. For comparison, the ENEL of 0.3 ppm for nasal cavity effects when expressed as human equivalent level (0.1 ppm) was the same as the human equivalent level for neurotoxicity after subchronic exposure (ENEL of 0.5 ppm). This implied that the actual NOEL for chronic exposure if based on neurotoxicity could be lower than that based on the effects in the nasal cavity. However, it is not possible to extrapolate such a NOEL at this time because the subchronic NOEL was already an estimated NOEL based on a LOEL which was reduced by a 10-fold uncertainty factor.

The oncogenicity of methyl bromide can not be evaluated at this time because experimental studies showed neither dose-related increased incidence of tumors after treatment nor sufficient data to determine the incidences. There is evidence that methyl bromide causes damage to the genetic material in experimental animals and humans, which is generally considered to play a significant role in the process of tumor formation.

A summary of the critical NOELs for inhalation exposure risk characterization is presented below:

Scenarios	Experimental NOEL	Human Equivalent NOEL ^a		Reference Concentration ^d	Effects in Animal Studies	Ref ^e
		Adult ^b	Child ^c			
Acute	40 ppm	21 ppm	na	210 ppb	Developmental toxicity (pregnant rabbit)	1*
	103 ppm ^f	45 ppm	25 ppm		Neurotoxicity (dog)	2
Subchronic 1 week	20 ppm	12 ppm	7 ppm	120 ppb(adult) 70 ppb (child)	Neurotoxicity (pregnant rabbit)	3
6 weeks	0.5 ppm (ENEL)	0.2 ppm	0.1 ppm	2 ppb (adult) 1 ppb (child)	Neurotoxicity (dog)	2
Chronic	0.3 ppm (ENEL)	0.2 ppm	0.1 ppm	2 ppb (adult) 1 ppb (child)	Nasal epithelial hyperplasia(rat)	4*

- a/ Experimental NOELs were converted to human equivalents using equations in Attachment G. na= child equivalent NOEL were not calculated because the effects were observed in pregnant animals. ENEL=estimated NOEL and is 1/10 of the LOEL in the study.
- b/ The adult equivalent NOELs are appropriate to address worker exposures. They are also used for residential exposures when child equivalent NOELs were not calculated.
- c/ The child equivalent NOELs are appropriate to address resident exposures (see footnote b).
- d/ The reference concentration was the ratio of the human equivalent NOEL and a default uncertainty factor of 100 since the NOEL was derived from experimental animal studies.
- e/ * indicates study was acceptable to DPR according to FIFRA guidelines. References: 1. Breslin *et al.*, 1990b; 2. Newton, 1994b; 3. Sikov *et al.*, 1981; 4. Reuzel *et al.*, 1987 and 1991.
- f/ The NOEL and human equivalents are presented in this Table for comparison purposes only. They are not used for risk characterization.

I.C.2. Exposure Assessment for Workers and Residents

Human exposure assessment was conducted for occupational and residential inhalation exposures to methyl bromide. Compared to the draft RCD/1999, this exposure assessment was revised to incorporate NRC recommendations and changes after re-evaluation of the database, methodology, and DPR regulations.

Occupational Exposure

The inhalation exposures of applicators in structural fumigation were not determined because they are required to wear self-contained breathing apparatus. No data were available for other workers such as tarp removers.

For field fumigation, monitoring studies were conducted primarily to determine the effectiveness of modifications to existing application procedures and aeration of treated fields. With shallow-shank and tarp fumigation, workers involved in the application with no modifications had higher exposures than those in other methods. The acute exposures of applicator, copilot, and shovel-man ranged from 188 ppb to 245 ppb. The best method involved both swept-back shank and closing shoes where the applicators, copilots, and shovel-men exposures were 1 ppb to 58 ppb. The driver (7 ppb) and copilot (62 ppb) of the tractor in the placement of tarp had lower acute exposures than those involved in the application. For tarp cutting and removal, one study showed acute exposures of 202 ppb and 215 ppb while another study showed workers with higher acute exposures (22 to 1058 ppb). With deep-shank injection, the applicators with only overhead fan had the highest acute exposure at 281 ppb. Lower acute exposures were measured for applicators in tractors with modifications such as overhead fan and scrapers and rollers (104 ppb), enclosed cab (161 ppb and 171 ppb), and enclosed cab with scrapers (13 ppb). When a second tractor with a disc or cultipacker was involved, the drivers had relatively lower exposure (13-181 ppb) than those for applicators, except for the disc driver (934 ppb). For both short-term and subchronic exposures in shallow-shank and deep-shank methods, the exposure patterns were similar to those for acute exposures which were the basis for the calculations. Chronic exposure was not expected for any of the work scenarios. For workers at adjacent fields, there were no data and their exposures were assumed to be at 210 ppb.

For workers with potting soil in greenhouses, the maximum acute exposure was 210 ppb. Their actual exposures were relatively low because tarp venters are required to wear self-containing breathing apparatus, and tarp removal occurs after 48 hours of venting. The short term exposures, based on measured values, were 0.001 ppb and 0.14 ppb for these two group of workers. No subchronic or chronic exposures were determined for this activity. No data were available for other workers, e.g., applicators, associated with this use.

For commodity fumigation workers, the acute exposure was 210 ppb and the exposures for other durations based on the average of measured values. For workers involved in the fumigation of grain products, the range of short-term exposures was 0.02 ppb to 11 ppb. The forklift drivers of sea containers/trailers had higher subchronic and chronic exposures (8 ppb) than those (3 ppb) for non-certifying fumigation chambers. For workers involved in the fumigation of raisins, the range of short-term exposures was 3 ppb to 180 ppb. For workers in a walnut processing plant, workers in clearing plant (178 ppb) and vacuum chamber (180 ppb) had

the highest short-term exposure compared to other areas. The lowest average short-term level (25 ppb) was measured in the special cracking area. For both raisin and walnut workers, the short-term and subchronic exposure levels were similar. Chronic exposure was considered for raisin processing workers but was not expected for most walnut processing workers.

For workers in a brewery, exposures were estimated for applicators and aerators at various locations. The acute exposure was assumed to be at 210 ppb. The short-term exposure level ranges were 7-49 ppb for aerators and 8-12 ppb for applicators. No seasonal or chronic exposures were expected.

For workers in the facilities but whose tasks were not directly related to commodity fumigation, data were available only for raisin and walnut fumigations. The exposure levels were either based on the acute level of 210 ppb or measured by ambient and area sampling. The range of short-term exposures ranged from 7 ppb to 180 ppb. The subchronic and chronic exposures (except for walnut processing) were comparable to those for short-term levels because of the frequency of exposure.

Residential Exposures

The exposures of residents returning to homes after fumigation and aeration were not estimated due to lack of data on current practices. DPR regulations limit the maximum acute exposure at 210 ppb.

Residential exposures to field fumigation were determined using monitoring data and computer modeling of the data. Maximum methyl bromide air concentration was related to the size of the field and emission rate (depending on the method of application). At the 95th percentile, the exposure ranges for each field sizes were: 161-174 ppb (1 acre), 163-215 ppb (10 acre), 201-225 ppb (20 acres), 213-230 ppb (30 acres), and 221-236 ppb (40 acres).

The acute exposure for residents living near commodity fumigation facilities was limited to 210 ppb. The exposures for the longer-term durations were 90-180 ppb (short-term), 70-175 ppb (subchronic), and 86-106 ppb (chronic).

For residents living in methyl bromide use areas which may include field, commodity, and structural fumigations, ambient air monitoring at the 95th percentile daily exposure levels ranged from 0.239 ppb (Mettler Fire Station) to 30.2 ppb (Pajaro Middle School in Watsonville). Levels at these two sites also provided the ranges for weekly (0.163 to 17.1 ppb), and 7-8 week (0.084 to 7.68 ppb) exposure durations. Additional monitoring has been conducted by the Air Resources Board and the registrant to characterize the exposures.

I.C.3. Risk Characterization for Inhalation Exposure

The NOEL at which adverse effects did not occur was used to assess the non-cancer hazard for potential human exposures to methyl bromide. The margin of exposure (MOE) was compared with a conventional benchmark level of 100. The MOEs varied from <1 to greater than 1000 for occupational and residential exposures.

Occupational Exposure

Margins of exposures were not calculated for workers involved in structural fumigation. The acute MOE for the applicators was assumed to be greater than 100 since these workers are required to be in a self-contained breathing apparatus.

With shallow-shank/tarp/broadcast fumigation, the acute MOEs were 112 (applicator), 86 (copilot), and 110 (shovel-man) for workers Noble plow and overhead fan. The MOEs were higher for the workers in shallow-shank/tarp/bed fumigation and various equipment modifications. The MOEs for these applicators were 144 to 5250 for swept-back shank and closing device. For copilots, the MOEs varied depending on the modification. The MOE was 69 when a conventional shank was used, even though scrapes/closing shoes were added. The MOEs were 111 when the copilot was in a raised platform and 362 when swept-back shank and closing device were used in the application. The MOEs for the driver and copilot in the second tractor for tarping were 3000 and 339, respectively. The MOEs for workers in tarp cutting and removal varied depending on the study even though similar procedures were used. In one study, the MOEs were 104 and 98; in the second study, the range of MOEs was 20 to 955. With deep-shank injection, the applicators with only overhead fan had the lowest MOE of 75. The range of MOEs were: 130 to 1614. The MOEs for driver in the second tractor with a cultipacker were also higher when scrapers were used after application. The MOE increased from 116 (no modifications) to 164-1615 (use of scrapers and/or rollers). The MOE was only 22 for the disc driver. For both shallow-shank and deep-shank methods, the MOEs for almost all short-term exposures were 100 while subchronic exposures were less than 100. Chronic exposure was not expected for any of the work scenarios. For workers at adjacent fields, the acute MOE could be assumed to be 100 with the exposure not to exceed 210 ppb.

The acute MOEs for all workers in commodity fumigation facilities were 100 because their upper exposure limit was 210 ppb. For tarp ventors and removers of potting soil fumigation in greenhouses, the MOEs for short-term exposures were greater than 80,000 because of their relatively low actual exposures. No data were available for other workers. In the fumigation of grain products, MOEs for these workers were greater than 100 for the aerators for all exposure periods. For forklift drivers, the short-term MOEs were > 1000 but the subchronic and chronic MOEs were less than 100 (MOEs of 25 and 67). For workers involved in the fumigation of raisins, the range of MOEs for short-term exposures was 67 to 4000. The MOE of 67 was based on the use of 210 ppb as the daily exposure value. The MOEs for subchronic and chronic exposures were less than 100, except for the forklift drivers with a MOE of 100. For workers in a walnut processing plant, the MOE was 67 for workers with the highest exposures (in clearing plant or vacuum chamber). This MOE was based on measured values (cleaning plant) and the 210 ppb limit (vacuum chamber). The highest MOE was 480 for workers at the special cracking area. The MOEs for subchronic and chronic exposures were less than 10. For workers in a brewery, the MOEs for applicators and aerators were ranged from 245 to 1714.

For workers in fumigation facilities, not directly related to fumigation, the short-term exposure MOEs were generally greater than 100 (MOE of 121 to 1714) for raisin facilities. The short-term MOE for walnut processing was 500 based on area sampling but was 67 based on 210 ppb as the daily exposure level in sorting and packaging areas. However, the subchronic and chronic exposure MOEs for both raisins and walnut processing facilities were less than 100 based on either measured values or 210 ppb.

Residential Exposure

For residents living in treated home after aeration, the acute MOEs were assumed to be at least 100 since regulations were based on the 210 ppb for acute exposure.

For residents living next to the buffer zone of field fumigation, the MOEs were 98 to 131 for the 95th percentile of methyl bromide air concentration determined for 1 and 10 acres field sizes and all emission rates. For 20 and 30 acres, the MOEs were around 100 (96 to 104) with the exception of 91 and 93 for 80 lbs emission rate. For 40 acres, the MOEs were 89 to 95 for all emission rates. At the 90th percentile air concentration, all MOEs were at or greater than 100.

The acute MOE for residents living near commodity fumigation facilities was 100 because the exposure was assumed to be 210 ppb. However, the MOEs were 39-78, 1, and 1, respectively, for short-term, subchronic, and chronic exposures based on 210 ppb as the average daily exposure levels.

For residents living around methyl bromide uses, ambient air monitoring of 12 sites showed MOEs ranged from 695 to >80,000 for acute exposure, and from 409 to > 40,000 for short-term exposures. For 7-8 weeks of exposure, the MOEs for 7 of the sites were greater than 100 (range from 126 to 1190). The MOEs for the remaining sites ranged from 13 (Pajaro Middle School) to 78 (Salinas Ambient Monitoring Station).

I.D. RISK APPRAISAL FOR INHALATION EXPOSURE

Certain limitations and uncertainties were incorporated into the hazard identification, exposure assessment, and risk characterization of methyl bromide.

I.D.1. Hazard Identification

For acute inhalation exposure to methyl bromide, the critical NOEL was based on developmental effects observed in rabbits with the assumption that methyl bromide will also cause developmental toxicity in humans. There are no data to support or refute this assumption. The reference concentration (210 ppb) for this NOEL was only 1.5-fold lower than that for neurotoxicity in humans (350 ppb). The endpoints for the critical short-term and subchronic exposures were based on neurotoxicity in the pregnant rabbit and dogs, respectively. There were uncertainties associated with the use of hyperplasia/degeneration to the nasal cavity of rats as the endpoint to evaluate chronic inhalation toxicity. One uncertainty was the interspecies variability in the nasal cavity between rodents and humans. Additional information on the pharmacokinetics of methyl bromide in the nasal cavity epithelium of animals and humans would permit additional consideration of this endpoint.

In this RCD, both the subchronic and chronic NOELs were estimated from the LOEL, the lowest dose tested. The estimated subchronic NOEL was 0.5 ppm based on neurotoxicity observed in two of eight dogs exposed to 5 ppm for 34 exposures. Due to limitation in the database, a default factor of 10 was used for the extrapolation. For chronic exposures, the estimated NOEL was 0.3 ppm based on a LOEL of 3 ppm for nasal epithelial hyperplasia and degeneration in the rat and an uncertainty factor of 10. The mildness of the lesion at the LOEL suggested that an UF of less than 10 might be sufficient to estimate the NOEL from the LOEL.

I.D.2. Inhalation Exposure Assessment

The major limitation in the worker (all uses) and residential (commodity fumigation) exposure assessment was that data were not available for many scenarios as some acute exposures were assumed to be or limited to 210 ppb. The use of 210 ppb exposures might be over- or underestimation of actual acute exposures. Of the available data, there were many deficiencies in the overall database and they included: small sample size, incomplete report, and short monitoring period. Potential areas of underestimation were the assumptions of single work task per day and no overtime worked. One area of overestimation was the use of 50% recovery value to adjust all data.

For residential exposure to field fumigation, there were also uncertainties in the determination of the maximum methyl bromide air concentration distribution along the buffer zone perimeter of fumigated fields. These uncertainties included: the precision and accuracy of the sampling and analytical methods, influence of environmental factors on air concentrations, application variability, use of default weather conditions, and use of default assumptions in estimating air concentrations associated with overlapping applications. Actual exposure may be underestimated or overestimated because of these uncertainties.

I.D.3. Risk Characterization

For risk characterization, the uncertainties included the use of uncertainty factors to address extrapolation of no-effects from experimental animals to humans (interspecies), and accounting for intraspecies variations. The sensitivity of humans and laboratory animals to methyl bromide toxicity was difficult to compare because of inadequate exposure information in human case reports. The current DPR default factor of 10-fold was used to address interspecies extrapolation. For intraspecies variation in the response to methyl bromide, the default uncertainty factor of 10 was also used because human illness/poisoning reports did not provide sufficient information to derive another factor. Studies on genetic polymorphism of glutathione-S-transferase (GST) in humans provided some evidence for variations in human response to methyl bromide. However, there were insufficient data to conclude that GSTT polymorphism leads to increased susceptibility to methyl bromide toxicity and to determine whether or not the variation is sufficiently addressed by the 10-fold default intra-individual uncertainty factor.

I.D.4. Issues related to the Food Quality Protection Act

There may be a potential for increased sensitivity of infants and children to the neurotoxicity of methyl bromide based on consideration of the maturity of the central nervous system. Given that methyl bromide is a potent neurotoxicant and there are no data on developmental toxicity, an additional uncertainty factor was suggested to address the potential increased sensitivity for infants and children. However, the NRC in the review of the draft RCD/1999 did not recommend such a factor mainly because the DPR selected NOELs for risk characterization that were considered adequately protective for these groups.

As for other Food Quality Protection Act issues, there could be a potential for aggregate exposure from occupation or residential exposures and dietary exposures. This aspect is being

addressed in a separate document. There is a potential for cumulative toxicity between methyl bromide and other alkylation agents. However, appropriate approaches are not available at this time. Based on available studies, methyl bromide has not been shown to cause endocrine disruption effects.

I.E. CONCLUSIONS FOR INHALATION EXPOSURE

The human health risk from potential inhalation exposure to methyl bromide was evaluated in this Volume I of Risk Characterization Document. The critical toxicity endpoints were derived from experimental animals: developmental toxicity for acute exposure, neurotoxicity for short-term and subchronic exposures, and tissue damage to the nasal cavity for chronic exposures. For acute and chronic exposure endpoints, neurotoxicity was also considered in the determination of the critical NOELs. The risks, expressed as the margins of exposure, were calculated for workers and residents involved or living in the vicinity of structural, field and commodity fumigations. Generally, a MOE of at least 100, which takes into account the possibility of 10-fold variations in susceptibility within the human population as well as between laboratory animals and humans, is considered adequate to protect humans from the effects of concern. Exposure scenarios with MOEs of less than 100 should be considered in the risk management process.

With structural fumigation, the acute MOEs for workers and residents were assumed to be at least 100 based on restrictions in the DPR regulations. However, data are needed to estimate actual exposures for acute and short-term exposures for workers and residents.

For field fumigation, the acute MOEs for workers were at or greater than 100 because of the most effective equipment modifications and work hour restrictions were placed in DPR regulations. However, there were work tasks with acute and short-term MOEs of less than 100 which are not specifically excluded in the regulations. They were: disc driver (acute MOE of 22, deep shank injection), and tractor drivers and basket-men in tarp removal (acute MOE of 20-21, tarp shallow with Noble plow shanks). For subchronic exposure, most of the worker tasks had MOEs of less than 100; many were less than 10 and included applicators, copilots, disc drivers, and tarp removers. The MOE for workers at adjacent fields was assumed to be 100 since they work outside of the buffer zone. Actual data are needed to verify this assumption as analyses for the effectiveness of buffer zones showed MOEs of less than 100 for some applications (in particular large fields and certain emission rates). For residents living at the buffer zone perimeter of fumigated fields, the acute MOEs were generally around 100 for the 95th percentile exposure except for a MOE of 91 for 30 acres and 80 lbs emission rate, and MOEs of 89-95 for 40 acres and all emission rates. The acute MOEs were generally greater than 100 at the 90% percentile exposure. No assessment was conducted for repeated exposures.

For commodity fumigation, the acute MOEs for workers involved in fumigation were at 100 because DPR regulation set work hour restrictions to limit the maximum exposure at 210 ppb. The actual MOEs were likely higher as the upper limit may not be reached in some scenarios. The short-term MOEs were greater than 100 for all work tasks based on actual measurements; the only exception was a MOE of 67 for the task of cleaning plant. The MOE was also 67 when the daily exposure was set at 210 ppb for raisin (clear chamber) and walnut (vacuum chamber) workers. The subchronic and chronic MOEs were generally less than 100

based on measured values and exposures amortized from 210 ppb.

For workers doing other tasks in commodity fumigation facilities, the acute MOEs and many of the short-term MOEs were at or greater than 100. The only exception was the short-term MOE of 67 for workers at the sorting or packaging areas and their exposures were based on 210 ppb as daily exposure. The subchronic and chronic MOEs for all workers were at or less than 67. Additional data are needed to characterize the exposures of these workers at the facilities. For residents living near fumigation facilities, the MOEs for all durations were based on 210 ppb used for acute exposure, and not actual measurements. The MOEs were between 1 and 78 for short-term, subchronic and chronic exposures.

The ambient air monitoring of three counties in California showed acute and short-term MOEs greater than 400. However, the 7-8 week MOEs were less than 100 (MOEs of 13 to 78) in some locations. Additional monitoring are being conducted to better characterize these exposures.

This risk assessment concluded that human inhalation exposure to methyl bromide resulted in margins of exposure of greater than 100 in some scenarios but less than 100 in other scenarios. The significance of these MOEs need to be viewed in the context of the limitations and uncertainties discussed. Many scenarios were based on exposure data with few samples or assumed exposure levels (i.e. 210 ppb for acute exposure). There were also scenarios which were not addressed in this document. Additional exposure data are needed to better characterize the exposure. In addition, the overall risk from methyl bromide exposure should consider the risks from other exposure routes. The risk characterization of dietary exposure and aggregate exposure is in Volumes II and III, respectively.

II. INTRODUCTION

A human health risk assessment for inhalation exposure to methyl bromide has been conducted because of adverse effects identified in chronic toxicity, oncogenicity, reproductive toxicity, developmental toxicity, genotoxicity, and neurotoxicity studies conducted with laboratory animals. The toxicity of methyl bromide in humans from occupational and accidental exposures also has been documented. Methyl bromide is regulated under the California Air Contaminant Act (AB 1807), The Food Safety Act (AB 2161), The Birth Defect Prevention Act of 1984 (SB 950), and Proposition 65. While the review of toxicology studies included all routes of exposure, the potential risk from dietary exposure to methyl bromide residues in the fumigated foods is addressed in a separate document.

II.A. CHEMICAL IDENTIFICATION

Methyl bromide has been used commercially since the 1890s (review by Alexeeff and Kilgore, 1983; WHO, 1995). Early uses were as an anesthetic agent, methylating agent, refrigerant, fire extinguishing agent, and fumigant. Currently, methyl bromide is used as a multipurpose fumigant for pest control in structures (warehouses, ships, freight cars, and homes) and in post-harvest treatment of commodities (Farm Chemicals Handbook, 1998). It is also used in the preplant treatment of soil in fields and greenhouses to control nematodes, insects, weeds, bacteria, and fungi. Methyl bromide is the primary fumigant for quarantine use on commodities exported to other countries (Attachment C).

The primary effect of methyl bromide after inhalation exposure is neurotoxicity which has been observed in both humans and laboratory animals (detailed discussion of the studies is in **III. TOXICOLOGICAL PROFILE**, and Attachment D). The signs and symptoms are dependent on concentration and exposure duration (von Oettingen, 1946; Rathus and Landy, 1961; Greenberg, 1971; Grant, 1974; Anger *et al.*, 1986; Gehring *et al.*, 1991; Uncini *et al.*, 1990; De Haro *et al.*, 1997).

With dermal exposure, vesication and swelling of the skin and increased plasma bromide levels were observed in workers exposed to high concentration of methyl bromide (Butler *et al.*, 1945; Jordi, 1953; Zwaveling, *et al.*, 1987; Hezemans-Boer *et al.*, 1988).

II.A.1. Mechanism of Action

The exact mechanism for the toxicity of methyl bromide via the inhalation route is not known. Methyl bromide is an alkylating agent and has been shown to bind irreversibly to sulfhydryl groups *in vitro* (Lewis, 1948; Price, 1985). Gehring *et al.* (1991) suggested that the depletion of glutathione (GSH) observed in the study by Alexeeff and Kilgore (1985) was a result of methyl bromide-GSH conjugate formation. However, conjugated metabolites of methyl bromide have not been reported. The depletion of GSH may also be due to the inhibition of glutathione reductase activity (Jaskot *et al.*, 1988; Davenport *et al.*, 1992).

The effect of methyl bromide on brain GSH and GSH transferase has been proposed as the mechanism of neurotoxicity (Davenport *et al.*, 1992). Methyl bromide-induced locomotor effects (tremors, ataxia, and limb paralysis) may be a result of changes in brain GSH

metabolism (Orlowski and Karkowsky, 1976). In a case study of two workers, methyl bromide conjugation with GSH by GSH transferase was hypothesized to account for the severity of neurotoxicity observed (Garnier *et al.*, 1996). Other investigators suggested that methyl bromide-induced neurotoxicity was due to the decrease of catecholamine (norepinephrine and dopamine) levels and the inhibition of tyrosine hydroxylase activity in the brain (Honma *et al.*, 1982, 1987, and 1991). The decrease in catecholamine levels may cause reductions in presynaptic neuronal activity, feeding, and body temperature. This effect would be consistent with the decreased locomotor activity and weight loss observed in rats. In addition, an increase in the sensitivity of dopamine receptors after methyl bromide exposure has been suggested as the mechanism for the neurotoxicity symptoms (hallucination, insomnia, and delusions) (Honma *et al.*, 1994). Other indications of neurotoxicity observed in the rats were conditioned taste aversion (Miyagawa, 1982) and increased thiopental-induced sleep time (Honma *et al.*, 1985).

The toxicity observed in human and animal studies with low concentrations of methyl bromide is likely due to methyl bromide *per se* and not bromide. First, methyl bromide is more toxic than bromide. The rat oral LD₅₀ (3,500 mg/kg) for sodium bromide is more than 15-fold higher than that (214 mg/kg) for methyl bromide (Smith and Hambourger, 1935; Danse *et al.*, 1984). For acute exposure, the lowest level of bromide in the blood that caused toxicity is 125 mg bromide/100 ml (Gosselin *et al.*, 1976). A no-effect level of 4 mg/kg based on electroencephalograph changes and increased thyroid activity in human volunteers and an average daily intake (ADI) of 1 mg/kg of sodium bromide has been proposed for humans (van Gelderen *et al.*, 1993). For chronic exposure to bromide, central nervous system effects (drowsiness, bizarre behavior, and hallucinations) were observed in a 60-year-old woman who ingested a bromide elixir daily for 7 years. The serum bromide level was 44.6 mEq/L (or 215 mg/100 ml based on 1 mEq=48 mg) (Blumberg and Neli, 1967).

Second, bromide level in the plasma, serum or urine is not an indicator of the severity of methyl bromide intoxication. The diet and past medicinal use of bromides contribute to the endogenous level of bromide (Harvey, 1985). Human studies and accidental poisoning cases showed that the bromide levels of affected individuals did not correlate with the symptoms (Drawneek *et al.*, 1964; Marraccini *et al.*, 1983; Squier *et al.*, 1992; Kishi *et al.*, 1991; Tanaka *et al.*, 1991). Hemodialysis did not alleviate the neurotoxic effects of methyl bromide in a worker accidentally exposed to methyl bromide while cleaning a rice silo (Moosa *et al.*, 1994). Hustinx *et al.* (1993) suggested that the severity of clinical signs is correlated more with previous exposures than serum bromide levels (more details about this study are in III.H. NEUROTOXICITY).

II.A.2. Chloropicrin

Chloropicrin, a lacrimator and a fumigant, is added to the formulations as a warning agent because methyl bromide is acutely toxic and is odorless. However, the efficacy of chloropicrin, which ranged from 0.25% to 67% depending on the formulation, has been questioned (WHO, 1995). Methyl bromide concentration may be 100-fold higher than that of chloropicrin because of the difference in vapor pressures and densities of these two compounds (Van Assche, 1971). The vapor pressure and density for methyl bromide are 1380 mm Hg and 3.78, respectively, and those for chloropicrin are 18.3 mm Hg and 5.68, respectively. At 1.3 ppm chloropicrin, which causes irritation, the calculated methyl bromide level was 115 ppm. The air

levels of these two compounds were measured simultaneously in a monitoring study conducted by the California Air Resources Board (Seiber *et al.*, 1987). After field fumigation with methyl bromide (194 lbs/acre) and chloropicrin (95 lbs/acre), the maximum methyl bromide and chloropicrin levels were: 1133 ppt for methyl bromide and 681 ppt for chloropicrin in the ambient air, and 900 ppb for methyl bromide and 23.8 ppb for chloropicrin 20 yards from the field.

The use of chloropicrin in California has increased from 2.1 million to 2.8 million pounds from 1993 to 1998 (DPR, 1993-1998). In 2000, a total of 3.9 million pounds were used (DPR, 2000a). Because of the increased use, in particular as a replacement for methyl bromide, there is concern about the potential health effects from exposure. The risk characterization of chloropicrin is being prepared as a separate document and a summary of use and toxicity information is provided in Attachment E.

II.B. REGULATORY HISTORY

The insecticidal activity of methyl bromide was first reported in 1932 (Le Goupil, 1932). Methyl bromide is a restricted use pesticide in the United States. Retail sale and uses are limited to certified applicators or persons under their direct supervision, and only for those uses covered by the applicator's certification.

II.B.1. Ozone Depletion

Methyl bromide is an ozone depleter with a calculated ozone depletion potential (ODP) of 0.7 (Watson *et al.*, 1992). In the 1994 Science Assessment of Ozone Depletion document, a panel of atmospheric scientists concluded that methyl bromide continued to be a significant ozone depleter with an ODP of at least 0.3 (NOAA/NASA/UNEP/WMO, 1995). The worldwide sources of methyl bromide include: anthropogenic (human made) agriculture (20-60 kilotons/year), biomass burning (forest fires, grass fires) (10-50 kilotons/year), leaded gasoline burning (0.5-22 kilotons/year), and oceans (60-160 kilotons/year). There is evidence that methyl bromide produced by open oceans is reabsorbed. Therefore, methyl bromide from agriculture use is a significant source for human exposure. The amounts (as % applied) of methyl bromide used which eventually reach the atmosphere have been estimated to be: 50-95% for soil, 80-95% for post-harvest commodity, and 90% for structural uses (U.S. EPA, 1997a).

The concern of methyl bromide and other chemicals with ozone depleting potential (ODP > 0.2) is currently being addressed by the U.S. Clean Air Act and the United Nations Environment Programme Montreal Protocol on Substances that Deplete the Ozone Layer (Montreal Protocol). Under the U.S. Clean Air Act, the U.S. Environmental Protection Agency (U.S. EPA) was required in 1994 to freeze the U.S. production and importation of methyl bromide at the 1991 level (U.S. EPA, 1993). A complete ban was scheduled for the year of 2001. However, the 1998 U.S. Congress passed legislation to extend the use until 2005. Recently, U.S. EPA determined that pesticide applicators using methyl bromide would not be required to use impermeable tarps to reduce air emissions from field fumigation because not enough was known about how the use of the tarps would affect crop production (U.S. EPA, 1998b). U.S. EPA recently published final rule on the exemptions for quarantine and preshipment uses of methyl bromide (U.S. EPA, 2001). These uses are permitted under the Montreal Protocol and exemptions are required by amendments to the Clean Air Act.

At the international level, the Parties (more than 125 nations) to the Montreal Protocol added methyl bromide to the list of depleters and agreed on deadlines for a freeze on the production and importation of methyl bromide (U.S. EPA, 1993). In 1997, Parties to the Montreal Protocol agreed to an extension of the use. The current deadlines for the 100% use reduction are 2005 and 2015 for developed and developing countries, respectively (UNEP, 1997). There are ongoing efforts to develop alternative approaches (GAO, 1996; USDA, 1993; CDFA, 1995; Braun and Supkoff, 1994).

II.B.2. Federal Regulations

The U.S. EPA established tolerances in commodities based on bromide level because of the assumption that methyl bromide is degraded completely to bromide (Federal Register, 1991a). However, residue studies have shown that fumigated commodities contain detectable levels (in ppm range) of methyl bromide especially immediately after fumigation. In 1986, the Methyl Bromide Industry Panel (MBIP) petitioned the U.S. EPA for tolerances for methyl bromide *per se* (U.S. EPA, 1986a). The proposed levels ranged from 0.1 ppm for certain vegetables to 5.0 ppm for green cocoa beans.

The U.S. EPA has established an oral chronic reference dose (RfD) and inhalation reference concentration (RfC) for methyl bromide (U.S. EPA, 1992a). The RfD is 0.0014 mg/kg/day based on the no-observed-effect level (NOEL) of 1.4 mg/kg/day for forestomach epithelial hyperplasia in a rat oral subchronic study (Danse *et al.*, 1984) and an uncertainty factor of 1000. The inhalation RfC is 5×10^{-3} mg/m³ (1.3 ppb) based on the LOAEL of 3 ppm for nasal olfactory epithelial hyperplasia from a rat chronic inhalation study (Reuzel *et al.*, 1987 and 1991) and an uncertainty factor of 100. For methyl bromide in the drinking water, the one-day, ten-day, and longer-term health advisory for a child is 0.1 mg/L assuming 1 L/day water consumption for a 10-kg child (U.S. EPA, 1992a). The longer-term health advisory for an adult is 0.5 mg/L assuming 2 L/day water consumption for a 70-kg adult. The lifetime health advisory is 0.01 mg/L assuming 20% of exposure by drinking water. Methyl bromide is classified as a "Group D" carcinogen (not classifiable as to human carcinogenicity) by U.S. EPA due to inadequate human and animal data (U.S. EPA, 1992a).

The Agency for Toxic Substances and Disease Registry (ATSDR) has established minimal risk levels (MRLs) for methyl bromide which may be of concern at hazardous waste sites and releases (ATSDR, 1992 and 1996). The acute MRL is 0.05 ppm based on an acute NOEL of 16 ppm for decreases of brain tyrosine hydroxylase activity in the rat after 8 hours of exposure to 31 ppm (Honma *et al.*, 1987 and 1991) and adjusted for daily exposure and a 100-fold uncertainty factor for interspecies and intraspecies extrapolation ($16 \text{ ppm} \times 8/24 \times 1/100$). The intermediate inhalation MRL is 0.05 ppm ($5 \text{ ppm} \times 1/100$) based on a NOEL of 5 ppm for a decrease in monoamines in the rat after 3 weeks of continuous daily exposure to 10 ppm (Honma *et al.*, 1982). The chronic MRL is 0.005 ppm ($2.3 \text{ ppm} \times 1/10 \times 8/24 \times 5/7 \times 1/10$) based on increased prevalence of muscle aching and fatigue, increased sensitivity threshold, and lowered recall ability in an epidemiological study of workers with an average exposure of 2.3 ppm for 8 hours per day and 5 days per week (Anger *et al.*, 1986) and an uncertainty factor of 100 for extrapolation of LOEL to NOEL and intraspecies variation. Respiration rate differences between animals and humans are not accounted for in these MRLs. The intermediate oral MRL is 0.003 mg/kg/day based on gastrointestinal effects.

The National Institute for Occupational Safety and Health has determined an Immediately Dangerous to Life and Health Concentration (IDLH) for immediate evacuation of workers exposed to methyl bromide (NIOSH, 1997). The IDLH of 250 ppm was supposedly based on an acute inhalation toxicity data in humans (Clarke *et al.*, 1945). However, the air concentration was not measured in the cited human report. The federal Occupational Safety and Health Administration permissible exposure level (PEL) is 20 ppm (CFR, 1989). The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a threshold limit value of 1 ppm (ACGIH, 1998).

II.B.3. California Regulations

In California, the use of methyl bromide is regulated by permit conditions and regulations promulgated by DPR².

Structural Fumigation

For occupational exposure to methyl bromide, the current California permissible exposure limit (PEL) for methyl bromide is 5 ppm or 20 mg/m³ and a ceiling limit of 20 ppm (California Code of Regulations, 1998). A reentry level of 5 ppm following fumigation of homes was established under the Label Improvement Program for Fumigants (U.S. EPA, 1986b). All persons are required to wear a self-contained breathing apparatus (SCBA) or combination air-supplied/SCBA respirators at concentrations higher than 5 ppm. In 1992, an evaluation of the monitoring data and toxicology studies showed that the 5 ppm reentry level in fumigated homes did not provide a sufficient safety margin for human exposure (DPR, 1992; Attachment A Preliminary Risk Assessment). The DPR promulgated emergency regulations to require a longer aeration period and lowered the reentry level to 1 ppm in the wall voids, and pest control operators had to hand out a Fact Sheet explaining the potential human hazards of methyl bromide fumigation. The Fact Sheet was prepared by the DPR in consultation with the Office of Environmental Health Hazard Assessment (OEHHA), California Department of Health Services, and U.S. EPA. A similar warning for developmental effects was subsequently required by U.S. EPA on methyl bromide product labels used for structural fumigation (U.S. EPA, 1992b).

On January 1, 1993, methyl bromide was administratively listed by OEHHA as a developmental toxicant under Proposition 65 via the provision for listing due to the federal label warning requirement. On December 21, 1993, OEHHA modified the listing from "methyl bromide" to "methyl bromide as a structural fumigant" because the Fact Sheet and label changes were limited to the use of methyl bromide as a structural fumigant. The Proposition 65 Developmental and Reproductive Toxicity Identification (DART) Committee of the OEHHA Science Advisory Board decided methyl bromide should not be listed for all uses since the evidence was considered equivocal³ and did not support the "clearly shown" criteria as mandated by the Proposition (OEHHA, 1994) (additional discussion under **IV. RISK ASSESSMENT A.1.a. Developmental Toxicity**).

² DPR web site: http://www.cdpr.ca.gov/docs/dprdocs/methbrom/mb_main.htm

³ The National Toxicology Program defines equivocal as "marginal evidence which may be chemical related."

In 2000, DPR adopted new regulations for structural fumigations (DPR, 2000b). The regulations set a minimum buffer zone of five feet (with longer buffer zones for larger applications), required tarpaulins of specific standards, and set specific safety standards for aeration of fumigated structures and tarp removal.

Field and Commodity Fumigation

Methyl bromide when used in agricultural production is classified as a restricted material. Possession and use of restricted materials are allowed only under a permit from the county agricultural commissioner. Before issuing a permit, the county agricultural commissioner must evaluate the application to determine whether it will cause environmental harm. Depending on the results of this review, the commissioner may deny the permit or impose permit conditions including the use of specified mitigation measures. In evaluating permit applications, commissioners must consider and, where appropriate, use information provided by DPR. For methyl bromide, DPR provides this information as suggested permit conditions. In 1993, DPR began developing new use practice restrictions for agricultural applications that would incorporate a one-day (24-hour) exposure level of 0.21 ppm for workers and public. The suggested permit conditions include equipment modifications, restrictions on work hours, limits on application rates, limits on acreage or volume treated, tarpaulin specifications, restricted entry requirements, enclosed space requirements, and establishment of buffer zones. A review of the restrictions on the use of methyl bromide was conducted in a report to the California legislature (DPR, 1996). Most of the permit conditions have been adopted as regulations (DPR, 2001a). The 2001 regulations also included a requirement of mandatory buffer zones for most applications. Additional protective measures were required when fumigation sites around schools, hospitals, and other "sensitive" sites, including a prohibition on fumigation when school is in session. A two-stage notification plan was devised for neighbors before fumigation. Additional restrictions and buffer zone requirements were determined to minimize the exposures of workers on nearby properties and property owners. DPR is now examining the potential for seasonal exposures by workers and person who live in the vicinity of recurring fumigations. Data from the air monitoring in 3 counties (Kern, Monterey, and Santa Cruz) showed high exposure levels in some areas (ARB, 2000 and 2001; DPR, 2001b⁴). DPR has placed methyl bromide into reevaluation and is requiring methyl bromide registrants to conduct ambient air quality monitoring in areas with highest seasonal use (DPR, 2001c).

II.C. TECHNICAL AND PRODUCT FORMULATIONS

In 2001, 54 methyl bromide-containing products were registered in California. The registrants of methyl bromide products are Ameribrom, Inc., Albemarle Corporation, Great Lakes Chemical Corporation, Soil Chemicals Corporation, Trical, and Shadow Mountain Products Corporation. The products are available as 100% methyl bromide and as mixtures with chloropicrin (range of 0.25% to 67% chloropicrin). Methyl bromide is used as a fumigant on raw and processed agricultural commodities, in structures, in soil, and on ornamentals.

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See Attachment H.

II.D. USAGE

There are two major types of methyl bromide fumigations: applications to an area of soil or applications to an enclosed volume (e.g., chamber, building). All applications to soil occur prior to planting the crop for control of a wide variety of pests. Most soil applications involve the injection of methyl bromide beneath the soil surface. Injection can either be shallow (12 inches or less) or deep (20 inches or more), depending on the crop to be planted. In many cases, but not all, the soil is covered with a plastic tarpaulin to retard methyl bromide off-gassing. For typical agricultural field applications, a tractor injects the methyl bromide through a set of chisels or shanks, and lays the tarpaulin all at the same time. Applications can either be to a flat field (broadcast application) or to a field with beds and furrows (bed application).

Applications to post-harvest commodities or other enclosed volumes are very different. The types of enclosures and their efficiency in retaining methyl bromide are quite varied. The more typical enclosures include chambers, transportation containers, tarpaulins, and buildings. Regardless of the enclosure, most applications follow a general three-step process: 1) introduction or injection of methyl bromide into the fumigated space—this step usually takes a few minutes; 2) a treatment or holding period—usually a few hours to a few days; 3) aeration of the fumigated space—also a few hours to a few days. The method of aeration can also be quite varied. Most chambers will have an elevated exhaust stack and release methyl bromide at a controlled rate, but tarpaulin applications are aerated simply by removing the tarpaulin.

From 1992-1999, about 14-18 million pounds of methyl bromide were used each year for soil, commodity, and structural fumigations in California (DPR, 2000a). In 2000, the reported pounds of pesticides used were reduced to 10.8 million pounds (DPR, 2000a). The major uses (% of total pounds used) in field fumigation were strawberry fields (39%), outdoor nursery uses (12%), and preplant soil fumigation (12%). The use of methyl bromide in structural fumigation has declined significantly to about 3% of total pounds used because of regulation that required extended aeration time before residents are permitted to reenter the homes.

II.E. ILLNESS REPORTS

Poisonings by inhalation exposure to methyl bromide have been reported as early as 1899 (von Oettingen, 1946). A review of the incidents published from 1939-1981 showed 115 incidences of fatalities and 843 incidences of non-fatal systemic or local injuries (Alexeeff and Kilgore, 1983). In California, illnesses associated with inhalation exposure to methyl bromide have been reported and are described in detail in Attachment F. Approximately 50% of the cases also involved another compound or compounds. In the work place, the most common cause of the illnesses was equipment failure. Exposure of the general population to methyl bromide was due primarily to drift from fumigated fields. Specific case studies and human epidemiological studies are presented in the **III.H. NEUROTOXICITY**.

II.F. PHYSICAL AND CHEMICAL PROPERTIES⁵

Chemical name:	bromomethane, monobromomethane
CAS Registry number:	74-83-9
Common name:	methyl bromide
Trade names:	Brom, Brom-O-Gas, M-B-R, Metabrom, Meth-O-Gas, Methyl Bromide, Pic-Brom, Terr-O-Gas, Tri-Brom, Tri-Con, Tri-Pan.
Molecular formula:	CH ₃ Br
Molecular weight:	94.95 g/mole
Chemical structure:	CH ₃ -Br
Physical appearance:	colorless gas, usually odorless; sweetish, chloroform-like odor at high concentrations (odor threshold at 80 mg/m ³ or 20.6 ppm); burning taste. It is nonflammable in air but does burn in oxygen.
Solubility:	1.75 g/100 g in water (20°C, 748 mm), forms a crystalline hydrate, CH ₃ Br·20 H ₂ O, below 4°C; freely soluble in alcohol, chloroform, ether, carbon disulfide, carbon tetrachloride, benzene.
Boiling point:	3.56°C
Melting point:	-93.66°C
Octanol/Water partition coefficient:	log P=1.19 (15.5:1 octanol:water)
Vapor pressure:	1420 mm Hg (20°C), 2600 mm Hg (40°C)
Specific gravity:	3.3 g/ml (gas), 1.7 g/ml (liquid)
Conversion factor:	1 ppm = 3.89 mg/m ³ at 25°C

⁵ Farm Chemical Handbook, 1998; The Merck Index, 1989; U.S. EPA, 1986b.

II.G. ENVIRONMENTAL FATE

Summary: Methyl bromide is degraded in the environment. The rate of hydrolysis was enhanced by elevated temperature, ultraviolet irradiation, aerobic conditions, and high organic matter in the soil. Once applied to the soil, methyl bromide volatilized into the air or adsorbed onto soil particles. Because of degradation, methyl bromide residues were not detected in the groundwater or commodities grown on fumigated soil. Residues were found in treated commodities after post-harvest fumigation.

II.G.1. Hydrolysis

Methyl bromide hydrolyzed to bromide in water (WIL, 1985a). The hydrolytic half-life was estimated to be 6 days for pH 9 at 35°C to 49 days for pH 7 at 25°C. There was leakage of methyl bromide from the flasks used in the experiments.

II.G.2. Photolysis or Photodegradation

Methyl bromide in solution (1.7×10^{-2} M) completely hydrolyzed to methanol, bromide, and hydrogen ion when irradiated at 254 nm for 40 days (Castro and Belser, 1981). The photolysis rate constant was $2 \times 10^{-6} \text{ sec}^{-1}$, 6.6-fold higher than without irradiation. However, experiments with incubation in the dark and in sterilized water were not performed.

In the upper stratosphere, methyl bromide was photo-dissociated, lost by diffusion, and reacted with hydroxyl radical (WHO, 1995). The products of these reactions were carbon dioxide, carbon monoxide, and bromide species. Photodegradation of methyl bromide was rapid in moist air (Gennari *et al.*, 1995). The half-lives were 22 minutes with irradiation at 250-420 nm and 15 mg/L moisture to 326 hours with irradiation at 366-750 nm and 15 mg/L moisture.

II.G.3. Microbial Degradation

There was no difference in the methyl bromide degradation half-lives between sterilized and unsterilized soils because methyl bromide decreased the microbial activity in both soils (Radian Corp., 1988). However, the half-lives under aerobic conditions were shorter than those for anaerobic conditions. The degradation in clay loam, with a higher organic content, was faster than in sandy loam. The average half-lives for sandy loam and clay loam soils were 35 and 3.8 hours, 47 and 2.5 hours, 144 and 39 hours, and 80 and 34 hours, under aerobic/ nonsterile, aerobic/sterile, anaerobic/nonsterile, and anaerobic/sterile conditions, respectively.

II.G.4. Mobility (Soil, Ground Water, Air, Plants)

II.G.4.a. Soil

The mobility of methyl bromide in soil, as with other soil fumigants, depends on many factors: chemical and adsorptive characteristics of the fumigant, temperature, moisture, organic matter, soil texture, and soil profile variability (Munnecke and Van Gundy, 1979; Kolbezen *et al.*, 1974; Abdalla *et al.*, 1974). The following section is a summary of some studies.

Thirty-two days after exposure to 200,000 ppm in the air, the soil contained less than 1.5 ppm methyl bromide (Radian Corp., 1988). This level was decreased by 10-fold after the soil was purged with nitrogen as methyl bromide was loosely associated with the soil. The proposed reaction of methyl bromide in the soil was: $\text{CH}_3\text{Br} + \text{O}_2 \rightarrow \text{HBr} + \text{H}_2\text{O} + \text{CO}$, then $2\text{CO} + \text{O}_2 \rightarrow 2\text{CO}_2$, with CO=carbon monoxide and CO_2 =carbon dioxide.

Under laboratory conditions, volatilization was the major route of dissipation from the soil (WIL, 1985b). The initial loss rate was $82.6 \text{ ug/cm}^2/\text{hour}$ and the steady state rate was $8.8 \text{ ug/cm}^2/\text{hour}$. Under similar conditions, the rate of loss for chloropicrin was much slower with a steady state rate of $1.8 \text{ ug/cm}^2/\text{hour}$.

Methyl bromide decomposed to bromide in all soil types (sand, peat, and loam) tested (Brown and Rolston, 1980). Decomposition was greatest in peat soil containing the most organic matter as the methyl group was transferred to the carboxyl groups and – and S-containing groups of the amino acids and proteins of soil organic matter. In loam soil, the decomposition reaction was first order depending on the air concentration. The retention of methyl bromide in soil depended on soil water content. In dry sand, the adsorption and desorption rates of methyl bromide were similar. In moist sand, the desorption was slower (30% of adsorption) than adsorption.

Methyl bromide in water adsorbed to Canfield silt loam, Holly silt loam, and Wooster silt loam more than agricultural sand (WIL, 1986). The methyl bromide concentrations were 18 ppm in Canfield, 17 ppm in Holly, and 14 ppm in Wooster loam soils; but only 6 ppm was in sand. When the treated soil was mixed with water, 89 to 97% of the adsorbed methyl bromide were released from the soil and the equilibrium was reached in 24 hours.

Methyl bromide concentration and half-lives in Reiff (fine sandy loam) and Yolo loam were similar after preplant injection (6-8 inches deep) into the soil and then tarped, (MBIP, 1986). The highest concentration was at the level (1 foot) of injection. The dissipation half-life was the fastest at 1 foot (0.9-1.2 days) and the slowest at 3 feet deep (4.1 to 5.9 days). With deep injection of 18-24 inches and nontarped preplant injection, the dissipation half-lives ranged from 2.8 days at 1 foot to 9.6 days at 8 feet deep. When methyl bromide-treated soil was drenched with water and steamed upon removal of the tarp, methyl bromide was detected as far as 2 feet below the surface. The dissipation half-lives ranged from 2.5 to 3.0 days for the application rate of 1 lb/100 square feet, and 2.5 to 11.0 days for 2 lb/100 square feet.

Methyl bromide was retained after application beneath concrete slabs (McKenry and Secara, 1990). Methyl bromide (128 kg) was introduced into the ground via holes drilled through the floor and then the floor was tarped for 4 days. After treatment, the highest concentration was approximately 9,000 ppm on day 2 at 30 cm from the house and 90 cm deep underneath the floor. The concentration in the soil declined as the distance from the injection point was increased; however, even at 150 cm away, the concentration was as high as 5,700 ppm on day 3. The use of an air compressor to deliver air to the soil air space on day 15 enhanced the dissipation of methyl bromide. The concentration of methyl bromide at 15 cm beneath the slab remained below 21 ppm and averaged 8 ppm one week after the final air compressor treatment. With continuous aeration, the methyl bromide concentration in the open portion of the house did not exceed 88 ppb. The ambient concentrations of the backyard and neighboring houses were

below 6 ppb during treatment and aeration.

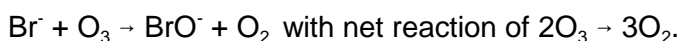
II.G.4.b. Ground Water

Methyl bromide was not detected (detection limit of 1 ppb) in ground water samples from fields (muck and sandy type soils) in Florida (Pickrell *et al.*, 1985) and wells in Florida and California (Golder Associates, Inc. 1985a and b). The wells in California had a history of more than 10 years of methyl bromide use with the last fumigation 5 to 17 months before the study (Golder Associates, Inc. 1985b).

II.G.4.c. Air

The major sources of bromide and methyl bromide in the air are marine aerosols and natural marine biological processes, respectively (Lovelock, 1975; Wofsy *et al.*, 1975). Methyl bromide from fumigation uses was estimated at 25% of the total emissions (natural and anthropogenic) (Watson *et al.*, 1992). A minor source of methyl bromide is the exhaust from cars that use leaded gasoline (Harsch and Rasmussen, 1977). Measurements of methyl bromide over the Atlantic Ocean showed average concentrations of 15.4 ± 1.9 parts per trillion (ppt) and 10.6 ± 0.9 ppt for the Northern and Southern Hemispheres, respectively (Penkett *et al.*, 1985). The calculated total lifetime in the atmosphere was 1.16 years (Lobert *et al.*, 1995). In a survey conducted in 1979, the mean levels of methyl bromide in the ambient air were 244 ppt in Los Angeles, CA; 66.8 ppt in Phoenix, AZ; and 54.7 ppt in Oakland, CA (Singh *et al.*, 1981). Worldwide environmental levels are in the review by WHO (1995).

Methyl bromide degradation in the air involved reactions with hydroxyl radicals and ozone. Based on an estimated hydroxyl radical concentration of 2×10^6 /cm³ in the daytime, the estimated residence time in the air was 289 days with a daily rate of loss of 0.4% (Singh *et al.*, 1981). In the winter months when hydroxyl radical concentration could be lowered, the residence time would increase. The bromide from the degradation reactions reacted with ozone by the following reaction (Wofsy *et al.*, 1975; Watson *et al.*, 1992).



The release of methyl bromide after structural fumigation was monitored in close proximity and nearby fumigated homes (Gibbons *et al.*, 1996 a and b). During fumigation, air levels ranged from less than 0.019 to 1.495 ppm when monitored at 10 feet from the fumigated houses. At the neighboring houses, the air levels ranged from 0.012 ppm (detection limit) to 0.351 ppm. During aeration, the concentrations inside the houses at 50 and 100 feet downwind from the fumigated house depended on the aeration method and time of sampling. Compared to the Standard Method, the Pest Control Operators of California Aeration Method resulted in lower concentrations (7.5 ppm versus 13.6 ppm) at the 10-foot distance after 1 hour of aeration, but not those after 24-hour aeration, or at greater distances.

Liscombe, *et al.* (1995 and 1996) tested alternative tarping and aeration methods to mitigate methyl bromide air concentrations from structural fumigations. During treatment, air concentrations ranged from 0.035 to 1.08 ppm five feet from the fumigated structure, depending on the method of tarping. During aeration, air concentrations ranged from 0.021 to 0.11 ppm.

Adding a second tarpaulin and aerating through an elevated stack were the most effective methods for reducing air concentrations.

Prior to 1992, limited monitoring of field fumigations was conducted. Methyl bromide levels in the air after tarpless fumigation of soil were determined in four farms (Soil Chemicals Corp., 1990). The shanks were placed 10 to 12 inches deep into the soil and the results are summarized below:

<u>Farms</u>	<u>Sampling site</u>	<u>Time</u>	<u>Methyl bromide level</u>
Belridge	60 ft downwind	several hours after fumigation	<30 ppb to 114 ppb
Kirschenman	150 ft downwind	0-11 hours after fumigation	<30 ppb (all times)
Major	200 ft downwind	during fumigation	<30 ppb to 211 ppb
Firini	in field	during fumigation	126 ppb
Firini	200 ft downwind	during fumigation	<30 ppb

In a monitoring study conducted by the Air Resources Board, Cal/EPA, air samples were collected on 3 off-sites close to strawberry fields and 4 sites in the nearby towns before and after application of methyl bromide (Seiber *et al.*, 1987). The fumigated field was tarped for 4 days. Methyl bromide levels were all below the MDL (1.1 ppb) for samples of ambient air in nearby towns. Methyl bromide was found in 3 off-sites (275, 76, and 175 meters from the field). The maximum levels (210-900 ppb) were detected on the day after application with a rapid decline on the next day. The highest average air concentration for an approximately 24-hour period was 450 ppb for site B, based on three 3-hour measurements. This level was used in the 1992 DPR Preliminary Risk Assessment (Attachment A).

Beginning in 1992, DPR, methyl bromide registrants, and academic researchers began more comprehensive monitoring of field and commodity fumigations. Details of the studies and the results are presented in Appendices F and H. The results were used to develop buffer zones for these uses.

II.G.5. Plant Residues/Metabolism

Methyl bromide residue in the food is generally analyzed by head-space gas chromatography (King *et al.*, 1981). This method requires the blending of macerated commodities in water. After the slurry is allowed to stand, methyl bromide which partitioned into the headspace is measured. The major uncertainty of this method is the time required for partitioning to reach an equilibrium that depends on the commodity composition and extent of methyl bromide interaction with endogenous components. The review of studies in the following section does not include some residue data submitted to DPR as part of the methyl bromide dietary risk characterization.

II.G.5.a. Field Fumigation

Methyl bromide *per se* is generally not found in commodities grown on soil pretreated with methyl bromide because of its dissipation and degradation (MBIP, 1988a; Trical, Inc., 1985, 1990, and 1991; WIL, 1984). When methyl bromide was injected into the soil 15 days before planting and the field was tarped for 6 days, low levels of methyl bromide were found (Trical, Inc., 1985). The sampled crops and levels were: lettuce (< 3 ppb-29 ppb), turnip roots (< 23

ppb-644 ppb), broccoli (< 250 ppb-1452 ppb), carrots (<16 ppb), green tomatoes (< 16 ppb), green beans (< 10 ppb). With cucumbers, two of the four samples contained residues at 5 and 34 ppb. In turnip leaves, methyl bromide levels ranged from < 9 ppb to 334 ppb; the control samples were all < 9 ppb. Matrix interference in the analysis was especially notable in broccoli and turnip roots. The levels of methyl bromide in two processed foods, tomatoes and dried beans, were below detection limits (10 ppb, and 6 ppb, respectively). Residues were also not detected in potatoes (< 5 ppb) and carrots in other studies (Trical, Inc., 1990 and 1991).

In a survey of methyl bromide residues after either broadcast application or bed treatment fumigation, 4 samples from each crop from 9 states (California, Florida, Oregon, Washington, Texas, Michigan, Arizona, Idaho, Hawaii, Wisconsin, and North Carolina) were analyzed (MBIP, 1988a). Most of the samples were collected in California. The crop groups and representative crops sampled were: root and tuber (carrot, potato, radish, and sugar beet); bulb vegetables (green onion, large bulb onion, small bulb onion, and garlic); leafy vegetables (head lettuce, leaf lettuce, celery, and spinach); Brassica vegetables (broccoli, cabbage, cauliflower, and mustard greens); legume vegetables (bush bean, green bean, soybean, succulent pea, and dry pea); fruiting vegetables (tomato, and pepper); cucurbit vegetables (cucumber, zucchini, watermelon, cantaloupe, and summer squash); citrus fruits (orange and grapefruit); pome fruits (apple); small fruits (raspberry, blueberry and strawberry); non-grass animal feed (alfalfa and clover); herbs and spices (basil, chives, dill, and marjoram); and miscellaneous (asparagus, ginger, grape, peanut, pineapple, corn, tobacco, and okra).

Almost all the samples contained residue levels below detection limits (ranged between 5 to 10 ppb). For mustard greens, the residue levels were 20.20 to 29.9 ppb (mean=24.9 ppb) for samples from California. In the Florida trial of cabbage, two of the four samples were 13.8 and 15.18 ppb and the other two were below the MDL (10 ppb). Since most of the samples did not contain residues, the levels above the MDL could be false positives due to dimethyl disulfide or other sulfur compounds. Bromide levels were determined in some crops and in general, were not indicative of methyl bromide application rates. For example, the mean bromide level in treated celery (442 ppm) was 4 times that of control (105 ppm). For pineapple, strawberry, and asparagus, bromide levels in the control and treated samples were similar (20 to 40 ppm).

II.G.5.b. Post-harvest Fumigation

The use of methyl bromide as a post-harvest fumigant on raw agricultural commodities and processed foods resulted in detectable levels of residues (Attachment C). Only residue data with adequate information of fumigation conditions and analysis method are included in Attachment C. In commercial practices, the fumigation condition is dictated by the pests of concern and the potential phytotoxicity by methyl bromide. In general, fresh fruits and vegetables are fumigated at short intervals (2 hours), and then stored at cool temperature.

The residue levels in fumigated foods were dependent on the nature of the commodity; load factor (volume of commodity to chamber size); application rate, temperature, frequency, and duration; as well as aeration and storage conditions. The half-lives of methyl bromide in fruits and vegetables were shorter than those for nuts and dried fruits. With cherries, there was an inverse relationship between load factor and initial residue levels such that an increase in the load factor from 1.6% to 32.0% resulted in lower residue levels (Sell *et al.*, 1988). Consequently,

a shorter aeration period was needed to achieve a certain residue level. In addition, an increase in pulp temperature enhanced the desorption of methyl bromide from the cherries. For example, the aeration period required to obtain 1 ppm methyl bromide remaining on the cherries was reduced from 18 hours to 9 hours when the pulp temperature was increased from 7°C to 27°C.

Likewise, an increase in temperature during fumigation or during aeration or storage resulted in the decrease of half-lives of methyl bromide in blueberries, walnuts, and strawberries (Attachment C). While an increase of the application rate from 2 to 4 lbs/1000 ft³ (plum, nectarine, or peach) or a doubling of exposure duration (avocado, peach, or pear) resulted in higher initial residue levels, there was no significant change in the half-lives. However, a 4-fold increase in an application rate (mango) resulted in an increase of both the initial residue levels and half-life.

Aeration lowered methyl bromide residues in fumigated strawberries (MBIP, 1984b). After 45 min, 1 hour, 2 hours, and 3 hours of aeration, the methyl bromide levels were 9.0 ppm, 7.0 ppm, 5.4 ppm, and 140 ppb, respectively. Samples which had been aerated for only 45 minutes before precooling contained 7.1 ppm of methyl bromide. The level then declined to 2.1 ppm and 1.6 ppb after 12 and 24 hours, respectively. Samples with 3 hours of aeration contained only 20-30 ppb after 2-3 hours at 34°F (1°C). No methyl bromide (MDL not specified) was detected in fumigated strawberries stored at 70°F (21°C) instead of 34°F (1°C). For asparagus, the mean residue level decreased from 2.14 ppm after fumigation to 0.016 ppm after 24 hours of aeration (Fieser and Conrath, 1993).

Because of the higher lipid content, the half-lives of methyl bromide in nuts (almonds, pistachio nut, and walnut) were longer than those for fruits (Attachment C). Methyl bromide absorbed into the almond shell and the kernel by dissolution of methyl bromide in the oil particles (Hartsell *et al.*, 1983). Some residues were released during aeration while others methylated amino acids or phenolic materials such as tannin and lignin. The shell generally contained higher levels of bromide and methyl bromide residues than the kernel. The highest bromide level was found in the Mission variety of almonds with the highest lignin and tannin contents, while lower levels were found in the Mercedes, Carmels, and Nonpareils varieties. Increase of temperature resulted in increased residues in the shell and kernels. During aeration, methyl bromide evaporated more rapidly from the shell than the kernel, but reached a similar concentration (< 2.5 ppm) in both compartments by about 50 hours.

Methyl bromide deposition in avocados was also related to the fat content (Singh *et al.*, 1982). The Fuerte variety absorbed 57% more methyl bromide and formed 22% more bromide than the Haas variety. Methyl bromide (21-36% conversion in Fuerte and 56-70% in Haas) was converted to bromide during storage.

Processing of fumigated grains reduced methyl bromide levels in the final product (MBIP, 1984a and 1988b; CMA, 1984). When wheat was processed to wheat flour, the levels ranged from below the detection limit (<1 ppb) to 2 ppb. For corn, grinding and baking at 350°C for 1 hour reduced the fumigated level (9.4 ppm) to 6.4 ppm and <0.01 ppm, respectively (MBIP, 1984a). Methyl bromide level in rice decreased from 5.2 ppm to < 0.01 ppm after 20 minutes of simmering. All flour and bakery mix samples had < 0.03 ppm methyl bromide.

Methyl bromide residues were higher (as much as 2-fold) in packaged dried fruits (dates, apricots, prunes) than in bulk form, except raisins (Attachment C). Because packaging provided limited off-gassing, the half-lives of methyl bromide in these commodities were also longer than those for bulk forms.

The dissipation half-lives provide only a qualitative estimate of the potential exposure by the consumers since multiple fumigations can occur to prevent reinfestation during processing and storage, either as bulk or packaged goods. A survey of nuts at the retail level showed methyl bromide levels ranged from 10 ppb to 3.7 ppm in 8 of 75 samples (Lindsay, 1985).

The U.S. Food and Drug Administration (FDA) collected samples of processed nuts, dried fruits, dried beans, and rice from the marketplace and analyzed them for methyl bromide (FDA, 1990-1991). Of the 1132 nut samples, only 2 pistachios samples contained detectable levels of residues (0.09 ppm and 0.03 ppm). Residues were not detected in 107 samples of rice, 347 samples of dried fruits, and 173 samples of dried beans; the MDL was 0.02 ppm (Ford *et al.*, 1992).

In a field-trial study, selected commodities were fumigated with methyl bromide at rates which ranged from 2-5 pounds/ 1000 ft³ for 2 to 24 hours according to the label uses (DFA, 1985; MBIP, 1985a). Methyl bromide residue levels were determined after 1, 3, or 7 days of aeration. The crop groups and selected commodities included: pome fruits (apple, pear), tree fruits (almond, walnut, and pistachios), root and tuber vegetables (carrot, potato, and sugar beet), legume vegetables (beans, peas, and soy beans), citrus fruits (orange, lemon, grapefruit), stone fruits (peach, plum), cereal grains (corn, rice, wheat), bulb vegetables (onion, garlic), fruiting vegetables (tomato, pepper), small fruits and berries (blackberry, blueberry, grape, and strawberry), herbs and spices (basil, chives, dill, and sage), leafy vegetables (broccoli and cabbage), cucurbits (cucumber, melon, and summer squash), processed (wheat, corn, rice), and miscellaneous (cocoa beans, dried fruits, and candy).

In wheat grown in sand containing ³⁵S-labeled sulfate and subsequently fumigated, the gluten or protein fraction contained N-methyl derivatives, dimethylsulfonium derivatives, as well as methoxy- and methythio- derivatives (Winteringham *et al.*, 1955). Further study with fumigated wheat flour showed that methyl bromide methylated the basic nitrogen residues (Bridges, 1955). The histidine residue was the primary site of methylation resulting in the formation of 1-methylhistidine, 3-methylhistidine and 1,3-dimethylhistidine (Bridges, 1955). Studies with diets containing high levels of methylated histidines (0.36% of the diet) showed that these residues are not available for nutritional use resulting in weight loss in mice (Friedman and Gumbmann, 1979).

II.G.5.c. Structural Fumigation

Foods remaining in the house during fumigation may also acquire methyl bromide residues (Scheffrahn *et al.*, 1992). Packaged foods (unopened or reclosed) were fumigated with methyl bromide at approximately maximum labeled rates. Of the 23 food items, the highest residues were found in fatty commodities such as peanut butter (106 ppm) and margarine (151 ppm). Residue levels were below the detection limit in foods unopened with the factory seal intact or vacuum-packed.

III. TOXICOLOGY PROFILE

Pharmacokinetic and toxicity studies of methyl bromide are summarized in this section. Acceptability of the studies (except genotoxicity studies) by DPR, where noted, was based on the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guidelines. The acceptability of the genotoxicity studies was based on the Toxic Substances Control Act guidelines (Federal Register, 1985 and 1987). The toxicology summary for studies reviewed for The Birth Defect Prevention Act of 1984 (SB 950) is included in Attachment D. In the toxicity studies, the no-effect levels may be expressed as NOELs or no-observed adverse effect levels (NOAELs). For the purpose of this document, endpoints under either designation are considered relevant for hazard identification.

Summary tables for selected toxicity studies considered for critical no-observed-effect levels (NOELs) and lowest-observed-effect levels (LOELs) are presented in Tables 5, 7, and 14 for acute, subchronic, and chronic exposures, respectively. Unless stated, concentrations are as measured concentrations from the studies. For comparison of toxicity between studies in these tables, the NOELs were also presented in terms of human equivalent NOEL. This human equivalent NOEL takes into consideration the air concentration, duration of exposure, and intake rate (respiration rate for inhalation exposure) differences between experimental animals and humans (adult and child) using equations in Attachment G. Since the experiments were conducted for various durations, the human equivalent NOEL is calculated on a per day basis to allow comparisons between studies. This approach follows the dose calculation methods outlined in the 1992 U.S. EPA Exposure Assessment guidelines, where the potential dose is a function of the concentration and intake rate (U.S. EPA, 1992c). It has generally been used for dietary exposure studies where the no-effect level is expressed as the dose (for example as mg/kg/day) accounted for consumption rate and duration of exposure, instead of concentration in the diet. Since the equivalent NOEL for children is lower than that for adults, only the children equivalents NOELs are presented in the summary tables. The only exceptions are the NOELs for developmental or reproductive toxicity studies since the endpoints are applicable only to adult exposures.

The internal doses for inhalation studies were assumed to be due to inhalation only. The inhalation pharmacokinetic studies were conducted with nose-only exposure while the toxicity studies (except where noted) were done with whole-body exposures. For laboratory animals in whole-body inhalation exposure studies, additional exposure was possible from oral ingestion due to licking of the fur and by dermal absorption. The internal dose from whole-body exposure may be higher than that calculated based only on the air concentration and respiration rates.

III.A. PHARMACOKINETICS

Summary: After inhalation, intraperitoneal, or oral administrations, methyl bromide was rapidly absorbed and radioactivity (^{14}C) was distributed to all tissues. With inhalation exposure, the percentages of the administered doses absorbed were similar in several species; they were 48% in the rat, 40% in the dog, and 52 to 55% in humans. In the rat, the highest levels in the tissues, principally in the lungs, were reached immediately after exposure. With oral and intraperitoneal administration to rats, more than 90% of the dose was absorbed with the highest radioactivity levels measured in the liver, kidneys, and testes. Methyl bromide was extensively

biotransformed into unidentified products and carbon dioxide. In the rat, within 1 hour after inhalation exposure, less than 10% of the radioactivity in the tissues was intact methyl bromide. In humans, both methyl bromide and inorganic bromide were detected in the tissues 5 hours after a lethal dose exposure. The primary routes of excretion were the exhaled air for inhalation and intraperitoneal exposures, and the urine for oral exposure. Carbon dioxide accounted for almost 50% (inhalation and intraperitoneal routes), and 30% (oral route) of the radioactivity in the exhaled air. After oral administration, biliary metabolites of methyl bromide were reabsorbed from the gut.

III.A.1. Absorption

Fischer-344 rats were exposed to methyl bromide (^{14}C , >98% pure; nominal concentrations of 1.6, 9.0, 170, or 310 ppm) by nose only inhalation for 6 hours (Medinsky *et al.*, 1985). For 1.6, 9.0, and 170 ppm, the percentages of the absorbed dose (the ratio of radioactivity in the whole body homogenate after 6 hours to the amount inhaled \times 100%) were 48%, 48%, and 38%, respectively. At 310 ppm, there were significant ($p \leq 0.05$) decreases in the tidal and minute volumes resulting in the absorption of only 27% of the total dose. At 66 hours after exposure, 17 to 26% of the total absorbed radioactivity remained in the body.

In beagle dogs, the calculated steady-state fractional, systemic uptake of the total inhaled methyl bromide (^{14}C , >98% pure, 174 to 361 ppb) was 39.5% after exposure for 3 hours by nose only, (Raabe, 1986). After the three-hour exposure, the blood concentration was 1.6% of the total amount inhaled and it declined to 1.2% at 117 hours after exposure.

In a human study, four volunteers (2 male and 2 female adults) were exposed to methyl bromide (^{14}C , >98% pure, 18 ± 6 ppb) for 2 hours by nose breathing and by mouth breathing (Raabe, 1988). Each subject was equipped with a two-stage demand regulator-based inhalation system that separated inhaled and exhaled air. The calculated steady-state, fractional systemic uptake of the total inhaled methyl bromide during nasal breathing and mouth breathing were 55.4% and 52.1%, respectively.

For oral and intraperitoneal administration in rats, the absorption was >90% when determined 72 hours after exposure (Medinsky *et al.*, 1984).

III.A.2. Distribution

After inhalation exposure to methyl bromide, radioactivity was found in the liver, kidneys, adrenal glands, lungs, thymus, brain, testes, and nasal turbinates in the rat (Medinsky *et al.*, 1985; Bond *et al.*, 1985; Jaskot *et al.*, 1988). The peak radioactivity levels in the tissues occurred immediately after exposure. The tissues with high radioactivity included the lungs, liver, and the nasal turbinates. In the study by Jaskot *et al.* (1988), the half-lives of tissue radioactivity were 2.71 hours (lung), 1.58 hours (liver), 0.58 hours (kidney), 1.37 hour (spleen), 6.54 hours (brain), and 5.29 hours (testes). In another study, the half-life of the radioactivity in the liver was 33 hours, while the half-lives were shorter in blood (7.7 hours), and in testes, small intestine, and brain (6 hours) (Bond *et al.*, 1985).

In a poisoning case, a man ingested and inhaled an unknown amount of methyl bromide

for approximately 1.5 hours and died 4 hours later (Michalodimitrakakis *et al.*, 1997). Tissues were sampled 1 hour after death during the autopsy. Except for the spleen, methyl bromide was found in all tissues. The methyl bromide levels were: subclavian blood (3.8 $\mu\text{g/ml}$), brain (3.5 $\mu\text{g/g}$), adrenal gland (3.4 $\mu\text{g/g}$), peripheral blood (3.3 $\mu\text{g/ml}$), lung (2.9 $\mu\text{g/g}$), testis (2.8 $\mu\text{g/g}$), kidney (2.6 $\mu\text{g/g}$), liver (1.9 $\mu\text{g/g}$), bile (1.2 $\mu\text{g/g}$), and epididymis (1.2 $\mu\text{g/g}$). The inorganic bromide levels were: subclavian blood (530 $\mu\text{g/mL}$), brain (30 $\mu\text{g/mL}$), peripheral blood (480 $\mu\text{g/ml}$), lung (410 $\mu\text{g/g}$), kidney (310 $\mu\text{g/kg}$), and bile and epididymis (none).

After intraperitoneal or oral administration of methyl bromide (^{14}C , >98% pure, 250 $\mu\text{mol/kg}$ or 23.7 mg/kg), the radioactivity levels (in decreasing order) in Fischer-344 rats tissues were: liver > kidney, testes > lung, heart, stomach > spleen (Medinsky *et al.*, 1984).

III.A.3. Biotransformation/Excretion

In rats exposed to methyl bromide by inhalation, 47 to 50% of the absorbed dose was exhaled as CO_2 and 0.4 to 4% as methyl bromide (Medinsky *et al.*, 1985). Excretion in the exhaled air was biphasic with a half-life of 4.1 hours in the initial phase and 17 hours in the second phase. Approximately 20% of the absorbed radioactivity was excreted in the urine, while only about 1% was found in the feces. The urinary half-life for radioactivity was 9.9 hours.

In another inhalation study with rats, methyl bromide was rapidly biotransformed and readily excreted in rats after inhalation exposure (Bond *et al.*, 1985). In all tissues examined, over 90% of the radioactivity was metabolites. The elimination half-life of radioactivity from the tissues was 1.5 to 8 hours. Nearly 75% of the absorbed dose was excreted by 65 hours with exhalation as the primary route. The excretion of $^{14}\text{CO}_2$ in the exhaled air was biphasic with the initial half-life at 3.9 hours, and a later half-life of 11.4 hours. The half-lives of radioactivity were 9.6 hours and 16.1 hours in the urine and feces, respectively. The percentages of the absorbed dose excreted in the expired air as CO_2 , in the expired air as methyl bromide, in the urine, feces, and retained in the body were 47%, 1%, 23%, 2%, and 28%, respectively. A similar excretion pattern was reported by Jaskot *et al.* (1988).

In dogs, the excretion of radioactivity was 1% (total inhaled) in the urine, 0.04% in the feces, and 9.86% in the lungs when measured 0 to 21 hours after exposure to methyl bromide (Raabe, 1986). At 69 hours after exposure, 5.7% and 0.7% of the total amount inhaled were excreted in the urine and feces (Raabe, 1986). The estimated total clearance half-life was 41 hours.

In humans, the amount exhaled as $^{14}\text{CO}_2$ ranged from 0.2 to 1.0% of the dose for mouth breathing, and 0.2 to 0.4% of the dose for nose breathing exposure when measured at the end of 2 hours of exposure and after 0.5 hour for clearance (Raabe, 1988). Radioactivity levels excreted in the urine ranged from 0.08 to 0.24% for mouth breathing, and from non-detected to 0.32% for nose breathing. The determination of urinary clearance was complicated by the variability in the volume. The net body retention for both exposure routes was 51.1% with a clearance half-life of 72 hours based on the amounts in the exhaled air and in the urine at 0.5 hour after inhalation exposure.

In rats after oral exposure, the distribution (as % of an absorbed dose) was 32% as

$^{14}\text{CO}_2$ and 4% as intact methyl bromide in exhaled air, 43% in the urine, and 14% in the carcass at 72 hours after exposure to methyl bromide (^{14}C , >98% pure, 250 $\mu\text{mol/kg}$ or 23.7 mg/kg) (Medinsky *et al.*, 1984). Only 2% of the dose was found in the feces. In cannulated rats, biliary excretion was a major pathway as 46% of the dose was found in the bile and only 12% and 7% in the exhaled CO_2 and urine, respectively, at 24 hours after dosing.

With intraperitoneal administration, the cumulative percentages of the doses in rats measured after 72 hours were: 45% as $^{14}\text{CO}_2$ and 20% as intact methyl bromide in exhaled air, 16% in the urine, 1% in the feces, and 17% in the carcass (Medinsky *et al.*, 1984).

III.B. ACUTE TOXICITY

Summary: Methyl bromide is a Toxicity Category I compound because of its acute inhalation toxicity (Federal Register, 1991b)⁶. Severe irritation to eyes, skin, and mucous membranes occur after acute exposure; therefore, acute oral, ocular and dermal studies are not required for registration. Neurotoxicity has been observed in humans and laboratory animals after inhalation exposure to methyl bromide with severity depending on the dose and duration of exposure. In humans exposed to high concentrations, neurological effects included ataxia, convulsion, and tremors. The nonlethal effects observed in laboratory animals included changes in brain catecholamines and tyrosine hydroxylase activity, tissue degeneration (nasal, brain, and adrenal glands), and neurotoxicity (ataxia and paralysis). Signs of oral toxicity in the dog included prostration, increased heart rates, lesions in multiple organs including the stomach and brain, hypoactivity, hypothermia, and death. Human dermal exposure resulted in skin lesions. The acute lethal toxicity of methyl bromide has been reviewed (Sayers *et al.*, 1929; Irish *et al.*, 1940; Alexeeff and Kilgore, 1983 and 1985; WHO, 1995). Studies considered for risk assessment are summarized in Table 5. NOELs and LOELs were determined only for those studies with adequate descriptions of the experimental protocol and results.

III.B.1. Inhalation - Rat

The first comprehensive study on the acute toxicity of methyl bromide in rats was conducted by Irish *et al.* (1940). Rats (strain not specified) were exposed to methyl bromide (99% pure, nominal concentrations of 0.42 to 50 mg/L or 100 to 13,000 ppm) continuously by inhalation, and the acute toxicity was determined. The lethal concentrations and exposure durations which resulted in 100% mortality rate are listed in Table 1. At 260 ppm for 20 hours, rats were excitable and jumped when stimulated. At concentrations < 2,600 ppm, they showed roughening of the fur, hunching of the back, drowsiness, heavy breathing, and occasionally lacrimation. After prolonged exposure, there were kidney damage, lung congestion and edema, and bronchopneumonia leading to death.

Fischer-344 rats were exposed to methyl bromide (99.9% pure; nominal concentrations of 0, 90, 175, 250, or 325 ppm) for 6 hours per day for 5 days (Hurt *et al.*, 1987). At 325 ppm, severe tissue degeneration in the nasal cavity, brain (cerebellar and cerebral), liver, and adrenal glands as well as minor alteration in testicular histology (delayed spermiation) were observed. Three of seven rats in the 325 ppm group died after 3 exposures. In addition, diarrhea, hemoglobinuria, ataxia, tremors and convulsions occurred in these animals (325 ppm). Ataxia and diarrhea were also observed in the 250 ppm treated animals. No death or tremors were observed in animals at this and lower concentrations. The degeneration in the nasal cavity and other tissues was concentration dependent. There was partial or complete destruction of the olfactory epithelium in the 325 and 250 ppm groups. At 175 ppm, there was moderate degeneration of the cerebellum, adrenal glands, and nasal cavity. The NOEL was 90 ppm.

⁶ The criteria for Toxicity Category I include an inhalation LD₅₀ of less than or equal to 0.05 mg/L, and fatal if swallowed, inhaled, or absorbed through the skin.

Table 1. The acute lethal toxicity of technical methyl bromide.

Species	Gender	Concentration ppm	Dosage mg/kg	Reference ^a
<u>Oral LD₅₀</u>				
Rat	M		214	1
Rat	M		104-133	2
<u>Subcutaneous LD₅₀</u>				
Rat	M		135	3
<u>Inhalation LC₁₀₀</u>				
Rat (6 min)	- ^b	13000		4
Rat (24 min)	- ^b	5200		4
Rat (42 min)	- ^b	2600		4
Rat (4 hr)	M	900		5
Rat (6 hr)	- ^b	520		4
Rat (26 hr)	- ^b	220		4
Rabbit (30 min)	- ^b	13000		4
Rabbit (1.4 hr)	- ^b	5200		4
Rabbit (11 hr)	- ^b	520		4
Rabbit (24 hr)	- ^b	260		4
Rabbit (32 hr)	- ^b	220		4
Guinea Pig (15 min)	- ^b	50000		6
Guinea Pig (1.5 hr)	- ^b	6950		6
Guinea Pig (3 hr)	- ^b	2290		6
Guinea Pig (8 hr)	- ^b	490		6
<u>Inhalation LC₅₀</u>				
Rat (15 min)	- ^b	5480		7
Rat (30 min)	- ^b	2700		8
Rat (4 hr)	M	780		5
Rat (8 hr)	M	310		8
Mouse (1 hr)	M	1200		9
Guinea Pig (5 hr)	- ^b	310		6
<u>Lethality</u>				
Human (5.5-7.5 hrs) ^c	M	8160		10
Human-adult (2 hr) ^d	M	60000		11

^{a/} References: 1. Danse *et al.*, 1984; 2. Kiplinger, 1994; 3. Tanaka *et al.*, 1988; 4. Irish *et al.*, 1940; 5. Kato *et al.*, 1986; 6. Sayers *et al.*, 1929; 7. AmeriBrom, Inc. 1983; 8. Honma *et al.*, 1985; 9. Alexeeff and Kilgore, 1985; 10. Miller, 1943; 11. Wyers, 1945.

^{b/} Gender was not specified in the study.

^{c/} This man was found in convulsions in a refrigerator car fumigated with methyl bromide 5.5 to 7.5 hours earlier. He was provided with life support but died 80 hours after removal from the car.

^{d/} This worker used methyl bromide to extinguish a fire and then continued to work for 2 hours. He was hospitalized and died one hour later.

In a subsequent study, Fischer-344 rats were exposed to methyl bromide (99.9% pure; nominal concentrations of 0, 90, or 200 ppm) for 6 hours per day for 1-5 days to determine regeneration and recovery of olfactory function (Hurtt *et al.*, 1988). No clinical signs of toxicity or olfactory epithelial damage in the 90 ppm group were observed. At 200 ppm, there was a transient significant decrease (9%) in body weight at the end of the fifth exposure. The body weights of the treated group returned to control values by day 47 after exposure. Extensive destruction of the olfactory epithelium of the dorsal meatus, nasal septum and lateral walls, and the complex ethmoid turbinates was evident after a single 6-hour exposure to 200 ppm. The olfactory degeneration was characterized by epithelial disruption, fragmentation, and exfoliation. The basal cell layer remained intact. Regeneration of the epithelium with the replacement by a squamous epithelium was evident by day 3 of exposure and was essentially complete by 10 weeks after exposure. However, some minor defects were not repaired such as: adhesions between the turbinates and adjacent structures, thinning of the olfactory epithelium due to a paucity of sensory cells, and respiratory metaplasia (conversion of the olfactory epithelium to a ciliated respiratory type). Olfactory function, as determined by the ability of food-deprived rats to find buried food pellets, was affected only in rats treated at 200 ppm. The impairment of the olfactory function was temporary with recovery by 4 to 6 days after exposure but before complete regeneration of the olfactory epithelium. The NOEL was 90 ppm based on olfactory damage at 200 ppm.

In a similar experiment, rats (strain not specified) were exposed to methyl bromide (purity not specified, a nominal concentration of 200 ppm) for only 4 hours per day, 4 days per weeks for 2 weeks (Hastings, 1990). After a single 4-hour exposure, the olfactory epithelium was extensively damaged, and olfactory function was impaired. After the end of exposure, no overt signs of toxicity were observed. The epithelium began to repair immediately after exposure but required more than 30 days for the restoration to a near normal appearance. Consistent with the findings of Hurtt *et al.* (1988), olfactory function returned to normal before complete epithelial regeneration.

CD rats (15/sex/group) were exposed to methyl bromide (>99% pure; nominal concentration of 0, 30, 100, or 350 ppm) for a single 6-hour inhalation exposure (Driscoll and Hurley, 1993). Testing was done at pre-exposure, within 3 hour post-exposure, 7 days post-exposure, and 14 days post-exposure using an automated assessment of motor activity and a Functional Observation Battery. Rats were sacrificed 16 to 19 days post-exposure. There were no effects on survival, body weight, and brain weight. No histological lesions were noted in the nervous system or the nasal tissues of the 350 ppm rats. Neurobehavioral effects were only seen in the 350 ppm group tested 3 hours post-exposure. Findings included: decreased arousal (both sexes); increased incidences of drooping or half-shut eyelids (both sexes); increased urination (females only); decreased rearing (both sexes); decreased tail pinch response (males only); increased incidences of piloerection (both sexes); decreased rectal temperature (both sexes); abnormal air righting reflex (females only); and decreased motor activity (both sexes). The NOAEL was 100 ppm based on neurobehavioral effects at 350 ppm.

The biochemical effects of methyl bromide were studied by Hurtt and Working (1988), Jaskot *et al.* (1988), and Davenport *et al.* (1992). Adult male Fischer 344 rats were exposed to methyl bromide (99.9% pure; 0, or a nominal concentration of 200 ppm) by inhalation for 6 hours per day for 5 days (Hurtt and Working, 1988). Rats were sacrificed on days 1 (first day of

exposure), 3, 5, 6, 8, 10, 17, 24, 38, 52, and 73. Methyl bromide did not affect testis weight, testicular and epididymal histology, daily sperm production, cauda epididymal sperm count, sperm morphology, sperm motility, and linear sperm velocity, or cause any observable toxicity. At day 5, the methyl bromide treated group weighed approximately 10% less than the control group and continued to weigh less until day 52. The nonprotein sulfhydryl levels of the testis and liver were significantly ($p \leq 0.05$) decreased after 1 and 3 days of treatment. The depression was transient as the levels returned to control values by day 8 (3 days after treatment). There was a transient decrease in the testosterone level during the 5-day exposure, as well as the day after exposure. The testosterone level was back to the control level by day 8.

CD rats were exposed to methyl bromide (99.5% pure, 0 or a nominal concentration of 30 ppm) for 5 or 10 days (Jaskot *et al.*, 1988). After either 5 or 10 days of exposure, there were significant ($p \leq 0.05$) decreases in the enzyme activities of glutathione (GSH) reductase and GSH transferase in the liver and increases of GSH transferase and glucose-6-phosphate dehydrogenase in the lung. The decreases were no more than 17% of the respective control values. In addition, serum chemistry showed significant ($p \leq 0.05$) decreases in the levels of blood urea nitrogen (BUN), uric acid, cholesterol, and erythrocyte cholinesterase activity, as well as an increase in leucine aminopeptidase activity.

Davenport *et al.* (1992) proposed that methyl bromide-induced neurotoxicity was due to an effect on GSH and glutathione-S-transferase in the brain. Fischer-344 rats were exposed to methyl bromide (99.9% pure; 150 ppm) for 6 hours per day for 5 days. The concentration was chosen because it did not induce brain lesions or signs of toxicity. The inhibition of GSH transferase ranged from 45 to 56% of control values and the depletion of GSH ranged from 51 to 86% for the different regions (frontal cortex, caudate nucleus, hippocampus, brain stem, and cerebellum). Pretreatment and post-treatment of rats with BW 755C (3-amino-1-[m-(trifluoromethyl)phenyl]-2-pyrazoline), an inhibitor of monohalomethane toxicity, protected against GSH transferase inhibition in all brain regions and gave partial protection against GSH depletion. Monoamines (dopamine and serotonin in the frontal cortex, caudate nucleus, and hippocampus) and amino acids were not affected by the treatment.

Another proposed mechanism for the neurotoxicity of methyl bromide was the alteration of catecholamine levels in the brain (Honma *et al.*, 1987). Male Sprague-Dawley rats (5/group) were exposed to methyl bromide (purity not specified; nominal concentrations 0, 31, 63, 100, 125, or 250 ppm) for 8 hours. Catecholamine levels (dopamine, DA; norepinephrine, NE; homovanillic acid, HVA; 3-methoxy-4-hydroxyphenylglycol, MHPG; serotonin, and 5-hydroxyindoleacetic acid, 5HIAA) were determined in the striatum, hypothalamus, frontal cortex, midbrain, and medulla oblongata after exposure (Table 2). Dopamine levels were decreased in all regions with a lowest-effect level (LEL) of 100 ppm for the striatum. Norepinephrine was decreased (87% of control, $p < 0.05$) with a LEL of 31 ppm in the hypothalamus. However, the decrease (84% of control) at the next dose of 63 ppm was not statistically significant. Homovanillic acid and MHPG were increased with a LEL of 63 ppm in the striatum, hypothalamus, and midbrain (MHPG only). Serotonin and 5HIAA were not significantly affected in any brain segment. Time course studies showed that the maximal effect was detected immediately or 2 hours after exposure for most catecholamines, and the levels returned to control levels 24 hours after exposure was stopped. There were inconsistencies in this study. First, decreased dopamine was measured in the striatum of rats exposed for 8 hours to 100 or

125 ppm methyl bromide whereas exposure at these same levels for a much longer period, 24 hours, did not affect dopamine content in Honma *et al.* (1982) (**III.C. SUBCHRONIC TOXICITY**). Second, if tyrosine hydroxylase was inhibited as proposed in Honma *et al.* (1991), one would expect that the metabolites such as HVA, “downstream” from tyrosine hydroxylase would be decreased. However, the HVA level was increased in this study.

The inhibition of tyrosine hydroxylase has been proposed as the mechanism for the reduction in dopamine levels. Male Sprague-Dawley rats (3-5/group) were exposed to methyl bromide (purity not specified; nominal concentrations of 0, 16, 31, 63, 125, or 250 ppm) for 8 hours (Honma *et al.*, 1991). Brain tyrosine hydroxylase activity (TH) in different brain segments was determined by *in vitro* (all doses) and *in vivo* (≥ 31 ppm) methods at 0, 1, 2, and 24 hours after exposure. Both assays indicated dose-responses for decreases in DOPA (3,4-dihydroxy phenylalanine) production. The segment with the LEL in the “*in vitro*” assay was the hypothalamus; the LEL was 16 ppm, the lowest dose tested (Table 2). The segments with the LEL in the “*in vivo*” assay were the striatum and hypothalamus; the LEL was 63 ppm, with a possible incipient effect at 31 ppm. The maximal inhibition of TH in both assays was seen with the rats sacrificed immediately after the 8 hour exposure period; significant recovery took place within two hours post-exposure and was complete by 24 hours post-exposure. The authors interpreted their findings as evidence that methyl bromide directly caused changes in the enzyme structure, presumably by methylation. However, DPR had significant questions about the findings and its relationship to other studies (additional discussion in **IV.A.1.b. Brain Monoamines and Enzyme Activity**).

The possible relationship between methyl bromide and dopamine was further investigated by testing whether rats exposed to methyl bromide were more sensitive (responsive) to the dopamine agonist apomorphine, which causes hyperactivity in rats (Honma *et al.*, 1994). Increased sensitivity to a dopamine agonist was expected if methyl bromide had damaged presynaptic neurons that use dopamine as the neurotransmitter. Also, the experiment tested whether methyl bromide affected the hypoactivity induced by the norepinephrine agonist clonidine. In the first of two assays, stereotypic oral behavior caused by an intraperitoneal injection of apomorphine was determined in male Sprague-Dawley rats (5/group) 7 days before exposure to methyl bromide and on days 1, 4, 7, 14, and 28 post-exposure. There were two types of inhalation exposure: 8 hours to 0, 25, 50, 100, or 200 ppm; and 8 hours per day for 7 consecutive days to 0, 5, 10, 25, or 50 ppm. There were no consistent dose responses for the supposed methyl bromide-induced increases in stereotypic behavior. The second assay involved measuring locomotor activity (automated-counting apparatus) after an intraperitoneal injection of apomorphine or clonidine. This assay (2 rats/dose) was conducted 7 days after exposure to 0, 10 or 50 ppm methyl bromide (8 hours/day for one day or for 7 consecutive days). Testing also was done the day before exposure to methyl bromide; in these instances, neither apomorphine nor clonidine were administered before the locomotor activity was recorded. The effect of methyl bromide on locomotor activity was uncertain as the data were only for 2 rats per dose and the variability in the mean value was not indicated.

Table 2. Alteration of catecholamine levels and tyrosine hydroxylase activity in the rat brain after acute inhalation exposure to methyl bromide.^a

Exposure (ppm)	16	31	63	100	125	250	63	125	250
Brain Region	% control (0 hour post-exposure)						% control (2 hours post-exposure)		
Striatum									
DA		92	94	76**	81*	70**			
HVA		106	144**	145**	132	137*			
NE		89	86	66*	89	78			
MHPG		107	127*	129*	139**	142**			
TH <i>in vitro</i>	98	87	72*		61**	60**	104	85*	77*
TH <i>in vivo</i>		90	62**		40**	26**	80	69*	81*
Hypothalamus									
DA		89	89	81**	82*	73**			
HVA		101	133*	137**	114	127			
NE		87*	84	79**	73**	70**			
MHPG		107	130*	126*	126	134*			
TH <i>in vitro</i>	82*	65**	65**		59**	57**	92	85	75*
TH <i>in vivo</i>		90	72*		50**	47**	104	96	79
Frontal cortex									
DA		87	92	90	91	75*			
HVA		102	121	144**	125*	125*			
NE		86	78	68**	72*	74*			
MHPG		101	127	110	115	146**			
TH <i>in vitro</i>	100	92	87*		84*	80**	105	89	80*
TH <i>in vivo</i>		103	90		62**	39**	106	101	97
Midbrain									
DA		95	88	86	87	77			
HVA		114	133	161**	148**	150**			
NE		96	80	73*	79**	73**			
MHPG		102	121*	132**	151*	140**			
TH <i>in vitro</i>	103	97	92		87	64**	106	100	97
TH <i>in vivo</i>		96	81*		68**	53**	104	102	99
Medulla									
DA		92	90	88	89	76*			
HVA		104	120	140**	149**	137*			
NE		94	91	86	83*	86			
MHPG		100	114	108	112	139**			
TH <i>in vitro</i>	97	89	91		85	72**	106	105	89
TH <i>in vivo</i>		111	92		69*	48**	104	99	104

^{a/} Data from Honma *et al.* (1987) for dopamine (DA), norepinephrine (NE), homovanillic acid (HVA), and 3-methoxy-4-hydroxyphenylglycol (MHPG) levels ; and Honma *et al.* (1991) for tyrosine hydroxylase activity (TH). Measurements were made immediately, 2 hours, or 24 hours after 8 hours of exposure. Some data were not shown (see details of the studies in the text). *, ** Significance level at $p < 0.05$ (*) or $p < 0.01$ (**) based on statistics as reported.

III.B.2. Oral- Rat

Albino rats (5/sex/group) were given methyl bromide (99.5% pure) either as a liquid or in microcapsules and mixed with corn oil (Kiplinger, 1994). In the liquid methyl bromide testing, methyl bromide was given once by gavage at 50, 100, or 150 mg/kg in initial testing and at 0, 80, 120 or 160 mg/kg in retesting. Only results from the retesting are presented in this Document. For the microcapsules groups, the reported doses were 98, 146, or 195 mg/kg. Rats were fasted for 18-20 hours prior to dosing and feed was made available 3-4 hours after dosing. Rats were observed at approximately 1, 3, and 4 hours after dosing (post-dosing day 0) and once in the morning and once in the afternoon on post-dosing days 1 through 14 (day of scheduled sacrifice). As shown in Table 3, clinical signs and death were reported for all treated groups. The mortality incidences were 0 for control groups, 2/10 (corn oil) and 1/10 (microcapsules) for low dose, 6/10 (corn oil) and 7/10 (microcapsules) for the mid-dose, and 10/10 (corn oil) and 9/10 (microcapsules) for the high dose groups. The clinical signs observed before death included: hypoactivity, ataxia, prostration, labored respiration, hypothermia, and tremors. Other findings with increased incidences included wet yellow urogenital staining and mucoid feces in the treated animals. Rats died on or before post-dosing day 2 with one death on post-dosing day 4. The LD50s for the liquid methyl bromide group were 86 mg/kg and between 120 and 160 mg/kg for females and males, respectively (combined LD50 of 104 mg/kg). The LD50s for the microencapsulated group were 105 mg/kg and 159 mg/kg for females and males, respectively (combined LD50 was 133 mg/kg).

For both the liquid and microcapsules methyl bromide groups, decreased food consumption and body weight gain were reported (Table 3). These effects were related to the dose in most cases. However, the food consumption reduction was greater for the first week than the second week. The stomach was the main organ affected regardless of how methyl bromide was mixed in corn oil. Hemorrhage, edema, and squamous cell hyperplasia were due to severe irritation of the stomach lining. To determine the relative toxicity between liquid and microencapsulated methyl bromide, DPR needs clarification on the following concerns: (1) whether the microcapsules dissolved before dosing and (2) whether the procedure for the methyl bromide content analyses was appropriate. The acute LOAELs were 80 mg/kg for liquid, and 98 mg/kg for microencapsulated methyl bromide for reduced food consumption, clinical signs, stomach lesions, and mortality in treated rats. This study was considered supplemental information by DPR.

Table 3. Clinical findings in rats after acute oral exposure.^a

Clinical Findings	Dosage (mg/kg)						
	Control 80 (----- Corn oil-----)	120	160	98	146	195	(----- Microcapsules-----)
MALES							
<u>Food Consumption</u>	Average (grams of feed /animal/day)						
Week 0-1	22	2	2	1	4	2	6
Week 1-2	33	15	9	1	21	11	15
<u>Body Weight Gain</u>	Average (grams/animal)						
Week 0-2	+32	-6	-6	NA	-7	-6	+1
<u>Clinical Signs</u>	Incidences^b						
Hypoactivity	0/5	4/5	4/5	5/5	0/5	4/5	5/5
Ataxia	0/5	1/5	2/5	3/5	0/5	1/5	2/5
Prostration	0/5	1/5	0/5	0/5	0/5	0/5	0/5
Labored respiration	0/5	1/5	1/5	1/5	0/5	1/5	0/5
Hypothermia	0/5	1/5	1/5	1/5	0/5	1/5	0/5
Tremors	0/5	0/5	0/5	1/5	0/5	1/5	0/5
Death	0/5	1/5	1/5	5/5	0/5	2/5	4/5
<u>Histology- Stomach</u>							
Squamous cell hyperplasia	0/5	3/5	4/5	0/5	4/5	3/5	1/5
Autolysis, hemorrhage, edema ^c	0/5	1/5	1/5	5/5	0/5	2/5	4/5
FEMALES							
<u>Food Consumption</u>	Average (grams of feed /animal/day)						
Week 0-1	15	2	1	NA	3	1	NA
Week 1-2	24	7	1	NA	9	NA	NA
<u>Body Weight Gain</u>	Average (grams/animal)						
Week 0-7	+6	-13	NA	NA	-7	NA	NA
<u>Clinical Signs</u>	Incidences^b						
Hypoactivity	0/5	2/5	5/5	5/5	0/5	5/5	4/5
Ataxia	0/5	1/5	2/5	4/5	0/5	3/5	4/5
Prostration	0/5	0/5	2/5	1/5	0/5	1/5	2/5
Labored respiration	0/5	1/5	2/5	2/5	0/5	1/5	3/5
Hypothermia	0/5	1/5	2/5	2/5	0/5	1/5	2/5
Death	0/5	1/5	5/5	5/5	1/5	5/5	5/5
<u>Histology- Stomach</u>							
Squamous cell hyperplasia	0/5	4/5	0/5	0/5	3/5	0/5	0/5
Autolysis, hemorrhage, edema ^c	0/5	1/5	5/5	5/5	1/5	5/5	5/5

a/ Data from Kiplinger, 1994. NA=not available, the animals died.

b/ Incidences were expressed as number of animals affected/ total animals in the group. Death was observed on day 0 (day of dosing) to post-dose day 2 (2 days after dosing) except for one death noted on post-dose day 4. Effects were those observed during the day of dosing to post-dose day 4.

c/ These animals were found dead before scheduled sacrifice.

III.B.3. Inhalation - Rabbit

Rabbits were exposed to methyl bromide (99% pure; nominal concentrations of 0.42 mg/L to 50 mg/L or 100-13,000 ppm) by inhalation (Irish *et al.*, 1940). Paralysis was observed in some rabbits exposed at 1 mg/L (260 ppm) for 20 hours. There was an indication of lung irritation at higher concentrations, though less pronounced than that observed in the rat. The concentrations and exposure times which resulted in 100% mortality are listed in Table 1.

III.B.4. Inhalation - Mouse

Swiss-Webster mice were exposed to methyl bromide (>99.5% pure) from 0.87 to 5.93 mg/L (223-1518 ppm) for 1 hour by nose only inhalation (Alexeeff and Kilgore, 1985). At all concentrations tested, the 24-hour weight gain of the treated mice was significantly ($p \leq 0.05$) decreased by 4-16% when compared to control group. Transient hyperactivity was observed in the 2.72 and 3.82 mg/L (696 and 978 ppm) groups. Abnormal gait, passivity, and lack of grooming were evident at 3.5 mg/L (896 ppm) and higher with the earliest onset at 3 hours for 4.7 to 5.93 mg/L. Additional clinical signs included: increased depth of respiration, decreased respiration rate, tremors, fasciculation, loss of righting reflex, splayed limbs, tonic seizures, and muscular rigidity. Death occurred at 3.82 mg/L and higher levels. There was also rectal hemorrhaging with diarrhea in those animals treated at 5.77 and 5.93 mg/L, occurring within 6 hours after treatment. One week after treatment, damage was observed in the kidneys (≥ 3.50 mg/L), liver (≥ 3.82 mg/L), brain (≥ 3.82 mg/L), and colon (≥ 3.82 mg/L). Glutathione levels in livers of the 4.7 and 5.93 mg/L groups were significantly ($p \leq 0.05$) lower than the control group. The NOEL was 2.72 mg/L (696 ppm) based on mortality and other effects at 3.82 mg/L.

III.B.5. Inhalation - Dog

Dogs were exposed to methyl bromide for one day, two days, and four days in range-finding studies to select doses for a one-year exposure study (Newton, 1994a). The average measured methyl bromide concentrations ranged from 55 to 394 ppm. The dogs were observed every 15 minutes for the first hour and hourly thereafter. The results for short-term exposures are summarized in Table 4.

In the one-day experiment, dogs (1/concentration, except 2 dogs used for 314 ppm) were exposed for 7 hours to methyl bromide (233, 314, 345, 350, and 394 ppm). All dogs exhibited neurotoxicity (including tremors, hunched appearance, and labored breathing) by the seventh hour, and the earliest onset was 3 hours in the 345, 350, and 394 ppm groups. The exposure of the 394 ppm dog ended at the 6th hour because of clinical signs (mucoid nasal discharge and labored breathing). One day after exposure, the 345 and 350 ppm dogs showed moderate white nasal discharge, while the 394 ppm dog was lethargic with excessive nasal discharge, salivation, and panting. At 314 ppm, one dog showed decreased activity after 4 hours of exposure. All the dogs were observed for 3 or more days and appeared normal before they were used for the two-day study. The NOAEL for the one-day exposure was < 233 ppm for neurotoxicity.

In the two-day exposure study, dogs (3/group) were exposed to 268 ppm and 283 ppm of methyl bromide (Newton, 1994a). These dogs had been used in the one-day experiment: 268 ppm group were previously exposed to either 233, 314, or 394 ppm; while the 283 ppm group were exposed to either 314, 350, or 345 ppm. At the start of this study, all dogs appeared

clinically normal. On the first day, one of the 283 ppm dogs showed excessive salivation, labored breathing, and emesis at the 6th hour of exposure. By the 7th hour, the dogs in this group showed labored breathing (3/3), excessive salivation (2/3), and emesis (2/3). By the second day, the 283 ppm group exposure was terminated because of the following observations: severe neurotoxicity (delirium, thrashing and vocalization, tremors, traumatizing behavior, depression, ataxia, irregular gait) and abnormal respiratory sounds. The 268 ppm group dogs appeared normal on the first day. One of the dogs showed labored breathing at the 3rd to 7th hour on the second day. All dogs showed decreased activity at the 7th hour of the second day. Also, increased blood urea nitrogen and serum aspartate aminotransferase were detected in both exposure groups. The NOAEL for the two-day exposure was < 268 ppm for neurotoxicity.

The four-day exposure study used dogs that had not been exposed to methyl bromide previously (Newton, 1994a). Beagle dogs (1/sex/group) were exposed to 55 ppm and 156 ppm by inhalation for four days (7 hours/day). In the 156 ppm group, one dog showed lacrimation at the fifth hour of exposure. Both dogs exposed to 156 ppm showed decreased activity, lacrimation and labored breathing during the third and fourth day of exposure. Irregular gait was observed in both dogs on the fourth day post-exposure. No abnormal signs were observed during or after exposure for the 55 ppm dogs. The NOAEL for neurotoxicity observed after 3 days of exposure was 55 ppm.

In addition to the above acute toxicity studies, the following subchronic studies were evaluated for the determination of an acute NOEL. The subchronic effects from methyl bromide exposure are further discussed in **III.C.5. Inhalation - Dog**. Beagle dogs (2-4 dogs/sex/group) were exposed to methyl bromide (100% pure) by whole body inhalation at 7 hours per day, 5 days per week, for two exposure durations (Newton, 1994b). The durations of exposure were: 23 to 24 exposure days (0, 26, 53, or 103 ppm) or 30 exposure days (24 exposure days at 11 ppm, then 6 exposure days at 158 ppm). Air concentrations stated were measured concentrations. Serum bromide levels increased with the dose at ≥ 26 ppm. The 158 ppm group showed decreased activity on the second exposure day (the first dose was on a Friday and the second dose was on the following Monday). They were reported in poor condition during the final (6th) exposure and showed severe neurotoxicity with lesions to the brain, adrenal, and olfactory tissues (Table 4). No effects were observed in the 103 ppm dogs after 8 days of exposure. On day 9, some of the dogs in this group showed decreased activity (3/8) and emesis (1/8). On day 10, tremor was noted in one dog. The acute NOEL was 103 ppm for decreased activity seen in the 158 ppm group after 2 exposures and severe neurotoxicity after 6 exposures, and lack of acute effects at 103 ppm.

Table 4. The neurotoxicity of methyl bromide in dogs after acute exposure.^a

Concentration mean \pm standard deviation (ppm)	Duration of exposure ^a	First signs of neurotoxicity and Incidence ^b	Clinical signs with additional exposure
394 \pm 20	3 hours	hunched appearance and tremors (1/1)	hunched appearance and tremors, mucoid nasal discharge, labored breathing
350 \pm 13	3 hours	labored breathing (1/1)	labored breathing, decreased activity, hunched appearance, tremors, excessive salivation and swallowing response
345 \pm 8	3 hours	tremors (1/1)	tremors, labored breathing, hunched appearance, excessive salivation, and gasping
314 \pm 6	4 hours	decreased activity (1/2)	tremors, hunched appearance, and restlessness (2/2)
283 \pm 13	6 hours	salivation, labored breathing, emesis (1/3)	excessive salivation (2/3), labored breathing (3/3), and emesis (2/3)
268 \pm 19	7 hours	no effects	day 2: labored breathing (1/3) and decreased activity (3/3)
233 \pm 21	5 hours	trembling (1/1)	panting, rapid eye blinks, and tremors
158 \pm 7 ^c	7 hours ^c	decreased activity (8/8)	day 3: decreased activity; day 6: severe neurotoxicity; brain, and adrenal lesions, olfactory degeneration (8/8)
156 \pm 15	5 hours	lacrimation (1/2)	day 3 and 4: lacrimation and labored breathing (2/2), prostrate (1/2), and decreased activity (2/2); day 4 post-exposure: irregular gait (2/2)
103 \pm 9 ^c	8 days	no effects	day 9: start of decreased activity (3/8) and emesis (1/8); day 10: tremor (1/8); week 5: cerebellar lesions (1/8) at sacrifice
53 \pm 4 ^c	13 days	no effects	day 14: decreased activity (2/8)
55	4 days	no effects	(experiment terminated after 4 days)

a/ Data from Newton (1994 a and b). Hours of exposure for onset of neurotoxicity.

b/ Incidences as number of dogs affected/ total are shown in parentheses.

c/ Data (Newton, 1994b) is under **III.C. SUBCHRONIC TOXICITY**. The first exposure was on a Friday with no effects reported. However, decreased activity was observed during the second exposure, on the following Monday.

III.B.6. Oral - Dog

Beagle dogs (1/sex/group) were given a single oral dose of methyl bromide (100% pure; 1, 3, 5, 50, or 500 mg/kg) in capsules in a corn oil solution (Naas, 1990). There was no control group. Emesis was observed in animals treated at 3 mg/kg or higher doses. The emesis was described as white foamy, containing food, with partially dissolved capsules, and/or red material. No vomiting was observed during one week post-dosing observation period. Clinical signs were observed at 50 and 500 mg/kg groups. At 50 mg/kg, both dogs showed hypoactivity, hypothermia (body cool to touch), no pain reflexes, and soft stools. Animals treated at 500 mg/kg showed prostration, rapid heart rates, hypothermia, and were dead within one day. Gross examination of the organs of these two dogs showed dark red adrenal glands (male only), dark red kidneys (both), slight hydrocephaly (female only), and marked reddened stomach mucosa (both). Necropsy was not performed on other dogs. Because of the few number of animals involved and that the effects may be due to dosing method, a NOEL was not determined. This study was considered supplemental information by DPR.

III.B.7. Inhalation - Guinea Pig

Guinea pigs were exposed to methyl bromide (purity not specified, nominal concentrations of 0.01 to 5%, with 1% =10,000 ppm) for 5 to 810 minutes (Sayers *et al.*, 1929). No tissue damage or death was observed when the guinea pigs were exposed to 0.06% for 90 minutes, or 0.03% for 270 minutes. The mortality was 100% at 5% of methyl bromide for 15 minutes, 1.3% for 68 minutes, 0.7% for 90 minutes, or 0.23% for 170 minutes. Death occurred within 21 hours after exposure at 2.2% of methyl bromide for 35 minutes, 0.23% for 90 minutes, and 0.05% for 480 minutes. Before death, lacrimation, difficulty in breathing, and weakness were observed. Necropsy showed congestion and tissue degeneration of multiple organs (including lungs, liver, heart, kidneys, and brain).

Guinea pigs (16/group) were exposed to methyl bromide (purity not specified; nominal concentration of 100 or 220 ppm for 7.5 to 8 hours per day for 1 to 3 days (Irish *et al.*, 1940). Guinea pigs at 220 ppm showed respiratory difficulty before death and lung damage. No effect was observed at 100 ppm.

III.B.8. Inhalation - Human

The effects of methyl bromide in humans after acute exposure is well-documented. A summary of the clinical signs and symptoms is provided in this section. Those studies which reported actual exposure levels are described in detail in **III.H. NEUROTOXICITY**. The signs and symptoms after methyl bromide exposure are dependent on concentration and exposure duration (von Oettingen, 1946; Rathus and Landy, 1961; Greenberg, 1971; Grant, 1974; Anger *et al.*, 1986; Gehring *et al.*, 1991; Uncini *et al.*, 1990; De Haro *et al.*, 1997). Acute exposures to lethal concentrations result in early symptoms of malaise, headache, visual disturbances, nausea, and vomiting. After the early symptoms, delirium, disorientation, and excitability may also occur. There is a delayed onset of symptoms that include numbness, ataxia, tremor, myoclonus, exaggerated (or absent) deep reflexes, positive Romberg's signs, paroxysmal abnormalities of the EEG, agitation, change of personality, coma, as well as clonic and tonic convulsions. Death usually occurs within 48 hours of exposure, due to pulmonary edema leading to respiratory failure or cardiovascular collapse. Postmortem examination of the brain

showed generalized swelling and lesions, including neuronal loss (Squier *et al.*, 1992).

Nonlethal exposures to methyl bromide result in neurological effects that include the early symptoms seen in lethal exposures as well as confusion, muscular weakness, tremors, convulsions, euphoria, delirium, and psychoses. Some symptoms may persist after exposure depending on the severity of toxicity. Ataxia and myoclonus continued to be experienced by a worker one year after exposure (Rathus and Landy, 1961). In severe chronic poisoning, endogenous chloride is replaced by bromide, the ionic form of bromine, from the biotransformation of methyl bromide in the body (Blumberg and Neli, 1967).

III.B.9. Dermal - Human

Six workers (1 woman and 5 men) were exposed to methyl bromide (estimated 35 g/m³, or 9,000 ppm) dermally during the fumigation of a castle (Hezemans-Boer *et al.*, 1988; Zwaveling *et al.*, 1987). They wore tight-fitting face masks, overalls over their daily clothing, work shoes, and polyvinylchloride gloves. Shortly after exposure, the primary complaint was burning sensation under the armpits and in the groin. No neurotoxicity was observed. Redness of the skin was noted. Approximately 8 hours after exposure, all workers developed skin lesions which consisted of sharply demarcated erythema with multiple vesicles and large bullae in areas of moisture (from perspiration) such as the axillae, groin, and submammary areas. Histopathological examination showed necrosis of keratinocytes, edema of the papillary dermis, subepidermal blistering, and preferential infiltration by neutrophils. Six days after exposure, there were signs of regeneration of the epidermis, but there was still evidence of cell necrosis and presence of neutrophils. One month after exposure, the skin lesions had disappeared with no significant scarring.

In a recent case report, a worker was exposed to methyl bromide dermally due to a leakage during a field fumigation application (Lifshitz and Gavrilov, 2000). In addition to the skin lesions (burns and blisters), peripheral neuropathy (weakness of the limbs, ataxia, paresthesia of limbs, hyperactive tendon reflexes and left Babinski sign) was observed one week following exposure. These signs persisted 3 months after exposure. While the worker was equipped with respiratory gear, the authors noted that its functionality was unknown and that the neurological effects may be due to both dermal and inhalation exposures.

III.B.10. Additional Acute Studies

Acute effects were also observed in studies described (in detail) in **III.C. SUBCHRONIC TOXICITY** and **III.G. DEVELOPMENTAL TOXICITY** and are included in Table 5.

Table 5. The no-observed-effect levels (NOELs) and lowest-observed-effect levels (LOELs) for acute effects of methyl bromide from selected studies.^a

Route/ Species	Exposure Duration ^b	Study NOEL/LOEL ppm	Human Equivalent ^c NOEL/LOEL ppm	Effects	Ref. ^d
<u>INHALATION</u>					
Rat	6h/dx5d	90/175	47/91	tissue degeneration (brain, adrenals, nasal cavity) neurotoxicity at higher doses (250 ppm)	1
Rat	6 h	90/200	47/104	olfactory epithelium degeneration, ↓ olfactory function	2
Rat	8h	31/63 <16/16	22/44 <11/11	altered brain catecholamines and tyrosine hydroxylase activity altered tyrosine hydroxylase activity (hypothalamus)	3
Rat	6 h	100/350	52/183	changes in neurobehavioral battery	4
Mouse	1 h	696/896	113/146	abnormal gait, passivity, no grooming	5
Dog	7h 7h/dx3d	<233/233 ^e 55/156	<58/58 14/39	neurotoxicity ↓ activity, labored breathing, prostrate	6
Dog^f	7h/dx1d	103/158	25/39	↓ activity on 2nd exposure day; brain lesions after 6 exposures (had previous exposure of 11 ppm for 24 days).	7
Guinea Pig	8h/dx1-3d	100/220	31/61	respiratory difficulty, death	8
<u>INHALATION-DEVELOPMENTAL TOXICITY STUDIES^g</u>					
Rat	7h/d, gd1-19	20/ 70	22/75	progeny-delayed skull ossification	9*
Rabbit	6h/d, gd7-19	40/ 80	21/42	progeny-fused sternebrae, gall bladder agenesis and other effects	10*
<u>ORAL</u>					
Rat/gavage	1 dose (corn oil)		mg/kg/day <80 / 80	Death, hypoactivity, ataxia, prostration, labored respiration, hypothermia, squamous cell hyperplasia in the stomach	11
Rat/gavage	1 dose (microcapsule)		<98 / 98	Death, squamous cell hyperplasia	11
<u>DERMAL</u>					
Human	few hours	-/9000 in air	na	skin lesions (erythema, vesicles)	12
a/	Bolded studies are those selected to derive the critical NOELs for risk characterization.				
b/	Duration: min=minutes, h=hours, d=days, w=weeks, and gd=gestation days.				
c/	Human equivalent NOEL/LOELs were calculated by adjusting for respiration rate differences and duration of exposure (Attachment G). The equivalent levels were those for children only (except references 9 and 10). The adult equivalent levels would be 2-fold higher since the adult respiration rate is lower (0.26 m ³ /kg/day compared to the child's 0.46 m ³ /kg/day). For references 9 and 10, the equivalent levels were those for adults since the effects were observed in pregnant animals.				
d/	* after reference number indicates the study was acceptable according to FIFRA guidelines. References: 1. Hurtt <i>et al.</i> , 1987; 2. Hurtt <i>et al.</i> , 1988; 3. Honma <i>et al.</i> , 1987 and 1991; 4. Driscoll and Hurley, 1993; 5. Alexeeff and Kilgore, 1985; 6. Newton, 1994a; 7. Newton, 1994b; 8. Irish <i>et al.</i> , 1940; 9. Sikov <i>et al.</i> , 1981; 10. Breslin <i>et al.</i> , 1990b; 11. Kiplinger, 1994; 12. Hezemans-Boer <i>et al.</i> , 1988.				
e/	The lowest dose tested.				
f/	Study described in III.C. SUBCHRONIC TOXICITY .				
g/	Studies described in III.G. DEVELOPMENTAL TOXICITY .				

III.C. SUBCHRONIC TOXICITY

Summary: Subchronic inhalation exposure of laboratory animals to methyl bromide resulted in altered brain catecholamine levels, decreased brain tyrosine hydroxylase activity, neurotoxicity, tissue degeneration (brain, nasal cavity, heart, testes, adrenal glands, thymus, spleen, and kidneys), and death. Based on overt signs of neurotoxicity, the dog, rabbit, and monkey were more sensitive to methyl bromide than other species (rat, mouse, and guinea pig). The primary finding after oral exposure by gavage in the rat was hyperplasia of the forestomach. A decrease in body weight gain and food consumption was observed in rats given microencapsulated methyl bromide mixed in the feed. A summary of selected subchronic studies is presented in Table 7.

III.C.1. Inhalation - Rat

Rats (strain not specified, 10-12/group) were exposed to methyl bromide (99% pure, nominal concentrations of 17 to 220 ppm) by inhalation for 7.5 to 8 hours per day, 5 days per week for 6 months or until toxicity was observed (Irish *et al.*, 1940). Methyl bromide at 220 ppm was lethal; all the rats died after 3 to 4 days. At 100 ppm after 6 or more exposures, the rats were in poor general appearance and some developed convulsions. Lung lesions were observed in 66% of the rats in the 100 ppm group. Except for the one death at 66 ppm (time of death not specified), no other effect was observed at this or lower doses.

Sprague-Dawley rats were exposed to methyl bromide (99.9% pure; nominal concentration of 65 ppm for 7.5 hours per day, 4 days per week for a total of 100 hours or 55 ppm for 6 hours per day, 5 days per week for 36 weeks (Anger *et al.*, 1981). There were no effects on sciatic and ulnar nerve conduction velocities, open field activity, or coordination.

Male Sprague-Dawley rats (5-6/group) were exposed to methyl bromide (99.94% pure; nominal concentrations 0, 1, 5, or 10 ppm) for 3 weeks (daily exposure duration not specified) (Honma *et al.*, 1982). Data were presented in graphs. There was no treatment-related change in the levels of acetylcholine in the whole brain or striatum, or cyclic AMP in the striatum. A marked decrease in cyclic GMP in the cerebellum at 5 and 10 ppm was not noted as statistically significant. The other effect at 5 ppm was an increase in dopamine in the striatum (~125% of control, $p < 0.05$). However at the next dose (10 ppm), the increase was only ~111% of control and was not statistically significant. Other monoamines were affected at 10 ppm. There was a decrease of norepinephrine in the hypothalamus (~35% of control, $p < 0.05$), and in the cortex and hippocampus (~30% of control, $p < 0.05$). Serotonin was decreased in the cortex and hippocampus (~70% of control, $p < 0.05$). The NOEL was 5 ppm for decreased monoamines in the brain at 10 ppm.

Sprague-Dawley rats were exposed to methyl bromide (purity not specified) for 4 hours per day, 5 days per week at nominal concentrations of 150 ppm for 11 weeks (Kato *et al.*, 1986). No clinical signs were observed. However, there was an increase in spleen weight (113% of control). Lesions in the heart were noted as small focal necrosis of heart muscle and fibrous replacement of heart muscle. In another experiment, rats were exposed to 200, 300, or 400 ppm for 6 weeks. Paralysis of the hind limb and death were observed in both the 300 and 400 ppm groups. The first death occurred after 3 weeks of exposure at 400 ppm. Voluntary movement was inhibited in all animals of the 400 ppm group by 2 weeks of exposure. Organ weights (brain, thymus, heart, liver and spleen) were significantly ($p \leq 0.05$) lower in one or both

dose groups. Histological examination of the brain of the 400 ppm group showed spongy nerve tissue and glial cell proliferation. Atrophy of the testes, sometimes accompanied by the appearance of giant cells in the seminal tubules, was observed in the 400 ppm group. Multiple and small focal necrosis or fibrosis were observed throughout the left and right ventricles and papillary muscle of the heart in all treated groups. A dose-related increase in bromide concentration was detected only in the liver.

The brain and heart were also target organs in Fischer-344 rats exposed to methyl bromide (99.8% pure, nominal concentration of 160 ppm) for 6 hours per day, 5 days per week for 6 weeks (Eustis *et al.*, 1988). Because there was more than 50% mortality, the male rats were sacrificed after 14 exposures. At the end of the 30 exposures, the survival of the female rats was 50%. There were no treatment related findings in the parameters measured in the clinical chemistry or urinalysis. The treated rats showed curling and crossing of hindlimbs, forelimb twitching, and tremors. There were significant ($p \leq 0.05$) decreases in the body weight (68% of control), and the weights of lungs, heart, spleen, right kidney, brain, liver, and right testes of the males. For the females, significant ($p \leq 0.05$) decreases in body weight (82% of control), and the weights of lungs, right kidney, brain, and liver were observed. Pathological lesions were found in the brain (necrosis and loss of neurons in the cerebral cortex, hippocampus, and thalamus), testes (degeneration and atrophy of the seminiferous tubules), nasal olfactory epithelium (necrosis and degeneration), heart (cardiomyopathy), adrenal cortex (cytoplasmic vacuolation), liver (hepatocellular necrosis), thymus (atrophy), and spleen (lymphoid depletion).

In a longer-term study, Fischer-344 rats were exposed to methyl bromide (99.8% pure, nominal concentrations of 0, 30, 60, or 120 ppm) for 6 hours per day, 5 days per week for 13 weeks (NTP, 1992; Eustis, 1992). No mortality was observed. The body weights were decreased as early as week 6 of exposure. By 13 weeks, the body weights of the 60 and 120 ppm males were 90% and 84% of control, respectively. The brain weights of the 120 ppm groups were significantly ($p \leq 0.01$) decreased to 92% (males) and 93% (females) of control values. There were occasional neurobehavioral effects (such as decreased startle response amplitude, increased startle response latency, and decreased grip strength) in the 120 ppm groups which were significantly ($p \leq 0.05$) different from control values; however, they were not related to exposure duration. Significant ($p \leq 0.05$) decreases in the mean hematocrit, hemoglobin, and erythrocyte counts were detected in the 120 ppm females only. A significant decrease in the erythrocyte count also was noted in the 60 ppm females. An increase in the incidences of olfactory epithelial dysplasia and cysts (irregularity in mucosal thickness and focal cavity spaces) was found in both sexes of the 120 ppm groups. The NOEL was 60 ppm for neurotoxicity and olfactory epithelial dysplasia at 120 ppm.

CD rats (15/sex/group) were exposed to methyl bromide (>99% pure; nominal concentrations of 0, 30, 70, or 140 ppm) by inhalation for 6 hours per day, 5 days per week for 90 days (Norris *et al.*, 1993 a and b). Neurobehavioral testing was done pre-exposure and at the end of study weeks 4, 8 and 13. Testing included automated assessments of motor activity and a Functional Observation Battery (FOB). Two 140 ppm males died on test (days 12 and 27); the latter had convulsions and tremors before dying. One other 140 ppm male that survived until the end of the study also exhibited clonic convulsions and tremors. The 140 ppm groups (both sexes) weighed significantly less than the controls, starting at study week 4 while the

70 ppm female group exhibited a body weight reduction, starting about study week 9. The mean body weights were 87% of control values on week 13 for 140 ppm groups, and 92% for the 70 ppm females.

FOB testing identified effects only in the 140 ppm groups; some effects were evident as early as study week 4. Findings included: ataxia (5 females, 1 male); decreased arousal (females only); decreased rearing activity (females only); increased hind leg splay (males only); and (possibly) abnormal air righting (males only). Motor activity testing identified effects only in the 70 ppm and 140 ppm female groups. Findings included decreased total motor activity and decreased rearing activity; both were evident as incipient effects in study week 8. Female groups exposed to methyl bromide exhibited a dose response for reduced absolute brain weight. The reductions were statistically significant ($p \leq 0.01$) for all dose levels and were 96%, 95%, and 90% of control for 30 ppm, 70 ppm, and 140 ppm, respectively. For the males, the brain weight of the 140 ppm group only was reduced (94% of control, $p \leq 0.05$). Histological findings included: brain lesions at multiple sites (four 140 ppm males; neuronal loss, neuronal necrosis, malacia); peripheral nerve degeneration and/or vacuolation (140 ppm, 2/sex affected; one 30 ppm female affected); and olfactory epithelium dysplasia (140 ppm, 3/sex affected). The NOAEL was < 30 ppm based on reduced brain weight at the lowest dose tested. Neuro-behavioral testing effects were observed at ≥ 70 ppm. Submission of "validation" training and positive control data (Gill, 1989 a, b, c, and d) generated 5 years before the methyl bromide testing using different personnel than those in the methyl bromide testing (Driscoll *et al.*, 1994) were considered inadequate. Therefore, this study is considered unacceptable and not upgradeable by DPR.

III.C.2. Oral - Rat

In a chronic toxicity range-finding study, Sprague-Dawley rats (15/sex/group) were given microcapsules containing methyl bromide (0, 0.1, 1.0, 10, or 100 ppm) mixed in the diet daily for 4 weeks (Tompkins, 1995). The reported average dosages for both sexes were 0.009, 0.09, 0.8, or 8 mg/kg/day. The highest nominal doses ranged from 6 to 9 mg/kg/day. All rats survived to scheduled sacrifice. No significant effects were observed in the following areas: clinical observations, hematology, serum chemistry, necropsy, absolute organ weights and organ weights relative to body weight, and histology. The NOEL for these parameters was > 100 ppm (> 8 mg/kg/day). The only statistically significant finding was decreased (91 to 92% of control) food consumption in the 100 male group for each of the four test weeks. However, the body weight gains of the 100 ppm males were significantly decreased (80% of control, $p < 0.05$) only for the first week. There was no effect on the food consumption in the female groups. There was a transient decrease (77% of control, $p < 0.05$) in the body weight gain of the 100 ppm females at 1 to 2 weeks.

Wistar rats were given methyl bromide (>98% pure; 0, 0.4, 2, 10, or 50 mg/kg/day) by gavage 5 days per week for 13 weeks (Danse *et al.*, 1984). At 50 mg/kg/day, there were significantly ($p \leq 0.05$) reduced body weight gain (69% and 73% of control values for 6 and 12 weeks, respectively) in the male, decreased food consumption (77-82% of control values) in both sexes, and decreased red blood cell concentration (93% of control values) in the males. Histological examination showed that there was an increase in the incidence and severity of hyperplasia of the stratified squamous epithelium of the forestomach. At 10 mg/kg/day, the hyperplasia was described as slight in 9 of 10 males and 6 of 10 females. At 50 mg/kg/day, the hyperplasia was predominantly strong and occurred in 8 of 10 of males and all females. In the original report, squamous cell carcinoma of the forestomach was reported for 13 of 20 animals treated with 50 mg/kg/day. However, re-analysis of the histological slides by a National Toxicology Program Panel concluded that the lesions were non-neoplastic (Boorman, 1984). Histological changes in the lungs were focal interstitial pneumonia in the 10 and 50 mg/kg/day groups, and slight atelectasis in the 50 mg/kg/day groups. The NOEL was 2 mg/kg/day (1.4 mg/kg/day as daily dose from adjustment for 5 days per week dosing) based on forestomach epithelial hyperplasia.

The reversibility of the lesions in the stomach was studied by Boorman *et al.* (1986). Wistar rats were given methyl bromide (>99% pure, 0 or 50 mg/kg) by gavage 5 days per week for 13, 17, 21 or 25 weeks. Pseudoepitheliomatous hyperplasia of the forestomach was observed in all treatment periods; however, there was no significant increase in the incidence with prolonged exposure. Evidence of early squamous cell carcinoma was detected in one animal after 25 weeks. In another experiment, rats were treated for 13 weeks and were sacrificed immediately afterward, 4 weeks, 8 weeks, or 12 weeks after treatment. There was an apparent regression of the hyperplasia formed at 13 weeks, as no incidence of hyperplasia was observed in animals sacrificed 12 weeks after treatment. However, adhesions, fibrosis, and mild acanthosis remained in the forestomach. The dosage for lowest-observed-effect level (LOEL) was 50 mg/kg/day (35.7 mg/kg/day as an adjusted daily dose).

In a study similar to that conducted by Boorman *et al.* (1986), Wistar rats were given methyl bromide (purity not specified) by gavage at 0, 25, or 50 mg/kg/day for 4 to 17 weeks (5 days/week) and allowed a recovery period of 4 to 9 weeks before necropsy was performed (Hubbs, 1986). In the non-glandular stomach, the squamous epithelial portion showed ulceration and pseudoepitheliomatous hyperplasia characterized by hyperkeratosis, acanthosis, and epithelial peg formation. Fibrosis was found in the muscularis mucosa or tunica muscularis. In the glandular stomach, there were submucosal lymphoid aggregates and non-lymphoid mononuclear cell infiltrates in the lamina propria. At 4 to 9 weeks after treatment, there was regression of the hyperplasia in the stomach but not the muscularis fibrosis. The LOEL was 25 mg/kg/day (17.9 mg/kg/day as an adjusted daily dose).

III.C.3. Inhalation - Mouse

In a range-finding study for a 90-day study, B6C3F1 mice (10/sex/group) were exposed to methyl bromide (99.8% pure; nominal concentrations of 0, 12, 25, 50, 100, or 200 ppm) for 6 hours per day, 5 days per week, for 14 days (NTP, 1992; Drew, 1983). Mortality occurred only at the 200 ppm groups with 4 of 10 females and 1 of 10 males surviving until terminal sacrifice. Bloody urine (both sexes) and mild hyperemia in the lungs, liver, and kidneys (females) were observed in the 200 ppm groups. No urinary bladder lesion was detected to account for the

hematuria. Neurotoxicity, manifested as trembling, jumpiness, and paralysis was noted for all exposed groups but was more prominent for the groups treated at 50 ppm and higher. There are questions as to the validity of the observations at the lower doses (12 and 25 ppm) since the observer had been cautioned to look for behavioral changes (Drew, 1983).

A decrease in body weight and neurotoxicity were also observed when B6C3F1 mice were exposed to methyl bromide (99.8% pure, a nominal concentration of 160 ppm) for 6 hours per day, 5 days per week for 2 weeks in a target organ toxicity study (Eustis *et al.*, 1988). The experiment was intended for 6 weeks but was terminated after 2 weeks since more than 50% of the animals were dead after 10 and 8 exposures for the males and females, respectively. Clinical signs included red urine, lethargy, and neurological effects (curling and crossing of the hindlimbs, forelimb twitching and tremors). Treated male and female body weights at termination were only 74% and 82% of the control values ($p \leq 0.001$, both sexes), respectively. Absolute organ weights which were significantly ($p \leq 0.05$) lower in both sexes (unless noted) included: lungs, heart, spleen (males), right kidneys (males), thymus, brain, and liver. Histological examination of the tissues showed lesions in the brain (necrosis and loss of neurons in the cerebellum and cerebral cortex), kidney (nephrosis, dilatation and increased cytoplasmic basophilia), testes (degeneration), nasal cavity (degeneration and atrophy, males), heart (cardiomyopathy), adrenal gland (atrophy of the inner-zone of the adrenal cortex, females), thymus (atrophy), and spleen (lymphoid depletion and hematopoiesis).

When B6C3F1 mice were exposed to methyl bromide (99.8% pure; nominal concentrations of 0, 10, 20, 40, 80, or 120 ppm) for 6 hours per day, 5 days per week for 13 weeks, the survival rates were 83% for the 120 ppm males and 100% for the females (NTP, 1992; Eustis, 1992). In the 120 ppm group, body weight gain was 58% of control ($p \leq 0.05$, males), and brain weights were 92 to 94% of control ($p \leq 0.01$, both sexes). Clinical signs (severe curling, crossing of the hindlimbs, and twitching of the forelimbs) were observed in the 120 ppm groups, with greater severity occurring in the males than in the females. Alterations in a few of the neurobehavioral responses were observed, primarily in the 80 ppm groups; no data were reported for the 120 ppm groups. Significant ($p \leq 0.05$) changes in the hematological parameters which were dose related included: decreased mean cell hemoglobin (40 to 120 ppm males, 120 ppm females), decreased mean cell volume (40 to 120 ppm males), increased erythrocyte count (40 to 120 ppm males), and increased hemoglobin (120 ppm males). No compound-related lesions were observed by histological examination. The NOEL was 20 ppm for changes in blood parameters at 40 ppm and neurobehavioral responses at 80 ppm.

III.C.4. Inhalation - Rabbit

Rabbits (strain unspecified) were exposed to methyl bromide (99% pure, nominal concentrations of 17, 33, or 66 ppm) by inhalation for 7.5-8 hours per day, 5 days per week during a 6-month period (Irish *et al.*, 1940). No adverse effects were observed at 17 ppm. Paralysis and lung damage occurred at the next dose (33 ppm) and higher. At 66 ppm after 14 to 46 exposures, 28 of 42 rabbits showed severe paralysis, and 14 of 42 rabbits died. Rabbits appeared to recover from the paralysis if they were removed from exposure at the first sign of paralysis.

New Zealand white rabbits (2/control, 6/treated) were exposed to methyl bromide (99.9% pure; a nominal concentration of 65 ppm for 7.5 hours per day, 25 hours per week for 4 weeks

(Anger *et al.*, 1981). The data were presented in graphs. After 4 weeks of exposure, the methyl bromide group showed a decrease in body weight which continued to decline at test week 5 (1 week after continuous exposure). After 4 days of exposure, eye blink amplitude were decreased in both control and treated groups. The decline in the control returned to pre-test level in the following week. However, in the treated group, eyeblink amplitude was decreased after additional exposure. Furthermore, during the fourth week of exposure, the rabbits did not use the hind limbs or groom themselves. The recovery of normal functions was complete for sciatic nerve conduction velocity and partial for ulner nerve conduction velocity and eyeblink amplitude when the treated rabbits were tested 6-8 weeks after exposure (Russo *et al.*, 1984).

Male New Zealand white rabbits (2 control, 6 treated) were exposed to methyl bromide (99% pure, a nominal concentration of 27 ppm) at 7.5 hours per day, 25 hours per week, for 30 weeks (Russo *et al.*, 1984). There were no treatment-related changes in sciatic and ulnar nerve conduction velocities and eyeblink reflex amplitude.

III.C.5. Inhalation - Dog

Beagle dogs (2-4 dogs/sex/group) were exposed to methyl bromide (100% pure) by whole body inhalation at 7 hours per day, 5 days per week, for three exposure durations. The durations of exposure were: 23 to 24 exposure days (0, 26, 53, or 103 ppm), 30 exposure days (24 exposure days at 11 ppm, then 6 exposure days at 158 ppm), or 34 exposure days (0 or 5 ppm) (Newton, 1994b). Air concentrations stated were measured concentrations. Serum bromide levels increased with the dose at ≥ 26 ppm. Body weight loss (25%) and neurotoxicity were seen in the dogs exposed to 158 ppm. These dogs showed decreased activity on the second exposure day (the first dose was on a Friday and the second dose was on the following Monday). They were reported in poor condition during the final (6th) exposure (Table 6). The next day, three 158 ppm males had to be sacrificed due to severe toxicity (opisthotonos, irregular gait, opening and closing of the jaws and convulsions). The remaining 158 ppm dogs exhibited: nystagmus, intention tremors, ataxia, irregular gait and depression. Elevated levels of protein and bilirubin were measured in the urine of the 158 ppm dogs. Histological examinations showed that each of the 158 ppm dogs had cerebellar lesions (vacuoles in the granular layer) and olfactory degeneration; the males also had adrenal cortex findings (zona fasciculata, cytoplasmic vacuoles).

A decrease in body weight gain and less severe neurotoxicity (tremors, emesis, decreased activity during exposure but not post-exposure) were seen in the 103 ppm dogs. The loss in body weight was statistically ($p \leq 0.05$) significant for all weekly measurements for males and from week 2 on for females. A decrease in activity was noted starting on exposure day 9 involving most or all of the animals. Tremors were observed in 1 of 8 dogs on day 10. Emesis was observed in 1 dog on days 9 and 10. One 103 ppm male exhibited a cerebellar lesion similar to that seen in the 158 ppm dogs. In the 53 ppm group, a decrease in activity during exposures also was noted (in 2 dogs), starting on exposure day 14. However, no abnormal findings were reported for the 53 ppm group in post-exposure examinations. The NOAEL for 23-24 exposure days was 53 ppm for neurotoxicity at 103 ppm and 158 ppm.

The female dogs which were exposed the longest to methyl bromide (5 ppm group) had reduced absolute spleen weights (55% of control compared to 75% of control for the male group) and two 5 ppm females were observed by an animal neurologist at the end of test week 6

to be less responsive than expected. The neurologist noted that one dog was “unresponsive and motionless”, and the other dog “stood quietly, appeared depressed.” He had examined the dogs in the study on two other occasions: pre-test and at the end of week 4. However, he did not examine the dogs during week 7 exposures. From exposure days 31 to 34 (end of exposure), the report noted no abnormal activities in these dogs. The LOAEL for 34 exposure days was 5 ppm for decreased spleen weight (females) and decreased responsiveness (females).

Acute and short-term NOELs were also established from these experiments (**III.B.5. Inhalation-Dog**). The acute NOEL was 103 ppm for decreased activity seen in the 158 ppm group after 2 exposures and severe neurotoxicity after 6 exposures (Table 4).

Table 6. The neurotoxicity of methyl bromide in dogs after subchronic exposure.^a

Concentrations mean \pm sd (ppm)	Onset	Clinical Signs and Incidences ^c	Clinical Signs with Additional Exposure
158 \pm 7 ^b	day 2	decreased activity (8/8)	severe neurotoxicity, cerebellar lesions (8/8)
103 \pm 9	day 9	decreased activity (3/8)	day 9 to 10: emesis (1/8), tremor (1/8), decreased activity (3/8); week 5: cerebellar lesions (1/8)
53 \pm 4	day 14	decreased activity (2/8)	
26 \pm 1	23-24 exposures	no effects observed	
5 \pm 0.4	30 exposures	decreased responsiveness (2/8)	

^a/ Data from Newton, 1994b.

^b/ The dogs were exposed to 11 ppm for 24 exposure days, then 158 ppm for 6 exposure days.

^c/ Incidences as number of dogs affected/total are shown in parentheses.

III.C.6. Inhalation - Guinea Pig

Guinea pigs exposed to methyl bromide (99% pure; nominal concentrations of 0, 33, 66, 100, or 220 ppm) for 7.5 to 8 hours per day and 5 days per week showed severe intoxication only at 100 ppm and higher concentrations (Irish *et al.*, 1940). At 100 ppm, 4 of 11 animals died after 64 to 91 exposures. However, pulmonary damage was insignificant. At 200 ppm, 14 of 16 animals died after only 1 to 3 days of exposure. All showed difficulty in breathing and lung damage.

III.C.7. Inhalation - Monkey

Monkeys were exposed to methyl bromide (99% pure; nominal concentrations of 0, 33, 66, 100 ppm) for 7.5 to 8 hours per day and 5 days per week (Irish *et al.*, 1940). At 100 ppm after 11 exposures, severe convulsions were observed in the one monkey tested. At the lower concentration (66 ppm), six monkeys were tested: one became paralyzed after 25 exposures and two others became paralyzed after 45 to 57 exposures. No toxicity was observed in four monkeys exposed to 33 ppm methyl bromide for 116 to 259 exposure days.

III.C.8. Additional Studies

Additional studies for the consideration of subchronic toxicity are described in the **III.D. CHRONIC TOXICITY**, **III.F. REPRODUCTIVE TOXICITY**, and **III.G. DEVELOPMENTAL TOXICITY** and are summarized in Table 7.

Table 7. The no-observed-effect levels (NOELs) and lowest-observed-effect levels (LOELs) for subchronic effects of methyl bromide.^a

Route/ Species	Exposure Duration ^b	Study NOEL/LOEL ppm	Human equivalent NOEL/LOEL ppm	Effects	Ref. ^d
INHALATION					
Rat	8h/dx5d/w ≥6 exposures	66/100	31/47	convulsions, lung lesion	1
Rat	7.5h/dx4d/w 100 h	65/- ^d	24/-	no effects on neurobehavioral tests	2
Rat	24 h/dx3w	5/10	10/21	↓ brain monoamine levels	3
Rat	4h/dx5d/wx6w	200/300	50/75	paralysis, death	4
Rat	6h/dx5d/wx3w	<160/160 ^e	<60/60	death, neurotoxicity, and tissue damage	5
Rat	6h/dx5d/wx13w	60/120	22/45	startle response, ↓ grip strength olfactory epithelial dysplasia	6
Rat	6h/dx5d/wx13w	<30/30 30/70	<11/11 11/26	↓ brain weight ↓ motor activity	7
Rat ^f	6h/dx5d/w 132-145 days	3/30 3/30	2/20 2/20	F ₁ parental-↓ fertility progeny-↓ body weight, ↓ brain weight (F ₁), ↓ cerebral cortex width (F ₁)	8*
Mouse	6h/dx5d/w x 2w	<160/160 ^d	<112/112	death, tissue degeneration, ↓ body and organ weights, neurotoxicity	5
Mouse	6h/dx5d/wx13w	20/40	14/28	hematology and neurobehavioral changes at higher doses	6
Mouse ^g	6h/dx5d/wx20w	33/100	23/98	brain, heart, sternum, and olfactory epithelium lesions, neurotoxicity	6

a/ Bolded studies are those selected to derive the critical NOELs for risk characterization.

b/ Duration of exposure is indicated as : h=hours, d=days, w=weeks, m=months.

c/ Human equivalent NOEL/LOELs were calculated by adjusting for respiration rate differences and duration of exposure (Attachment G). The equivalent levels were those for children only (except reference 8). The equivalent levels would be 2-fold higher since the adult respiration rate is lower (0.26 m³/kg/day compared to the child's 0.46 m³/kg/day). For reference 8, the equivalent levels were those for adults since the effects were related to pregnancy.

d/ * after the reference number indicates the study was acceptable to DPR according to FIFRA guidelines. References: 1. Irish *et al.*, 1940; 2. Anger *et al.*, 1981; 3. Honma *et al.*, 1982; 4. Kato *et al.*, 1986; 5. Eustis *et al.*, 1988; 6. NTP, 1992 and Eustis, 1992; 7. Norris *et al.*, 1993a and b; 8. American Biogenics, Corp., 1986.

e/ The only dose studied or the dose at which an effect was observed at the specified duration but not necessarily the LOEL.

f/ Study described in **III.F. REPRODUCTIVE TOXICITY**.

g/ Study described in **III.D. CHRONIC TOXICITY**.

Table 7. The no-observed-effect levels (NOELs) and lowest-observed-effect levels (LOELs) for subchronic effects of methyl bromide (continued).^a

Route/ Species	Exposure Duration ^b	Study NOEL/LOEL ppm	Human equivalent NOEL/LOEL ppm	Effects	Ref. ^c
INHALATION					
Rabbit	8h/dx5d/w x<6 mon	17/33	4/9	paralysis, lung lesion	1
Rabbit	8h/dx5d/w x 14-46 exp	33/66	9/17	paralysis, death	1
Rabbit	7.5h/dx4d/wx4w	<65/65 ^e	<14/14	↓ nerve conduction velocity, ↓ eyeblink reflex, paralysis	2
Rabbit	7.5h/dx4d/wx30w	27/>27	7/>7	no change in nerve conduction velocity, or eyeblink reflex 3	
Rabbit^f	7h/d, gd1-15	20/ 70	7/24	convulsion, paresis, death after 1 week	4
Rabbit ^f	6h/d, gd 7-17	70/140	21/41	neurotoxicity	5
Rabbit ^f	6h/d, gd 7-19	40/80	12/23	neurotoxicity on gd 19	6*
Dog	7h/dx14d	26/53	5/9	↓ activity	7
Dog	7h/dx34d (6w)	<5/5^e	<1/1	↓ responsiveness, ↓ spleen weight	7
Guinea Pig	8h/dx5d/wx47 exp	33/66	7/14	death	1
Monkey	8h/dx5d/wx11 exp	66/100	14/21	convulsion	1
Monkey	8h/dx5d/wx25 exp	33/66	7/14	convulsion, paralysis	1
ORAL		NOEL/LOEL in unadjusted	mg/kg/day adjusted ^g		
Rat	gavage, 5d/wx13w	2/10	1.4/7.1	forestomach-hyperplasia	9
Rat	gavage, 5d/wx13-25w	<50/50	<35.7/35.7	forestomach-hyperplasia, tumor	10
Rat	gavage, 5d/wx4-17w	<25/25	<17.9/17.9	forestomach-hyperplasia	11

^{a/} Bolded studies are those selected to derive the critical NOELs for risk characterization.

^{b/} Duration of exposure is indicated as : h=hours, d=days, w=weeks, exp=exposures, gd=gestational day.

^{c/} Human equivalent NOEL/LOELs were calculated by adjusting for respiration rate differences and duration of exposure (Attachment G). The equivalent levels were those for children only. The equivalent levels for adults would be 2-fold higher since the adult respiration rate is lower (0.26 m³/kg/day compared to the child's 0.46 m³/kg/day).

^{d/} * after the reference number indicates the study was acceptable to DPR according to FIFRA guidelines.

References: 1. Irish *et al.*, 1940; 2. Anger *et al.*, 1981; 3. Russo *et al.*, 1984; 4. Sikov *et al.*, 1981; 5. Breslin *et al.*, 1990a; 6. Breslin *et al.*, 1990b; 7. Newton, 1994b; 8. Danse *et al.*, 1984; 9. Boorman *et al.*, 1986; 10. Hubbs, 1986.

^{e/} The only dose studied or the dose at which an effect was observed at the specified duration.

^{f/} Studies described in **III.G. DEVELOPMENTAL TOXICITY**.

^{g/} The dosages were adjusted for experiments with dosing 5 days per week to 7 days per week.

III.D. CHRONIC TOXICITY AND ONCOGENICITY

Summary: The nasal cavity, brain, and heart were major target organs in rodents after chronic inhalation exposure to methyl bromide. Olfactory epithelial damage (hyperplasia, metaplasia, and necrosis) and myocardial degeneration were observed in rats and mice. Cerebellar and cerebral degenerations were detected in mice while reduced brain weight was observed in rats. When rats were exposed to methyl bromide in microcapsules mixed in the feed, the primary effect was body weight reduction. Possible treatment-related lesions were found in the spleen, liver, pancreas, and lungs. In male dogs fed methyl bromide-fumigated feed, decreased hematocrit and hemoglobin levels were observed. A summary of the chronic toxicity studies is presented in Table 14.

III.D.1. Inhalation - Rat

Wistar rats (90/sex/group) were exposed to methyl bromide (98.8% pure; nominal concentrations of 0, 3, 30, or 90 ppm) 6 hours per day, 5 days per week (Reuzel *et al.*, 1987 and 1991). The main group for each dose consisted of 50 rats of each sex and were exposed to methyl bromide for 29 months. There were 4 satellite groups (10/sex/group except noted): week 13-14 hematology and blood chemistry analyses, week 41 behavioral effects, 1 year interim sacrifice, and 2 years interim sacrifice.

In the 90 ppm group, the 2 year and 2.5 year mortality rates for both sexes (male/female) were 52%/46% and 84%/86%, respectively. These rates were considered higher than those for the control groups which were 32% for 2 years and about 72% for 2.5 years, for both sexes. The mean body weight of the 90 ppm female group was significantly ($p \leq 0.05$) lower than that of the controls throughout most of the study with the maximal reduction (12%) at the end of the study. The mean body weight of the 90 ppm male group was significantly ($p \leq 0.05$) decreased (maximum of 6%) on occasion. Absolute kidney weights were significantly ($p \leq 0.05$) decreased in the 30 ppm (89% of control) and 90 ppm (84% of control) females, and in the 90 ppm males (85% of control) when compared to control values at the 1 year sacrifice. Absolute brain weights of the 90 ppm females were reduced at the 1-year and 2-year sacrifices (Table 8). At 29 months, the absolute brain weights were significantly decreased in the 30 ppm males and females, and the 90 ppm females. Brain weight reduction also was seen in the 90 ppm male group at 29 months but was not statistically significant probably due to the small number of survivors ($n=8$). The NOAEL was 3 ppm for brain weight reduction.

There were increased incidences of heart thrombi and myocardial degeneration in rats that died or were killed when moribund (Table 8). These lesions may be the cause of increased mortality in the high dose groups. Statistical comparison to the control group did not identify any increased tumor incidences. Few tumors were observed: brain glioma in the 30 ppm group (1 male and 1 female), granular cell myoblastoma in the 30 ppm group (2 males), and 90 ppm group (1 male, and 2 females), spinal cord glioma in the control (1 male) and 90 ppm group (1 female). The historical control data (1974-1988) for Wistar rats showed the following incidences (male and female, respectively): 8/873 and 3/876 for brain glioma, 2/685 and 1/701 for spinal cord glioma, and 2/873 and 8/876 for granular cell myoblastoma.

At 12-24 months, the incidences of nasal cavity lesions of the 30 and 90 ppm groups were significantly ($p \leq 0.05$) different from those of the control group (Table 8). At 24-29

months, there was a dose-related increase in the incidences of nasal cavity degeneration/hyperplasia, heart lesions (thrombus, myocardial degeneration, and cartilaginous metaplasia), esophageal hyperkeratosis, and stomach hyperkeratosis in all treatment groups. The finding of epithelial cell degeneration/basal cell hyperplasia in the olfactory epithelium of the nasal cavity was both dose- and time-related in incidence and severity (Table 8). The lesions were described as very slight at the lower doses to moderate at the higher doses. There was thinning (atrophy) of the epithelial layer and the formation of cyst-like glandular structures in the submucosa layer. The LOAEL for the basal cell hyperplasia/degeneration were >90 ppm, 30 ppm, and 3 ppm for exposures lasting 12 months, 12-24 months, and 24-29 months, respectively. The results from the reexamination of the nasal cavity histological slides (Hardisty, 1997) did not change the LOAELs because: (1) the rereading of the slides was not conducted in accordance with standard procedures for a peer review, (2) dose response for incidence and severity remained the same with effects observed at 3 ppm. This study was considered acceptable to DPR according to FIFRA guidelines.

Fischer-344/DuCrj rats (50/sex/group) were exposed to methyl bromide (99.9% pure; 0, 4, 20, or 100 ppm) by inhalation 6 hours per day, 5 days per week for 104 weeks (Gotoh *et al.*, 1994). Results in this study were reported as summary data in a brief publication. There were no effects on survival. The mean body weights of the 100 ppm (both sexes) and 20 ppm (males) were stated to be lower than controls; however, no data were included in the report. The primary effect was increased incidences ($p \leq 0.05$) of necrosis (100 ppm males), inflammation (≥ 4 ppm males; 100 ppm females), and respiratory metaplasia (100 ppm males; 4 ppm females) of the olfactory epithelium. These effects occurred in the males at lower doses than in the females. The LOEL for nasal cavity inflammation and respiratory metaplasia was 4 ppm. Histological examination of the tissues showed increased incidences of pituitary adenoma (100 ppm males) and adrenal gland pheochromocytoma (4 ppm females). The significance of these findings as well as non-neoplastic findings require the evaluation of individual data, historical control data, and subchronic studies. The study was considered unacceptable and upgradeable by DPR.

Table 8. The effects of methyl bromide in rats after chronic inhalation exposure.^a

Exposure duration		Methyl Bromide Concentration (ppm)			
		0	3	30	90
MALE					
		Mean Absolute Organ weight (g)^b			
Brain Weight:	1 year	2.01±0.03	2.12±0.01*	2.03±0.03	1.93±0.03
	2 year	2.09±0.07	2.15±0.02	2.08±0.03	1.99±0.06
	29 months	2.15±0.02	2.11±0.03	2.03±0.04*	2.02±0.05
Nasal Cavity:		Incidences			
Degeneration/ hyperplasia	12-24 months	6/30++ (20%)	1/26 (4%)	11/35 (31%)	22/39** (56%)
	24-29 months	4/36++ (11%)	12/37* (32%)	16/32*** (50%)	20/28*** (71%)
Heart:		Incidences			
died before end of study ^c					
Cartilaginous metaplasia		1/33++	2/25	5/34	12/41**
Myocardial degeneration -moderate/severe		21/33++	16/25	8/34	36/41*
Thrombus		4/33++	3/25	10/34	20/41**

FEMALE					
		Mean Absolute Organ weight (g)^b			
Brain Weight:	1 year	1.94±0.02	1.95±0.03	1.85±0.04	1.81±0.03**
	2 year	1.97±0.02	1.91±0.01	1.88±0.03	1.84±0.05*
	29 months	2.01±0.02	1.96±0.02	1.92±0.02*	1.77±0.06**
Nasal Cavity		Incidences			
Degeneration/ hyperplasia	12-24 months	7/38++ (18%)	5/34 (15%)	16/39* (41%)	26/42*** (62%)
	24-29 months	5/40++ (13%)	16/42** (38%)	15/38** (39%)	25/35*** (71%)
Heart:		Incidences			
died before end of study ^c					
Cartilaginous metaplasia		4/41	10/33	2/35	14/51*
Myocardial degeneration -moderate/severe		13/41++	5/33	5/35	38/51**
Thrombus		5/41++	8/33	1/35	20/51*

a/ Data from Reuzel *et al.* (1987, 1991). Incidence rates were the number of animals affected/number of animals examined. Rats in the 12-24 month group were those in the 1-year and 2-year sacrifice groups, and in the main group which died before two years. Rats in the 24-29 month group were those in the main group which died between days 736 and terminal sacrifice, and those at terminal sacrifice. *, **, ***; +, ++ Level of statistical significance, $p \leq 0.05$ (* or +), $p \leq 0.01$ (** or ++), or $p \leq 0.005$ (***). Significance for incidences was based on a dose-weighted chi-square trend test and the Fisher's Exact Test. For brain weights, significance was based on ANOVA and Dunnett tests.

b/ The number of animals per group for the 29 months data were: 15, 25, 16, and 8 for the males; and 18, 25, 24, and 9 for the females for 0, 3, 30, and 90 ppm, respectively.

c/ Incidences of heart lesions in those animals dead before the end of the study.

III.D.2. Dietary - Rat

Sprague-Dawley rats (70/sex/group, except for 0.5 and 2.5 ppm with 50/sex/group) were given methyl bromide in microcapsules dispersed into the granular feed for presentations to the animals for two years (Mertens, 1997). Corn oil containing methyl bromide was micro-encapsulated using starch and sucrose. Two types of microcapsules were produced. One was a blend of 7 production runs; it had a methyl bromide content of 0.48% w/w. The second type was a blend of five production runs; its methyl bromide content was 3.44% w/w. The two types of microcapsules differed also in terms of corn oil, starch, and sucrose content and age of the material at start of testing. Nominal methyl bromide concentrations in the diet were as follows: 0 (basal diet), 0 (diet containing placebo microcapsules), 0.5, 2.5, 50 or 250 ppm. The blend containing 0.48% methyl bromide was used to prepare the two low doses while the blend containing 3.44% was used to prepare the two high doses. The highest dose tested was selected on the basis of a two-week range-finding study. The daily ration of feed varied as follows: for test weeks 0-65, males and females each received 30 and 23 g, respectively; for test weeks 66 -104, males and females received 35 and 30 g, respectively. One outcome of this feeding strategy appeared to have been that a fraction of the animals in the control and 0.5 to 50 ppm groups had their feed consumption restricted during the first 65 weeks of the study. In test week 53, interim sacrifices were performed on 18-20 rats/sex for the following dose levels: 0 (basal diet), 0 (placebo microcapsules), 50 and 250 ppm. The reported dosages (male/female) were 0, 0.02/0.03, 0.11/0.15, 2.20/2.92, or 11.10/15.12 mg/kg/day for 0, 0.5, 2.5, 50, or 250 ppm, respectively.

Survival was statistically increased in the 250 ppm male group and in the 50 and 250 ppm female groups when compared to the placebo-microcapsule groups. Body weight was reduced in the 250 ppm groups; the reduction reached a maximum (about 90% of control) in the early weeks of testing in both sexes (Table 9). A further reduction in body weight relative to the controls (placebo-microcapsule groups) did not occur despite continued exposure and reduced food consumption throughout the study (Table 9). Since a reduction in feed consumption occurred in the 250 ppm groups (both sexes) starting with the first exposure week, the body weight reduction would appear to be due mainly to the reduced feed consumption.

No treatment-related effects were reported in the following areas: clinical observations, ophthalmology, hematology, serum chemistry or urinalysis. Effects on absolute organ weights (only brain, kidneys, liver, testes/ovaries were measured) and organ weights relative to body weight appeared to be due to the body weight reduction in the 250 ppm groups; this was true for animals sacrificed at test week 52 as well as for the survivors at the end of the study. An increased incidence of dark red areas was observed on the livers of the 50 ppm females surviving to test week 104 (0 ppm, basal: 5/20; 0 ppm, placebo: 3/19; 0.5 ppm: 8/22; 2.5 ppm: 4/24; 50 ppm: 14/27; and 250 ppm, 8/29). No statistical analyses were supplied for the histology data. Also, the lesion-incidence summary table did not present autolysis and lesion-grade data and may not have been corrected for tissues lost to autolysis. Possible treatment-related effects include: increased incidence of pancreatic acinar atrophy at 250 ppm (both sexes), increased incidence of adrenal cortical hypertrophy at 250 ppm (females), and increased incidence of pulmonary arterial mineralization at 50 ppm (females). Two rare tumor types, adenocarcinoma of the prostate and endometrial stromal sarcoma of the cervix, were seen at 4% incidence only at 250 ppm. By experimental design, the histological examinations of the pancreas, prostate, spleen, adrenal glands, cervix, and uterus at the 0.5 to 50 ppm dose levels were limited to those

rats that did not survive to terminal sacrifice. Autolysis was a frequent observation in the gastrointestinal organs in rats that did not survive to the end of the study (all groups, both sexes). While an increased incidence of spongiosis hepatitis was seen in the 50 ppm females, the relationship of this lesion to angiectasis and the necropsy finding of dark red liver spots that also occurred at the 50 ppm dose level needs clarification.

A possible, treatment-related findings at necropsy was an increasing incidence of splenomegaly in the 2.5 ppm and 50 ppm group; however, not all spleens were sectioned (Table 10). Histological findings on the enlarged spleens included extramedullary hematopoiesis, congestion, and lymphoma. The NOEL was 0.5 ppm (0.02 mg/kg/day for males) for increased incidences of enlarged spleens at 2.5 and 50 ppm. The incidence of splenomegaly in the 250 ppm group was not statistically different from the control groups. When first reviewed, the study was considered unacceptable pending the submission of the supplemental information regarding: range-finding study; analytical methods; cause and extent of autolysis; histological examinations for the lower dose groups; and clarification of liver gross and histological findings. Additional information was submitted and this study is considered marginally acceptable to DPR. The NRC in the review of the draft RCD/1999 considered a NOAEL of 50 ppm for this study based on decreased body weight (NRC, 2000). The enlarged spleen was not considered to be treatment-related since there was no clear dose-response relationship, histological correlates in the spleen, and effects on hematology and clinical chemistry parameters. The U.S. EPA also established a NOEL of 50 ppm for this study based on reduced body weight, body weight gain, and food consumption in both genders during the first 18 months of the study (Gross, 1999).

Fischer-344 rats were fed daily for 2 years feed fumigated with methyl bromide (99.5% purity) (Mitsumori *et al.*, 1990). After fumigation, the feed was exposed to air for 21 days until the methyl bromide level was < 20 ppm and the total bromide level was approximately 500 ppm. Diets containing 80 ppm and 200 ppm total bromide were prepared from the 500 ppm feed. Another group of rats was maintained on a diet containing 500 ppm potassium bromide. In the methyl bromide groups, there were no major adverse effects reported, except for a significant ($p \leq 0.05$) decrease in body weight (3-6% from week 60 onward). Significant increases ($p \leq 0.05$) in food and water consumption and urobilinogen were observed in both 500 ppm methyl bromide and potassium bromide treated diet groups. Since the purpose of the study was to determine the effects of residual bromide, not methyl bromide itself, this study was considered supplemental information by DPR.

Table 9. Food consumption and body weight in rats during chronic exposure to methyl bromide.^a

Duration (weeks)	Methyl Bromide concentration (ppm)					
	Microcap 0 ppm	0.5	2.5	50	250 ppm	
Male	0	0.02	0.11	2.20	11.10 mg/kg/day	
Food Consumption (mean, g/animal/day)						<u>% Control</u>
0 to 1	26	26	26	25	23**	88
26 to 27	27	27	27	26	24**	89
52 to 53	27	27	28	27	25**	93
78 to 79	28	27	27	27	26	93
103 to 104	25	25	19	23	23	92
Body Weight (mean, g)						
1	252	256	252	250	242**	96
26	589	600	589	575	521**	88
52	683	697	684	661	595**	87
78	760	773	762	737	691*	91
104	685	725	673	667	700	102
Female	0	0.03	0.15	2.92	15.12 mg/kg/day	
Food Consumption (mean, g/animal/day)						
0 to 1	18	18	18	19	17**	94
26 to 27	20	20	20	19	18**	90
52 to 53	21	21	21	21	20*	95
78 to 79	24	23	23	23	21	87
103 to 104	20	20	19	19	19	95
Body Weight (mean, g)						
1	171	169	170	173	166	97
26	305	303	300	305	281**	92
52	360	359	353	359	330**	92
78	462	449	443	465	418	90
104	488	455	445	489	454	93

^{a/} Only selected values are presented in this Table (Mertens, 1997). There were 60 to 70 animals (Microcap, 50 ppm, and 250 ppm) or 48 to 50 animals (0.5 ppm and 2.5 ppm) per group for the first 53 weeks. From week 53 to week 104, the number of male rats per group decreased from 57 to 17 (Microcap), 49 to 16 (0.5 ppm), 50 to 16 (2.5 ppm), 59 to 22 (50 ppm), and 60 to 30 (250 ppm) for the groups. For week 53 to week 104, the number of female rats decreased from 59 to 19 (Microcap), 50 to 22 (0.5 ppm), 48 to 22 (2.5 ppm), 48 to 24 (50 ppm), and 59 to 30 ppm (250 ppm) for the groups. Statistical significance was based on the Dunnett's test with *, ** for p < 0.05 and p < 0.01, respectively. % Control was based on values for Microcapsules only as the control.

Table 10. Effects of methyl bromide in spleens of rats fed microcapsules containing methyl bromide in the feed for two years.^a

	Micro-capsules 0 ppm	Methyl Bromide Concentrations			
		0.5 ppm	2.5 ppm	50 ppm	250 ppm
		0.02	0.11	2.2	11.0 mg/kg/day
ALL EXAMINED SPLEENS					
Enlarged ^b Male	2/50 (4%) (p<0.05)+	7/50 (14%) (p=0.08)	10/50 (20%) (p=0.014)**	11/50 (22%) (p=0.007)**	3/50 (6%)
Female	6/50 (12%)	4/50 (8%)	4/50 (8%)	2/52 (4%)	5/50 (10%)
Congestion Male	1/47 (2%)	0/34 (0%)	2/35 (6%)	2/28 (7%)	1/50 (2%)
Female	2/50 (4%)	0/28 (0%)	0/24 (0%)	0/21 (0%)	0/49 (0%)
Extramedullary hematopoiesis Male	8/47(17%)	9/34(27%)	10/35(29%)	7/28(25%)	12/50(24%)
Female	14/50(28%)	11/28(39%)	6/24(25%)	3/21(14%)	12/49(25%)
Lymphoma/ Leukemia Male	0/47 (0%)	1/34 (3%)	1/35 (3%)	1/28 (4%)	0/50 (0%)
Female	0/50 (0%)	0/28 (0%)	0/24 (0%)	0/21 (0%)	0/49 (0%)
ENLARGED SPLEENS - histological findings in male rats					
Extramedullary hematopoiesis	2/2	4/7	3/10	4/11	3/3
Congestion	0/2	0/7	0/10	2/11	0/3
Lymphoma/ Leukemia	0/2	1/7	1/10	1/11	0/3
Not Sectioned	0/2	2/7	6/10	4/11	0/3

a/ Data from Mertens, 1997.

b/ Incidence= number of animals affected/total animals examined. With the 250 ppm dose excluded, statistical significance was determined by the Fisher Exact Test with ** for $p \leq 0.01$, and the Cochran-Armitage Trend test with * for $p \leq 0.05$. Histological examination of the spleens in the 0.5, 2.5, and 50 ppm groups was limited to those rats which did not survive to terminal sacrifice. The first male rat with enlarged spleen was in the 2.5 ppm group and was found dead on day 394 of the study. Spleens dimensions were provided only for those considered enlarged. The report did not provide the criteria for the determination of enlargement.

III.D.3. Inhalation - Mouse

B6C3F1 mice (86/sex/group) were exposed to methyl bromide (99.8% pure; nominal concentrations of 0, 10, 33, or 100 ppm) 6 hours per day, 5 days per week, for 2 years (NTP, 1992; Eustis, 1992). There were interim sacrifices (~ 10/sex/group) at 6 and 15 months for the control, 10, and 33 ppm groups; and at 15 months for the 100 ppm females. Another group (10 mice/sex/group) was used for neurobehavioral testing every 3 months. The exposure of the 100 ppm group was stopped after only 20 weeks because of neurotoxicity and mortality. In this group, clinical signs indicative of neurotoxicity (tremors, paralysis, unusual gait, abnormal posture) were observed in 78% of the males and 43% of the females. The surviving animals in the 100 ppm group were observed for the duration of the study (2 years). Neurological signs in the 100 ppm groups often began to appear well after their exposure had stopped.

At the interim sacrifice of 6 months, there were no significant findings in the 10 and 33 ppm groups. At the 15-month interim sacrifice, treatment-related lesions in the brain, sternum, and heart were observed. These changes were similar to those observed after 2 years. While there was no evidence of carcinogenic effects, methyl bromide caused increased incidences of cerebellar and cerebral degeneration, myocardial degeneration, cardiomyopathy, sternal dysplasia, and olfactory epithelial necrosis and metaplasia (Table 11). Cerebellar degeneration, cerebral degeneration, myocardial degeneration, and olfactory epithelium necrosis were considered fatal lesions since higher incidences occurred in animals which died before terminal sacrifice. Heart lesions, either cardiac degeneration or chronic cardiomyopathy, were observed in 80% of the males and 69% of the females exposed to 100 ppm methyl bromide; also, the incidence of chronic cardiomyopathy in the male 33 ppm group (20%) was greater than that seen in the controls (8%). Sternal dysplasia was observed at low incidences (4-6%) in the 10 ppm and 33 ppm female groups and the 33 ppm male group but higher incidences (15-20%) in the 100 ppm groups (both sexes). Because of the rarity of this lesion, the finding at 10 ppm was considered significant. Degenerative lesions in the cerebellum were observed in 44% and 18% of the male and female 100 ppm groups, respectively. Cerebellar degeneration, sternal dysplasia, chronic cardiomyopathy, and olfactory metaplasia were observed in the 100 ppm survivors which were sacrificed at study week 104 (Table 12).

Despite the neurotoxicity observed in the 100 ppm mice before week 20, neurobehavioral testing at 3 months resulted in significant ($p \leq 0.01$) findings for only 5 and 3 of the 9 endpoints studied in the 100 ppm male and female groups, respectively. However, testing of the 100 ppm female group at 6 months resulted in significant ($p \leq 0.01$) findings in 3 of the endpoints though the survivors had not been exposed to methyl bromide for about one month. Neurobehavioral testing also found a significant ($p \leq 0.05$) decrease in locomotor activity in the 10 ppm and 33 ppm groups (both sexes) when tested at 6 months as well as 12 months (females only). Based on the neurobehavioral testing changes in locomotor activity and sternal dysplasia, the LOAEL was established at 10 ppm, the lowest test dose. This study was considered acceptable to DPR according to FIFRA guidelines. The NRC in the review of this study considered a LOEL of 100 ppm for this study since the incidences for spinal dysplasia at 10 and 33 ppm were not statistically significant from the control (NRC, 2000). In addition, the incidences of decreased locomotor activity occurred at only 1 of 8 time periods for each sex and the significance of the decrease was offset by increases (nonstatistically significant) compared to control values at other times. This difference in LOEL has no impact on the risk characterization since the critical study (Reuzel *et al.*, 1987 and 1991) has a lower NOEL compared to this study (NRC, 2000).

BDF1 mice (50/sex/group) were exposed to methyl bromide (99.9% pure; 0, 4, 16, or 64 ppm) by inhalation 6 hours per day, 5 days per week for 104 weeks (Gotoh *et al.*, 1994). There were no significant differences in survival between the groups. Results in this study were reported as summary data in a brief publication. The mean body weights of the 64 ppm (both sexes) were stated to be lower than controls; however, no data were included in the report. The primary effect was increased incidences (30% compared with 0% in controls; $p \leq 0.05$) of atrophy (slight) of the granular layer of the cerebellum of the 64 ppm group. The NOEL for cerebellar lesion was 16 ppm. Histological examination of the tissues showed increased incidences of liver adenoma (4 ppm females) and lymphoma in lymph nodes (4 ppm females). However, the significance of these findings as well as non-neoplastic findings require the evaluation of individual data, historical control data, and subchronic studies. The study was considered unacceptable and upgradeable to DPR.

Table 11. The incidences of histological lesions in mice after chronic inhalation exposure to methyl bromide.^a

	Methyl Bromide Concentration (ppm)			
	0	10	33	100 ^b
Male				
Cerebellar degeneration	0/50++	0/50	0/50	31/70** (44%)
Cerebral degeneration	0/50++	0/50	0/50	11/70** (16%)
Sternal dysplasia ^c	0/50++	0/50	3/50 (6%)	14/70** (20%)
Myocardial degeneration	0/50++	0/50	0/50	32/70** (46%)
Chronic cardiomyopathy	4/50++ (8%)	7/50 (14%)	10/50 (20%)	24/70** (34%)
Olfactory epithelium, metaplasia	0/50	0/50	1/50 (25%)	2/69 (3%)
Olfactory epithelium, necrosis	0/50++	0/50	0/50	6/69* (9%)
% Survival at the end of the study ^d	82	74	80	23
Female				
Cerebellar degeneration	0/50++	0/50	0/50	11/60** (18%)
Cerebral degeneration	0/50+	0/50	0/50	2/60 (3%)
Sternal dysplasia ^c	0/50++	2/50 (4%)	2/50 (4%)	9/60** (15%)
Myocardial degeneration	1/50++ (2%)	0/50	0/50	7/59 (12%)
Chronic cardiomyopathy	2/50++ (4%)	4/50 (8%)	2/50 (4%)	34/59** (57%)
Olfactory epithelium, metaplasia	0/50++	0/50	0/50	5/60* (9%)
Olfactory epithelium, necrosis	0/50	0/50	0/50	1/60* (2%)
% Survival at the end of the study ^d	71	82	90	65

a/ Data were from NTP, 1992 and Eustis, 1992. Overall incidence was the number of animals with lesions/number of animals examined at site. Level of statistical significance, $p \leq 0.05$ (* or +) or $p \leq 0.01$ (** or ++), is indicated after each incidence. Significance indicated at the control value was based on a dose-weighted chi-square trend test; significance at the dosed group was based on the logistic regression test or the life table test when a lesion was considered to be fatal.

b/ Because of high mortality, exposure of the 100 ppm group was stopped at 20 weeks. The incidence rates are for all animals in this group and included incidences before and after the termination of exposure.

c/ Sternal dysplasia also was observed at the 15 month sacrifice (one male and one female from the 33 ppm group and one female in the 100 ppm group).

d/ The percentage of survival represented the survival rates adjusted for interim evaluation, neurobehavioral study animals, and accidental deaths.

Table 12. The incidences of histological lesions in survivors of chronic inhalation exposure to methyl bromide.^a

	Methyl Bromide Concentration (ppm)			
	0	10	33	100 ^b
Male Mice				
Cerebellar degeneration	0/40++	0/37	0/40	3/16** (19%)
Sternal dysplasia	0/40++	0/37	2/40 (5%)	12/16** (75%)
Chronic cardiomyopathy	4/40++ (10%)	4/37 (11%)	9/40 (23%)	9/16** (56%)
Olfactory epithelium, metaplasia	0/40++	0/37	1/40 (3%)	2/16 (13%)
Female mice				
Cerebellar degeneration	0/36++	0/41	0/45	4/40 (10%)
Sternal dysplasia	0/36++	2/41 (5%)	2/45 (4%)	7/40** (18%)
Chronic cardiomyopathy	1/36++ (3%)	4/41 (10%)	2/45 (4%)	27/39** (69%)
Olfactory epithelium, metaplasia	0/36++	0/41	0/45	5/40* (13%)

^{a/} Data were from NTP, 1992 and Eustis, 1992. Overall incidence was the number of animals with lesions/number of animals examined at terminal kill. Level of statistical significance, $p \leq 0.05$ (* or +) or $p \leq 0.01$ (** or ++), is indicated after each incidence. Significance indicated at the control value was based on a dose-weighted chi-square trend test; the pair-wise significance at the dosed group was based on the Fisher's Exact Test.

^{b/} Because of high mortality, exposure of the 100 ppm group was stopped at 20 weeks. Incidence rates indicated are those of the survivors at 2 years.

III.D.4. Dietary - Dog

Methyl bromide (purity not specified) fumigated feed with bromide levels of 0, 35, 75, or 150 mg/kg/day was fed to beagles (4/group) daily for 1 year (Rosenblum *et al.*, 1960). Concentrations of methyl bromide *per se* were not determined. Lethargy and lower weight gain were observed in the high dose group; these findings were absent in the sodium bromide (100 mg/kg/day) group. Salivation, diarrhea, and death occurred in both the high dose methyl bromide and sodium bromide treated diet groups. This study was considered unacceptable to DPR due to too few animals, as well as the lack of feed analysis and necropsy/pathology data.

Beagle dogs (4/sex/dose except 8 dogs/sex at high dose) were given feed fumigated with methyl bromide 5 days per week for one year (Newton, 1996). Granular feed containing 10% corn oil was fumigated with methyl bromide at concentrations of 0, 7092, 20,000 or 116,279 ppm for one hour and degassed for one hour. One hour after the feed had been presented to the dogs, the nominal residual methyl bromide levels in the feed-corn oil admixture were: 0, 0.5, 1.5 or 5.0 ppm. Reported dosages (male/female) were: 0, 0.06/0.07, 0.13/0.12, and 0.27/0.27 mg/kg/day. In addition, test feeds presumably contained fumigation-derived products (bromide, methylation adducts, methyl chloride). While the concentrations of reaction products were not measured, because of the experimental design, their concentrations in the low-dose feed versus high-dose feed may have varied by a factor of 16. Residual methyl bromide levels were selected on the basis of discussions between the Registrant and the U.S. EPA to achieve a "safety" study (i.e., the high dose was not set on the basis of toxicity data). A new analytical procedure was developed to determine residual methyl bromide; however, the adequacy of the new procedure could not be assessed pending submission of supplemental information.

There were no clear effects on survival, cage side observations, body weight or food consumption. Possible treatment-related effects included: decreased hemoglobin and (or) hematocrit levels at 3, 6 and (or) 12 months in the high-dose male group; and decreased serum calcium (94-96% of control) at 6 and 12 months in the mid- and high-dose male group (Table 13). The incidence of thyroid C-cell hyperplasia in the male control group was 1/4 versus 5/8 in high-dose male group. Mean absolute kidney weight (82-86% of control, $p < 0.05$) of the mid- and high-dose female groups were reduced; however, the effects were not statistically significant relative to terminal body weight or brain weight. Due to the experimental design, the effects seen in this study may be due to residual methyl bromide and (or) its reaction products. The NOEL was 1.5 ppm (0.13 mg/kg/day for males) based on statistically significant decrease in hemoglobin and/or hematocrit at 5 ppm (0.27 mg/kg/day). When first reviewed, this study was considered unacceptable and upgrading would require the submission of the following: 1) supplemental information regarding the analytical method; 2) historical control data for thyroid C-cell hyperplasia in males; 3) histological examination of the thyroid in the low- and mid-dose male groups and the parathyroid in three high-dose females whose tissues were not examined originally; and 4) the statistical analyses of the hemoglobin, hematocrit and serum phosphate data. Subsequently, the registrant submitted data on the analytical method, histological data for the thyroid and parathyroid, and historical control data for the thyroid (CMA Methyl Bromide Industry Panel, 1998; Auletta, 1998). Based on these data, C-cell hyperplasia was no longer considered a possible adverse effect. Validation for the analytical method used in this study has been requested. This study is considered supplemental information by DPR. The U.S. EPA did not consider the reduction in hemoglobin and hematocrit levels to be biologically significant since the mean values were within 10% of control values and within the normal range (Hansen, 1998). U.S. EPA established a NOEL of ≥ 5 ppm for no effects in this study.

Table 13. Selected hematology and clinical chemistry parameters in dogs exposed to methyl bromide fumigated feed.^a

Parameters	Months	Nominal concentration in the diet (ppm)			
		0	0.5	1.5	5.0
Males					
Hematocrit %	pretest ^b	(43.8-60.7)	(43.7-49.4)	(46.1-52.3)	(43.7-52.5)
	3	51.7 (50.3-54.3)	50.7 (49.7-51.1)	50.5 (46.4-55.3)	47.7* (44.6-49.5)
	6	50.8 (49.0-52.8)	51.0 (49.2-52.4)	49.1 (47.2-50.1)	46.8* (44.0-50.8)
	12	57.2 (54.5-60.0)	54.9 (54.4-55.4)	51.7 (42.7-58.6)	51.5* (45.9-55.7)
Hemoglobin g/dL	pretest	(14.5-19.5)	(14.7-16.3)	(15.0-16.8)	(14.4-17.0)
	3	17.4 (17.0-18.2)	17.1 (16.4-17.3)	17.0 (15.7-18.6)	16.2* (15.0-17.0)
	6	17.7 (17.1-18.4)	18.0 (17.0-18.5)	17.3 (16.6-17.5)	16.6* (15.5-18.0)
	12	19.1 (18.3-20.1)	18.3 (18.2-18.5)	17.5 (14.4-19.7)	17.3* (15.6-18.2)
RBC 10 ⁶ /μL	3	(6.40-8.49)	(6.45-7.16)	(6.74-7.26)	(6.47-7.66)
	6	7.69 (7.48-8.13)	7.41 (7.07-7.70)	7.41 (7.23-7.74)	7.24 (6.54-7.78)
	12	7.64 (7.35-7.99)	7.62 (7.16-7.95)	7.40 (7.15-7.64)	7.23 (6.73-8.07)
		8.22 (7.93-8.68)	7.81 (7.65-8.00)	7.45 (6.44-8.04)	7.59 (6.74-8.33)
Females					
Hematocrit %	3	45.9	48.4	47.9	49.6
	6	45.4	45.3	49.5	48.9
	12	48.0	49.2	53.7*	48.3
Hemoglobin g/dL	3	15.6	16.4	16.3	16.8
	6	15.9	16.0	17.4	16.9
	12	15.8	16.3	18.0*	16.2
RBC 10 ⁶ /μL	3	6.76	7.21	7.26	7.46
	6	6.80	6.82	7.53	7.33
	12	6.79	7.04	7.85*	7.03

a/ Data from Newton, 1996. *, ** Statistically different from control value at p<0.05 and p<0.01, respectively. There were 4 dogs/sex at all dose levels except 8 dogs/sex at the high dose.

b/ Values in parenthesis are range for all animals. Pre-test values for weeks -3, -2 and -1 before the start of the experiment were combined.

Table 14. The no-observed-effect levels (NOELs) and lowest-observed-effect levels (LOELs) of methyl bromide from chronic oral and inhalation studies.^a

Species	Duration ^b	Study NOEL/LOEL ppm	Human equivalent ^c NOEL/LOEL ppm	Effects	Ref. ^d
<u>INHALATION</u>					
Rat	6h/dx5d/w x24-29m x12-24m	<3/3 3/30	<1/1 1/11	olfactory epithelial hyperplasia/ degeneration	1*
Rat	6h/dx5d/w x24m	<4/4	<1/1	nasal inflammation and respiratory metaplasia	2
Mouse	6h/dx5d/w x24m	<10/10	<7/7	neurobehavioral changes and sternal dysplasia	3*
Mouse	6h/dx5d/w x 104w	16/64	11/45	cerebellum atrophy	2
<u>ORAL</u>					
		ppm	mg/kg/day		
Rat	2 years	0.5/2.5 50/250	0.022/ 0.11 2.2 /11.1	enlarged spleens (males) decreased body weight	4 ^e
Dog ^f	1 year	1.5/5.0	0.13 / 0.27	decreased hemoglobin and hematocrit (males)	5

a/ Bolded studies are those selected to derive the critical NOELs for risk characterization.

b/ Duration of exposure is indicated as: d=days, w=weeks, m=months.

c/ Human equivalent NOEL/LOELs were calculated by adjusting for respiration rate differences and duration of exposure (Attachment G). The equivalent levels were those for children only. The equivalent levels would be 2-fold higher since the adult respiration rate is lower (0.26 m³/kg/day compared to the child's 0.46 m³/kg/day).

d/ * after the reference number indicates the study was acceptable to DPR according to FIFRA guidelines.

References: 1. Reuzel *et al.*, 1987 and 1991; 2. Gotoh *et al.*, 1994; 3. NTP, 1992; Eustis, 1992; 4. Mertens, 1997; 5. Newton, 1996.

e/ Methyl bromide was in microcapsules mixed in the feed. This study was considered marginally acceptable to DPR (see study summary for details) .

f/ The feed was fumigated with methyl bromide and then allowed to offgas.

III.E. GENOTOXICITY

Summary: Methyl bromide was genotoxic in several *in vitro* and *in vivo* assays. It was a base-pair substitution mutagen in the *Salmonella* assays. It was a direct-acting mutagen since a liver S-9 fraction was not required for mutagenicity. It caused micronuclei formation in female mice and an increased frequency of sister chromatid exchanges in CHO cells and in mouse bone marrow cells *in vivo*. It did not induce unscheduled DNA synthesis in rat hepatocytes or cause sperm abnormalities in mice. DNA alkylation was detected in both rats and mice after *in vivo* exposure by oral, intraperitoneal, or inhalation routes while DNA damage was found in the germ cells of rats after inhalation exposure. There was some evidence of genotoxicity in workers exposed to methyl bromide. Elevated levels of sister chromatid exchanges in lymphocytes and S-methylcysteine adducts in the blood were measured in soil fumigators. An increased frequency of hypoxanthine-guanine phosphoribosyl transferase gene (*hprt*) mutations in the lymphocytes and an increased incidence of micronuclei in oropharyngeal cells were observed in structural fumigators. The genotoxicity studies are summarized in Table 15.

III.E.1. Gene Mutation

Methyl bromide was mutagenic to *Salmonella typhimurium* strains TA100 and TA1535, but not TA98, TA1537 or TA1538 (Simmon *et al.*, 1977; Kramers *et al.*, 1985; Moriya *et al.*, 1983; NTP, 1992). It was also mutagenic to *Escherichia coli* strains Sd-4 and WP2 hcr (Djalali-Behzad *et al.*, 1981; Moriya *et al.*, 1983), and *Saccharomyces cerevisiae* (Mortelmans and Shepherd, 1980). The positive mutagenic response was independent of the presence of rat liver S9 fraction (Kramers *et al.*, 1985; Mortelmans and Shepherd, 1980; NTP, 1992) or hamster liver S9 fraction (NTP, 1992). Methyl bromide induction of sex-linked recessive lethality in *Drosophila melanogaster* was dependent on the exposure duration (Kramers *et al.*, 1985; and McGregor, 1981). Methyl bromide was also positive for the induction of forward mutations in the mouse lymphoma L5178Y assay at both the TK and HGPRT loci (Kramers *et al.*, 1985). Of all the studies summarized above, only the study by Mortelmans and Shepherd (1980) was considered acceptable to DPR. The basis for unacceptability in other studies are given in Attachment D.

III.E.2. Structural Chromosomal Aberrations

B6C3F1 mice were exposed to methyl bromide (0, 12, 25, 50, 100, and 200 ppm) for 6 hours per day, 5 days per week for 10 exposure days (NTP, 1992). Peripheral blood from female mice of the 100 and 200 ppm groups showed increased frequencies of micronuclei formation. No effect was observed in the male mice. In the second experiment, mice were exposed to methyl bromide (0, 10, 20, 40, 80, and 120 ppm) for 6 hours per day, 5 days per week for 4, 8, or 12 weeks. No increase in the frequency of micronucleated red blood cells was observed for either sex at any sampling times. This study was considered acceptable to DPR.

No induction of micronuclei formation was observed in rats (both sexes) given methyl bromide up to 123 mg/kg by a single intraperitoneal injection (Putman and Morris, 1991). This study was considered acceptable to DPR.

Methyl bromide did not cause dominant lethal mutations in male rats nor structural chromosomal aberrations in the bone marrow cells of rats (both sexes) exposed to methyl bromide by inhalation up to 70 ppm for 5 days (McGregor, 1981).

III.E.3. Other Genotoxic Effects in Experimental Animal Studies

Methyl bromide did not induce unscheduled DNA synthesis in rat hepatocytes (Kramers *et al.*, 1985) or human embryonic intestinal cells (McGregor, 1981) under *in vitro* conditions, or cause sperm abnormalities in mice after inhalation exposure (McGregor, 1981).

Methyl bromide caused a dose-related increase in the frequency of sister chromatid exchanges in Chinese hamster ovary cells *in vitro* (Rounds, 1980) and in bone marrow cells in female mice after inhalation exposure (6 hours/day and 5 days/week) to methyl bromide at 100 and 200 ppm for 10 exposures (NTP, 1992). There was a small increase noted for the male mice and this result was considered equivocal. When another group of mice was exposed to methyl bromide (up to 120 ppm) for a longer duration (12 weeks), there was no further increase in the frequency of sister chromatid exchanges in the bone marrow cells and of micronuclei in peripheral erythrocytes (NTP, 1992). Methyl bromide did not have any effect on the bone marrow cell kinetics or erythropoiesis. The author suggested that the longer duration of exposure (12 weeks compared to 10 exposure days) may have caused changes in the metabolism or sensitivity of the bone marrow cells and resulted in a reduction of response. The NTP (1992) study was considered acceptable to DPR.

In vivo exposure of mice to methyl bromide resulted in the alkylation of tissue DNA. After exposure to methyl bromide (>98% pure; 36 ppm for 4 hours) by either inhalation or intraperitoneal routes, 7-methyl-guanine in liver and spleen DNA and methylated cysteine in hemoglobin and liver protein were detected (Djalali-Behzad *et al.*, 1981).

In the study by Gansewendt *et al.* (1991), rats were exposed to methyl bromide (96% pure) by inhalation for 6 hours (263 ppm for females, and 131 ppm for males), or by gavage (8.3 μ moles or 0.8 mg/kg for females and 0.58 mg/kg for males). From both routes of exposure, 7-methyl guanine and O⁶-methyl guanine were detected in the DNA from the liver, lung, stomach, and forestomach. The DNA adducts were considered a systemic genotoxic effect since high concentrations of the adducts were found in the stomach and forestomach DNA for both routes.

Methyl bromide (>99% purity; 0, 77, 153, or 258 ppm) was administered to Fischer 344 rats (5/group) by whole body inhalation (6 hours/day for 5 days) (Bentley, 1994). Animals were sacrificed one hour or one day after the 5th exposure. Damage to testicular DNA was determined by the alkaline-elution assay. The positive control group consisted of rats given methyl methanesulfonate. Mean body weights for the 150 and 250 ppm groups were reduced during the experiment. On the day after the 5th exposure, the mean body weight of the 150 and 250 ppm groups were 97% and 78%, respectively, of the pretreatment levels. On days 5 and 6, two rats in the 250 ppm group died, and a third rat was moribund. Signs of neurotoxicity seen in the 250 ppm group included: ataxia, spasms, diarrhea, lethargy, and prostration. Colored nasal discharge was reported for all groups (including 40% incidence in the control), but was not explained. DNA from the 250 ppm group (both sacrifice times) eluted faster (breakage of DNA into smaller pieces) than DNA from the 0 ppm group but at a comparable rate to that for the positive control. While it is clear that inhalation exposure to methyl bromide at 250 ppm resulted in DNA damage in male germ cells, the results for DNA elution rates for the 150 and 75 ppm groups was not consistent. The elution of DNA from the 150 ppm group (1 hour post-treatment sacrifice) was significantly slower (DNA as more intact or cross-linking) than the rate seen with the 0 ppm group (both sacrifice times). In the 75 ppm group, DNA from the one-day post-

treatment sacrifice groups, but not DNA from the one-hour post-treatment group, eluted faster than the DNA from the control. Also, the amount of DNA from the one-day group retained on the filters at the end of the elution was significantly less than that seen with the control. A NOEL cannot be determined at this time pending submission of the following information: protocol and raw data; historical control data; explanation of the time frame per group for inhalation exposures, sacrifices, and alkaline elution runs; and data analysis. This study is considered unacceptable by DPR according to FIFRA guidelines. The U.S. EPA concurred with the study author that the result for the 75 ppm group (one-day) did not represent a treatment-related effect (Hansen, 1994). The result at 250 ppm was considered positive for genotoxic potential to the DNA of testicular cells after inhalation exposure.

DNA methylation was studied in rats and mice after single or multiple dose exposures (Pletsa *et al.*, 1999). Sprague-Dawley rats (female, 2-4/group) were exposed to methyl bromide by gavage for 4 hours (80 or 160 mg/kg) or for 4 days (30 or 60 mg/kg). O⁶-methylguanine adducts were detected in several tissues (liver, glandular stomach, and forestomach) by either treatments, and in spleens, lung, bone marrow, and blood leukocytes from multiple dosing. The multiple dosing regiment also resulted in a decrease of O⁶-alkylguanine-DNA alkyltransferase, a repair enzyme, in the tissues examined. This decrease was hypothesized to be the result of inactivation by methyl bromide or reduced de novo synthesis. O⁶-methylguanine adducts were also found in tissues of lamda lacZ transgenic mice after single (5 or 12.5 mg/kg) or multiple doses (25 mg/kg for 10 days). There was no increase in mutant frequency with either regiments. The hypothesis was that the adduct levels were at pre-mutagenic level and that other events, such as cell proliferation, also need to be activated for mutagenesis to occur.

III.E.4. In vitro and In vivo Human Studies

Hallier *et al.* (1993) showed a polymorphism in human blood for glutathione-S-transferase activity and methyl bromide. Of the individuals studied, 75% of them were considered conjugators; that is, there was an apparent enzyme-mediated disappearance of methyl bromide when their erythrocyte cytoplasm was incubated with methyl bromide (99% pure; 5,000 ppm) and glutathione. Individuals whose blood did not show such a reaction were considered non-conjugators. The conjugation reaction was apparently a detoxification mechanism because sister chromatid exchanges in the peripheral lymphocytes of non-conjugators were increased by approximately twofold over untreated control levels. Under identical testing conditions, lymphocytes from conjugators showed little or no increase in sister chromatid exchanges.

In a report on biomonitoring, S-methylcysteine adducts in the blood and sister chromatid exchanges in lymphocytes were measured in methyl bromide soil fumigators (Goergens *et al.*, 1994). Methyl bromide exposure levels and duration of exposure were not provided. The adduct levels in the blood ranged from 23 to 42 nmoles/g protein for 8 soil fumigators and 13-18 nmoles/g protein for 4 controls with no methyl bromide exposure. For 14 soil fumigators, there was an increase of sister chromatid exchange rates in the lymphocytes collected in September (the end of use season) compared to those collected in June (beginning of the season).

In another biomonitoring study, hemoglobin S-methylcysteine levels in 14 methyl bromide workers showed a range of 5 to 35 nmoles/g protein compared to 5-10 nmoles/g protein (estimated from graph in the report) (Iwasaki *et al.*, 1989). The methyl bromide concentration in the work place was less than 2 ppm, the detection limit of the gas detector tube.

In a study on the genotoxicity of methyl bromide in humans, blood and oropharyngeal cells were collected from 32 workers involved in structural fumigation (Calvert *et al.*, 1998a). Oropharyngeal cells were used to indicate recent exposure since the average lifespan for these cells is 14 days. Compared to individuals with no history of methyl bromide exposure (28 referents), samples from workers showed an increased incidence of micronuclei in oropharyngeal cells, and an increased frequency of hypoxanthine-guanine phosphoribosyl transferase gene (*hprt*) mutations in lymphocytes. No consistent differences were observed for the frequencies of kinetochore-negative lymphocyte micronuclei, or kinetochore-positive lymphocyte micronuclei. The limitations of the study included: small sample size, inadequate exposure information, and short duration of exposure (median length was 4 hours). The authors did conclude that the findings provided some evidence of genotoxicity in humans after short-term exposure to methyl bromide.

Table 15. The genotoxicity of methyl bromide.

Test types	Route/ Exposure Duration ^a	Dose ^b	Effects/Comments	References ^c
<u>I. Gene Mutation</u>				
<u>Bacterial mutagenicity tests</u>				
S. typhimurium, TA100	air, x 21 h	≥ 0.01%	+, dose-related increase in revertants	1
S. typhimurium, TA100	air, x 5 d	≥ 1900 mg/m ³	+, ± rat liver S9 fraction	2
S. typhimurium, TA100	air	≥ 500 mg/m ³	+	3
S. typhimurium, TA100	air	≥ 0.004 moles/L	+, ± rat or hamster liver S9 fraction	4
S. typhimurium, TA98	air	> 50,000 mg/m ³	-	2
S. typhimurium, TA98	air	> 2.4 moles/L	-	4
S. typhimurium, TA1535	air, x 2 d	≥ 5000 µg/plate	+	3
S. typhimurium, TA1537, TA1538, TA98	air	> 5000 µg/plate	-	3
E. coli Sd-4	solution	≥ 4 mM	+	5
E. coli WP2 hcr	air, x 2 d	5000 µg/plate	+	3
<u>Mitotic recombination</u>				
S. cerevisiae	solution, x 4 d	≥ 0.2%	+, ± rat liver S9 fraction	6*
<u>Sex-linked recessive lethal test</u>				
D. melanogaster	air, x 5 h	> 70 ppm	-	7
D. melanogaster	air, x 6 h/d x 5 or 15 d	≥ 200 mg/m ³	+	2
<u>Forward mutation test (Mouse lymphoma L5178Y)</u>				
TK locus and HGPRT locus	solution, x 24 h	0.3 mg/L	+	2
<u>II. Structural Chromosomal Aberrations</u>				
<u>Micronucleus test</u>				
Mouse	intraperitoneal	> 123 mg/kg	-, in bone marrow cells	8*
Mouse	inhalation, 6h/dx5d/wx2w	≥ 100 ppm	+, in peripheral red blood cells (females)	4*
Mouse	inhalation, 6h/dx5d/wx12w	> 120 ppm	-, in peripheral red blood cells	4*

a/ The duration of exposure was: h= hrs, d=days, and w=weeks.

b/ Dose was the concentration of methyl bromide which resulted in a positive response or the highest dose tested with a negative response.

c/ * indicates the study was acceptable to DPR according to FIFRA guidelines. References: 1. Simmon *et al.*, 1977; 2. Kramers *et al.*, 1985; 3. Moriya *et al.*, 1983; 4. NTP, 1992; 5. Djalali-Behzad *et al.*, 1981; 6. Mortelmans and Shepherd, 1980; 7. McGregor, 1981; 8. Putman and Morris, 1991.

Table 15. The genotoxicity of methyl bromide (continued).

Test types	Route/ Exposure Duration ^a	Dose ^b	Effects/Comments	References ^c
<u>Chromosomal aberration test</u>				
Rat	inhalation, 7 h/dx5d	> 70 ppm	–, in bone marrow cells	1
<u>Dominant lethal test</u>				
Rat	inhalation, 7 h/dx5d	> 70 ppm	–, no genotoxicity or reproductive effects	1
III. Other Genotoxic Effects				
<u>Unscheduled DNA synthesis</u>				
Rat hepatocytes	solution, x 24 h	> 0.3 mM	–, no increase in nuclear grain counts	2
Human embryonic intestinal cell	air, x 3 h	> 70%	–, no increase in nuclear grain counts	1
<u>Sister chromatid exchange</u>				
CHO cells	air, x 18 h	≥ 1 ppm	+, dose related ↑ in frequency	3
Mouse	inhalation, 6h/dx5d/wx2w	≥ 100 ppm	+, dose related ↑ in frequency (females)	4*
Mouse	inhalation, 6h/dx5d/wx12w	> 120 ppm	–	4*
Human lymphocytes	air, x 1hr	5,000 ppm	+, non-conjugators	5
<u>Alkylation</u>				
Mouse	inhalation x 4 h	36 ppm ^d	+, N-7-methylguanine in liver and spleen DNA and methylated cysteine in hemoglobin and liver protein	6
Mouse	intraperitoneal	417 ug/kg	+, alkylation protein in hemoglobin and liver	6
Rat	inhalation x 6 h or single dose by gavage	131-263 ppm 0.58-0.8 mg/kg	+, methylated guanine in liver, lung, stomach and forestomach	7
<u>Sperm abnormality</u>				
Mouse	inhalation, 7h/dx5d	> 70 ppm	–, no increase in frequency of abnormally shaped sperm	1
<u>Micronuclei and hprt mutation</u>				
Humans	inhalation, not reported	not reported	+ (weak), micronuclei and hprt mutations	8

a/ The duration of exposure was: h= hrs, d=days, and w=weeks.

b/ Dose was the concentration of methyl bromide which resulted in a positive response or the highest dose tested with a negative response.

c/ * after the reference number indicates the study was acceptable to DPR according to FIFRA guidelines. References: 1. McGregor, 1981; 2. Kramers *et al.*, 1985; 3. Rounds, 1980; 4. NTP, 1992; 5. Hallier *et al.*, 1993; 6. Djalali-Behzad *et al.*, 1981; 7. Gansewendt *et al.*, 1991; 8. Calvert *et al.*, 1998a.

d/ Static exposure.

III.F. REPRODUCTIVE TOXICITY

Summary: In a 2-generation reproductive toxicity study in rats by inhalation, methyl bromide reduced the fertility rate of the F₁ parents during the second mating trial. While the body weights of the treated pups at birth showed varied responses, their body weights were significantly lowered during lactation. Brain weight and cerebral cortex width were reduced in the F₁ adults.

III.F.1. Inhalation - Rat

Methyl bromide (99.9% pure) was administered to Sprague Dawley rats of both sexes by whole-body inhalation 6 hours per day and 5 days per week at the nominal concentrations of 0, 3, 30, or 90 ppm (American Biogenics Corp., 1986; Hardisty, 1992; Busey, 1993). Parental animals were exposed for about 40 or 55 days and 90 to 105 days before their first and second matings, respectively, and were exposed for a total of 132-145 days before they were sacrificed. There was no exposure to methyl bromide between gestation day 21 and lactation day 4 in any of the four birthing periods. The pups were not directly exposed to methyl bromide until after weaning (post-natal day 28). Body weights (91-95% of control values) and body weight gain (76% of control values) during the pre-mating periods were significantly decreased only in the F₀ males of the 90 ppm group. For the 30 and 90 ppm F₁ groups, the body weights at pre-mating and during reproduction were consistently lower than those of controls. The absolute brain (wet) weights of the F₀ males, F₁ males, and F₁ females in the 90 ppm groups were significantly ($p \leq 0.05$) decreased by 5%, 6%, and 6%, respectively, compared with controls (Table 16). The brain weight of the F₁ females of the 30 ppm group was also reduced by 5% ($p > 0.05$). Fertility indices (the ratio of the number of pregnancies to the number of copulations) were comparable among the four treatment groups (85-100% of control) for the F_{1a}, F_{1b}, and F_{2a} mating trials. However, in the F_{2b} mating trial, the fertility indices decreased from 90.9 of the controls to 66.7% ($p=0.056$, Fisher's Exact test) and 68.2% ($p=0.066$, Fisher's Exact test) in the 30 and 90 ppm groups.

At birth, the pup body weights of the treated groups were either higher or not significantly different from controls; the only exception was the lowered body weight of the F_{2a} 90 ppm group (Table 16). During lactation, the F_{1a} and F_{1b} pups of the 30 and 90 ppm groups showed significantly reduced body weights on lactation days 14 to 28. The F_{2a} 90 ppm pup body weights were lower at birth than the controls and remained reduced throughout lactation. The F_{2a} 30 ppm pup body weights showed significant reduction on lactation days 14 to 28. The F_{2b} 30 and 90 ppm pup body weights were decreased, starting as early as 4 days after birth. The reduction in body weight was greater in the F_{2a} and F_{2b} progeny (reduction of 9 to 21% at 90 ppm) compared respectively to the F_{1a} and F_{1b} pups (reduction of 5 to 11% at 90 ppm). Since the pups were not exposed to methyl bromide during the lactation period, except perhaps via the maternal milk, the finding of reduced body weights suggested that growth retardation might be an effect due to the 14 to 15 days of *in utero* exposure.

For the female F_{2b} progeny from the 90 ppm group, the absolute weights of the brain, heart, kidneys, and liver were reduced significantly ($p \leq 0.05$) by 7%, 15%, 18%, and 23% when compared to control values, respectively. The absolute weights of the kidneys, liver, and testes of the corresponding male progeny were also reduced, though to a lesser degree. The organ to body weight ratios were generally not significantly different from control values.

Histomorphometric data showed a decrease in the width of the cerebral cortex (parameters IIIh and IVb in the sectioning scheme of Rodier and Gramann, 1979) of the F₁ 90 ppm groups (both sexes) (Table 16). Measurements for other parameters also were decreased in the F₁ 90 ppm females (IIh, IVb) or F₁ males (IIIa and IIIc). Since the mid- and low-dose F₁ groups were not examined, no NOAEL was established for these effects. However, the reduced brain (fixed) weights for the F₁ 30 ppm females suggested that the LOAEL for the reduced cerebral-cortex width was 30 ppm. Histomorphometric parameters were not affected in the F₀ 90 ppm adults which suggested that the F₁ effects were the result of the *in utero* exposure of the F₁ animals or via feeding in the milk. However, there are no published studies on the excretion of methyl bromide in the milk. Disse *et al.* (1996) showed the presence of bromide in the milk of rats exposed to sodium bromide (250 mg/%) in the drinking water, *ad libitum*, from gestation day 5 to 15.

The parental NOAEL was 3 ppm based on reduced fertility. The progeny NOEL was 3 ppm based on the decreased pup body weights and organ weights, reduced F₁ adult brain weight, and reduced cerebral cortex width assumed at 30 ppm. This study was considered marginally acceptable to DPR according to FIFRA guidelines. In the evaluation of this study, U.S. EPA established the NOEL for maternal toxicity at 30 ppm based on reduced body weights. Reduced fertility was considered a treatment-related finding and an indicator of reproductive toxicity (U.S. EPA, 1992a).

III.F.2. Oral - Rat

In a published study to investigate the effects of methyl-bromide fumigated feeds, Crj:CD (SD) rats (24/sex/group) were given either basal diet or fumigated feed (80 ppm, 200 ppm, or 500 ppm total bromine) for 18 weeks for each generation (Kaneda *et al.*, 1993). The methyl bromide concentration was reported as < 20 ppb but no details were given. Using the average consumption rates provided in the report, the exposure in terms of methyl bromide was approximately 200 ng/kg/day using average body weights of 0.35 kg and 0.25 kg for males and females, respectively, and consumption rates of 25 g/week and 20 g/week for males and females, respectively. The only significant effects were reduced food consumption in the 500 ppm total bromide F1 parental females during the weeks 9 and 10 of the premating period and on days 0 to 21 of lactation (87-93% of controls), and lowered body weights throughout the lactation period of 500 ppm total bromide F2 female pups (91-95% of controls). A NOEL for reproductive effects for methyl bromide can not be established since methyl bromide levels in the feed were not determined.

Table 16. Body weight changes in rats after inhalation exposure to methyl bromide in a 2-generation reproductive toxicity study.^a**Mean Body Weights (grams)^b**

Lactation Days	F _{1a} litter				F _{1b} litter			
	0	3	30	90 ppm	0	3	30	90 ppm
0	6.0	6.2**	6.2**	6.0	6.2	6.4**	6.2	6.5**
4	9.5	9.4	9.3	9.3	9.3	9.9**	9.5	9.7*
7	13.5	13.7	13.0*	13.1	13.7	14.9**	14.1	14.3
14	23.2	22.9	21.5**	21.6**	24.1	24.2	22.5*	22.5*
21	37.8	37.7	34.3**	33.8**	39.3	39.4	36.0**	36.4**
28	68.4	66.9	62.1**	61.8**	70.1	69.3	64.1**	66.4

Lactation Days	F _{2a} litter				F _{2b} litter			
	0	3	30	90 ppm	0	3	30	90 ppm
0	5.6	6.1**	5.5	5.4**	6.4	6.7**	6.2	6.2
4	8.1	8.4	7.8	7.4**	10.1	9.9	9.2**	9.2**
7	11.6	12.2*	11.6	10.6**	14.3	14.7	13.4*	13.3*
14	21.9	22.6	20.4**	18.6**	24.1	23.7	19.8**	19.6**
21	35.4	36.2	31.4**	29.1**	40.3	39.8	32.4**	32.0**
28	64.3	64.2	58.6**	53.8**	71.6	70.6	58.4**	58.2**

Mean Absolute Brain (wet) Weight (grams)^c

ppm	F0 Adults		F1 Adults		F2 Weanlings	
	males	females	males	females	males	females
0	2.26	2.11	2.16	2.05	1.57	1.53
3	2.25	2.09	2.15	2.04	1.54	1.48
30	2.20	2.11	2.14	1.95	1.51	1.45
90	2.14*	2.07	2.02*	1.93*	1.49	1.42 **

Mean Cerebral Cortex Width (mm, mean ± standard deviation)^d for F1 Adults

ppm	Males		Females	
	IIIh	IVb	IIIh	IVb
0	1.41±0.130	1.47±0.149	1.38±0.163	1.43±0.092
90	1.30±0.143*	1.42±0.121	1.28±0.115*	1.37±0.086*

^{a/} Data from American Biogenics Corp., 1986. Fetuses were exposed *in utero* to methyl bromide for 5 days/week during gestation days 0 to 19. Offspring were not placed in the inhalation chambers during the lactation period.

^{b/} Values were mean body weights for both sexes. Statistical significance levels were * at $p \leq 0.05$, and ** at $p \leq 0.01$ levels using ANOVA and Scheffe's Multiple comparisons reported by the investigators.

^{c/} Statistical significance levels were * at $p \leq 0.05$, and ** at $p \leq 0.01$ levels.

^{d/} Data from Busey, 1993. IIIh and IVb are sections of the brain based on Rodier and Gramann (1979).

III.G. DEVELOPMENTAL TOXICITY

Summary: Methyl bromide caused developmental effects in both rats and rabbits after inhalation exposure. The findings in the fetuses included delayed skull ossification in rats and fused sternebrae, gall bladder agenesis, and other effects in rabbits. Methyl bromide did not cause any significant developmental effects in rats and rabbits after oral exposure.

III.G.1. Inhalation - Rat

Pregnant Wistar rats were exposed to methyl bromide (99.5% pure; nominal concentrations of 0, 20, or 70 ppm) for 7 hours per day from days 1 to 19 of gestation (Sikov *et al.*, 1981). Additional groups received a pre-gestational exposure to methyl bromide (20 and 70 ppm) for 5 days per week for the three weeks before mating. There was no significant maternal toxicity, with and without pre-mating exposure, and the NOEL was greater than 70 ppm. The only developmental effect was an increased incidence of delayed skull ossification in the fetuses of both 70 ppm groups, with the developmental NOEL at 20 ppm. This study was considered acceptable to DPR according to FIFRA guidelines.

III.G.2. Inhalation - Rabbit

Pregnant New Zealand white rabbits (26/group) were exposed to methyl bromide (99.5% pure; nominal concentrations of 0, 20, or 70 ppm) 7 hours per day from days 1 to 24 of gestation (Sikov *et al.*, 1981). Maternal toxicity was observed only in the 70 ppm group. After 3 days of exposure and throughout the study, food consumption of the 70 ppm group was lower than the other groups. After approximately 1 week of exposure, the 70 ppm does showed a decrease in body weight and signs of neurotoxicity (convulsive movements, severe to partial paresis of the hind limb). The first doe died on gestation day 9, and two more does died on gestation day 10. Even though dosing stopped on gestation day 15 for all treatment groups (Hardin *et al.*, 1981), all but one of the 70 ppm does were dead by gestation day 30. The NOEL for maternal neurotoxicity was 20 ppm. No developmental toxicity was observed in the fetuses of the 20 ppm group or those (8 fetuses/1 litter) of the one survivor from the 70 ppm group. Because of the loss of the 70 ppm group and the abbreviated duration of gestational exposure in the 20 ppm group, this study was not a valid developmental toxicity study according to FIFRA guidelines.

In a probe study to determine the maternal toxicity and embryo lethality of methyl bromide, pregnant New Zealand white rabbits (7/group) were exposed to methyl bromide (99.6% pure; nominal concentrations of 0, 10, 30, or 50 ppm in Part I; and 0, 50, 70, or 140 ppm in Part II) 6 hours per day by inhalation on days 7 to 19 of gestation (Breslin *et al.*, 1990a). All animals were sacrificed on gestation day 20 except for the 140 ppm group which was sacrificed on gestation day 17 due to their moribund state. No toxicity was observed in Part I.

In Part II, the does in the 140 ppm group showed early signs of toxicity (lethargy and decreased food consumption) after 8 exposures. With continued exposure, the treatment related effects were: decreased body weights and body weight gains; and neurotoxicity (lethargy, labored breathing, ataxia, right-sided head tilt, reduced sensations in the extremities, dilated pupils, lateral recumbency, loss of placing or righting reflex, and rear leg splay). Histological examination of the brains from the 140 ppm group showed pathological lesions in

all animals (multi-focal areas of inflammation of the meninges overlying most regions of the brain and/or bilaterally symmetrical necrosis or spongiosis of the midbrain dorsolateral to the pyramidal tracts). Fetal examinations were limited to counting the number of implantations and resorptions. In the 70 ppm group, there appeared to be a reduction in litter size in association with an increase in pre-implantation loss. However, the loss was not considered treatment-related since implantation occurred before treatment. No examination of the 140 ppm group was reported. This study was considered supplemental information to DPR.

In the definitive study by the same group of investigators, pregnant New Zealand white rabbits were exposed to methyl bromide (99.6% pure; nominal concentrations of 0, 20, 40, or 80 ppm in Part I; and 0 or 80 ppm in Part II) for 6 hours per day by inhalation from days 7 to 19 of gestation (Breslin *et al.*, 1990b). The Part II experiment was designed to determine if the gall bladder agenesis observed in Part I was associated with a particular male used for artificial insemination. Rabbits (in Part II) designated as naive controls were inseminated with sperm from the suspect male.

Maternal effects were observed only in the 80 ppm group and included: decreased body weight gain (Parts I and II), decreased feces, and neurotoxicity (3 of 26 rabbits in Part I only; lethargy, right-sided head tilt, slight ataxia, and slight lateral recumbency). Neurotoxicity was observed on gestation day 19, the last day of exposure. The body weight gain was reduced in both Part I and II 80 ppm groups, but only the reduction in Part II was statistically significant ($p \leq 0.05$). This reduction in maternal body weight gain in the 80 ppm group in Part II was seen in the presence of reduced fetal weight. DPR estimated the maternal body weight as the difference between terminal body weight and gravid uterine weight and showed that there was no difference between the control and treated groups (Table 17). In addition, the significance of any maternal body weight gain reduction is uncertain because body weight changes in rabbits during pregnancy are more variable than other species (U.S. EPA, 1991). The maternal NOEL was 40 ppm based on neurotoxicity.

Fetal effects were also observed primarily in the 80 ppm groups (Table 17). The fetal effects included omphalocele, hemorrhaging (with or without generalized edema), retro-esophageal right subclavian artery, gall bladder agenesis, fused sternebrae, and decreased fetal body weight (13% in Part II). In the 80 ppm group (Part I), the incidences of gall bladder agenesis and fused sternebrae were significantly ($p \leq 0.05$) different from the controls. The increased incidences of gall bladder agenesis and fused sternebrae were independent of maternal toxicity because these effects were observed in fetuses from both normally behaving and affected (with neurotoxicity) does. The finding of gall bladder agenesis was confirmed in Part II with approximately the same litter incidence (29%) as for Part I (26%). Additionally, gall bladder agenesis was not associated with a particular male since the malformation was not observed in the naive controls (in Part II) which had been inseminated only with sperm from the suspect male. The historical control incidences of gall bladder agenesis are in Attachment B. The distribution of affected fetuses with respect to neurotoxicity in the does is shown in the footnotes of Table 17. The developmental NOEL was 40 ppm based on omphalocele, hemorrhaging, retro-esophageal right subclavian artery, gallbladder agenesis, fused sternebrae and decreased fetal body weight at 80 ppm. This study was considered acceptable to DPR according to FIFRA guidelines.

Table 17. The incidences of fetal effects in rabbits after inhalation exposure to methyl bromide during gestation.^a

Effects ^b	Methyl bromide Concentrations Part I				Part II		
	0	20	40	80ppm	0	0 ^c	80ppm
# Examined:							
fetuses	190	137	143	159	114	102	92
litters	21	15	19	19	16	13	14
<u>Fetal body weight</u> (g)	31.8	32.2	35.0	30.4	36.2	33.8	31.4*
<u>External Effects</u>							
omphalocele	0	0	0	2/2 (11%) ^d	0	0	0
hemorrhage (with or without edema)	0	0	0	2/2 (11%) ^d	0	0	1/1 (7%) ^d
<u>Soft Tissues</u>							
retro-esophageal right subclavian artery	0	0	0	2/2 (11%) ^d	0	0	0
gall bladder agenesis	2/1 (5%)	1/1 (7%)	1/1 (5%)	13/5 ^{*e} (26%) ^d	1/1 (6%)	0	4/4 ^e (29%) ^d
<u>Skeletal Effects</u>							
fused sternebrae	0	0	3/2 (11%)	20/10 ^{*f} (53%) ^d	NA ^g	NA ^g	NA ^g
<u>Maternal</u>							
Terminal body weight- gravid uterine weight (grams, day 28)	3863	3659	3805	3636	3428	3391	3344

a/ Incidence data were expressed as the number of fetuses affected/number of litters affected. Data were from Breslin *et al.* (1990b) with does exposed to methyl bromide 6 hours/day on days 7 to 19 of gestation. Parts I and II were two separate experiments. Statistical significance in comparison to the controls, * ($p \leq 0.05$), is indicated after each incidence.

b/ Omphalocele is the protrusion of intestines through a defect in the abdominal wall at the umbilicus. Hemorrhage is subdermal hematoma with either multiple petechiae or edema. Retro-esophageal right subclavian artery refers to the placement of the artery posterior to the esophagus. Fused sternebrae is the premature fusion of the sternum segments.

c/ These rabbits were designated as naive controls and were inseminated with sperm from suspect male.

d/ Percent of litters affected= (affected litters/total litters examined) x 100.

e/ Of the 13 fetuses with missing gall bladder in Part I, 6 were from 3 does without neurotoxicity and 7 were from 2 does with neurotoxicity. In part II, all 4 affected fetuses were from 4 does without neurotoxicity.

f/ Of the 20 fetuses with fused sternebrae, 19 were from 9 does without neurotoxicity, and 1 from 1 doe with neurotoxicity.

g/ NA=skeletal examination was not performed.

III.G.3. Oral - Rat

Pregnant rats (Crj:CD (SD), 23-24 rats/dose) were given methyl bromide (purity 99.5%; 0, 3, 10, or 30 mg/kg) dissolved in corn oil by gavage on gestation days 6-15 and sacrificed on day 20 (Kaneda *et al.*, 1998). No clinical signs were observed. Food consumption and weight gain were reduced in the dams of the 30 mg/kg group. Food consumption was also reduced in the control group given corn oil; this suggested that the effect may be related to the large volume of corn oil used (10 mL/kg) or the method of administration. At necropsy, all dams in the 30 mg/kg group showed erosion and thickening of the wall in the nonglandular part of the stomach and adhesions between the stomach and the spleen, liver or diaphragm. In the fetuses from the 30 mg/kg dams, there were increased incidences of microphthalmia in 2 fetuses (two litters, 8% incidence), and having 25 (not 26) presacral vertebrae count in 5 fetuses (two litters, 8% incidence). While neither effect was statistically significant, no cases were observed in the control group. This study was considered supplemental information by DPR.

III.G.4. Oral - Rabbit

Pregnant rabbits (Kbl:JW, 15-18 rabbits/dose) were given methyl bromide (purity 99.5%; 0, 1, 3, or 10 mg/kg) dissolved in corn oil by gavage on gestation days 6-18 and sacrificed on day 27 (Kaneda *et al.*, 1998). No clinical signs were observed. Food consumption and weight gain were reduced in the does of the 10 mg/kg group. In the fetuses, total litter resorption occurred in 2 does of the 10 mg/kg groups and one control doe; the number of resorptions involved were not indicated. Skeletal malformations involving 2-3 litters in at least one methyl bromide-treated group included: splitting of the nasal/frontal/parietal bones; hemivertebra; fusion of the ribs/sternabrae; and absence of the metacarpal and phalangeal bones. While the number of fetuses with malformation were higher in the treated groups than the control groups; the increase was neither statistically significant at the litter level nor related to the dose. This study was considered supplemental information by DPR.

III.H. NEUROTOXICITY

Methyl bromide is a known neurotoxicant to both humans and experimental animals. The neurotoxicity of methyl bromide in laboratory animals was described **II.A. CHEMICAL IDENTIFICATION** and in previous sections of the **III. TOXICOLOGY PROFILE**. Delayed neurotoxicity study under the FIFRA guidelines is not currently required.

For neurotoxicity in humans, information was available primarily from accidental poisonings. The following selected reports from residential and occupational exposures were those where methyl bromide levels were available or effects adequately described.

III.H.1. Occupational Exposure

One of the earliest reports on the effects of methyl bromide from occupational exposure was those from a 2-week observation in a repackaging plant (Watrous, 1942). The workers manually filled, sealed, inspected, recovered, and packaged methyl bromide from a tank into glass ampules. It is not known whether these workers had previous exposure to methyl bromide. During the first week of the study, the workers had potentially high exposures to methyl bromide due to handling of ampules by hand, spillage during filling, inadequate hood exhaust, and two reported accidents (broken ampules from a packaged box and broken pipe from the methyl bromide tank). While gross methyl bromide leaks were detected by the flame detector, actual measurements were not recorded. In the second week, the work environment was better controlled in that ampules were held by clamps, spillage was vented, and a larger blower was installed for the hoods. Methyl bromide air concentrations were measured hourly at the breathing level of the workers by the flame detector (detection limit of 35 ppm). The recorded methyl bromide air concentration was generally less than 35 ppm. During this 2-week period, twenty-two cases of skin lesions were reported. These were attributed to direct contact of methyl bromide on the skin (i.e. from spillage) and resulted in blisters and/or dermatitis. Seventeen of these 22 cases also complained of systemic symptoms. Overall, 31 of the 90 workers in the filling and sealing rooms developed systemic effects over the 2-week period. The onset of the symptoms as to time after exposure was noted as "variable...sometimes occurring at work after a few hours exposure, and sometimes being delayed until several hours after..the shift." The most common symptoms were anorexia and nausea with variable onset and duration. Headaches were reported to occur only during exposure and were often elicited only after specific questioning of the workers. Vertigo and faintness were reported following "known exposure." The relationship between methyl bromide exposure and other symptoms such as sensations in the eyes, sleepiness, spigastric or substernal pain, and muscular pain were considered questionable.

An investigation was initiated in a date packing plant when 15-20 more workers were absent within a period of 2 to 10 days (Johnstone, 1945). Neurotoxicity was reported in 34 workers exposed to methyl bromide between 100 to 500 ppm for an unknown amount of time while working in the plant. Visual disturbance was present in every case and other symptoms were speech disturbance (23/34), numbness of the extremities (18/34), mental confusion (15/34), hallucination (7/34), melancholia (2/34), coma (4/34), convulsion (1/34), apathy (1/34), tremor (4/34), neurosis (3/34), and fainting attacks (3/34).

Neurobehavioral functions were evaluated in 128 California structural and soil

fumigators who had been working with methyl bromide, sulfuryl fluoride, or the combination for at least one year (Anger *et al.*, 1986). The following summary of the report describes only the results for the methyl bromide group. Exposure data for the various work activities are summarized below:

<u>Occupation (number of workers)</u>	<u>Estimated Work hours/day</u>	<u>Exposure Mean (range) ppm</u>	<u>Source of Data</u>
soil fumigator (4)	8	2.3 (0-6.2)	NIOSH
soil fumigator (30)	not given	2.6 (0-7.4)	DPR
tarp remover (4)	variable	4.5 (0-8.6)	NIOSH
shoveler (11)	variable	0.8 (0-2.3)	DPR
structural fumigator (10)	1.5	0.8 (0-2.2)	NIOSH

There was a higher prevalence of muscle aching and fatigue, increased threshold for the two-point test for finger sensitivity, and a lower number of facts recalled in the Wechsler Memory Scale for the methyl bromide group. This group also consistently showed lower performance on neurobehavioral test measures. Mild neurologic dysfunctions were observed in some subjects; they included increased tremors, unsteadiness on standing with eyes closed, ataxia, and poor grip strength. The authors offered the following caveats for the interpretation of the results: (1) lack of information on participation rates and bias; (2) group differences in age, educational level, race, alcohol consumption, use of prescription drugs, and use of "illegal drugs"; and, (3) the possibility of over-reporting of the symptoms.

In an acute exposure, four nursery workers were exposed to methyl bromide while untarping a field (6 acres) which had been treated with methyl bromide (350 lbs/acre) and covered for 10 days (Herzstein and Cullen, 1990). None of the workers had a history of exposure to methyl bromide or had used pesticides during the 6-week period before the incident. During the days of untarping, the workers experienced fatigue and light-headedness. After work, they developed severe coughing, chest tightness, nausea, vomiting, frontal headaches, tremulousness, ataxia, and tremor. The symptoms were less severe over the next 2 to 3 weeks. By 3 weeks, two of the workers reported upper- and lower-extremity paresthesia and reduced hand dexterity. Clinical tests conducted after exposure and follow-up visits were within normal limits. No long-term adverse health effects were reported after 18 months.

In the Netherlands, 9 greenhouse workers were exposed to methyl bromide from an adjacent fumigated area via poor seals around a door and open pipes (Hustinx *et al.*, 1993). Methyl bromide used (200 g/m²) was 5 times the legal use. Some workers were previously exposed to methyl bromide and had experienced symptoms (nausea, vomiting, dizziness, and poor memory). On the first day of fumigation, the methyl bromide level was 25 ppm in the non-fumigated side. On the second day when the workers were poisoned, the methyl bromide levels ranged from 150 to 200 ppm. All, except one worker, experienced extreme nausea, repeated vomiting, and dizziness. The other one felt only a burning sensation in the throat. Two workers later developed seizures. Others complained of headache, nausea, ataxia, slurred speech, and a sensation described as "floating." The serum bromide levels ranged from 51 to 363 mg/L and were higher than the general population. Most of the levels (5-119 mg/L) remained elevated 19 days after exposure. The severity of the symptoms did not correlate with the bromide levels, but was associated with known previous exposures to methyl bromide.

Two workers were exposed to a high concentration (4400 ppm) of methyl bromide for 45 minutes when aerating a fumigated mill (Deschamps and Turpin, 1996; Garnier *et al.*, 1996). Both experienced nausea, vomiting, headache and dizziness after exposure. Two hours later, one (44 years old) of them had severe myoclonic seizures. This worker was hospitalized and still had ataxia, debilitating action/intention myoclonus, bilateral cortical deafness, and mental deterioration upon discharge after 52 days in the hospital. One year later, the worker remained affected and was confined to a wheel chair. The second worker (39 years old) was less affected and did not develop seizures or myoclonus. One year after the accident, he showed only a mild deficit in verbal memory. Analysis of the blood collected 7 weeks after the accident showed that the difference in response between these two workers may be due to a difference in glutathione transferase level. The more severe neurotoxicity experienced by the older worker was attributed to two factors. First, glutathione transferase activity was higher in this worker (Garnier *et al.*, 1996). The formation of S-methyl-glutathione was hypothesized to be involved in the neurotoxicity observed. On the other hand, the second worker had higher levels of S-methylcysteine adducts in the erythrocyte proteins. Second, the filter mask of this individual was considered "inefficient" which resulted in a 3-fold higher blood bromide level than that for the younger worker.

In a cross-sectional study conducted in 1992 and 1993 by the National Institute for Occupational Safety and Health (NIOSH) and the University of Miami, potential chronic health effects of 123 structural fumigation workers in South Florida were evaluated (Calvert *et al.*, 1998b). A majority of the workers (112) were exposed to methyl bromide and sulfuryl fluoride, with the remaining workers exposed to sulfuryl fluoride only. The median year for employment in the structural fumigation was 4 years (range 0.5 to 32 years). The medians for years worked with methyl bromide and sulfuryl fluoride were 1.2 years (range 0-22.1 years) and 2.85 years (0.11 to 20.5 years), respectively. The tests for neurological function included those for: nerve conduction, vibration, neurobehavioral tests from the Neurobehavioral Evaluation System, vocabulary, Santa Ana Dexterity, posture, contrast sensitivity, color vision, and olfactory function. In addition, urine analysis, lung function, and physical examination were conducted. Pattern memory and olfactory function were the only tests which showed significant difference between workers with high sulfuryl fluoride exposures and the referents. Reduced performance in the Santa Ana Dexterity test by the workers was attributed to the physical damage due to the use of heavy-duty spring clamps to fasten tarps. The authors found few health effects associated with methyl bromide but noted that the study had limited power to assess the exposure.

III.H.2. Residential Exposure

A woman was exposed to methyl bromide after returning to her home which had been fumigated and cleared for reentry (Reidy *et al.*, 1994). Initially, she had trouble breathing and developed headaches, diarrhea, continued nausea, and rashes over uncovered portions of the body for 2 days. The headache continued for several months after the initial exposure. Air sampling done 9 weeks after reentry showed the highest measurements were 3 ppm in the air above the bathroom carpet pad, and 2 ppm in the air above the front door. It was determined that an excessive amount of methyl bromide was used during fumigation. The actual peak exposure on the first day of reentry was estimated to be 400 to 1500 ppm. The woman continued to live in the home for 14 weeks after the fumigation. She showed impairments in

concentration, information processing, learning, and memory as well as emotional stress in a comprehensive neuro-psychological evaluation administered a few days after she moved out of the home.

In another fumigation, a family (a couple with a 3-1/2 month old infant) was exposed to methyl bromide from a neighboring house through emptied sewage pipes (Langard *et al.*, 1996). The estimated air concentration was 6430 ppm in the fumigated house. After about 2.5 hours of exposure, the infant cried vigorously, vomited, and had severe diarrhea. The symptoms persisted until the infant died on the next day. The autopsy showed inflammation in the lungs, blood vessels, heart, and brain. The parents were also affected as they sensed burning in their eyes, throat, and mouth and vomited. However, they recovered with no apparent neurological deficits when tested about 1 week later. The bromide levels were 170 mg/L (36 hours after exposure) for the infant, and 110-130 mg/L (39 hours) for the parents.

Another fatal case of exposure through an open connection was reported in California where a fumigated room was connected to an unattached guest house via 8 uncapped electrical conduits (Swenson *et al.*, 1997). The occupant of the guest house initially complained of flu-like symptoms and was found unconscious and convulsing on the next day. Blood and urine samples collected at the emergency room showed serum bromide levels of 27 mg/dL and 6.2 mg/dL, respectively. Air analysis of one adjoining tube on the 6th day after fumigation showed 15 ppm methyl bromide.

IV. RISK ASSESSMENT FOR INHALATION EXPOSURE

IV.A. HAZARD IDENTIFICATION

The most appropriate data for the hazard identification of methyl bromide are those from human studies. However, human case reports (**III.H. NEUROTOXICITY**) did not provide sufficient detail on the dose-response relationship. In the absence of human data, results from animal studies were extrapolated to humans assuming that the effects observed in laboratory animals would also be observed in humans. Toxicity endpoints and critical NOELs for risk characterization are discussed in this section (details of the studies are in **III. TOXICOLOGY PROFILE**). The no-effect levels may be expressed in terms of NOAELs or NOELs. Only those endpoints considered of toxicological significance were used for risk characterization.

The study to evaluate the chronic inhalation toxicity of methyl bromide in a nonrodent species (*i.e.* dogs), as part of the SB 950 data requirement, has not been submitted to DPR. While a chronic inhalation study in the dog would further characterize the neurotoxicity of methyl bromide, the requirement was waived by DPR based on the evaluation of short-term studies in the dog (Newton, 1994 a and b) which showed that a chronic study would have to be conducted at relatively low dose levels (Oshima, 1995; Gee, 1995). These levels would be in the range of the estimated NOELs from the rat (Reuzel *et al.*, 1987 and 1991) and mouse oncogenicity studies (NTP, 1992; Eustis, 1992). The chronic inhalation study would be required by DPR if the basis for the waiver is changed.

IV.A.1. Selection of Toxicity Endpoints

The selection of a toxicity endpoint and its associated NOEL involved the review of the published literature and registrant-submitted studies for the most appropriate endpoint to assess human exposure. The NRC in the review of the draft RCD/1999 agreed with DPR selection of endpoints for risk characterization (NRC, 2000).

IV.A.1.a. Developmental Toxicity

One endpoint DPR considered for risk assessment is the development toxicity observed in experimental animals after methyl bromide exposure. In a developmental toxicity study, the pregnant animals are exposed continuously to methyl bromide during a specified period of gestation (when organ formation occurs). Any adverse effect observed in the fetus is considered an acute effect under the current assumption that only a single exposure at a critical time is necessary for the induction of developmental adverse effects according to the U.S. Environmental Protection Agency Guidelines for Developmental Toxicity Risk Assessment. Since this endpoint is the result of exposure during pregnancy, it is only used for the assessment of exposure by women of childbearing age.

The critical NOEL for developmental toxicity was 40 ppm from a study with rabbits. The result from this study was the basis for the emergency regulation and permit conditions currently used in California. U.S. EPA also considered these endpoints of concern and has used the same study in a Section 18 evaluation on the use of methyl bromide on imported fruits at ports of entry. In this rabbit developmental toxicity study, fetuses exposed to 80 ppm *in utero* showed gall bladder agenesis (no gall bladders), fused sternbrae (early fusion of the

sternebrae), and lowered body weights. The missing gallbladder finding was seen in Part I of the experiment, which by itself is a complete study and fulfilled FIFRA guidelines for an acceptable study. The investigator was concerned with the finding as it was rarely observed in the negative-control litters in the conducting laboratory as well as in other laboratories using the same rabbit strain. When the experiment (Part II) was repeated three months later, missing gall bladders were again observed in fetuses exposed to methyl bromide *in utero*. The fused sternebrae found in Part I was not confirmed since skeletal examination was not performed in Part II.

The developmental toxicity effects observed in fetuses should not be discounted because of maternal toxicity (body weight changes and neurotoxicity) reported at the same dose level. Consideration must be given to when the effects were observed. First, the decrease in the body weight gain of the 80 ppm group does was not a consistent finding. Statistically significant decreases were reported for gestation days 13-16 in Part I and gestation days 7-20 and 10-13 periods in Part II. The reduced weight gain in the does of Part II occurred concomitantly with a reduction in the mean fetal body weight. Second, there was no significant difference in the strictly maternal parameter calculated as the terminal body weight minus gravid uterine weight. Third, body weight changes in pregnant rabbits are known to be more variable than rodents. As a result, body weight changes in rabbits often do not carry as much weight as an indicator for maternal toxicity as for rodents as discussed in the U.S. EPA Developmental Toxicity Risk Assessment guidelines. Fourth, maternal neurotoxicity was characterized by clinical signs; including lethargy, head tilt, slight ataxia and slight lateral recumbency. These signs were observed in only 3 of 43 does (7%) dosed at 80 ppm and they did not appear until gestation days 19-20 (the last days of the 13-day exposure period). Based on the description and comparison with observations reported in other studies, DPR did not consider these signs as indicators of excessive toxicity.

Furthermore, the failure of gall bladders to form in some fetuses was independent of maternal neurotoxicity. In Part I, 6 of the fetuses with missing gallbladders were from 3 does without neurotoxicity while the remaining 7 affected fetuses were from 2 does with neurotoxicity. In Part II, none of the does showed neurotoxicity while 4 fetuses (from 4 does) had missing gallbladders. In addition, the development of the gall bladder in rabbits can be considered an acute event since it takes place in one to two days after its onset on gestation day 11.5 (Hoar and Monie, 1981). The maternal neurotoxicity reported on gestation days 19-20 would have occurred too late to have been a factor in the agenesis of the gall bladder.

Similar findings have not been reported in the rat developmental toxicity studies. While it is worth noting that rats do not have gall bladders, the absence of these findings in another species should not negate their significance as indicators of the potential for methyl bromide to cause developmental toxicity in humans. Species specificity in developmental effects has been demonstrated for some chemicals. Developmental toxicity testing under the FIFRA guidelines requires two species to be tested, a rodent and a non-rodent species, typically the rabbit, for the purpose of identifying species susceptibility. The need to test non-rodent species arose from the findings of thalidomide where it was demonstrated that this human teratogen did not exhibit significant teratological effects in rats but caused at least some significant effects in rabbits (Schardein, 1985). As stated in the U.S. EPA Developmental Toxicity Risk Assessment guidelines, developmental effects may not be evident in more than one species. The findings from the most sensitive species are appropriate to use to estimate human risk.

The significance of the developmental toxicity findings was discussed in a 1994 Proposition 65 meeting to determine whether methyl bromide should be listed for all uses. The emergency regulation in 1992 resulted in methyl bromide being listed as a chemical known to the state to be a reproductive toxicant for structural fumigation use only. The Developmental and Reproductive Toxicity Identification (DART) Committee was presented with results from animal developmental toxicity (absence of gall bladders and fused sternebrae) and reproductive toxicity (decreased pup body weight) studies. After much discussion, the Committee voted not to expand the listing of methyl bromide from structural fumigation to all uses because there was not enough evidence to support the "clearly shown" criteria as mandated by the Proposition. However, the members expressed several concerns: the need for more experimental studies to clarify the findings, potential for exposure to methyl bromide via the milk during lactation, and the lack of information on human exposure especially during pregnancy.

After this meeting, DPR received additional data to support the consideration of reproductive or developmental toxicity as a pertinent endpoint for risk assessment and regulatory actions. First, supplemental data on the rat reproductive toxicity study showed that methyl bromide caused a reduction in the width of a certain part of the brain (cerebral cortex) in the F₁ adults exposed to methyl bromide *in utero* (American Biogenics Corp., 1986). Second, a study received by DPR in 1998 showed that methyl bromide caused a breakage of DNA in the testicular cells isolated from rats after inhalation exposure (Bentley, 1994). It is not known whether the effect was due to methyl bromide or a metabolite.

In the review of the draft RCD/1999, the NRC concluded that methyl bromide may be a developmental and possibly a reproductive toxicant (NRC, 2000). The NRC also agreed with the DPR rationale for the selection of developmental toxicity as an endpoint for acute toxicity. This use could be considered a conservative approach but justifiable in the absence of data which show that gall bladder agenesis requires multiple days of exposure.

IV.A.1.b. Neurotoxicity

Methyl bromide caused neurotoxicity in all animal species studied. There are four aspects to the methyl bromide-induced neurotoxicity: (1) species sensitivity, (2) exposure duration dependency, (3) persistency of effects, and (4) cumulative toxicity.

Of the laboratory animals studied, there was a species sensitivity to the neurotoxicity of methyl bromide after short-term exposure. Based on the comparisons of the lowest-observed effect level (LOEL) for neurotoxicity, the dog and rabbit showed greater sensitivity than the guinea pig, mouse and rat. For example, dogs exposed to 156 ppm (human equivalent level of 68 ppm) showed severe neurological effects in 2 to 7 days of exposure while rats exposed to the same concentration in terms of human equivalent level (65 ppm; 70 ppm actual air concentration) for the same exposure duration did not show any neurotoxicity. In pregnant animals, the rabbit was more sensitive to methyl bromide than the rat. For pregnant rabbits, severe neurotoxicity was observed at the LOEL of 70 ppm (Sikov *et al.*, 1981; Breslin *et al.*, 1990) while no neurotoxicity was reported in the pregnant rats at the same level (Sikov *et al.*, 1981).

Although the dog inhalation toxicity studies were not designed to be one of the FIFRA guideline study types, they were conducted under Good Laboratory Practices and DPR

considered the results valid for hazard identification. These same data were used by the MBIP to support their position that a chronic inhalation toxicity study in the dog should not be required (CMA, 1994). The selection of results from the most sensitive species based on the review of the database, in this case the dog, is consistent with the U.S. EPA Neurotoxicity Risk Assessment guidelines (U.S. EPA, 1998a).

Methyl bromide-induced neurotoxicity was dependent on the dose and duration of exposure. As shown in Tables 1 and 3, there was a relatively steep dose-response relationship. The data which best illustrate this point are the results from the dog studies (Newton, 1994 a and b). No effects were observed at 103 ppm (NOEL) for up to 5 days of exposure. However, lacrimation was noted on the first day when the concentration was increased to 156 ppm (1.5 times the NOEL), and the dogs had to be sacrificed after day 6 due to neurotoxic effects. At 314 ppm (3 times the NOEL), tremors and hunched appearance were observed in both dogs after only 7 hours of exposure.

Another aspect of the methyl bromide-induced neurotoxicity is the persistence of the effect after the termination of exposure. In the NTP study, mice were treated with methyl bromide at 100 ppm (NTP, 1992). The exposure was stopped after 20 weeks because of neurotoxicity (tremors, paralysis, and other signs) and mortality. However, neurotoxicity continued to be observed in the survivors for the remainder of the 2-year study. In some cases, the first signs of neurotoxicity appeared one month or more after the last exposure to methyl bromide. Also, at the terminal sacrifice (84 weeks after the last exposure), brain lesions were found in some 100 ppm survivors suggesting that these lesions, which may have been induced during exposure, were not repaired. In rabbits, the neurotoxicity observed was shown to be associated with lesions in the midbrain and meninges (Breslin *et al.*, 1990a). Another example of persistence of effect is the neurotoxicity observed in dogs (Newton, 1994b) and in rabbits after the last exposure to methyl bromide (Sikov *et al.*, 1981).

The persistence of effect may be due to cumulative toxicity after repeated exposure to low doses. In dogs, a comparison of the clinical signs showed that the 158 ppm group was more affected than the 156 ppm by methyl bromide exposure (Newton, 1994 a and b). Decreased activity was noted in the second day (<14 total hours; hourly observations not available) of exposure to 158 ppm compared to the third day (17 total hours) for 156 ppm. The 158 ppm group was previously exposed to 11 ppm for 24 days and appeared normal during the exposure. In a study of California structural and soil fumigators working at air concentration of less than 5 ppm methyl bromide for at least one year, the workers showed lower performance on neurobehavioral test measures and some also showed mild neurological dysfunctions (Anger *et al.*, 1986).

IV.A.1.c. Brain Monoamines and Enzyme Activity

Methyl bromide was shown to decrease tyrosine hydroxylase activity in the rat brain after acute exposure (Honma *et al.*, 1991). This decreased activity was hypothesized by the authors to be due to methyl bromide-induced structural changes to the enzyme. This endpoint and a NOEL of 16 ppm were used by the ATSDR to establish the minimum risk levels for methyl bromide (ATSDR, 1992 and 1996). The intent of the MRL was to raise concerns for additional studies rather than for regulatory action.

DPR determined that the LOELs were 16 ppm and 63 ppm based on *in vitro* and *in vivo* assay methods, respectively, for reduced tyrosine hydroxylase activity in the brain segments. It was not possible to determine which LOEL was valid since the publication was incomplete in explaining how important parts of the study were conducted.

Furthermore, the proposed hypothesis was not well substantiated by the investigators. First, there were other plausible explanations for the decreased tyrosine hydroxylase activity in the assays besides direct effects on the enzyme. Second, a decrease in tyrosine hydroxylase activity should result in a decrease in dopamine, the next metabolite in the pathway after DOPA. However, studies done earlier by Dr. Honma's group (Honma *et al.*, 1982 and 1987) either indicated that brain dopamine was not affected or that it was decreased only after levels of its catabolite, homovanillic acid, had increased. Third, the subsequent research in Dr. Honma's group (Honma *et al.*, 1994) did not corroborate or extend the findings of the 1991 paper (Honma *et al.*, 1991). More studies are needed that show the effects on tyrosine hydroxylase and brain dopamine are reproducible. Therefore, the effect of methyl bromide on tyrosine hydroxylase and catecholamines was not selected by DPR as the critical endpoint at this time. While the effect of methyl bromide on tyrosine hydroxylase, by itself, is not considered an adverse effect, the effect on catecholamines in more than one region of the brain (Table 2) was a significant finding for the consideration of critical NOELs for risk characterization. The NRC agreed with the DPR conclusion that the Honma *et al.* studies were not suitable for use in risk characterization (NRC, 2000).

IV.A.1.d. Nasal Cavity Toxicity

Another important toxicity endpoint is the methyl bromide-induced damage to the olfactory epithelium of rats and mice after inhalation exposure (Reuzel *et al.*, 1987 and 1991; NTP, 1992). This endpoint is used by the U.S. EPA in the determination of the chronic reference inhalation concentration (RfC) (U.S. EPA 1992a) and by the Office of Environmental Health and Hazards Assessment (OEHHA) for chronic toxicity reference exposure levels (RELs) (OEHHA, 1996). With acute exposure to 200 ppm, the damage to the rat olfactory epithelium included epithelial disruption, fragmentation, and exfoliation (Hurt *et al.*, 1988). Repair of the epithelium included replacement by a squamous epithelium, loss of sensory cells, and respiratory metaplasia (conversion of the olfactory epithelium to a ciliated respiratory type). In other short-term studies, the damage to the nasal epithelium was described as necrosis and degeneration (Eustis *et al.*, 1988) and dysplasia (NTP, 1992; Eustis, 1992). In the chronic inhalation toxicity study, basal cell hyperplasia and degeneration in the olfactory epithelium were observed in the rat (Reuzel *et al.*, 1987 and 1991).

While the effect on the nasal cavity may generally be considered a finding limited to the rat due to anatomical considerations, it is not the case with methyl bromide. Dogs exposed to 156 ppm methyl bromide for only 6 days showed moderate to moderately severe olfactory degeneration (Newton, 1994b). Boorman *et al.* (1990) suggested that the specificity for the toxicity of methyl bromide to this region was due to an abundance of endoplasmic reticula with high metabolic (biotransformation) activity. The greater susceptibility of the olfactory epithelium to pyridine-induced lesions has also been attributed to metabolic activation at this site (Nikula and Lewis, 1994). Air flow to this area, which amounts to 8 to 12% of inspired air (Morris *et al.*, 1993; Kimbell *et al.*, 1993), was considered too slow to be a factor as a target site.

Epithelial hyperplasia of the basal cell layer observed in rats and mice may be a regenerative response or an early indication of neoplasia (Boorman *et al.*, 1990). The olfactory epithelium has remarkable regenerative capacity with a turnover time of 28 days. The basal cells are the stem cells for olfactory neurons. If the basal cells are destroyed, then olfactory epithelium cannot be reconstituted and olfactory function is impaired or lost. The regenerative ability of the basal cells does decline with age (Hastings, 1990). As part of the reparative process, prolonged injury may result in squamous metaplasia and respiratory metaplasia. Squamous metaplasia is characterized by multiple layers of epithelial cells with eosinophilic cytoplasm (Boorman *et al.*, 1990; Haschek and Witschi, 1991). Squamous cell neoplasms have been shown to develop from areas of squamous metaplasia in the olfactory epithelium (Boorman *et al.*, 1990). Respiratory metaplasia, the conversion of olfactory epithelium to a ciliated respiratory type, after exposure to methyl bromide indicates a permanent change in the cell type (Hurt *et al.*, 1988; NTP, 1992; Eustis, 1992). Olfactory epithelial reconstitution after methyl bromide exposure has been used as the model to study the mechanism of recovery of the olfactory system (Schwob *et al.*, 1995 and 1999).

The nasal effects represented the most sensitive endpoint for chronic exposure. In the rat, lesions in the heart, and decreased brain weights were observed at higher concentrations than that for nasal effects (Table 8). In the mice, the no-effect levels were the same for nasal cavity, brain, sternum, and heart lesions (Table 11).

IV.A.2. Selection of Critical No-Observed-Effect Level

Humans are exposed to methyl bromide by inhalation (occupational, residential, and ambient air) and by oral (dietary) routes. In the evaluation of the potential effects after exposure to methyl bromide, route-specific critical NOELs were derived because the toxicity and pharmacokinetics are different between inhalation and oral exposures. After oral administration, liver and kidneys were the major organs of deposition, and there was reabsorption of biliary metabolites and/or reaction products from the gut. Toxicity was limited to the stomach and forestomach in the rat. For inhalation, the effects were systemic and involved several organs including the nasal cavity, brain, and heart. The primary routes of excretion were via the exhaled air (50% of the dose) as $^{14}\text{CO}_2$ for inhalation and intraperitoneal routes, and the urine (43% of the dose) for oral routes of administration. The NRC in the review of the draft RCD/1999 agreed with DPR on the selection of NOELs for risk characterization (NRC, 2000).

IV.A.2.a. Acute Toxicity- Inhalation

Studies with animals showed that there is a relatively steep dose-response relationship in which the difference between 100% survival and 100% mortality was only a 2- to 10-fold increase in concentration. The sublethal effects of methyl bromide included neurotoxicity, biochemical alterations, and tissue degeneration (Table 5).

The critical NOEL for acute exposure was selected from neurotoxicity and developmental toxicity studies. For the adult population, especially for women of childbearing age, the lowest NOEL was from the rabbit developmental study by Breslin *et al.* (1990b) since the dosage was lower than that used in the rat study (Sikov *et al.*, 1981). Even though in the developmental study the exposure was repeated during the gestation period, the primary

assumption is that only a single exposure at a critical time is necessary for the induction of developmental adverse effects according to the U.S. EPA Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991).

In the rabbit developmental study, the NOEL was 40 ppm (human/adult equivalent of 21 ppm) (Breslin *et al.*, 1990b). Fetal malformations (omphalocele, retro-esophageal right subclavian artery, and gall bladder agenesis), variations (fused sternebrae), and decreased fetal body weights were observed in the fetuses of does exposed to methyl bromide at 80 ppm. Since these malformations are rarely seen in litters of untreated rabbits, they were considered treatment-induced in this study. The occurrence of these effects in a single group by chance was unlikely given the historical control data for the conducting laboratory (for more discussion, see Attachment B). The increased incidences of gall bladder agenesis and fused sternebrae were statistically significant ($p \leq 0.05$) (Table 17). Furthermore, gall bladder agenesis was confirmed when the experiment was repeated. Skeletal examinations were not done in the second experiment. Both adverse effects were observed in fetuses from does with and without neurotoxicity, indicating that maternal toxicity was unlikely to be the determining factor in the development of the defects.

Developmental effects were also observed in the rat, though to a lesser extent compared to the rabbit. In rats, the fetuses of the two groups exposed to 70 ppm methyl bromide showed increased delayed skull ossification, and the NOEL was 20 ppm (human/adult equivalent NOEL of 22 ppm) (Sikov *et al.*, 1981). No maternal toxicity was observed in this study.

For other population groups, including infants and children, the most appropriate endpoint for risk assessment is neurotoxicity. The lowest NOEL was <16 ppm (human/child equivalent of <11 ppm) for a decrease in tyrosine hydroxylase activity in the rat hypothalamus (Honma *et al.*, 1987 and 1991). This NOEL from the *in vitro* assay was not selected for risk assessment because of the inconsistencies in the findings and interpretation of the results **(IV.A.1.b. Brain Monoamines and Enzyme Activity)**. However, the NOEL (31 ppm or human/child equivalent of 22 ppm) for altered catecholamines in more than one region of the brain was considered as a support for the critical NOEL derived from the dog studies.

The critical acute NOELs for neurotoxicity were considered from clinical observations in dogs (Table 4; Newton, 1994 a and b). The selection of the 103 ppm dose (human/child equivalent of 25 ppm) as the acute NOEL considered three major factors: subjectiveness of the observations, severity of the neurotoxicity at higher concentrations, and possibility of delayed neurotoxicity. The NOEL of 103 ppm in the dogs was based on gross observations. Neurotoxicity may be present but not detected unless more refined methods such as the Functional Observation Battery were used. It is possible that the actual NOEL may be lower than 103 ppm. Furthermore, severe neurotoxicity was observed at higher doses (1.5 times the NOEL) with a few additional days of exposure. At 156 ppm, one of two dogs showed lacrimation (tearing) on the first day. This finding by itself may arguably be considered less significant with respect to adversity. However, there were only two dogs in this group. With 2-3 days of additional exposure, both dogs showed significant toxicity manifested as difficulty in breathing and decreased activity. In another study, all dogs (8 in the group) exposed to 158 ppm showed decreased activity before the end of the second exposure day (the first dose was on a Friday and the second dose was on the following Monday). With 5 additional days of

exposure, all showed severe neurotoxicity and brain lesions. The selection of 103 ppm as the acute NOEL also addresses, indirectly, the possibility of delayed neurotoxicity which has been reported in humans after accidental poisonings. Since no effects were observed in the dogs at 103 ppm for 7 days of continuous exposure, it is unlikely that there would be delayed neurotoxicity within one week after a single exposure to the same level. The human equivalent NOEL (25 ppm) from the dog study is only two-fold or less than those for the acute effects observed in the rats and guinea pigs (Table 7).

From the two critical acute NOELs selected to address human population groups, the critical NOEL of 40 ppm (human/adult equivalent of 21 ppm) for developmental toxicity in the rabbit was most appropriate for workers and residents since women of child bearing age are in both groups. For children, the critical NOEL was 103 ppm (human/child equivalent of 25 ppm) for neurotoxicity in the dog (Newton, 1994a). Since the developmental toxicity NOEL was lower than that for neurotoxicity, this NOEL was selected for risk characterization to address occupational and residential exposures and would also be protective of the children population.

IV.A.2.b. Subchronic Toxicity- Inhalation

From occupational and residential uses of methyl bromide, there is a potential for subchronic inhalation toxicity from short-term exposure periods due to a single application, and from multiple applications during a season. One example of potential short-term exposure is from the release of methyl bromide from wall space of fumigated homes. Current label allows residents to reenter treated homes when the methyl bromide concentration reached ≤ 1 ppm in the wall space. Residents living next to fumigation chambers or fields with consecutive application may also experience short-term exposures.

For continuous exposure of 1 week, methyl bromide effects on the brain and clinical signs of neurotoxicity were the endpoints used to select the critical NOEL (Table 7). For this duration of exposure, the lowest and the critical NOEL was 20 ppm (human/child equivalent of 7 ppm) for neurotoxicity and death in pregnant rabbits (Sikov *et al.*, 1981). After approximately 1 week (exact number of days not reported), the 70 ppm does showed a decrease in body weight and signs of neurotoxicity (convulsive movements, severe to partial paresis of the hind limb). One of 26 does died on gestation day 9, and two more does died on gestation day 10. Though dosing stopped on gestation day 15, all but one of the 70 ppm does were dead by gestation day 30. Neurotoxicity was also observed in pregnant rabbits in two other studies (Breslin *et al.*, 1990 a and b). The NOELs (70 ppm and 40 ppm) were higher in these latter studies compared to that from Sikov *et al.* (1981). The lower NOEL from the Sikov *et al.* (1981) study may be due to longer exposure as the rabbits were exposed earlier (gestation day 1 compared to gestation day 7) and longer each day (7 hours instead of 6 hours).

The NOEL of 26 ppm (human/child equivalent of 5 ppm) for decreased activity in the dog after 14 days of exposure to 53 ppm was also considered for the short-term critical NOEL. The decreased activity was considered an early sign of neurotoxicity since decreased activity and more severe signs of neurotoxicity were observed in the 103 ppm group during the 1-2 weeks of exposure. However, the time to effect (14 days) was much longer than the duration (7 days) for the scenarios of concern.

For subchronic exposures of longer duration (90 days, seasonal), the critical NOEL was

an estimated NOEL (ENEL) of 0.5 ppm (human/child equivalent of 0.1 ppm) based on a LOAEL of 5 ppm for decreased responsiveness in two of eight dogs during a neurological examination after 6 weeks of exposure (30 exposure days). A default uncertainty factor of 10 was used to calculate the NOEL from a LOAEL (Dourson and Stara, 1983). While the duration is shorter than the 13-week generally considered for subchronic exposure, it was chosen because of the endpoint (neurotoxicity) and species sensitivity (the dog is a more sensitive species than the rat to methyl bromide). It is possible that the NOEL might be lower if the dogs were exposed to methyl bromide for 13 weeks. The NRC considered this NOEL as conservative and the endpoint to be equivocal because of the lack of a dose-response curve, non-standard testing protocol, and low number of replications (NRC, 2000). However, the NRC concluded that the endpoint was reasonable because of neurotoxicity concerns and the use of this NOEL would probably be protective even for longer exposure durations.

This ENEL (child equivalent of 0.1 ppm) was lower than the NOEL (3 ppm, human/adult equivalent of 2 ppm) for lowered body weights of rat pups from dams exposed to methyl bromide before mating and during part of the pregnancy in the reproductive toxicity study (American Biogenics Corp., 1986) (Table 16). The reduction of pup body weight was both dose- and time- dependent with respect to the adult exposure, with the highest reduction occurring in the F_{2b} 30 ppm and 90 ppm litters. There was also decreased brain weight in the F₁ adults at 30 ppm. This study and the endpoint are appropriate to evaluate the potential effects in humans exposed to methyl bromide during pregnancy. The potential post-natal toxicity was, therefore, accounted for by the use of the lower ENEL for neurotoxicity in the dog. Another study also showed an estimated NOEL of 3 ppm (human/child equivalent of 1.1 ppm) based on a significant decrease in the absolute brain weight in female rats exposed to 30 ppm and higher concentrations of methyl bromide for 13 weeks (Norris *et al.*, 1993 a and b). This effect on the brain weight was considered biologically significant since the brain is a target organ of methyl bromide. The absence of neurotoxicity by Functional Observation Battery testing at the same dose (30 ppm) does not diminish the importance of the brain weight finding since the etiology of the two effects are not necessarily related.

IV.A.2.c. Chronic Toxicity- Inhalation

For chronic inhalation exposure, all chronic studies conducted with rodents (rats and mice), the reproductive toxicity study, and the subchronic dog inhalation toxicity study were considered in the determination of the chronic critical NOEL. While the exposure duration in chronic toxicity studies generally lasted for the life-time for rodents, the actual duration of the testing was two years. Since humans may be exposed to methyl bromide on a yearly basis, not just one or two years in the lifetime, the NOEL from the chronic toxicity study after two years of exposure was, therefore, appropriate for use. This NOEL may underestimate the risk of repeated yearly exposure as there is evidence of cumulative toxicity for this endpoint, as well as for neurotoxicity.

After chronic inhalation exposure, tissue damage was noted in the nasal cavity, brain, and heart of rodents. The most significant finding after chronic exposure was the dose-dependent increase in the incidences of nasal olfactory epithelial hyperplasia and respiration metaplasia found in rodents (Reuzel *et al.*, 1987 and 1991; NTP, 1991; Eustis, 1992; Gotoh *et al.*, 1994). In the Reuzel *et al.* study (1987 and 1991), the incidences of hyperplasia were dependent on the exposure duration as there was an increase in the number of rats affected

from 1 year to 2.5 years of exposure. The LOAELs were >90 ppm, 30 ppm, and 3 ppm for exposures lasting 12 months, 12-24 months, and 24-29 months, respectively (Table 8). At 30 ppm, there was also a reduction of absolute brain weight with a NOEL of 3 ppm. Using a standard default uncertainty factor of 10 for the calculation of an estimated NOEL from the LOEL (Dourson and Stara, 1983) for the 24-29 months of exposure, the critical ENEL for basal cell hyperplasia/ degeneration in the rat olfactory epithelium was 0.3 ppm (human/child equivalent of 0.1 ppm).

The LOAEL of 3 ppm from the rat inhalation study by Reuzel *et al.* (1987 and 1991) was supported by the study of Gotoh *et al.* (1994). In the Gotoh *et al.* study, the estimated NOEL was 4 ppm (human/child equivalent of 0.1 ppm) for nasal cavity inflammation (\geq 4ppm males) and respiratory metaplasia (4 ppm females) in rats exposed to methyl bromide by inhalation for 104 weeks. Other long-term studies showed higher NOELs or ENELs than the critical ENEL. In the mouse chronic toxicity study, the LOEL was 10 ppm for neurobehavioral effects and sternal dysplasia (NTP, 1992; Eustis, 1992). Using a default uncertainty factor of 10 for the calculation of a NOEL from a LOEL, the ENEL would be 1 ppm (human/adult equivalent of 0.7 ppm). In the reproductive toxicity study, pregnant rats showed a reduction in fertility indices (American Biogenics Corp., 1986). However, the NOEL of 3 ppm (human equivalent of 2 ppm) was higher than the 0.3 ppm ENEL for olfactory epithelial hyperplasia observed in the rat oncogenicity study (Reuzel *et al.*, 1987 and 1991).

Another comparison of the NOELs was made with the results from the subchronic neurotoxicity study. The ENEL of 0.3 ppm for nasal cavity effects when expressed as human/child equivalent level (0.1 ppm) was the same as the human equivalent level for neurotoxicity after subchronic exposure (ENEL of 0.5 ppm). This implied that the actual NOEL for chronic exposure if based on neurotoxicity could be lower than that based on the effects in the nasal cavity. However, it is not possible to extrapolate such a NOEL at this time because the subchronic ENEL was already an estimated NOEL based on a LOEL which was reduced by a 10-fold uncertainty factor. The use of two 10-fold uncertainty factors to the subchronic LOEL may result in a no-effect level well below the threshold for neurotoxicity after chronic exposure.

IV.A.2.d. Oncogenicity

The genotoxicity studies showed that methyl bromide is a direct-acting mutagen. It has been shown to alkylate DNA in different organs in *in vivo* studies (Djalali-Behzad *et al.*, 1981; Gansewendt *et al.*, 1991) and was positive for genotoxicity in several *in vitro* and *in vivo* assays (Table 15). A recent report showed genotoxicity in workers exposed to methyl bromide (Calvert *et al.*, 1998). In addition, methyl bromide belongs to the methyl halide group (methylating agents) which includes methyl chloride and methyl iodide. These chemicals have been shown to be genotoxic in *in vitro* assays and do not require exogenous metabolic activation systems (Bolt and Gansewendt, 1993).

While the positive findings in genotoxicity studies suggest that methyl bromide is potentially oncogenic, the current toxicology database did not provide clear evidence of oncogenicity for methyl bromide. After chronic inhalation exposure to methyl bromide, dose-related responses were identified only for non-neoplastic lesions and included nasal epithelial hyperplasia in Wistar rats (Reuzel *et al.*, 1987 and 1991) and B6C3F1 mice (NTP, 1992; Eustis, 1992). Other studies showed various tumors but were limited to some dose groups or low

incidences. Adrenal gland pheochromocytoma in Fischer rats and lymphoma in BDF1 mice (Gotoh *et al.*, 1994) and glioma and granular cell myoblastoma in Wistar rats (Reuzel *et al.*, 1987 and 1991) were reported in the low dose female group only. In a chronic oral study with rats using methyl bromide microcapsules mixed in the feed, various tumors detected were lymphoma (males only, low dose groups only at 3-4%), prostate adenocarcinoma (high dose male at 4%) and cervical endometrial stromal sarcoma (high dose female at 4%). It should be noted that these tumor incidences for this study are not overall incidences for the study. While histological examinations of organs were performed on all rats of the control and high dose groups, they were conducted only on those rats that did not survive to the end of the study for the other dose groups. In a subchronic study, an early squamous cell carcinoma in the forestomach was detected in one animal after gavage treatment (only one dose tested) for 25 weeks (Boorman *et al.*, 1986). Since methyl bromide is a known irritant and hyperplasia of the forestomach epithelium was observed throughout the experiment, the carcinoma could be due to a direct contact effect.

In addition to genotoxicity, methyl bromide is expected to be oncogenic because chemicals of similar structures, such as methyl chloride and methyl iodide, are oncogenic in experimental animals (Bolt and Gansewendt, 1993). Methyl chloride induced renal tumors in male mice but not in rats after inhalation exposures. Methyl iodide caused lung adenomas in mice after intraperitoneal administration and local sarcomas after subcutaneous injection. The difference in the tumor sites suggests that different mechanisms for oncogenicity for these two chemicals. The lack of oncogenicity in the experimental studies with methyl bromide may be related to the exposure duration and cellular response to the genotoxic effects. In studies comparing the incidence of sister chromatid exchanges in the bone marrow between after 10 exposure days and 12 weeks at similar concentrations of methyl bromide, there was a decrease in response in the 12 week experiment (NTP, 1992). The author suggested that the lower response may be due to changes in metabolism or sensitivity of the bone marrow cells from prolonged exposure. This possibility may explain why there is no oncogenicity observed in the chronic toxicity studies where the doses used were similar to those used in the genotoxicity studies (noting that different strains were used). In the rat (Wistar rats) chronic toxicity study, the highest dose tested was 90 ppm without any evidence of oncogenicity (Reuzel *et al.*, 1987, 1991). In comparison, male rats (F-344) exposed to 131 ppm after a single 6 hours of exposure showed DNA adducts in various tissues (Gansewendt *et al.*, 1991). For mice, the highest dose in the oncogenicity study was 33 ppm for 2 years and without any tumors (B6C3F1 mice: NTP, 1992) compared with 36 ppm for 4 hours resulting in DNA adducts in the liver and spleen (CBA mice; Djalali-Behzad *et al.*, 1981). Another possibility is that the DNA adduct levels were below the threshold required for mutagenesis and oncogenesis. In the studies by Pletsa *et al.* (1999), the presence of O⁶-methylguanine adducts were detected in several tissues of Sprague-Dawley rats and lamda lacZ transgenic mice after exposure to methyl bromide. The multiple dosing regiment also resulted in a decrease of O⁶-alkylguanine-DNA alkyltransferase, a repair enzyme, in the tissues examined. However, the presence of these adducts did not lead to increased mutation frequency. The hypothesis was that the adduct levels were at pre-mutagenic level and that other events, such as cell proliferation, also need to be activated for mutagenesis to occur.

Therefore, the oncogenic risk for methyl bromide was not considered based on the currently available data. The NRC agreed with the DPR conclusion that the current database did not show methyl bromide to be oncogenic (NRC, 2000). Another concern on the

oncogenicity of methyl bromide is the possibility that certain people in the population with genetic polymorphism for glutathione-S-transferase may be more susceptible than others to the oncogenicity of methyl bromide. A discussion on this topic is included in **V.D.2. Intraspecies Extrapolation**.

A summary of the critical NOELs for risk characterization is presented in Table 18.

Table 18. The critical no-observed-effects levels (NOELs) for the risk characterization of inhalation exposures to methyl bromide.

Scenarios	Experimental NOEL	Human Equivalent NOEL ^a		Reference Concentration ^d	Effects in Animal Studies	Ref ^e
		Adult ^b	Child ^c			
Acute	40 ppm	21 ppm	na	210 ppb	Developmental toxicity (pregnant rabbit)	1*
	103 ppm ^f	45 ppm	25 ppm		Neurotoxicity (dog)	2
Subchronic 1 week	20 ppm	12 ppm	7 ppm	120 ppb(adult) 70 ppb (child)	Neurotoxicity (pregnant rabbit)	3
6 weeks	0.5 ppm (ENEL)	0.2 ppm	0.1 ppm	2 ppb (adult) 1 ppb (child)	Neurotoxicity (dog)	2
Chronic	0.3 ppm (ENEL)	0.2 ppm	0.1 ppm	2 ppb (adult) 1 ppb (child)	Nasal epithelial hyperplasia/ degeneration (rat)	4*

a/ Experimental NOELs were converted to human equivalents using equations in Attachment G. na= child equivalent NOEL were not calculated because the effects were observed in pregnant animals.

b/ The adult equivalent NOELs are appropriate to address worker exposures. They are also used for residential exposures when child equivalent NOELs were not calculated.

c/ The child equivalent NOELs are appropriate to address resident exposures (see footnote b).

d/ The reference concentration is the ratio of the human equivalent NOEL and a default uncertainty factor of 100 since the NOEL was derived from experimental animal studies.

e/ * indicates study was acceptable to DPR according to FIFRA guidelines. References: 1. Breslin *et al.*, 1990b; 2. Newton, 1994b; 3. Sikov *et al.*, 1981; 4. Reuzel *et al.*, 1987 and 1991.

f/ The NOEL and human equivalents are presented in this Table for comparison purposes only. They are not used for risk characterization.

IV.B. INHALATION EXPOSURE ASSESSMENT

Human exposure assessment was conducted for occupational and residential inhalation exposures to methyl bromide (Tables 19-23 based on Attachments F, H, and references within). This assessment addressed only exposure scenarios where there were available data or when the exposure could be estimated based on DPR permit conditions or regulations (referred to as DPR regulations⁷). The exposure levels were expressed as methyl bromide concentration in the air (ppb). Exposure durations considered were: acute (daily exposure), short-term (referred to as 7 day or subacute in Attachment F), subchronic, and chronic (annual) exposures. All exposure estimates based on monitoring studies were adjusted for 50% recovery (discussed in Attachment F). Dermal exposure was not considered because published studies showed that dermal exposure was significant at much higher methyl bromide air concentration than those estimated from occupational and residential exposures (Attachment F). Skin lesions were observed in workers exposed to high concentrations of methyl bromide (Zwaveling *et al.*, 1987; Hezemans-Boer, 1988; Lifshitz and Gavrilov, 2000). There are no data on the dermal absorption of methyl bromide.

Compared to the draft RCD/1999, this exposure assessment was revised to incorporate some of the NRC recommendations (NRC, 2000) as well as other changes needed (Specific details are provided under **IV.B.1.** and **IV.B.2.**). The NRC recommended collection of additional data to better characterize the exposures of workers and residents. Due to limited resources, DPR focused on residential exposure and collected ambient monitoring data for three California counties. These additional data were incorporated in this assessment (**IV.B.1.**). No additional worker exposure data were collected by DPR or submitted by the registrant. The NRC recommended re-analysis of the worker and residential data to more accurately assess the exposure as well as to determine the variability and uncertainty of the data. As a result, major changes were made in this section and the exposures were re-calculated to reflect current DPR regulations. Since no additional worker exposure data were available, the assessment of worker exposures continued to be based on point estimates. The variability and uncertainty in the data still could not be quantified. A distributional analysis of methyl bromide air concentration along the buffer zone perimeter was performed to assess residential exposure; however, it was limited to a single field application using both monitored data (Attachment H) and computer modeling (Johnson, 2001).

The NRC commented that the chronic exposure should include lifetime in the definition (NRC, 2000). DPR defines repeated exposures on an annual basis as chronic exposure. It does not account for the number of years of potential exposure in a lifetime because it is unknown how many years a worker or resident may be exposed to the pesticide of concern.

⁷

DPR field regulations include general requirements (tarps, acre limit, etc.), notification, minimum buffers, application methods, work hour limits, reentry intervals, tarp repair and removal procedures. The field permit conditions include procedures, guidance, and specifics for determining buffer zones. Structural fumigation regulations include tarp requirements, buffer zones, aeration and tarp removal procedures. The permit conditions for commodity, greenhouse, and potting soil fumigations include buffer zones, application methods, and work hours limitations. This list is not intended to be all inclusive and the full text of the permit conditions and regulations should be consulted.

The toxicological endpoint for risk characterization is selected from repeated 1- or 2-year exposure studies. Lifetime exposure is considered when a pesticide of concern showed a potential to cause tumors. For lifetime exposure, the workers are assumed to work and be exposed for 40 years in a 75-year lifetime, and the residents are assumed to be exposed for the entire lifetime of 75 years.

IV.B.1. Occupational Exposures

The database used to determine occupational exposures was the same as that used in the draft RCD/1999. However, the worker exposure estimates were substantially revised after re-evaluation of the database, examination of the methodology to estimate the exposure, and incorporation of current DPR regulations (Tables 19 to 21 based on Appendix E of Attachment F). Some occupational exposure scenarios were eliminated because of various reasons including change in use practices (detailed discussion in Attachment F). Others were not included because of lack of data or the type exposure was not anticipated. For example, chronic exposure of workers associated with field fumigation was not considered because methyl bromide is used primarily during pre-planting. The exposures for tarp removers measured on the same day as tarp was cut as well as pipe laying activity during fumigation were eliminated because such practices were no longer in compliance with the DPR regulations.

In terms of the methodology to estimate the exposure levels, an upper bound value was used, instead of the only measured value or the highest value, to estimate the acute exposures of workers in field fumigations. This change was necessary to be consistent with the upper bound approach used to determine work hour restrictions in the DPR regulations (Gibbons and Thongsinthusak, 2000). The equation used to calculate the upper bound values was defined as:

$$\text{upper bound} = \text{mean or only measured level} + (1.645 \times \text{standard deviation})$$

It should be noted, the upper bound values for most work scenarios were based on a single or two measurements (n values indicated in Tables 19-21). In these cases, the standard deviation was assumed to be equal to that data point or the average of two data points. In almost all cases, the upper bound values were greater than the values in the draft RCD/1999.

In addition, the upper bound exposures were adjusted based on the work hours restrictions in the DPR regulations with the maximum daily exposure not to exceed 210 ppb. For example, the field fumigation applicator exposure was calculated based on the permitted work hour of 4 hours instead of the 5.8 hours determined from the surveys (see Attachment F). For commodity fumigation, the acute exposure for all workers was set at 210 ppb. The DPR regulations required monitoring of the work site and reduction of work hours accordingly to meet the 210 ppb daily limit. For durations longer than acute exposure, the exposures were either based on 210 ppb (n=0 in Tables 20 and 21) as the daily exposure or the average measured values when they do not exceed 210 ppb. These exposures were then amortized by the number of days work within the specified period. The total duration for these periods were 7, 90, and 365 days for short-term, subchronic, and chronic exposures, respectively.

Structural Fumigation

The inhalation exposures of applicators in structural fumigation were not determined because they are required to wear self-contained breathing apparatus. No data were available for other workers such as tarp removers.

Field Fumigation

For pre-treatment of soil before planting, two groups of fumigation were assessed: shallow-shank injection with tarp and deep-shank injection without tarp. General duties of the workers were: (1) Applicator drives application rig with the cab which could be enclosed or equipped with an overhead fan, (2) Copilot assists the applicator. He may be on a raised platform, (3) Shovel-man turns the rig around at the end of a row and seals row ends, (4) Cultipacker driver- drives a cultipacker which compacts the soil after application, (5) Disc driver- drives a second tractor which a disc to compact the soil after application, (6) Tarp cutter or tractor driver drives a vehicle which cuts the tarp, and (7) Tarp remover (basket-man, end puller) removes and gathers the cut tarp from the field. For both groups of fumigation, the monitoring studies were conducted primarily to determine the effectiveness of modifications to existing application procedures and aeration of treated fields. As such, these studies generally contained only 1 to 2 samples. Collectively, they showed that some modifications were effective in reducing exposure and those modifications were subsequently included in the regulations for the use of methyl bromide in field fumigation.

With shallow-shank and tarp fumigation (Table 19a to f), workers involved in the application with no modifications (Table 19a) had higher exposures than those in other methods (Table 19b to d). The applicator, copilot, and shovel-man acute exposures were 188 ppb, 245 ppb, and 191 ppb, respectively, based on 8 to 10 measurements. With the addition of scrapers (closing shoes), rollers, and/or raised platforms (Table 19b to d), these devices appeared to lowered the exposures for these workers. The best method involved both swept-back shank and closing shoes (Table 19d) where the applicators, copilots, and shovel-men exposures were 4 ppb, 58 ppb, and 1 ppb, respectively. The driver (7 ppb) and copilot (62 ppb) of the tractor in the placement of tarp had lower acute exposures than those involved in the application. For tarp cutting and removal, one study showed acute exposures of 202 ppb (cutter, 3 samples) and 215 ppb (puller, 12 samples) (Table 19e). Another study showed cutters, tractor drivers, basket-men, and end pullers with higher acute exposures; they were 138 ppb, 1058 ppb, 1003 ppb, and 22 ppb, respectively (Table 19f). These were based on single measurements.

With deep-shank injection, the applicators with only overhead fan had the highest acute exposure at 281 ppb (Table 19g). Lower acute exposures were measured for applicators in tractors with modifications. These included overhead fan and scrapers and rollers (104 ppb, Table 19h), enclosed cab (161 ppb and 171 ppb, Table 19i), and enclosed cab with scrapers (13 ppb, Table 19j). When a second tractor with a disc or cultipacker was involved, the drivers had relatively lower exposure (13-181 ppb) than those for applicators, except for the disc driver (934 ppb Table 19i).

For both short-term and subchronic exposures in shallow-shank and deep-shank methods, the exposure patterns were similar to those for acute exposures which were the basis for the calculations. Chronic exposure was not expected for any of the work scenarios.

For workers at adjacent fields, there were no data for their exposures. Since the buffer zone for acute exposure is set at 210 ppb and they are only allowed to work outside of the buffer zone, their exposures could be assumed to be at or less than 210 ppb.

Commodity/Brewery Fumigation

For workers with potting soil in greenhouses, the maximum acute exposure was set at 210 ppb (Table 20a). Their actual exposures were relatively low because tarp venters are required to wear self-containing breathing apparatus and tarp removal occurs after 48 hours of venting. The short term exposures, based on measured values, were 0.001 ppb and 0.14 ppb for these two group of workers. No subchronic or chronic exposures were determined for this activity. No data were available for other workers, e.g., applicators, associated with this use.

The acute exposure of all workers in commodity fumigation facilities was also limited 210 ppb (Table 20b and c). The exposures for other exposure durations were based on the average of measured values. The workers included those who were directly involved with the fumigation (applicators, aerators, leak checkers), those who handled fumigated products (forklift drivers, sorters, packaging workers), and those who worked in the facilities doing other jobs.

For workers involved in the fumigation of grain products, the range of short-term exposures was 0.02 ppb (aerator of tarpaulin fumigation) to 11 ppb (forklift driver emptying sea containers/truck trailers) (Table 20b). These forklift drivers also had the highest exposure of 8 ppb for subchronic and chronic exposures. In comparison, forklift drivers emptying non-certifying fumigation chambers had much lower exposures (3 ppb) for these durations.

For workers involved in the fumigation of raisins, the range of short-term exposures was 3 ppb (Table 20c. forklift driver) to 180 ppb (Table 20c. worker involved in clear chamber for raisins). For workers in a walnut processing plant (Table 20c2), potential exposures were based on air sampling of work stations rather than specific tasks. Workers in clearing plant (178 ppb) and vacuum chamber (180 ppb) had the highest methyl bromide levels for short-term exposure compared to other areas. The lowest average short-term level (25 ppb) was measured in the special cracking area. For both raisin and walnut workers, the short-term and subchronic exposure levels were similar because the fraction of time worked (6 days per 7 days short-term, 63-75 days per 90 days seasonal) during those periods was almost the same. Chronic exposure was considered for raisin processing workers but was not expected for most of walnut processing workers.

For workers in a brewery, exposures were estimated for applicators and aerators at various locations (Table 20d). This type of fumigation is similar to structural fumigation and no other workers are allowed in the facility during fumigation. The exposure levels were slightly higher during aeration than fumigation. The short-term exposure level ranges were 7-49 ppb for aerators and 8-12 ppb for applicators. No seasonal or chronic exposures were expected.

For workers in the facilities but whose tasks were not directly related to commodity fumigation, data were available only for raisin and walnut fumigations. The exposure levels were either based on the acute level of 210 ppb or measured by ambient and area sampling (Table 21). The range of short-term exposures was 7 ppb (hopper area for raisins, Table 21a) to 180 ppb (walnut sorting and packaging areas, Table 21b2). The subchronic and chronic

exposures (except for walnut processing) were comparable to those for short-term levels because of the frequency of exposure. The estimated number of work days were 6 days per 7 day period, 63-75 days per 90 day period, and 150 per 365 day period, for short-term, subchronic, and chronic exposures, respectively.

IV.B.2. Residential Exposures

Structural Fumigation

The exposures of residents returning to homes after fumigation and aeration were not estimated due to lack of data on current practices. The durations of exposure expected are acute and short-term as methyl bromide off-gas from confined air space such as the wall space. DPR regulations limit the acute exposure at or less than 210 ppb by modification of application methods, aeration time (72 hours of active aeration or 7 days for nonmechanical or natural ventilation instead of the 24 hours used previously), and buffer zones around the fumigated homes (DPR, 2000b).

Field Fumigation

Residential exposures were determined along the buffer zone perimeter to determine the effectiveness of the buffer zone (Table 22a). Two types of distributional analyses were performed: the maximum concentration along the buffer zone perimeter, and the maximum distance required to keep the air concentration at or below the 210 ppb reference concentration for acute exposure (Johnson, 2001⁸). In these analyses, available field monitoring data (data summarized in Attachment H) were combined with computer modeling to generate the maximum air concentration or distance under a wide variety of conditions due to the field size, flux (emission rate), and meteorological conditions. The cumulative frequency distribution reflected the maximum concentrations or distances under the 24-hour meteorological data sets (7166 days from 20 years of data). It should be noted that the maximum concentration determined in these analyses occurred only on a portion of the buffer zone perimeter, and these analyses addressed only acute exposure. For longer durations, the exposures were not simulated at this time because of the complexity involved in determining the methyl bromide air levels from multiple field applications and different durations of exposure. Potential exposures from multiple uses are addressed in part by ambient air monitoring projects as described under All Uses and Table 22c.

The result of the maximum air concentration analysis was used in the exposure assessment to determine the acute residential exposure at the buffer zone perimeter after field fumigation. The data from Johnson (2001) were interpolated/extrapolated to derive emission rates representing the different fumigation methods (Attachment F). The emission rates (lbs mebr/acre-day) and the corresponding fumigation methods were: 80 (nontarp/ shallow/bed), 160 (tarp/deep/broadcast; nontarp/deep/broadcast), 200 (tarp/shallow/bed), 225 (drip system-

⁸ The executive summary of the Johnson (2001) report is in Attachment H. The report contained additional analyses and responses to NRC questions on buffer zones. Only a limited amount of information of the report is contained in this document. The reader is referred to the complete report for details.

hot gas), and 320 (tarp/shallow/broadcast). The magnitude of the methyl bromide maximum air concentration was related to the size of the field and emission rate (depending on the method of application) (Table 22a). The maximum methyl bromide air concentrations from the 90th to the 99th percentiles (cumulative frequency of 0.9 to 0.99) were presented. For example, the maximum concentration along the buffer zone perimeter was 143 ppb for 1 acre fumigation and 80 lbs emission rate under 6449 (90% of 7166 input) different 24-hour meteorological data sets. At this same 90th percentile, the air concentrations were at or less than 210 ppb for other emission rates and acreage. At the 95th percentile, a level generally selected for risk characterization, the exposure ranges for each field sizes were: 161-174 ppb (1 acre), 163-215 ppb (10 acre), 201-225 ppb (20 acres), 213-230 ppb (30 acres), and 221-236 ppb (40 acres).

Commodity Fumigation

The acute exposure for residents living near commodity fumigation facilities was limited to 210 ppb (Table 22b). The exposures for the longer-term durations were based on the 210 ppb level and adjusted by the number of exposure days during the exposure period. They were broadly divided into two categories of low range (3/7 days, 30/90 days, and 150/365 days) and high (6/7 days, 75/90 days, and 185/365 days) range depending on the number of exposed days during the duration period. The exposures were 90-180 ppb (short-term), 70-175 ppb (subchronic), and 86-106 ppb (chronic).

All Uses

For residents living in methyl bromide use areas which may include field, commodity, and structural fumigations, the exposures were based on ambient air monitoring by the Air Resources Board (7-8 weeks of monitoring) at Kern, Monterey and Santa Cruz counties (ARB, 2000 and 2001) (Table 22c). For each monitoring site, the 95th percentile of all daily (24-hour) monitoring was calculated using lognormal methods (Powell, 2001). The weekly exposure values indicated in the Table were the 95th percentile of all weekly means using normal methods for each site. The 7-8 week exposure values were the arithmetic means of the weekly means. The data showed that the magnitude of the detected levels corresponded to the use (field and commodity fumigations) during the monitored period (DPR, 2001d). The 95th percentile daily exposure levels ranged from 0.239 ppb (Mettler Fire Station) to 30.2 ppb (Pajaro Middle School in Watsonville) (Table 22c). Levels at these two sites also provided the ranges for weekly (0.163 to 17.1 ppb), and 7-8 week (0.084 to 7.68 ppb) exposure durations. While there may be a potential for longer duration of exposure, a quantitative determination of the exposure cannot be made at this time (Attachment F). Since these studies showed some sites with methyl bromide levels 2- to almost 8-folds higher than the 7-week reference concentrations of 1 to 2 ppb (Table 18), additional monitoring has been conducted by the Air Resources Board (DPR, 2001b). DPR has also required the registrants to conduct ambient air quality monitoring in 2001-2002 (DPR, 2001c).

Table 19. Estimates of occupational exposures to methyl bromide in field fumigation.^a

Table 10: Estimates of occupational exposures to methyl bromide in field fumigation					
Type of Application	n ^b	Acute	Short-term	Subchronic	Chronic
		upper bound (ppb)	mean (ppb)	mean (ppb)	mean (ppb)
a. Shallow-shank/ tarp / broadcast - (Noble plow, 10-12" injection, open cab and overhead fan for applicators; <i>Table B1,2,3</i>)					
Applicator	8	188	66	34	n/a
Copilot	7	245	99	51	n/a
Shovel-man	10	191	33	n/a	n/a
b. Shallow shank/ tarp/ bed - Scrapers (6-8" injection, conventional shank, copilot on raised platform in one case, scrapers/closing shoes and rollers to compress the soil after injection in the other case; <i>Table B9</i>)					
1. Raised platform					
Applicator	1	146	47	25	n/a
Copilot	2	190	61	32	n/a
2. Closing shoes					
Applicator	1	80	26	13	n/a
Copilot	2	305	99	51	n/a
c. Shallow shank/ tarp/ bed - Drip tape (12-14" injection; swept-back shank, first tractor forms bed, injects methyl bromide, and puts on drip tape; second tractor lays on tarp; <i>Table B10</i>)					
1. Tractor fumigation					
Driver	1	51	17	9	n/a
Applicator	1	82	27	14	n/a
Drip tape layer	1	119	19	n/a	n/a
2. Tractor with tarp					
Driver	1	7	2	1	n/a
Copilot	2	62	20	10	n/a
d. Shallow shank/ tarp/ bed - Closing device (6-8" injection, swept-back shank, use of a closing device and compaction roller to compress the soil before tarp application; <i>Table B11</i>)					
Applicator	1	4	1	1	n/a
Copilot	2	58	19	10	n/a
Shovel-man	2	1	0.2	n/a	n/a
e. Shallow shank/ tarp - Tarp removal study 1 (10-12" injection, Noble plow, tarp cut 5 days after fumigation and removed after 1 day of aeration; <i>Table B12</i>)					
Cutter	3	202	39	18	n/a
Puller	12	215	28	13	n/a
f. Shallow shank/ tarp - Tarp removal study 2 (10" injection, Noble plow, tarp cut 5 days after fumigation and removed after 1 day of aeration; <i>Table B13</i>)					
Cutter	1	138	37	17	n/a
Remover:tractor driver	1	1058	286	133	n/a
Remover:basket-man	1	1003	271	126	n/a
Remover:end puller	1	22	6	3	n/a

Table 19. Estimates of occupational exposures to methyl bromide in field fumigation (continued).^a

Type of Application	n ^b	Acute	Short-term	Subchronic	Chronic
		upper bound (ppb)	mean (ppb)	mean (ppb)	mean (ppb)
g. Deep-shank/ non-tarp - Overhead fan (20-24" injection, open cab and overhead fan for applicators, <i>Table B6</i>)					
Applicators	2	281	91	47	n/a
Copilot	1	89	29	15	n/a
Cultipacker	1	181	59	n/a	n/a
h. Deep-shank/ non-tarp - Overhead fan and scrapers (20-24" injection, open cab and overhead fan for applicators, scrapers and press wheels to compress the soil after injection; <i>Table B6</i>)					
Applicator	1	104	34	17	n/a
Cultipacker	1	128	41	n/a	n/a
i. Deep-shank/ non-tarp - Enclosed cab (24" injection, enclosed cab for applicators, closing scrapers, second tractor equipped with either a disc or cultipacker; <i>Table B7</i>)					
1. Disc					
Applicator	1	161	52	27	n/a
Disc driver	1	934	303	157	n/a
2. Cultipacker					
Applicator	2	171	56	29	n/a
Supervisor	1	122	40	21	n/a
Cultipacker	2	62	20	n/a	n/a
j. Deep-shank/ non-tarp - Enclosed cab and scrapers (27" injection, enclosed cab for applicators, scrapers and rollers to compress the soil after injection; <i>Table B8</i>)					
Applicator	1	13	4	2	n/a
Cultipacker	1	13	4	n/a	n/a

^{a/} Detailed description of the exposure scenarios are provided in Attachment F and values from Appendix E. with Table number indicated in italics for cross reference. n/a= not applicable or no exposure data available. General duties of the workers: Applicator- drives application rig and inside the cab with or with enclosure or overhead fan. Copilot- assists the applicator. He may be on a raised platform as in f. Shovel-man- turns rig around at the end of a row and seals row ends. Cultipacker driver- drives a cultipacker which compacts the soil after application. Disc driver- drives a second tractor which a disc to compact the soil after application. Tarp cutter- drives a tractor which cuts the tarp. Tarp remover- removes the tarp from the field (tractor driver, basket-man, end puller).

^{b/} n=number of measurements. These measured value(s) were used to determine the upper bound value for acute exposure. The average of measured values was amortized for other exposure durations.

Table 20. Estimates of occupational exposures to methyl bromide in commodity fumigation.^a

Type of Application	n ^b	Acute ^c	Short-term	Subchronic	Chronic
		upper bound (ppb)	mean (ppb)	mean (ppb)	mean(ppb)
a. Greenhouse potting soil-hot gas method					
Tarp venter	4	210	0.001	n/a	n/a
Tarp remover	4	210	0.14	n/a	n/a
b. Fumigation of grain products					
Aerator (container/trailer)	3	210	0.43	0.3	0.3
Aerator (tarp)	3	210	0.02	0.01	0.01
Forklift driver (container)	3	210	11	8	8
Forklift driver (chamber)	3	210	4	3	3
c. Fumigation of dried fruit and tree nut products					
1. Raisins					
Fumigator	2	210	54	44	26
Aerator	2	210	40	33	19
Clear chamber	0	210	180	147	86
Stem picker	2	210	24	20	12
Forklift driver	1	210	3	2	1
Hopper operator	1	210	16	13	8
2. Walnut processing					
Bulk packaging	2	210	29	28	n/a
Cleaning plant	12	210	178	173	n/a
Fumigatorium	3	210	75	73	43
Packaging	1	210	38	37	n/a
Vacuum chamber	0	210	180	175	n/a
Sorting	6	210	27	27	n/a
Special cracking	4	210	25	24	n/a
d. Fumigation and aeration at a brewery facility					
1. Applicator					
Entry to open canister	4	210	8	n/a	n/a
Area sample	1	210	12	n/a	n/a
2. Aerator					
Aerator	2	210	7	n/a	n/a
Area sample (entrance)	1	210	49	n/a	n/a
Area sample (truck)	1	210	29	n/a	n/a

^{a/} Data from Attachment F. n/a= not applicable or no exposure data available.

^{b/} n=number of measurements. The average measured value(s), if they do not exceed 210 ppb, were used to determine the exposures for durations longer than that for acute. For n=0, 210 ppb was used as the average value.

^{c/} The worker exposure was set at 210 ppb, the maximum limit in the DPR regulations.

Table 21. Ambient and area air sampling of methyl bromide in commodity fumigation facilities.^a

Type of Application	n ^b	Acute ^c	Short-term	Subchronic	Chronic
		upper bound (ppb)	mean (ppb)	mean (ppb)	mean (ppb)
a. Chambers (raisins)					
Chamber	1	210	75	62	36
Cage	1	210	46	38	22
Leak checker	2	210	n/a	n/a	n/a
Aeration	2	210	99	81	48
Clearing	2	210	39	32	19
Hopper area	2	210	7	6	3
Stem picker area	4	210	23	19	11
b. Walnut processing facility					
1. Area samples					
Sorting line	2	210	24	n/a	n/a
2. Compliance monitoring					
Sorting line	0	210	180	175	n/a
Cello packaging	0	210	180	175	n/a
Bulk packaging	0	210	180	175	n/a

a/ Detailed description of the exposure scenarios are provided in Attachment F. n/a= not applicable or no exposure data available.

b/ n=number of measurements. The average measured value(s), if they do not exceed 210 ppb, were used to determine the exposures for durations longer than that for acute. For n=0, 210 ppb was used as the average value.

c/ The worker exposure was set at 210 ppb, the maximum limit in the DPR regulations.

Table 22. Residential exposures to methyl bromide from living near field or commodity fumigation activities.

a. At buffer zone perimeter of fumigated fields- Acute exposure ^a						
Field size	Cumulative frequency	Methyl bromide concentration (ppb) for different emission rates (80-320 lbs methyl bromide /acre-day)				
		80	160	200	225	320
1 acre	0.9	143 ppb	152 ppb	151 ppb	150 ppb	148
	0.95	161	174	174	174	173
	0.97	175	191	191	192	195
	0.99	211	239	241	241	243
10 acres	0.9	190	175	170	163	138
	0.95	215	203	198	190	163
	0.97	236	224	219	212	186
	0.99	290	283	276	268	236
20 acres	0.9	198	183	178	176	171
	0.95	225	212	207	206	201
	0.97	248	234	230	229	225
	0.99	304	297	290	289	286
30 acres	0.9	204	183	183	183	186
	0.95	230	213	213	214	218
	0.97	255	235	236	238	242
	0.99	312	298	299	301	309
40 acres	0.9	210	190	189	190	196
	0.95	236	222	221	223	229
	0.97	263	246	245	247	255
	0.99	321	312	310	313	324
b. Near commodity fumigation facilities ^b						
Type of Application	Acute	Short-term	Sub-chronic	Chronic		
	upper bound (ppb)	mean (ppb)	mean (ppb)	mean (ppb)		
low range	210	90	70	86		
high range	210	180	175	106		

Table 22. Residential exposures to methyl bromide from living near field or commodity fumigation activities (continued).

c. Ambient monitoring in three California counties ^c					
Sites in California	Daily (ppb)	Weekly (ppb)	7-8 weeks (ppb)	Chronic	
Monterey					
Chualar School, Chualar	2.26	1.63	0.644	No data	
La Joya Elementary School, Salinas	18.5	11.1	3.79		
Oak Avenue School, Greenfield	1.21	0.918	0.387		
Pajaro Middle School, Watsonville	30.2	17.1	7.68		
Ambient Monitoring Station, Salinas	6.17	3.14	1.29		
Santa Cruz					
Salsepuedes Elementary School, Watsonville	12.2	7.45	2.6	No data	
Kern					
Ambient Monitoring Station, Bakersfield	0.556	0.507	0.189		
Cotton Research Station, Shafter	25.4	5.54	2.16		
Mettler-Fire Station, Mettler	0.239	0.163	0.084		
Mountain View School, Lamont	0.262	0.195	0.092		
Shafter-Walker Ambient Monitoring Station	3.98	2.05	0.792		
Vineland School District, Bakersfield	0.292	0.181	0.099		

a/ Based on air concentrations in Johnson, 2001. The emission rates (lbs mebr/acre-day) and the fumigation methods are in Attachment F and are: 80 (nontarp/shallow/bed), 160 (tarp/deep /broadcast; nontarp/deep/broadcast), 200 (tarp/shallow/bed), 225 (drip system-hot gas), and 320 (tarp/shallow/broadcast). The concentrations in ug/m³ was converted to ppb using a factor of 3.89. Bolded values are at the 95th percentile.

b/ Low range= 3 days/7 days, 30 days/90 days, and 150 days/365 days for short-term, subchronic, and chronic exposure, respectively, as described in Attachment F. High range= 6 days/7 days, 75 days/90 days, and 185 days/365 days for short-term, subchronic, and chronic exposure, respectively.

c/ Data from Attachment F. Air monitoring was done for 7-8 weeks. Daily=95th percentile of all measured values, weekly=mean values, 7-8 weeks= means of weekly means.

Table 23. Summary of occupational and residential exposures to methyl bromide.^a

Scenarios	Workers at specific tasks (ppb) ^b				Workers around the use of methyl bromide (ppb) ^c				Residential exposures (ppb) ^d			
	acute	short-tem	sub-chronic	chronic	acute	short-term	sub-chronic	chronic	acute	short-term	sub-chronic	chronic
Structural Fumigation												
Houses	No exposure since SCBA is required. No data on tarp removers				NA				assume 210 ppb	No data		
Field Fumigation												
Shallow-shank Deep-shank	1-1058	1-286	0.2-133	NA	assume 210 ppb	No data		NA	161-236 at 95 th %	No data		
	13-934	4-303	2-157	NA								
Commodity Fumigation												
Green-house soil	210*	0.001-0.14	NA	NA	No data				210*	90*-180*	70*-175*	86*-106*
Grains	210*	0.02-11	0.01-8	0.01-8	No data							
Raisins	210*	3-180*	2-147*	1-86*	210*	7-99	6-81	3-48				
Walnut	210*	25-180*	24-175*	43	210*	24-180*	175*	NA				
Brewery	210*	8-49	NA	NA	NA							
Other uses	No data				No data							
All Uses												
Ambient air	NA								0.239-30.2	0.163-17.1	0.084-7.68	No data

^{a/} Data were presented in Tables 19-22. NA=not applicable as exposure was not expected. * =exposure was based on 210 ppb as the acute exposure or the daily exposure value for amortization to calculate other durations of exposure.

^{b/} Table 19 for field fumigations and Table 20 for commodity fumigation.

^{c/} Table 21 for commodity fumigation.

^{d/} Table 22a for field fumigations, 22b for commodity fumigation, and 22c for ambient air monitoring.

IV.C. RISK CHARACTERIZATION

The potential health hazard associated with the use of methyl bromide was considered for occupational and residential exposures. Non-oncogenic effects were characterized in terms of a margin of exposure (MOE), defined as the ratio of the critical human equivalent NOEL to the estimated human exposure levels. The oncogenic risk of exposure to methyl bromide was not evaluated since methyl bromide has not been shown to be oncogenic based on the current database. The human equivalent NOELs are listed in Table 18 and the exposure levels for the various exposure scenarios are presented in Tables 19 to 22 and summarized in Table 23. The calculated MOEs are shown in Tables 24 to 27 and a summary is presented in Table 28.

IV.C.1. Occupational Exposure

Structural Fumigation

Margins of exposures were not calculated for workers involved in structural fumigation. The acute MOE for the applicators was assumed to be greater than 100 since these workers are required to be in a self-contained breathing apparatus.

Field Fumigation

With shallow-shank/tarp/broadcast fumigation (Table 24a to f), the acute MOEs were 112 (applicator), 86 (copilot), and 110 (shovel-man) for workers Noble plow and overhead fan (Table 24a). The MOEs were higher for the workers in shallow-shank/tarp/bed fumigation and various equipment modifications. The MOEs for these applicators were 144 and 263 (Table 24b, conventional shank and scrapers), 256 (Table 24c with swept-back shank), and 5250 (Table 24d swept-back shank and closing device). For copilots, the MOEs varied depending on the modification. The MOE was 69 when a conventional shank was used, even though scrapes/closing shoes were added. The MOEs were 111 when the copilot was in a raised platform (Table 24b) and 362 when swept-back shank and closing device were used in the application (Table 24d). The MOEs for the driver and copilot in the second tractor for tarping were 3000 and 339, respectively. The MOEs for workers in tarp cutting and removal varied depending on the study even though similar procedures were used. However, there were more measurements in the first study (3 to 12 samples) compared to the second study (1 sample each). In study 1 (Table 24e), the MOEs were 104 and 98 for cutters and pullers. In the second study (Table 24f), the MOEs were 152 (cutter), 20 (remover:tractor driver), 21 (remover:basket-man), and 955 (remover:end puller).

With deep-shank injection, the applicators with only overhead fan had the lowest MOE of 75 (Table 24g). The MOEs were higher with modifications and were: 202 (Table 24h, open cab with scrapers), 130 and 123 (Table 24i, enclosed cab), and 1614 (Table 24j, enclosed cab and scrapers/rollers). The MOEs for driver in the second tractor with a cultipacker were also higher when scrapers were used after application. The MOE increased from 116 (no modifications, Table 24g) to 164-1615 (use of scrapers and/or rollers, Table 24h-j). The MOE was only 22 for the disc driver (Table 24i1).

For both shallow-shank and deep-shank methods, the MOEs for almost all short-term exposures were 100 while subchronic exposures were less than 100. Chronic exposure was not expected for any of the work scenarios.

For workers at adjacent fields, the acute MOE could be assumed to be 100 with the exposure not to exceed 210 ppb.

Commodity/Brewery Fumigation

The acute MOEs for all workers in commodity fumigation facility were 100 because their upper exposure limit was 210 ppb (Tables 25 and 26). For tarp ventors and removers of potting soil fumigation in greenhouses, the MOEs for short-term exposures were greater than 80,000 because of their relatively low actual exposures (Table 25a). No data were available for other workers.

In the fumigation of grain products, MOEs for these workers were greater than 100 for the aerators for all exposure periods (Table 25b). For forklift drivers, the short-term MOEs were > 1000 but the subchronic and chronic MOEs were less than 100 (MOEs of 25 and 67). For workers involved in the fumigation of raisins, the range of MOEs for short-term exposures was 4000 (Table 25c1. forklift driver) to 67 (Table 25c1. worker involved in clear chamber for raisins). The MOE of 67 was based on the use of 210 ppb as the daily exposure value. The MOEs for subchronic and chronic exposures were less than 100, except for the forklift drivers with a MOE of 100. For workers in a walnut processing plant, the MOE was 67 for workers with the highest exposures (in clearing plant or vacuum chamber, Table 25c2). This MOE was based on measured values (clearing plant) and the 210 ppb limit (vacuum chamber). The highest MOE was 480 for workers at the special cracking area. The MOEs for subchronic and chronic exposures were less than 10. For workers in a brewery, the MOEs for applicators and aerators were ranged from 245 to 1714 (Table 25d).

For workers in fumigation facilities not directly related to fumigation, the short-term exposure MOEs were generally greater than 100 (MOE of 121 to 1714) for raisin facilities. The short-term MOE for walnut processing was 500 based on area sampling but was 67 based on 210 ppb as the daily exposure level in sorting and packaging areas (Table 26b.2). However, the subchronic and chronic exposure MOEs for both raisins and walnut processing facilities were less than 100 based on either measured values or 210 ppb.

IV.C.2. Residential Exposure

Structural Fumigation

For residents living in treated home after aeration, the acute MOEs were not calculated due to lack of exposure data. They were expected to be at least 100 since regulations were based on the 210 ppb for acute exposure.

Field Fumigation

For the 95th percentile exposure at the buffer zone perimeter, the acute MOE ranged from 89 (40 acres/80 lbs) to 131 (10 acres/80 lbs) (Table 27a). The interpretation of these MOEs is not as straight forward as those based on point estimates since they are based on a frequency distribution and on maximum air concentrations along the perimeter. When the MOE is less than 100 based on a 95th percentile value, it means that the reference concentration of 210 ppb was exceeded in less than 5% of the 7166 24-hour meteorological data sets and only along the portion of the buffer zone perimeter with the maximum methyl bromide air

concentration. At the 90th percentile methyl bromide air concentration, all MOEs were at or greater than 100. At the 95th percentile, the MOEs were at least 100 (98 to 131) for 1 and 10 acres and all emission rates. For 20 and 30 acres, the MOEs were around 100 (96 to 104) with the exception of 91 and 93 for 80 lbs emission rate. For 40 acres, the MOEs were 89 to 95 for the specified emission rates.

Commodity Fumigation

The acute MOE for residents living near commodity fumigation facilities was 100 because the exposure was assumed to be 210 ppb (Table 27b). However, the MOEs were 39-78, 1, and 1, respectively, for short-term, subchronic, and chronic exposures based on 210 ppb as the average daily exposure levels.

All Uses

For residents living around methyl bromide uses, ambient air monitoring of 12 sites showed MOEs ranged from 695 to >80,000 for acute exposure, and from 409 to > 40,000 for short-term exposures (Table 27c). For 7-8 weeks of exposure, the MOEs for 7 of the sites were greater than 100 (range from 126 to 1190). The MOEs for the remaining sites ranged from 13 (Pajaro Middle School) to 78 (Salinas Ambient Monitoring Station).

Table 24. Margins of exposure for occupational exposures to methyl bromide in field fumigations.^a

Type of Application	n ^b	Acute	Short-term	Subchronic	Chronic
a. Shallow-shank/ tarp / broadcast - (Noble plow, 10-12" injection, open cab and overhead fan for applicators; <i>Table B1,2,3</i>)					
Applicator	8	112	182	6	n/a
Copilot	7	86	121	4	n/a
Shovel-man	10	110	364	n/a	n/a
b. Shallow shank/ tarp/ bed - Scrapers (6-8" injection, conventional shank, copilot on raised platform in one case, scrapers/closing shoes and rollers to compress the soil after injection in the other case; <i>Table B9</i>)					
1. Raised platform					
Applicator	1	144	255	8	n/a
Copilot	2	111	197	6	n/a
2. Closing shoes					
Applicator	1	263	462	15	n/a
Copilot	2	69	121	4	n/a
c. Shallow shank/ tarp/ bed - Drip tape (12-14" injection; swept-back shank, first tractor forms bed, injects methyl bromide, and puts on drip tape; second tractor lays on tarp; <i>Table B10</i>)					
1. Tractor fumigation					
Driver	1	412	706	22	n/a
Applicator	1	256	444	14	n/a
Drip tape layer	1	176	632	n/a	n/a
2. Tractor with tarp					
Driver	1	3000	6000	200	n/a
Copilot	2	339	600	20	n/a
d. Shallow shank/ tarp/ bed - Closing device (6-8" injection, swept-back shank, use of a closing device and compaction roller to compress the soil before tarp application; <i>Table B11</i>)					
Applicator	1	5250	12000	200	n/a
Copilot	2	362	622	20	n/a
Shovel-man	2	21000	60000	n/a	n/a
e. Shallow shank/ tarp - Tarp removal study 1 (10-12" injection, Noble plow, tarp cut 5 days after fumigation and removed after 1 day of aeration; <i>Table B12</i>)					
Cutter	3	104	308	11	n/a
Puller	12	98	429	15	n/a
f. Shallow shank/ tarp - Tarp removal study 2 (10" injection, Noble plow, tarp cut 5 days after fumigation and removed after 1 day of aeration; <i>Table B13</i>)					
Cutter	1	152	324	12	n/a
Remover:tractor driver	1	20	42	2	n/a
Remover:basket-man	1	21	44	2	n/a
Remover:end puller	1	955	2000	67	n/a

Table 24. Margins of exposure for occupational exposures to methyl bromide in field fumigation (continued).^a

Type of Application	n ^b	Acute	Short-term	Subchronic	Chronic
g. Deep-shank/ non-tarp - Overhead fan (20-24" injection, open cab and overhead fan for applicators; <i>Table B6</i>)					
Applicators	2	75	132	4	n/a
Copilot	1	236	414	13	n/a
Cultipacker	1	116	203	n/a	n/a
h. Deep-shank/ non-tarp - Overhead fan and scrapers (20-24" injection, open cab and overhead fan for applicators, scrapers and press wheels to compress the soil after injection; <i>Table B6</i>)					
Applicator	1	202	353	12	n/a
Cultipacker	1	164	293	n/a	n/a
i. Deep-shank/ non-tarp - Enclosed cab (24" injection, enclosed cab for applicators, closing scrapers, second tractor equipped with either a disc or cultipacker; <i>Table B7</i>)					
1. Disc					
Applicator	1	130	231	7	n/a
Disc driver	1	22	40	1	n/a
2. Cultipacker					
Applicator	2	123	214	7	n/a
Supervisor	1	172	300	10	n/a
Cultipacker	2	339	600	n/a	n/a
j. Deep-shank/ non-tarp - Enclosed cab and scrapers (27" injection, enclosed cab for applicators, scrapers and rollers to compress the soil after injection; <i>Table B8</i>)					
Applicator	1	1615	3000	100	n/a
Cultipacker	1	1615	3000	n/a	n/a

^{a/} Margins of exposure were based on exposure levels in Table 19 and human equivalents of the critical NOELs in Table 18 for each of the durations. The critical NOELs were: acute, 40 ppm (adult equivalent of 21 ppm) for developmental toxicity in rabbits; short-term, 20 ppm (adult equivalent of 12 ppm) for neurotoxicity in rabbits; subchronic, 0.5 ppm (adult equivalent of 200 ppb) for neurotoxicity in dogs; and chronic, 0.3 ppm (adult equivalent of 200 ppb) for nasal epithelial hyperplasia/degeneration in rats.

^{b/} n=number of measurements.

Table 25. Margins of exposure for occupational exposures to methyl bromide in commodity fumigation.^a

Type of Application	n ^b	Acute	Short-term	Subchronic	Chronic
a. Greenhouse potting soil- hot gas method					
Tarp ventor	4	100	>100000	n/a	n/a
Tarp remover	4	100	85714	n/a	n/a
b. Fumigation of grain products					
Aerator (sea container/trailer)	3	100	27907	667	667
Aerator (tarp)	3	100	>100000	20000	20000
Forklift driver (container/trailer)	3	100	1091	25	25
Forklift driver (chamber)	3	100	3000	67	67
c. Fumigation of dried fruit and tree nut products					
1. Raisins					
Fumigator	2	100	222	5	8
Aerator	2	100	300	6	11
Clear chamber	0	100	67	1	2
Stem picker	2	100	500	10	17
Forklift driver	1	100	4000	100	200
Hopper operator	1	100	750	15	25
2. Walnut processing facility					
Bulk packaging	2	100	414	7	n/a
Cleaning plant	12	100	67	1	n/a
Fumigatorium	3	100	160	3	5
Packaging	1	100	316	5	n/a
Vacuum chamber	0	100	67	1	n/a
Sorting	6	100	444	7	n/a
Special cracking	4	100	480	8	n/a
d. Fumigation and aeration at a brewery facility					
1. Applicator					
Entry to open canisters	4	100	1500	n/a	n/a
Area sample	1	100	1000	n/a	n/a
2. Aerator					
Aerator	2	100	1714	n/a	n/a
Area sample	2	100	245-414	n/a	n/a

a/ Margins of exposure were based on exposure levels in Table 20 and human equivalents of the critical NOELs in Table 18 for each of the durations. The critical NOELs were: acute, 40 ppm (adult equivalent of 21 ppm) for developmental toxicity in rabbits; short-term, 20 ppm (adult equivalent of 12 ppm) for neurotoxicity in rabbits; subchronic, 0.5 ppm (adult equivalent of 200 ppb) for neurotoxicity in dogs; and chronic, 0.3 ppm (adult equivalent of 200 ppb) for nasal epithelial hyperplasia/degeneration in rats.

b/ n=number of measurements.

Table 26. Margins of exposure for occupational exposures to ambient and area air sampling of methyl bromide in commodity fumigation facilities.^a

Type of Application	n ^b	Acute	Short-term	Subchronic	Chronic
a. Chambers (raisins)					
Chamber	1	100	160	3	6
Cage	1	100	261	5	9
Leak checker	2	100	n/a	n/a	n/a
Aeration	2	100	121	2	4
Clearing	2	100	308	6	11
Hopper area	2	100	1714	33	67
Stem picker area	4	100	522	11	18
b. Walnut processing facility					
1. Area samples					
Sorting line	2	100	500	n/a	n/a
2. Compliance monitoring					
Sorting line	0	100	67	1	n/a
Cello packaging	0	100	67	1	n/a
Bulk packaging	0	100	67	1	n/a

a/ Margins of exposure were based on exposure levels in Table 21 and human equivalents of the critical NOELs in Table 18 for each of the durations. The critical NOELs were: acute, 40 ppm (adult equivalent of 21 ppm) for developmental toxicity in rabbits; short-term, 20 ppm (adult equivalent of 12 ppm) for neurotoxicity in rabbits; subchronic, 0.5 ppm (adult equivalent of 200 ppb) for neurotoxicity in dogs; and chronic, 0.3 ppm (adult equivalent of 200 ppb) for nasal epithelial hyperplasia/degeneration in rats.

b/ n=number of measurements.

Table 27. Margins of exposure for residential exposures to methyl bromide from living near field or commodity fumigation activities.^a

a. At buffer zone perimeter of fumigated fields- Acute exposure						
Field size	Cumulative frequency	Margins of exposure for different emission rates (80-320 lbs methyl bromide /acre-day)				
		80	160	200	225	320
1 acre	0.9 0.95	146 131	138 121	139 121	140 121	142 122
10 acres	0.9 0.95	111 98	120 103	124 106	129 110	152 129
20 acres	0.9 0.95	106 93	115 99	118 101	119 102	122 104
30 acres	0.9 0.95	103 91	115 99	115 98	115 98	113 96
40 acres	0.9 0.95	100 89	110 95	111 95	110 94	107 92
b. Near commodity fumigation facilities						
Type of Application	Acute		Short-term	Sub-chronic	Chronic	
	upper bound (ppb)		mean (ppb)	mean (ppb)	mean (ppb)	
low range	100		78	1	1	
high range	100		39	1	1	

Table 27. Margins of exposure for residential exposures to methyl bromide from living near chamber or field fumigation activities (continued).^a

c. Ambient monitoring in three California counties					
Sites in California	Daily (ppb)	Weekly (ppb)	7-8 weeks (ppb)	Chronic	
Monterey					
Chualar School, Chualar	9292	4294	155	n/a	
La Joya Elementary School, Salinas	1135	631	26		
Oak Avenue School, Greenfield	17355	7625	258		
Pajaro Middle School, Watsonville	695	409	13		
Ambient Monitoring Station, Salinas	3404	2229	78		
Santa Cruz					
Salsepuedes Elementary School, Watsonville	1721	940	38	n/a	
Kern					
Ambient Monitoring Station, Bakersfield	37770	13807	529		
Cotton Research Station, Shafter	827	1264	46		
Mettler-Fire Station, Mettler	87866	42945	1190		
Mountain View School, Lamont	80153	35897	1087		
Shafter-Walker Ambient Monitoring Station	5276	3415	126		
Vineland School District, Bakersfield	71918	38674	1010		

^{a/} Margins of exposure were based on exposure levels in Table 22 and human equivalents of the critical NOELs in Table 18 for each of the durations. The critical NOELs were: acute, 40 ppm (adult equivalent of 21 ppm) for developmental toxicity in rabbits; short-term and weekly, 20 ppm (child equivalent of 7 ppm) for neurotoxicity in rabbits; subchronic and 7-8 weeks, 0.5 ppm (child equivalent of 100 ppb) for neurotoxicity in dogs; and chronic, 0.3 ppm (child equivalent of 100 ppb) for nasal epithelial hyperplasia/degeneration in rats.

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Table 28. Summary of margins of exposure for occupational and residential exposures to methyl bromide.^a

Scenarios	Workers at specific tasks (ppb) ^b				Workers around the use of methyl bromide (ppb) ^c				Residential exposures (ppb) ^d			
	acute	short-term	sub-chronic	chronic	acute	short-term	sub-chronic	chronic	acute	short-term	sub-chronic	chronic
Structural Fumigation												
Houses	Assume > 100 for applicators since SCBA is required. No data on tarp removers				No data				assume 100*	No data		
Field Fumigation												
Shallow-shank	20->1000	42->1000	2-200	n/a	assume 100*	No data		NA	89-131 at 95th%	No data		
Deep-shank	22->1000	40->1000	1-100	n/a								
Commodity Fumigation												
Green-house soil	100*	>1000	NA	NA	No data				100*	39*-78*	1*	1*
Grains	100*	>1000	25->1000	25->1000	No data							
Raisins	100*	67*->1000	1*-100	2*-200	100*	121->1000	2-33	4-67				
Walnut	100*	67*-480	1*-8	5	100*	67*-500	1*	NA				
Brewery	100*	245->1000	NA	NA	NA							
Other Uses	No data				No data							
All Uses												
Ambient air	NA								695->1000	409->1000	13->1000	No data

a/ Data were presented in Tables 24 to 27. n/a=not applicable or exposure data were not available. ">1000" was used as the upper limit for this Table, actual MOEs are indicated in Tables 24 to 27. *= MOE was based on 210 ppb for acute exposure or average daily exposure.

b/ Table 24 for field fumigation and Table 25 for commodity fumigation.

c/ Table 26 for commodity fumigation.

d/ Table 27a for field fumigation, 27b for commodity fumigation, and 27c for ambient air monitoring levels.

V. RISK APPRAISAL FOR INHALATION EXPOSURE

V.A. INTRODUCTION

The human health risk assessment of methyl bromide was conducted for occupational and residential exposures. Risk assessment is the process used to evaluate the potential for human exposure and the likelihood that the adverse effects of a substance will occur in humans under specific exposure conditions. Every risk assessment has inherent limitations on the application of existing data to estimate the potential risk to human health. Therefore, certain assumptions and extrapolations are incorporated into the hazard identification, dose-response assessment, and exposure assessment processes. This, in turn, results in uncertainty in the risk characterization which integrates all the information from the previous three processes. Qualitatively, risk assessments for all chemicals have similar uncertainties. However, the degree or magnitude of the uncertainty can vary depending on the availability and quality of the data, and the types of exposure scenarios being assessed. Specific areas of uncertainty associated with this risk assessment of methyl bromide are delineated in the following discussion.

V.B. HAZARD IDENTIFICATION

The uncertainties associated with the selection of the endpoints and the NOELs have already been discussed in some details (IV.A. HAZARD IDENTIFICATION).

V.B.1. Acute Toxicity

For acute inhalation exposure to methyl bromide, one of the critical NOELs was based on developmental effects observed in rabbits. The assumption was that methyl bromide will also cause developmental toxicity in humans. Epidemiological data were not available to support or refute this assumption for methyl bromide. Comparative studies of other agents showed that laboratory animal data were generally predictive of adverse developmental effects in humans (U.S. EPA, 1991). There are agents which caused developmental toxicity in laboratory animals but have not been clearly shown to be human developmental toxicants. Available human data were too limited to establish cause-effect relationships.

The risk for adults, based on developmental toxicity, may be overestimated because of the approach used to determine the human equivalent NOEL to calculate the margins of exposures. Consistent with the U.S. EPA Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991), the developmental effects (gall bladder agenesis and fused sternebrae) observed at the end of the gestation (after 12 days of exposure) were assumed to be due a single day's exposure. The actual NOEL for a single day's exposure may be higher than that for 12-days of exposure. Furthermore, DPR determined a 24-hour time-weighted average dose by amortizing the NOEL from 6 hours to 24 hours of exposure using Haber's Rule ($C^n \times T = \text{effect}$ where $n=1$). This calculation resulted in an amortized dose that is one-fourth of the 6-hour NOEL and assumed that the dose would remain above the threshold for developmental effects. In an interim toxicology assessment for methyl bromide, the U.S. EPA also used amortization to determine the dose for the same endpoint. The calculated dosage (14 mg/kg/day) was different than the DPR dosage (21 mg/kg/day) because rabbit respiration rates used by DPR (0.54 m³/kg/day) and U.S. EPA (0.37 m³/kg/day) were different (Hansen, 1993;

Lewis, 1995). The NRC in the review of the draft RCD/1999 stated that the amortization method used by DPR was conservative since methyl bromide is likely to be less toxic at lower concentrations over a day (50 ppm for 24 hours) than a higher concentration within a shorter time period (6 hours at 200 ppm) (NRC, 2000). The DPR approach was considered to provide more protection for the residential exposures and not a factor for worker exposures.

On the other hand, a comparison of NOELs for neurotoxicity in the dog and human showed that the extrapolated level may not be an overestimation of the risk. As discussed in the Hazard Identification section (**IV.A. HAZARD IDENTIFICATION**), the human equivalent NOEL for neurotoxicity observed in the dog was 25 ppm for children. This level was comparable to the 21 ppm based on developmental toxicity in the rabbits. For comparison with neurotoxicity in humans, a report of worker exposure showed a LOEL of 35 ppm (Watrous, 1942) (**III.H.1. Occupational Exposure**). In that study, workers experienced anorexia, nausea, and headaches when exposed to an overall methyl bromide concentration of <35 ppm during a 2 week period (Watrous, 1942). If the actual no effect in one day is assumed to be 1/10 of the 35 ppm, then the NOEL would be 3.5 ppm. Using a default factor of 1/10 for intraspecies extrapolation, the regulatory level would be 0.35 ppm (or 350 ppb), a level only 1.5-fold higher than the 210 ppb (21 ppm x 1/10 for interspecies x 1/10 for intraspecies variations) for developmental toxicity used by DPR for regulation. However, there are uncertainties in determining whether the symptoms were associated with acute exposure in the Watrous (1942) study. First, the report did not specify whether the workers had previous exposures to methyl bromide. It is unlikely that inexperienced workers were used since all tasks were manually performed. Second, the report was not specific as to the relationship between actual exposure concentration and duration and symptoms observed. Higher exposures were likely to have occurred in the first week compared to the second week when control measures were instituted. It would have been useful to have individual data on the onset of symptoms as well as measured exposure concentrations for both weeks. Workers with both dermal and systemic effects due to methyl bromide spillage and other accidents, especially during the first week, were likely to be exposed to levels higher than 35 ppm.

Another comparison of the critical acute NOEL is with the OEHHA Hot Spots reference levels (OEHHA, 1999). The current DPR acceptable level for acute exposure is 0.21 ppm, as an average over 24 hours. The equivalent concentration for a one-hour period is 5 ppm. This level is higher than the 1 ppm, one-hour REL for mild effects issued by OEHHA. While the DPR level of 5 ppm may not appear to be protective of human health, there are several considerations that need to be taken into account. RELs are determined by OEHHA for airborne toxicants under the mandate of the Air Toxics "Hot Spots" Information and Assessment Act of 1987 (AB 2588). This program has different objectives and procedures than DPR. For example, OEHHA issues three different RELs, a level protective against mild adverse effects, a level protective against severe adverse effects, and a level protective against life-threatening effects. DPR regulates based on a single level. The basis of the OEHHA one-hour REL of 1 ppm also needs to be considered. The 1 ppm was determined from the Watrous study (1942). As discussed in the previous paragraph, there are several problems with this study. OEHHA assumed that the toxicity experienced by the workers was due to a single exposure to 35 ppm methyl bromide for two hours. It is the opinion of DPR that the systemic effects reported are likely due to cumulative toxicity of these workers with previous exposure to high levels of methyl bromide at the plant before and during the first week of the study. The actual one-hour peak exposure level for mild effects is likely to be higher than the REL of 1 ppm.

V.B.2. Subchronic Toxicity

The endpoints for the critical short-term and subchronic exposures were based on neurotoxicity in the pregnant rabbit (Sikov *et al.*, 1981) and dogs (Newton, 1994b), respectively. Since methyl bromide is a known neurotoxicant, these endpoints are appropriate to use for hazard identification and risk characterization. The severity of the effects (convulsion and paresis) observed in the pregnant rabbits at 70 ppm and death after treatment had stopped suggested that a margin of exposure greater than the conventional benchmark of 100 might have to be considered.

It has been suggested that the decreased responsiveness observed in the dog after 30 exposures to 5 ppm should not be considered a treatment-related effect and is thus not appropriate for use as the critical NOEL for subchronic exposure. This suggestion was based on the assumption that effects after repeated exposure were only related to total dosage. The calculated total dosage for "decreased responsiveness" was less than those for "decreased activity" which was considered a treatment-related effect. DPR considers the analysis an oversimplification of the biological processes involved in the manifestation of the observed effects since the mechanism is unknown. The most important consideration is that the decreased responsiveness was specifically reported by an animal neurologist who had examined all 48 dogs on test previously on two occasions.

V.B.3. Chronic Toxicity

There were uncertainties associated with the use of hyperplasia/degeneration to the nasal cavity as the endpoint to evaluate chronic inhalation toxicity. One uncertainty was the interspecies variability in the nasal cavity between rodents and humans. Compared to humans, the increased complexity of the nasal turbinates, the straighter nasopharyngeal region, and the lower regional flow rates of rats might alter the toxicity at given exposure concentrations (Schreider, 1986). Additional information on the deposition, reactivity, solubility, absorption, metabolism, and clearance of methyl bromide in the nasal cavity epithelium of animals and humans would permit additional consideration of interspecies dosimetric adjustment (Jarabek *et al.*, 1990; U.S. EPA, 1990). Such information would also help define the relative contributions of regional versus systemically absorbed methyl bromide in the etiology of nasal damage.

As already discussed in the **IV.A. HAZARD IDENTIFICATION 2.c. Chronic Toxicity-Inhalation**, the use of the chronic NOEL based on effects in the nasal cavity may underestimate the risk since this NOEL expressed as human equivalents (0.1 ppm) is the same as that for the NOEL based on neurotoxicity after subchronic exposure.

V.B.4. Extrapolation of Estimated No-Effect Level from the Lowest-Effect Level

In this RCD, both the subchronic and chronic NOELs were estimated from the LOEL, the lowest dose tested. It is the DPR policy to use the 10-fold uncertainty factor (UF) to estimate the NOEL from a LOEL. Therefore, the estimated subchronic NOEL was 0.5 ppm based on neurotoxicity observed in two of eight dogs exposed to 5 ppm for 34 exposures. For chronic exposures, the estimated NOEL was 0.3 ppm based on a LOEL of 3 ppm for nasal epithelial hyperplasia and degeneration in the rat.

Instead of using a default 10-fold UF, two approaches have generally been discussed. One approach is to use the NOEL/LOEL ratios from the database. The problem with this approach is that these ratios reflect largely the dose selection of the studies, instead of toxicity. Two examples are provided.

(1) Methyl bromide is lethal to all species and shows a steep dose-response relationship in most cases. In one study, all rats exposed to 220 ppm methyl bromide died (100% mortality) but none died at 100 ppm (Irish, 1940). This implied that the UF could be 2-fold. However, the data also showed that the rats at 100 ppm suffered severe neurotoxicity and some were moribund. Obviously, neither the dose with no mortality can be used as the NOEL for risk assessment, nor can the factor of 2 be used as the UF for this study or other studies.

(2) With the developmental toxicity study (Breslin *et al.*, 1990), the NOEL and LOEL were 40 ppm and 80 ppm, respectively, for increased incidences of gall bladder agenesis and other effects. This also implied a 2-fold UF for extrapolation. On the other hand, the NOEL and LOEL ratio was 10-fold for parental (decreased fertility) and progeny (decreased pup body weights) effects in the reproductive toxicity study (American Biogenics Corp., 1986).

A more appropriate approach is the consideration of the magnitude of the response at the LOEL (Dourson *et al.*, 1996). The 10-fold UF may be excessive if the response rate at the LOEL is marginal or low. On the other hand, the 10-fold UF may not be sufficient when the response at the LOEL is considered severe. If data are sufficient for determining the slope of the dose-response, a benchmark dose approach might be considered for estimating the NOEL.

In the case with the dog study used to derive the critical subchronic NOEL, there was a qualitative dose-response relationship between the exposure duration and concentration and the severity of neurotoxicity (Table 6). However, the magnitude of the response at the lowest dose (5 ppm) can not be compared with those at the higher doses since those experiments were not conducted for the same duration. Therefore, it is appropriate to use the 10-fold default factor as the UF for this study.

For the critical chronic NOEL, there was also a dose-response relationship between the exposure duration and concentration and the severity of the nasal cavity lesions in the rat (Table 8). At the LOEL (the lowest dose tested), the incidence was significantly elevated ($p \leq 0.05$), for both sexes, when compared to that in the controls. However, the lesion was described as very slight. The mildness of the lesion suggested that an UF of less than 10 might be sufficient to estimate the NOEL from the LOEL. While the default factor of 10-fold for the extrapolation was used as per DPR policy, a benchmark dose approach may be considered when guidelines for the use of the approach are established. The NRC in the review of the draft RCD/1999 concurred with the DPR discussion and suggested a factor of 3 (NRC, 2000). However, the NRC also pointed out that the current use of a factor of 10 and a different methodology resulted in reference concentrations (1 ppb and 2 ppb for children and adults, respectively) similar to that (1.3 ppb) determined by the U.S. EPA.

V.C. INHALATION EXPOSURE ASSESSMENT

As discussed in **IV.B. INHALATION EXPOSURE ASSESSMENT**, a limited number of exposure scenarios was assessed. Data were not available for many scenarios as some acute

exposures were assumed to be or limited to 210 ppb (Table 23). The 210 ppb limit was used for exposures of both workers (commodity fumigation) and residents (structural and commodity fumigations). Depending on the factors such as distance and frequency of fumigation, the use of 210 ppb as a default exposure might over- or underestimate the actual acute exposures. However, it could be an over-estimation of exposures for longer durations as it is unlikely that the limit of 210 ppb is reached everyday during the specified period.

Of the available data, there were many deficiencies in the overall database (except for residential exposure to field fumigation and ambient air monitoring). They included: (1) studies not in compliance with Good Laboratory Practices, in particular, absence of field fortification recovery studies; (2) some data are from interim, internal, or draft reports; (3) missing application rate and field fortification recovery information; and (4) lack of duration and frequency of exposure values for some work scenarios. Many exposure data were obtained from studies employing short monitoring periods and then amortized to the 24-hour time-weighted average. These amortized exposure data could overestimate or underestimate the actual exposures. Two potential areas of underestimation were the assumptions that (1) workers of specific work task will not have additional exposure from working in other work task(s) for the remainder of the workday, and (2) there was no overtime work during peak use season. The magnitude of these uncertainties can not be quantified at this time. One area of overestimation was the use of 50% recovery value to adjust all data. In some field studies, the adjustment resulted in more methyl bromide volatilized than was applied.

With respect to specific studies in field fumigation, one uncertainty in the exposure estimates was that they were largely based on studies conducted in an effort to devise equipment modifications to decrease exposure. As such, many of the studies had only one or two measurements. In Subdivision U, U.S. EPA required data for 3 locations and 5 replicates per location for each work task monitored (U.S. EPA, 1986c). But collectively, the data indicated that the modifications were effective in reducing worker exposures. Some of these exposures were further decreased by work hour restrictions in the DPR regulations. In addition, the assessment of acute exposure was based on "upper bound" values as defined in **IV.B.1. Occupational Exposures**. These upper bound values were not true statistical upper bounds because they were based on few measured values and the coefficient (1.645) in the equation was not adjusted for sample size. Nevertheless, these values were higher than the highest values obtained in each study for almost all cases. The use of the highest measured value is a general default approach for acute exposure when the database is limited. For workers involved in commodity fumigation, the sample size was also small (1 to 2 samples) for almost all cases. Since the acute exposure was limited to 210 ppb, the reference level, this sample size problem applied mainly to the short-term, subchronic, and chronic exposure durations. Exposure data from studies conducted in compliance with the DPR regulations are needed.

For residential exposure to field fumigation, there were also uncertainties in the determination of the maximum methyl bromide air concentration distribution along the buffer zone perimeter of fumigated fields (Johnson, 2001). Once applied, methyl bromide levels in the air depend on many factors including wind, air temperature, barometric pressure, and soil conditions. The simulated exposures considered only one variable that is currently amenable to quantification: meteorology. This variable was based on the weather conditions of areas (4 counties) of heaviest methyl bromide use. While the analyses used 7166 inputs representing varied conditions during the 20 years, they may still not accurately represent statewide

conditions. Regional differences in weather conditions may also produce different exposure estimates. However, it is not possible to do extensive monitoring in every region of California because DPR has limited resources, and methyl bromide is used under a wide variety of use, field, and weather conditions. Targeted ambient air monitoring high methyl bromide use areas and computer modeling remain the most cost-effective mean of determining exposure. Additional monitoring by the ARB and the registrant will be used to re-evaluate the exposure. The potential risk from repeated exposures was not addressed due to lack of data. While DPR has implemented regulatory controls to require time and distance separation between fumigations, monitoring data are needed to determine the effectiveness of these measures.

V.D. RISK CHARACTERIZATION

The MOEs for potential acute, subchronic, and chronic exposures were based on NOELs for toxicity observed in laboratory animals. When the NOEL for non-oncogenic effects is based on animal data, a MOE of 100 is generally considered adequate for protection against potential acute or chronic toxicity of a chemical. This benchmark of 100 includes an uncertainty factor of 10 for interspecies extrapolation and a factor of 10 for intraspecies variability. These uncertainty factors assume that the average human is 10 times more sensitive to the effects of a chemical than the most sensitive laboratory animal, and that a sensitive individual is 10 times more susceptible than an average individual (Davidson *et al.*, 1986; Dourson and Stara, 1983).

V.D.1. Interspecies Extrapolation

The sensitivity of humans and laboratory animals to methyl bromide toxicity was difficult to compare because of inadequate exposure information in human case reports. For endpoints such as developmental toxicity and nasal hyperplasia/degeneration, there were no data for these effects in humans. For other endpoints such as death, human exposure levels were generally very high (> 1000 ppm) and the exposure durations were determined by the circumstance of cases and were limited to one individual in most cases. In addition, it is difficult to estimate the exposure since methyl bromide at high concentration tends not to be evenly distributed (Holling and Clarke, 1944). As a result, human case reports can not be used for comparison to the LC100 data from animal testing since the latter were experimentally determined and involved a large number of animals (Table 1). At lower concentrations of methyl bromide, a limited comparison was made with neurotoxicity observed in humans and dogs. In the following example, symptoms in humans appeared to be more severe than those in the dogs under similar exposure concentrations and durations (Table 29). However, a quantitative determination can not be made because of the scarcity of human data.

The current DPR default for interspecies extrapolation is a factor of 10-fold with respect to the dose. The NRC in the review of the draft RCD/1999 agreed with DPR on the use of the 10-fold interspecies uncertainty factor (NRC, 2000). Accordingly, methyl bromide air concentrations were converted to the "dose" by taking into account the exposure concentration and duration, as well as the intake rate (respiration rate) of the exposed population. This approach is similar to that generally used for dietary exposure studies. The no-effect level is expressed as the dose after taking into account the consumption rate, instead of the concentrations in the diet. Thus, the net interspecies adjustment included the interspecies ratio of the intake rate, duration, and the 10-fold uncertainty factor.

Table 29: Comparison of neurotoxicity in humans and dogs.

Dose and duration	Human	Dog
156 ppm for 5 hours		lacrimation (Newton, 1994a)
400 ppm for 24 hours	difficulty in breathing, headaches, nausea, skin rash (Reidy <i>et al.</i> , 1994)	
150 ppm for 8 hours	nausea, vomiting, dizziness; later seizures, headaches, nausea, ataxia, and others (Hustinx <i>et al.</i> , 1993)	
103 ppm for 9 days		↓ activity and emesis (Newton, 1994b)
53 ppm for 14 days		↓ activity (Newton, 1994b)
overall <35 ppm over a 2 week period; onset and duration not specified	anorexia, nausea, headaches, vertigo, and other effects (Watrous, 1942)	

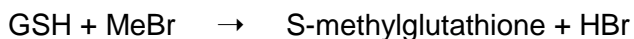
V.D.2. Intraspecies Extrapolation

For intraspecies variation in the response to methyl bromide, the default uncertainty factor of 10 was used because human illness/poisoning reports did not provide sufficient information to derive another factor. In these reports (discussed in **III.H. Neurotoxicity**), some individuals showed more severe symptoms than others. However, this difference in response was not quantified, and may only be quantified in well-conducted experimental studies. The NRC in the review of the draft RCD/1999 agreed with DPR on the use of the 10-fold intraspecies uncertainty factor (NRC, 2000).

Studies on the role of glutathione-S-transferase (GST) in methyl bromide metabolism and toxicity also provided evidence for variations in human response to methyl bromide. The glutathione-S-transferases are a multi-gene family of enzymes involved in the metabolism (activation and detoxification) of a wide variety of chemicals (Eaton and Bammler, 1999). They catalyze the general reaction: $\text{GSH} + \text{R-X} \rightarrow \text{GSR} + \text{HX}$. The mammalian soluble GSTs are divided into 4 main classes, alpha (A), mu (M), pi (P), and theta (T). The role of these enzymes in individual susceptibility to chemical exposure and toxicity is difficult to determine because of the large number of isozymes in the body. Second, GST expression varies among tissues. Not all isoforms are found in every tissue or all species. One important example, with respect to methyl bromide, is GSTT which is found in human erythrocytes but not in rodent erythrocytes. Third, GSTs have been found to be polymorphic in the human population. There are individuals who do not have the gene for certain GSTs. It has been determined that 50% of the Caucasian population do not have GSTM1, and 16% do not have GSTM3. GSTT has been found to be

variable among different ethnic groups. The percentages of the population without the GSTT gene ranged from 9.7% (Mexican-Americans) to 64.6% (Chinese-Americans), as cited by Garnier *et al.* (1996). With GSTP, the different variants of the enzyme are due to the transition mutation of a codon (s) such that other amino acids are substituted.

Methyl bromide has been identified as a substrate for GSTT (Eaton and Bammler, 1999). In 1990, Hallier *et al.* (1990) showed that when human erythrocyte cytoplasm was incubated with methyl bromide, there was a loss of methyl bromide in the gas phase with the formation of S-methylglutathione via an enzymatic reaction. Individuals which showed this activity were designated as “conjugators” while those with activity level comparable to boiled erythrocyte cytoplasm were “non-conjugators”.



This interaction of methyl bromide with sulfhydryl groups has been used in the study of methyl bromide workers. Iwasaki *et al.* (1989) and Goergens *et al.* (1994) showed methylcysteine levels in hemoglobin proteins were higher in some methyl bromide workers compared to controls (Details of these studies are in **III.E.4.**). However, a quantitative relationship between adduct level and exposure was not determined.

There is evidence which shows conjugators, individuals with GSTT, may be more protected than non-conjugators from the genotoxicity of methyl bromide. In the study by Hallier *et al.* (1993), methyl bromide was incubated with whole blood from conjugators and non-conjugators. Lymphocytes from conjugators had lower number (range of 6.51 to 7.95) of sister chromatid exchanges per cell than non-conjugators (range of 10.19 to 13.97). The lower level of SCEs in the conjugators, compared to the non-conjugators, was attributed to the reduced amount of methyl bromide available to interact with lymphocyte DNA because of reaction with erythrocyte proteins mediated by GSTT.

On the other hand, there is evidence that shows methyl bromide reaction with GST may be involved in the manifestation of neurotoxicity. In Davenport *et al.* (1992), GST activity was inhibited in the brain of rats exposed to methyl bromide (details in **III.B.1.**). The GST activity was protected when the rats were either pre- or post-treated with an inhibitor of monohalomethane toxicity. In a report of poisoning of two workers, the non-conjugator had fewer neurotoxic effects when compared to the conjugator (Garnier *et al.*, 1996) (details in **III.H.1. Occupational Exposure**). The formation of S-methylglutathione, via conjugation of methyl bromide with GSH, in the brain of the conjugator was hypothesized to be involved in the neurotoxicity. The non-conjugator also had 2-fold higher concentrations of S-methylcysteine adduct in the erythrocytes; but the reaction was considered non-enzymatic. However, in another report of the same study, the worker designated as a conjugator may have been exposed to higher levels of methyl bromide because of an “inefficient” filter mask (Deschamps and Turpin, 1996).

It is unknown how these results on GST polymorphism and genotoxicity may be extrapolated to cancer susceptibility after methyl bromide exposure. First, there is no association between genotoxicity and oncogenicity of methyl bromide in experimental animals. Methyl bromide has been found to be genotoxic in rodents; yet, long-term studies in rodents have not shown methyl bromide to be oncogenic. Second, the relationship between GST polymorphism on cancer susceptibility remains unclear. While many studies showed a role for

GST enzymes in the detoxification of chemicals, there are few studies on the relationship between GST and cancers (d'Errico *et al.*, 1999); however, most of these studies have limited number of subjects. In the epidemiological studies reviewed, there was no association between GSTT1 polymorphism and the risk of bladder cancer, lung cancer and gastric cancer (d'Errico *et al.*, 1999). When GST polymorphism was combined with smoking as a factor, some reported association with between GSTM1 and GSTT1 null genotypes with the risks of lung, bladder and colon cancers (Strange and Fryer, 1999). However, other studies showed contrary results (Strange and Fryer, 1999). The potential influence of GSTT activity on cancer susceptibility is further complicated by the role of other isozymes of GST and other enzymes in the activation and/or detoxification of the substrate. The combination of GSTM1 null and CYP1A1 rare alleles have been associated with increased cancer risk due to smoking (Fryer and Jones, 1999).

In conclusion, the data show that the interaction of methyl bromide and GST is complex. While the polymorphism of GSTT in the human population is important to consider, it is not possible to conclude that GSTT polymorphism leads to increased susceptibility to methyl bromide toxicity and to determine whether or not the variation is sufficiently addressed by the 10-fold default intra-individual uncertainty factor.

V.E. ISSUES RELATED TO THE FOOD QUALITY PROTECTION ACT

The Food Quality Protection Act of 1996 mandated U.S. EPA to “upgrade its risk assessment process as part of the tolerance setting procedures” (U.S. EPA, 1997b and c). The improvements to risk assessment were based on the recommendations from the 1993 National Academy of Sciences report, “Pesticides in the Diets of Infants and Children” (NRC, 1993). The Act required an explicit finding that tolerances are safe for children. U.S. EPA was required to use an extra 10-fold safety factor to take into account potential pre- and post-natal developmental toxicity and the completeness of the data unless U.S. EPA determined, based on reliable data, that a different margin would be safe. In addition, U.S. EPA must consider available information on: 1) aggregate exposure from all non-occupational sources; 2) effects of cumulative exposure to the pesticide and other substances with common mechanisms of toxicity; 3) the effects of *in utero* exposure; and 4) the potential for endocrine disrupting effects.

In recent documents, U.S. EPA used 3 criteria for the determination of the factor: (1) completeness and reliability of the toxicology database, (2) completeness and reliability of the exposure database, and (3) potential pre- and post-natal toxicity (U.S. EPA, 1999 a, b, and c). The latter criterion requires the consideration of evidence for developmental and reproductive toxicity, and developmental neurotoxicity.

V.E.1. Pre- and Post-natal Sensitivity

In recent years, issues have been raised on the adequacy of the risk assessment process to address the potential increased sensitivity of infants and children to pesticides. The basis of this concern was discussed in detail in the 1993 National Research Council report: *Pesticides in the Diets of Infants and Children* (NRC, 1993). In the 1994 DPR report: *A Joint Review of Existing Federal and State Pesticide Registration and Food Safety Programs* (also known as the PECC report), the PECC recommendation was to address the susceptibility issue on a case-by-case basis when specific data become available (DPR, 1994). A review of recent time-limited tolerances for pesticides showed that U.S. EPA generally applied an additional

uncertainty factor of 10 for an incomplete database where one or more FIFRA required reproductive or developmental toxicity studies were not available. An additional uncertainty factor of 3 (MOE of 300) was used when the NOEL for developmental or reproductive effects was lower than that for maternal toxicity, or when there was no developmental neurotoxicity study. The criteria for the developmental toxicity testing included findings of teratogenicity to the central nervous system, neuropathology and neurotoxicity, hormone-like activity, and developmental toxicity (for effects other than structural abnormalities of the CNS) (Levine and Butcher, 1990). USEPA recently proposed that a development neurotoxicity study be included in the core toxicology data set (U.S. EPA, 1998c).

There was some evidence for increased sensitivity to the prenatal and post-natal toxicity of methyl bromide when NOELs for developmental or reproductive toxicity were compared with those for maternal toxicity. In the rabbit developmental toxicity study, the NOEL was 20 ppm for both effects in the fetus and neurotoxicity in the dam (Breslin *et al.*, 1990b). However, it should be noted that the neurotoxicity was observed toward the end of the experiment while effects on the fetus were likely to have occurred earlier during organogenesis. In the developmental study conducted with rats, increased incidence of delayed skull ossification was reported in rat fetuses with a NOEL of 20 ppm compared to a NOEL of >70 ppm for maternal toxicity (Sikov *et al.*, 1981). In the rat reproductive toxicity study, the NOEL was 3 ppm for reduced fertility in the F2b mated rats and for effects in the pups (decreased pup body weights and organs weights) (American Biogenics Corp., 1986). It is not known whether the reduced fertility in these F2b rats was due to exposure as adults or a manifestation of effects from previous *in utero* exposure (as fetuses from the F1 mating).

There may be a potential for increased sensitivity of infants and children to the neurotoxicity of methyl bromide based on consideration of the maturity of the central nervous system. In the young, the central nervous system is not fully developed at birth. Neuron proliferation and migration, blood-brain barrier, synaptic connections, as well as receptor and transmitter systems development continue after birth and into childhood (Rodier, 1995). Furthermore, there is a difference in the maturity of the brain development between laboratory animals and humans (Hoar and Monie, 1981; Dobbing and Sands, 1973). At birth, the rat brain is considered to be more developed than the human brain.

The potential impact of methyl bromide on the developing nervous system has not been evaluated. The toxicity studies for methyl bromide have only been conducted with adult animals and a developmental neurotoxicity study is not available. There is one case report in humans which showed that methyl bromide is more toxic to the young. In an acute exposure to methyl bromide in a home, an infant died while the parents recovered without apparent neurological deficits (Langard *et al.*, 1996). It is not known whether the severity of the effects on the infant was from increased exposure due to physiological differences (*i.e.* increased respiration rates) or increased sensitivity. Another concern is the potential cumulative toxicity from low level exposure to methyl bromide. As discussed in **IV.A.1.b. Neurotoxicity**, the dogs with prior exposure to relatively nontoxic level of methyl bromide (11 ppm) showed decreased activity earlier than those with no previous exposure when both groups were exposed to similar methyl bromide levels (156-158 ppm).

In this risk assessment for methyl bromide, inter-individual differences were accounted for by an uncertainty factor of 10. Given that methyl bromide is a potent neurotoxicant and there

are inadequate toxicity information for infants and children, it may be prudent to consider an additional uncertainty factor to address the potential increased sensitivity for these population subgroups. However, the NRC in the review of the draft RCD/1999 concluded that the available database was sufficient to identify appropriate NOELs for risk characterization (NRC, 2000). Furthermore, the NRC indicated that this additional uncertainty factor was not necessary since the DPR selected NOELs for risk characterization were adequately conservative.

V.E.2. Aggregate Exposure

There could be a potential for aggregate exposure from occupation or residential exposures and dietary exposures. The risk characterization for aggregate exposure is in Volume III.

V.E.3. Cumulative Toxicity

Since the mechanism of methyl bromide toxicity is possibly due to alkylation of reactive groups, there is potential cumulative toxicity between methyl bromide and other chemicals with such a general mechanism of toxicity. The approach to address the cumulative risk of chemicals is being discussed by the U.S. EPA Scientific Advisory Panel. The main focus of the discussion at this time is the toxicity of organophosphate pesticides.

V.E.4. Endocrine Effects

Based on the studies reviewed, methyl bromide has not been shown to cause endocrine disruption effects.

VI. CONCLUSIONS FOR INHALATION EXPOSURE

The human health risk from potential inhalation exposure to methyl bromide was evaluated in this Volume I of Risk Characterization Document. The critical toxicity endpoints were derived from experimental animals: developmental toxicity for acute exposure, neurotoxicity for short-term and subchronic exposures, and tissue damage to the nasal cavity for chronic exposures. For acute and chronic exposure endpoints, neurotoxicity was also considered in the determination of the critical NOELs. The risks, expressed as the margins of exposure, were calculated for workers and residents involved or living in the vicinity of structural, field and commodity fumigations. Generally, a MOE of at least 100, which takes into account the possibility of 10-fold variations in susceptibility within the human population as well as between laboratory animals and humans, is considered adequate to protect humans from the effects of concern. Exposure scenarios with MOEs of less than 100 should be considered in the risk management process.

With structural fumigation, the acute MOEs for workers and residents were assumed to be at least 100 based on restrictions in the DPR regulations. However, data are needed to estimate actual exposures for acute and short-term exposures for workers and residents.

For field fumigation, the acute MOEs for workers were at or greater than 100 because of the most effective equipment modifications and work hour restrictions were placed in DPR regulations. However, there were work tasks with acute and short-term MOEs of less than 100 which are not specifically excluded in the regulations. They were: disc driver (acute MOE of 22, deep shank injection), and tractor drivers and basket-men in tarp removal (acute MOE of 20-21, tarp shallow with Noble plow shanks). For subchronic exposure, most of the worker tasks had MOEs of less than 100; many were less than 10 and included applicators, copilots, disc drivers, and tarp removers. The MOE for workers at adjacent fields was assumed to be 100 since they work outside of the buffer zone. Actual data are needed to verify this assumption as analyses for the effectiveness of buffer zones showed MOEs of less than 100 for some applications (in particular large fields and certain emission rates). For residents living at the buffer zone perimeter of fumigated fields, the acute MOEs were generally around 100 for the 95th percentile exposure except for a MOE of 91 for 30 acres and 80 lbs emission rate, and MOEs of 89-95 for 40 acres and all emission rates. The acute MOEs were generally greater than 100 at the 90% percentile exposure. No assessment was conducted for repeated exposures.

For commodity fumigation, the acute MOEs for workers involved in fumigation were at 100 because DPR regulation set work hour restrictions to limit the maximum exposure at 210 ppb. The actual MOEs were likely higher as the upper limit may not be reached in some scenarios. The short-term MOEs were greater than 100 for all work tasks based on actual measurements; the only exception was a MOE of 67 for the task of cleaning plant. The MOE was also 67 when the daily exposure was set at 210 ppb for raisin (clear chamber) and walnut (vacuum chamber) workers. The subchronic and chronic MOEs were generally less than 100 based on measured values and exposures amortized from 210 ppb.

For workers doing other tasks in commodity fumigation facilities, the acute MOEs and many of the short-term MOEs were at or greater than 100. The only exception was the short-term MOE of 67 for workers at the sorting or packaging areas and their exposures were based on 210 ppb as daily exposure. The subchronic and chronic MOEs for all workers were at or less

than 67. Additional data are needed to characterize the exposures of these workers at the facilities. For residents living near fumigation facilities, the MOEs for all durations were based on 210 ppb used for acute exposure, and not actual measurements. The MOEs were between 1 and 78 for short-term, subchronic and chronic exposures.

The ambient air monitoring of three counties in California showed acute and short-term MOEs greater than 400. However, the 7-8 week MOEs were less than 100 (MOEs of 13 to 78) in some locations. Additional monitoring are being conducted to better characterize these exposures.

This risk assessment concluded that human inhalation exposure to methyl bromide resulted in margins of exposure of greater than 100 in some scenarios but less than 100 in other scenarios. The significance of these MOEs need to be viewed in the context of the limitations and uncertainties discussed. Many scenarios were based on exposure data with few samples or assumed exposure levels (i.e. 210 ppb for acute exposure). There were also scenarios which were not addressed in this document. Additional exposure data are needed to better characterize the exposure. In addition, the overall risk from methyl bromide exposure should consider the risks from other exposure routes. The risk characterization of dietary exposure and aggregate exposure is in Volumes II and III, respectively.

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VIII. ATTACHMENTS

ATTACHMENT A
PRELIMINARY RISK ASSESSMENT

M e m o r a n d u m

To : Jim Wells
Director

Date : February 11, 1992

Place : Sacramento

4-1285

From : Department of Pesticide Regulation - Larry Nelson, Chief
Medical Toxicology Branch

Subject : Methyl Bromide Preliminary Risk Characterization

We have completed a preliminary risk characterization of methyl bromide to evaluate the significance of ambient air levels resulting from structural fumigation and agricultural uses. Attached are evaluations, conducted by the Branch, which provide the specifics of our analysis.

Results indicate inadequate margins of safety exist from methyl bromide exposure for both existing uses.

Attachment

Memorandum

To : Larry Nelson, Chief

Date : February 11, 1992

via Keith Pfeifer, Senior Toxicologist

Place : Sacramento, CA

From : Department of Pesticide Regulation Lori O. Lim
Staff Toxicologist

Subject : Methyl Bromide- Preliminary risk assessment for inhalation exposure in structural fumigation

INTRODUCTION

Methyl bromide is used in structural, soil, and commodity fumigation. In 1991, more than 60 products as technical material or formulations were registered in California. The major registrants are Ameribrom, TriCal Soil Chemical Corp., Ethyl Corp., and Great Lakes Chemical Corp. The use of methyl bromide has been increasing in the last 5 years. The amount applied doubled from 10 million pounds in 1986 to over 20 million pounds in 1991.

The current label for the use of methyl bromide in domestic dwellings specifies re-entry at an air concentration below 5 ppm. However, there were two Section 24 (c) SLN issued in 1990 for scale broom roots in buildings (CA-900033 and CA-900045) where the re-entry level should not exceed 30 ppb. This level was recommended by Worker Health & Safety Branch based on the NOEL of 3 ppm from the rat reproductive study to achieve a Margin of Safety (MOS) of 100.

Since its use commercially, worker illnesses have been reported as early as 1899 (von Oettingen, 1946). Dermal exposure to high concentrations of methyl bromide results in vesication and swelling of the skin (Butler, et al., 1945 and Jordi, 1953). Signs and symptoms of methyl bromide from inhalation exposure are dependent on the amount and duration of exposure (Greenberg, 1971; Gehring, et al., 1991). Mild and chronic exposure results in polyneuropathy which may be reversible. Acute exposure to high concentrations results in: malaise, headache, visual disturbances, nausea, and vomiting. There is a delayed onset of symptoms indicative of central nervous system involvement: numbness, ataxia, tremor, convulsion, and coma. Death is usually due to pulmonary edema leading to respiratory failure or cardiovascular collapse.

In a study of workers in a repackaging plant where the methyl bromide was estimated to be less than 35 ppm (or approximately 12 mg/kg-day), clinical symptoms of anorexia, nausea, headache, vertigo, abnormal sleepiness were reported (Watrous, 1942).

ACUTE EXPOSURE

In animal studies, acute exposure to methyl bromide resulted in central nervous system depression and loss of righting reflex (Honma, et al., 1985) and decreased body weight gain (Honma, et al., 1985; Alexeeff and Kilgore, 1985). At higher concentrations, there were decrease in body temperature, lethargy (Honma, et al., 1985; Alexeeff and Kilgore, 1985), excitability (Irish, et al., 1940), and paralysis (Irish, et al., 1940). The alteration in body temperature, anorexia resulting in lower body weight gain, and inactivity has been attributed to methyl bromide inhibition of tyrosine hydroxylase activity (Honma, et al., 1991). Developmental toxicity studies indicate that methyl bromide is a developmental toxin in the rat and rabbit (Breslin, et al., 1990; Sikov, et al., 1981).

The lowest acute NOEL was 40 ppm (155 mg/m³) from the rabbit teratology study (Breslin, *et al.*, 1990). The endpoints (30 ppm, or 310 mg/m³) (in the fetus) were omphalocele, hemorrhaging with or without hydrops, retroesophageal right subclavian artery, gall bladder agenesis, fused sternbrae and decreased fetal body weights. The duration adjusted dosage (amortized over 24 hrs exposure, 7 days per week, and respiration rate of ~~960~~ ⁵⁴⁰ L/kg/day) for the NOEL is 21 mg/kg-day.

Based on the NOEL of 21 mg/kg-day and the exposure at the re-entry level of 5 ppm, the margin of safety for human exposure is 4 and is inadequate. Generally, when animal data is used, an MOS of 100 is considered adequate. Although teratogenic endpoints are only relevant for women of child-bearing age, the assumption that all other population subgroups are as sensitive results in MOSs that protect the health of other population subgroups.

<u>Subgroup</u>	<u>Breathing rate</u> <u>m³/kg-day</u>	<u>Human equivalent</u> <u>NOEL (ppm)</u>	<u>MOS</u>
Adult	0.26	21	4

SUBCHRONIC EXPOSURE

After structural fumigation, the residents of the houses can potentially be exposed to methyl bromide for a short term as it is released from the structure and furnishings.

In animal studies, inhalation exposure to methyl bromide subchronically resulted in tissue degeneration (Hurtt, *et al.*, 1987), lung lesions (Irish, *et al.*, 1940), decreased body and organ weights (American Biogenics Corp., 1986), reduced fertility (American Biogenics Corp., 1986), fetal variations (Sikov, *et al.*, 1981; Breslin, *et al.*, 1990), and neurotoxicity and convulsions (Irish, *et al.*, 1940; Breslin, *et al.*, 1990; Sikov, *et al.*, 1981; NTP, 1990).

The lowest NOEL was 20 ppm (78 mg/m³, adjusted dosage of 12 mg/kg-day) for neurotoxicity (convulsion, paresis, and death) observed in rabbits exposed to methyl bromide for more than 1 week (Sikov, *et al.*, 1981). Neurotoxicity after methyl bromide exposure has also been reported in the monkey (NOEL of 13 mg/kg-day), mouse (NOEL of 31 mg/kg-day), and in another rabbit study (NOEL of 21 mg/kg-day).

The reproductive study used previously in the SLN application is not used in this assessment because the effects were not observed until after more than 100 days of treatment. The re-entry level is evaluated based on a shorter duration of exposure for normal fumigation as compared to subfloor methyl bromide injection which demonstrated air levels > 30 ppb for up to 21 days post treatment.

Based on the NOEL of 12 mg/kg-day and the exposure at the re-entry level of 5 ppm, the margins of safety for human exposure are inadequate. Again, an MOS of 100 is generally considered adequate.

<u>Subgroups</u>	<u>Breathing rate</u> <u>m³/kg-day</u>	<u>Human equivalent</u> <u>NOEL (ppm)</u>	<u>MOS</u>
Adult	0.26	12	2
Child	0.46	7	1

RECOMMENDATION

As indicated in this preliminary assessment, the current re-entry level of 5 ppm does not provide adequate margins of safety. Based on the subchronic exposure of children, the highest potential exposure population subgroup, an air concentration not to exceed 60 ppb in 24 hours is needed to provide an MOS of 100.

M e m o r a n d u m

To : Larry Nelson, Chief
Medical Toxicology Branch

Date : February 11, 1992

via Keith Pfeifer, Senior Toxicologist *Keith Pfeifer*
Health Assessment Section

Place : Sacramento

From : Department of Pesticide Regulation *Nu-may Reed*
Nu-may R. Reed
Staff Toxicologist

Subject : Acute exposures to airborne Methyl Bromide

The potential health effects of airborne methyl bromide was re-evaluated.

Background Information

A report documenting air monitoring data by the Air Resources Board (ARB) under the mandate of AB1807 was received by Medical Toxicology Branch in November, 1990. Using these data, a preliminary risk assessment was initially conducted in December, 1990. Based on the toxicological data available at the time, an interim NOEL of 90 ppm (6 hr/day; 5 days) established in a rat subchronic study (DPR Vol. 123-109) was used in the assessment. The margin of safety (MOS) ranged from 104 (child) to 185 (adult). The toxicological database has since been updated.

In a recent evaluation of the potential health hazards associated with the label-approved use for structural fumigation, the staff established an inhalation NOEL to evaluate acute exposure scenarios. Consequently, the potential health hazard associated with the occurrence of methyl bromide in the air was re-assessed.

Air monitoring data

The air monitoring for field application was conducted in Monterey county, at town sites and sites adjacent to the application field (off-site). Air samples were also taken after enclosure fumigation in Stockton. The results are given in the attached Summary table from the ARB report.

Based on this report, the air concentrations of 1.1 ppb (Minimum Detection Limit, MDL) and 450 ppb were used for assessing the exposures for town sites and off-sites, respectively. The 450 ppb was the average air concentration for an approximately 24-hour period (Sept. 12, 9:45 am to Sept. 13, 1:15 pm), based on three 3-hour measurements for site 3 at Fennell farm (67 meter from the edge of an application site). A summary table (ARB report, Table 3) of the air measurements at this site is also attached. The highest single measurement at the Stockton sites was 1.6 ppb.

Toxicological data

The acute inhalation NOEL was established at 21 ppm for women of child-bearing age. These values were calculated from the NOEL of 21 mg/kg/day (40 ppm; 6 hr/day), for developmental effects established in a rabbit teratology study. Using this NOEL to evaluate the risk of women of child-bearing age will provide the lowest MOS among all population subgroups. The supporting

toxicological database is presented in greater detail in the memo from Lori Lim to Larry Nelson (February 11, 1992) concerning structural fumigation.

Risk Characterization

Based on the human NOEL of 21 ppm and the ARB monitoring data, the margins of safety (MOSs) for the Monterey county town sites (air concentration at the MDL of 1.1 ppb) and sites at Stockton (highest concentration at 1.6 ppb) are at least 13,000 and indicate no potential health concern. The MOS for the acute off-site exposures at 450 ppb is 47. An MOS of 100, based on a NOEL established in animal studies, is generally considered adequate. The off-site air measurement, taken 67 meters from the edge of an application site, represents a realistic exposure scenario, since no buffer zone is currently required for methyl bromide field application.

Recommendation

Reduction of the air levels to an equivalence of 210 ppb for 24 hours would result in an MOS of 100, which is generally considered adequate based on a NOEL established in animal studies.

Attachment

Attachment Summary tables of ARB's air monitoring report

Summary Table

Summary of Air Concentrations of Methyl Bromide in Parts Per Billion Volume

(4-hour samples collected in September and October 1986)

Monitoring Site	Maximum Positive ^a	Second Highest Positive ^a	Average All Samples above MDL	Total # of Samples	# Above MDL ^b
Aromas	<MDL	<MDL	<MDL	48	2
Elkhorn	<MDL	<MDL	<MDL	46	0
Flax Market	<MDL	<MDL	<MDL	48	0
M. P. Hospital	<MDL	<MDL	<MDL	42	0
Pannell Farms ^c					
Site A	210	52	76.8	22	8
Site B	900	280	111	38	25
Site C	530	110	59.4	36	20
Stockton	1.6	0.92	1.0	87	3

^aAverage of two replicates, rounded to two significant figures.

^bMDL = minimum detection limit (1.1 ppb; 0.5 ppb for Stockton samples).

^cSites A-C were adjacent to a strawberry field application.

Table 3. METEOR BROMIDE AT FARNELL FARMS APPLICATION SITE
(average values)

DATE	START TIME	(µg/Cu m) SITE				(P.P.B.) SITE		
		A	B	C		A	B	C
=====								
9/11/86	7:10		197				51	
	8:54	200				52		
	11:25		254				73	
	11:37			422				110
	13:30	< 4.2				< 1.1		
9/12/86	6:20		< 4.2				< 1.1	
	6:23			< 4.2				< 1.1
	7:00	800				210		
	9:45		1100				250	
	10:15			325				84
	10:57	< 4.2				< 1.1		
	13:02		3500				900	
	13:30			2060				330
9/13/86	10:15		662				170	
	10:45			400				100
	13:45		409				110	
	14:18			275				70
9/14/86	8:45		29				23	
	8:50			29				7.0
	9:18	< 4.2				< 1.1		
	12:50		621				160	
	13:30			212				55
9/15/86	7:00		< 4.2				< 1.1	
	7:25			< 4.2				< 1.1
	7:55	157				41		
	11:12		230				39	
	11:38			52				16
	11:59	< 4.2				< 1.1		
	13:25		315				31	
	13:45			215				55
	19:46		449				116	
	20:02			122				42
9/16/86	7:22		< 4.2				< 1.1	
	7:52			< 4.2				< 1.1
	8:16	17				4.0		
	11:19		< 4.2				< 1.1	
	12:29			< 4.2				< 1.1
	12:55	< 4.2				< 1.1		
	17:05		50				12	
	17:26			4.2				< 1.1
9/17/86								

Table 8 (con't). ~~METHYL~~ BROMIDE AT FENDALL FARMS APPLICATION SITE
(average values).

		(Hq/Cu m)			:	(P.P.E.)		
		SITE			:	SITE		
DATE	START TIME	A	B	C	:	A	B	C
=====								
	9:47			< 4.2	:			< 1.1
	10:11		< 4.2		:		< 1.1	
	10:36	< 4.2			:	< 1.1		
	14:16			< 4.2	:			< 1.1
	15:22		38		:		10	
9/18/86					:			
	8:56	< 4.2			:	< 1.1		
	9:36		< 4.2		:		< 1.1	
	9:59			< 4.2	:			< 1.1

Attachment B

METHYL BROMIDE

Department of Pesticide Regulation

California Environmental Protection Agency

March 7, 1994

This document is prepared for the Developmental and Reproductive Toxicant Identification Committee for the consideration of methyl bromide as a developmental toxicant under Proposition 65.

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METHYL BROMIDE

I. INTRODUCTION

Methyl bromide is a restricted use pesticide for pest control in structural, soil, and commodity fumigations. In 1991, more than 60 products containing methyl bromide were registered and more than 18 million pounds were used in California (DPR, 1991). Since methyl bromide is acutely toxic at low concentrations, chloropicrin, a lacrimator, is added to some of the methyl bromide formulations as a warning agent.

In 1991, the Methyl Bromide Industry Panel submitted the rabbit developmental toxicity studies conducted by Breslin *et al.* (1990a and 1990b) as required by the California Birth Defect Prevention Act of 1984 (Senate Bill 950). The studies were reviewed by the Medical Toxicology Branch of the Department of Pesticide Regulation (DPR). Significant developmental effects (gall bladder agenesis, fused sternebrae, and decreased fetal body weights) were identified and a No-Observed-Effect Level (NOEL) of 40 ppm was established. This NOEL was used to evaluate the reentry level of 5 ppm established for structural fumigation, and resulted in the conclusion that the reentry level did not provide an adequate margin of safety. In addition, monitoring studies conducted by the DPR's Worker Health and Safety Branch showed that, after structures were cleared for re-occupancy and windows and doors were closed, methyl bromide levels tended to rise above the 5 ppm level. Several days were required for complete dissipation. A preliminary risk assessment was conducted to determine the acceptable level of acute exposure for humans. Using the NOEL from the rabbit developmental study (Breslin *et al.*, 1990b), the acceptable level for acute exposure was calculated to be 210 ppb with a margin of safety of 100. Even though in the developmental study the exposure was continuous during a selected period during gestation (e.g. from gestation days 7 to 19), the assumption is that only a single exposure at a critical time is necessary for the induction of developmental adverse effects according to the U.S. Environmental Protection Agency (USEPA) Guidelines for Developmental Toxicity Risk Assessment (USEPA, 1991).

DPR promulgated emergency regulations which required a longer aeration period after fumigation, and required pest control operators to hand out a fact sheet explaining the potential hazards of methyl bromide fumigation. The fact sheet was prepared by DPR in consultation with the Office of Environmental Health Hazard Assessment (OEHHA), California Department of Health Services, and USEPA. A summary of the animal toxicology was included in the fact sheet describing the effects to the central nervous system, eyes, respiratory system, and fetal development. The section on fetal development is reproduced below:

"In recent animal studies, methyl bromide caused birth defects when pregnant animals were exposed under experimental conditions. There is no evidence that methyl bromide affects human reproduction, although some chemicals which cause birth defects in animals may also cause birth defects in humans. Any person, including pregnant women, should avoid unnecessary exposure."

A similar warning for developmental effects was subsequently required by USEPA on methyl bromide product labels used for structural fumigation. On January 1, 1993, methyl bromide was administratively listed as a developmental toxicant by OEHHA under Proposition

65. The Proposition 65 statute requires the listing of a chemical when the state or federal government has formally required the labeling or identification of the chemical as a carcinogen or a reproductive toxicant. Warning would have been required for all uses of methyl bromide as of January 1, 1994.

An administrative petition from the growers and users of methyl bromide to rescind the listing of methyl bromide was submitted and subsequently denied by OEHHA in October, 1993. A Safe Use Determination (SUD) was requested by the Alliance of the Methyl Bromide Industry. A workshop on the SUD was conducted on November 30, December 1, and a public hearing was held on December 20, 1993. On December 21, 1993, OEHHA modified the listing from "methyl bromide" to "methyl bromide as a structural fumigant". The broader question of whether methyl bromide should be listed for all uses was to be referred to the Developmental and Reproductive Toxicant Identification Committee of the OEHHA Science Advisory Board.

II. TOXICOLOGY PROFILE

The following is a brief discussion of the pharmacokinetic and toxicity studies of methyl bromide in humans and in laboratory animals. Pharmacokinetic studies with ^{14}C -methyl bromide showed that methyl bromide equivalents are distributed to all tissues in the body. Acute, subchronic, and chronic studies showed toxic effects in multiple organs. After methyl bromide inhalation exposure, neurotoxicity has been reported in humans, rats, mice, rabbits, guinea pigs, and monkeys. Specific studies which showed developmental and reproductive effects are presented in section **III. DEVELOPMENTAL AND REPRODUCTIVE TOXICITY**. Additionally, genotoxicity studies which showed that methyl bromide is a direct acting mutagen and that it can alkylate DNA and proteins are also presented in this section.

A. Pharmacokinetic studies

After inhalation, intraperitoneal, and oral routes of administrations, methyl bromide (^{14}C -methyl bromide) is rapidly absorbed and radioactivity is detected in all tissues (Medinsky *et al.*, 1985; Bond *et al.*, 1985; Jaskot *et al.*, 1988; Raabe, 1986, Raabe, 1988; Medinsky *et al.*, 1984). After inhalation exposure, the percentages of administered doses absorbed were similar in several species; 48% in the rat, 40% in the dog, and 51-55% in human. In the rat, the highest levels in the tissues, principally in the lungs, were reached immediately after exposure. Following oral or intraperitoneal administration, the highest levels of radioactivity were found in the liver and kidneys of the rat. Methyl bromide was extensively biotransformed into unidentified products and carbon dioxide. In the rat within 1 hour after exposure, less than 10% of the radioactivity in the tissues was intact methyl bromide. Carbon dioxide accounted for almost 50% (inhalation and intraperitoneal routes), and 30% (oral route) of the radioactivity excreted in the exhaled air. After inhalation exposure, the percent of absorbed doses excreted in the air and urine were much lower in the human study than those found in the rat study. The difference may be due to the time when samples were taken. In the human study, the samples were taken after only 0.5 hour of clearance and not at steady state. The primary routes of excretion were the exhaled air for inhalation and intraperitoneal exposures, and the urine for the oral route of administration. After oral administration, there was reabsorption of biliary metabolites of methyl bromide from the gut.

B. Toxicity Studies

1. Humans

The primary route of exposure to methyl bromide by the general population and workers is via inhalation. In California, there were 148 illness associated with methyl bromide reported in 1982 through 1990 (Worker and Health Safety Branch, 1993). In the work place, systemic illnesses in the workers are generally due to equipment failure or other accidents. For the general population, exposure is due to drift or leakage of methyl bromide from fumigated fields, chambers, or homes; or due to residual levels of methyl bromide in fumigated homes. The general population also may be exposed to methyl bromide by dietary exposure from ingestion of fumigated commodities. However, the residue levels are relatively low or below the analytical detection limit.

Signs and symptoms in humans from inhalation exposure to methyl bromide are dependent on concentration and exposure duration (von Oettingen, 1946, Rathus and Landy, 1961; Greenberg, 1971; Grant, 1974; Anger *et al.*, 1986; Gehring *et al.*, 1991). Acute exposure to lethal concentrations results in early symptoms of malaise, headache, visual disturbances, nausea, and vomiting. Later symptoms include delirium, convulsions, and respiratory failure or cardiovascular collapse leading to death. Nonlethal exposures result in neurological effects similar to the early symptoms for fatal exposure. Symptoms may persist after exposure, depending on the severity of the toxicity. Dermal exposure of workers to concentrated methyl bromide as a liquid results in vesication and swelling of the skin (Butler *et al.*, 1945; Jordi, 1953; Zwaveling *et al.*, 1987).

Recently, Hallier *et al.* (1993) showed that there is a polymorphism in human blood for glutathione-S-transferase activity directed at methyl bromide. Of the individuals studied, 75% of them are considered conjugators; that is, there was an apparent enzyme-mediated disappearance of methyl bromide when their erythrocyte cytoplasm was incubated with methyl bromide and glutathione. Individuals whose blood did not show such a reaction are called non-conjugators. The conjugation reaction is apparently a detoxification mechanism because the levels of sister chromatid exchanges in the peripheral lymphocytes of non-conjugators were increased by approximately two-fold over untreated control levels when their whole blood was incubated in the presence of methyl bromide. Under identical testing conditions, lymphocytes from conjugators showed little or no increase in their levels of sister chromatid exchanges.

2. Laboratory Animals

a. Acute Toxicity

Methyl bromide is a Toxicity Category I compound because of its acute inhalation toxicity (Federal Register, 1991). The lethal air concentrations for 100% death (LC100) are 220 ppm for rats after 26 hours (Irish *et al.*, 1940), 220 ppm for rabbits after 32 hours (Irish *et al.*, 1940) and 490 ppm for guinea pigs after 8 hours (Sayers *et al.*, 1929), compared to 1583 ppm for humans after 10-20 hours (USEPA, 1986).

The nonlethal effects in laboratory animals exposed acutely to methyl bromide involve multiple organs. These effects include alteration in glutathione transferase activity,

catecholamine levels, and tyrosine hydroxylase activity (Jaskot *et al.*, 1988; Davenport *et al.*, 1992; Honma *et al.*, 1987, Honma *et al.*, 1991). Tissue damage has been found in the lungs, nasal cavity, brain, kidneys, testes, and adrenal glands (Irish *et al.*, 1940; Hurtt *et al.*, 1987; Hurtt *et al.*, 1988; Hurtt and Working, 1988; Hastings, 1990; Sayers *et al.*, 1929). Clinical signs of neurotoxicity include ataxia, paralysis, tremor, and convulsion (Hurtt *et al.*, 1987; Irish *et al.*, 1940; Alexeeff and Kilgore, 1983 and 1985; Sayers *et al.*, 1929). Signs of acute oral toxicity include prostration, increased heart rate, lesions in multiple organs including the stomach and brain, hypoactivity, hypothermia, and death (Naas, 1990).

b. Subchronic Toxicity

Subchronic inhalation exposure of laboratory animals to methyl bromide also results in neurotoxicity, tissue degeneration (such as brain, nasal cavity, heart, adrenal glands, thymus, spleen, kidneys, and testes), and death (Irish *et al.*, 1940; NTP, 1992; Eustis, 1992; Eustis *et al.*, 1988; Kato *et al.*, 1986; Drew, 1983; Anger *et al.*, 1981). Based on overt signs of neurotoxicity, the rabbit was more sensitive than other species to methyl bromide; and the sensitivity in decreasing order is rabbit > monkey > guinea pig > rat (Irish *et al.*, 1940). For subchronic oral exposure, the primary finding was hyperplasia in the forestomach (Danse *et al.*, 1984; Boorman *et al.*, 1986; Hubbs, 1986).

c. Chronic Toxicity and Oncogenicity

The nasal cavity, brain, and heart were also target organs in rodents after chronic inhalation exposure to methyl bromide. Olfactory epithelial damage (hyperplasia, metaplasia, and necrosis) and myocardial degeneration were observed in rats and mice (Reuzel *et al.*, 1987 and 1991; NTP, 1992; Eustis, 1992). Cerebellar and cerebral degeneration was detected in mice (NTP, 1992; Eustis, 1992).

3. Genotoxicity Studies

Methyl bromide was mutagenic in in vitro mutation assays and was a base-pair substitution mutagen in the Salmonella assays (Simmon *et al.*, 1977; Kramers *et al.*, 1985; Moriya *et al.*, 1983; NTP, 1992; Eustis, 1992). It is considered a direct acting mutagen since liver S-9 fraction was not required for mutagenicity (Kramers *et al.*, 1985; NTP, 1992; Eustis, 1992). There was micronuclei formation in the female mice (NTP, 1992 and Eustis, 1992) and increased frequency of sister chromatid exchanges in CHO cells, mouse bone marrow cells in vivo, and lymphocytes (Rounds, 1980; NTP, 1992; Eustis, 1992; Garry *et al.*, 1990). Methyl bromide did not induce unscheduled DNA synthesis in rat hepatocytes, or cause sperm abnormalities in mice (Kramers *et al.*, 1985; McGregor, 1981).

Methyl bromide is a direct-acting alkylating agent. In vivo exposure of rats and mice to methyl bromide resulted in the alkylation of tissue DNA. After exposure to methyl bromide by either inhalation or intraperitoneal routes, 7-methylguanine in liver and spleen DNA, as well as methylated cysteine in hemoglobin and liver protein, were detected (Djalali-Behzad, *et al.*, 1981). In a study by Gansewendt, *et al.* (1991), 7-methyl guanine and O⁶-methyl guanine were detected in the DNA from the liver, lung, stomach, and forestomach of rats exposed to methyl bromide by inhalation or by gavage. The formation of DNA adducts indicated a systemic genotoxic effect since the highest concentrations of the DNA adducts were found in the

stomach and forestomach DNA for both routes.

C. Structure-Activity Relationship

Methyl chloride, the chloro analog of methyl bromide, is a known developmental toxicant. Heart defects were found in fetuses of pregnant mice exposed by inhalation to methyl chloride during gestation (Wolkowski-Tyl *et al.* 1983a). The significance of the finding was further discussed (John-Greene *et al.* 1985 and Tyl, 1985). Exposure of pregnant rats to the same methyl chloride concentration did not result in any developmental effects (Wolkowski-Tyl *et al.*, 1983b). Further studies with mice and rats showed a reduction of nonprotein sulfhydryl concentrations in fetal tissues, which suggested transplacental passage of methyl chloride and/or its metabolites (observations discussed in Wolkowski-Tyl *et al.*, 1983b)

III. DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

In this section, studies which showed developmental and reproductive toxicological effects are discussed and a summary is presented in Table 1. Work sheets for each of the studies are available from DPR. In the evaluation of the data and the determination of whether regulatory action to decrease methyl bromide exposure was appropriate, DPR used the basic assumptions in the USEPA Guidelines for Developmental Toxicity (USEPA, 1991) and Kimmel *et al.* (1993), and they are:

1. An agent that produces an adverse developmental effect in experimental animal studies will potentially pose a hazard to humans following sufficient exposure during development.
2. All of the four manifestations of developmental toxicity (death, structural abnormalities, growth alterations, and functional deficits) are of concern.
3. The types of developmental effects seen in animal studies are not necessarily the same as those that may be produced in humans.
4. The most appropriate species is used to estimate human risk when data are available. In the absence of data, it is assumed that the most sensitive species is appropriate for use, based on observations that humans are as sensitive or more so than the most sensitive animal species tested for the majority of agents known to cause human developmental toxicity.
5. In general, a threshold is assumed for the dose-response curve for agents that produce developmental toxicity.

A. Rats

1. American Biogenics Corp., 1986

In a study conducted by American Biogenics Corp. (1986), parental rats were exposed to methyl bromide 6 hrs/day, 5 days/week at 0, 3, 30, or 90 ppm at pre-mating, mating, gestation, and lactation, except from gestation day 21 to lactation day 4. There was a total of 4

matings, generating F1a and F1b offspring from the F0 parents and F2a and F2b offspring from the F1 parents. The first and second generation pups were exposed to methyl bromide only in utero for 5 days per week from gestation days 0 to 20, resulting in a total exposure of 15 days. Offspring were not exposed to methyl bromide during the lactation period. The F1 parents were selected from the F1b offspring. The F1 animals were then exposed to methyl bromide after weaning. The offspring from the F1 parents are called the F2a and F2b litters.

Absolute brain weights were decreased in the 90 ppm F0 males, F1 males, and F1 females, and possibly in the 30 ppm F1 females as well. In the second mating of the F1 adults, the fertility index decreased from 90.9% in the controls to ? 68% in the 30 and 90 ppm groups.

The results on pup body weights are shown in Table 3. At birth, the F1a and F1b pup body weights for the treated groups were either higher or not significantly different from controls. However, the pups from the 30 and 90 ppm groups in the F1a and F1b showed significantly reduced body weights on lactation days 14 to 28. The F2a pup body weights of the 90 ppm group were lower at birth than the controls and remained reduced throughout lactation. The F2a pup body weights of the 30 ppm group showed significant reduction on lactation days 14 to 28. The F2b litter body weights for the 30 and 90 ppm groups were decreased, starting as early as 4 days after birth. The reductions in body weight tended to be greater in the F2a and F2b progeny (reduction of 9 to 21% at 90 ppm) compared respectively to the F1a and F1b pups (reduction of 5 to 11% at 90 ppm). Since the pups were not exposed to methyl bromide during the lactation period, except perhaps via the maternal milk, the finding of reduced body weights suggests that growth retardation may be an effect due to in utero exposure. Except for a reduction of food consumption in the first week of exposure of the parents of the first generation, the food consumption of all the parents were comparable to the control animals. No change in nursing behavior was reported. Pending the submission of additional information on exposure conditions and histological examinations of target organs, the tentative NOEL is 3 ppm for decreased body weights in the neonates, and decreased fertility in the dams.

2. Sikov *et al.*, 1981

In the developmental study by Sikov *et al.* (1981), nonpregnant Wistar rats were exposed to methyl bromide concentrations of 0 (air), 20, or 70 ppm for 7 hours/day for 3 weeks. These rats were then allowed to mate with untreated males. Upon evidence of mating, females were then assigned to gestational exposure groups in the following manner. Females exposed to 0 ppm methyl bromide pregestationally were proportioned into groups that would be exposed to 0, 20, or 70 ppm methyl bromide during their gestational periods. Females exposed pregestationally to 20 or 70 ppm methyl bromide were proportioned into groups that would be exposed to 0 ppm or to the same methyl bromide concentration that was used pregestationally. Gestational exposures were for 7 hours/day and were continuous from gestation days 1 through 19.

There was no maternal toxicity at any of the doses. The only developmental effect identified by DPR was an increase in the incidences of delayed skull ossification of the supraoccipital plate in the fetuses of both groups exposed to 70 ppm during gestation (Table 2), an effect considered a skeletal variation. The authors of the report had noted an increase in the incidences of delayed ossification for several skeletal structures, but these were considered not to be treatment-related. However, since the skull effect was noted in both groups exposed to the high dose (70 ppm) during gestation, DPR did not consider the dismissal appropriate as a NOEL can be established at 20 ppm. It has also been suggested that the skeletal results in this

study were highly variable and, therefore, no treatment-induced effect can be inferred. DPR evaluated all of the skeletal results and only identified the skull ossification defect as a treatment-induced effect. Other skeletal endpoints were not considered treatment-related because there was no indication of an increased incidence of the effects in the treated groups (e.g., rudimentary rib), or the increased incidence was seen only in one of the 70 ppm groups, but not the other 70 ppm group (e.g. unossified sternebrae).

It has been suggested that since there were 5 treated groups in this study, the likelihood of a statistically significant effect by chance was proportionately increased. DPR does not believe that the increased incidence of skull ossification defects was due to chance since the effect was observed at the same litter incidence in both 70 ppm groups (Table 2).

That the delayed ossification effect in this study is only a skeletal variation and that other skeletal effects were not noted is acknowledged. However, this effect appears to be treatment-induced and was seen in the absence of any maternal toxicity. That is, the highest dose tested, 70 ppm, was not a maximum tolerated dose. Results from Eustis *et al.* (1988) suggested that the maximum tolerated dose would be between 90 and 160 ppm. Results from the rat reproduction study showed no parental toxicity in rats exposed to methyl bromide at 90 ppm for two matings per generation for two generations for a total of 132-145 days of exposure. Therefore, if the methyl bromide concentration in the Sikov *et al.* study were higher, then more severe developmental effects might be expected.

B. Rabbits

1. Sikov *et al.*, 1981

Sikov *et al.* (1981) also conducted a study with rabbits. Pregnant New Zealand white rabbits were to be exposed to methyl bromide concentrations of 0, 20, or 70 ppm, 7 hours/day, on gestation days 1 to 24. Neurotoxicity (convulsion and paresis in the hind limb) was observed in the 70 ppm group after 1 week of exposure and deaths started to occur starting on gestation day 9. Because of neurotoxicity and mortalities in the 70 ppm group, exposures of all the groups were stopped on gestation day 15 (Hardin *et al.*, 1981). By gestation day 30, all but one of the 70 ppm does were dead. No developmental effects were observed in the fetuses of the 20 ppm does or those of the one survivor from the 70 ppm group. Because of the loss of the 70 ppm group and the abbreviated duration of gestational exposure in the 20 ppm group, this study is not a valid developmental study and should not be interpreted as "negative" evidence for developmental toxicity. This study does serve to illustrate that pregnant rabbits are significantly more susceptible than pregnant rats to the neurotoxic effects of methyl bromide. That is, neurotoxicity and death occurred within 9 days of continuous exposure of rabbits to 70 ppm in the Sikov *et al.* study whereas no maternal toxicity was observed in rats exposed to methyl bromide at the same concentration pregestationally as well as from gestation days 1 to 19.

2. Breslin *et al.*, 1990a

In a probe study conducted by Breslin *et al.* (1990a) to determine the maternal toxicity and embryoletality of methyl bromide, pregnant New Zealand white rabbits were exposed to methyl bromide 6 hours/day on gestation days 7 to 19, with sacrifice on gestation day 20. There were two parts to this study. In Part I, the methyl bromide concentrations were 0, 10, 30, or 50 ppm. No maternal or fetal effects were observed. In Part II, the methyl bromide concentrations were 0, 50, 70, or 140 ppm. All does in the 140 ppm group showed signs of

toxicity (lethargy and decreased food consumption) after 8 exposures. With continued exposure, severe neurotoxicity was observed, including the following: lethargy, labored breathing, ataxia, right-sided head tilt, reduced sensation in the extremities, dilated pupils, lateral recumbency, loss of placing or righting reflex, and rear leg splay. As a result, all rabbits in this group were sacrificed on gestation day 17. Histological examination was done on brains from all treatment groups. Only brains from the 140 ppm group showed pathological lesions. Fetal examinations were limited to counting the number of implantations and resorptions. In the 70 ppm group, the only possible effect was a reduction in litter size that was associated with an increased incidence of preimplantation loss. However, this was not considered to be treatment-related because treatment-related preimplantation loss would not be expected with this study design, since treatments did not start until after implantation had occurred. Also, an increase in preimplantation loss was not seen in either of the 80 ppm groups that were part of the definitive study (Breslin *et al.*, 1990b).

3. Breslin *et al.*, 1990b

In the definitive study by the same group of investigators, there were also two parts to the study (Breslin *et al.*, 1990b). In the first part (Part I), pregnant rabbits were exposed to methyl bromide concentrations of 0, 20, 40, or 80 ppm for 6 hours/day on gestation days 7 to 19 and were sacrificed on gestation day 28. The second part (Part II) was designed to determine if the gall bladder agenesis observed in Part I was associated with a particular male that was one of several males whose sperm were mixed together and used for artificial insemination. The methyl bromide concentrations were 0 or 80 ppm.

Maternal effects were observed in the 80 ppm group. In Part I, signs of neurotoxicity (right-sided head tilt, ataxia, slight lateral recumbency, lethargy) were observed in 3 of 26 does in the 80 ppm group. The severity of these neurological effects in these three affected does was much less than that seen in the 140 ppm does in the probe study. Also, the onset of these signs was later (Table 1). In Part II, none of the 17 does in the 80 ppm group exhibited signs of neurotoxicity.

Decreased body weight gain was observed in the does across treatment groups in a variable fashion. The body weight gain for gestation days 7 to 20 was reduced in both 80 ppm groups but only the reduction in Part II was statistically significant. This reduction in maternal body weight gain in the 80 ppm group in Part II was seen in the presence of reduced fetal weight. The biological significance of the maternal body weight gain reduction is uncertain because body weight changes in rabbits during pregnancy are more variable than other species (USEPA, 1991).

The incidences of fetal effects considered by DPR are shown in Table 4. The effects observed included omphalocele, retroesophageal right subclavian artery, hemorrhage with or without generalized edema, gall bladder agenesis, fused sternebrae, and decreased fetal body weight.

Omphalocele and retroesophageal right subclavian artery were seen only in the 80 ppm group in Part I whereas hemorrhage (with or without generalized edema) was seen in both 80 ppm groups. Although their incidences were low and not statistically different from the incidences in the concurrent controls, these effects were considered to be possibly treatment-related because each of these effects has been rarely seen at the Dow laboratory in its control groups (Table 5). The Dow laboratory database, from 1974 to 1991, did not record a control group with two affected litters for any of these three endpoints (omphalocele, retroesophageal

right subclavian artery, and hemorrhage, with or without generalized edema) nor a control group wherein these three findings were made in the same group. Data in the database compiled by the Middle Atlantic Reproduction and Teratology Association (MARTA, Lang 1993) also corroborated that these are rare findings in control groups (Table 7).

The incidences of gall bladder agenesis and fused sternebrae were significantly different from the controls at $p \leq 0.05$ level. These effects were considered independent of maternal toxicity because these effects were observed in fetuses from both normally behaving and affected (with neurotoxicity) does. The finding of gall bladder agenesis was confirmed in Part II of the experiment with approximately the same litter incidence (29%) as for Part I (26%). No maternal toxicity was reported in Part II. The possibility that gall bladder agenesis was associated with a particular male was discounted since the malformation was not observed in the naive controls (in Part II) which had been inseminated with the sperm from a suspect male.

It has been suggested that the finding of gall bladder agenesis is biologically insignificant. It has been noted that some species, like the rat, do not have a gall bladder. DPR considers the absence of the gall bladder a significant biological finding. First, humans do have gall bladders. Second, gall bladder agenesis is a malformation; that is, the entire organ did not form. Histological investigation done on one case of gall bladder agenesis from the 80 ppm group (Part I) confirmed the failure of the gall bladder to form, including the absence of the common bile duct. As stated earlier, it is assumed when using animal data for identification of human hazards, that a chemical will not necessarily cause the same defect in different species. If a chemical is shown to cause a malformation in one species, it is assumed, unless proven otherwise, that the chemical has the potential for causing a malformation (not necessarily the same malformation) in the human population (USEPA, 1991; Kimmel *et al.*, 1993).

It has been suggested that since gall bladders vary in size and shape, the lack of a gall bladder is only part of a continuum of effects; therefore, gall bladder agenesis should be considered a variation. DPR does not concur with this conclusion in that the results from the Breslin study clearly identified the absence of gall bladder, not a reduction in size or change in shape. For the same reason, the fact that the spontaneous incidence of hypoplastic gall bladders may be considerably greater and more variable than that for gall bladder agenesis is considered inconsequential to interpreting the results of the Breslin *et al.* study.

It has been suggested that developmental effects should be compared with historical control databases because the evaluation of these effects are subjective and variable. Because of the variability, DPR believes the use of in-house historical control data (Dow Chemical Company as the contract laboratory for the study) is most appropriate, especially those data generated closest in time to the study in question. The in-house historical control data would be more relevant than historical control data generated outside of the facility in question. DPR specifically considered the historical control data from the contracting laboratory of the Breslin *et al.* study. With regard to gall bladder agenesis, the facility did not record a single case in its control groups between 1974 and 1989 when the methyl bromide study was conducted. However during this time, the facility did identify hypoplastic gall bladder and gall bladder agenesis as possible treatment-induced effects in studies of other chemicals. The overall litter incidence for the control groups is 0.35% for rabbits used at the facility between 1974 and 1991 (i.e., including two years after the methyl bromide study was conducted; Table 5). This incidence rate is comparable to the 0.67% (7 affected litters/1051 litters) calculated for the absence of gall bladder in the negative control groups for 37 studies performed between 1985 and 1993 at the WIL Research Laboratories (Holson, 1993a, 1993b, and 1993c, Table 6). In addition, DPR examined the historical control databases compiled by MARTA (Table 7,

Lang, 1993) and those published by Stadler *et al.* (1983) (Table 8). These databases showed that the spontaneous litter incidence for gall bladder agenesis is less than one percent. They supported the DPR conclusion that the finding of ? 26% litter incidence for gall bladder agenesis in the Breslin *et al.* study is significant.

There was a dose-related increase in the incidences of fused sternebrae in the fetuses of the methyl bromide treated groups. While DPR considered this a significant finding, others have questioned it because the Breslin *et al.* study facility's historical control database contained an entry for "unfused sternebrae", a term that could be considered unconventional. Therefore, a question was raised regarding what was considered to be "fused" sternebrae. DPR examined the historical control database supporting the Breslin *et al.* study. A total of only 22 fetuses (involving 21 litters) had this entry. These "unfused" sternebrae entries involved studies conducted between 1974 (earliest study in the database) and 1982, whereas the Breslin *et al.* study was not conducted until 1989. Dr. Breslin was contacted to determine the definition of "unfused" sternebrae. He indicated that this term referred to a type of delayed ossification wherein the sternebrae present as two parts separated longitudinally; it is also called a bipartite sternebrae (Figure 1). The reason that there are no findings of unfused sternebrae after 1982 is because it was decided in that time period to simply include this finding in the general tally of sternebrae exhibiting delayed ossification. The reason the database still has unfused sternebrae as an entry is to maintain its completeness and authenticity as a historical record. The litter incidence for fused sternebrae was 53% for the 80 ppm group. The litter incidence rates in the historical control databases are 4.46% for the Breslin *et al.* study facility (Table 5), 1.58% for the WIL Research Laboratories (Table 6), and 4.58% for the MARTA database (Table 7). Therefore, the DPR concludes that there is no basis to discount the finding of an increased incidence of fused sternebrae in this study. Also, the fact that skeletal examinations were not conducted in Part II of the study has no consequence on how the skeletal findings of Part I are interpreted.

In Part II of the experiment, at 80 ppm, there was also a significant decrease in the fetal body weight. This decrease in fetal body weight also resulted in a significant decrease (79% of control values) in gravid uterine weight (the total weight of the uterus and fetuses) of does in this group. It has been suggested that this effect should be discounted since the decrease was statistically significant only in Part II and not Part I. Also, when the Part II-80 ppm fetal body weight data are compared to the Part I control (0 ppm) data, there is no significant difference between the two values. This conclusion is not valid since the proper control group for Part II for the 80 ppm group is its concurrent group. It is not known why fetal body weights were affected significantly in Part II and not in Part I, but it may be due to the following differences between Parts I and II: (1) animals in Part II were from a different shipment of rabbits (albeit from the same supplier); (2) animals in Part II were 2-3 months younger than used in Part I; in fact, their body weights (3.3-3.4 kg) suggest that they had just reached puberty; and (3) the reduced number of animals on test in Part II resulted in a different loading pattern for the inhalation chamber compared to Part I. In addition, mean litter sizes were different between Parts I and II. The mean litter sizes were 9.0 fetuses/litter in the 0 ppm group in Part I versus 6.6 fetuses/litter in the 80 ppm group in Part II. Since litter size may affect fetal weight (Romero *et al.*, 1992; Duncan, 1969), it would not be appropriate to compare results from the two Parts for fetal weight comparisons.

Therefore, the results from both Parts I and II were taken into consideration in the determination of the NOEL and establishment of a NOEL at 40 ppm.

IV. CONCLUSION

DPR evaluated toxicity studies submitted and those reported in the literature and determined that methyl bromide caused developmental effects in animals. The Breslin *et al.* study (1990b) was selected as the definitive study for the establishment of a NOEL for acute exposure because the study was conducted under USEPA Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guidelines, and the results showed statistical significance for the increased incidences of gall bladder agenesis and fused sternebrae and for the decreased fetal weight. DPR considered these developmental effects to be treatment-related and biologically significant. These effects can not be dismissed as being due to maternal toxicity since they were observed in does that did not exhibit neurotoxicity or other evidence of maternal toxicity. In addition, these effects observed in the 80 ppm treated groups were statistically significant when compared to the concurrent control group, the most appropriate group for comparison. Historical control data from the conducting laboratory, WIL Research Laboratories, MARTA (Lang, 1993), and Stadler *et al.* (1983) also supported the conclusion that the effects were treatment-related.

Further evidence of developmental toxicity can be found in the rat developmental toxicity study (Sikov *et al.*, 1981) wherein no maternal toxicity was evident. Delayed skull ossification was observed at equal litter incidence in both groups exposed to a concentration of methyl bromide at less than a maximum tolerated dose.

Methyl bromide also caused reproductive toxicity in rats. In the rat reproductive toxicity study, there was a reduction in the fertility index of the treated groups. There was also decreased pup body weights during the lactational periods for each of the four birthing periods in pups from methyl bromide treated dams. It is important to note that the pups were only exposed to methyl bromide in utero. Moreover, the in utero exposure was not continuous; that is, they were exposed to methyl bromide only 5 days per week (for a total of 15 days) instead of the daily exposure during the selected period of gestation as in the developmental toxicity protocol.

It has been suggested that developmental effects should be observed in more than one species to be confirmative. To the contrary, it is known that for some chemicals, there is species specificity in developmental effects. Developmental toxicity testing under the FIFRA guidelines requires two species to be tested, a rodent and a non-rodent species, typically the rabbit, for the purpose of identifying species susceptibility. The need to test non-rodent species arose from the findings of thalidomide where it was demonstrated that this unequivocal human teratogen did not exhibit significant teratological effects in rats but caused at least some significant effects in rabbits (Schardein, 1985a). In the absence of human data and when animal data are used, it is assumed that the most sensitive species is appropriate for use to determine regulatory action (USEPA, 1991).

Consideration should also be given to the results from genotoxicity studies which have shown that methyl bromide is an alkylating agent capable of reacting with biological nucleophiles (proteins and DNA) and is a direct-acting mutagen in a variety of test systems. While the mechanism for the developmental effects observed from the exposure to methyl bromide is unknown, it has been shown that many of the anticancer alkylating agents are teratogenic in laboratory species, and several of them have elicited malformations in humans (Schardein, 1985b). In addition, methyl chloride, the chloro analog of methyl bromide, has been shown to cause developmental effects in mice.

DPR evaluated available toxicity studies and found that methyl bromide caused developmental effects in rabbits and rats, and reproductive effects in rats. Therefore, DPR

concluded that the developmental and reproductive effects observed in laboratory animals were significant and warranted regulation on the use of methyl bromide to decrease human exposure.

V. References

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Table 1. The NOELs and LOELs of methyl bromide by inhalation from developmental and reproductive toxicity studies.

Studies	Species	Duration ppm	NOEL/LOEL ^a	Effects
1. American Biogenics Corp. (1986)	Rat	6h/d	3 /30 3 /30	maternal-reduced fertility fetal-reduced body weights
2. Sikov <i>et al.</i> , (1981)	Rat	7h/d	70/ - 20/ 70	maternal-no significant effects fetal-delayed skull ossification
3. Sikov <i>et al.</i> , (1981)	Rabbit	7h/d	20/ 70	maternal-convulsion, paresis, and death (after 1 week)
4. Breslin <i>et al.</i> , (1990a,probe, Part I)	Rabbit	6h/d	50/-	maternal and fetal- no effects at the highest dose studied
5. Breslin <i>et al.</i> , (1990a,probe, Part II)	Rabbit lesions	6h/d	70/140	maternal- neurotoxicity (after 8 exposures), brain
6. Breslin <i>et al.</i> , (1990b,Part I)	Rabbit	6h/d	40/ 80 40/ 80	maternal-neurotoxicity in some does (after 12 exposures) fetal-fused sternebrae, gall bladder agenesis, and other effects
7. Breslin <i>et al.</i> , (1990b,Part II)	Rabbit	6h/d	- / 80 - / 80	maternal-decreased body weight gain fetal-gall bladder agenesis and decreased body weights

^{a/} See text for full explanation of the results.

Table 2. The incidence of delayed ossification of the supraoccipital plate in rat fetuses after inhalation exposure to methyl bromide during gestation^a.

Exposure conditions ^b <u>Premating-Gestation</u>	<u>Affected litters/Total litters</u>
air - air	1/37
air - 20 ppm	2/31
air - 70 ppm	7/36 ^c
20 ppm - air	4/34
20 ppm - 20 ppm	2/38
70 ppm - air	0/36
70 ppm - 70 ppm	7/36 ^c

^{a/} Data were from Sikov *et al.*, 1981.

^{b/} There were 2 exposure periods: 3 weeks prior to mating, and during gestation. The does were exposed to various combinations of air or methyl bromide concentrations during those periods.

^{c/} p= 0.025 using Fisher's Exact Test.

Table 3. The body weights of rat pups after inhalation exposure in a 2-generation reproductive study^a.

Body Weight (grams) ^b								
Lactation Days	0	F1a litter				F1b litter		
		3	30	90 ppm		0	3	30 90 ppm
0	6.0	6.2**	6.2**	6.0	6.2	6.4**	6.2	6.5**
4	9.5	9.4	9.3	9.3	9.3	9.9**	9.5	9.7*
7	13.5	13.7	13.0*	13.1	13.7	14.9**	14.1	14.3
14	23.2	22.9	21.5**	21.6**	24.1	24.2	22.5*	22.5*
21	37.8	37.7	34.3**	33.8**	39.3	39.4	36.0**	36.4**
28	68.4	66.9	62.1**	61.8**	70.1	69.3	64.1**	66.4

Lactation Days	0	F2a litter				F2b litter		
		3	30	90 ppm		0	3	30 90 ppm
0	5.6	6.1**	5.5	5.4**	6.4	6.7**	6.2	6.2
4	8.1	8.4	7.8	7.4**	10.1	9.9	9.2**	9.2**
7	11.6	12.2*	11.6	10.6**	14.3	14.7	13.4*	13.3*
14	21.9	22.6	20.4**	18.6**	24.1	23.7	19.8**	19.6**
21	35.4	36.2	31.4**	29.1**	40.3	39.8	32.4**	32.0**
28	64.3	64.2	58.6**	53.8**	71.6	70.6	58.4**	58.2**

^{a/} Data were from American Biogenics Corp., 1986. Fetuses were exposed in utero to methyl bromide for 5 days/week during gestation day 0 to gestation day 19. Offspring was not placed in the inhalation chambers during the lactation period.

^{b/} Values were mean body weights for both sexes. Statistical significance levels were * at $p \leq 0.05$, and ** at $p \leq 0.01$ levels using ANOVA and Scheffe's Multiple comparisons reported by the investigators.

Table 4. The incidence of fetal effects in rabbits after inhalation exposure to methyl bromide during gestation^a.

Effects	Concentration (ppm)							
	Part I				Part II			
	0	20	40	80	0	0 ^b	80	
# Examined:								
fetuses	190	137	143	159	114	102	92	
litters	21	15	19	19	16	13	14	
<u>Mean litter size</u>	9.0	9.1	7.5	8.4	7.1	7.8	6.6	
<u>Mean fetal body weight (g)</u>	31.8	32.2	35.0	30.4	36.2	33.8	31.4*	
<u>External Effects</u>								
omphalocele	0	0	0	2/2 (11%) ^d	0	0	0	
hemorrhage (with or without generalized edema)	0	0	0	2/2 (11%) ^d	0	0	1/1 (7%)	
<u>Soft Tissues</u>								
retroesophageal right subclavian artery	0	0	0	2/2 (11%) ^d	0	0	0	
gall bladder agenesis	2/1 (5%)	1/1 (7%)	1/1 (5%)	13/5* ^c (26%) ^d	1/1 (6%)	0	4/4 ^c (29%) ^d	
<u>Skeletal Effects</u>								
fused sternebrae	0	0	3/2 (11%)	20/10* ^e (53%) ^d	NA ^f	NA ^f	NA ^f	

^{a/} Incidence data were expressed as the number of fetuses affected/number of litters affected. Data were from Breslin, *et al.* (1990b) with does exposed to methyl bromide 6 hours/day on days 7 to 19 of gestation. Parts I and II were two separate experiments. Statistical significance in comparison to the controls, * ($p \leq 0.05$), is indicated after each incidence.

^{b/} These rabbits were not placed in an inhalation chamber. All does in this group had been inseminated with semen from one male that was suspected from Part I of selectively contributing to the increased incidences of gall bladder agenesis.

^{c/} Of the 13 fetuses with missing gall bladder in Part I, 6 were from 3 does without neurotoxicity and 7 were from 2 does with neurotoxicity. In part II, all 4 affected fetuses were from 4 does without neurotoxicity.

^{d/} Percent of litters affected = (affected litters/total litters examined) x 100.

^{e/} Of the 20 fetuses with fused sternebrae, 19 were from 9 does without neurotoxicity, and 1 from 1 doe with neurotoxicity.

^{f/} NA=not analyzed, i.e., skeletal examinations were not performed.

Table 5. Historical control data for developmental effects in rabbits for Dow Chemical Company 1974-1991.^a

<u>Effects</u>	<u>Fetuses^b</u>	<u>Litters^c</u>
omphalocele	5/8956 (0.06) ^d	5/1159 (0.43) ^d
petechial hemorrhage	1/8956 (0.01)	1/1159 (0.09)
subdermal hematoma	2/8956 (0.02)	2/1159 (0.17)
generalized edema	1/8956 (0.01)	1/1159 (0.09)
retroesophageal right subclavian artery	7/5333 (0.13)	7/1158 (0.60)
gall bladder agenesis	5/5333 (0.09)	4/1158 (0.35)
fused sternebrae	55/8502 (0.65)	49/1099 (4.46)

^{a/} Data were from Breslin *et al.*, 1990b.

^{b/} Number of affected fetuses/total number of fetuses.

^{c/} Number of affected litters/total number of litters.

^{d/} Percent of total number of fetuses or litters in database affected is in parenthesis.

Table 6. Historical control data for developmental effects in rabbits for WIL Research Laboratories 1982-1992 (except as noted otherwise)^a

<u>Effects^b</u>	<u>Fetuses^c</u>	<u>Litters^d</u>
gall bladder agenesis	7/7232 (0.10)	7/1051 (0.67) ^e
fused sternebrae ^f	21/7855 (0.27)	18/1136 (1.58)
omphalocele	11/7855 (0.14)	11/1136 (0.97)
edema	1/7855 (0.01) ^g	1/1136 (0.09) ^g

^{a/} Data were from WIL Research Laboratories supplied to DPR (Holson, 1993a, 1993b, 1993c).
^{b/} The WIL database does not contain specific entries for hemorrhage/subdermal hematoma or retroesophageal right subclavian artery. The latter may be included under entries in which several separate blood vessel findings are grouped.

^{c/} Number of affected fetuses/total number of fetuses examined. Percent of incidence is in parenthesis.

^{d/} Number of affected litters/total number of litters examined. Percent of incidence is in parenthesis.

^{e/} Values are based on negative control groups from 37 studies done between February, 1985 and November, 1993.

^{f/} Fused sternebrae is classified as a skeletal malformation in the WIL database.

^{g/} Values are for localized fetal edema. An entry for generalized edema, hydrops, or words to that effect does not appear in the database.

Table 7. Historical control data for New Zealand white rabbits from the Middle Atlantic Reproduction and Teratology Association (MARTA).^a

<u>Effects</u>	<u>Fetal % Incidences Average</u>	<u>Litter % Incidences Average</u>	<u>Number of Studies</u>	<u>Total Litters</u>	<u>Total Fetuses</u>
Gall bladder agenesis	0.14	0.92	178	2890	19310
Fused sternebrae	0.92	4.58	172	2794	18762
Omphalocele	0.07	0.32	225	2776	20071
Retroesophageal right subclavian	0.055	0.23	178	2890	19310
Hematoma	0.01	0.07	225	2776	20071
Local edema	0.02	0.18	225	2776	20071

^{a/} Data were from Lang, 1993. The historical control data were compiled from 21 companies as provided by members of MARTA. Since all participating laboratories conduct studies under Good Laboratory Practices, it was assumed that conditions meet or exceed federal regulations for the care and housing of laboratory animals. Dow Chemical Company and WIL Research Laboratories were not listed as participants. In this table, only the arithmetic means of the percentage of incidences from all studies are included. These studies included rabbits which were sacrificed on gestation days 28, 29, and 30. Incidence data for effects observed in each of the gestation days are also available.

Table 8. Historical control data of New Zealand rabbits from Stadler *et al.* (1983)^a

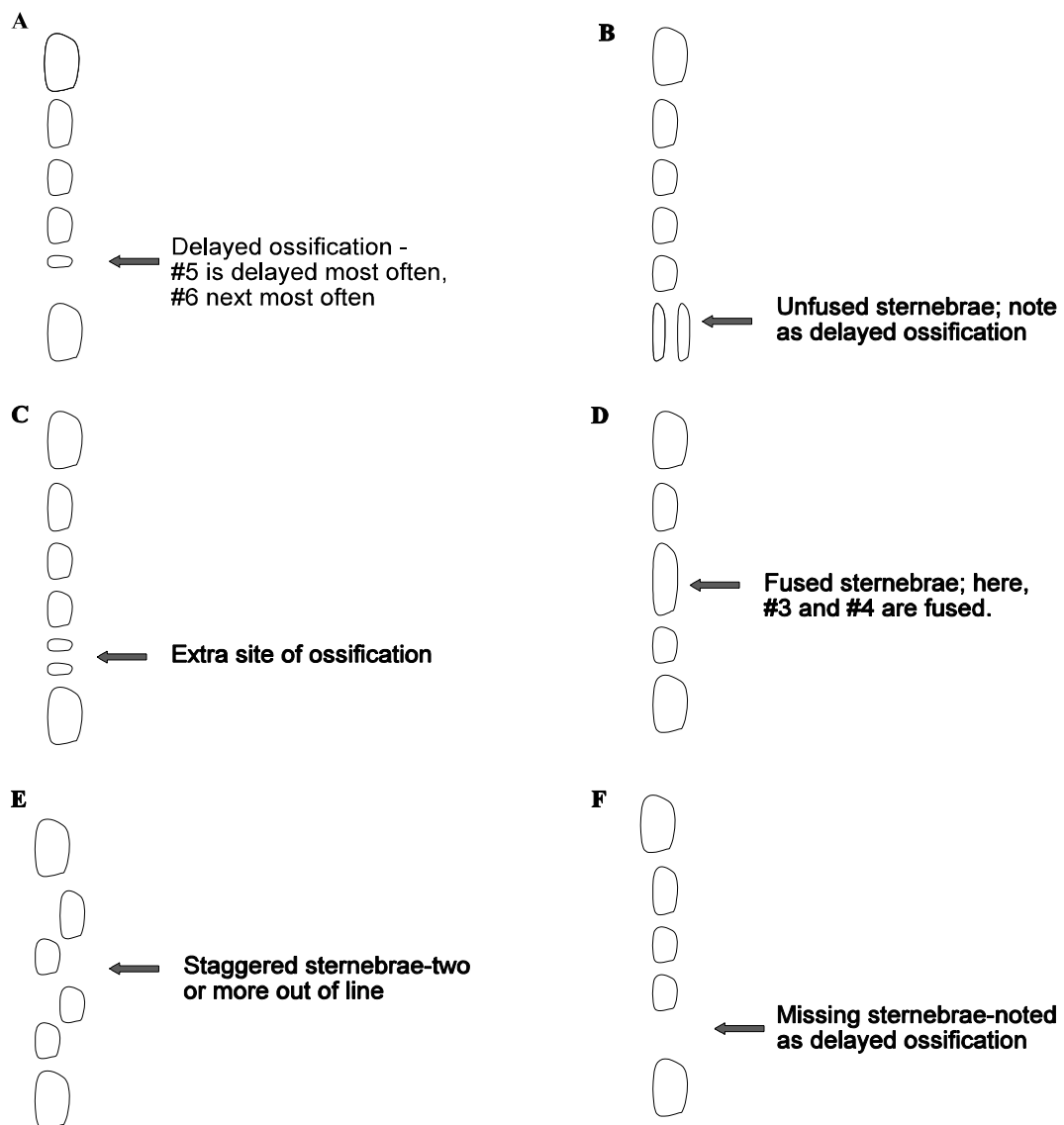
<u>Effects^b</u>	<u>Fetuses^c</u>
Gall bladder agenesis	6/3185 (0.19%)
Subcutaneous edema	1/5592 (0.02%)

^{a/} Data were from Stadler *et al.* (1983).

^{b/} The following endpoints did not have entries in this database: omphalocele, hemorrhaging (visible externally), retroesophageal right subclavian artery, and fused sternbrae.

^{c/} Values are expressed as number of fetuses affected/ total number of fetuses examined. Percent affected is included in the parenthesis. Litter incidence data were not provided in this publication.

Figure 1. Common anomalies of the sternebrae.^a



^{a/} Adapted from a figure provided by The Dow Chemical Company upon request from DPR.

Attachment C: The half-lives of methyl bromide residues in commodities after post-harvest fumigation

Commodities	rate (lbs/1000 ft ³)	Fumigation time /temperature	When samples were collected for analysis ^a	Analysis Method ^b	Initial residue level ^c	Half-life ^d	References
Fresh Fruits							
Apple	5	2 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	6.8 ppm	19 hrs	MBIP, 1985a; Hazel, 1988
Avocado (ripe, Fuerte var.)	2	2 hrs/20°C	after 30 min aeration, during 0 to 5 days of storage	F	7.2 ppm	4.6 hrs	Singh <i>et al.</i> , 1982
Avocado (ripe, Fuerte var.)	2	4 hrs/20°C	after 30 min aeration, during 0 to 5 days of storage	F	7.5 ppm	5.2 hrs	Singh <i>et al.</i> , 1982
Blueberry	3	3 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	3.8 ppm	15.6 hrs	MBIP, 1985a; Hazel, 1988
Blueberry	2	3.5 hrs/16.6°C	during aeration (1-24 hrs)	A	50.8 ppm	1.6 hrs	IR-4, 1983
Blueberry	2	2 hrs/27.2°C	during aeration (1-24 hrs)	A	26.6 ppm	0.8 hrs	IR-4, 1983
Cherry	3	2 hrs/21°C	after 2 hrs aeration, during 2 to 48 hrs of storage at 2.5°C	B	18.1 ppm	4.7 hrs	Tebbetts <i>et al.</i> , 1983
Cherry	2	4 hrs/21°C	after 2 hrs aeration, during 2 to 48 hrs of storage at 2.5°C	B	14.0 ppm	4.9 hrs	Tebbetts <i>et al.</i> , 1983
Grape	4	2.5 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	3.3 ppm	23.5 hrs	MBIP, 1985a; Hazel, 1988
Grapefruit	3	3 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	4.4 ppm	2.5 days	MBIP, 1985a; Hazel, 1988
Grapefruit	2	2 hrs	after 15 min aeration, during 2 to 48 hrs of storage at 24 °C	B	9.0 ppm	8.7 hrs	King <i>et al.</i> , 1981
Lemon	2.7	2 hrs/20°C	after 2 hrs aeration, during 2 hrs to 31 days of storage	B	4.9 ppm	3.3 days	Hartsell <i>et al.</i> , 1989
Lemon	3	3 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	5.0 ppm	1.8 days	MBIP, 1985a; Hazel, 1988
Mango	1	2 hrs/20°C	after 5 min aeration, during 0.17 to 3 hrs storage in fume hood with fan on (24.4 m/min face velocity)	B	4.7 ppm (peel) 2.2 ppm (pulp)	0.3 hrs (peel) 0.4 hrs (pulp)	Stein and Wolfenbarger, 1989

Mango	4	2 hrs/20°C	after 5 min aeration, during 0.17 to 3 hrs storage in fume hood with fan on (24.4 m/min face velocity)	B	21.2 ppm (peel) 20.6 ppm (pulp)	1.8 hrs (peel) 2.4 hrs (pulp)	Stein and Wolfenbarger, 1989
Nectarine	3	2 hrs/21°C	after 2 hrs aeration, during 2 to 48 hrs of storage at 2.5°C	B	24.4 ppm	3.1 hrs	Tebbets <i>et al.</i> , 1983
Nectarine	2	4 hrs/21°C	after 2 hrs aeration, during 2 to 48 hrs of storage at 2.5°C	B	24.8 ppm	3.0 hrs	Tebbets <i>et al.</i> , 1983
Nectarine	2	2 hrs/15.5°C	after 2 hrs aeration, during 2 to 168 hrs of storage at 2.5°C	B	13.8 ppm	18.9 hrs	Harvey <i>et al.</i> , 1982
Nectarine	4	2 hrs/15.5°C	after 2 hrs aeration, during 2 to 168 hrs of storage at 2.5°C	B	26.7 ppm	17.0 hrs	Harvey <i>et al.</i> , 1982
Orange	3	3 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	4.7 ppm	2.4 days	MBIP, 1985a; Hazel, 1988
Peach	5	2 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	2.2 ppm	15.8 hrs	MBIP, 1985a; Hazel, 1988
Peach	3	2 hrs/21°C	after 2 hrs aeration, during 2 to 24 hrs of storage at 2.5°C	B	24.4 ppm	2.5 hrs	Tebbets <i>et al.</i> , 1983
Peach	2	4 hrs/21°C	after 2 hrs aeration, during 2 to 24 hrs of storage at 2.5°C	B	15.8 ppm	2.7 hrs	Tebbets <i>et al.</i> , 1983
Peach	2	2 hrs/15.5°C	after 2 hrs aeration, during 2 to 168 hrs of storage at 2.5°C	B	18.4 ppm	18 hrs	Harvey <i>et al.</i> , 1982
Peach	4	2 hrs/15.5°C	after 2 hrs aeration, during 2 to 168 hrs of storage at 2.5°C	B	37.6 ppm	17.5 hrs	Harvey <i>et al.</i> , 1982
Pear	5	2 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	10 ppm	22 hrs	MBIP, 1985a; Hazel, 1988
Pear	3	2 hrs/21°C	after 2 hrs aeration, during 2 to 48 hrs of storage at 2.5°C	B	44.0 ppm	8.4 hrs	Tebbets <i>et al.</i> , 1983
Pear	2	4 hrs/21°C	after 2 hrs aeration, during 2 to 48 hrs of storage at 2.5°C	B	58.1 ppm	7.1 hrs	Tebbets <i>et al.</i> , 1983
Plum	4	2.5 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	6.3 ppm	21.8 hrs	MBIP, 1985a; Hazel, 1988

Plum	3	2 hrs/21 °C	after 2 hrs aeration, during 2 to 48 hrs of storage at 2.5 °C	B	34.2 ppm	12.5 hrs	Tebbets <i>et al.</i> , 1983
Plum	2	4 hrs/21 °C	after 2 hrs aeration, during 2 to 48 hrs of storage at 2.5 °C	B	30.4 ppm	13.9 hrs	Tebbets <i>et al.</i> , 1983
Plum	2	2 hrs/15.5 °C	after 2 hrs aeration, during 2 to 168 hrs of storage at 2.5 °C	B	18.0 ppm	17.7 hrs	Harvey <i>et al.</i> , 1982
Plum	4	2 hrs/15.5 °C	after 2 hrs aeration, during 2 to 168 hrs of storage at 2.5 °C	B	26.7 ppm	17.8 hrs	Harvey <i>et al.</i> , 1982
Raspberry	3	3 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	0.28 ppm	1.5 days	MBIP, 1985a; Hazel, 1988
Strawberry	3	3 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	0.32 ppm	1.6 days	MBIP, 1985a; Hazel, 1988
Strawberry	3	2 hrs	during 1 to 24 hrs aeration at 0 °C	C	60 ppm (Tioga) 44.2 ppm (Tuft)	1 hr (Tioga) 2 hrs (Tuft)	IR-4, 1982
Strawberry	3	3 hrs	after 45 min aeration, during 0-24 hrs of storage	B	7.1 ppm	2.0 hrs	MBIP, 1984b
Strawberry	3	3 hrs	during 0.75 to 3 hrs aeration	B	9.0 ppm	0.4 hrs	MBIP, 1984b
<u>Vegetables and Herbs</u>							
Basil	3	12 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	2.2 ppm	1.7 days	MBIP, 1985a; Hazel, 1988
Bean-dry	3.5	24 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	0.77 ppm	9.2 days	MBIP, 1985a; Hazel, 1988
Broccoli	3	3 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	0.004 ppm	3.1 days	MBIP, 1985a; Hazel, 1988
Carrot	3	6 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	2.0 ppm	21.7 hrs	MBIP, 1985a; Hazel, 1988
Chive	3	12 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	0.13 ppm	1.7 days	MBIP, 1985a; Hazel, 1988
Corn	3	24 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	3.4 ppm	5.4 days	MBIP, 1985a; Hazel, 1988

Cucumber	3	4 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	0.34 ppm	2.0 days	MBIP, 1985a; Hazel, 1988
Dill	3	12 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	1.9 ppm	1.5 days	MBIP, 1985a; Hazel, 1988
Garlic	3	3 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	0.16 ppm	1.4 days	MBIP, 1985a; Hazel, 1988
Melon	3	3 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	2.9 ppm	1.6 days	MBIP, 1985a; Hazel, 1988
Pea-dry	2	24 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	0.29 ppm	7 days	MBIP, 1985a; Hazel, 1988
Potato	3	6 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	1.2 ppm	1.2 days	MBIP, 1985a; Hazel, 1988
Sage	3	12 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	2.5 ppm	2.1 days	MBIP, 1985a; Hazel, 1988
Soy bean	2	24 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	0.32 ppm	5.4 days	MBIP, 1985a; Hazel, 1988
Sugar beet	3	4 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	0.61 ppm	1.0 day	MBIP, 1985a; Hazel, 1988
Tomato	3	4 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	1.8 ppm	1.3 days	MBIP, 1985a; Hazel, 1988
<u>Dried Fruits</u>							
Date (bulk, non-pitted)	1.5	24 hrs/10°C	after 24 hrs aeration, during 1 to 9 days of storage	B	1.5 ppm	2.0 days	Hartsell <i>et al.</i> , 1989
Date (packaged, pitted)	1.5	24 hrs/10°C	after 24 hrs aeration, during 1 to 9 days of storage	B	3.0 ppm	2.2 days	Hartsell <i>et al.</i> , 1989
Dried Apricot (bulk)	1.5	24 hrs/10°C	after 24 hrs aeration, during 1 to 6 days of storage	B	2.4 ppm	1.2 days	Hartsell <i>et al.</i> , 1989
Dried Apricot (packaged)	1.5	24 hrs/10°C	after 24 hrs aeration, during 1 to 13 days of storage	B	5.4 ppm	2.7 days	Hartsell <i>et al.</i> , 1989
Fig	1.5	24 hrs/10°C	after 24 hrs aeration, during 1 to 13 days of storage	B	3.4 ppm	2.1 days	Hartsell <i>et al.</i> , 1989

Prune (bulk)	1.5	24 hrs/10°C	after 24 hrs aeration, during 1 to 6 days of storage	B	3.3 ppm	1.6 days	Hartsell <i>et al.</i> , 1989
Prune (packaged)	1.5	24 hrs/10°C	after 24 hrs aeration, during 1 to 9 days of storage	B	4.2 ppm	2.0 days	Hartsell <i>et al.</i> , 1989
Raisin (bulk)	1.5	59.5 hrs/13-14°C	after 8 hrs aeration, during 1 to 8 days of storage	B	4.5 ppm	1.6 days	Hartsell <i>et al.</i> , 1989
Raisin (packaged with liner)	1.5	24 hrs/10°C	during 1 to 13 days of storage	B	1.8 ppm	4.3 days	Hartsell <i>et al.</i> , 1989
Raisin (bulk)	1.5	24 hrs/10°C	during 1 to 8 days of storage	B	2.2 ppm	3.3 days	Hartsell <i>et al.</i> , 1989
Nuts and Beans							
Almond	1	12 hrs/10°C	during 4 to 72 hrs of aeration with the first 8 hrs aeration with a fan, and then the door was left open	B	9 ppm (kernel) 28 ppm (shell)	1.5 days (kernel) 12.6 hrs (shell)	Hartsell <i>et al.</i> , 1983
Cocoa bean	2.2	24 hrs	during storage at 1 to 17 days at ambient temperature	D	1.7 ppm	4.2 days	Schumacher, 1985
Cocoa bean	8.7	20 hrs/15°C	during "airing" 0 to 72 hrs	E	22.9 ppm	1.8 days	Fairall and Scudamore, 1980
Pecan	3.5	24 hrs/10°C	after 24 hrs of aeration, during 1 to 8 days of storage	B	3.4 ppm	2.1 days	Hartsell <i>et al.</i> , 1989
Pistachio nut	2	24 hrs/15.5°C	after 24 hrs of aeration, during 1 to 13 days of storage at 15.5°C	B	28.9 ppm	1.9 days	Hartsell <i>et al.</i> , 1986
Pistachio nut	1.5	24 hrs/26.6°C	after 24 hrs of aeration, during 1 to 13 days of storage at 26.6°C	B	10.1 ppm	2.2 days	Hartsell <i>et al.</i> , 1986
Pistachio nut	2.5	24 hrs/26.7°C	after 24 hrs of aeration to 120 hrs of storage	B	14.9 ppm	1.6 days	MBIP, 1985b
Walnut (inshell)-small scale trial	3.5	4 hrs/15.5°C	after aeration, during 4 hrs to 13 days of storage under ambient conditions 14-24°C	B	53.8 ppm	1.7 days	Nelson <i>et al.</i> , 1984
Walnut (inshell)-large scale trial	3.5	4 hrs/15.5°C	after 4 hrs of aeration, during 0 to 21 days of storage at 10°C	B	74.4 ppm	4.1 days	Hartsell <i>et al.</i> , 1984
Walnut (inshell)-large scale trial	3.5	4 hrs/15.5°C	after 4 hrs of aeration, during 0 to 21 days of storage at 32°C	B	74.4 ppm	1.2 days	Hartsell <i>et al.</i> , 1984

Grains							
Maize (white)	0.45	90 hrs/15 °C	during "airing" 0 to 48 hrs	E	18.0 ppm	14.4 hrs	Fairall and Scudamore, 1980
Oats	0.45	90 hrs/15 °C	during "airing" 0 to 48 hrs	E	18.8 ppm	14.8 hrs	Fairall and Scudamore, 1980
Rice	3	24 hrs	after 18 hrs aeration, during 1 to 7 days of storage	B	0.41 ppm	9.2 days	MBIP, 1985a; Hazel, 1988
Rice	0.45	90 hrs/15 °C	during "airing" 0 to 7 hrs	E	8.7 ppm	3.8 hrs	Fairall and Scudamore, 1980
Wheat	1.5	24 hrs/21 °C	after aeration of 4 hrs, during 0 to 24 hrs of storage	B	91.3 ppb	19.5 hrs	CMA, 1984
Wheat	8.7	20 hrs/15 °C	during "airing" 0 to 72 hrs	E	27.6 ppm	24.8 hrs	Fairall and Scudamore, 1980

- ^a When indicated as aeration, a high velocity fan or blower was used to enhance the off-gassing of methyl bromide from the commodity. During storage, a fan of lower velocity or none was used to circulate the air. "Airing" conditions were not specified in the data reported by Fairall and Scudamore, 1980.
- ^b Analysis Methods were: A. not specified; B. head-space method by King *et al.*, 1981; C. partition with methylene chloride, Heuser and Scudamore, 1970; D. hexane volatile trap reflux; and E. partition with acetone/pentane.
- ^c Initial residue level was the residue level at the earliest sampling time.

SUMMARY OF TOXICOLOGY DATA

NAME OF ACTIVE INGREDIENT:
METHYL BROMIDE

Chemical Code # 385, SB 950 # 078, Tolerance # 123

October 20, 1987

Revised May 10, 1989; July 12, 1991; Jan. 17, 1992; Feb. 5, 1993;
July 24, 1995; October 29, 1997; and March 5, 1999

I. DATA GAP STATUS

Chronic rat: ¹	No data gap, possible adverse effect
Chronic dog:	No data gap, possible adverse effect ²
Onco rat: ¹	No data gap, possible adverse effect ³
Onco mouse:	No data gap, possible adverse effect ³
Repro rat:	No data gap, possible adverse effect
Terato rat:	No data gap, possible adverse effect
Terato rabbit:	No data gap, possible adverse effect
Gene mutation:	No data gap, possible adverse effect
Chromosome:	No data gap, possible adverse effect
DNA damage:	No data gap, possible adverse effect
Neurotox:	Inadequate study, possible adverse effect indicated ⁴

¹ Record 158746 was a chronic toxicity-oncogenicity study using feed containing microencapsulated methyl bromide.

² See Note under "Chronic, Dog" dated 3/5/99 by Gee

³ A summary publication of 2-y bioassays done by inhalation with F344 rats and B6C3F1 mice (record 143994) suggests that methyl bromide increased some tumor incidences; other bioassays using Wistar rats (record 059184) and B6C3F1 mice (record 116243) did not indicate an onco-genic effect for inhalation exposure.

⁴ Under SB950, this category is for acute delayed neuropathy testing in hens for agents with anti-cholinesterase activity. Since this does not apply to methyl bromide, there is no data requirement. The study in question here refers to an 827-type, 90-d rat study that USEPA called in.

Note: Toxicology one-liners are attached.

** indicates acceptable study.

Bold face indicates possible adverse effect.

Revised file name: T990305

Revised by: Stephen J. Rinkus and Joyce Gee (3/5/99)

EPA Reregistration guidance document dated August, 1986 contains EPA findings.

CHRONIC, RAT

****123-179 158746** "A 24-Month Chronic Dietary Study of Methyl Bromide in Rats" (Dr. Jozef J.W.M. Mertens; WIL Research Laboratories, Inc.; laboratory study number: WIL-49014; 12/9/97). Corn oil containing methyl bromide was microencapsulated using starch and sucrose. Two types of microcapsules were produced. One was a blend of 7 production runs; it had a methyl bromide content of 0.48% w/w. The second type was a blend of five production runs; its methyl bromide content was 3.44% w/w. The two types of microcapsules differed also in terms of corn oil, starch, and sucrose contents and age of the material at start of testing. The microcapsules were dispersed into granular feed for presentation to the animals. Nominal methyl bromide concentrations in the diet were as follows: 0 (basal diet), 0 (diet containing placebo microcapsules), 0.5, 2.5, 50 and 250 ppm. The blend containing 0.48% methyl bromide was used to prepare the two low doses while the blend containing 3.44% was used to prepare the two high doses. The highest dose tested was selected on the basis of a two-week range-finding study that also is on file (record 162360). The daily ration of feed varied as follows: for test weeks 0-65, males and females each received 30 and 23 g, respectively; for test weeks 66-104, males and females received 35 and 30 g, respectively. One outcome of this feeding strategy appears to have been that a fraction of the animals in the control and 0.5 to 50 ppm groups had their feed consumption restricted during the first 65 weeks of the study. The number of rats/sex/dose level was 50-70 at the start of the study. In test week 53, interim sacrifices were performed on 18-20 rats/sex for the following dose levels: 0 (basal diet), 0 (placebo microcapsules), 50 and 250 ppm. Survival was statistically increased in the 250 ppm male group and in the 50 and 250 ppm female groups when compared to the placebo-microcapsule groups. Bodyweight was reduced in the 250 ppm groups; the reduction reached a maximum in the first weeks of testing in both sexes; a further reduction in body-weight relative to the controls (placebo microcapsule groups) did not occur despite continued exposure. Since a reduction in feed consumption occurred in the 250 ppm groups (both sexes) starting with the first exposure week, the bodyweight reduction would appear to be due mainly to the reduced feed consumption. No treatment-related effects were reported in the following areas: clinical observations, ophthalmology, hematology, serum chemistry or urinalysis. Effects on absolute organ weights (brain, kidneys, liver, testes/ovaries) and organ weights relative to bodyweight appeared to be due to the bodyweight reduction in the 250 ppm groups; this was true for animals sacrificed at test week 52 as well as for the survivors at the end of the study. Possible, treatment-related findings at necropsy were an increasing incidence of splenomegaly in the males (0 ppm, basal: 2/50; 0 ppm, placebo: 2/50; 0.5 ppm: 7/50; 2.5 ppm: 10/50; 50 ppm: 11/50; and 250 ppm, 3/50) and an increased incidence of dark red areas on the liver in the 50 ppm females surviving to test week 104 (0 ppm, basal: 5/20; 0 ppm, placebo: 3/19; 0.5 ppm: 8/22; 2.5 ppm: 4/24; 50 ppm: 14/27; and 250 ppm, 8/29). No statistical analyses were supplied for the histology data. Also, the lesion-incidence summary table did not present autolysis and lesion-grade data and may not have been corrected for tissues lost to autolysis. Possible treatment-related effects include: increased incidence of pancreatic acinar atrophy at 250 ppm (both sexes), increased incidence of adrenal cortical hypertrophy at 250 ppm (females), and increased incidence of pulmonary arterial mineralization at 50 ppm (females). Two rare tumor types, adenocarcinoma of the prostate and endometrial stromal sarcoma of the cervix, were seen at 4% incidence at 250 ppm. By experimental design, the histological examinations of the pancreas, prostate, spleen, adrenal glands, cervix, and uterus at the 0.5 to 50 ppm dose levels were limited to those rats that did not survive to terminal sacrifice. Autolysis was a frequent observation in the GI-tract organs in rats that did not survive to the end of the study (all groups, both sexes). While an increased incidence of spongiosis hepatitis was seen in the 50 ppm females, the relationship of this lesion to angiectasis and the necropsy finding of dark red liver spots that also occurred at the 50 ppm dose level needs clarification. When first reviewed (Rinkus, 3/20/98), the study was considered unacceptable pending the submission of the supplemental information described in worksheet W158746.835 regarding: range-finding study;

analytical methods; cause and extent of autolysis; histological examinations for the lower dose groups; and clarification of liver gross and histological findings. Subsequently, records 160305, 162360, 162361 and 165140 were submitted. For the reasons discussed in worksheet W158746.S03, this study is now considered marginally **ACCEPTABLE, with a LOEL = 0.5 ppm**. This is a conservative call based on the following: in the absence of histological data to the contrary, the instances of splenomegaly in the 0.5, 2.5 and 50 ppm male groups that have not been examined histologically are assumed to be due to lymphoma. (Rinkus, 3/5/99)

123-182 160305 This record was the response from the Registrant to the February 20, 1998 re-view of record 158746. It was received at DPR on March 30, 1998. The initial section consisted of 11 pages of narrative, two small tables, and one large table showing group bodyweight gains as a percentage of feed consumed on weekly basis from test week -2 to test week 104 (both sexes). The initial section addressed the following issues related to the first DPR MT review: selection of 250 ppm as the high dose; why decreased bodyweight in the 250 ppm groups would not be explained by a decrease in feed consumption due to an olfactory-aversion mechanism; the bioavailability of the methyl bromide in the microcapsules; clarification of analytical methods; and a defense of the practice of not examining all gross lesions in the study. The final section of record 160305 concerned the analytical method. It further explained the methods, addressed specific issues raised in the first DPR MT review and provided five "exhibits," which were sets of raw data and chromatograms in support of positions taken in the narrative portion. This record is discussed in worksheet W158746.S03.

Supplementary information. (Rinkus, 3/5/99).

123-187 162361 "Determination of the Stability of Microencapsulated Methyl Bromide in Diet" (Severs, L. W.; laboratory study number: WIL-49010; May 9, 1994). This is an analytical study that was referenced in record 160305. This study was supposed to be the basis for the strategy in record 158746 of heating at 100°C for 15 minutes preinjection when assaying feed containing microencapsulated methyl bromide. This record is a short report in the form of a letter (6 pages of narrative, 2 tables) from Loren W. Severs (Manager of Analytical Chemistry, WIL Research Laboratories) to Kathryn Rosica (Methyl Bromide Industry Panel, Chemical Manufacturers Association). It is notable for the following: 1) it provides no data or discussion per se supporting the selection of 100°C for 15 minutes as the preinjection heating procedure; 2) the stability analysis indicated that after 24 h at room temperature, the methyl bromide content of feed containing microencapsulated methyl bromide (100 ppm) was 80% of the content after preparation whereas no loss of methyl bromide occurred in this interval when the feed was stored in the freezer; and 3) ≥ 10 minutes of heating feed containing microencapsulated methyl bromide at 54°C results in the formation of methyl chloride. This record is discussed in worksheet W158746.S01. **Supplemental information.** (Rinkus, 11/17/98).

123-186 162360 "A Two Week Dietary Range-Finding Toxicity Study of Methyl Bromide in Rats" (Mertens, J.J.W.M.; laboratory study number: WIL-49015; April 9, 1996). This study was the basis for the selection of the high dose in record 158746. For 18 days, 5 Crl:CD@BR rats/sex/dose were fed basal diet or a diet containing 250 ppm methyl bromide presented as microcapsules dispersed in feed. The microencapsulated material was ill defined; apparently, it was obtained from Pharma-co LSR, Inc. and had a methyl bromide content of 6.1%. All rats survived to scheduled sacrifice and were necropsied. The only treatment-related effects were decreased bodyweight and decreased food consumption in the 250 ppm male group. The relevance of this study in terms of the selection of 250 ppm as the high dose in record 158746 is questionable due to the following considerations: the duration of exposure was only 18 days; it is not clear if the methyl bromide content of the microcapsules was determined; and it was not addressed whether the microencapsulated material used in this study was comparable to the microcapsules used in record 158746. This record is also notable because the analytical strategy was similar to that used in record 158746 and involved headspace analysis with heating for 15 minutes at 100°C preinjection. It was indicated that as part of the quantitation of methyl bromide, the conversion to methyl chloride was taken into account. **Supplemental information.** This record is discussed in worksheet W158746.S02. (Rinkus, 11/20/98).

123-207 165140 This record was the response from the Registrant to the March 20, 1998 review of record 158746. The initial section was a 6-page narrative addressing: the bioavailability of methyl bromide when using microencapsulated material; and specific items discussed in memo-randum M980512, dated May 12, 1998, from the DPR MT reviewer (Dr. Rinkus) to Gary Patter-son (Medical Toxicology Branch Chief) regarding the analytical methods used in record 158746. Following the initial section were four attachments concerning: 1) literature citations for other toxi-cological studies wherein an agent was tested using microencapsulation; 2) a discussion of the pathology data as a justification for not conducting the histological examinations requested in the March 20, 1998 review of record 158746; 3) data from Midwest Research Institute for the Febru-ary, 1994 titering of the 0.48% microcapsules; and 4) data from Midwest Research Institute for the January, 1995 titering of the 3.44% microcapsules. This record is discussed in worksheet W158746.S03. **Supplementary information.** (Rinkus, 3/5/99).

123-127 095929 "Two-Year Oral Chronic Toxicity and Carcinogenicity Study in Rats of Diets Fum-igated with Methyl Bromide," (Mitsumori et al., Fd. Chem. Toxic. 28:109-119, 1990). This study used F344 rats (both sexes) to examine the chronic toxicity and carcinogenicity of methylation products and bromine residues resulting from fumigation of rat feed with methyl bromide. After fumigating the feed to attain ~500 ppm total bromine, the feed was exposed to air for 3 weeks; this feed was then pulverized and mixed with untreated feed to achieve dose levels of total bromine of 200 and 80 ppm. Actual organic methyl bromide levels were not determined in this study, except to note that at the end of the 3-weeks airing, the level of organic methyl bromide in the feed con-taining ~500 ppm total bromine was < 20 ppm. The only effect observed in this study was body weight depression in males fed the diet containing 500 ppm total bromine; the effect was attributed to methylation products generated in the feed since a comparable effect was not seen in rats fed a diet containing 500 ppm KBr. **Supplementary information. No worksheet.** (Rinkus, 5/3/91).

123-157 131601 "Draft Protocol: A 24-Month Oral Chronic Toxicity Study of Methyl Bromide in Rats" (no author identified; WIL Research Laboratories, Inc.; no study/project/report number; April 27, 1993). This record is an unsigned "draft" protocol for a chronic toxicity study in Crl:CD(SD)BR rats (both sexes). The proposed route of administration is by gavage using corn oil solutions through which methyl bromide has been bubbled. Not reviewed (unsigned draft proposal). **Sup-plementary information. No worksheet.** (Rinkus, 7/24/95).

SUBCHRONIC, RAT

123-043 913094 A 90-day subchronic rat study (Danse et al., Tox. Appl. Pharm. 72: 262-271, 1984) indicated a carcinogenic response in forestomach at 50 mg/kg. (Wong, 4-8-85). However, a reanalysis of the histological slides of Danse et al. by a NTP panel concluded that the lesions appeared to be nonneoplastic only (inflammation and hyperplasia) (see letter of 5/9/84 from Dr. Boorman [NTP] to Dr. Vos [National Institute of Public Health, The Netherlands] in front of CDFA document 123-103). (Rinkus, 4/25/89). However, while Hubbs (record 059183 in CDFA docu-ment 123-083) also did not find any carcinogenicity in rats treated up to 17 weeks with 50 mg/kg, Boorman et al. (Toxicol. Applied Pharmacol. 86: 131-139, 1986) did observe an early carcinoma in one of 11 rats treated for 25 weeks at 50 mg/kg. (Rinkus, 4/17/90).

NOTE The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/17/89) notes EPA classification as "Core Minimum". CDFA reviewer (Aldous) pre-sumes this to refer only to the subchronic study data requirement, since the 1986 Regis-tration Standard did not consider the chronic rodent study data gap filled. [Aldous, 1/5/90].

123-109 087805 "Histopathology of Acute Toxic Responses in Selected Tissues from Rats Exposed by Inhalation to Methyl Bromide," (Hurtt et al., *Fund. Applied Toxic.* 9:352-365, 1987). Methyl bromide (99.9% pure) was given by inhalation to groups of 10 adult male Fischer 344 rats at 0 (air), 90, 175, 250, and 325 ppm for 6 h/day for 5 days; an additional untreated group received feed quantities identical to those consumed by the rats in the 325 ppm group. After the 5th expo-sure or *in extremis* (325 ppm, 4 days), rats were sacrificed and the following sites were examined histologically: nasal cavity, brain, liver, kidney, adrenal glands, testes, and epididymides. Ataxia and diarrhea were observed in the rats exposed to ≥ 250 ppm; tremors and/or convulsions were observed in a few rats exposed to 325 ppm; reddish perineal staining (hemaglobinuria ?) in some rats exposed to ≥ 175 ppm; no clinical effects were cited for rats exposed to 90 ppm. Histological findings were: degeneration of the nasal olfactory epithelium (≥ 175 ppm); degeneration in the cerebellar cortex (≥ 175 ppm; two lesions noted: large to small foci of granule cells, with edema-tous distension of the cytoplasm; and a diffuse granule cell degeneration without the edematous cytoplasm); degeneration in the cerebral cortex (325 ppm) and the dorsolateral regions of the thalamus (325 ppm); hepatocellular degeneration (325 ppm); lipid accumulation in parenchymal cells of adrenal cortex (≥ 175 ppm); and delayed spermiation (325 ppm). No lesions were noted in the kidneys or the epididymides; the former finding indicates that the presumed hemoglobinuria is not due to a renal lesion. The authors compared these lesions to similar lesions seen in rats ex-posed to methyl chloride (which presumably was at much greater concentrations, e.g., 3000 ppm). Supplemental information. No worksheet. (Rinkus, 2/28/90).

ACUTE, RAT

123-162 132699 "Acute Oral Toxicity Comparison of Microencapsulated Methyl Bromide and Li-liquid Methyl Bromide in Albino Rats" (Kiplinger, G.R.; laboratory study number: WIL-49011; Sep-tember 22, 1994). Two types of corn oil solutions were compared: one made with methyl bromide (added as a liquid) and the other made with microencapsulated methyl bromide. In the liquid meth-yl bromide testing, methyl bromide, 99.5% purity, was given once by gavage to 5 Crl:CD®BR rats per sex per dose level at 50, 100 and 150 mg/kg in initial testing and at 0, 80, 120 and 160 mg/kg in retesting. The initial dose levels were chosen on the basis of range-finding testing which also was discussed in the report. Rats were fasted 18-20 hours prior to dosing and feed was made available 3-4 hours after dosing. Rats were observed for mortality and clinical signs at approxi-mately 1, 3 and 4 h after dosing (postdosing day 0) and once in the morning and once in the after-noon on postdosing days 1 through 14 (day of scheduled sacrifice). All rats in the initial testing and retesting were necropsied. In the retesting, microscopic examination of the stomach, duoden-um, jejunum and ileum also was performed. With one exception, rats that died did so on or before postdosing day 2. At necropsy, the main organ affected was the stomach. The findings were con-sistent with severe irritation of the lumen surface. The mortality data indicated a slight sex differ-ence; for example, LD50 values (method of Litchfield and Wilcoxon) for males and females in the initial testing were, respectively, 139 mg/kg (125-155 mg/kg as 95% confidence interval) and 107 mg/kg (97-119 as 95% confidence interval). The lowest LD50 value was 86 mg/kg (77-96 mg/kg as 95% confidence interval); this was seen in the females in the retesting. The testing of microen-capsulated methyl bromide can not be evaluated pending clarification of the following: 1) whether the microcapsules dissolved before dosing; 2) whether the procedure for the methyl bromide con-tent analyses was appropriate; and 3) whether the microencapsulated material was comparable to the material used in the two-year microencapsulated methyl bromide feed study, record 158746. **Supplemental information.** (Rinkus, 11/13/98).

CHRONIC, DOG

Note: As has been done with other active ingredients, the collective data for toxicity studies with a non-rodent were evaluated. Although no single study has been found acceptable, no further studies are being required at this time and the data gap is considered filled, with possible adverse effects noted in several studies, as indicated in the following summaries of the in-dividual studies (Gee, 3/5/99).

Note: Chronic-toxicity testing using inhalation as the route of exposure is no longer being required (see rebuttal response of July 24, 1995). (Rinkus, 10/29/97).

123-175 143945 "A Chronic (12-Month) Toxicity Study of Methyl Bromide Fumigated Feed in the Dog" (Newton, P.E.; Pharmaco LSR.; study no. 94-3186; 1/4/96). Granular feed containing 10% corn oil was fumigated with methyl bromide at concentrations of 0, 7092, 20,000 or 116,279 ppm for one hour. After one hour of degassing, the feeds were presented to four beagle dogs/sex/dose level (except 8 dogs/sex at the high dose). Fumigated feeds were presented five d/week for one year. Nominal residual methyl bromide levels in the feed-corn oil admixture one hour after the feed had been presented to the dogs were: 0, 0.5, 1.5 and 5.0 ppm. In addition, test feeds presumably contained fumigation-derived products (bromide, methylation adducts, methyl chloride). While the concentrations of reaction products were not measured, because of the experimental design, their concentrations in the low-dose feed versus high-dose feed may have varied by a factor of 16. Re-sidual methyl bromide levels were selected on the basis of discussions between the Registrant and the USEPA to achieve a "safety" study (i.e., the high dose was not set on the basis of toxicity data). A new analytical procedure was developed to determine residual methyl bromide; however, the adequacy of the new procedure could not be assessed pending submission of supplemental information. There were no clear effects on survival, cageside observations, bodyweight or food consumption. Possible treatment-related effects included: decreased hemoglobin and (or) hematocrit at 3, 6 and (or) 12 months in the high-dose male group; and decreased serum calcium at 6 and 12 months in the mid- and high-dose male group. The incidence of thyroid C-cell hyperplasia in the male control group was 1/4 versus 5/8 in high-dose male group; histological examination of thyroids from mid- and low-dose males was not done. Statistically reduced absolute kidney weight was seen in the mid- and high-dose female groups; when viewed relative to terminal bodyweight or brain weight, kidney effects were not statistically significant. Due to the experimental design, the effects seen in this study may be due to residual methyl bromide and (or) its reaction products. **NOEL = 1.5 ppm (anemia)**. When first reviewed (Rinkus, 9/5/97), this study was considered un-acceptable and upgrading would require the submission of the following: 1) supplemental information regarding the analytical method; 2) historical control data for thyroid C-cell hyperplasia in males; 3) histological examination of the thyroid in the low- and mid-dose male groups and the parathyroid in three high-dose females whose tissues were not examined originally; and 4) the statistical analyses of the hemoglobin, hematocrit and serum phosphate data. Subsequently, the Registrant submitted records 165489 and 165490 (dated 12/23/98 and 12/29/98). The former contains data regarding the analytical method; the latter contains histological data for the thyroid and parathyroid and historical-control data for the thyroid. Based on the newly submitted data, C-cell hyperplasia has been dropped as a possible adverse effect. Validation for the analytical method is requested (discussed in worksheet W143945.S01). **Supplemental information.** (Rinkus, 2/22/99).

123-208 165489 This consists of the following: 1) separate responses to issues discussed in worksheet W143945.831 regarding the analytical method; 2) an attachment containing typical chromatograms for the analyses of untreated feed samples; 3) an attachment containing handwritten data sheets and chromatograms for time-course studies of the loss of methyl bromide from dog feed after it had been fumigated; 4) an attachment containing handwritten data sheets and chromatograms for headspace analyses of methyl bromide after it had been spiked into polypropylene containers that were empty or that contained feed; and 5) an attachment containing the daily log sheets for the fumigation of the dog feed. This record is discussed in worksheet W143945.S01. **Supplemental information.** (Rinkus, 3/5/99).

123-209 165490 This consists of the following: 1) a narrative that discusses the hematology and serum chemistry data in record 143945 as well as the newly submitted histological data for the thyroid and parathyroid contained in record 165490; 2) individual animal data sheets for all dogs on test regarding the microscopic examination of the thyroid and parathyroid glands; 3) historical control data from the conducting laboratory for the microscopic examination of the thyroid in 1-, 3-and 12-month studies; 4) the protocol for the study; and 5) protocol amendments for record 143945. This record is discussed in worksheet W143945.S01. **Supplemental information.** (Rin-kus, 3/5/99).

048 913193(4110) "Chronic Ingestion by Dogs of Methyl Bromide Fumigated Food." (Albany Medical College, 1960) Methyl bromide fumigated food was fed to beagles, 4/group, daily at 0, 150, 75 or 35 mg/kg/day. **No adverse effect indicated:** Apparent NOEL = 75 mg/kg/day (lethargy, obesity, and one death at high dose). **Unacceptable.** Test article not characterized, no analysis of feed over the 6 to 8-week periods in which a given batch of test article was used, no necropsy/pathology data presented, too few animals (only 4 females at all treatment levels combined). J. Wong, 4-8-85.

123-161 132895 This record is an addendum to a letter from the Registrant to Jim Wells (director, DPR) dated October 19, 1994 (contained in the front of document 123-161). The letter and the addendum were submitted as a petition to DPR to drop its requirement for a dog inhalation chronic toxicity study. Record 132895 (and the letter) are reviewed in a memorandum from Dr. Rinkus to Dr. Gee dated January 19, 1995 (M950119). **Supplemental information. No worksheet.** (Rin-kus, 7/24/95).

ACUTE/SUBACUTE, DOG

123-124 091578 "Acute Oral Toxicity Study in Beagle Dogs with Methyl Bromide," (Naas, D.; WIL Research Laboratories, Inc.; project no. WIL-49006; 10/9/90). Methyl bromide, 100% purity, was administered one time orally (corn-oil solutions in gelatin capsules) to beagle dogs (1/sex/treatment level) at 500, 50, 5, 3, and 1 mg/kg; no negative controls were used. Testing at 5 and 3 mg/kg consisted of using two different concentrations of methyl bromide: high concentration (HC), 158 and 138 mg/ml, respectively; and low concentration (LC), 63 and 64 mg/ml, respectively. Dogs were observed daily for clinical signs for 1-2 weeks postdosing, depending on the treatment level. Both dogs treated at 500 mg/kg exhibited severe signs of toxicity and vomiting and were found dead the next day; necropsy indicated toxicological effects in the stomach, kidneys, adrenal glands, and brain. No other dogs in the study died and no other dogs were necropsied. Severe signs of toxicity and vomiting of reddish material (presumably blood) were seen in the dogs treated at 50 mg/kg. The only other clinical sign seen in the other groups was vomiting, which in some cases contained reddish material. No vomiting was seen during the one week postdosing observation period in two dogs treated at 1 mg/kg or the females treated at 5 (LC) and 3 (HC) mg/kg. Supplementary data. (Rinkus, 11/2/90).

123-124 091577 This record is a letter from the contract laboratory that conducted the acute oral dog study in record 091578 to Great Lakes Chemical Corp. (member company in the MBIP); it describes the observation of vomiting in two dogs treated once with methyl bromide at 5 mg/kg, using gelatin capsules that contained **microencapsulated** methyl bromide. Supplementary information. No worksheet. (Rinkus, 11/2/90).

123-163 132818 "An Up-and-Down Acute Inhalation Toxicity Study of Methyl Bromide in the Dog" (Newton, P.E.; Pharmaco LSR, Inc.; study number 93-6067; 9/14/94). One-day, two-day and four-day exposures were conducted as part of a range-finding process to select doses for an one-year exposure study. Dogs (one per concentration) were exposed for 7 h in the following order: 314 ppm, 233 ppm, 314 ppm, 394 ppm (6 h only due to severity of effects), 350 ppm and 345 ppm.

Tremors and (or) trembling extremities were seen during exposure in each of the one-day experiments. **NOAEL (one day) = <233 ppm.** In the two-day exposure study, the six dogs used in the one-day exposure study were divided into two groups of three: one group was exposed to 268 ppm and the other, 283 ppm. At the start of this study, all dogs appeared clinically normal. The dogs were supposed to be exposed for four days (7 h/d) but the study had to be terminated after two days due to the observation of the following: severe neurotoxicity (delirium, thrashing and vocalization, tremors, traumatizing behavior [defined as slamming the head and body into the cage walls], depression, ataxia, irregular gait), rales and a cachectic appearance. Also, increased blood urea nitrogen and serum aspartate aminotransferase were serum chemistry findings for the dogs in both exposure groups. **NOAEL (two days) = <268 ppm.** The four-day exposure study used dogs that had not been exposed to methyl bromide previously. One male and one female were exposed to 55 ppm and 156 ppm for four days (7 h/d) and the dogs were terminated after the 4th exposure. Both dogs exposed to 156 ppm showed decreased activity during exposure on exposure days 3 and 4 and irregular gait during the postexposure observation period on exposure day 4. No abnormal signs were observed during or after exposure for the 55 ppm dogs. **NOAEL (four days) = 55 ppm.** Based on these results, the authors of record 132818 concluded that the cumulative effect for methyl bromide induced neurotoxicity made it difficult to estimate an exposure level which the dogs could tolerate for a 28-day or 1-year exposure study. **Supplemental information.** (Rinkus, 7/21/95).

123-164 132821 "A Four Week Inhalation Toxicity Study of Methyl Bromide in the Dog" (Newton, P.E.; Pharmaco LSR, Inc.; study no. 93-6068; 9/14/94). Methyl bromide (100% purity) was administered to beagle dogs (2-4 dogs per sex per treatment level) by whole body inhalation at 7 h/d, 5 d/week, for 23-24 exposure days (0, 25, 50 and 100 ppm), 30 exposure days (24 exposure days at 10 ppm, then 6 exposure days at 150 ppm), and 34 exposure days (0 and 5 ppm). Treatment levels were selected on the basis of a four-day exposure study (record 132818). Serum bromide levels were increased in a dose-response fashion in dogs exposed to ≥ 25 ppm. Bodyweight loss and neurotoxicity were seen in the dogs exposed to 150 ppm. Decreased activity was seen during exposure, starting on the 2nd exposure day to 150 ppm; and the dogs were in a poor condition during the final (6th) exposure. The next day three 150 ppm males had to be sacrificed due to exhibiting opisthotonos, irregular gait, opening and closing of the jaws and convulsions. The remaining 150 ppm dogs exhibited: nystagmus, intention tremors, ataxia, irregular gait and depression. Urinalysis indicated elevated levels of protein and bilirubin in the urine of the 150 ppm dogs. Histological examinations indicated that each of the 150 ppm dogs had cerebellar lesions (vacuoles in the granular layer) and olfactory degeneration; the males also had adrenal cortex findings (zona fasciculata, cytoplasmic vacuoles). Decreased bodyweight gain and less severe neurotoxicity (tremors, emesis, decreased activity during exposure but not postexposure) were seen in the 100 ppm dogs. One 100 ppm male exhibited a cerebellar lesion like that seen in the 150 ppm dogs. Decreased activity during exposures also was noted in two dogs exposed to 50 ppm, starting exposure day 14; but no findings were made for the 50 ppm group in postexposure examinations, including those done by a neurologist. **NOAEL (23-24 exposure days) = 50 ppm.** The female dogs exposed the longest to methyl bromide (5 ppm group) had reduced absolute spleen weight and two 5 ppm females were observed by the neurologist at the end of test week 6 to be less responsive than expected. Whether the latter constitutes an incipient neurological effect remains to be seen. **LOAEL (34 exposure days) = 5 ppm.** Major deficiencies include: inadequate conduct and reporting of the nervous system histological analysis (no *in situ* perfusion of brain; no musculature examination; possibly an inadequate number and selection of brain tissues examined); inadequate reporting of animal observations; and failure to secure organ weights, hematology, and serum chemistry data on the three 150 ppm males exhibiting the greatest neurotoxicity. **Supplemental information.** (Rinkus, 12/5/94).

123-156 130781 This record is a letter dated June 8, 1994 from the Registrant to the Office of Pesticide Programs of USEPA, informing them that neurotoxicity had been observed in a 5-7 week dog inhalation study (record 132821). The letter indicates that the NOAEL was 100 ppm. The fact that DPR MT has set the NOAEL at 50 ppm is discussed in the rebuttal response of July 24, 1995 (R950724). **Supplemental information. No worksheet.** (Rinkus, 7/24/95).

ONCOGENICITY, RAT

Note: The one-liner for record 158746, a combined chronic toxicity-oncogenicity study using feed containing microcapsules of methyl bromide dissolved in corn oil, appears in the section "CHRONIC, RAT"

****084 059184** "Chronic (29-Month) Inhalation Toxicity and Carcinogenicity Study of Methyl Bromide in Rats," (Civo Institutes TNO, The Netherlands; report no. V86.469/221044, 1/87). Methyl Bromide, purity 98.8%, administered by whole body inhalation at concentrations of 0, 3, 30 or 90 ppm to 90 Wistar rats/sex per treatment level, 6 hours/day, 5 days/week for 29 months. Decreased bodyweight in the females and decreased survival in both sexes were observed in the high-dose groups. Nonneoplastic effects included: irritation of the epithelium of the nasal cavity (hyperplastic changes) in all treatment groups, decreased brain weight for high-dose females; and increased incidence of thrombi in the heart for both sexes in the high-dose groups. When first reviewed (Rinkus, 3/29/89), this study was considered unacceptable but upgradable upon submission of individual data and more information regarding the histological analyses of several organs (nasal cavity, thymus, hemopoietic system and brain). Individual data were submitted in record 116337 and historical control data were discussed in record 120402. Based on the brain weight data in record 116337, another adverse effect was identified: decreased absolute brain weight in both sexes surviving to terminal sacrifice, with a NOAEL of 3 ppm. In the second review (worksheet W059184.S01), the study was still considered unacceptable, but upgradable upon submission of histological data for the brains of rats in the interim sacrifice groups that died prematurely and other supplemental information regarding: the histological findings for the brain; the observation of neurological signs; and the historical control database (discussed in the rebuttal response R930205). The requested data were supplied in record 133417 and reviewed in worksheet W059184.S02. Since two neoplastic lesions from the 30 ppm female group originally diagnosed as gliomas had been reclassified as granular cell myoblastomas, the induction of gliomas was dropped as a possible adverse effect finding. Pursuant to the registrant's request, the setting of the LOAEL for olfactory-epithelium effects was revisited. It was concluded that the LOAEL for the increased incidence of basal-cell hyperplasia in the olfactory epithelium was dependent on the duration of the exposure: for exposures lasting 12 months, 12-24 months and 24-29 months, the respective LOAELs were >90 ppm, 30 ppm and 3 ppm. Also, it was noted that degenerative changes (thinning of the overlying epithelium) accompanied the basal cell hyperplasia. Based on record 133417, record 059184 was upgraded to an **ACCEPTABLE** study (Rinkus, 7/10/95). In record 156300, the Registrant provided the results of a reexamination of the nasal-cavity histological slides from record 059184 by Drs. Jerry F. Hardisty (Experimental Pathology Laboratories, Inc.) and C.F. Kuper (TNO). Based on the reexamination, it was proposed that the LOAEL for olfactory epithelium effects be set at 30 ppm. However, this has not been accepted by DPR MT for reasons that include the following (discussed in worksheet W059184.S03): 1) the reexamination was not conducted in accordance with standard procedures for a peer review; and 2) even with the revised data, a dose response for incidence and severity was still evident, starting with the 3 ppm dose. (Rinkus, 9/23/97).

123-109 087806, 087807 IARC Monograph on methyl bromide (Vol. 41, pp. 187-212, 1986). No worksheet. (Rinkus, 3/2/90).

123-109 087798 Computer search of the IRIS data base on methyl bromide (bromomethane). No worksheet. (Rinkus, 6/4/90).

123-147 116337 This record contains the individual data for record 059184. It also contains organ-weight data for those rats from the main groups surviving to terminal sacrifice; these data were not mentioned in record 059184. **Supplemental information.** (Rinkus, 1/19/93).

123-148 120402 This record uses a question-and-answer format to address matters concerning record 059184 that were raised in the original review of this study (worksheet W059184.832) and in the rebuttal response R910712. The authors of this record are scientists at the Dutch-government laboratory that conducted the study reported in record 059184 (TNO-CIVO Toxicology and Nutrition Institute). **Supplemental information. No worksheet.** (Rinkus, 2/5/93).

123-148 120406 This record is a 2-page letter from Dr. Til of the TNO-CIVO Toxicology and Nutrition Institute to Dr. McAllister of Great Lakes Chemical Corporation. It contains corrections to the individual data (record 116337) and the original report (record 059184) that resulted from an audit of these records by the conducting laboratory. **Supplemental information. No worksheet.** (Rinkus, 2/5/93).

123-148 120408 This record is a photocopy of the first 9 pages of record 116337. **Supplemental information. No worksheet.** (Rinkus, 2/5/93).

123-166 133417 "Reevaluation of Pathology and Related Data Generated as Part of a Methyl Bromide Oncogenicity Study in Rats: Response to Questions Raised by the California Department of Food and Agriculture, Medical Toxicology Branch Document No. 123-147 (Addendum to Document 123-084)" (Bos-Kuijpers, M.H.M., Kuper, C.F., and Feron, V.J.; Civo Institutes TNO, The Netherlands; report no. V94.594; Nov., 1994). This record uses a question-and-answer format to address matters raised in R930205 concerning the histological, historical and neurological data contained in records 058194 and 116337. This record is discussed in worksheet W059184.S02. **Supplemental information. No worksheet.** (Rinkus, 7/24/95).

123-178 156300 "Chronic (29-Month) Inhalation Toxicity and Carcinogenicity Study of Methyl Bromide in Rats--Reexamination of Nasal Cavity" (J.F. Hardisty; Experimental Pathology Laboratories, Inc.; study number B-91-8213/002; July 21, 1997). At the request of the Registrant, Dr. Hardisty examined all nasal-cavity sections generated in the TNO rat inhalation study, record 059184. The intent was to determine "the accuracy and consistency of the initial diagnoses reported by the study pathologist," Dr. C.F. Kuper (TNO). All differences between the two pathologists were reconciled; i.e., agreement was reached on the final diagnoses in each case. Based on the reexamination, it was concluded that the LOAEL for the olfactory epithelium effects should be changed to 30 ppm. This record is reviewed in worksheet W059184.S03. **Supplemental information.** (Rinkus, 9/23/97).

123-174 143944 "Two-year Toxicological and Carcinogenesis Studies of Methyl Bromide in F344 Rats and BDF1 Mice" (Gotoh et al.; Japan Bioassay Laboratory; In: "Proceedings -- Second Asia-Pacific Symposium on Environmental and Occupational Health -- 1994", pp. 185-191). This is a 7-page report. It summarizes longterm studies done by inhalation (6 h/d, 5 d/w for 104 weeks) using F344/DuCrj rats and Crj:BDF1 mice; in both species, 50 animals per sex per dose were tested. Rats were exposed to 0, 4, 20 and 100 ppm; mice were exposed to 0, 4, 16 and 64 ppm. The authors indicated that there were no effects on survival in either species, that bodyweight reduction was mainly limited to the high-dose groups (both sexes) in both studies, that nonneoplastic effects were seen in the nasal cavity and cerebellum of the rats and mice, respectively, but that "evidence of carcinogenicity of methyl bromide was not obtained" in either species. However, inspection of the summary data indicates that the incidence of the following achieved statistical significance at the 0.01 level: pituitary adenoma in the 100 ppm male rats; adrenal-gland pheochromocytoma in the 4 ppm female rats; and liver adenoma in the 4 ppm female mice. Also, increased tumor incidences in some methyl bromide-treated groups are a concern either due to the (presumed) rarity of the tumor (thyroid follicular-cell adenocarcinoma in the 100 ppm male rats; mesothelioma in the 20 ppm male rats) or the

(apparent) failure to analyze tumor incidences for all sites combined (he-mangioma/hemangiosarcoma in male mice; lymphoma in female mice). In order to do a complete evaluation of these studies, the full databases, including individual data, historical control data and subchronic studies, need to be submitted. **UNACCEPTABLE, UPGRADEABLE.** (Rinkus, 9/29/97).

ONCOGENICITY, MOUSE

****123-146 116243** "Toxicology and Carcinogenesis Studies of Methyl Bromide in B6C3F1 Mice (Inhalation Studies)," (Brookhaven National Laboratories, NTP Technical Report 385, March, 1992). Methyl bromide, purity 99.8%, was administered by whole body inhalation at concentrations of 0, 10, 33 and 100 ppm to 86 B6C3F1 mice/sex/treatment level, 6 h/day, 5 days/week for 2 years. Exposures to 100 ppm had to be stopped after 20 weeks due to debilitating neurotoxicity and mortalities, especially among the males; these groups (both sexes) were exposed only to un-treated air for the remainder of the study. Treatment levels were chosen on the basis of subchronic testing which was included in the report. Interim sacrifices of ~10 mice/sex/treatment level were performed at 6 months and 15 months; also, 16 mice/sex/treatment level primarily were used for neurobehavioral testing every 3 months. Clinical signs indicative of neurotoxicity (tremors, paralysis, unusual gait, abnormal posture) were observed in 78% of the males and 43% of the females exposed to 100 ppm methyl bromide and were observed in 2-3% of the mice (both sexes) exposed to 33 ppm methyl bromide. In many cases, the clinical signs in the 100 ppm groups began to appear well after their exposure to methyl bromide had stopped. Neurobehavioral testing identified effects in the 100 ppm groups at 3 months (both sexes) and later (only females could be tested). Neurobehavioral testing also found effects in the 10 ppm and 33 ppm groups starting after 6 months of exposures. Decreased bodyweight was observed in the 33 ppm and 100 ppm female groups and the 100 ppm male group. Heart lesions, either cardiac degeneration or chronic cardiomyopathy, were observed in 80% of the males and 69% of the females exposed to 100 ppm methyl bromide; also, the incidence of chronic cardiomyopathy in the male 33 ppm group (20%) was greater than that seen in the controls (8%). Sternal dysplasia was observed at low incidence (4-6%) in the 10 ppm and 33 ppm female groups and the 33 ppm male group and was observed at a higher incidence (15-20%) in the 100 ppm groups (both sexes). The rarity and the late onset for the sternal lesion raises the possibility that it is the result of some type of neuromuscular toxicity, as opposed to a direct effect on the sternum. Degenerative lesions in the brain were observed in 44% and 18% of the male and female 100 ppm groups, respectively. The lesions were located in the cerebellum (internal granular layer cells) and sometimes were accompanied by degenerative lesions in the cerebrum. Since some brain lesions were seen in 100 ppm mice surviving till terminal sacrifice (therefore not exposed to methyl bromide since test week 20), some damage caused by methyl bromide to the brain is not repairable. Olfactory epithelium lesions, either necrosis or metaplasia, were observed in 12% of the mice exposed to 100 ppm methyl bromide (both sexes). **NOAEL < 10 ppm (neurobehavioral testing changes, sternal dysplasia).** No evidence of any carcinogenicity was observed. This study is considered **ACCEPTABLE.** (Rinkus, 11/6/92).

123-145 076659 This record is an exact duplicate of record 116243. **Supplemental information. No worksheet.** (Rinkus, 7/24/95).

123-174 143944 "Two-year Toxicological and Carcinogenesis Studies of Methyl Bromide in F344 Rats and BDF1 Mice" (Gotoh *et al.*; Japan Bioassay Laboratory; In: "Proceedings -- Second Asia-Pacific Symposium on Environmental and Occupational Health -- 1994", pp. 185-191). This is a 7-page report. It summarizes longterm studies done by inhalation (6 h/d, 5 d/w for 104 weeks) using F344/DuCrj rats and Crj:BDF1 mice; in both species, 50 animals per sex per dose were tested. Rats were exposed to 0, 4, 20 and 100 ppm; mice were exposed to 0, 4, 16 and 64 ppm. The authors indicated that there were no effects on survival in either species, that bodyweight reduction was mainly limited to the high-dose groups (both sexes) in both studies, that nonneoplastic effects were seen in the nasal cavity and cerebellum of the rats and mice, respectively, but that "evidence of

carcinogenicity of methyl bromide was not obtained" in either species. However, inspection of the summary data indicates that the incidence of the following achieved statistical significance at the 0.01 level: pituitary adenoma in the 100 ppm male rats; adrenal-gland pheochromocytoma in the 4 ppm female rats; and liver adenoma in the 4 ppm female mice. Also, increased tumor incidences in some methyl bromide-treated groups are a concern either due to the (presumed) rarity of the tumor (thyroid follicular-cell adenocarcinoma in the 100 ppm male rats; mesothelioma in the 20 ppm male rats) or the (apparent) failure to analyze tumor incidences for all sites combined (hemangioma/hemangiosarcoma in male mice; lymphoma in female mice). In order to do a complete evaluation of these studies, the full databases, including individual data, historical control data and subchronic studies, need to be submitted. **UNACCEPTABLE, UPGRADEABLE.** (Rinkus, 9/29/97).

REPRODUCTION, RAT

****123-082 058196** "Two-Generation Reproduction Study Via Inhalation in Albino Rats Using Methyl Bromide," (American Biogenics Corporation, Decatur, IL; laboratory study number 450-1525, 2/19/86). Methyl Bromide (lot and purity not stated) was administered to Sprague Dawley rats of both sexes by whole body inhalation 6 h/day for 5 days/week at the nominal levels of 0, 3, 30 or 90 ppm. Parental animals were exposed for about 40 or 55 days and 90-105 days before their first and second matings, respectively, and were exposed for a total of 132-145 days before they were sacrificed. Premating bodyweights were decreased statistically only in F0 males in the 90 ppm group. Absolute brain weights were decreased in F0 males, F1 males, and F0 females in the 90 ppm groups. In the second mating of the F1 parents, the fertility index decreased from 90.9% in the controls to $\leq 68\%$ in the 30 and 90 ppm groups. The progeny from the 30 and 90 ppm groups exhibited statistically reduced bodyweights at weaning in each of the four litters produced by these groups. For the female F2b progeny from the 90 ppm group, the absolute weights of the brain, heart, kidneys, and liver were reduced statistically; weight reductions of a lesser degree also occurred for the kidneys, liver, and testes of the corresponding male progeny. When first reviewed (3/21/89), the parental NOEL was tentatively set at 3 ppm based on the reduced fertility seen at 30 ppm and the study was considered unacceptable but upgradeable upon submission of: 1) lot number and purity of test article; 2) more details about exposure conditions and monitoring; and 3) microscopic examination of target organs in parents per EPA guidelines. Items 1 and 2 were satisfied by the submission of DPR documents 123-109 (attachment 6 [no record number]) and 123-139, respectively. Item 3 was marginally satisfied by the submission of record 125516. Items 1-3 are discussed in worksheet W058196.S01. The quantitative histological data indicate that in the F1 90 ppm groups (both sexes), there was a decrease in the width of the cerebral cortex (section III-h in the sectioning scheme of Rodier and Gramann [*Neurobehavioral Toxicology*, 1:129-135, 1979]). Other parameters also were decreased in the F1 90 ppm females (parameters IIh and IVb) or F1 males (parameters IIIa and IIIb). Since the mid- and low-dose F1 groups have not been examined, no NOAEL has been established for these effects per se. However, the reduced brain weights for the F1 30 ppm females will be used to assume that the LOAEL for the reduced cerebral-cortex width is 30 ppm. Quantitative histological parameters were not affected in the F0 90 ppm adults, thus indicating that the F1 effects were the result of the perinatal exposure of the F1 rats. No gliosis or other brain lesions were noted in any F1 or F0 adults. **Parental NOAEL = 3 ppm (reduced fertility). Progeny NOAEL = 3 ppm (decreased pup bodyweight and some organ weights; reduced F1 brain weight/reduced width of the cerebral cortex).** It should be noted that the pregnant dams in this study were only exposed 5 d/w (for a total of 14-15 d) during their pregnancy and that the pups were not directly exposed until after weaning (postnatal day 28). This study is now considered marginally **ACCEPTABLE.** (Rinkus, 5/26/95).

094 059912 Protocol to 082 058916. No worksheet; not reviewed. (Kishiyama, 3/21/89).

123-139 111505 This record concerns the analytical measurements of the methyl bromide atmospheres generated in record 058196. This record is discussed in worksheet W058196.S01. **Sup-**

plemental information. No worksheet. (Rinkus, 7/24/95).

123-142 113606 "Histopathological Evaluation of Brains from Rats--Inhalation Study of Methyl Bromide," (Hardisty, J.F.; Experimental Pathology Laboratories, Inc., Research Triangle Park, NC; EPL Project Number: 303-007; 3/2/92). This record contains qualitative histological data from the analyses of the brains of the F1 adults generated in record 058196. This record is discussed in worksheet W058196.S01. **Supplemental information. No worksheet.** (Rinkus, 7/24/95).

123-153 125516 "Chemical Manufacturer's Association Study Number 450-1525: Neuropathological Evaluation of Brains from F0 and F1 Rats in a Two-Generation Reproduction Study with Methyl Bromide--Pathology Report" (W. M. Busey; Experimental Pathology Laboratories, Inc.; EPL project number 303-007; Feb. 25, 1993). This record contains quantitative histological data for the brains of the F1 and F0 adults exposed to 0 ppm or 90 ppm (only dose levels considered) from record 058196. These data indicate that in the F1 90 ppm groups (both sexes), there was a decrease in the width of the cerebral cortex (section III-h in the sectioning scheme of Rodier and Gramann [Neurobehavioral Toxicology, 1:129-135, 1979]). Other parameters also were decreased in the F1 90 ppm females (parameters IIh and IVb) or F1 males (parameters IIIa and IIIc). Quantitative histological parameters were not affected in the F0 90 ppm adults, thus indicating that the F1 effects were the result of the perinatal exposure of the F1 rats. This record was reviewed in worksheet W058196.S01. **Supplemental information. No worksheet.** (Rinkus, 7/24/95).

123-152 124863 This record is an unsigned, "draft" version of record 125516. This record has not been reviewed since it was superseded by record 125516. **Supplemental information. No worksheet.** (Rinkus, 7/24/95).

No Record Number. "Protocol for the Neuropathological Evaluation of Brains from F0 and F1 Rats in a Two-Generation Reproduction Study with Methyl Bromide, Toxigenics Study Number 450- 1525," (W. M. Busey; Experimental Pathology Laboratories, Inc.; May 8, 1992). This protocol, which was sent by fax as a response to a telephone conference between the representatives of the MBIP and DPR MT on May 5, 1992, is the protocol for record 125516. This protocol was discussed in the rebuttal response of May 13, 1992 (R920513). **Supplemental information. No worksheet.** (Rinkus, 7/24/95).

123-109 087804 "Evaluation of Spermatogenesis and Sperm Quality in the Rat Following Acute Inhalation Exposure to Methyl Bromide," (Hurt, M.E. & Working, P.K., Fund. Applied Toxicol. 10: 490-498, 1988). Methyl bromide (99.9% pure) was given by inhalation to adult male Fischer 344 rats at 0 (air) or 200 ppm for 6 h/day for 5 days. Rats from both treatment groups were sacrificed (5 or 10 per group, depending on the day) at the following times: days 1 (first day of exposure), 3, 5, 6, 8, 10, 17, 24, 38, 52, and 73. At day 5, the methyl bromide-treated group weighed ~10% less than the control group and continued to weigh less till day 52. The methyl bromide group exhibited lower plasma testosterone on days 1, 3, 5, and 6 and a decrease in nonprotein sulfhydryl in the testis and liver on days 1 and 3. Endpoints that were not affected were: clinical signs; testis weight; testicular and epididymal histology; daily sperm production; cauda epididymal sperm count; sperm morphology; sperm motility; and linear sperm velocity. However, CDFA notes spermatocytes and differentiating spermatogonia were sampled only once each (days 52 and 73, respectively); this could be important for sperm parameters like sperm count, morphology, and motility. The authors compared these test results with those seen in rats inhaling 3000+ ppm methyl chloride in a similar acute exposure. **Supplemental information. No worksheet.** (Rinkus, 2/26/90).

TERATOGENICITY, RAT

****123-039 026866** "Teratologic Assessment of Butylene Oxide, Styrene Oxide and Methyl Bromide (Rats)" (Battelle, Pacific Northwest Laboratory, contract no. 210-78-0025; NIOSH Technical Report, July 1981). Pure methyl bromide was administered to Wistar rats by whole body inhalation 7 hrs/day

on days 1 to 19 of gestation at 0, 20 or 70 ppm. Some groups received pregestational exposure for 5 days/week over three weeks immediately prior to mating. The following combinations of pre- and post-mating treatments were employed: 0/0, 0/20, 0/70, 20/0, 20/20, 70/0, and 70/70 ppm pre/post-treatment. Initially reviewed as: no apparent adverse effects indicated; maternal NOEL = 20 ppm (diminished body weight gain in early to mid gestation); apparent developmental NOEL = 20 ppm (treatment-related skeletal and delayed ossification effects); unacceptable, upgrade possible; J. Remsen (Gee), 9-4-85; C. Aldous, 10/20/87. In the second review by Rinkus (4/13/89), it was concluded that the high dose did not obviously affect dam bodyweights; maternal NOEL was revised to: > 70 ppm and developmental NOEL remained 20 ppm. The study was considered unacceptable, but upgradeable upon submission of: evidence that test material was technical grade; evidence that a MTD essentially was tested; and individual data for mothers and fetuses. The study is now considered ACCEPTABLE because: technical grade material typically is of high purity like that used in this study; while 70 ppm probably is less than half of a MTD, this is a moot point since the high-dose did exert an effect (delayed skull ossification); and the re-view of the individual data to see if the effect is being mediated by maternal toxicity will be done if necessary in the risk assessment phase. (Rinkus, 5/24/91).

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/17/89) notes EPA classification as having been changed from "Core Minimum" to "Core Supplementary" (but upgradeable).

092 059690 Partial duplicate to 039 026866. No worksheet. (Kishiyama, Rinkus, 4/13/89)

039 026867 "Teratogenicity Investigation of Orally Administered Methyl Bromide." (An investigation "conducted by Dutch authorities" translated for EPA by Great Lakes Chemical Company, 6-81) Methyl bromide, no purity given, was administered to rats by gavage on day 5 to 20 of gestation at 0 (peanut oil), 0.5, 5, 25 or 50 mg/kg. **Unacceptable.** Poor translation, incomplete with no data. J. Remsen (Gee), 9-4-85.

NOTE: This study was not available to EPA for review as of 2/17/89.

No Record Number. "Oral Teratogenicity Studies of Methyl Bromide in Rats and Rabbits" (Kane-da, M, Hojo, H., Teramoto, S. & Maita, K.; Institute of Environmental Toxicology, Tokyo, Japan; Food Chem. Toxicol. 36:421-427, 1998). Methyl bromide (purity 99.5%) dissolved in corn oil was administered by gavage to 23-24 pregnant Crj:CD (SD) rats/dose at 0 (corn oil), 3, 10 and 30 mg/kg on gestation days 6-15 and to 15-18 pregnant Kbl:JW rabbits at 0 (corn oil), 1, 3 and 10 mg/kg on gestation days 6-18. Rats and rabbits were sacrificed on gestation days 20 (ether inhalation) and 27 (pentobarbital iv injection), respectively. The highest doses tested were selected (apparently) on the basis of preliminary studies that included dosing rats and rabbits at 25 and 30 mg/kg, respectively. The dosing volumes were 10 mL/kg for rats and 0.5 mL/kg for rabbits; as a result, the high-dose rats were gavaged with a 3 mg/mL solution while the high-dose rabbits were gavaged with a 20 mg/mL solution. In both species, maternal effects were observed only in the high-dose groups. Both species exhibited decreased bodyweight gain; but only rabbits lost body-weight relative to predosing. Decreased food consumption occurred in both species; in the case of the rats, the fact that the negative control group also exhibited decreased food consumption suggests that the large volume of corn oil used (10 mL/kg) or the act of being gavaged constituted a stress on the animals. At necropsy, only the high-dose rats had findings: all dams exhibited erosion and thickening of the wall in the nonglandular part of the stomach and adhesions between the stomach and the spleen, liver or diaphragm. In both species, no clinical signs were observed (i.e., no neurotoxicity). In rats, the only fetal findings of interest were seen in the high-dose group: microphthalmia in two fetuses (two litters [8% incidence]) and having 25 (not 26) presacral vertebrae in five fetuses (two litters [8% incidence]); no cases of microphthalmia or decreased vertebrae count were seen in the negative-control group. While neither effect was statistically significant, typically both of these findings are seen infrequently in negative-control litters using Sprague Dawley rats (i.e., $\leq 1\%$ litter incidence). In rabbits, total litter resorption occurred with two high-dose does and one negative-control doe; the number of resorptions involved in these instances was not indicated. In rabbits, the only fetal finding of interest was the observation that each of the three methyl bromide-treated groups had more fetuses with skeletal

malformations than what was observed in the negative-control group. Skeletal malformations involving 2-3 litters in at least one methyl bromide-treated group included: splitting of the nasal/frontal/parietal bones; hemivertebra; fusion of the ribs/sternebrae; and absence of the metacarpal and phalangeal bones. At the litter level, no increased incidence was statistically significant nor were there any dose responses. Notwithstanding that historical negative-control data for Kbl:JW rabbits are not generally available in the open literature, the differences between the negative-control and methyl bromide-treated groups appear too small to warrant further concern. **Supplemental information.** (Rinkus, 12/23/98).

TERATOGENICITY, RABBIT

039 026865 "Teratologic Assessment of Butylene Oxide, Styrene Oxide and Methyl Bromide - Rabbits." (NIOSH, 9-82) Methyl bromide, 99.5%, was administered by whole body inhalation to New Zealand White rabbits, 7 hrs/day, day 1 to 24 of gestation at 0, 20 or 70 ppm, 24/group. **Un-acceptable.** No individual data, 2 doses only with one too high. J. Remsen (Gee), 9-4-85. It should be noted that neurotoxicity and death were observed in the rabbits inhaling 70 ppm methyl bromide in this study. The onset of the neurotoxicity and death occurred concurrently after about 1 week of exposures. Out of a group of 25 does, 3 were dead by gestation day 10, increasing to a total of 9 dead by gestation day 15, when exposures were stopped; all does in this group except one were dead by gestation day 30. (Rinkus, 1/17/92).

NOTE: EPA did not accept this study for regulatory purposes (see EPA Re-registration Guidance document of Aug., 1986, 123-071, p. 9).

092 059690 Partial duplicate to 039 026865. No worksheet. (Kishiyama, Rinkus, 4/13/89)

104 066800 Protocol (draft). A letter from Hazleton Laboratories dated January 28, 1988 for a rabbit teratology study indicates a final protocol is pending. No worksheet. (Kishiyama, 1/24/89)

****123-127 095930** "Methyl Bromide Inhalation Teratology Study in New Zealand White Rabbits," (Breslin *et al.*; The Toxicology Research Laboratory, Dow Chemical Company; Laboratory Project Study ID number K-000681-033; 6/18/90). Methyl bromide was administered by whole body inhalation 6 h/d on days 7-19 of gestation at concentrations of 0, 20, 40 and 80 ppm to 15-21 pregnant New Zealand White rabbits/treatment level (part I) or 0 and 80 ppm to 15-16 pregnant does/treatment level (part II); does were sacrificed on day 28. Treatment levels were chosen on the basis of a pilot study, which is now on file at CDPR (record 111266). Maternal effects were limited to the 80 ppm groups and consisted of decreased bodyweight gains and clinical signs indicative of neurotoxicity (part I only, 3 does: right-sided head tilt, ataxia, slight lateral recumbency, lethargy). **Maternal NOAEL = 40 ppm (neurotoxicity).** Fetal bodyweight was decreased statistically in the 80 ppm group in part II. Fetal effects that appeared to be the results of treatments included: omphalocele (80 ppm group, part I); hemorrhaging with or without hydrops (80 ppm, parts I & II); retroesophageal right subclavian artery (80 ppm group, part I); gall bladder agenesis (80 ppm, parts I & II); and fused sternebrae (80 ppm, part I; no skeletal analysis in part II). When first reviewed (5/3/91), this study was considered **UNACCEPTABLE**, with a developmental NOAEL of 20 ppm (fused sternebrae; omphalocele); and to upgrade the following had been requested: 1) necropsy data of pups/fetuses of 80 ppm does that delivered early or were found dead; 2) the pilot study; and 3) clarification of matters concerning historical control data, umbilical hernia/omphalocele & number bred in part II. These data have now been submitted (records 111265 and 111266) and, as discussed in worksheet W095930.S01, the matters that they address are now considered resolved. **Developmental NOAEL = 40 ppm (omphalocele, hemorrhaging with or without hydrops, retroesophageal right subclavian artery, gall bladder agenesis, fused sternebrae and decreased fetal bodyweight).** This study now is considered **ACCEPTABLE.** (Rinkus, 1/15/92).

123-137 111265 This record contains the following supplementary information to record 095930: individual responses to the matters raised in W095930.833; the protocol to record 095930; raw da-

ta regarding animal observations and (or) the gross pathology examination of two 80 ppm does which either delivered early or was found dead; a table identifying the route of administration used in the studies that comprise the historical control database for the conducting laboratory; an updated version of this historical control database; and some text regarding the management of mucoid enteritis in rabbits. Discussion of this record is contained in the worksheet W095930.S01 **Supplementary information. No worksheet.** (Rinkus, 1/16/92).

123-138 111266 "Methyl Bromide Inhalation Teratology Probe Study in New Zealand White Rabbits," (Breslin et al.; The Toxicology Research Laboratory, Dow Chemical Company; Laboratory Project Study ID numbers K-000681-032 & K-000681-032A; 4/2/90). This study was not a teratology study; rather, it was designed only to evaluate maternal toxicity and embryoletality so that the high dose in a standard teratology study (record 095930) could be set; also histological examinations of the brain (parts I & II) and spinal cord (part II) were performed. Methyl bromide was administered by whole-body inhalation 6 h/d on days 7-19 of gestation at concentrations of 0, 10, 30, and 50 ppm to 4-7 pregnant New Zealand White rabbits/treatment level (part I) or 0, 50, 70, and 140 ppm to 6-7 pregnant does/treatment level (part II). Does were sacrificed on day 20, with the exception of the 140 ppm group: these does were sacrificed on day 17 (i.e., after 10 exposure days) due to their moribund state. Clear maternal effects were limited to the 140 ppm group and included: decreased bodyweights and bodyweight gains and clinical signs of neurotoxicity (lethargy, labored breathing, ataxia, right-sided head tilt, reduced sensations in the extremities, dilated pupils, lateral recumbency, loss of placing or righting reflex, and rear leg splay). Histological examinations of the brains of all does on test indicated that only the 140 ppm group had pathological lesions (multifocal areas of inflammation of the meninges overlying most regions of the brain and/or bilaterally symmetrical necrosis or spongiosis of the midbrain dorsolateral to the pyramidal tracts). Fetal examinations were limited to counting the number of implantations and resorptions. A reduction in litter size for the 70 ppm group in association with an increase in preimplantation loss was suggested by the data (no evaluation of 140 ppm group was provided). The authors noted that these effects were not observed again in the full study (record 095930). **Supplemental information. No worksheet.** (Rinkus, 1/16/92).

123-141 112841 This record contains the protocol for record 095930; this protocol also is found in record 111265. **No worksheet.** (Rinkus, 2/5/93).

123-141 (no record number) The front of this document contains a follow-up response dated 1/9/92 by Dr. Breslin regarding his responses contained in record 111265 regarding 095930. It addresses: why animal identification numbers were noncontinuous; the number of uteri stained with sodium sulfide; and corrections in the historical control data regarding frequency of umbilical hernia. **No worksheet.** (Rinkus, 2/5/93).

No Record Number. "Oral Teratogenicity Studies of Methyl Bromide in Rats and Rabbits" (Kane-da, M, Hojo, H., Teramoto, S. & Maita, K.; Institute of Environmental Toxicology, Tokyo, Japan; Food Chem. Toxicol. 36:421-427, 1998). Methyl bromide (purity 99.5%) dissolved in corn oil was administered by gavage to 23-24 pregnant Crj:CD (SD) rats/dose at 0 (corn oil), 3, 10 and 30 mg/kg on gestation days 6-15 and to 15-18 pregnant Kbl:JW rabbits at 0 (corn oil), 1, 3 and 10 mg/kg on gestation days 6-18. Rats and rabbits were sacrificed on gestation days 20 (ether inhalation) and 27 (pentobarbital iv injection), respectively. The highest doses tested were selected (apparently) on the basis of preliminary studies that included dosing rats and rabbits at 25 and 30 mg/kg, respectively. The dosing volumes were 10 mL/kg for rats and 0.5 mL/kg for rabbits; as a result, the high-dose rats were gavaged with a 3 mg/mL solution while the high-dose rabbits were gavaged with a 20 mg/mL solution. In both species, maternal effects were observed only in the high-dose groups. Both species exhibited decreased bodyweight gain; but only rabbits lost bodyweight relative to predosing. Decreased food consumption occurred in both species; in the case of the rats, the fact that the negative control group also exhibited decreased food consumption suggests that the large volume of corn oil used (10 mL/kg) or the act of being gavaged constituted a stress on the animals. At necropsy, only the high-dose rats had findings: all dams exhibited ero-

sion and thickening of the wall in the nonglandular part of the stomach and adhesions between the stomach and the spleen, liver or diaphragm. In both species, no clinical signs were observed (i.e., no neurotoxicity). In rats, the only fetal findings of interest were seen in the high-dose group: microphthalmia in two fetuses (two litters [8% incidence]) and having 25 (not 26) presacral vertebrae in five fetuses (two litters [8% incidence]); no cases of microphthalmia or decreased vertebrae count were seen in the negative-control group. While neither effect was statistically significant, typically both of these findings are seen infrequently in negative-control litters using Sprague Dawley rats (i.e., $\leq 1\%$ litter incidence). In rabbits, total litter resorption occurred with two high-dose does and one negative-control doe; the number of resorptions involved in these instances was not indicated. In rabbits, the only fetal finding of interest was the observation that each of the three methyl bromide-treated groups had more fetuses with skeletal malformations than what was observed in the negative-control group. Skeletal malformations involving 2-3 litters in at least one methyl bromide-treated group included: splitting of the nasal/frontal/parietal bones; hemivertebra; fusion of the ribs/sternae; and absence of the metacarpal and phalangeal bones. At the litter level, no increased incidence was statistically significant nor were there any dose responses. Notwithstanding that historical negative-control data for Kbl:JW rabbits are not generally available in the open literature, the differences between the negative-control and methyl bromide-treated groups appear too small to warrant further concern. **Supplemental information.** (Rinkus, 12/23/98).

GENE MUTATION

Note: Document 123-109 contains various published reports regarding the mutagenic potential of methyl bromide. In each case, the experimental details for the mutagenicity testing were not reported adequately, which is often observed with reports published in the open literature. Inadequate documentation of methods is viewed by CDFA as a significant reason for officially rejecting a study. However, CDFA also recognizes that these studies collectively indicate that methyl bromide is a direct-acting mutagen. Since this opinion now is endorsed by the Sponsor also (see Attachment 1 in document 123-109), these studies have been considered collectively as satisfying this data requirement, despite their individual shortcomings. (Rinkus, 2/23/90).

103 066722 "Sex-Linked Recessive Lethal Test in *Drosophila Melanogaster*," (Inveresk Research International Ltd., Scotland; report no. 1190, 5/30/81). Two separate stocks of wild-type male fruit flies (*D. melanogaster*; Oregon K) were exposed to air containing either 20 or 70 ppm of test material for 5 h and subsequently were mated to Muller-5 females to produce F1 females, which were mated to produce the F2 progeny in which the frequency of lethal mutations was scored (Muller-5 test). Treatments with test material did not produce any signs of toxicity or affect fertility. An increased frequency of lethals that was observed for the 20 ppm group using one stock of males was not similarly observed in the corresponding group of the second stock of males nor in either stocks treated at the 70 ppm level with test material. UNACCEPTABLE and not upgradable because testing up to a MTD clearly was not achieved and the testing failed in other ways to meet the EPA guidelines for this assay. (Kishiyama, 2/2/89; Rinkus, 4/6/89).

123-109 087801 "Mutagenic Activity of Chemicals Identified in Drinking Water," (Simmon et al., In: *Progress in Genetic Toxicology*, Scott et al. (Eds.), pp. 249-258, Elsevier/North Holland Biomedical Press, 1977). Methyl bromide (purity not stated) was tested in the Ames test using TA100; testing did not involve the use of any metabolic activation system like S-9. The experimental details were not described adequately. Agar plates containing bacteria were incubated for 21 h at 37°C in 9-liter dessicators that contained methyl bromide concentrations of 0 (air), 0.01, 0.02, 0.05, 0.10, and 0.20 % (i.e., 0, 100, 200, 500, 1000, and 2000 ppm). Stirring bars were used as fans to achieve an even distribution of vapors, but the number of plates per dessicator was not stated. A

doubling in the spontaneous number of revertants was seen at the lowest concentration tested; and the number of revertants continued to increase with increasing concentration, up to a maximum effect at the 0.1% treatment level. **UNACCEPTABLE**. No worksheet. (Rinkus, 2/23/90).

123-109 087802 "Mutagenicity of Methyl Bromide in a Series of Short-Term Tests," (Kramers et al., Mutation Res. 155: 41-47, 1985). Methyl bromide of 99% purity was tested for genotoxicity in the following assays: a fluctuation test using Klebsiella pneumoniae; the Ames test using Salmonella typhimurium strains TA100 and TA98; the induction of forward mutations at the TK locus and at the HGPRT locus using L5178Y mouse lymphoma cells; the induction of unscheduled DNA synthesis (UDS) using freshly isolated rat liver cells; and the induction of sex-linked recessive leth-al mutations using Drosophila melanogaster. The experimental details were not described adequately. Exposures to methyl bromide were accomplished by: exposing the tester organisms to vapors formed in closed containers into which an ethanolic solution had been introduced (fluctuation test, Ames test); adding an ethanolic solution directly to gas-tight bottles ~90% filled with cell media (mouse lymphoma assay, UDS assay); or exposing the tester organisms in a chamber to a continuous flow of methyl bromide-containing atmospheres (Drosophila). Methyl bromide was active in all tests, except the UDS testing. Lowest treatments that exhibited a positive effect were: 1) fluctuation test, 4750 mg/m³ (1271 ppm; the estimated concentration of methyl bromide in the nutrient broth was 250 µM); 2) TA100, 1900 mg/m³ (508 ppm) (no mutagenicity seen with TA98); 3) L5178Y cells, ~0.3 µM; and Drosophila, 3 weeks of 6 h/day, 5 day/week using 200 mg/m³ (52 ppm). UDS testing conducted up to a maximum concentration of 0.3 mM did not detect an effect, but it was not stated whether the HDT was sufficient to cause cytotoxicity. **UNACCEPTABLE**. No worksheet. (Rinkus, 2/23/90).

123-109 087803 Abstract to work discussed in record 087802. No worksheet. (Rinkus, 2/26/90).

123-109 087808 "Further Mutagenicity Studies on Pesticides in Bacterial Reversion Assay Systems," (Moriya et al., Mutation Res. 116: 185-216, 1983). Methyl bromide (purity not stated) was tested for mutagenicity using the Salmonella typhimurium strains TA100, TA1535, TA1537, TA1538, and TA98 and the Escherichia coli strain WP2 hcr. Experimental details were not reported adequately. Testing involved placing one bacteria-containing agar plate without its lid upside down in a glass container, injecting gaseous methyl bromide into the container, and incubating for 2 days at 37°C while an electric fan stirred the atmosphere in the container. The lowest test concentration to increase the revertant frequency of TA100 was ~500 mg/m³ (134 ppm). Other strains listed as showing a positive response were: TA1535 and WP2 hcr. It was stated without data that the mutagenicity of methyl bromide was not greatly affected by the use of a S-9 mix. This study also indicates that chloropicrin, which is often combined with methyl bromide in formulated fumigant products, was mutagenic in WP2 hcr and TA98 in the absence of S-9 and in TA100 in the presence of S-9; the chloropicrin testing involved the standard plate assay. **UNACCEPTABLE**. No worksheet. (Rinkus, 3/2/90).

123-109 087809 "Estimation of Genetic Risks of Alkylating Agents. VI. Exposure of Mice and Bacteria to Methyl Bromide," (Djalali-Behzad et al., Mutation Res. 84: 1-9, 1981). Methyl bromide (purity not stated) was tested for mutagenicity using Escherichia coli Sd-4, but the experimental details were not reported adequately. Also, adduct formation of methyl bromide with hemoglobin and DNA in test-tube reactions and in mice exposed to methyl bromide by either inhalation or by intraperitoneal injection was determined. Inhalation exposure involved the use of a static system in which 9 mice in an 11-liter chamber inhaled an atmosphere for 4 h that initially contained 36 or 17 ppm (CDEA calculation of ppm concentration). Intraperitoneal exposure involved the single injection of a corn-oil solution to give a dose of 417 µg/kg bodyweight. Bacterial mutagenicity was observed at test concentrations of ≥ 4 mM; the LD50 for these test conditions was 6-8 mM. N-7-methylguanine formation was 10 times greater in DNA isolated from the spleen than that measured in the liver (only organs sampled) of mice inhaling the high dose; DNA adduct formation was not assayed for the low inhalation dose or for the intraperitoneal exposure. Protein alkylation was 22 times greater in RBCs than in the liver for mice inhaling the high dose; protein alkylation was

also measured at the low inhalation dose and in the intraperitoneal experiment. **UNACCEPT-ABLE.** No worksheet. (Rinkus, 3/8/90).

123-146 116243 "Toxicology and Carcinogenesis Studies of Methyl Bromide in B6C3F1 Mice (Inhalation Studies)--Ames Test," (National Toxicology Program Technical Report 385; March, 1992). As part of the National Toxicology Program, the mouse inhalation cancer bioassay, record 116243, also contained data for mutagenicity testing using the Ames test. Testing was performed using dessicators into which methyl bromide/air mixtures were introduced. These data indicated a positive and reproducible response. However, the supposed lowest test concentration, 0.004 moles per liter, would be equivalent to a methyl bromide atmosphere of 100,000 ppm and such a concentration should be much too high to allow for any survival. Possibly, the reporting of the test concentrations is a typographical error. **UNACCEPTABLE.** No worksheet. (Rinkus, 2/5/93).

CHROMOSOME EFFECTS

Note: EPA is requiring both bone marrow and sister chromatid exchange tests (see EPA Re-registration Guidance document of Aug., 1986).

044 035750 [Previous Record # = 913095-1] "Effect of Methyl Bromide on the Frequency of Sister Chromatid Exchanges (SCE) in Chinese Hamster Ovary (CHO) Cells." (Pasadena Foundation for Medical Research, 1980) Methyl bromide, purity not given, was assayed with Chinese Hamster Ovary cells at 0, 1, 6, 13 or 26 ppm for SCEs. **Possible adverse effect:** dose-related increase in SCEs. **Unacceptable.** Protocol not provided, criteria for scoring SCEs not provided. J. Wong, 4-8-85. [There is no apparent merit in seeking to "upgrade" this study, as EPA is requiring additional studies of this type in any case].

103 066721 "Cytogenetic Analysis of Rat Bone Marrow Cells," (Inveresk Research International Ltd., Scotland; report no. 1190, 5/30/81). Methyl bromide was administered by whole body inhalation at concentrations of 0 (air), 20 and 70 ppm to Sprague Dawley rats of both sexes. One group of 30 rats/treatment level received only one 7-h exposure and another group of 10 rats/treatment level received 5 consecutive daily exposures of 7 h/day. The former were sampled at 6, 24 and 48 hours posttreatment whereas the latter were sampled 6 hours posttreatment. There was no obvious treatment-related increase in the frequencies of chromosomal aberrations in any of groups receiving test material. NOEL > 70 ppm. **UNACCEPTABLE** and not upgradeable because the HDT is at least half of a MTD. (Kishiyama, 1/30/89; Rinkus, 4/4/89).

103 066719 "Dominant Lethal Testing in Male Rats," (Inveresk Research International Ltd., Scotland; report no. 1190, 5/30/81). Methyl bromide was administered by whole body inhalation at concentrations of 0 (air), 20 and 70 ppm to 10 male Sprague Dawley rats/treatment level for 7 h/day for 5 consecutive days. After the fifth exposure, males were housed with pairs of virgin, non-treated females for 7 days, with a different pair of females being used weekly for a total of 10 consecutive weeks. Examination of the ovaries and the uterine contents indicated no genotoxic effects or reproductive effects, as can be measured in this assay. NOEL > 70 ppm. **UNACCEPTABLE** and not upgradeable because the number of males per treatment level was only 10 and the HDT was at least half of a MTD. (Kishiyama, 2/1/89; Rinkus, 4/4/89).

****123-136 099090** "Micronucleus Cytogenetic Assay in Mice" (Putman, D.L. & Morris, M.J.; Microbiological Associates, Inc.; study number T9413.122; 5/17/91). Methyl bromide (purity not stated) was tested for the induction of micronuclei in bone-marrow polychromatic erythrocytes of ICR mice of both sexes. Testing involved one-time intraperitoneal injections of 5 mice/sex/dose and sacrificing them 24, 48 or 72 hours later. Doses based on analytical determinations were: 0 (corn oil), 28, 57, and 123 mg/kg; the targeted low, mid and high doses had been 34, 68, and 136 mg/kg, respectively. The selection of the high dose was based on LD50 data that were contained in the re-

port. **No induction of micronuclei was observed** whereas the negative control and positive control (triethylenemelamine, 0.25 mg/kg IP) gave appropriate results. This study is considered **ACCEPTABLE**. (Rinkus, 1/14/92).

123-108 085429 Proposed protocol for conducting a micronucleus test in mice, using intraperitoneal injection as the route of exposure. No worksheet. (Rinkus, 4/20/90).

****123-146 116243** "Toxicology and Carcinogenesis Studies of Methyl Bromide in B6C3F1 Mice (Inhalation Studies)--Micronucleated Peripheral Red Blood Cells," (National Toxicology Program Technical Report 385; March, 1992). Testing was performed at the Brookhaven National Laboratories in New York; the testing was done in two parts using whole-body inhalation. In the initial testing, methyl bromide was administered at concentrations of 0 (air), 12, 25, 50, 100 and 200 ppm for 6 h/d, 5 d/week for a total of 10 exposure days to 5 B6C3F1 mice per sex per treatment level. In subsequent testing, the treatment levels were 0 (air), 10, 20, 40, 80 and 120 ppm for 6 h/d, 5 d/week for 12 weeks, using 8 mice per sex per treatment level. Peripheral blood was collected at the end of exposures in the initial testing and at 4, 8 and 12 weeks during the 12-week studies. Smears were made and processed in a standard manner using acridine orange for staining; and the frequencies of polychromatic and normochromatic red blood cells (RBCs) with micronuclei were determined. In the initial testing, female mice exposed to 100 and 200 ppm exhibited mean frequencies of 9.0 and 16.0 micronucleated RBCs per 1000 cells scored, respectively; these were in comparison to mean frequencies of 3.0-7.0 per 1000 cells scored for the other treatment groups, including the negative controls. **NOAEL = 50 ppm for an 10-day exposure period.** In the 12-week study, no increase in the frequency of micronucleated RBCs was observed for either sex at any of the sampling times. **NOAEL > 120 ppm for exposure periods of 4-12 weeks.** While it may be unexpected that a response would only be seen in the initial testing, without replicate testing or other supplemental information, there presently is no substantial reason to discount this effect. **ACCEPTABLE.** (Rinkus, 1/19/93).

****123-146 116243** "Toxicology and Carcinogenesis Studies of Methyl Bromide in B6C3F1 Mice (Inhalation Studies)--Sister Chromatid Exchanges Testing," (National Toxicology Program Technical Report 385; March, 1992). Testing was performed at the Brookhaven National Laboratories in New York; testing was done in two parts, using in both cases whole-body inhalation and four B6C3F1 mice per sex per treatment level. In the initial testing, methyl bromide was administered at concentrations of 0 (air), 12, 25, 50, 100 and 200 ppm for 6 h/d, 5 d/week for a total of 10 exposure days. In subsequent testing, the treatment levels were 0 (air), 10, 20, 40, 80 and 120 ppm for 6 h/d, 5 d/week for 12 weeks. Twenty-four hours before being sacrificed, the mice received a tablet of bromodeoxyuridine as an implant under their skin; and two hours before being sacrificed, they received an IP injection of colchicine. Bone marrow cells were isolated from the femurs and processed in a standard manner for examination of metaphase spreads for sister-chromatid exchanges (SCEs). Twenty-five second division metaphase cells were scored per mouse. In the initial testing, female mice exposed to 100 and 200 ppm exhibited mean frequencies of 4.8 and 5.3 SCEs/cell, respectively; these were in comparison to mean frequencies of 3.2-3.8 SCEs/cell in the other treatment groups, including the negative controls. **NOAEL = 50 ppm for an 10-day exposure period.** In the 12-week study, no increase in the frequency of SCEs/cell was observed for

either sex. **NOAEL > 120 ppm for a subchronic exposure.** While it may be unexpected that a response would only be seen in the initial testing, without replicate testing or other supplemental information, there presently is no substantial reason to discount this effect. **ACCEPTABLE.** (Rinkus, 1/19/93).

DNA DAMAGE

Note: EPA is requiring an unscheduled DNA synthesis test using rat hepatocytes and a test to determine the effects on germ cells (see EPA Re-registration Guidance document of Aug., 1986). Presumably, record 162362 was done to satisfy the latter. (Rinkus, 3/5/99).

****044 913095** "In vitro Microbiological Mitotic Recombination Assay of Methyl Bromide Using *S. cerevisiae* D3." (SRI International, 4-80) Methyl bromide, purity not stated, was assayed for mitotic recombination with *Saccharomyces cerevisiae* D3 at 0, 0.05, 0.075, 0.1, 0.15, 0.2, 0.3, or 0.4 % w/v. The study was conducted on 4 days, total of 5, 10 or 15 plates per concentration, with and without activation. Increase in number of mitotic recombinants with increasing dose. **Acceptable.** J. Wong, 4-8-85.

103 066718 "Unscheduled DNA Synthesis Assay," (Inveresk Research International Ltd., Scotland; report no. 1190, 5/30/81). Unscheduled DNA synthesis was measured in human embryonic intestinal cell after exposure to methyl bromide gas in air at concentrations of 5, 10, 20, 30, 40, 50, 60, or 70%. None of the methyl bromide treatments induced any increase in UDS. **UNACCEPTABLE** but upgradeable upon submission of a more detailed explanation of how the cells were exposed to test material, the number of cultures per treatment level, and cytotoxicity data. (Kishiyama, 1/30/89; Rinkus, 4/6/89).

103 066720 "Sperm Abnormalities Test in Mice," (Inveresk Research International Ltd., Scotland; report no. 1190, 5/30/81). Methyl bromide was administered by whole-body inhalation at concentrations of 0 (air), 20, and 70 ppm to 10 B6C3F1 hybrid male mice per treatment level. Mice were sacrificed 5 weeks later and their sperm were categorized in terms of the frequencies of abnormally shaped sperm. There was no significant increase in the frequency of abnormally shaped sperm in the mice treated with test material. **NOEL > 70 ppm.** **UNACCEPTABLE** but may be upgraded upon submission of purity of test material and toxicity data that supports the conclusion that 70 ppm is a reasonable approximation of a MTD. (Kishiyama, 2/2/89; Rinkus, 4/5/89).

123-109 087799 "Methylated Purines in Human Liver DNA after Probable Dimethylnitrosamine Poisoning," (Herron, D.C. and Shank, R.C., Cancer Res. 40: 3116-3117, 1980). DNA isolated from the liver and kidneys of a single victim of methyl bromide poisoning (no details at all on this poisoning) did not contain any detectable amounts of 7-methylguanine or O⁶-methylguanine. Supplemental information. No worksheet. (Rinkus, 2/22/90).

123-109 087800 "Evaluation of Genetic Risks of Alkylating Agents. IV. Quantitative Determination of Alkylated Amino Acids in Haemoglobin as a Measure of the Dose after Treatment of Mice with Methyl Methanesulfonate," (Segerback et al., Mutation Res. 49: 71-82, 1978). Article does not contain any testing results for methyl bromide per se, but it does explain methods and logic for this approach as applied to methyl bromide in record 087809. Supplemental information. No worksheet. (Rinkus, 2/23/90).

123-108 085428 Proposed protocol for measuring DNA single-strand breakage in the DNA of testicular cells isolated from rats exposed by inhalation. No worksheet. (Rinkus, 4/20/90).

123-155 129996 This record is a letter dated February 1, 1994 from the Registrant to the Office of Pesticide Programs of USEPA, informing them that DNA damage had been observed using the alkaline elution technique on DNA isolated from testes of male F344 rats. Animals were exposed to 0, 75, 150 or 250 ppm methyl bromide 6 h/d for 5 days, with sacrifice one hour and one day after the 5th exposure. DNA damage was detected with this technique at the high dose at both sacrifice times. Review of tabular data indicates that the effect at 250 ppm was comparable to that produced by the positive control, methyl methanesulfonate at 50 mg/kg (route and total dose not specified). **Supplemental information. No worksheet.** (Rinkus, 7/24/95).

123-188 162362 "Detection of Single Strand Breaks in Rat Testicular DNA by Alkaline Elution Following In Vivo Inhalation Exposure to Methyl Bromide" (K.S. Bentley; Medical Research Project No.: 9714-001 [Sponsor Study No.: MBIP-21.0-ALK-HASK]; March 23, 1994). Methyl bromide (>99% purity) was administered by whole body inhalation for 6 h/day for 5 days to 5 Fischer 344 males/treatment level/sacrifice time. Rats were sacrificed 1 hour or 1 day after the 5th exposure and testicular cells were isolated and analyzed for single-strand DNA breakage using the alkaline elution procedure and a fluorometric assay for DNA determination. Nominal dose levels were: 0, 75, 150 and 250 ppm; the corresponding analytical values were: 0, 77, 153, and 258 ppm. The high dose was selected based on record 087805 (Fund. Appl. Toxicol. 9:352-365, 1987). Also, as controls for the alkaline-elution assay, testicular DNA was processed from 5 males/control/trial that had been injected ip with phosphate-buffered saline or 50 mg/kg methyl methanesulfonate (MMS) and sacrificed two hours posttreatment; two trials were necessitated by equipment failure in the initial trial. The first exposure day resulted in a loss in mean bodyweight for the 150 and 250 ppm groups. On the day after the 5th exposure, the mean bodyweights of the 250 ppm and 150 ppm groups were 78% and 97%, respectively, of what they had been before the onset of exposures; the 0 and 75 ppm groups showed little or no gain in bodyweight over this interval. Two rats from the 250 ppm group died before scheduled sacrifice (test days 5 & 6) and a third rat from this group was sacrificed ahead of schedule (test day 5) due to its moribund state. Signs of neurotoxicity seen in the 250 ppm included ataxia, spasms, diarrhea, lethargy and prostration. Colored nasal discharge was seen in all treatment groups involved in inhalation exposures, including a 40% incidence in the 0 ppm group prior to the final exposure period (not explained). The alkaline-elution curves indicated that the DNA from the 250 ppm group (both sacrifice times) eluted significantly faster than the DNA from the 0 ppm groups and at a rate comparable to that seen with the DNA from the MMS-treated males. The alkaline-elution curves also indicated that the DNA elution rate for the 150 ppm group (1-h posttreatment sacrifice) was significantly slower than the rate seen with the corresponding 0 ppm group (both sacrifice times) and that the amount of DNA retained on the filters at the end of the 15 h of elution for the 75 ppm group (24-h posttreatment sacrifice) was significantly less than that seen with the corresponding 0 ppm group. **LOEL = 75 ppm** (this is a conservative call based on the statistically significant findings reported for the rats sacrificed 24 h posttreatment). This study is considered **UNACCEPTABLE**. Upgrading will require the submission of the following: protocol and raw data for the study; historical control data (negative and positive) from the conducting laboratory; explanation of the time frames per group for inhalation exposures, sacrifices, and alkaline elution runs; slope recalculations with statistical analysis using the combined data for the four negative-control groups. The supplemental information that is being sought is for the purposes of setting the NOEL. Although record 162362 presently is unacceptable, it is sufficient for concluding that inhalation exposure to methyl bromide resulted in DNA damage in rat male germ cells. This is true even after taking into consideration the Registrant's waiver petition to the USEPA (contained in document 123-186) regarding extra testing that was being required based on the results of this alkaline-elution study (discussed in worksheet W162362.844). **Supplemental information.** (Rinkus, 12/14/98).

NEUROTOXICITY

Note: The brain is clearly a target organ for inhaled methyl bromide (e.g., reviewed in records 059183 & 064742). Comparison of the results of inhalation studies conducted with dogs (records 132821 & 132818), rabbits (records 026865/026866, 095930 & 111266; Irish *et al.*, *J. Industr. Hyg. Toxicol.* 22:218-230, 1940; Anger *et al.*, *Scand. J. Work Environ. Health*, 7 [Suppl. 4]: 40-47, 1981; and Russo *et al.*, *J. Toxicol. Environ. Health*, 14:247-255, 1984), monkeys (Irish *et al.*, *J. Industr. Hyg. Toxicol.* 22: 218-230, 1940), rats (records 026866/026865, 059184, 087805, 131609 & 131619; Irish *et al.*, *J. Industr. Hyg. Toxicol.* 22:218-230, 1940; and Anger *et al.*, *Scand. J. Work Environ. Health*, 7 [Suppl. 4]:40-47, 1981), and mice (record 116243) indicates that there is a significant species difference in sensitivity to the neurotoxic effects of inhaled methyl bromide, with nonrodents (dogs, rabbits, monkeys) being more sensitive than rodents. (Rinkus, 7/24/95).

123-158 131609 "Methyl Bromide: Single Exposure Vapor Inhalation Neurotoxicity Study in Rats" (Driscoll, C.D. & Hurley, J.M.; Bushy Run Research Center; laboratory project ID no. 92N1197; 5/27/93. Methyl bromide (100% purity) was administered to 15 CD® rats/sex/treatment level by whole body inhalation at 0, 30, 100 and 350 ppm, for 6 h. The high dose was selected based on the study by Honma *et al.* (*Tox. Appl. Pharm.* 81:183-191, 1985). Neurobehavioral testing utilized 15 rats/sex/group and included automated assessments of motor activity and testing in a functional observation battery. Testing was done: preexposure; within 3 h postexposure; 7 d postexposure; and 14 d postexposure. Rats were sacrificed 16-19 d postexposure. Ten rats/sex/group underwent perfusion fixation. Six rats/sex/group for the 0 ppm and 350 ppm groups had their nervous system and nasal tissue examined histologically. Neurobehavioral effects were only seen in the testing done within 3 h postexposure and only the rats exposed to 350 ppm were affected. Findings included: decreased arousal (both sexes); increased incidence of drooping or half-shut eyelids (both sexes); increased urination (females only); decreased rearing (both sexes); decreased tail pinch response (males only); increased incidence of piloerection (both sexes); decreased rectal temperature (both sexes); abnormal air righting (females only); and decreased motor activity (both sexes). No effects on bodyweight or brain weight were noted. Vacuolation that was seen in the cerebellar white matter and the white matter tracts of the spinal cord for 0 ppm and 350 ppm rats was dismissed as an incidental finding. Otherwise, no histological lesions were noted in the nervous system or the nasal tissues of the 350 ppm rats. **NOAEL = 100 ppm. Supplemental Information.** (Rinkus, 1/3/95).

123-159 131619 "Methyl Bromide: Ninety-Day Vapor Inhalation Neurotoxicity Study in CD® Rats" (Norris, J.C., Driscoll, C.D. & Hurley, J.M.; Bushy Run Research Center; laboratory project ID no. 92N1172; 9/29/93 [1/5/94 for amendment 1]). Methyl bromide (100% purity) was administered to 15 CD® rats per sex per treatment level by whole body inhalation at 0, 30, 70 and 140 ppm, for 6 h/d, 5 d/week, for 13 weeks. Treatment levels were selected on the basis of subchronic studies conducted previously by the NTP (contained in record 116243). Neurobehavioral testing was done preexposure and at the end of study weeks 4, 8 and 13. Testing included automated assessments of motor activity (13-15 rats/sex/group) and testing in a Functional Observation Battery (9-10 rats/sex/group). Rats used in the FOB testing underwent perfusion fixation. Six rats/sex/group had their nervous system examined histologically in two phases: first phase, 0 and 140 ppm groups; second phase, 30 and 70 ppm groups (amendment 1 [record 131621]). Two 140 ppm males died on test (study days 12 and 27); the latter had convulsions and tremors before dying. One other 140 ppm male that survived till the end of the study also exhibited clonic convulsions and tremors. The 140 ppm groups (both sexes) weighed significantly less than the controls, starting study week ~4; and the 70 ppm female group exhibited a bodyweight reduction, starting study week ~9. FOB testing identified effects only in the 140 ppm groups; some effects were evident as early as study week 4. Findings included: ataxia (five females, one male); decreased arousal (females only); decreased rearing activity (females only); increased hind leg splay (males only); and (possibly) abnormal air righting (males only). Motor activity testing identified effects only in the 70 ppm and 140 ppm female groups. Findings included decreased total motor activity and decreased rearing activ-

ity; both were evident as incipient effects in study week 8. Female groups exposed to methyl bromide exhibited a dose response for reduced brain weight whereas only the 140 ppm male group had reduced brain weight. Histological findings included: brain lesions at multiple sites (140 ppm, four males affected: neuronal loss, neuronal necrosis, malacia); peripheral nerve degeneration and/or vacuolation (140 ppm, two/sex affected; 30 ppm, one female affected); and olfactory epithelium dysplasia (140 ppm, three/sex affected). White matter vacuolation was seen in the second-phase examination of all males and some females and was considered by the authors to be a storage/pressure artifact. **NOAEL < 30 ppm (reduced brain weight at the lowest dose tested).** When first reviewed (Rinkus, 12/30/94), this study was considered unacceptable and upgrading would require the submission of positive control data. Subsequently, the Registrant submitted records 143173, 143175, 143176 and 143178. These contain results for neurotoxicity testing done by the conducting laboratory using amphetamine, chlorpromazine, acrylamide and (or) iminodipropionitrile. These data did not suffice as positive-control data primarily because the data were too old to be considered contemporary data; also, there were inconsistencies in some of the submissions (discussed in worksheet W131619.S01). Subsequently, the Registrant submitted record 161564 (draft report), which was the "validation" training for the two FOB observers from records 131619 and 131609. These data do not suffice as positive control data, for the reasons discussed in worksheet W131619.S02. Therefore, record 131619 remains **UNACCEPTABLE**. Also, because records 131619, 143173, 143175, 143176, 143178 and 161564 collectively indicate that it is unlikely that adequate positive control data exist to support this study, record 131619 is now considered **NOT UPGRADEABLE**. **Supplemental Information.** (Rinkus, 1/7/99).

123-160 131621 "Methyl Bromide: Ninety-Day Vapor Inhalation Neurotoxicity Study in CD® Rats: Amendment 1" (Norris, J.C., Driscoll, C.D. & Hurley, J.M.; Bushy Run Research Center; laboratory project ID no. 92N1172 amendment 1; 1/5/94). The histological examination of the rats in record 131619 was done and reported in two phases. Initially, the control and high-dose groups (both sexes) were examined and the results were reported in record 131619. In the second phase, the low and mid-dose groups (both sexes) were examined and the results, combined with the data from record 131619, were reported in record 131621. In this second phase of examinations, vacuolation was noted in the white matter at several sites (e.g., cerebellum, brain stem, trigeminal tract). The authors of amendment 1 dismissed the vacuolation as a "pressure artifact" which developed during storage. This amendment is discussed in worksheet W131619.827. **Supplemental information. No worksheet.** (Rinkus, 7/24/95).

123-170 143173 "Single-Dose Functional Observational Battery Validation Study with Chlorpromazine (CPZ) and Amphetamine (AMP) in Rats" (M.W. Gill; Bushy Run Research Center; BRRC Developmental Project Report 51-902; May 9, 1989). The testing was done with female Sprague-Dawley rats. This record, along with records 143175, 143176 and 143178, were submitted to satisfy the requirement for positive-control data for record 131619 (discussed in worksheet W131619.827). These records are reviewed in worksheet W131619.S01. **Supplemental information.** (Rinkus, 10/15/97).

123-170 143175 "Two-Week Repeated Dose Limb Grip Strength Validation Study with Acrylamide (ACR) in Rats" (Gill, M.W. and Boystein, L.A.; Bushy Run Research Center; BRRC Developmental Project Report 51-905; Sept. 18, 1989). The testing was done with female Sprague-Dawley rats. This record, along with records 143173, 143176 and 143178, were submitted to satisfy the requirement for positive-control data for record 131619 (discussed in worksheet W131619.827). These records are reviewed in worksheet W131619.S01. **Supplemental information.** (Rinkus, 10/15/97).

123-171 143176 "Single-Dose Motor Activity Validation Study with Chlorpromazine (CPZ) and Amphetamine (AMP) in Rats" (M.W. Gill; Bushy Run Research Center; BRRC Developmental Project Report 51-904; Sept. 18, 1989). The testing was done with F344 rats (both sexes). This record, along with records 143173, 143175 and 143178, were submitted to satisfy the requirement for positive-control data for record 131619 (discussed in worksheet W131619.827). These records

are reviewed in worksheet W131619.S01. **Supplemental information.** (Rinkus, 10/15/97).

123-171 143178 “Two-Week Repeated Dose Functional Observation Battery Validation Study with Acrylamide (ACR) and Iminodipropionitrile (IDP) in Rats” (M.W. Gill; Bushy Run Research Center; BRRC Developmental Project Report 51-903 Revised; Sept. 18, 1989). The testing was done with female Sprague-Dawley rats. This record, along with records 143173, 143175 and 143176, were submitted to satisfy the requirement for positive-control data for record 131619 (discussed in worksheet W131619.827). These records are reviewed in worksheet W131619.S01.

Supplemental information. (Rinkus, 10/15/97).

123-205 161564 This was a training exercise conducted in November, 1992. One part was intended to train 7 people to perform a functional observation battery (FOB), including the two observers who did the FOB testing in records 131619 and 131609. It was indicated that record 161564 was their “validation” training, qualifying them to do FOB testing in a definitive study. For the FOB “validation” training, 9 male CD rats were used; and d-amphetamine (3 rats; 10-15 mg/kg, ip), carbaryl (2 rats; 19 and 21 mg/kg, ip) and ethanol (2 rats; 7 g/kg, po) served as the neurotoxic standards, with saline (2 rats; po) as the negative control. The other testing in record 161564 exclusively involved the two observers who did the FOB testing in records 131619 and 131609. They measured grip strength (fore and hind) and hind leg splay in untreated male CD rats. Record 161564 was marked “draft” on each page. There were no signatures on the GLP page nor in the “Review and Approval” section; and there was no QA page. **Supplemental information.** (Rinkus, 3/5/99).

SUPPLEMENTAL STUDIES

BRAIN TYROSINE HYDROXYLASE AND BRAIN CATECHOLAMINE STUDIES

No Record Number. “Inhibition of Tyrosine Hydroxylase Activity by Methyl Bromide Exposure” (Honma *et al.*, *Neurotoxicology and Teratology* 13:1-4, 1991). Male Sprague-Dawley rats (3 to 5 rats/dose level/sacrifice time) were exposed to methyl bromide (0 to 250 ppm) for 8 h using inhalation chambers. The animals were sacrificed 0, 1, 2 or 24 hours postexposure. Brain tyrosine hydroxylase (THase) activity was quantitated in an “*in vitro*” assay and in an “*in vivo*” one. Both assays indicated dose-responses for decreases in DOPA production in various brain segments. The segment with the lowest effect level (LEL) in the “*in vitro*” assay was the hypothalamus; its LEL was 16 ppm, the lowest dose tested. The segments with the lowest effect level (LEL) in the “*in vivo*” assay were the striatum and hypothalamus; their LEL was 63 ppm, with a possible incipient effect at 31 ppm. The maximal inhibition of THase activity in both assays was seen with the rats sacrificed immediately after the 8 h exposure period; significant recovery took place within two hours postexposure and was complete by 24 h postexposure. The authors interpreted their findings as evidence that methyl bromide directly caused changes in the enzyme structure, presumably by methylation. However, as reviewed in worksheet “whonma1.sup,” there are significant questions about the findings of Honma *et al.* (1991) and its relationship to other studies. **Supplemental information.** (Rinkus, 1/26/98).

No Record Number. “Significant Changes in Monoamines in Rat Brain Induced by Exposure to Methyl Bromide” (Honma *et al.*, *Neurobehavioral Toxicology and Teratology* 4:521-524, 1982). In one part of this study, male Sprague-Dawley rats were exposed for 24 h to 0, 10, 20, 40, 60, 100 or 120 ppm methyl bromide. In another part, rats were exposed for 3 weeks to 0, 1, 5 or 10 ppm methyl bromide. In both parts, rats were sacrificed immediately after exposure using a focussed microwave pulse directed at the head. The brain was sectioned into segments and several neurotransmitters (norepinephrine, dopamine, serotonin, acetylcholine) and cyclic nucleotides (cAMP and cGMP) were assayed. The main finding was that significant reductions in norepinephrine occurred

in the hypothalamus and in a segment consisting of the cortex plus hippocampus. The reductions were seen in the groups exposed to 100 and 120 ppm for 24 h and in the group exposed to 10 ppm for 3 weeks. Although norepinephrine was reduced, dopamine in the striatum was un-changed or possibly increased. The lack of a reduction in dopamine is inconsistent with the main premise of Honma *et al.* (1991), which is that methyl bromide affects THase, causing a decrease in DOPA, which in turn leads to decreases in dopamine and norepinephrine. **Supplemental in-formation. No worksheet.** (Rinkus, 4/15/98).

No Record Number. "Methyl Bromide Alters Catecholamine and Metabolite Concentrations in Rat Brain" (Honma *et al.*, *Neurotoxicology and Teratology* 9:369-375, 1987). In the first part of this study, male Sprague-Dawley rats were exposed for 8 h to 0 or 100 ppm methyl bromide and sacrificed at 0, 2, 8 or 24 hours postexposure. In the second part, rats were exposed for 8 h to 0, 31, 63, 125 and 250 ppm methyl bromide and sacrificed immediately afterwards. A focussed microwave pulse to the head was used to sacrifice the animals. The brain was sectioned into the same segments used in Honma *et al.* (1991). The following neurotransmitters and their respective metabolites were assayed: dopamine and homovanillic acid; norepinephrine and 3-methoxy-4-hydroxyphenylglycol (MHPG); and serotonin and 5-hydroxyindoleacetic acid (5HIAA). The findings from the study were: a) dopamine was decreased (LEL = 100 ppm [striatum]) whereas homovanillic acid was increased (LEL = 63 ppm [striatum, hypothalamus]); b) norepinephrine was decreased (LEL = 31 ppm [hypothalamus]) whereas MHPG was increased (LEL = 63 ppm [striatum, hypothalamus, midbrain]); c) serotonin and 5HIAA were not significantly affected in any brain segment (LEL > 250 ppm); and d) return of dopamine, homovanillic acid, norepinephrine and MHPG to their respective control values was complete by 24 h postexposure. Some inconsistencies that this study presents include the following. First, decreased dopamine was measured in the striatum of rats exposed for 8 h to 100 or 125 ppm methyl bromide whereas exposure at these same levels for a much longer period, 24 h, did not affect dopamine content in Honma *et al.* (1982). Second, if THase is inhibited as proposed in Honma *et al.* (1991), one would expect that the metabolites "downstream" from THase would be decreased. That is, the DOPA decrease should lead to a decrease in dopamine, which in turn should cause a decrease in the dopamine catabolite, homovanillic acid. This is what occurs when α -methyl tyrosine (methyl ester), a known THase inhibitor, is given to rats (Aust. J. Biol. Sci. 36:519-523, 1983). However, the opposite occurred in this study: homovanillic acid increased, with a LEL (63 ppm) that was lower than the LEL for the dopamine decrease (100 ppm). **Supplemental information. No worksheet.** (Rinkus, 4/15/98).

No Record Number. "Behavioral Evidence for Modified Receptor Sensitivity in Rat Brain Induced by Methyl Bromide Exposure" (Honma *et al.*, *Industrial Health* 32:1-16, 1994). This study was a follow-up to the work reported in Honma *et al.* (1991). The intent was to test whether male Sprague-Dawley rats exposed to methyl bromide were more sensitive (responsive) to the dopamine agonist apomorphine, which causes hyperactivity in rats. Increased sensitivity to a dopamine agonist was expected if methyl bromide had damaged presynaptic neurons that use dopamine as the neurotransmitter. The increased sensitivity was thought to be a way to compensate for the presynaptic damage, by having the postsynaptic neurons increase their density of dopamine receptors and (or) increase the affinity of their receptors for dopamine. Also, whether methyl bromide affected the hypoactivity induced by the norepinephrine agonist clonidine was tested. Two assays were used. One assay involved a blind scoring of the stereotypic oral behavior (defined as abnormal sniffing, licking and biting) caused by an i.p. injection of apomorphine. This assay used five rats/dose level and was conducted 7 days before exposure to methyl bromide and on days 1, 4, 7, 14 and 28 postexposure. There were two types of inhalation exposure: 8 h to 0, 25, 50, 100 or 200 ppm; and 8 h/day for 7 consecutive days to 0, 5, 10, 25 or 50 ppm. The second assay involved measuring locomotor activity in an automated-counting apparatus after an i.p. injection of apomorphine or clonidine. This assay used only two rats/dose level and was conducted 7 days after exposure to 0, 10 or 50 ppm methyl bromide (8 h/day for one day or for 7 consecutive days). Testing also was done the day before exposure to methyl bromide; in these instances, neither apomorphine nor clonidine were administered before the locomotor activity was recorded. The DPR MT reviewer's concerns about this study are contained in the review of Honma *et al.* (1991) (i.e., worksheet

SINGLE AND (OR) REPEATED INHALATION EXPOSURE STUDIES

No Record Number. "The Response Attending Exposure of Laboratory Animals to Vapors of Methyl Bromide" (Irish et al., J. Ind. Hyg. Tox., 22:218-230, 1940). This study involved single exposures of rats and rabbits and repeated exposures for up to 6 months (7.5-8 h/d, 5 d/w) to rats, guinea pigs, rabbits, and rhesus monkeys (rodent and rabbit strains not specified). The study is notable for its findings of neurotoxicity and species differences. The results suggest the following decreasing order of sensitivity to the neurotoxic effects of repeated exposure to methyl bromide-containing atmospheres: rabbits \geq monkeys > guinea pigs \geq rats. Literature reference. (Rinkus, 1/17/92).

4-17 WEEK GAVAGE STUDY, MALE RATS

083 059183 "The Subchronic Effects of Oral Methyl Bromide Administration in the Rat," (Purdue University, Masters Thesis, Ann Frances Hubbs, December, 1986). Methyl bromide was administered by gavage at the nominal concentrations of 0 (peanut oil), 25, and 50 mg/kg/day (5 days/week) to 71, 41, and 71 male Wistar rats, respectively. Rats received treatments until sacrificed at 4, 9, 13, or 17 weeks, with 7-10/group/sacrifice; however, rats in the 25 mg/kg/day group were not sacrificed at the two earliest times. Also, some rats in each group stopped receiving treatments after 13 weeks and remained untreated for either 4 or 9 weeks before being sacrificed. Toxicological examination mainly consisted of histological examination of blood, bone marrow and stomach. Food consumption and bodyweights were reduced in both groups receiving methyl bromide. Gross and histological changes were observed in the stomach of most rats receiving methyl bromide and were consistent with damage and inflammation of the squamous epithelium, but no tumorigenesis was indicated. NOEL, MTD < 25 mg/kg/day. Supplemental information. (Kishiya-ma, 1/24/89; Rinkus, 4/17/89).

Note: record 059183, as a thesis, contains an extensive literature review on methyl bromide. Topics include: poisoning in man by dermal, ocular (?), inhalation, and oral exposure; experimental animal studies; and in vitro studies (mutagenicity, transformation, and cytotoxicity). (Rinkus, 4/25/89).

TOXICOLOGY LITERATURE REVIEW

099 64742 "Toxicology of Methyl Bromide" is some sort of collaborated review, 29 pages long, plus 7 pages of references (with first two pages missing). Authors have affiliations with Toxicology and Pharmacology, Inc., Georgetown University, and Virginia Commonwealth University Medical College of Virginia. The authors' purpose in preparing the review (e.g., as a submission for publication) is not indicated; also, there is no date on the manuscript. Topics include: exposure, pharmacokinetics, human health effects, experimental studies, teratogenic activity, mutagenic activity, carcinogenic activity, and mechanism of action. It was noted that the most recognized effect of methyl bromide was neurotoxicity. No worksheet. Supplemental information. (Rinkus, 4/25/89).

RESIDUE STUDIES

Note: Record 126281 demonstrated that methyl bromide is readily converted to methyl chloride in the presence of water and sodium chloride. Given the facile production of methyl chloride when animal feed is fumigated, these data indicate that methyl chloride may be a concomitant residue after methyl bromide fumigation of organic matrices containing water and chloride (e.g., feeds and foods). (Rinkus, 7/24/95).

123-109 087810 "Methyl Bromide Residue Study (Pre-Plant)--Revised Draft," (Bolsa Research Associates; B.R. #10:87, 4/11/88). This record is some sort of partial report on results of measuring organic methyl bromide and inorganic bromide in a variety of crops grown on soil fumigated with methyl bromide. Apparently, no methyl bromide was detected in any crops grown on fumigated soil, while inorganic bromide levels were increased. Supplemental information. Not reviewed; no worksheet. (Rinkus, 4/20/90).

123-109 087811 "Section E: Removal of Residues," (no author or other identification given). This record is some sort of partial report regarding "additional means of reducing methyl bromide residues," presumably after commercial fumigation. Supplemental information. No Worksheet. (Rinkus, 4/20/90).

123-109 087812 "Fumigant Survey: Flour and Flour Products, April-June 1984," (Oregon Department of Agriculture, Laboratory Services Division, Food and Dairy Division; no date). No methyl bromide was detected in 100 flour and bakery mix products. The analytical method that was used had a detection limit of 0.03 ppm. Supplemental information. No worksheet. (Rinkus, 4/20/90).

123-109 087813 "Determination of Methyl Bromide Residues in Strawberries after Commercial Fumigation," (no author or other identification given). This record is some sort of partial report regarding the loss of organic methyl bromide residues from strawberries fumigated at the Driscoll Strawberries Associates fumigation facility in Watsonville, CA. The analytical method that was used was the headspace gas-chromatography assay of King et al. Data which were not provided were said to indicate an exponential loss in organic residues, such that only 3×10^{-6} ppm would be expected after 8 hours of some sort of unspecified aeration. Supplemental information. No worksheet. (Rinkus, 4/20/90).

123-151 124366 This record is a letter dated June 8, 1993 from the Registrant to the Office of Pesticide Programs at USEPA. An accompanying letter (no record number) in the front of 123-151 (dated June 16, 1993 and addressed to Dr. Larry Nelson [DPR MT Branch Chief]) indicates that the ecotoxicity testing data in record 124366 on the stability of methyl bromide in water is relevant to the discussion of how to conduct the rat chronic feeding study. Although it is stated that the rapid loss of methyl bromide from water makes it unacceptable to perform a chronic toxicity study using drinking water, no data concerning the losses incurred using drinking-water bottles were provided. Tabular data indicate that 10 mg/L solutions of methyl bromide in "well water" contained 86-89% of their initial content 48 h later (experimental conditions not described--apparently a closed system). **Supplemental information. No worksheet.** (Rinkus, 7/24/95).

123-154 126281 "Study to Determine the Feasibility of Preparing Dog and Rodent Diet with a Controlled Methyl Bromide Residual" (Ariano, J.; Great Lakes Chemical Corp.; technical report number: 1-93-10; Aug. 21, 1993). This record is notable for the following: its analytical studies utilized a modification of the headspace assay of King et al. (*J. Agric. Food Chem.* 29:1003-1005, 1981); it documented that in the fumigation of animal feed, there is sufficient water and chloride content to result in the formation of methyl chloride, presumably through some halide exchange reaction. DPR MT's concerns about the modified assay of King et al. are discussed in the rebuttal response of July 24, 1995 (R950724). **Supplemental information. No worksheet.** (Rinkus, 7/24/95).

123-151 124373 This record is a "working draft" (dated 5/9/93) of record 126281 (dated 8/21/93). This record has not been reviewed since it was superseded by record 126281. **Supplemental information. No worksheet.** (Rinkus, 7/24/95).

MISCELLANEOUS

123-140 112312 This record contains a letter (dated 1/2/92) from Dee Kuhn (the Chemical Manufacturers Association Manager for the MBIP). The letter summarizes a variety of matters discussed at the meeting of October 30, 1991 in Sacramento between the representatives of the MBIP and CDPR MT staff. This record also contains some written text and tables regarding the presentation made on methyl bromide neurotoxicology at the aforementioned meeting by Dr. Michael Gill. **Supplemental information. No worksheet.** (Rinkus, 1/17/92).

NOTE: All studies received by the DPR Medical Toxicology Branch up to 4/15/98 have been considered in this SUMMARY OF TOXICOLOGY DATA. The following also have been received but have not been reviewed:

- 1) 123-172 143942 "A Four Week Dietary Range-Finding Toxicity Study of Methyl Bromide in Rats" (E. Crosby Tompkins; project number WIL-49013; Aug. 16, 1995 [Susan Lewis's signature]).
- 2) 123-173 143943 This is a copy of a memorandum from Dr. Vince Piccirillo (NPC, Inc.) to Dr. Sue Lewis (CMA/MBIP) dated Nov. 27, 1995. The subject matter is identified as: "Six-Month Status for WIL Research Laboratories Study No. WIL-49014: A 24-Month Chronic Dietary Toxicity Study of Methyl Bromide in Rats."
- 3) 123-176 146039 This is an interim letter report regarding the one-year status of project number WIL-49014 (A 24-Month Chronic Dietary Toxicity Study of Methyl Bromide in Rats). The report is from J.J.W.M. Mertens (Study Director, WIL) to Susan A. Lewis (Methyl Bromide Industry Panel/CMA). It is dated March 26, 1996. Presumably, it is a synopsis of record 149113.
- 4) 123-177 149113 This is a 1767-page presentation of the data through test week 52 for project number WIL-49014 (A 24-Month Chronic Dietary Toxicity Study of Methyl Bromide in Rats). It is dated August 15, 1996 The author is J.J.W.M. Mertens (Study Director, WIL).

CHLOROPICRIN (CCl₃NO₂)

Attachment E.1. Introduction

This Attachment contains general information on chloropicrin which is used as a warning agent in some of the methyl bromide products. More extensive review will be presented in the risk characterization document for chloropicrin as an active ingredient. References cited in this Attachment are included in **VII. REFERENCES**.

Chloropicrin (trichloronitromethane, nitrochlorform, nitrotrichloromethane) is a colorless, slightly oily, heavy liquid with an intense irritating tear gas odor (The Merck Index, 1989; Farm Chemicals Handbook, 1998). In a mixture with methyl bromide, it volatilizes readily when released from the tanks (Exttoxnet, 1999). Chloropicrin has been used as an insecticide since 1917 and as a soil fumigant since 1920 (Exttonet, 1999). As a pesticide for space and soil fumigation, it controls nematodes, bacteria, fungi, insects, and weeds. In 1999, there are 44 active registered products with chloropicrin in California. The registrants for these products are: Ameribrom, Inc.; Great Lakes Chemical Corp.; Soil Chemicals Corp.; Niklor Chemical Co.; Holtrachem Manufacturing Co.; Trical, Trinity Manufacturing, Inc.; Osmose Wood Preserving, Inc.; and Shadow Mountain Products Corp. Twenty-six of the products are in combination with methyl bromide, while 8 of the products are in combination with 1,3-dichloropropene (Telone^R).

From 1993 to 1998, the use of chloropicrin increased from 2.1 million pounds in 1993 to 3.0 million pounds in 1998. The majority of the total use (>67%) was for strawberry fields in efforts to decrease the amount of methyl bromide applied. The use of methyl bromide for all uses are under strict use permit conditions requiring a minimum buffer zone of 100 feet for residents and 30 feet for workers.

From 1982 to 1996, there were a total of 363 cases with health effects “definitely”, “probably”, or “possibly” related to chloropicrin exposure reported in the California Pesticide Illness Surveillance Program (Mehler, 1999). Systemic effects (such as headache, nausea) as well as local effects to the eye and skin were reported. Some of the reported cases were due to drift from application sites. The highest number of cases was reported in 1987 where 71 residents in a nearby labor camp were exposed to chloropicrin being applied to a 9 acre field. Fumes were detected and the residents exhibited symptoms of exposure.

As a warning agent, the odor threshold is 1.1 ppm while 0.3 to 0.37 ppm resulted in painful irritation to the eyes in 3-30 seconds (ACGIH, 1997). For occupational exposure, the American Conference of Governmental Industrial Hygienists (ACGIH) has recommended a Threshold Limit Value (TLV^R) of below 0.1 ppm for occupational exposure and measured as an 8-hour time-weighted average air concentration. This level would protect for eye irritation. This level has been adopted as the Permissible Exposure Limit (PEL) by the Occupational Safety and Health Administration and the California Occupational Safety and Health Administration. Respiratory protection for workers is required if the air level exceed 0.1 ppm. National Institute of Occupational Safety and Health has established 2 ppm as the Immediately Dangerous to Life and Health (IDLH) level (NIOSH, 1999). In California, the Reference Exposure Levels are 4.4 ppb and 13 ppb for mild and severe effects, respectively (OEHHA, 1999).

Attachment E.2. Toxicology

2.a. Acute Toxicity

Because of its acute toxicity, chloropicrin is in toxicity category I, under FIFRA toxicity classification, and is a restricted use pesticide. Undiluted liquid or concentrated chloropicrin is a severe irritant to the eye, skin, and upper respiratory tract. The dose response for chloropicrin is considered steep. In humans, the no observable effect is 100 ppb (ACGIH, 1997). At 300 ppb, cough, nausea, and vomiting occur, and severe skin irritation from direct skin contact. A summary list of the air concentrations for lethality and acute effect is presented in Table E1.

2.b. Other Toxicity Studies

Toxicity studies submitted for the fulfillment of SB 950 data requirement and reviewed under FIFRA guidelines are summarized in Table E2. The review of all submitted studies in the Summary of Toxicology Data is available upon request to the Registration Branch of DPR.

Table E1. Acute toxicity of chloropicrin in experimental animals and human.

Species	Inhalation LC 50	Inhalation (non-lethal)	Oral LD50	Dermal LD50	Ref ^a
Human	2000 ppm (10 min), lethal		5 to 50 mg/kg as lethal dose		1
Human	200 ppm (10 min), lethal				2
Rat	25.5 ppm (1 hr) ^b		37.5 mg/kg ^b	100 mg/kg ^b	3
Rat	11.9 ppm (4 hr) ^c				4
Rat	16.7-20.1 ppm (4 hr)				5
Rat	(4 hr) whole body 14.4 ppm nose only 6.6 ppm				6
Mouse		7.98 ppm (10 min) ^d			7
Mouse	9.9 ppm (4 hr)				1
Mouse		2.34 ppm(30 min)			8
Dog	111-131ppm (30 min) 53% dead				9, 10
Cat	120 ppm (20 min)				1
G. Pigs	120 ppm (20 min)				1

a/ References: 1. HSDB, 1994; 2. Prentiss, 1937; 3. Harton and Rawl, 1976; 4. Yoshida et al., 1987a; 5. Hoffman, 1999a; 6. Yoshida et al., 1991; 7. Kane et al., 1979; 8. Hoffman, 1999b; 9. Lambert and Jackson, 1920; 10. Underhill, 1920.

b/ Lethal doses were based on deaths within 14 days.

c/ Rats were exposed to chloropicrin (0, 8.8 to 16 ppm) for 4 hours. Necropsy showed lung lesions (edema, emphysema) and gastric distension. All animals showed reduced body weights.

d/ RD50= dose which caused 50% decrease in the respiration rate.

Table E2. Summary of findings from toxicity studies in the SB 950 database.

Species /Route (Dose)	NOEL	Effects	Ref
Subchronic Toxicity			
Rat / inhalation (0.37-2.93 ppm)	0.67 ppm	↓ Body weights, food consumption; ↑ lung weights; lung epithelial hypertrophy	1
Rat/ oral gavage (10-80 mg/kg/day for 10 days)	<10 mg/kg/day	Forestomach lesions	2
Rat/ oral gavage (2-32 mg/kg/day for 90 days)	8 mg/kg/day	↓ Body weight, hematological changes and forestomach histological changes	2
Chronic Toxicity/Oncogenicity			
Rat / oral gavage (0.1- 10 mg/kg/day for 2 years)	0.1mg/kg/day	↓ Body weight, periportal vacuolization of hepatocytes Stomach papilloma (1 male), ↑ mammary fibroadenomas in 10 mg/kg females	3*
Dog / oral capsule (0.1- 5.0 mg/kg/day for 1 year)	1.0 mg/kg/day	↓ Body weight (male), clinical signs and clinical pathology	4*
Rat / inhalation (0.1-1.0 ppm for 107 weeks)	0.1 ppm (0.12 mg/kg/day)	↓ Survival	5
Mouse/ inhalation (0.1-1.0 ppm for at least 78 weeks)	0.1 ppm (0.22 mg/kg/day)	↓ Body weight/ gain, food consumption; ↑ lung weights; and lung lesions. No oncogenic effects	6*
Reproductive Toxicity			
Rat / inhalation (0.5-1.5 ppm for 2 generations)	Maternal 0.5 ppm Repro. ≥ 1.5 ppm	↓ Body weight, and lung lesions No pup or reproductive effects	7*
Developmental Toxicity			
Rat / inhalation (0.4-3.5 ppm, gd 6 to 15)	Maternal 1.2ppm Fetal 0.4 ppm	↓ Body weight, body weight gain, and food consumption; ↑ clinical sign ↑ Skeletal variations	8*
Rabbit / inhalation (0.4-2.0 ppm, gd 7 to 20)	Maternal 0.4 ppm Fetal 0.4 ppm	↑ Clinical signs, abortions, and mortality ↑ Skeletal variations	9*
Genotoxicity			
Mouse lymphoma cells	NA	No increase in forward mutation frequency	10*
<i>S. typhimurium</i> 5 strains	NA	↑ revertant colonies ± rat liver S9	11*
Chinese hamster ovary cells	NA	↑ chromosomal aberrations	12*
Rat primary hepatocytes	NA	No effect on unscheduled DNA synthesis	13*

a/ * Studies were considered acceptable under FIFRA guidelines. Reference: 1. Yoshida *et al.*, 1987b; 2. Condie *et al.*, 1994; 3. Slauter, 1995; 4. Wisler, 1994; 5. Burleigh-Flayer and Benson, 1995; 6. Burleigh-Flayer *et al.*, 1995; 7. Schardein, 1994; 8. Schardein, 1993; 9. York, 1993; 10. San and Sigler, 1990a; 11. San and Sigler, 1990b; 12. Putman and Morris, 1990; and 13. Curren, 1990. NA= not applicable.

ATTACHMENT F

ESTIMATION OF EXPOSURE OF PERSONS TO METHYL BROMIDE

ESTIMATION OF EXPOSURE OF PERSONS TO METHYL BROMIDE
DURING AND/OR AFTER AGRICULTURAL AND NONAGRICULTURAL USES

By

Thomas Thongsinthusak, Staff Toxicologist
David Haskell, Associate Environmental Research Scientist*

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California Environmental Protection Agency
Department of Pesticide Regulation
Worker Health and Safety Branch
*Pesticide Registration Branch
1001 I Street, P. O. Box 4015
Sacramento, California 95812

EXECUTIVE SUMMARY

Methyl bromide (MB) has been used extensively to fumigate soil, agricultural commodities and structures in California. Total reported use of MB from 1996 to 1999 was 16.0, 15.7, 13.6 and 15.3 million pounds, respectively. In 1999, strawberry, soil application (preplant-outdoor) and outdoor container/field grown plants accounted for 55% of the total annual use.

This exposure document was prepared as part of the Department of Pesticide Regulation's risk assessment process. The document contains information, including physical/chemical properties, regulatory history, formulations, usage, label precautions, human illnesses, dermal toxicity and sensitization, animal/human metabolism, inhalation uptake/dermal absorption, and exposure assessment. MB exposure estimates for workers and other persons were calculated, if applicable, using air concentrations of MB, duration and frequency of exposures. Exposure estimates are shown as the 24-hour Time-Weighted Average (TWA) unless indicated otherwise.

Due to its high vapor pressure, the major route of exposure is by inhalation. Major excretion routes in rats after inhalation exposure occurred in exhaled air and urine. From 1991 to 1999, illnesses in California caused by MB alone were 90 cases (average 10.0 cases/year) and those caused by MB in combination with chloropicrin were 106 cases (average 11.7 cases/year). From 1982 to 1999, there were six accidental exposures where 253 people were evacuated. From the same period, there were 19 deaths resulting entirely from structural fumigation.

Exposure assessments for MB were determined for occupational workers and other persons, including residents of nearby homes. Examples of average (or range of average) acute exposure estimates (part per billion, ppb) calculated as the 24-hour TWA are:

- preplant soil injection fumigation, 0.6 – 835,
- soil fumigation in greenhouses, 0.009 (tarpaulin (tarp) venters) and 0.95 (tarp removers),
- fumigation of grain products, 0.03 - 16.0,
- dried fruit and tree nut fumigation, 4 - 1,434,
- a walnut processing facility, 29 - 239,
- a brewery facility, 25 - 173.

The 95th percentile acute MB exposures of persons at the buffer zone distance range from 163 to 239 ppb, depending on field sizes (1 to 10 acres) and soil application methods (such as nontarp/shallow/bed, tarp/deep/broadcast, tarp/shallow/broadcast). For example, the MB air concentration for a 10-acre field when nontarp/shallow/bed fumigation method was used was 217 ppb and that when tarp/shallow/broadcast fumigation method was used was 165 ppb. The maximum ambient MB concentrations (ppb) in the high use counties (Monterey, Santa Cruz and Kern) were 30.8 (daily), 15.5 (weekly), and 7.68 (mean of weekly means). The meaning of ambient MB concentrations are: 1) maximum daily MB concentration represents the highest observed 24-hour MB concentrations in one of the sampling stations; 2) maximum weekly mean represents the highest observed weekly average in one of the sampling stations; 3) maximum mean of weekly means represents the highest observed weekly average in one of the sampling stations. The sampling period lasted 7 or 8 weeks.

Several applications of MB such as soil fumigation in nurseries and greenhouses, fumigation of homes and fumigation of noncertified chambers, which were used in exposure monitoring studies, were not conducted in accordance with permit conditions/regulations. Thus, exposure data from these studies are not included in this document because the influence of factors required by permit conditions/regulations to MB concentrations is not known. These studies were performed during fumigation of potting soil, greenhouse (except tarp venters and removers), grain products (except aerators and forklift drivers), dried fruits and tree nuts (except chamber-raisins), cherries, walnut processing facility (except fumigation in 1994), residents/bystanders in fumigated homes and reentry studies for fumigated homes.

Some MB exposure data are grouped based on types of fumigation and exposure scenarios. The purpose of grouping of exposure data is to show the magnitude of the exposure data and whether mitigation measures would cover a wide range of exposure. Examples of the average (range) of acute MB concentrations (ppb) for soil fumigation are 136 (3 - 515) for nonbedded, 93 (1 - 334) for bedded), and 123 (1 - 518) for bedded and nonbedded, and 83 (1 - 404) for commodity fumigation (other workers).

Acute and nonacute MB exposures (7-day, 90-day, and 365-day exposure periods) of persons during soil, commodity, and structural (brewery facility) fumigations were recalculated using work hours allowed by the current soil fumigation regulations or permit conditions, instead of using work hours from a survey. Examples of the ranges of the adjusted average exposures during field fumigations are: 0.4 – 974 ppb for acute exposure, 0.2 – 696 ppb for subacute exposure (7-day exposure period), and 1.0 – 595 ppb for subchronic exposure (90-day exposure period). Upper bound MB concentrations for acute exposures were also calculated. The upper bound acute exposures range from 1 to 2,118 ppb for soil fumigation. The maximum MB exposure of persons during greenhouse, commodity, and structure (brewery facility) fumigations was assumed to be 210 ppb because MB concentrations in work areas must be monitored and work hours be adjusted accordingly so that the daily MB exposure is not greater than 210 ppb, which is the target exposure level.

The Department of Pesticide Regulation does not have data to assess all worker exposure scenarios or potential exposure to the public from all MB applications. Nonacute exposures were also estimated for different work tasks and exposure scenarios. These exposures were estimated from acute exposure, duration and frequency of exposure for each specific exposure scenario. Ambient air concentrations were shown as daily (maximum 24-hour and 95th percentile), weekly (maximum and 95th percentile weekly mean) and mean of weekly means (7- or 8-week).

Adverse effects of MB, which were used to establish the endpoints for the critical no-observed-effect levels for risk assessment, were developmental toxicity (acute), neurotoxicity (subchronic), and nasal epithelial hyperplasia and degeneration (chronic).

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ROAD MAPS FOR APPENDICES, TABLES AND CALCULATIONS

The National Research Council peer reviewed the exposure document for MB and recommended that a road map of the information in the appendices and a more systematic presentation of the data would be helpful to the reader. Two road maps are provided for this purpose in the form of flow diagrams as follows:

a) A road map for appendices and tables of the MB exposure document: This flow diagram indicates appendices and tables contained in this exposure document. The authors also provide a brief description of contents in these appendices and tables. However, a road map within an appendix is deemed unnecessary because each appendix is self-explanatory in nature.

This flow diagram also shows the arrangement of tables. Basically, these tables are arranged according to the document format for sections. Summary tables (Tables 11 to 14) for exposure data are located ahead of other tables that contain exposure data from individual study because of the recommendation from the reviewers.

b) A road map for calculations of subacute, subchronic and chronic exposures of MB: This road map provides a quick glance for exposure calculations. Basically, the exposure data are adjusted to reflect the recovery and maximum application rate allowed by product labels. The magnitude of exposures for acute, subacute, subchronic and chronic exposures are also dependent on duration and frequency of exposure. Duration and frequency of exposure were obtained from surveys as well as from default values, if data were not available. These data are shown in Appendix A. Stepwise calculations are shown in the flow diagram.

Figure 1. A Road Map for Appendices and Tables of the Methyl Bromide Exposure Document

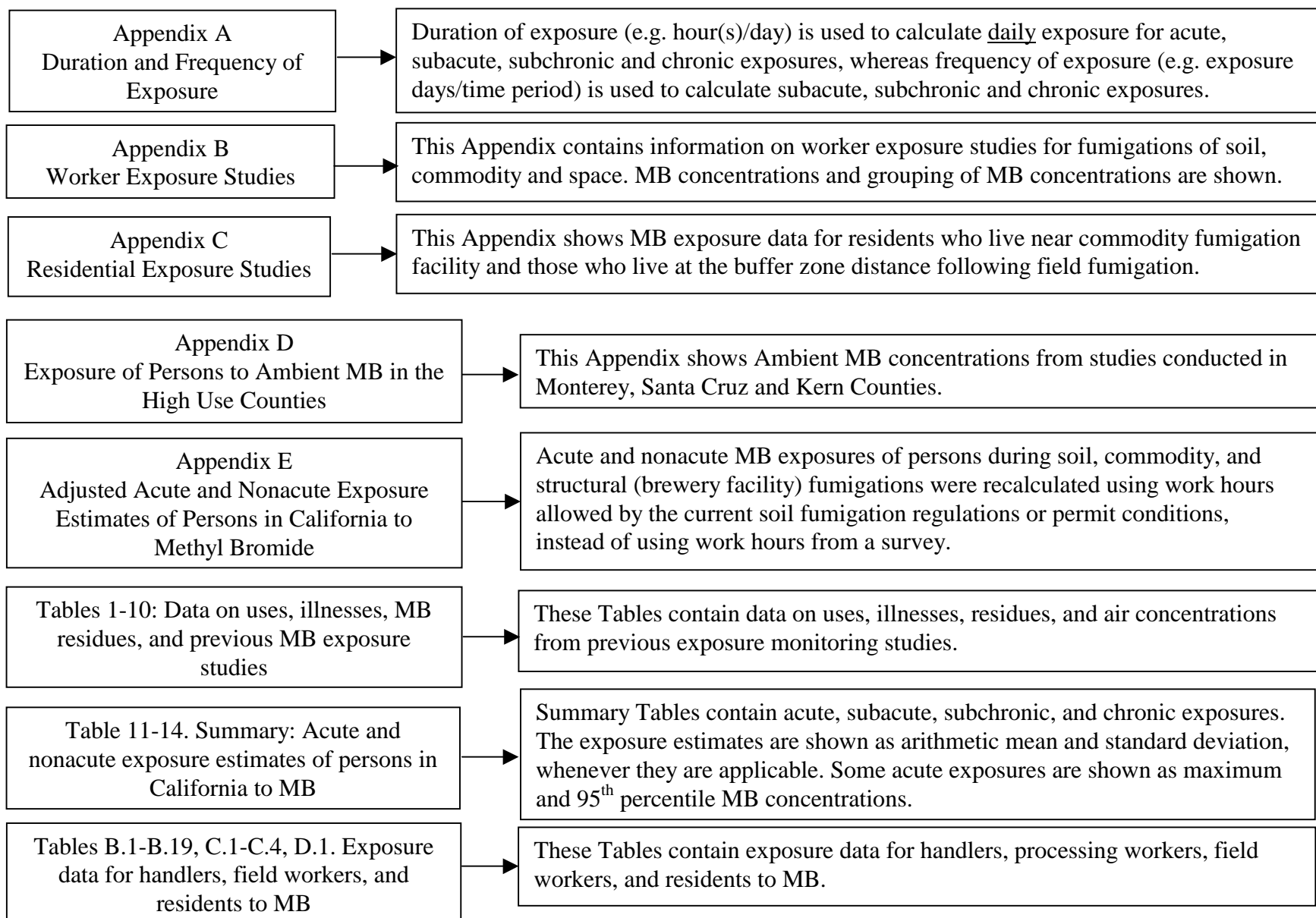
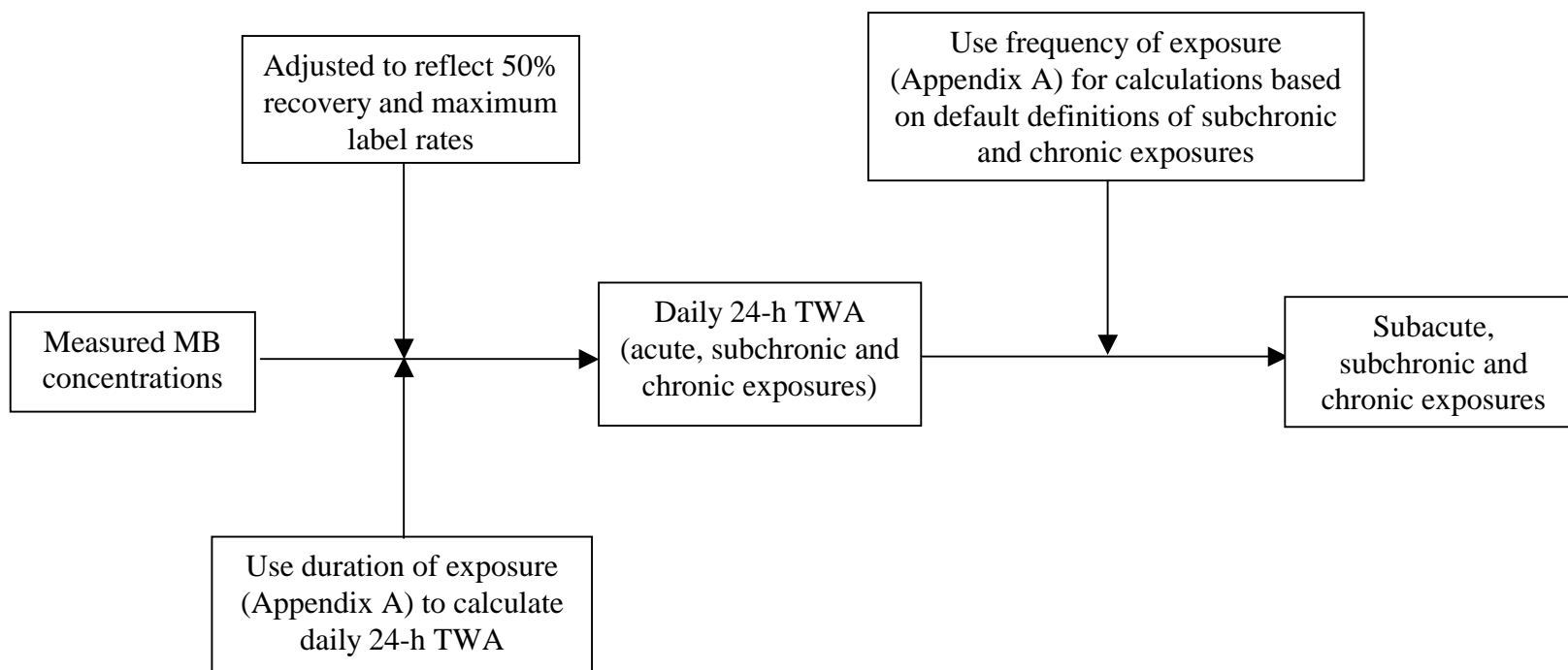


Figure 2. A Road Map for Calculations of Subacute, Subchronic and Chronic Exposures of Methyl Bromide



Example of subchronic exposure calculation:

Measured MB Concentration (ppb)	Application rate (lbs MB/A) (maximum/applied)	Field spike recovery (%)	Duration of exposure 5 hours/day	Frequency of exposure (exposure days/90-day period)
397	400/280	50	5/24	55/90

Daily subchronic exposure (24-h TWA): $\frac{397 \times 400 \times 100 \times 5}{280 \times 50 \times 24} = 236 \text{ ppb}$

Subchronic exposure: $\frac{236 \times 55}{90} = 144 \text{ ppb}$

Department of Pesticide Regulation
Worker Health and Safety Branch

Human Exposure Assessment

HS-1659 February 5, 2002

INTRODUCTION

Methyl bromide is widely used as a fumigant to control pests in soil, fresh and dry agricultural products, residences and other structures. This fumigant is acutely toxic to humans from excessive inhalation exposure. In order to reduce potentially harmful exposures to users and residents/bystanders, the Department of Pesticide Regulation (DPR) issued permit conditions for soil injection fumigation, soil fumigation within the greenhouse, fumigation of tarped potting soil, and commodity fumigation. Recently, DPR adopted regulations pertaining to the use of methyl bromide in structural fumigations and the use of methyl bromide in soil fumigations prior to the planting of agricultural crops. Currently, DPR is working on the risk assessment of MB under the provision of the Birth Defects Prevention Act of 1984. The Worker Health and Safety Branch (WH&S) is responsible for the preparation of the MB exposure assessment document, which is an integral part of the risk assessment process.

Many exposure monitoring studies were conducted prior to the implementation of permit conditions/regulations and may not reflect exposure after restrictions were implemented; these studies were soil fumigation, nursery potting soil fumigation, greenhouse soil fumigation, fumigation of grain products, fumigation of dried fruit and tree nut products, fumigation at a walnut processing and a brewery facility, and fumigation of houses. DPR does not have data to assess all worker exposure scenarios or potential exposure to the public from all MB applications.

The exposure assessment document contains sections dealing with physical and chemical properties, regulatory history, formulations, usage, label precautions, human illnesses, dermal toxicity/sensitization, animal/human metabolism, inhalation uptake and dermal absorption. Information from these sections enhances better understanding of the nature, usage, and potential for exposure. Exposure estimates are presented as the 24-hour time-weighted-average (TWA) air concentration of MB. These estimates are grouped as acute exposure (daily exposure) and nonacute exposures (subacute, subchronic, and chronic exposures).

The Subcommittee on Methyl Bromide of the National Research Council reviewed the 1999 MB risk characterization document, which included the exposure document (October 5, 1999). The Subcommittee provided comments and recommendations in the report (NRC, 2000). This revision of the exposure document incorporates comments from the Subcommittee when they warrant changes.

On December 3, 2001, the exposure for applicators and co-pilots during shallow shank, tarped-bed fumigation (Table 11, g) was changed to reflect correct methyl bromide concentrations. The exposure for irrigation pipe tractor drivers and pipelayers were deleted because these work tasks are not allowed during MB soil fumigation until the restricted entry interval has expired.

PHYSICAL AND CHEMICAL PROPERTIES

Physical and chemical properties of MB as mentioned below were obtained from the Farm Chemicals Handbook (Meister, 1995), the Merck Index (Budavari *et al.*, 1989), and United States Environmental Protection Agency (U.S. EPA, 1986a).

Chemical name: Bromomethane, monobromomethane

CAS Registry number: 74-83-9

Common name: Methyl bromide

Trade names: Brom, Brom-O-Gas, M-B-R, Metabrom, Meth-O-Gas, Methyl Bromide, Pic-Brom, Terr-O-Gas, Tri-Brom, Tri-Con, Tri-Pan.

Molecular formula: CH₃Br

Molecular weight: 94.95 g/mole

Chemical structure: CH₃-Br

Physical appearance: Colorless gas, usually odorless; sweetish, chloroform-like odor at high concentrations (odor threshold at 80 mg/m³ or 20.6 ppm); burning taste. It is nonflammable in air but does burn in oxygen.

Solubility: 1.75 g/100 g water (20 °C, 748 mm Hg), forms a crystal hydrate, CH₃Br.20H₂O, below 4 °C; freely soluble in alcohol, chloroform, ether, carbon disulfide, carbon tetrachloride, benzene.

Boiling point: 3.56 °C

Melting point: -93.66 °C

Octanol/Water partition coefficient: Log P = 1.19 (15.5:1)

Vapor pressure: 1420 mm Hg (20 °C), 2600 mm Hg (40 °C)

Specific gravity: 1.7 g/mL (liquid)

Vapor density: 3.3 g/L (gas)

Conversion factor: 1 ppm = 3.89 mg/m³ at 25 °C

REGULATORY HISTORY INCLUDING U.S. EPA STATUS

The insecticidal activity of MB was first reported in 1932 (Le Goupil, 1932). MB is a restricted use pesticide in the United States. Retail sale and use are limited to certified applicators or persons under their direct supervision, and only for those uses covered by the applicator's certification.

Ozone depletion:

1. MB is an ozone depleter with a calculated ozone depletion potential (ODP) of 0.7 (Watson *et al.*, 1992).
2. The worldwide sources of MB include: Anthropogenic (human made) agriculture, biomass burning (forest fires, grass fires), leaded gasoline burning, and oceans.
3. U.S. Clean Air Act mandated that by the year of 2005, no production or importation of MB is allowed. However, the Act does not restrict the use, which is regulated under the Federal Insecticide, Fungicide and Rodenticide Act in the U.S. EPA, Office of Pesticide Programs.
4. At the 1997 meeting, Parties (over 125 nations) to the Montreal Protocol amended the previous deadlines. The new deadlines on complete phase-out of use are 2015 and 2005 for developing and industrial nations, respectively.

Federal Regulations:

1. The U.S. EPA established tolerances in commodities based on inorganic bromide level because of the assumption that MB is degraded completely to bromide (Federal Register, 1991).

2. The oral reference dose (RfD) was determined to be 0.0014 mg/kg/day based on the no-observed-effect level (NOEL) of 1.4 mg/kg/day for forestomach epithelial hyperplasia in a rat oral subchronic study (Danse *et al.*, 1984) and an uncertainty factor of 1,000. The inhalation reference concentration (RfC) was 5×10^{-3} mg/m³ (1.3 parts per billion, ppb) based on the lowest-observed-adverse-effect level (LOAEL) of 3 ppm for nasal olfactory epithelial hyperplasia from a rat chronic inhalation study (Reuzel *et al.*, 1987 and 1991) and an uncertainty factor of 100.
3. The drinking water health advisories for MB for one-day, ten-day, and longer-term health advisory for a child is 0.1 mg/L assuming 1 L/day water consumption for a 10-kg child (U.S. EPA, 1992). The longer-term health advisory for an adult is 0.5 mg/L assuming 2 L/day water consumption for a 70-kg adult. The lifetime health advisory is 0.01 mg/L assuming 20% of exposure by drinking water.
4. MB is classified as a "Group D" carcinogen (not classifiable as to human carcinogenicity) by U.S. EPA due to inadequate human and animal data (U.S. EPA, 1992).

California Regulations:

1. For occupational exposure to MB, the current permissible exposure limit (PEL) for MB is 5 ppm or 20 mg/m³ and a ceiling limit of 50 ppm.
2. In 1992, monitoring data caused the DPR to be concerned regarding the risk from short-term exposures to MB both to structural workers and residents returning to recently fumigated structures. The DPR promulgated emergency regulations to decrease the exposure and required pest control operators to hand out a Fact Sheet explaining the potential human hazards of MB fumigation. Permit conditions were developed for soil, and commodity fumigation.
3. On January 1, 1993, MB, as structural fumigant, was administratively listed by the Office of Environmental Health Hazard Assessment (OEHHA) as a developmental toxicant under Proposition 65 via the provision for listing due to the federal label warning requirement.
4. The Proposition 65 Developmental and Reproductive Toxicity Identification (DART) Committee of the OEHHA Science Advisory Board decided that evidence from experimental animals had not "clearly shown" that MB caused developmental and reproductive toxicity. MB remains listed under Proposition 65 for structural fumigation uses only.
5. The regulation for the use of methyl bromide in structural fumigations was approved on August 15, 2000 and effective on September 14, 2000.
6. The regulation for the use of methyl bromide in soil fumigations prior to the planting of agricultural crops was approved on December 15, 2000 and effective on January 14, 2001.

FORMULATIONS

In 2001, 54 MB-containing products were registered in California. Table 1 shows % active ingredient (a.i.) and trade (product) names of these products. Some products contain chloropicrin as a warning agent. Chloropicrin is also a fumigant similar to MB in controlling pests. Detailed information on application rate and sites is available from the DPR home page. There is too much information to summarize or provide as hard copy in this document. Table 1 presents a DPR database search of MB active products as of April 26, 2001.

Table 1. Methyl bromide products registered in California in 2001.

Product Name	Formulation	Company	% MB	% Chloropicrin listed as a.i.
50-50	P	A	50	50
57-43	P	A	58	43
67-33	P	G	67	33
67-33 Preplant Soil Fumigant	P	A	67	33
75-25	P	A	75	25
80-20	PG	A	79	19
98-2	P	G	98	0
98-2 Contains 2% Chloropicrin	P	A	97.6	0
Brom-76	PG	S	75	1
Bromo-O-Gas (Liquid)	PG	G	98	0
Bromo-O-Gas 0.5%	PG	G	99.5	0
Bromo-O-Gas 0.25%	P	G	99.75	0
Bromo-O-Gas 2%	P	G	98	0
MBC-33 Soil Fumigant	P	T	67	33
MBC Concentrate Soil Fumigant	P	T	98	0
M-B-R 98	P	AL	98	0
M-B-R 98 Technical	P	AL	98	0
Metabrom 100	P	A	99.7	0
Metabrom 99	P	A	99.65	0.25
Metabrom Q	PG	A	100	0
Meth-O-Gas 100	PG	G	100	0
Meth-O-Gas Q	P	G	100	0
Methyl Bromide	P	G	100	0
Methyl Bromide 100	PG	S	100	0
Methyl Bromide 100	PG	A	100	0
Methyl Bromide 89.5%	PG	T	89.5	0
Methyl Bromide 98%	P	S	98	0
Methyl Bromide 98%	PG	T	98	0
Methyl Bromide 99.5%	PG	G	99.5	0
Methyl Bromide 99.5%	PG	S	99.5	0
Methyl Bromide 99.5%	PG	T	99.5	0.5
Methyl Bromide 99.75%	PG	S	99.75	0
Methyl Bromide Quarantine Fumigant	PG	S	100	0
Pic-Brom 25	PG	S	75	25
Pic-Brom 33	PG	S	67	33
Pic-Brom 43	PG	S	57	43
Pic-Brom 50	PG	S	50	50
Pic-Brom 55	PG	S	45	55
Pic-Brom 67	PG	S	33	67
Terr-O-Gas 57	PG	G	57	41.5
Terr-O-Gas 67	PG	G	67	33
Terr-O-Gas 75	PG	G	75	25

Table 1 (cont.). MB products registered in California in 2001.

Product Name	Formulation	Company	% MB	% Chloropicrin listed as a.i.
Terr-O-Gas 80	PG	G	80	20
Terr-O-Gas 98	P	G	98	2
Tri-Brom	P	T	99	0
Tri-Con 45/55	P	T	45	55
Tri-Con 50/50	PG	T	50	50
Tri-Con 57/43	PG	T	57	42.6
Tri-Con 67/33	PG	T	67	32.7
Tri-Con 75/25	PG	T	75	24.8
Tri-Con 80/20	P	T	80	19.8
Tri-Con 80/20	P	SM	80	19.8
Tri-Pan 76/24	PG	T	75	24.0
TriCal Methyl Bromide 99.5%	P	SM	99.5	0

P = pressurized liquid/sprays/foggers; PG = pressurized gas; A = Ameribrom, G = Great Lakes, S = Soil Chemical Corp; AL = Albermarle; T = TriCal; SM = Shadow Mountain (part of TriCal)

USAGE

The annual top-ten uses of MB (DPR, 1999a, 1999b, 2000a, 2000b) are shown in Tables 2-5. The highest percentages of MB use in those years were for strawberry planting, ranging from 26% to 34% of the total annual reported use. The percentages of annual top-ten uses from 1996-1999 calculated based on the total annual reported use were 72%, 76%, 74%, and 76%, respectively.

Table 2. Summary of methyl bromide usage in 1996 from the DPR database:^a Top ten uses.

Usage	Lbs methyl bromide	% Total
Strawberry (All or Unspecified)	4,375,225	27
Grapes, wine	1,479,859	9
Soil application, preplant-outdoor (seedbeds, etc.)	1,407,539	9
Outdoor container/field grown plants	1,118,593	7
Sweet potato	611,586	4
Structural pest control	594,902	4
Almond	532,007	3
Outdoor grown transplant/propagative material	515,267	3
Walnut (English walnut, Persian walnut)	459,301	3
Outdoor grown cutflowers or greens	414,520	3
Total	11,508,799	72

^a DPR, 1999a. Total methyl bromide use in 1996 was 16,022,069 pounds

Table 3. Summary of methyl bromide usage in 1997 from the DPR database:^a Top ten uses.

Usage	Lbs methyl bromide	% Total
Strawberry (All or Unspecified)	4,050,264	26
Soil application, preplant-outdoor (seedbeds, etc.)	2,153,566	14
Outdoor container/field grown plants	922,659	6
Grapes, wine	897,380	6
Almond	893,299	6
Sweet potato	766,042	5
Grapes	579,120	4
Outdoor grown cutflowers or greens	545,718	3
Outdoor grown transplant/propagative material	509,527	3
Structural pest control	504,221	3
Total	11,821,796	76

^a DPR, 1999b. Total methyl bromide use in 1997 was 15,663,832 pounds.

Table 4. Summary of methyl bromide usage in 1998 from the DPR database:^a Top ten uses.

Usage	Lbs methyl bromide	% Total
Strawberry (All or Unspecified)	4,252,131	31
Soil application, preplant-outdoor (seedbeds, etc.)	1,522,344	11
Outdoor container/field grown plants	1,062,682	8
Outdoor grown transplant/propagative material	546,740	4
Sweet potato	541,923	4
Grapes, wine	478,247	4
Almond	459,260	3
Outdoor grown cutflowers or greens	429,620	3
Peppers (fruiting vegetable), (Bell, chili, etc.)	403,079	3
Structural pest control	360,618	3
Total	10,056,644	74

^a DPR, 2000a. Total methyl bromide use in 1998 was 13,569,875 pounds.

Table 5. Summary of methyl bromide usage in 1999 from the DPR database:^a Top ten uses.

Usage	Lbs methyl bromide	% Total
Strawberry (All or Unspecified)	5,171,766	34
Soil application, preplant-outdoor (seedbeds, etc.)	2,159,084	14
Outdoor container/field grown plants	1,095,489	7
Grapes, wine	823,720	5
Outdoor grown transplant/propagative material	517,498	3
Peppers (fruiting vegetable), (Bell, chili, etc.)	544,962	4
Sweet potato	445,731	3
Walnut (English walnut, Persian walnut)	344,730	2
Almond	336,671	2
Peach	332,440	2
Total	11,772,091	76

^a DPR, 2000b. Total methyl bromide use in 1999 was 15,342,080 pounds.

LABEL PRECAUTIONS/PERSONAL PROTECTIVE EQUIPMENT

All MB products are classified as Toxicity Category I pesticides bearing a signal word "Danger/Poison." The general precautionary statements for MB read: *"Hazard to humans and domestic animals: Danger. Extremely hazardous liquid and vapor under pressure. Inhalation may be fatal or cause serious acute illness or delayed lung or nervous system injury. Do not breathe vapors. Liquid or excessive vapor can cause serious skin or eye injury, which may have a delayed onset. Do not get liquid on skin, in eyes, or on clothing."* If the product contains chloropicrin, it further gives these statements: *"This product contains chloropicrin as a warning odorant. Chloropicrin may be irritating to the upper respiratory tract, and even lower levels can cause painful irritation to the eyes, producing tearing. If these symptoms occur, leave the fumigation area immediately."*

The labels also give the following restrictions: *Do not fumigate with MB when soil temperature is below approximately 50 °F at 6 inches, do not wear jewelry, gloves, goggles, tight fitting clothing, rubber protective clothing, or rubber boots when handling. MB and chloropicrin are heavier than air and can be trapped inside clothing and cause skin injury.*

Product labels specify required personal protective clothing and equipment for workers. For example, applicators and other handlers must wear loose-fitting or well-ventilated long-sleeved shirts and long pants. The label requires respiratory protection when the air concentration level is above 5 ppm (20 mg/m³) at any time. DPR has established the target 24-hour TWA of 210 ppb (Nelson, 1992). The respiratory protection must be one of the following types: 1) a supplied air-respirator (MSHA/NIOSH approval number prefix TC-19C) or 2) a self-contained breathing apparatus (SCBA) (MSHA/NIOSH approval number prefix TC-13F). Under normal soil fumigation conditions, if the concentration of MB in the working area will not generally exceed 5 ppm, no respiratory protection is required. However, there is a possibility of a spill or leak during soil fumigation. Therefore, respiratory protection of a type specified above must be available and will be required for entry into the affected area in the event of a leak or spill.

HUMAN ILLNESSES

MB can cause serious human illness, especially when health protection and regulations are lax. In the past, MB was used as a refrigerant and a basic chemical in fire extinguishers. Some published literature revealed a history of serious illnesses caused by these uses or by accidental exposure to MB. Watrous (1942) reported a case where 33 out of 90 workers experienced systemic symptoms. These workers were involved in a packaging process where they placed liquid MB in glass ampoules, sealed the ampoules and inspected them for leakage. The air concentration of MB in the work area was generally less than 35 ppm. Workers experienced symptoms of anorexia, nausea, vomiting, headache, vertigo, difficulty in focusing the eye, lethargy, muscular pains, and dimness of vision. Johnstone (1944) reported 34 known cases of MB intoxication that developed in the date-packing industry in Indio, California. An estimated 15 to 20 more packers were absent from work for a period of two to 10 days but did not consult with a physician. The maximum allowable air concentration of MB at that time was 50 ppm. The high level of exposure was caused by leakage of chambers. Many of the fumigation chambers were not

constructed tightly enough to prevent leakage of MB into the workroom area. The majority of workers had neurologic disturbances involving vision, speech, tremors, and numbness of the extremities. There was a high incidence of mental confusion and some hallucinations. Depressive states lasted as long as five months. Other published reports revealed symptoms of different severity and fatalities among workers and residents (von Oettingen, 1946; Mezel *et al*, 1948; MacDonald, *et al.*, 1950; Ingram, 1951; Rathus and Randy, 1961; Longley and Jones, 1965; Alexeeff and Kilgore, 1983). Even though current California laws and regulations regarding the use of MB are more stringent than those in the 1940s and 1950s, illnesses still occur as a result of exposure to MB from various uses.

The Pesticide Illness Surveillance Program (PISP) of DPR maintains credible records of illnesses caused by MB. In California, physicians are required to report any illness or injury they suspect of being related to pesticide exposure. Data in Tables 6 and 7 show illnesses associated with exposure to MB and MB in combination with other pesticides from 1991 to 1999 (Mehler, 2001).

Table 6. Occupational and nonoccupational illnesses associated with exposure to methyl bromide alone in California (1991-1999).^a

Methyl bromide alone	Illness/injury type				Total		
Activity	Systemic	Eye	Skin	Eye/skin	Def ^b	Prob ^c	Pos ^d
1. Occupational (occup.)							
Fumigation, field	1	0	11	1	10	2	1
Fumigation, tarpaulin	4	0	0	0	0	1	3
Fumigation, chamber	9	0	0	0	2	5	2
Exposed to drift	15	0	0	0	2	1	12
Residue and other	7	0	4	0	5	2	4
Emergency response	8	0	0	0	2	3	3
Exposed to concentrate	3	1	0	0	1	3	0
Total occupational	47	1	15	1	22	17	25
2. Nonoccupational							
Exposed to residues	15	3	0	0	2	15	1
Other	8	0	0	0	3	0	5
Total nonoccupational	23	3	0	0	5	15	6
Occup. + nonoccup.	70	4	15	1	27	32	31
Yearly average	7.8	0.4	1.7	0.1	3.0	3.6	3.4

^a Mehler, 2001.

^b The "definite (Def)" classification indicates the signs and symptoms exhibited by the affected person are such as would be expected to result from the exposure described and medical or physical evidence is available to substantiate the exposure.

^c The "probable (Prob)" classification indicates that there is close correspondence between the exposure and the illness experienced.

^d The "possible (Pos)" classification indicates some correspondence between the exposure described and the illness/injury experienced.

Table 7. Occupational and nonoccupational illnesses associated with exposure to methyl bromide in combination with other pesticides in California (1991-1999).^a

Methyl bromide in combination with other pesticides	Illness/injury type				Total		
	Systemic	Eye	Skin	Eye/skin	Def ^b	Prob ^c	Pos ^d
1. Occupational							
Fumigation, field	11	2	3	1	8	5	4
Fumigation, drift	8	1	0	0	1	5	3
Other residues	28	2	4	2	3	7	26
Emergency response	1	4	1	0	0	5	1
Total occupational	48	9	8	3	12	22	34
2. Nonoccupational							
Exposed to drift or residue	35	3	0	0	0	23	15
Total nonoccupational	35	3	0	0	0	23	15
Occup. + nonoccup.	83	12	8	3	12	45	49
Yearly average	9.2	1.3	0.9	0.3	1.3	5.0	5.4

^a Mehler, 2001.

^b The "definite (Def)" classification indicates the signs and symptoms exhibited by the affected person are such as would be expected to result from the exposure described and medical or physical evidence is available to substantiate the exposure.

^c The "probable (Prob)" classification indicates that there is close correspondence between the exposure and the illness experienced.

^d The "possible (Pos)" classification indicates some correspondence between the exposure described and the illness/injury experienced.

The 9-year average illnesses associated with exposure to MB alone and MB in combination with other pesticides are 10.0 and 11.7 cases per year, respectively (Tables 6 and 7). The overall average is 21.7 cases per year. This average includes cases classified as "possible," accounting for about 40.8% of the overall average. The "possible" classification indicates some correspondence between the MB exposure described and the illness/injury experienced; whereas, the "definite" classification indicates the signs and symptoms exhibited by the affected person are such as would be expected to result from the exposure described and medical or physical evidence is available to substantiate the exposure. The "probable" classification indicates that there is close correspondence between the exposure and the illness experienced.

Affected people described a variety of illness/injury symptoms associated with exposure to MB alone or MB in combination with chloropicrin. Table 8 shows some symptoms reported by affected people in California from 1991 to 1999 for "definite" relationship category.

Table 8. Symptoms described by patients exposed to methyl bromide alone and in combination with chloropicrin in California (1991-1999).^a

Illness/injury type	Observed symptoms ^b
Systemic/respiratory	Dizziness, lightheadedness, coughing, choking, nausea, headache, fever, shaking, sore throat, shortness of breath, vomiting, slurred speech, chest tightness and burning, disorientation, numbness on the cheek
Eye	Burning, irritation, tearing, double vision, itching, mild conjunctival inflammation, photophobia, moderate conjunctival irritation
Skin	Burning, pain, chemical burn, first and second degree burn, itching, painful swelling, redness, pruritic rash, blisters

^a Mehler, 2001.

^b symptoms are not arranged according to the degree of severity

Evacuations after the use of MB:

From 1982 to 1999, there were six evacuations of people after the use of MB and chloropicrin (Richmond, 1997; Mehler, 2001). Summary of evacuations are as follows:

1. An evacuation occurred after a field was treated with MB and chloropicrin. The investigative report indicated that the apparent cause for the concentration of fumigants over the evacuation area was the lack of wind and a temperature inversion during and after the application, causing poor wind dilution and dispersion. As a result, 35 people were seen at local hospitals during evacuation. These people experienced systemic symptoms.
2. Seventy-one people at a labor camp were evacuated after a nearby nine-acre field was tarp fumigated. These people detected fumes and exhibited symptoms of exposure (tearing and burning eyes). This incident was caused by a gas leak. The seriousness of the gas leak involved two main factors, which were vandalism and poor wind movement.
3. Twenty-five people were evacuated from an area after four cylinders of MB fell off a pallet. One of the cylinders leaked gas. An employee was exposed and suffered from lightheadedness. Only this employee developed illness symptoms.
4. Approximately 100 people were evacuated from apartments when an adjacent apartment complex, which had been tarped and fumigated with MB, emitted white smoke from a vent pipe. It was found out later that the source of the smoke was the water heater closet in the back of the building. The Hazardous Materials Team later declared the building was free of toxic gases. There were no illness/injury from this incident.
5. One family of four was evacuated after they complained of odor and eye irritation subsequent to a field fumigation 434 feet upwind. The fire department responded to the complaint, and fire department personnel also experienced irritation. They noted that the problem was very spotty. It came and went, and was much more noticeable in some locations than at other nearby locations. The application of MB violated the applicable buffer zone requirement of 200 feet on other side of the field, but the people who lived within the buffer zone were not affected.

6. Eighteen workers were evacuated from a packinghouse after two workers removed the custom locking caps from a methyl bromide cylinder. Accidentally, the valve was opened and released MB. Seven of the employees developed symptoms.

From 1982-1999, PISP received 25 reports involving people (generally seeking shelter) who entered enclosed areas treated with MB and one report involving a neighbor of the fumigated building. The atmosphere in these areas contained a lethal level of MB. Eighteen of the 24 people died. In 1997, one death occurred when MB diffused through unsealed conduits from a fumigated building to an occupied guest house a short distance away. The guest house occupant mentioned feeling poorly during the fumigation, and was found comatose and having seizures the day after the fumigation was complete. The blood bromine level was 27 mg/dl 5 days later. She died after 16 days in the hospital.

DERMAL TOXICITY AND SENSITIZATION

Symptoms observed in illness incidents indicate that liquid MB can cause severe eye and skin burns. The DPR's database does not have any submitted reports on dermal sensitization studies. Given the acute dermal toxicity of MB liquid, a sensitization study is not feasible.

ANIMAL/HUMAN METABOLISM

MB was rapidly biotransformed and readily excreted in rats after inhalation exposure (Bond *et al.*, 1985). In all tissues examined, over 90% of radioactivity was metabolites. The elimination half-life of radioactivity from the tissues was 1.5 to 8 hours. Almost 50% of the absorbed dose was excreted by the lungs as CO₂. The pulmonary excretion was biphasic with half-lives of 3.9 hours and 11.4 hours. The half-lives of radioactivity were 9.6 hours and 16.1 hours in the urine and feces, respectively. In another inhalation study with rats, Bond *et al.* (1985) revealed that the percentages of the absorbed dose in the urine and feces were 23% and 2%, respectively. In other studies, Medinsky *et al.* (1985) and Jaskot *et al.* (1988) observed similar results (exhalation and excretion of the absorbed dose, and excretion half-lives) after inhalation exposure with rats.

In humans, the amount exhaled as ¹⁴CO₂ ranged from 0.2 to 1.0% of the dose for mouth breathing, and 0.2% to 0.4% of the dose for nose breathing exposure when measured at the end of 2 hours of exposure and after 2 hours of clearance (Raabe, 1988). The net body retention for both exposure routes was 51.1% with a clearance half-life of 72 hours based on the amounts in the exhaled air and in the urine at 0.5 hour after inhalation exposure.

In rats after oral exposure, the distribution (as % of an absorbed dose) was 32% as ¹⁴CO₂ and 4% as intact MB in exhaled air, 43% in the urine, and 14% in the carcass at 72 hours after exposure to MB (Medinsky *et al.*, 1984). Only 2% of the dose was found in feces. With intraperitoneal administration, the cumulative percentages of the doses in rats measured after 72 hours were: 45% as ¹⁴CO₂ and 20% as intact MB in exhaled air, 16% in the urine, 1% in the feces, and 17% in the carcass (Medinsky *et al.*, 1984).

INHALATION UPTAKE/DERMAL ABSORPTION

Inhalation uptake:

Inhalation uptake of MB was determined in beagles (Raabe, 1986), in humans (Raabe, 1988), and in rats (Medinsky *et al.*, 1985). Inhalation uptake of MB in adult nose-breathing beagle dogs was determined to be 39.8 percent (Raabe, 1986). In humans, the results were obtained from two males and two females in which uptake was evaluated by inhaling MB through mouth or nose. Means of the corrected inhalation uptake (observed uptake fraction x dead space correction factor) when breathing by mouth and nose are 52.1 and 55.4 percent, respectively (Raabe, 1988). Inhalation uptake of MB (1.6-9.0 ppm) in rats was determined to be about 48 percent, which is similar to inhalation uptake in beagles and humans (Medinsky *et al.*, 1985). Whenever it is necessary to estimate an absorbed dose from inhalation exposure, an inhalation absorption of 50% will be used. However, exposure estimates for MB in this document are shown as air concentrations instead of absorbed doses.

Dermal absorption:

The DPR library database showed an article titled "Absorption of MB through the intact skin (Jordi, 1953)." Upon reviewing this article, there was no actual dermal absorption study of MB as indicated by the title of the article. This article reported the incidence of one fatal and two nonfatal cases of poisoning, which occurred after the fumigation of a flour mill. Results of the investigation revealed that the workers wore oxygen-supplying apparatus and there was adequate oxygen during the fumigation period. All workers experienced illness symptoms at least one hour after the fumigation, which took one hour and 30 minutes.

On March 26, 1985, Great Lakes Chemical Corporation submitted a request to the U.S. EPA for a waiver of dermal exposure data (TriCal, 1987). The registrant provided several reasons with the request. However, the U.S. EPA did not grant a waiver because the registrant provided insufficient evidence to the Agency for consideration. The registrant resubmitted a request after a meeting with the U.S. EPA personnel about the type of a closed system for MB application. The registrant claimed that workers would not be exposed to liquid MB under normal usage. Additionally, the only possible dermal exposure would come from a spill situation and under these conditions the inhalation route would still be the most important means of exposure (TriCal, 1987). Hence, a dermal absorption study is not needed for MB. On February 24, 1986, the agency granted the waiver of dermal exposure data based upon reasons that MB is applied in a closed system and the volatile nature of MB (boiling point = 4 °C). However, some questions still exist because there is a possibility that dermal absorption of MB is increased in areas with partly lipophilic character, such as armpit, groin, genitals, and the skin under the waist belt. This suggestion was substantiated by observations that skin lesions were limited to those areas where perspiration is relatively high (Zwaveling *et al.*, 1987). However, these effects are only observed with extremely high ambient MB concentrations.

Dermal exposure may be important for those exposure scenarios in which dermal contact is the primary source of exposure, such as for workers who wear respiratory protection in areas with relatively high concentrations of MB. Based upon illness reports in the literature, there is potential for significant dermal exposure of workers who wear self-contained-breathing apparatus

(SCBA) in high MB concentration environment and work in the area for extended periods. Zwaveling *et al.* (1987) and Hezemans-Boer (1988) reported skin lesions in six workers eight hours after exposure for 40 minutes to high concentration of MB of approximately 40 g/m³ or 10,000 ppm during the fumigation of an enclosed building. These workers wore coveralls on top of normal daily clothing, PVC gloves, and work shoes. During the actual fumigation, these workers breathed pressurized air from a portable container through a tight fitting facemask. The skin lesions consisted of sharply demarcated erythema with multiple vesicles and large bullae. The lesions were limited to parts of the skin that were relatively moist and/or subjected to mechanical stress such as the armpits, groin, labia, vulva, penis, scrotum, rima ani, navel, and skin under the waistbelt. The mean plasma bromide concentration for samples collected immediately after the exposure and 12 hours after the exposure were 95 ± 15 and 72 ± 24 µmol/L, respectively. It is possible that MB absorption is increased in this partly lipophilic (sebaceous glands) and partly hydrophilic (sweat glands) environment (Zwaveling *et al.*, 1987). The percentage of dermal absorption could not be determined. Healing of the skin lesions of these workers occurred in 2 weeks. Deschamps and Turpin (1996) reported illnesses of two experienced fumigators who wore a cartridge respirator with activated charcoal. They entered a building where the concentration of MB was 17g/m³. Under the very high MB concentration environment, it is likely that the respirator was rapidly saturated with MB. It is for this reason that NIOSH does not recommend any air-purifying respirator for MB.

Dermal absorption of chemical vapors other than MB was studied. Four human volunteers (naked excepted shorts) were exposed to styrene vapors in the air within the concentration range of 1,300 to 3,200 mg/m³ for 2 hours (Wieczorek, 1985). These volunteers (3 men and 1 woman aged 25-35) breathed pure air from outside through a respirator. The results showed that dermal absorption of the styrene vapors contributed about 5% to the amount absorbed in the respiratory tract under the same conditions when the subjects did not wear a respirator. Riihimaki and Pfaffli (1978) studied percutaneous absorption of xylene, styrene, toluene, 1,1,1-trichloroethane, and tetrachloroethane vapors employing restricted numbers of human volunteers (n = 2-3 for each kind of vapor). The percutaneous absorption when the volunteers were exposed to moderate air concentrations of 300 and 600 ppm for 3.5 hours were about 0.1 to 2% of the amount estimated to be absorbed from the unprotected respiratory tract.

McDougal *et al.* (1985) studied dermal absorption of dibromomethane (DBM, 500 to 10,000 ppm) and bromochloromethane (BCM, 2,500 to 40,000 ppm) vapors in rats. The percentages of body burden, which was due to penetration of the skin, were 5.8% for DBM and 4.2% for BCM. The observed permeability constants in rats for styrene, xylene, toluene, perchloroethylene, benzene, halothane, hexane, and isoflurane were estimated to be two to four times greater than the human permeability constants calculated from the available literature data (McDougal *et al.*, 1990). Based upon the difference in absorption of various chemical vapors in rats and humans, the percentage of body burden in humans was assumed to be 1.5 to 2.9% for DBM and 1.1 to 2.1% for BCM.

In conclusion, the dermal absorption of MB can be significant based upon reported illnesses of individuals with SCBA exposed to high concentration of MB for extended periods. Dermal exposures of other gases in humans such as styrene, xylene, styrene, toluene, 1,1,1-

trichloroethane, tetrachloroethane, dibromomethane, and bromochloromethane can be in the range of 0.1-5% of the unprotected respiratory exposure. However, there is no chemical-specific dermal absorption study for MB; we cannot meaningfully estimate dermal exposure at this time.

FARM COMMODITY RESIDUES

MB is used to fumigate fresh fruits, vegetables, and raw agricultural and processed food commodities. These treatments are needed to control pests and to comply with U.S. import requirements and quarantines of other nations. Applications are usually made to fresh produce before it is loaded for export or to harvested crops before they are processed further. If the raw or processed commodity is stored for an extended period of time, additional fumigations may be necessary to control infestations of Indian meal moth and other pests. MB applications are made by treating the whole structure containing the commodity, covering the commodity with tarps or placing the commodity in a fumigation chamber. The treatment is a function of the application rate of the gas (pounds (Lbs) of MB per 1,000 ft³ of commodity or space being treated), temperature of the commodity, exposure time and the load factor (percentage of the chamber area filled by the commodity). After the exposure period has expired, the commodity is aerated to remove the gas. Aeration can be done passively where the chamber doors are left open or the tarps are removed to allow the gas to dissipate. It can involve active ventilation where fans are used to exhaust the gas from chambers or to blow through the treated commodity.

The data in the Table 9 were derived from studies concerning the fumigation of various commodities. MB residues were detected in treated commodities using the headspace analytical method (King *et al.*, 1981) with the exception of treated wheat, which was analyzed using the derivative method (Fairall and Scudamore, 1980), the reflux method (Malone, 1970) and FDA methodology (CDFA, 1984b). Half-lives were calculated for the rates of dissipation of the organic bromide residues remaining after each treatment. These values were derived from the linear regression analysis of the time versus residue data points presented in the studies. The natural log of 2 was divided by the rate constant (slope) to estimate the half-life from the start of aeration.

Table 9 shows commodities that are representative of general fumigation. This table also contains information indicating how physical conditions and aeration can affect the amount of organic bromide residues left in the treated commodity. The temperature at which the commodity was treated and subsequently aerated and stored was the primary factor in determining the rate of dissipation of MB residues left in the treated commodity. As demonstrated in the residue data for "cherries," the greater the temperature, the more rapid the dissipation rate as expressed in the shorter half-life. This relationship is expressed by the following Arithmetic equation: $\log(\text{rate constant}) = a + b(1/K)$, where K is temperature in degrees Kelvin. Cherries fumigated at lower temperatures had greater amounts of organic bromide residues at the start of aeration than that treated at the same rate, but at a higher temperature.

The majority of the studies were conducted in the laboratory with fumigation chambers ranging in size from 1-28 ft³, with almonds and walnuts fumigated in larger chambers (100-110 ft³). Only the strawberry and wheat studies involved sampling for MB residues under actual commercial

usage. Studies were conducted to test the hypothesis that chambers of various sizes might produce different dissipation rates. There may be some reservations regarding the use of this data to estimate commercial use conditions. MB fumigation studies were conducted comparing commercial and laboratory treatments of commodities at the same rates. The concentrations of MB were monitored in chambers of various sizes (0.028-5,494 m³) during an inshell almond fumigation study (Hartsell *et al.*, 1992). The levels of fumigant from an application of 24 g/m³ at 26 °C for four hours were similar at various times: 28.3 L (0.028 m³) chamber, 14.8-15.1 g/m³ at 1.0 hour, 13.1-13.5 g/m³ at 4 hours and the 5,494 m³ chamber, 16.8 g/m³ at 1.0 hour, 12.5 g/m³ at 4 hours. A similar study was conducted during the fumigation and subsequent aeration of raisins (Hartsell *et al.*, 1992). The regression analysis of the data points derived comparable rate constants (slopes) for the dissipation rates for up to eight days for the lab and commercial chambers.

A 1975 study of tarp fumigations with hull almonds in piles at the harvest site observed the temperature variability that occurs when commodities are fumigated outdoors (Nelson *et al.*, 1975). During the 24-hour fumigations, temperatures ranged from 69-79 °F at the bottom of the pile near the edge to 83-120 °F for one of the top corners at a depth of 1-2 feet. This temperature variability makes it difficult to predict the dissipation rate for the organic bromide residues.

The almond fumigation study (Hartsell *et al.*, 1984b) researchers observed that wooden bins with slots cut in the sides allowed the MB gas to dissipate faster than bins with solid sides. Harris *et al.* (1983) found that polystyrene foam boxes desorbed larger quantities of MB gas compared to cartons constructed of wood or fiberboard. When a fumigation chamber (49.6 ft³) containing empty polystyrene foam grape boxes was fumigated, aerated and resealed, MB levels in the chamber reached a maximum of 3.0 g/m³. Sinclair and Lindgen (1952) noted that during the fumigation of empty flats, the excelsior packing material absorbed 20% of the applied MB in the chamber.

Table 9. A log-linear regression analysis of residue data over time from methyl bromide chamber fumigation of various commodities.^a

Crop	Fumigation method				Storage temp. (°C)	Rate constant ^c	Residues at aeration ^d (ppm)	t _{1/2} ^e (hours)
	Rate ^b	Time (hr)	Temp. (°C)	% Load				
In shell almonds (shells)	1	12	10	70-75	n/a	0.054	46.7	12.8
In shell almonds (shells)	1	8	15.6	70-75	n/a	0.051	17.3	13.6
In shell almonds (shells)	1	4	26.7	70-75	n/a	0.044	15.5	15.7
In shell almonds (meats)	1	12	10	70-75	n/a	0.018	9.5	38.4
In shell almonds (meats)	1	8	15.6	70-75	n/a	0.027 _j	4.4	26.4
In shell almonds (meats)	1	4	26.7	70-75	n/a	0.023 _j	4.9	31.2
Almond meats in cartons	1	8	15.6	70-75	n/a	0.047	13.4	14.8
In shell walnuts (meats) ^f	3.5	4	15.6	50-55	1.7	0.127	56.5	132
In shell walnuts (meats) ^f	3.5	4	15.6	50-55	10	0.162	50.2	103.2
In shell walnuts (meats) ^f	3.5	4	15.6	50-55	32	0.563	31.0	28.8
Fresh strawberries ^g	3	3	18.3	n/r	n/a	1.149 _j	26.4	0.60
Fresh strawberries ^h	3	3	18.3	n/r	1.1	0.037 _j	n/a	18.7
Lemons	2.75	2	21	50	10	0.021	2.2	33
Grapefruit	4	2	20	80	24	0.085 _j	26.8	8.2
Wheat in storage	1.5	24	21	100	21	0.035 _j	0.111	19.8
Wheat in storage	1.5	24	21	100	21	0.049 _j	0.519	14.2
Wheat in storage	1.5	24	21	100	21	0.087 _j	0.648	8.0
Wheat in storage	1.5	24	21	100	21	0.061 _j	1.149	11.3
Avocados (Hass) whole fruit	2	2	20	40	22	0.108 _j	3.0	6.4
Avocados (Hass) whole fruit	2	4	20	40	22	0.112 _j	4.4	6.2
Cherries	3	2	3	32	3	0.296	83.5	2.3
Cherries	3	2	9	32	9	0.398	76.0	1.7
Cherries	3	2	23	32	23	0.636	59.2	1.1
In shell pistachio meats ⁱ	1	24	15.5	80	15.5	0.016	12.5	62.5
In shell pistachio meats ⁱ	1.5	24	15.5	80	15.5	0.014	20.6	49.5
In shell pistachio meats ⁱ	1.5	24	26.6	80	26.6	0.013	10.6	53.3
In shell pistachio meats ⁱ	3.5	24	26.6	80	26.6	0.014 _j	20.1	49.5
Peaches	3	3	21	50-60	2.5	0.168 _j	15.4	4.1
Plums	3	3	21	50-60	2.5	0.045	34.1	15.4
Pears	3	3	21	50-60	2.5	0.047	22.7	14.8
Raisins	1.5	24	10	50	10	0.005	1.3	139
Dried apricots in bulk	1.5	24	10	50	10	0.023	4.1	30.1
Dried apricots in packages	1.5	24	10	50	10	0.011	7.3	63
Nonpitted prunes in bulk	1.5	24	10	46	10	0.018 _j	4.8	38.5
Pitted prunes in bulk	1.5	24	10	46	10	0.018 _j	4.9	38.5
Brown rice in 2 lb boxes	1.5	16	21	not known	21	0.046 _j	143.0	15.0
Milled rice in 2 lb boxes	1.5	16	21	not known	21	0.064 _j	1.9	10.8

n/a-not applicable or no data available; n/r-not reported

Table 9 (cont.). A log-linear regression analysis of residue data over time from MB chamber fumigation of various commodities.

^a References for various commodities are:

- | | |
|--|---|
| 1. almonds-Hartsell <i>et al.</i> , 1984b. | 9. pears-Tebberts <i>et al.</i> , 1983. |
| 2. pistachios-Hartsell <i>et al.</i> , 1986. | 10. plums-Tebberts <i>et al.</i> , 1983. |
| 3. walnuts-Hartsell <i>et al.</i> , 1984a. | 11. strawberries-CDFA, 1984a. |
| 4. avocados-Singh <i>et al.</i> , 1982. | 12. wheat-CDFA, 1984b. |
| 5. cherries-Sell <i>et al.</i> , 1987. | 13. lemons-Soderstrom <i>et al.</i> , 1991. |
| 6. grapefruit-King <i>et al.</i> , 1981. | 14. apricots-Hartsell <i>et al.</i> , 1992. |
| 7. prunes-Obenauf, 1992. | 15. rice-Anonymous, 1992. |
| 8. peaches-Tebberts <i>et al.</i> , 1983. | 16. raisins-Hartsell <i>et al.</i> , 1992. |

^b pounds MB per 1,000 ft³.

^c same as the regression coefficient (slope of the regression line) for natural log of MB concentration as a function of time.

^d estimated residues at start of aeration. Residues were calculated based on y-intercept of the regression line.

^e half-life ($t_{1/2}$) = \log_2 /rate constant.

^f fumigated at reduced pressure of 100 mm Hg.

^g calculated as the mean from two replications.

^h calculated with 1.0 ppb as 50% of the minimum detectable level.

ⁱ mean value of residues after three sequential treatments made at the listed rate, 20 days apart.

^j the regression performed for this crop was found to be insignificant (with P-value >0.05).

Several fumigation trials observed the MB residues remaining in commodities when two different percents of load (10% versus 50%) were used in the chamber for the same treatment (Hartsell *et al.*, 1992). A t-test of the differences in residues from the two load factors indicated that the percent load may affect the amount of residues remaining in the fumigated commodity. However, the t-test may not be an appropriate method for determining if the difference is significant because the samples were not randomly taken.

EXPOSURE ASSESSMENT

MB exposure estimates include those determined for workers during fumigation of preplant soil, agricultural commodities or structures as well as for residents or persons who live or work at the buffer zone distance of commodity or field fumigation. Ambient MB concentrations in the high use counties (Monterey, Santa Cruz and Kern) are also shown in this document. Air concentrations of MB at specified periods are shown as ppb or ppm (parts per million) whenever they are appropriate.

Some of the exposure estimates are grouped into acute and nonacute exposures depending on the nature of each work task or exposure scenario. Acute exposure is the exposure that occurs daily or within 24 hours. Nonacute exposures, as used in this document, are those exposures that occur in these specified periods: 7 days (subacute), 90 days (subchronic), and 365 days (chronic). Definitions of subchronic and chronic exposures are adopted from Sanders (1998). Duration (daily exposure time, e.g. 4 hours per day) and frequency (days of exposure in a specified period, e.g. 45 days in a 90-day period) of exposure for each work task or exposure scenario are used to determine whether the exposure is acute or nonacute exposure. These exposure scenarios also reflect toxicological endpoints observed in experimental animals as determined by DPR.

Calculations of exposure rely on factors, including application rates, work periods specified in the current California permit conditions and duration and frequency of exposure. Types of tarpaulins, application equipment, and injection depth are used in the permit conditions to determine the maximum daily work time for each type of soil injection fumigation. DPR requested MB registrants to provide duration and frequency of exposure for acute and nonacute exposures (Donahue, 1997). Several registrants provided some data as requested. Consequently, default duration and frequency of exposure for many exposure scenarios were generated from data obtained from various sources and the use of professional judgment (Haskell, 1998a, 1998b). These default values are shown in Appendix A (Table 12).

As shown in the previous section on formulations, many MB products contain chloropicrin. However, the exposure assessment of chloropicrin has not been initiated at this time. This chemical has been placed in the high priority list under the Birth Defect Prevention Act of 1984. The exposure assessment may be initiated depending on the priority of the Department's risk assessment.

Exposure calculation procedures:

MB exposure estimates are calculated for acute and nonacute exposures for applicable exposure scenarios. In each case, the air concentration is shown as the 24-hour TWA. (*Notes:* Lbs a.i. as used in this document is equivalent to Lbs MB unless mentioned otherwise. Lbs formulated product may include only MB or MB and chloropicrin.)

a) Acute exposures

Procedures used to estimate the 24-hour TWA concentration are as follows:

- a.1) Volume of air sample at standard temperature and pressure of 25 °C and 760 mm Hg

$$VS = \frac{V \times P \times 298}{760 \times (T + 273)}$$

where VS is volume of air (L) at standard conditions,
V is volume of air sample (L) as measured,
P is measured barometric pressure in mm Hg, and
T is measured temperature of air in °C,

a.2) Calculation of MB concentrations (ppm) in air

$$\text{MB (ppm)} = \frac{\mu\text{g} \times 24.45}{\text{VS} \times 94.94} = \frac{\mu\text{g} \times 0.2576}{\text{VS}}$$

Where one mole of MB occupies 24.45 liters at 25 °C and the molecular weight is 94.94.

a.3) Conversion of MB from $\mu\text{g}/\text{m}^3$ to ppb and vice versa

$$1 \text{ ppb} = \frac{24.45}{94.94} \times \mu\text{g}/\text{m}^3 = 0.26 \times \mu\text{g}/\text{m}^3$$

$$1 \mu\text{g}/\text{m}^3 = \frac{94.94}{24.45} \times \text{ppb} = 3.88 \times \text{ppb}$$

a.4) Calculation of the 24-hour TWA concentration

$$\text{TWA} = \frac{C_1T_1 + C_2T_2 + C_nT_n}{24 \text{ hours}}$$

where TWA is MB concentration (ppb, ppm, $\mu\text{g}/\text{m}^3$, or mg/m^3 ,
C is concentration of MB during an increment of exposure, and
T is incremental exposure time in 24 hours.

b) Nonacute exposures

The nonacute exposure estimates shown in this document represent subacute, subchronic, and chronic exposures. The underlying reason for nonacute exposure is that workers or residents may be exposed to airborne MB either continuously or intermittently for longer than 24 hours. Exposure duration and frequency for nonacute exposures were used to estimate exposure. Exposure for the subacute or subchronic exposure period is that period during the maximum or peak use of MB for fumigation purposes. Basically, the nonacute exposure estimates are determined from daily exposures either as acute, subchronic, or chronic exposure as shown below.

$$\text{Nonacute exposure estimate (ppb)} = \frac{\text{Daily exposure (ppb)} \times \text{Days of exposure (days)}}{\text{Exposure period (7, 90 or 365 days)}}$$

Definitions:

The "**High Barrier**" tarpaulin must have a permeability factor of less than 8 milliliters MB per hour, per square meter, per 1,000 ppm of MB under tarp at 30 °C. Any polyethylene tarp of 6-mil thickness or greater meets this criterion.

The "**Very High Barrier**" tarpaulin must have a permeability factor of less than 5 milliliters MB per hour, per square meter, per 1,000 ppm of MB under tarp at 30 °C.

Availability of worker exposure studies:

Before 1992 studies were conducted using then-current soil injection equipment, which often resulted in high air concentrations of MB near the worker's breathing zone. These studies are summarized in (a) below. Subsequently, DPR required registrants to conduct many exposure studies in order to determine short-term air concentrations of MB in various uses and exposure scenarios. Starting in 1992, registrants of MB conducted exposure monitoring studies during the fumigation of preplant soil, agricultural commodities, and other structures. Submitted reports indicated that many studies were not conducted in compliance with Good Laboratory Practice (GLP) standards as indicated in 40 CFR 160 (U.S. EPA, 1998). The main reason why these studies were not in GLP compliance was due to no valid field or laboratory fortification recovery study. Field exposure studies conducted in and after 1992 are summarized in (b) below. Many of these studies were used to estimate exposures for risk assessment.

a) Summary of MB exposure studies conducted before 1992

In 1987, TriCal, Inc. submitted reports of several worker exposure studies (TriCal, 1987). The first data set consisted of exposure data generated during fumigations of a flour mill, processing and handling silo, grain silo, shipping container, transportation vehicle (barge loaded with oak logs), furniture covered with tarpaulin, and flat storage fumigation (corn, soybeans). The analytical and exposure monitoring methods were based on NIOSH method No. S372. Air samples were collected from the worker's breathing zone using a sampling train that consisted of two 600 mg coconut shell charcoal sampling tubes and a personal air sampling pump. The principle of quality control/quality assurance was observed during the studies. The analytical recovery for MB ranged from 95 to 117%. Results were reported as the 8-hour TWA (Table 10). The application rates for most uses were not noted, but the report indicated that label instructions were followed.

Table 10. Air concentrations of methyl bromide near the worker's breathing zone.^a

Type of fumigation	Work task	n	8-hr TWA (ppm) Average \pm STDEV (range)
1. Flour mill			
a) Applicators opened gas tanks located inside the building.	Applicators	9	4.1 \pm 4.4 (0.04-13)
	Aerators	7	7.8 \pm 6.9 (0.01-15)
	Tape removers	1	0.4
b) Applicators opened gas tanks located outside the building.	Applicators	4	0.2 \pm 0.27 (0.06-0.61)
	Aerators	3	5.5 \pm 7.3 (1.1-14)
2. Processing and handling silo (enclosed conveyer and storage bins)	Applicators	3	7.3 \pm 5.0 (2.7-12.6)
	Aerators	2	0.07 (0.03 and 0.1)
3. Grain silo, elevator, or bin	Applicators	3	0.5 \pm 0.1 (0.4-0.6)
	Aerators	3	0.2 (ND) ^b
	Grain loaders	2	0.2 (ND) ^b
4. Shipping containers (trailers or rail cars)	Applicator	1	0.02
	Aerator	1	6.8
5. Transportation vehicle (barge loaded with oak logs)	Applicator	3	0.6 \pm 0.3 (0.05-0.9)
	Supervisor	1	0.04
	Inspectors	1	0.02
	Aerators	2	16.1 (7.1 and 25)
	Tarp removers	2	0.4 (0.3 and 0.5)
6. Tarpaulin (wooden furniture and a pallet of flour)	Applicators	2	0.1
	Tarp remover	1	0.2
	Aerator	1	1.3
7. Flat storage building (filled to the ceiling with corn, soybeans)	Applicator	3	0.25 \pm 0.1 (0.2-0.3)
	Helpers	2	0.1 (0.02 and 0.2)
	Aerators	2	0.1 (0.02 and 0.2)

^a n is number of replicates; TWA is Time-Weighted Average; STDEV is standard deviation.

^b Minimum detectable level (MDL) ranged from 0.01 to 0.4 ppm depending on sample volume; one-half of the high MDL or 0.2 ppm was used whenever the result indicated "nondetects (ND)."

TriCal, Inc. also conducted worker exposure studies to determine exposures of tractor drivers and co-pilots to MB during tarpless bed fumigation (TriCal, 1990). Application rates ranged from 50 to 360 pounds MB per acre and the injection depth ranged from 4 to 18 inches under the soil surface. Air concentrations at various distances from treated fields were also measured. The application of MB in these studies presumably used unmodified application equipment, unlike those currently used to reduce worker exposure. Exposure ranges (ppm) for drivers obtained from four studies were 0.009-1.500 (carrots), 2.952-4.772 (potatoes), 0.648-1.704 (seedbed), and 1-2.1 (broccoli), and those for co-pilots were 0.270-1.524 (carrots), and 2.544-3.212 (seedbed). These air concentrations are high compared to the current target exposure level of 210 ppb for acute toxicity. The downwind air concentrations, measured 60 to 200 feet from treated fields, ranged from 0.03-0.211 ppm.

TriCal, Inc. also submitted several other studies that measured MB air concentrations near the worker's breathing zone (TriCal, 1987). These studies are listed below:

1. Deep tarpless application, Wasco, California. April 2, 1986. DPN 123-099, record number 64750.
2. Deep tarpless application, Delano, California. May 30, 1986. DPN 123-099, record number 64750.
3. Tarped field fumigation, Ducor, California. April 2, 1984. DPN 123-099, record number 64750.
4. Driscoll chamber fumigation, Watsonville, California. March 26, 1984. DPN 123-099, record number 64750.
5. Driscoll chamber fumigation (strawberries for export), Watsonville, California. July 18, 1984. DPN 123-099, record number 64750.
6. A study of the inhalation exposure of workers to MB and chloropicrin during preplant soil fumigations (shallow injection) in 1982 - A preliminary report. DPN 123-099, record number 64751 (or HS-1076, June 10, 1983, DPR).
7. A study of the inhalation exposure of workers to MB during preplant soil fumigations (shallow injection) in 1980 and 1981. DPN 123-099, record number 64752 (or HS-900, May 20, 1982, DPR).
8. A study of the levels of MB and chloropicrin in the air downwind from a field during and after a preplant soil fumigation (shallow injection) - A preliminary report. DPN 123-099, record number 64753 (or HS-1061, April 15, 1983, DPR).

Results from these studies are not employed for estimation of worker exposure due to one or more reasons listed below.

1. The report does not contain adequate information concerning fumigation method, sample collection and processing, and analysis (QA/QC) to ensure correct calculation of the TWA air concentrations.
2. The study used unacceptable analytical methods.
3. There are better studies conducted in and after 1992.
4. The studies conducted before 1992 do not reflect current work practices.

b) Summary of MB exposure studies conducted after 1992

MB exposure estimates and results of grouping of exposure estimates are shown in Tables 11, 12, 13 and 14. Table 11 shows exposures for handlers and other workers calculated as acute, subacute, subchronic and chronic exposures. Table 12 shows acute exposures for persons at the buffer zone distance. Table 13 shows results of grouping of some acute exposures. Table 14 shows ambient MB concentrations in three high use counties in CA. Details of studies and calculations are presented in Appendices B, C and D. Factors concerning duration and frequency of exposure for various work tasks and exposure scenarios are shown in Appendix A (Table 12).

Table 11. Summary: Acute and non-acute exposure estimates of persons in California to methyl bromide*.

Number/ Type of application (Data from Table)**	Acute exposure (ppb)			Subacute exp. (ppb)			Subchronic exp. (ppb)			Chronic exp. (ppb)		
	/24-hour period			/7-day period			/90-day period			/365-day period		
	Avg.	STDEV	Range***	Days	Avg.	STDEV	Days	Avg.	STDEV	Days	Avg.	STDEV
a) Shallow shank-tarped soil injection fumigation (T. B.1) Applicators: Noble plow shanks	111	98	3-303	6	95	84	40	49	44	n/a	n/a	n/a
a) Shallow shank-tarped soil injection fumigation (T. B.2) Co-pilots: Noble plow shanks	224	152	34-518	6	192	130	40	100	68	n/a	n/a	n/a
a) Shallow shank-tarped soil injection fumigation (T. B.3) Shovelmen: Noble plow shanks (by growers)	147	135	52-515	3	63	58	n/a	n/a	n/a	n/a	n/a	n/a
a) Shallow shank-tarped soil injection fumigation Tarp removers (by PCOs) (T. B.4)	835	596	3-1659	5	596	426	55	510	364	n/a	n/a	n/a
Tarp removers (by growers) (T. B.5)	278	199	1-553	2	79	57	n/a	n/a	n/a	n/a	n/a	n/a
b) Nontarp deep shank injection fumigation (T. B.6) Applicators	154	n/a	126&181	6	132	n/a	40	68	n/a	n/a	n/a	n/a
Co-pilots	49	n/a	n/a	6	42	n/a	40	22	n/a	n/a	n/a	n/a
Cultipacker	99	n/a	n/a	6	85	n/a	n/a	n/a	n/a	n/a	n/a	n/a
b) Nontarp deep shank injection fumigation (improved) (T. B.7) Applicator	57	n/a	n/a	6	49	n/a	40	25	n/a	n/a	n/a	n/a
Cultipacker	70	n/a	n/a	6	60	n/a	n/a	n/a	n/a	n/a	n/a	n/a
c) Nontarp deep shank injection fumigation (T. B.7) Appl: Basic + a second tractor with a disc	88	n/a	n/a	6	75	n/a	40	39	n/a	n/a	n/a	n/a
Disc driver: Basic + a 2nd tractor with a disc	512	n/a	n/a	6	439	n/a	40	228	n/a	n/a	n/a	n/a
Applicator: Basic + a cultipacker	94	n/a	22&165	6	81	n/a	40	42	n/a	n/a	n/a	n/a
Supervisor: Basic + a cultipacker	67	n/a	n/a	6	57	n/a	40	30	n/a	n/a	n/a	n/a
Cultipack.: Basic + a cultipacker (by growers)	34	n/a	10&58	6	29	n/a	n/a	n/a	n/a	n/a	n/a	n/a
d) Nontarp deep shank injection fumigation (T. B.8) Applicator: With 4 forward curved shanks	7	n/a	n/a	6	6	n/a	40	3	n/a	n/a	n/a	n/a
Cultipack: 4 forward curved shanks (grower)	7	n/a	n/a	6	6	n/a	n/a	n/a	n/a	n/a	n/a	n/a
e) Shallow shank-tarped bed fumigation (T. B.9) Appl: Conv.+ raised platform&inj. 8"	80	n/a	n/a	6	69	n/a	40	36	n/a	n/a	n/a	n/a
Co-pilots: Conv.+ raised platform&inj. 8"	104	n/a	98&111	6	89	n/a	40	46	n/a	n/a	n/a	n/a
Applicators: Conv. + closing shoes	44	n/a	n/a	6	38	n/a	40	20	n/a	n/a	n/a	n/a
Co-pilots: Conv. + closing shoes	167	n/a	125&209	6	143	n/a	40	74	n/a	n/a	n/a	n/a

* acute exposure is the exposure that occurs daily or within 24 hours; subacute exposure is the exposure that occurs in a seven-day period; subchronic exposure is the exposure where days of exposure is 30 days or longer in a 90-day period; chronic exposure is the exposure where days of exposure is 120 days or longer in a 365-day period.

** where applicable, the daily average and standard deviation for subchronic and chronic exposure were taken from the table as indicated for use in the calculation of subchronic and chronic exposures shown in this table.

*** when there are only two data points, these two data points are shown as, e.g. 34&24, and the standard deviation was not calculated.

Notes: 1. A standard deviation (STDEV) was not calculated when there were only two exposure values.

2. Abbreviations: T. = (from) Table; exp. = exposure; by growers or pest control operators (PCOs) = employed by growers or PCOs; Avg. = average; conv. = conventional; inj. = injection; Tr. = tractor; n/a = not applicable (data are not available or cannot be calculated).

Table 11. (continued 1). Acute and non-acute exposures of persons in California to methyl bromide*.

Number/ Type of application (Data from Table)**	Acute exposure (ppb)			Subacute exp. (ppb)			Subchronic exp. (ppb)			Chronic exp. (ppb)		
	/24-hour period			/7-day period			/90-day period			/365-day period		
	Avg.	STDEV	Range***	Days	Avg.	STDEV	Days	Avg.	STDEV	Days	Avg.	STDEV
f). Shallow shank-tarped bed fumigation (T. B.10)												
Driver: Tr. was equipped for fum. (by PCOs)	28	n/a	n/a	6	24	n/a	40	12	n/a	n/a	n/a	n/a
Appl: Tractor was equipped for MB fum.	45	n/a	n/a	6	39	n/a	40	20	n/a	n/a	n/a	n/a
Tape layer: Tr. was equipped for MB fum.	65	n/a	n/a	3	28	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Driver: Tractor was equipped for laying tarp	4	n/a	n/a	6	3	n/a	40	1.8	n/a	n/a	n/a	n/a
Co-pilot: Tr was equipped for laying tarp	34	n/a	4&65	6	29	n/a	40	15	n/a	n/a	n/a	n/a
g). Shallow shank, tarped-bed fumigation (T. B.11)												
Applicator	2	n/a	n/a	6	2	n/a	40	1	n/a	n/a	n/a	n/a
Co-pilot	32	n/a	31&32	6	27	n/a	40	14	n/a	n/a	n/a	n/a
Shovelman (by growers)	0.6	n/a	0.6&0.6	3	0.3	n/a	n/a	n/a	n/a	n/a	n/a	n/a
h). Tarp shallow with Noble plow shanks (T. B.12)												
Cutter: From broadcast appl. (by growers)	27	45	2-79	2	8	13	n/a	n/a	n/a	n/a	n/a	n/a
Cutter: From broadcast appl. (by PCOs)	82	134	3-237	5	59	96	30	27	45	n/a	n/a	n/a
Puller: From broadcast appl. (by growers)	11	31	1-108	2	3	9	n/a	n/a	n/a	n/a	n/a	n/a
Puller: From broadcast appl. (by PCOs)	33	92	3-324	5	24	66	30	11	31	n/a	n/a	n/a
i). Tarp shallow with Noble plow shanks (T. B.13)												
From use of high barrier (HB) tarp												
Cutter: By PCOs	78	n/a	n/a	5	56	n/a	30	26	n/a	n/a	n/a	n/a
Remover: Tractor driver (by PCOs)	343	n/a	n/a	5	245	n/a	30	114	n/a	n/a	n/a	n/a
Remover: Basketman (by PCOs)	325	n/a	n/a	5	232	n/a	30	108	n/a	n/a	n/a	n/a
Remover: End puller (by PCOs)	7	n/a	n/a	5	5	n/a	30	2	n/a	n/a	n/a	n/a
Cutter (by growers)	26	n/a	n/a	5	19	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Remover: Tractor driver (by growers)	114	n/a	n/a	5	81	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Remover: Basketman (by growers)	108	n/a	n/a	5	77	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Remover: End puller (by growers)	2	n/a	n/a	5	1	n/a	n/a	n/a	n/a	n/a	n/a	n/a
2.a. Worker exposure assessment during potting soil fumigation (no usable data)												
2.b. Greenhouse soil fumigation (T. B.14)												
Tarp venters	0.009	0.02	0.00006-0.03	1	0.0013	0.003	n/a	n/a	n/a	n/a	n/a	n/a
Tarp removers	0.95	0.89	0.23-2.2	1	0.1357	0.1271	n/a	n/a	n/a	n/a	n/a	n/a
3. Fumigation of grain products (chambers, sea containers) (T. B.15)												
Initiation of aeration of sea containers/truck trailers												
Aerator	0.6	0.41	0.13-0.85	5	0.43	0.29	45	0.33	0.22	180	0.25	0.17
Initiation of aeration of tarpaulin fumigation												
Aerator	0.025	0.041	0.001-0.07	5	0.02	0.03	45	0.01	0.02	180	0.01	0.02
Emptying sea containers/truck trailers												
Forklift driver	16	24	2-43	5	11	17	45	4	6	180	4	6
Emptying non-certifying fumigation chambers												
Forklift driver	6	2	4-8	5	4	1	45	2	1	180	1	0.5

Table 11. (continued 2). Acute and non-acute exposures of persons in California to methyl bromide*.

Number/ Type of application (Data from Table)**	Acute exposure (ppb)			Subacute exp. (ppb)			Subchronic exp. (ppb)			Chronic exp. (ppb)		
	/24-hour period			/7-day period			/90-day period			/365-day period		
	Avg.	STDEV	Range***	Days	Avg.	STDEV	Days	Avg.	STDEV	Days	Avg.	STDEV
4. Fumigation of dried fruit and tree nut products (T. B.16)												
Chamber (raisins):												
Fumigators	63	n/a	19&107	6	54	n/a	63	44	n/a	150	17	n/a
Aerators	47	n/a	30&64	6	40	n/a	63	33	n/a	150	13	n/a
Clear chambers 1-2	1434	n/a	1406-1463	6	1229	n/a	63	1004	n/a	150	393	n/a
Stem pickers	28	n/a	26&30	6	24	n/a	63	20	n/a	150	12	n/a
Forklift driver	3	n/a	n/a	6	3	n/a	63	2	n/a	150	0.4	n/a
Hopper operator	19	n/a	n/a	6	16	n/a	63	13	n/a	150	8	n/a
Area sampling:												
Fumigation chambers	88	n/a	n/a	6	75	n/a	63	62	n/a	150	24	n/a
Fumigation cage	54	n/a	n/a	6	46	n/a	63	38	n/a	150	15	n/a
Leak checkers-chambers 4-5	4	n/a	2&6	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Aeration-chambers 4-5	116	n/a	47&186	6	99	n/a	63	81	n/a	150	32	n/a
Clearing-chambers 4-5	46	n/a	26&66	6	39	n/a	63	32	n/a	150	13	n/a
Hopper areas	8	n/a	2&13	6	7	n/a	63	6	n/a	150	3	n/a
Stem picker	27	3	24-30	6	23	3	63	19	2	150	11	1
5. Measurement of MB exposure to the fumigators, forklift drivers, cherry sorters and other workers (no usable data)												
6. Methyl bromide air monitoring studies at a walnut processing facility (T. B.17)												
a) Worker exposure studies												
Bulk packaging	34	n/a	24&44	6	29	n/a	75	28	n/a	n/a	n/a	n/a
Cleaning plant	208	155	1-404	6	178	133	75	173	129	n/a	n/a	n/a
Fumigatorium	87	32	50-106	6	75	27	75	53	19	180	19	7
Packaging	44	n/a	n/a	6	38	n/a	75	28	n/a	n/a	n/a	n/a
Vacuum chamber	239	200	92-466	6	205	171	75	199	167	n/a	n/a	n/a
Sorting	32	16	14-54	6	27	14	75	27	13	n/a	n/a	n/a
Special cracking	29	9	16-34	6	25	8	75	24	8	n/a	n/a	n/a
b) Area samples												
Sorting line	83	n/a	80&86	2	24	n/a	n/a	n/a	n/a	n/a	n/a	n/a
d) Compliance monitoring:												
Sorting line in cleaning plant	318	28	287-343	6	273	24	75	265	23	n/a	n/a	n/a
Cello pack. of in-shell walnuts in main bldg.	355	26	326-375	6	304	22	75	296	22	n/a	n/a	n/a
Bulk pack. of in-shell walnuts in main bldg.	243	n/a	242&245	6	208	n/a	75	203	n/a	n/a	n/a	n/a
7. Fumigation and aeration at a brewery facility (T. B.18)												
a) Applicators												
Entry and reentry to open canisters/cylinders	28.9	n/a	n/a	2	8.3	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Area sample (door to buffer zone)	42	n/a	n/a	2	12	n/a	n/a	n/a	n/a	n/a	n/a	n/a
b) Aerators												
Aerators	25	n/a	24&25	2	7	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Area sample (left of entrance door)	173	n/a	n/a	2	49	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Area sample (on applicator's truck)	100	n/a	n/a	2	29	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Table 11. (continued 3). Acute and non-acute exposures of persons in California to methyl bromide*.

Number/ Type of application (Data from Table)**	Acute exposure (ppb)			Subacute exp. (ppb)			Subchronic exp. (ppb)			Chronic exp. (ppb)		
	/24-hour period			/7-day period			/90-day period			/365-day period		
	Avg.	STDEV	Range***	Days	Avg.	STDEV	Days	Avg.	STDEV	Days	Avg.	STDEV
Appendix C (3). Exposure of residents to MB during commodity fumigation (T. C.1)												
Low range of exposure days	210	n/a	n/a	3	90	n/a	30	70	n/a	150	86	n/a
High range of exposure days	210	n/a	n/a	6	180	n/a	75	175	n/a	185	106	n/a

Table 12. Acute methyl bromide exposures (95th percentile) of persons at the buffer zone distance following field fumigation.

Field	1 acre					10 acres					20 acres					30 acres					40 acres				
Emission rate*	80	160	200	225	320	80	160	200	225	320	80	160	200	225	320	80	160	200	225	320	80	160	200	225	320
Buffer zone (ft)	110	290	380	420	580	410	1100	1400	1600	2100	610	1600	2000	2300	3100	770	2000	2600	2900	3900	900	2400	3000	3400	4600
MB (ug/m3)	625	677	677	676	672	835	790	769	741	633	874	825	807	802	783	895	827	830	834	849	918	863	860	866	889
MB (ppb)	163	176	176	176	175	217	205	200	193	165	227	215	210	209	204	233	215	216	217	221	239	224	224	225	231

* The emission rate of 80 lbs MB/acre-day was determined for nontarp/shallow/bed fumigation method.
The emission rate of 160 lbs MB/acre-day was determine for tarp/deep/broadcast fumigation method.
The emission rate of 160 lbs MB/acre-day was determine for nontarp/deep/broadcast fumigation method.
The emission rate of 200 lbs MB/acre-day was determine for tarp/shallow/bed fumigation method.
The emission rate of 225 lbs MB/acre-day was determine for drip system-hot gas fumigation method.
The emission rate of 320 lbs MB/acre-day was determine for tarp/shallow/broadcast fumigation method.

Table 13. Summary: Grouping of methyl bromide acute exposure estimates for workers during fumigations of soil, commodity and brewery facility^a.

Types of fumigation	Methyl bromide concentration (ppb)			
	Replicate	Mean \pm STDEV	Range	95 th percentile ^c
Soil: Bedded + nonbedded ^b	57	123 \pm 120	1 - 518	324
Soil: Bedded ^b	17	93 \pm 87	1 - 334	245
Soil: Nonbedded ^b	40	136 \pm 131	3 - 515	356
Commodity: Handlers	15	48 \pm 56	0.001 - 186	146
Commodity: Other workers	52	83 \pm 119	1 - 404	283
Greenhouse: Tarp venters	4	0.01 - 0.02	0.0001 – 0.03	0.05
Greenhouse: Tarp removers	4	1.0 \pm 0.9	0.4 – 2.2	3.1
Brewery facility ^d	Exposure replicates are not sufficient for grouping purposes			

^a exposure estimates were grouped according to types of fumigations. Data were taken from Table B.19.

^b exposure of handlers.

^c arithmetic mean + $t_{(95; n-1)}$ x standard deviation (or STDEV).

^d was not grouped because there are only 1 to 2 replicates for each exposure scenario.

Table 14. Methyl bromide concentrations (ppb) based on the Air Resources Board 2000 monitoring studies in Monterey and Santa Cruz and Kern Counties.^a

		Daily		Weekly		7 or 8-week
Site ^b	Monitoring days	Maximum 24-hour	95 th percentile 24-hour	Maximum weekly mean	95 th percentile weekly mean	Mean of weekly means
Monterey and Santa Cruz Counties (8 monitoring weeks, September 11 – November 3, 2000)						
		-----ppb-----				
CHU	31	2.41	2.26	1.61	1.63	0.644
LJE	30	24.0	18.5	10.5	11.1	3.79
OAS	31	1.84	1.21	1.01	0.918	0.387
PMS	31	30.8	30.2	15.5	17.1	7.68
SAL	31	7.91	6.17	3.01	3.14	1.29
SES	31	16.4	12.2	8.30	7.45	2.60
Kern County (7 monitoring weeks, July 19 – September 1, 2000)						
		-----ppb-----				
ARB	25	0.996	0.556	0.507	0.507	0.189
CRS	24	14.2	25.4	4.59	5.54	2.16
MET	26	0.224	0.239	0.145	0.163	0.084
MVS	26	0.487	0.262	0.201	0.195	0.092
SHA	26	3.52	3.98	1.77	2.05	0.792
VSD	26	0.347	0.292	0.175	0.181	0.099

^a Methods and equations used to derive different categories of air concentrations are shown in Appendix D, section 4 - Calculations of MB air concentrations. Data were taken from Table D.1.

^b Names of ambient sampling sites (Monterey and Santa Cruz): Chualar School (CHU), La Jolla Elementary School (LJE), Oak Avenue School (OAS), Pajaro Middle School (PMS), MBUAPCD Ambient Monitoring Station, Salinas (SAL), Salspuedes Elementary School (SES); (Kern): ARB Ambient Monitoring Station (ARB), Cotton Research Station (CRS), Mettler-Fire Station (MET), Mountain View School (MVS), Shafter-Walker Ambient Monitoring Station (SHA), Vineland School District-Sunset School (VSD).

EXPOSURE APPRAISALS

The exposure appraisal section contains information regarding the quality of exposure studies and the adequacy of submitted reports. This section also briefly describes uncertainty of default factors used in the calculation of exposure estimates. The section also provides some suggestions on how to obtain better exposure estimates for the MB risk assessment.

None of the submitted MB exposure studies met the requirements set forth in Subdivision U (U.S. EPA, 1986b) regarding the number of replicates and locations of the studies, i.e., three locations and five replicates per location for each work task monitored. Many studies provided more than five replicates for each work task, but a majority of the field studies provide replicates ranging from one to three replicates. In most cases, these replicates were from one location. This occurred because DPR had requested expedited development of exposure monitoring data to revise the use permits. Additionally, many studies were not conducted in compliance with GLP standards indicated in 40 CFR 160 (U.S. EPA, 1998).

Reports of the studies were gradually submitted to the Department in the form of interim, internal, or draft reports. Only a few reports were finalized using a format similar to the PR Notice 86-5 (U.S. EPA, 1986c). Currently, many reports are still classified as interim or internal reports; registrants may not accomplish finalizing these reports in the foreseeable future. Nonetheless, these exposure data are shown in this exposure assessment document because registrants were asked by DPR to produce them and the studies were conducted in California.

A field fortification recovery study was not carried out in many of the exposure studies. This may be due to the fact that MB has very high vapor pressure. It is extremely difficult to conduct a field fortification recovery study. Several laboratory recovery studies were performed and the monitoring data were adjusted for recoveries. However, the air concentrations were readjusted by DPR to reflect a recovery of 50% (Biermann and Barry, 1999; Helliker, 1999). Reports of several studies did not disclose application rates of MB. Authors could not make corrections regarding application rates and field fortification recoveries. Thus, MB concentrations for some of those studies shown in this document could be lower or higher than what they would be in actual work environment.

Duration and frequency of exposure are important factors employed in the calculation of nonacute exposure estimates. DPR realizes that MB registrants can provide data on duration and frequency of exposures because they have close contacts or business relationships with dealers, pest control operators or other users. That was why DPR issued several requests to registrants in November of 1997 for such data. The Department has received some information essential for the estimation of acute and nonacute exposures. DPR has made it clear in those letters that if registrants fail to provide requested data; the Department will derive default factors based upon available information and professional judgment. Authors of this document have conducted data searches, utilized survey results, as well as, consulted with knowledgeable persons on the use of MB. The default factors were established and used in the calculation of subacute and nonacute exposure estimates.

Many exposure data were obtained from studies employing short monitoring periods and then amortized to the 24-hour time-weighted average. These amortized exposure data could overestimate or underestimate the actual exposure.

Exposure estimates shown in this document are generally for specific work tasks and exposure scenarios. In other words, the exposure estimated for forklift drivers in a commodity fumigation or for shovelmens in a soil fumigation was based on a specific time period used to perform those work tasks. It did not take into account the exposure to MB the remainder of the workday if those workers performed other duties. Also, the calculated maximum duration of a workday for acute exposure was based on sources other than current permit conditions. There is a good possibility that the acute exposure was underestimated because workers might work overtime during the peak use season. In contrast, we do not know the degrees of overestimation of exposure when a study was not conducted in compliance with current permit conditions or regulations. Several MB exposure monitoring studies are not included in this document because the fumigation methods used in those studies were not performed in compliance with the permit conditions or regulations. Those studies or parts of those studies were nursery/greenhouse, commodity, potting soil, grain products, dried fruit and tree nuts, and residential reentry studies. It is desirable for the Department to obtain exposure data from studies that are conducted in compliance with the permit conditions or regulations.

MB air concentrations obtained from several studies are grouped based on types of fumigation methods and exposure scenarios. The purpose of grouping of MB concentrations is to show the magnitude of the exposure data and whether a proposed mitigation measure would cover a wide range of exposures. However, a mitigation proposal may not be developed based on grouped MB concentrations if a fumigation method is specific to particular fumigation tools.

Information on some of the variables that is mentioned in this section is intended to be qualitative in nature. It is difficult to judge quantitatively how these variables might affect MOE. For example, if the application rate was not mentioned, the rate could be at the maximum application rate. Hence, this variable would have no effect on exposure or MOE. Furthermore, we do not know if more data on duration and frequency of exposure would affect MOE and to what extent. We do not have sufficient background information to assign numbers to those variables. If we do so, it will cause some uncertainty concerning those assigned numbers.

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Dr. Lori O. Lim, Staff Toxicologist, Toxicology Branch, DPR provided preliminary or summary of the following sections: Physical and chemical properties, regulatory history including U.S. EPA status, animal/human metabolism, and a portion of usage and formulations. Readers may obtain complete information of these sections from the current MB Risk Characterization Document.

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Appendix A

Duration and frequency of acute and nonacute exposures for workers and residents^a

Section ^b	Work task ^c	Adjustment rate (ref) ^d	Hours/workday (ref.) ^e		Workdays (ref.)		
		(lb. MB/A)	Acute	Subc-chronic	/7 days	/90 days	/365 days
a	<i>Shallow shank-tarped soil fumigation (broadcast)</i>						
	<i>Applicators (used Noble Plow shanks, 10-12")</i>	400 (1)	5.8 (7)	5.8-n/a (7)	6 (7)	40 (7)	n/a (7)
	Co-pilots	400 (1)	5.8 (7)	5.8-n/a (7)	6 (7)	40 (7)	n/a (7)
	Shovelmen: Employed by growers	400 (1)	5.8 (7)	n/a-n/a (6)	3 (8)	n/a (6)	n/a (6)
	Tarpaulin removers: Employed by private companies	400 (1)	6 (6)	6-n/a (6)	5 (8)	55 (8)	n/a (6)
	Tarpaulin removers: Employed by growers	400 (1)	2 (6)	n/a-n/a (6)	2 (8)	n/a (6)	n/a (6)
b	<i>Nontarp deep shank injection fumigation (broadcast)</i>						
	<i>Applicators (used improved shank, 20-24")</i>	400 (1)	5.8 (7)	5.8-n/a (7)	6 (7)	40 (7)	n/a (7)
	Co-pilots: Employed by application rigs	400 (1)	5.8 (7)	5.8-n/a (7)	6 (7)	40 (7)	n/a (7)
	Cultipacker tractor drivers: Employed by growers	400 (1)	5.8 (7)	n/a-n/a (6)	6 (8)	n/a (6)	n/a (6)
c	<i>Nontarp deep shank injection fumigation (Traver, etc., CA)</i>						
	<i>Applicators (used forward curving inj. shank, cl. scraper, 24")</i>	400 (1)	5.8 (7)	5.8-n/a (7)	6 (7)	40 (7)	n/a (7)
	Disc drivers: Employed by PCOs	400 (1)	5.8 (7)	5.8-n/a (7)	6 (7)	40 (7)	n/a (7)
	Cultipacker tractor drivers: Employed by growers	400 (1)	5.8 (7)	n/a-n/a (6)	6 (7)	n/a (6)	n/a (6)
	Supervisor: Employed by PCOs	400 (1)	5.8 (7)	5.8-n/a (7)	6 (7)	40 (7)	n/a (7)
d	<i>Nontarp deep shank injection fumigation (Helm, CA)</i>						
	<i>Applicators (used forward curving shank, 24")</i>	400 (1)	5.8 (7)	5.8-n/a (7)	6 (7)	40 (7)	n/a (7)
	Cultipackers: Employed by growers	400 (1)	5.8 (7)	n/a-n/a (6)	6 (7)	n/a (6)	n/a (6)
e	<i>Shallow shank-tarped bed fumigation</i>						
	<i>Applicators (used modified shanks, 6-8")</i>	250 (1)	5.8 (7)	5.8-n/a (7)	6 (7)	40 (7)	n/a (7)
	Co-pilots	250 (1)	5.8 (7)	5.8-n/a (7)	6 (7)	40 (7)	n/a (7)
f	<i>Tarped-bed fumigation: Mitigation of exposure</i>						
	<i>Applicators (used Kennco Combi Superbedder, 14")</i>	250 (1)	5.8 (7)	5.8-n/a (7)	6 (7)	40 (7)	n/a (7)
	Co-pilots	250 (1)	5.8 (7)	5.8-n/a (7)	6 (7)	40 (7)	n/a (7)
	Drip tape layers: Employed by growers	250 (1)	5.8 (7)	n/a-n/a (6)	3 (8)	n/a (6)	n/a (6)

^a nonacute exposures include subacute, subchronic and chronic exposures.

^b section corresponds to that in Appendices B and C.

^c PCO = Pest control operator; BH = high barrier; VHB = very high barrier; PE = polyethylene.

^d an application rate that was used to adjust MB concentrations obtained from a study using a different application rate.

^e exposure times as indicated were used for the calculation of daily acute, subchronic (subchr.) and chronic (chr.) exposures (Tables B.1-B.18, C.1). n/a = not applicable.

Appendix A (Continued 1)

Section ^b	Work task ^c	Adjustment rate (ref) ^d (lb. MB/A)	Hours/workday (ref.) ^e		Workdays (ref.)		
			Acute	Subc-chronic	/7 days	/90 days	/365 days
g	<i>Shallow shank, tarped bed fumigation</i>						
	Applicators (used sweptback shank, 8")	250 (1)	5.8 (7)	5.8-n/a (7)	6 (7)	40 (7)	n/a (7)
	Co-pilots	250 (1)	5.8 (7)	5.8-n/a (7)	6 (7)	40 (7)	n/a (7)
	Shovelmen: Employed by growers	250 (1)	5.8 (7)	n/a-n/a (6)	3 (8)	n/a (6)	n/a (6)
h	<i>Tarp removers (shallow shank, broadcast, HB, 10-12")</i>						
	Cutters: Growers	400 (1)	2 (6)	n/a-n/a (6)	2 (8)	n/a (8)	n/a (6)
	Cutter: Employed by independent companies	400 (1)	6 (6)	6-n/a (6)	5 (8)	30 (8)	n/a (6)
	Pullers: Employed by growers	400 (1)	2 (6)	n/a-n/a (6)	2 (8)	n/a (8)	n/a (6)
	Puller: Employed by independent companies	400 (1)	6 (6)	6-n/a (6)	5 (8)	30 (8)	n/a (6)
i	<i>Tarp cutters and removers</i>						
	Cutters (Fum. Shallow, broadcast, VHB, Noble Plow shank, 10")	400 (1)	2 (6)	n/a-n/a (6)	5 (8)	n/a (6)	n/a (6)
	Removers: Employed by growers	400 (1)	2 (6)	n/a-n/a (6)	5 (8)	n/a (6)	n/a (6)
	Cutters and removers: Employed by independent companies	400 (1)	6 (6)	6-n/a (6)	5 (8)	30 (8)	n/a (6)
2.a	<i>Nursery potting soil fumigation</i>						
	Applicators (used perforated plastic hoses, 6-mil PE)	0.6/yd ³ (3)	1 (6)	n/a-n/a (6)	1 (6)	n/a (6)	n/a (6)
	Applicator assistants	0.6/yd ³ (3)	1 (6)	n/a-n/a (6)	1 (6)	n/a (6)	n/a (6)
	Tarp removers	0.6/yd ³ (3)	1 (6)	n/a-n/a (6)	1 (6)	n/a (6)	n/a (6)
	Tractor drivers	0.6/yd ³ (3)	1 (6)	n/a-n/a (6)	1 (6)	n/a (6)	n/a (6)
	Truck drivers	0.6/yd ³ (3)	1 (6)	n/a-n/a (6)	1 (6)	n/a (6)	n/a (6)
	Potters	0.6/yd ³ (3)	3 (6)	n/a-n/a (6)	1 (6)	n/a (6)	n/a (6)
2.b	<i>Greenhouse soil fumigation</i>						
	Applicators (used perforated plastic hoses, 1 mil HDT)	450 (2)	2 (6)	n/a-n/a (6)	1 (6)	n/a (6)	n/a (6)
	Tarp venters	450 (2)	1 (6)	n/a-n/a (6)	1 (6)	n/a (6)	n/a (6)
	Tarp removers	450 (2)	1 (7)	n/a-n/a (6)	1 (6)	n/a (6)	n/a (6)
3	<i>Fumigation of grain products (chambers, vans, etc.)</i>						
	Applicators (6 mil PE, if used)	6/1,000 ft ³ (4)	6 (6)	6.5-5 (6)	5 (6)	45 (6)	180 (6)
	Aerators	6/1,000 ft ³ (4)	6 (6)	6.5-5 (6)	5 (6)	45 (6)	180 (6)
	Forklift drivers	6/1,000 ft ³ (4)	1 (6)	0.5-0.5 (6)	5 (6)	45 (6)	180 (6)
	Rice processing workers (Warehouse)	6/1,000 ft ³ (4)	6 (8)	n/a-n/a (6)	5 (8)	n/a (6)	n/a (6)

^a nonacute exposures include subacute, subchronic and chronic exposures.

^b section corresponds to that in Appendices B and C.

^c PCO = Pest control operator; BH = high barrier; VHB = very high barrier; PE = polyethylene.

^d an application rate that was used to adjust MB concentrations obtained from a study using a different application rate.

^e exposure times as indicated were used for the calculation of daily acute, subchronic (subchr.) and chronic (chr.) exposures (Tables B.1-B.18, C.1). n/a = not applicable.

Appendix A (Continued 2)

Section ^b	Work task ^c	Adjustment rate (ref) ^d (lb. MB/A)	Hours/workday (ref.) ^e		Workdays (ref.)		
			Acute	Subc-chronic	/7 days	/90 days	/365 days
4	<i>Fumigation of dried fruit & tree nut products</i>						
	<i>1. Sea van</i>						
	Fumigators	1.5/1,000 ft ³ (4)	1 (6)	n/a-n/a (6)	2 (6)	n/a (6)	n/a (6)
	Fumigator observers	1.5/1,000 ft ³ (4)	1 (6)	n/a-n/a (6)	2 (6)	n/a (6)	n/a (6)
	Aerators	1.5/1,000 ft ³ (4)	1 (8)	n/a-n/a (8)	2 (6)	n/a (8)	n/a (8)
	Area sampling (15-foot downwind)	1.5/1,000 ft ³ (4)	1 (8)	n/a-n/a (8)	2 (8)	n/a (8)	n/a (8)
	<i>2. Chamber (dried prunes)</i>						
	Forklift operators	1.5/1,000 ft ³ (4)	0.5 (7)	n/a-n/a (6)	3 (7)	n/a (7)	n/a (7)
	Fumigators	1.5/1,000 ft ³ (4)	0.5 (7)	n/a-n/a (6)	3 (7)	n/a (7)	n/a (7)
	1-m from door	1.5/1,000 ft ³ (4)	0.5 (7)	n/a-n/a (6)	3 (7)	n/a (7)	n/a (7)
	2 & 15 m from chamber	1.5/1,000 ft ³ (4)	0.5 (7)	n/a-n/a (6)	3 (7)	n/a (7)	n/a (7)
	Leak check, side seal	1.5/1,000 ft ³ (4)	0.5 (7)	n/a-n/a (6)	3 (7)	n/a (7)	n/a (7)
	<i>3. Big chamber fumigation (raisins)</i>						
	Primary fumigators	1.5/1,000 ft ³ (4)	3 (6)	2.5-2.5 (6)	5 (6)	60 (6) ^f	20&170 ^g (6)
	Secondary fumigators	1.5/1,000 ft ³ (4)	3.5 (6)	2.5-2.5 (6)	5 (6)	60 (6) ^f	20&170 ^g (6)
	Aerators	1.5/1,000 ft ³ (4)	3 (6)	2.5-2.5 (6)	5 (6)	60 (6) ^f	20&170 ^g (6)
	Forklift drivers	1.5/1,000 ft ³ (4)	2.5 (6)	2-2 (6)	5 (6)	60 (6) ^f	20&170 ^g (6)
	Catchall operators	1.5/1,000 ft ³ (4)	8 (6)	8-8 (6)	5 (6)	60 (6) ^f	20&170 ^g (6)
	Hopper operators	1.5/1,000 ft ³ (4)	8 (6)	8-8 (6)	5 (6)	60 (6) ^f	20&170 ^g (6)
	Capper dumpers	1.5/1,000 ft ³ (4)	8 (6)	8-8 (6)	5 (6)	60 (6) ^f	20&170 ^g (6)
	Inspectors	1.5/1,000 ft ³ (4)	8 (6)	8-8 (6)	5 (6)	60 (6) ^f	20&170 ^g (6)
	Moisture checkers	1.5/1,000 ft ³ (4)	8 (6)	8-8 (6)	5 (6)	60 (6) ^f	20&170 ^g (6)
	Stem pickers	1.5/1,000 ft ³ (4)	8 (6)	8-8 (6)	5 (6)	60 (6) ^f	20&170 ^g (6)
	Packers	1.5/1,000 ft ³ (4)	8 (6)	8-8 (6)	5 (6)	60 (6) ^f	20&170 ^g (6)
	Shed-green forklift	1.5/1,000 ft ³ (4)	2.5 (6)	2-2 (6)	5 (6)	60 (6) ^f	20&170 ^g (6)
	Shed-blue tractor	1.5/1,000 ft ³ (4)	2.5 (6)	2-2 (6)	5 (7)	60 (6) ^f	20&170 ^g (6)
	Aeration-shed 604-606	1.5/1,000 ft ³ (4)	3 (8)	2.5-2.5 (8)	5 (8)	60 (8)	20&170 ^g (6)
	Capper area	1.5/1,000 ft ³ (4)	8 (8)	8-8 (6)	5 (6)	60 (6)	20&170 ^g (6)
	Hopper area	1.5/1,000 ft ³ (4)	8 (8)	8-8 (6)	5 (6)	60 (6)	20&170 ^g (6)

^a nonacute exposures include subacute, subchronic and chronic exposures.

^b section corresponds to that in Appendices B and C.

^c PCO = Pest control operator; BH = high barrier; VHB = very high barrier; PE = polyethylene.

^d an application rate that was used to adjust MB concentrations obtained from a study using a different application rate.

^e exposure times as indicated were used for the calculation of daily acute, subchronic (subchr.) and chronic (chr.) exposures (Tables B.1-B.18, C.1). n/a = not applicable.

^f average value from three large commodity fumigation facilities.

^g each average value represents three small chambers (30, 20, and 20 days/year) and three large chambers (90, 200, and 220 days/year) for commodity fumigation facilities. The higher value was used for the estimation of MB exposure in this document.

Appendix A (Continued 3)

Section ^b	Work task ^c	Adjustment rate (ref) ^d (lb. MB/A)	Hours/workday (ref.) ^e		Workdays (ref.)		
			Acute	Subc-chronic	/7 days	/90 days	/365 days
	<i>3. Big chamber fumigation (raisins) (continued)</i>						
	Catchoff area	1.5/1,000 ft ³ (4)	8 (8)	8-8 (6)	5 (6)	60 (6)	20&170 ^g (6)
	Side hopper area	1.5/1,000 ft ³ (4)	8 (8)	8-8 (6)	5 (6)	60 (6)	20&170 ^g (6)
	Stem picker area	1.5/1,000 ft ³ (4)	8 (8)	8-8 (6)	5 (6)	60 (6)	20&170 ^g (6)
	Filler area, E-line	1.5/1,000 ft ³ (4)	8 (8)	8-8 (6)	5 (6)	60 (6)	20&170 ^g (6)
	<i>4. Chamber (raisins)</i>						
	Fumigators	1.5/1,000 ft ³ (4)	1.5 (6)	1.5-1 (6)	6 (6)	63 (6)	150 (6)
	Aerators	1.5/1,000 ft ³ (4)	1.5 (6)	1.5-1 (6)	6 (6)	63 (6)	150 (6)
	Forklift drivers	1.5/1,000 ft ³ (4)	1 (6)	1-0.4 (6)	6 (6)	63 (6)	150 (6)
	Hopper operators	1.5/1,000 ft ³ (4)	8 (6)	8-8 (6)	6 (6)	63 (6)	150 (6)
	Stem picker	1.5/1,000 ft ³ (4)	8 (6)	8-8 (6)	6 (6)	63 (6)	150 (6)
	Fumigation area, cage	1.5/1,000 ft ³ (4)	1.5 (8)	1.5-1 (8)	6 (8)	63 (8)	150 (6)
	Leak check	1.5/1,000 ft ³ (4)	0.5 (8)	n/a-n/a (8)	n/a (8)	n/a (8)	n/a (8)
	Aeration chambers	1.5/1,000 ft ³ (4)	1.5 (6)	1.5-1 (6)	6 (6)	63 (6)	150 (6)
	Clearing chamber	1.5/1,000 ft ³ (4)	1.5 (8)	1.5-1 (8)	6 (8)	63 (8)	150 (8)
	Hopper area	1.5/1,000 ft ³ (4)	8 (8)	8-8 (8)	6 (8)	63 (8)	150 (8)
	<i>5. Fumigation of noncertified chambers (nuts)</i>						
	Fumigators	3.5/1,000 ft ³ (4)	5.5 (6)	4-2.5 (6)	6 (6)	70 (6)	185 (6)
	Cleaning fumigator	3.5/1,000 ft ³ (4)	5.5 (8)	4-2.5 (8)	6 (8)	70 (8)	185 (8)
	Cracking, sorting, cleaning, packing	3.5/1,000 ft ³ (4)	8 (6)	8-n/a (6)	6 (6)	70 (6)	n/a (6)
	Bulk casing worker	3.5/1,000 ft ³ (4)	8 (8)	8-n/a (8)	6 (8)	70 (8)	n/a (8)
	Hopper operator	3.5/1,000 ft ³ (4)	8 (8)	8-n/a (8)	6 (8)	70 (8)	n/a (8)
	Area sampling: Fumigatorium	3.5/1,000 ft ³ (4)	5.5 (8)	4-2.5 (8)	6 (8)	70 (8)	185 (8)
	Area sampling: Sorting, cracking,	3.5/1,000 ft ³ (4)	8 (8)	8-n/a (8)	6 (8)	70 (8)	n/a (8)
	Vacuum chamber area	3.5/1,000 ft ³ (4)	8 (8)	8-n/a (8)	6 (8)	70 (8)	n/a (8)
	Cleaning building fumigator	3.5/1,000 ft ³ (4)	4 (8)	4-2.5 (8)	6 (8)	70 (8)	185 (8)
	<i>6. Sea van aeration</i>						
	Upwind and downwind areas	3.5/1,000 ft ³ (4)	0.5 (8)	0.5-n/a (8)	6 (8)	70 (8)	n/a (8)

^a nonacute exposures include subacute, subchronic and chronic exposures.

^b section corresponds to that in Appendices B and C.

^c PCO = Pest control operator; BH = high barrier; VHB = very high barrier; PE = polyethylene.

^d an application rate that was used to adjust MB concentrations obtained from a study using a different application rate.

^e exposure times as indicated were used for the calculation of daily acute, subchronic (subchr.) and chronic (chr.) exposures (Tables B.1-B.18, C.1). n/a = not applicable.

^f average value from three large commodity fumigation facilities.

^g each average value represents three small chambers (30, 20, and 20 days/year) and three large chambers (90, 200, and 220 days/year) for commodity fumigation facilities. The higher value was used for the estimation of MB exposure in this document.

Appendix A (Continued 4)

Section ^b	Work task ^c	Adjustment rate (ref) ^d (lb. MB/A)	Hours/workday (ref.) ^e		Workdays (ref.)		
			Acute	Subc-chronic	/7 days	/90 days	/365 days
5	<i>Fumigation of cherries for export</i>						
	Control room: Start-up	5/1,000 ft ³ (4)	1 (6)	n/a-n/a (6)	5 (6)	n/a (6)	n/a (6)
	Control room: Left overnight	5/1,000 ft ³ (4)	1 (6)	n/a-n/a (6)	5 (6)	n/a (6)	n/a (6)
	Fumigators	5/1,000 ft ³ (4)	1 (6)	n/a-n/a (6)	5 (6)	n/a (6)	n/a (6)
	Closing-up, opening-up	5/1,000 ft ³ (4)	1 (6)	n/a-n/a (6)	5 (6)	n/a (6)	n/a (6)
	Forklift drivers	5/1,000 ft ³ (4)	0.75 (6)	n/a-n/a (6)	5 (6)	n/a (6)	n/a (6)
	Sorters	5/1,000 ft ³ (4)	8 (6)	n/a-n/a (6)	5 (6)	n/a (6)	n/a (6)
	Dump station	5/1,000 ft ³ (4)	8 (6)	n/a-n/a (6)	5 (6)	n/a (6)	n/a (6)
6	<i>Fumigation at a walnut processing facility</i>	Study rate-not known					
	Meats pool, bulk packaging, cleaning plant, cracking	no adjustment	8 (6)	8-n/a (6)	6 (6)	75 (6)	n/a (6)
	Warehouse workers (storage area)	no adjustment	8 (6)	8-8 (6)	6 (6)	75 (6)	180 (6)
	Warehouse aisle	no adjustment	8 (6)	8-n/a (6)	6 (6)	75 (6)	n/a (6)
	Sorting line	no adjustment	8 (6)	8-n/a (6)	6 (6)	75 (6)	n/a (6)
	Fumigatorium	no adjustment	5.5 (6)	4-2.5 (6)	6 (6)	75 (6)	180 (6)
	Cleaning plant	no adjustment	8 (6)	8-n/a (6)	6 (6)	75 (6)	n/a (6)
	Vacuum chamber	no adjustment	8 (6)	8-n/a (6)	6 (6)	75 (6)	n/a (6)
	Nonwork areas (vicinity of fumigation chambers, fence line, alleyway, lamp posts, etc.)	no adjustment	0.5 (8)	n/a-n/a (8)	2 (8)	n/a (8)	n/a (8)
	<i>Compliance monitoring study:</i>						
	Foreman's desk top	Study rate-not known	8	8-8 (8)	6 (8)	75 (8)	180 (8)
	Foreman's desk, phone box shelf	no adjustment	8	8-8 (8)	6 (8)	75 (8)	180 (8)
	Fence between chambers	no adjustment	0.5	n/a-n/a (8)	6 (8)	75 (8)	180 (8)
7	<i>Warehouse fumigation at a brewery facility</i>	Study rate-not known					
	Applicators (structural PCOs)	no adjustment	1.1(study)	n/a-n/a (8)	2 (8)	n/a (8)	n/a (8)
	Aerators (structural PCOs)	no adjustment	0.6 (study)	n/a-n/a (8)	2 (8)	n/a (8)	n/a (8)
	Work areas (workers in fumigated building)	no adjustment	8 (6)	8-n/a (8)	3 (8)	n/a (8)	n/a (8)
Appen. C	<i>2. Exposure of residents to MB from living near commodity fumigation facility</i>						
	Low range of exposure days	no adjustment	24	24-n/a (8)	3 (6)	30 (6)	150 (6)
	High range of exposure days	no adjustment	24	24-n/a (8)	6 (6)	75 (6)	185 (6)

^a nonacute exposures include subacute, subchronic and chronic exposures.

^b section corresponds to that in Appendices B and C.

^c PCO = Pest control operator; BH = high barrier; VHB = very high barrier; PE = polyethylene.

^d an application rate that was used to adjust MB concentrations obtained from a study using a different application rate.

^e exposure times as indicated were used for the calculation of daily acute, subchronic (subchr.) and chronic (chr.) exposures (Tables B.1-B.18, C.1). n/a = not applicable.

References for those indicated under "Hours/workday" and "Workdays" in this table.

1. Methyl bromide proposed or suggested soil injection fumigation permit conditions (issued between 6/94 to 7/97).
2. Suggested permit conditions for methyl bromide soil fumigation within a greenhouse (issued between 9/94 to 9/96).
3. Suggested permit conditions for methyl bromide fumigation of tarped potting soil (issued between 12/95 to 9/96).
4. Based on MB product labels.
5. Based on Gibbons, 1994.
6. Based on Haskell, 1998a.
7. Based on Haskell, 1998b.
8. Assumed exposure times were based on Haskell (1998a, 1998b) or Gibbons (1994) for similarity in work practices. Only acute and subacute exposures were assumed for exposure in nonwork areas, such as fence line, lamp post, alleyway.
9. Sansone, 1998.
(study) = from the study conducted by Gibbons, 1994.

Appendix B

Worker Exposure Studies

Methyl bromide studies conducted in and after 1992

Daily acute, subchronic and chronic exposures for each of the following studies were calculated based upon appropriate MB air concentrations and daily duration of exposure for acute, subchronic and chronic exposures as shown in Appendix A. These exposure estimates and frequency of exposure (Appendix A) were used to calculate subacute, subchronic, and chronic exposures, which are shown in Table 11.

In the course of reviewing submitted exposure monitoring studies, numerous meteorological conditions (factors) in respect to air and soil temperatures, relative humidity, and wind conditions are available in several studies. However, it is rather impossible to determine the relationship or the effect of these conditions to MB concentrations that were used to estimate the exposure of workers. This is because collections of air samples were not sequentially made and the sample collection times were generally too short. Consequently, the analysis on the influence of meteorological conditions to MB concentrations was not conducted.

Also, some exposure monitoring studies were conducted before DPR issued suggested MB permit conditions. Some conditions used in these studies were not in compliance with current suggested permit conditions/regulations, such as an application of MB was done inside a greenhouse, an aeration period was shorter than that recommended in permit conditions, chambers were not pressure tested, or chambers did not have standard stacks. Data from these studies are not included in this exposure document. Detailed explanations are shown in the text of this document.

Methyl bromide studies conducted in and after 1992 are shown as follows:

1. Preplant soil injection fumigation (including aeration, tarp removal)

Worker exposure studies during preplant soil injection fumigation with MB were conducted in treated fields, nurseries or greenhouses. The soil was typically prepared and was ready for planting crops. The tarpaulin was either used or not used depending on methods of fumigation. Information regarding fumigation methods are provided below.

a) Shallow-shank tarp method for MB fumigation: Worker exposure (Siemer & Associates, 1992a)

Report No. SM924096A-D (Final report).

Study director: S.R. Siemer, Ph.D. (Siemer & Associates, Inc.).

Compliance with GLP standards (40 CFR Part 160): This study was not conducted in compliance with GLP.

Application information

Formulation: MB 99.5%, Tricon 67-33, Tricon 57-43, Tricon 80-20.

Application rate: 214-398 Lbs a.i./A.

Date of application: July 14, 1992 to August 6, 1992.

Location (area treated, acres): Hayward (12), Wasco (78, 78, 18.76), Salinas (20, 20), Union City (10-13, 10-13), Wasco (78, 78), Watsonville (17-20, 17-20, 17-20, 9-10).

Crops to be planted: Strawberries, roses, gladiolus.

Use of tarpaulin: Dow or Cadillac high barrier tarpaulin.

Application method: MB was injected into the soil using one type of application equipment. A tractor was equipped with a pair of Noble Plow shanks (horizontal V-shaped blades), which were used to inject MB at a depth of 10-12". The Noble Plows were mounted to the tool bar. The injection spacing was 12" between injection outlets, which were evenly spaced across the trailing edge of each Noble Plow blade. The effective swath width was 7 feet. Each end of the tool bar had a conventional vertical shank that was injecting MB into the soil. This tractor was also equipped with an overhead fan above the head of the applicator. The fan chamber was 17" in diameter by 21" in height and was attached to the canopy of the tractor directly over the seat of the applicator. The fan was approximately 11 feet above the ground. There was a pair of plastic air supply pipe ducts for co-pilot positioned to either side of applicator. In addition, there was an opening and closing shovel on the field side of the tool bar to open and close the soil over the leading edge of the plastic tarp.

The thickness of the plastic tarpaulin used to seal the MB in the soil was 1.0 mil (Dow HB, Cadillac HB or Armin). The end of the tarp was buried with soil at the beginning and ending of swath. The lapping edge of the tarp was continuously glued to the previously laid adjacent strip. The other side was covered with a continuous band of soil.

MB air monitoring study

Work activities (monitoring time, replicates):

1. Applicator (tractor driver of application rig) (5.08-7.38 hrs, n=8)
2. Co-pilot (applicator assistant) (5.35-7.37 hrs, n=7)
3. Shovelman (assist in turning rig around at the end of row and sealing of row end and start of next) (4.1-7.08 hrs, n=9)
4. Tarp removers (5-6 days post-fumigation; tarp was cut using an ATV equipped with a cutting wheel; exposure was monitored for supervisor, tarp cutter, roper, truck loader) (1.83-1.93 hrs, n=3)

Exposure monitoring equipment:

1. Sample collection tubes-400/200 mg petroleum charcoal (A and B tubes, SKC #226-38-02).
2. Personal air sampling pumps-SKC model #222-3 or 224-PCXR7. The flow rate was set at approximately 20 mL/min.
3. Air inlet of tube A was set at about 8 inches from the worker's mouth.
4. Sampling tubes were kept on dry ice during storage and transportation.

Recovery study: An average recovery was 69%.

Exposure assessment

Air concentrations of MB in submitted reports were pre-adjusted using an average recovery of 69%. However, the air concentrations were readjusted by DPR to reflect a recovery of 50% (Biermann and Barry, 1999; Helliker, 1999). MB concentrations were adjusted for an application rate of 400 Lbs a.i./acre. One-half (10 ppb) of the MDL was used for any values reported as none detected. Results are shown in Tables B.1 to B.5. Acute and nonacute exposure estimates are shown in Table 11.

Table B.1. Exposure of applicators to methyl bromide (MB) during shallow shank-tarped soil injection fumigation.

Test No.	Lbs MB /A	Hours monitored	MB conc. ppm, v/v	Adjusted MB conc. ppm, v/v*	24-hour TWA (ppb)		
					Noble Plow shanks **		
					Acute	Subchr.***	Chr.***
924096A-1	398	5.32	0.903	1.25	303	303	n/a
924096A-3	398	5.4	ND	0.01	3	3	n/a
924096A-4	398	6.5	0.423	0.59	142	142	n/a
924096A-5	235	5.08	0.052	0.12	30	30	n/a
924096A-7	398	5.8	0.251	0.35	84	84	n/a
924096A-9	398	5.43	0.245	0.34	82	82	n/a
924096A-11	214	7.38	0.087	0.22	54	54	n/a
924096A-13	280	5.92	0.397	0.78	189	189	n/a
AVERAGE					111	111	n/a
STDEV					98	98	n/a

Lbs MB/A is Lbs active ingredient/A; TWA is time-weighted average; STDEV is standard deviation.

*adjusted by DPR for 400 lbs MB/A and 50% recovery (Biermann and Barry, 1999; Helliker, 1999).

One-half of the MDL (0.01 ppm) was used for non-detects.

***with a fan operating over the applicator's head; a reduced number of conventional shanks; the system consisted of a pair of horizontal V-shaped blades (Noble Plow shanks); injection depth was 10-12"; had opening and closing shovels to open and close soil over the leading edge of the plastic tarpaulin.

***subchr. (subchronic) and chr. (chronic) were used for the calculation of subchronic and chronic exposures (Table 11); hours/workday and workdays for subchronic and chronic exposures are shown in Appendix A.

Table B.2. Exposure of co-pilots to methyl bromide (MB) during shallow shank-tarped soil injection fumigation.

Test No.	Lbs MB /A	Hours monitored	MB conc. ppm, v/v	Adjusted MB conc. ppm, v/v*	24-hour TWA (ppb)		
					Noble Plow shanks**		
					Acute	Subchr.***	Chr.***
924096A-1	398	5.35	1.546	2.14	518	518	n/a
924096A-3	398	5.4	0.102	0.14	34	34	n/a
924096A-4	398	6.5	0.792	1.10	265	265	n/a
924096A-5	235	6.05	0.220	0.52	125	125	n/a
924096A-7	398	5.77	0.772	1.07	259	259	n/a
924096A-9	398	5.43	0.559	0.78	187	187	n/a
924096A-11	214	7.37	0.285	0.74	178	178	n/a
AVERAGE					224	224	n/a
STDEV					152	152	n/a

Lbs MB/A is Lbs active ingredient/A; TWA is time-weighted average; STDEV is standard deviation.

*adjusted by DPR for 400 lbs MB/A and 50% recovery (Biermann and Barry, 1999; Helliker, 1999).

**with a fan operating over the co-pilot's head.

***subchr. (subchronic) and chr. (chronic) were used for the calculation of subchronic and chronic exposures (Table 11); hours/workday and workdays for subchronic and chronic exposures are shown in Appendix A.

Table B.3. Exposure of shovelmen to methyl bromide (MB) during shallow shank-tarped soil fumigation.

Test No.	Lbs MB /A	Hours monitored	MB conc. ppm, v/v	Adjusted MB conc. ppm, v/v*	24-hour TWA (ppb)		
					Noble Plow shanks		
					Acute	Subchr.**	Chr.**
924096A-1	398	5.47	0.459	0.64	154	n/a	n/a
924096A-1	398	5.3	0.490	0.68	164	n/a	n/a
924096A-4	398	5.77	0.337	0.47	113	n/a	n/a
924096A-4	398	5.83	0.201	0.28	67	n/a	n/a
924096A-5	235	5.6	0.184	0.43	104	n/a	n/a
924096A-7	398	4.1	0.366	0.51	123	n/a	n/a
924096A-9	398	5.02	1.536	2.13	515	n/a	n/a
924096A-11	373	7.08	0.146	0.22	52	n/a	n/a
924096A-13	280	4.53	0.252	0.50	120	n/a	n/a
924096A-13	280	4.47	0.122	0.24	58	n/a	n/a
AVERAGE					147	n/a	n/a
STDEV					135	n/a	n/a

Lbs MB/A is Lbs active ingredient/A; TWA is time-weighted average; STDEV is standard deviation.

*adjusted by DPR for 400 lbs MB/A and 50% recovery (Biermann and Barry, 1999; Helliker, 1999).

**subchr. (subchronic) and chr. (chronic) are used for the calculation of subchronic and chronic exposures (Table 11); hours/workday and workdays for subchronic and chronic exposures are shown in Appendix A.

Table B.4. Exposure of tarpaulin removers employed by pest control operators to methyl bromide (MB) during collection of tarp from shallow shank-tarped soil injection fumigation.

Test No.	Lbs MB /A	Hours monitored	MB conc. ppm, v/v	Adjusted MB conc. ppm, v/v*	24-hour TWA (ppb)		
					Conventional shanks		
					Acute	Subchr.**	Chr.**
924096A-1	398	1.93	2.006	2.78	696	696	n/a
924096A-1	398	1.87	2.921	4.05	1013	1013	n/a
924096A-1	398	1.83	ND	0.01	3	3	n/a
924096A-1	398	1.8	2.321	3.22	805	805	n/a
924096A-1	398	0.63	4.785	6.64	1659	1659	n/a
AVERAGE					835	835	n/a
STDEV					596	596	n/a

Lbs MB/A is Lbs active ingredient/A; TWA is time-weighted average; STDEV is standard deviation.

*adjusted by DPR for 400 lbs MB/A and 50% recovery (Biermann and Barry, 1999; Helliker, 1999).

One-half of the MDL (0.01 ppm) was used for non-detects.

**subchr. (subchronic) and chr. (chronic) are used for the calculation of subchronic and chronic exposures (Table 11); hours/workday and workdays for subchronic and chronic exposures are shown in Appendix A.

Table B.5. Exposure of tarpaulin removers employed by growers to methyl bromide (MB) during collection of tarp from shallow shank-tarped soil injection fumigation.

Test No.	Lbs a.i. /A	Hours monitored	MB conc. ppm, v/v	Adjusted MB conc. ppm, v/v*	24-hour TWA (ppb)		
					Conventional shanks		
					Acute	Subchr.**	Chr.**
924096A-1	398	1.93	2.006	2.78	232	n/a	n/a
924096A-1	398	1.87	2.921	4.05	338	n/a	n/a
924096A-1	398	1.83	ND	0.01	1	n/a	n/a
924096A-1	398	1.8	2.321	3.22	268	n/a	n/a
924096A-1	398	0.63	4.785	6.64	553	n/a	n/a
AVERAGE					278	n/a	n/a
STDEV					199	n/a	n/a

Lbs MB/A is Lbs active ingredient/A; TWA is time-weighted average; STDEV is standard deviation.

*adjusted by DPR for 400 lbs MB/A and 50% recovery (Biermann and Barry, 1999; Helliker, 1999).

One-half of the MDL (0.01 ppm) was used for non-detects.

**subchr. (subchronic) and chr. (chronic) were used for the calculation of subchronic and chronic exposures (Table 11); hours/workday and workdays for subchronic and chronic exposures are shown in Appendix A.

b) Nontarp deep injection for measurement of MB exposure to the applicator, applicator assistant and cultipacker tractor driver (Siemer & Associates, 1992b).

Report No. SM924096B (interim report).

Study Director: S. R. Siemer (Siemer & Associates, Inc.).

Compliance with GLP standards: There was no GLP compliance statement in the report.

Application information

Formulation: MB 99.5%.

Application rate: 398 Lbs a.i./A.

Date of application: (1992): July 15 (Chowchilla), July 28 (Shafter), October 21 (Shafter).

Location (area treated, acres): Chowchilla (25), Shafter (15), Shafter (15.2).

Use of tarpaulin: No.

Crop to be planted: Almond.

Application method: An application tractor was equipped with mounted tool bar. Shank injectors were set 20-24" deep, spaced up to 66" apart with a wing welded to the shank to break up the chisel chimney. The application tractor was followed by a disc-cultipacker to compact seal the soil surface. The tractor was equipped with a fan over an applicator's head.

MB air monitoring study

Work tasks (monitoring time, replicates): Applicators (4.71-7.88 hrs, n=3), co-pilot (4.72, n=1), cultipacker tractor drivers (4.6-6.52, n=2).

Exposure monitoring equipment: Similar to those for shallow shank tarp fumigation.

Recovery study: An average recovery was 69%.

Exposure/data assessment

Air concentrations of MB in submitted reports were pre-adjusted using an average recovery of 69%. However, the air concentrations were readjusted by DPR to reflect a recovery of 50% (Biermann and Barry, 1999; Helliker, 1999). MB concentrations were adjusted for an application rate of 400 Lbs a.i./acre. Results are shown in Table B.6. Acute and nonacute exposure estimates are shown in Table 11.

Table B.6. Exposure of applicators, applicator assistants and cultipacker tractor drivers to methyl bromide (MB) during deep shank injection.

Work task	Lbs MB /A	Monitoring time (hrs)	MB conc. ppm, v/v*	Adjusted MB conc. ppm, v/v**	24-hr TWA (ppb)		
					Acute	Subchronic***	Chronic***
Conventional deep shank injection (the tractor was equipped with a fan over an applicator's head)							
Applicator 1	398	4.72	0.377	0.52	126	126	n/a
Applicator 2	398	7.88	0.539	0.75	181	181	n/a
				Average	154	154	n/a
Co-pilot	398	4.72	0.146	0.20	49	49	n/a
Cultipacker 1	398	4.6	0.294	0.41	99	n/a	n/a
Improved deep shank injection (the tractor was equipped with a fan over an applicator's head; used scrapers and press wheels on an application rig and the disc and drag bar on the second tractor pulling a cultipacker)							
Applicator 3	398	7.25	0.170	0.24	57	57	n/a
Cultipacker 2	398	6.52	0.210	0.29	70	n/a	n/a

Lbs MB/A is Lbs active ingredient/A; TWA is time-weighted average.

* adjusted by the study director for an average recovery of 69%.

** adjusted by DPR for 400 lbs MB/A and 50% recovery (Biermann and Barry, 1999; Helliker, 1999).

*** subchronic and chronic were used for the calculation of subchronic and chronic exposures (Table 11); hours/workday and workdays for subchronic and chronic exposures are shown in Appendix A.

c) Exposure of workers to MB during a deep shank, nontarp soil fumigation near Traver, Hanford, and Madera in California (Siemer & Associates, 1993a).

Report No.: SR934100.1A1 (April 16, 1993, interim report).

Study Director: S. R. Siemer (Siemer & Associates, Inc.).

Compliance with GLP standards: No detailed statement of GLP compliance.

Application information

Formulation: 99% MB.

Application rate: 396 Lbs a.i./A.

Date of application: February 16, 1993.

Location (area treated): Traver, Hanford, and Madera in California.

Use of tarpaulin: No.

Crops to be planted: Not specified.

Application method (Basic equipment): An application tractor equipped with three forward curved shanks with 2x width of shank thickness chisel points (60" spacing) to inject MB to a depth of approximately 24 inches. The fumigation tractor was equipped with closing scrapers behind each of the three shanks, but not equipped with an overhead fan above the applicator.

The application tractor was equipped with a Type 2 air conditioned enclosed cab. Specific equipment used at each location is as follows:

- a) near Traver - used basic equipment plus a second tractor with a disc that followed the application tractor.
- b) near Hanford - used basic equipment plus a second tractor pulling a cultipacker that followed the application tractor.
- c) near Madera - used basic equipment plus a second tractor pulling a cultipacker that followed the application tractor.

MB air monitoring study

Work tasks (monitoring time, replicates): Applicator (2.72-6.53 hrs, n=3), disc driver (2.95 hrs, n=1), supervisor (3.28 hrs, n=1), cultipacker driver (2.95-6.2 hrs, n=2)

Exposure monitoring study: The exposure of workers to MB was measured by collecting air samples from the workers' breathing zone using charcoal sampling tubes during work activities.

Recovery: The average recovery was 69%.

Exposure/data assessment

MB concentrations were adjusted for an application rate of 400 Lbs a.i./acre and a recovery of 69%. However, the air concentrations were readjusted by DPR to reflect a recovery of 50% (Biermann and Barry, 1999; Helliker, 1999). Results are shown in Table B.7. Acute and nonacute exposure estimates are shown in Table 11.

Table B.7. Methyl bromide (MB) air concentrations near the workers' breathing zone and the estimation of worker exposure (non-tarp soil fumigation near Traver, Hanford and Madera in California).

Work task	Lbs MB /A	Monitoring time (hrs)	MB conc. ppm, v/v*	Adjusted MB conc. ppm, v/v**	24-hr TWA (ppb)		
					Acute	Subchr.***	Chr.***
Traver: Basic injection equipment plus a second tractor with a disc							
Applicator 1	396	2.72	0.26	0.36	88	88	n/a
Disc driver	396	2.95	1.52	2.12	512	512	n/a
Hanford and Madera: Basic injection equipment plus a second tractor pulling a cultipacker							
Applicator 2	396	3.4	0.491	0.68	165	165	n/a
Applicator 3	396	6.53	0.066	0.09	22	22	n/a
				Average	94	94	n/a
Supervisor	396	3.28	0.198	0.28	67	67	n/a
Cultipacker 1	396	2.95	0.173	0.24	58	n/a	n/a
Cultipacker 2	396	6.2	0.03	0.04	10	n/a	n/a
				Average	34	n/a	n/a

Lbs MB/A is Lbs active ingredient/A; TWA is time-weighted average.

* adjusted by the study director for an average recovery of 69%.

** adjusted by DPR for 400 lbs MB/A and 50% recovery (Biermann and Barry, 1999; Helliker, 1999).

*** subchr. (subchronic) and chr. (chronic) were used for the calculation of subchronic and chronic exposures shown in Table 11; hours/workday and workdays for subchronic and chronic exposures are shown in Appendix A.

d) Deep shank, nontarp fumigation: Mitigation of MB worker exposure (near Helm, California)
(Siemer and Associates, 1993b).

Report No.: SM934104.1-2, SM934104.2-1 (interim report)

Study Director: S. R. Siemer (Siemer & Associates, Inc.)

Compliance with GLP standards: Not in compliance with GLP standards

Application information

Formulation: 97.6% MB/2.4% chloropicrin.

Application rate: 392 Lbs a.i./A.

Date of application: March 8, 1993.

Location (area treated, acres): Near Helm, California (40).

Use of tarpaulin: No.

Crop to be planted: Grapes.

Application method: An application tractor was equipped with four forward curved shanks, each having a chisel point 2x wider than the width of the shank and an injector port forward of the leading edge of the shank body, behind the chisel point. The shanks were spaced 40 inches apart. The application tractor was equipped with a Type 2 air conditioned enclosed cab. Injection depth was approximately 27 inches. The shanks were each equipped with closing scrapers and followed by a gauge roller and a rolling cultipacker. During fumigation, shank slices were covered with soil from the use of closing scrapers. The soil was then compressed by the gauge roller. The soil in shank slices was further compressed by a cultipacker, which followed the application tractor within 5 minutes. In this improved deep soil injection fumigation method, a fan overhead of the applicator was not used.

MB air monitoring study

Work tasks (monitoring time, replicates): Applicator (9.18 hrs, n=1, cultipacker driver (8.38 hrs, n=1).

Exposure monitoring study: The exposure of workers to MB was measured by collecting air samples from the workers' breathing zone (approximately 8 inches from the mouth) using charcoal sampling tubes (400/200 mg charcoal) during work activities.

Recovery: The average recovery was 69%.

Exposure/data assessment

Air concentrations of MB in submitted reports were pre-adjusted using a recovery of 69%.

However, the air concentrations were readjusted by DPR to reflect a recovery of 50% (Biermann and Barry, 1999; Helliker, 1999). MB concentrations were adjusted for an application rate of 400 Lbs a.i./acre. Results are shown in Table B.8. Acute and nonacute exposure estimates are shown in Table 11.

Table B.8. Methyl bromide (MB) air concentrations near the workers' breathing zone and the estimation of worker exposure (deep shank non-tarp soil fumigation near Helm, California).

Work task	Lbs MB /A	Monitoring time (hrs)	MB conc. ppm, v/v*	Adjusted MB conc. ppm, v/v**	24-hr TWA (ppb)		
					Acute	Subchr.***	Chr.***
Applicator	392	9.18	0.02	0.03	7	7	n/a
Cultipacker	392	8.38	0.02	0.03	7	n/a	n/a

Lbs MB/A is Lbs active ingredient/A; TWA is time-weighted average.

* adjusted by the study director for an average recovery of 69%.

** adjusted by DPR for 400 lbs MB/A and 50% recovery (Biermann and Barry, 1999; Helliker, 1999).

*** subchr. (subchronic) and chr. (chronic) were used for the calculation of subchronic and chronic exposures shown in Table 11; hours/workday and workdays for subchronic and chronic exposures are shown in Appendix A.

e) Shallow shank, tarped-bed soil fumigation: Worker exposure (Siemer & Associates, 1992c).

Report No. (status): SM924096 C, M (Interim report)

Study Director: S. R. Siemer & Associates, Inc.

Compliance with GLP standards: There was no information on GLP compliance.

Application information

Formulation: 75% MB.

Application rate: 187.5 Lbs a.i./A.

Date of application: 10/92 and 11/17-18/92.

Location: Santa Maria.

Use of tarpaulin: Yes.

Crop to be planted: Strawberries.

Application methods: An application rig was equipped with three 6- to 8-inch shanks, closing rollers, and tarp-laying equipment plus scrapers (closing shoes) mounted between the trailing edge of each shank and the closing roller. The scrapers were mounted to be rigid laterally and

pivot vertically; their leading edge was forward of the trailing edge of each shank. The scrapers kept soil heaped on the base of each shank and traveled just under the soil surface so that soil and trash flowed over them. Soil injection was 6-8 inches below bed top.

MB air monitoring study

Work tasks (monitoring time, replicates): Applicator (6.07-7.83 hrs, n=6), co-pilot (6.05-7.7 hrs, n=8), shovelman (7.1 hrs, n=2).

Exposure monitoring equipment: The exposure of workers to MB was measured by collecting air samples from the workers' breathing zone using charcoal sampling tubes (400/200 mg charcoal) during work activities.

Recovery study: An average recovery was 69%.

Exposure assessment

Air concentrations of MB in submitted study reports were adjusted using a recovery of 69%. However, the air concentrations were readjusted by DPR to reflect a recovery of 50% (Biermann and Barry, 1999; Helliker, 1999). MB concentrations were further adjusted by DPR for an application rate of 250 Lbs a.i./acre. Results are shown in Table B.9. Acute and nonacute exposure estimates are shown in Table 11.

Table B.9. Exposure of workers to methyl bromide during (MB) fumigation using conventional and modified injection shanks.

Work task	Lbs MB /A	Monitoring time (hrs)	MB conc. ppm, v/v*	Adjusted MB conc. ppm, v/v**	24-hr TWA (ppb)		
					Acute	Subchr.***	Chr.***
Conventional injection shanks plus the raised co-pilot platform and an injection depth of 8"							
Applicator	187.5	7.33	0.18	0.33	80	80	n/a
Co-pilot	187.5	7.3	0.25	0.46	111	111	n/a
Co-pilot	187.5	7.25	0.22	0.40	98	98	n/a
				Average	104	104	n/a
Conventional injection shanks plus closing shoes							
Applicator	187.5	6.07	0.10	0.18	44	44	n/a
Co-pilot	187.5	6.22	0.47	0.86	209	209	n/a
Co-pilot	187.5	6.05	0.28	0.52	125	125	n/a
				Average	167	167	n/a

Lbs MB/A is Lbs active ingredient/A; TWA is time-weighted average.

* adjusted by the study director for an average recovery of 69%.

** adjusted by DPR for an application rate of 250 lbs MB/A (soil injection fumigation permit conditions, 12/95) and 50% recovery (Biermann and Barry, 1999; Helliker, 1999).

***subchr. (subchronic) and chr. (chronic) were used for the calculation of subchronic and chronic exposures (Table 11); hours/workday and workdays for subchronic and chronic exposures are shown in Appendix A.

f) Tarped-bed fumigation: Mitigation of MB worker exposure (Siemer & Associates, 1993c).

Report No. (status): SM934104.1M (interim report).

Study Director: S. R. Siemer (Siemer & Associates, Inc.)

Compliance with GLP standards: There was no information on GLP compliance.

Application information

Formulation: 75% MB/25% chloropicrin (Tri-Con 75/25).

Application rate: 262.5 Lbs a.i./A.

Date of application: February 15, 1993.

Location (area treated, acres): Arvin, Kern County, CA (\cong 20 acres).

Use of tarpaulin: 1.5 mil black mulch film.

Crop to be planted: Peppers.

Application method: MB was applied by a two-stage method. One tractor, Kennco Combi Superbedder, was equipped with swept back shanks spaced approximately 10" apart. This Superbedder formed three beds (height-10," width-36") and injected MB to finished beds from outlets at the end of each shank at a depth of 10-14". The shanks were positioned so that they would extend between the bed puller blades, just ahead of the bed shaper, with soil covering them to a depth of 18 to 24" during bed formation. The finished bed injection depth was approximately 12-14". Drip tape was laid from the fumigation tractor. The 6 foot wide plastic tarp was carried on a bar on the second tractor. The plastic tarp was unrolled and covered the beds. Press wheels held the tarp in place on the sides of the beds while shovels threw soil over the edge of the plastic.

MB air monitoring study

Work tasks (monitoring time, replicates): a) fumigation tractor-driver (7.77 hrs, n=1), applicator (7.72 hrs, n=1), tape layer (7.17 hrs, n=1); b) tarp laying tractor-driver (7.73 hrs, n=1), co-pilot (7.5 hrs, n=2).

Exposure monitoring equipment: The exposure of workers to MB was measured by collecting air samples from the workers' breathing zone using charcoal sampling tubes (400/200 mg charcoal) during work activities.

Recovery: A recovery of 88% was obtained by fortifying control samples with injecting standard.

Exposure assessment

Air concentrations of MB in submitted study reports were adjusted using a recovery of 88%.

However, the air concentrations were readjusted by DPR to reflect a recovery of 50% (Biermann and Barry, 1999; Helliker, 1999). MB concentrations were further adjusted by DPR for an application rate of 250 Lbs a.i./acre. Results are shown in Table B.10. Acute and nonacute exposure estimates are shown in Table 11.

Table B.10. Exposure of workers to methyl bromide (MB) during application using exposure mitigation method.

Work task	Lbs MB /A	Monitoring time (hrs)	MB conc.* ppm, v/v	Adjusted MB conc.** ppm, v/v	24-hr TWA (ppb)		
					Acute	Subchr.***	Chr.***
The tractor was equipped for methyl bromide fumigation							
Driver	262.5	7.77	0.07	0.12	28	28	n/a
Applicator	262.5	7.72	0.11	0.18	45	45	n/a
Drip tape layer	262.5	7.17	0.16	0.27	65	65	n/a
The tractor was equipped for laying tarp							
Driver	262.5	7.73	ND	0.02	4	4	n/a
Co-pilot 1	262.5	7.5	0.16	0.27	65	65	n/a
Co-pilot 2	262.5	7.5	ND	0.02	4	4	n/a
				Average	34	34	n/a

Lbs MB/A is Lbs active ingredient/A; TWA is time-weighted average.

*adjusted by the study director for an a recovery of 88%. One-half of the MDL (10 ppb) was used for nondetects.

** adjusted by DPR for an application rate of 250 lbs MB/A (soil injection fumigation permit conditions, 12/95) and 50% recovery (Biermann and Barry, 1999; Helliker, 1999).

***subchr. (subchronic) and chr. (chronic) were used for the calculation of subchronic and chronic exposures (Table 11); hours/workday and workdays for subchronic and chronic exposures are shown in Appendix A.

g) Tarp-bed fumigation for measurement of MB exposure to the applicator, applicator assistant, and shovelman (Siemer & Associates, 1994)

Report No. (status): SM934110 (Interim report).

Study Director: S. R. Siemer (Siemer & Associates, Inc.).

Compliance with GLP standards: This study was conducted in compliance with GLP standards (40 CFR Part 160) with some exceptions. A signed copy of the compliance statement was attached to the submitted report.

Application information

Formulation: 98% MB

Application rate: 287 Lbs a.i./treated acre

Date of application: July 13, 1993

Location (area treated, acres): Santa Maria, CA (9 acres)

Use of tarpaulin: 1.75 mil tarp

Crops to be planted: Strawberries

Application method: The soil was fumigated by using a modified method of injection with swept-back shanks and a closing device for sealing off the shank slice. Three sweptback-style shanks were spaced approximately 10 inches apart. MB was injected through a series of hoses, valves and tubing to an outlet at the end of each shank. The shanks were positioned so that the injection port was extended backwards underneath the compaction roller. A closing device was situated to close the shank slice between the shank and the press roller. The injection depth was 6-8 inches. The closing device moved soil over the shank slice and the

compaction roller pressed the soil into the shank slice ahead of the plastic tarpaulin simultaneously laid over the top and side of the bed. The preformed beds measured 12-14 inches high and approximately 41 inches wide. The application tractor was not equipped with an overhead fan.

MB air monitoring study

Work tasks (monitoring time, replicates): Applicator (10.33 hrs, n=1), applicator assistant (7.98 and 8 hrs, n=2), and shovelmen (9.32 and 7.83 hrs, n=2).

Exposure monitoring equipment: Air samples were collected by using a sampling train that consisted of two charcoal tubes containing 400 and 200 mg of charcoal and a personal sampling pump. Air intake ends of the sampling tube was positioned approximately 8 inches from the worker's mouth. The pump flow rate was approximately 20 mL/min.

Recovery study: An average recovery was 69%.

Exposure/data assessment

Air concentrations of MB in submitted study reports were adjusted using a recovery of 69%. However, the air concentrations were readjusted by DPR to reflect a recovery of 50% (Biermann and Barry, 1999; Helliker, 1999). MB concentrations were further adjusted by DPR for an application rate of 250 Lbs a.i./acre. Results are shown in Table B.11. Acute and nonacute exposure estimates are shown in Table 11.

Table B.11. Exposure of handlers to methyl bromide (MB) during shallow shank, tarped-bed fumigation.

Work task	Lbs MB /A	Monitoring time (hrs)	MB conc. ppm, v/v*	Adjusted MB conc.** ppm, v/v	24-hr TWA (ppb)		
					Acute	Subchr.***	Chr.***
Applicator	287	10.33	0.012	0.01	2	2	n/a
Co-pilot A	287	7.98	0.108	0.13	31	31	n/a
Co-pilot B	287	8.00	0.109	0.13	32	32	n/a
				Average	32	32	n/a
Shovelman A	287	9.32	0.002	0.002	0.6	n/a	n/a
Shovelman B	287	7.83	0.002	0.002	0.6	n/a	n/a

Lbs MB/A is Lbs active ingredient/A; TWA is time-weighted average; STDEV is standard deviation.

* adjusted by the study director for an average recovery of 69%.

** adjusted by DPR for an application rate of 250 lbs MB/A (soil injection fumigation permit conditions, 12/95) and 50% recovery (Biermann and Barry, 1999; Helliker, 1999).

***subchr. (subchronic) and chr. (chronic) were used for the calculation of subchronic and chronic exposures (Table 11); hours/workday and workdays for subchronic and chronic exposures are shown in Appendix A.

On July 7, 1998, DPR issued a memo to county agricultural commissioners informing them that the installation of sprinkler irrigation pipe during soil fumigation is not recognized in the current suggested soil permit conditions for MB (Sanders and Andrews, 1998). Some growers would like to continue the practice because the water from the sprinkler system may help keep the tarpaulin in place in windy conditions. However, the memo mentioned that preliminary data collected early in the permit condition development showed this procedure could result in serious overexposure to workers involved in pipe installation. Therefore, exposure data for irrigation pipe tractor drivers and pipelayers in the submitted report are not included in this exposure assessment document.

h) MB exposure to the tarpaulin cutter and remover positions from tarped-shallow broadcast fumigation (TriCal, 1993a).

Report No. (status): TC211 (interim report).

Study Director: TriCal, Inc.

Compliance with GLP standards: This study was not conducted in compliance with GLP standards (40 CFR Part 160).

Application information

Formulation: MB 99.5% (Burrell and Corcoran), 80% (Watsonville).

Application rate (Lbs a.i./A): 298.5 (Burrell), 398 (Corcoran), and 280 (Watsonville).

Date of application: April 4, 12, and 28, 1993

Location (area treated, acres): Burrell (10.74 acres), Corcoran (10.48 acres), Watsonville (8.07 acres).

Use of tarpaulin: Dow HB or Cadillac HB.

Crops to be planted: Grapes, flowers, turf.

Application method: The broadcast fumigation of MB was made with Noble Plow shanks at the depth of 10-12". The tarpaulin was left in place for a minimum of five days after the completion of fumigation. After the five-day waiting period, each tarp panel was cut by a four wheeler using a cutting coulter. The aeration period for MB after the tarp cutting was completed in one day. At the end of the aeration period, tarp removal proceeded by windrowing the plastic panels and then pulling these panels into a truck for disposal.

MB air monitoring study

Work tasks (monitoring time, replicates): Tarpaulin cutters (driver) (0.52-1.23 hrs, n=3), tarpaulin pullers or removers (e.g. tractor drivers, end rollers) (1.09-2.1 hrs, n=12).

Exposure monitoring equipment: Air samples were collected by using a sampling train consisting of two charcoal tubes containing 400 and 200 mg of charcoal and a personal sampling pump. Samples were taken from the breathing zones of the tarpaulin cutter and puller positions.

Recovery: The average recovery was 69%.

Exposure/data assessment

Air concentrations of MB in submitted study reports were adjusted using the average recovery of 69%. However, the air concentrations were readjusted by DPR to reflect a recovery of 50% (Biermann and Barry, 1999; Helliker, 1999). MB concentrations were further adjusted by DPR for an application rate of 400 Lbs a.i./acre. Results are shown in Table B.12. Acute and nonacute exposure estimates are shown in Table 11.

Table B.12. Exposure of tarp cutters and removers to methyl bromide (MB).

Work task	Lbs MB /A	Monitoring time (hrs)	MB conc. ppm, v/v*	Adjusted MB conc.** ppm, v/v	24-hr TWA (ppb)		
					Acute	Subchr.***	Chr.***
(By PCOs - work time is 6 hours/day)							
Cutter 2	298.5	0.52	ND	0.02	5	5	n/a
Cutter 1	398	1.1	ND	0.01	3	3	n/a
Cutter 1	280	1.23	0.48	0.95	237	237	n/a
				Average	82	82	n/a
				STDEV	134	134	n/a
(By growers - work time is 2 hours/day)							
Cutters				Average	27	n/a	n/a
				STDEV	45	n/a	n/a
(By PCOs - work time is 6 hours/day)							
Puller 1(a)	298.5	2	ND	0.02	5	5	n/a
Puller 2(b)	298.5	2	ND	0.02	5	5	n/a
Puller 3(b)	298.5	2	0.7	1.29	324	324	n/a
Puller 1	398	2.1	0.04	0.06	14	14	n/a
Puller 2	398	2.08	ND	0.01	3	3	n/a
Puller 3	398	1.6	ND	0.01	3	3	n/a
Puller 1	280	1.17	ND	0.02	5	5	n/a
Puller 2	280	1.21	0.03	0.06	15	15	n/a
Puller 3	280	1.2	ND	0.02	5	5	n/a
Puller 4	280	1.12	ND	0.02	5	5	n/a
Puller 5	280	1.09	ND	0.02	5	5	n/a
Puller 6	280	1.1	ND	0.02	5	5	n/a
				Average	33	33	n/a
				STDEV	92	92	n/a
(By growers - work time is 2 hours/day)							
Pullers				Average	11	n/a	n/a
				STDEV	31	n/a	n/a

Lbs MB/A is Lbs active ingredient/A; TWA is time-weighted average; STDEV is standard deviation.

(a) end roller (b) tractor driver

* adjusted by the study director for an average recovery of 69%.

** adjusted by DPR for an application rate of 400 lbs MB/A and 50% recovery (Biermann and Barry, 1999; Helliker, 1999). One half of the MDL (0.01 ppm) was used for nondetects.

***subchr. (subchronic) and chr. (chronic) were used for the calculation of subchronic and chronic exposures (Table 11); hours/workday and workdays for subchronic and chronic exposures are shown in Appendix A.

i) Worker exposure to MB during tarp cutting and removal (TriCal, 1993b).

Report No. (status): TC233.3 (interim report).

Study Director: Kirk Fowler (TriCal, Inc.).

Compliance with GLP standards: This study was not conducted in compliance with GLP standards (40 CFR Part 160).

Application information

Formulation: 99.5% MB.

Application rate: 390.2 Lbs a.i./A.

Date of application: October 19, 1993.

Location (area treated, acres): Gonzales, California (7.09 acres).

Use of tarpaulin: 1.0 mil high barrier test film.

Crops to be planted: Head lettuce.

Application method: MB was injected into the soil at a depth of 10 inches using Noble Plow shanks. The fumigated area was thereafter covered with high barrier test film. The tarpaulin was left in place for at least five days after the complete of the application. After the five-day waiting period, each panel of the tarp was cut along the tape by an ATV equipped with a cutting wheel. After cutting and a 24-hour waiting period had elapsed, the tarpaulin was removed by workers.

MB air monitoring study

Work tasks (monitoring time, replicates): Tarp cutter (0.36 hrs, n=1), Tarp remover (Tractor driver, basketman, end puller) (1.20-1.23 hrs, n=3).

Exposure monitoring equipment: MB levels were measured by collecting air samples from the workers' breathing zone using charcoal tubes (400/200 mg charcoal) for the duration of the work period.

Recovery: The average recovery was 69%.

Exposure/data assessment

Air concentrations of MB in submitted study reports were adjusted using the average recovery of 69%. However, the air concentrations were readjusted by DPR to reflect a recovery of 50% (Biermann and Barry, 1999; Helliker, 1999). MB concentrations were further adjusted by DPR for an application rate of 400 Lbs a.i./acre. Results are shown in Table B.13. Acute and nonacute exposure estimates are shown in Table 11.

Table B.13. Exposure of tarp cutters and removers to methyl bromide (MB) following the use of high barrier tarpaulin.

Work task	Lbs MB /A	Monitoring time (hrs)	MB conc. ppm, v/v*	Adjusted MB conc.** ppm, v/v	24-hr TWA (ppb)		
					Acute	Subchr.***	Chr.***
(By PCOs - work time is 6 hours/day)							
Tarp cutter	390.2	0.36	0.22	0.31	78	78	n/a
(By PCOs - work time is 6 hours/day)							
Tarp remover 1 (Tractor driver)	390.2	1.2	0.97	1.37	343	343	n/a
Tarp remover 2 (Basketman)	390.2	1.21	0.92	1.30	325	325	n/a
Tarp remover 3 (End puller)	390.2	1.23	0.02	0.03	7	7	n/a
(By growers - work time is 2 hours/day)							
Tarp cutter					26	n/a	n/a
(By growers - work time is 2 hours/day)							
Tarp remover 1 (Tractor driver)					114	n/a	n/a
Tarp remover 2 (Basketman)					108	n/a	n/a
Tarp remover 3 (End puller)					2	n/a	n/a

Lbs MB/A is Lbs active ingredient/A; TWA is time-weighted average.

* adjusted by the study director for an average recovery of 69%.

** adjusted by DPR for an application rate of 400 lbs MB/A and 50% recovery (Biermann and Barry, 1999; Helliker, 1999).

***subchr. (subchronic) and chr. (chronic) were used for the calculation of subchronic and chronic exposures (Table 11); hours/workday and workdays for subchronic and chronic exposures are shown in Appendix A.

2. Soil fumigation in nurseries and greenhouses

a) Worker exposure assessment during potting soil fumigation (Siemer & Associates, 1992d)

Exposure study assessment

Exposure data from this study are not included in this exposure assessment document because the application of MB was not conducted according to current permit conditions/regulations.

Examples:

- The soil pile size was 6,000 yd³ (permit conditions allow 400 yd³).
- The soil pile was tarped for 2 days (permit conditions require 3 days).

b) Exposure of workers to MB during soil fumigation in greenhouses (Siemer & Associates, 1992e)

Exposure study assessment

Exposure data from this study, except exposure of tarp venters and tarp removers, are not included in this exposure assessment document because the application of MB was not conducted according to current permit conditions/regulations. Examples:

- MB was introduced from inside the greenhouse (permit conditions require introduction of MB from outside the greenhouse).
- No information on leak checking of all fittings, connections, and valves of the introduction plumbing.

Details of the study are as follows:

Report No. (status): SM924099A1 (interim report).

Study Director (company): S. R. Siemer (Siemer and Associates, Inc.).

Compliance with GLP standards: There was no information to determine whether the study was conducted in compliance with GLP standards.

Application information

Formulation: 99.5% MB.

Application rate: 447.75 Lbs a.i./A.

Date of application: August and September, 1992.

Location (area treated, acres): Oxnard, Ventura County (approximately 3/4 acres).

Use of tarpaulin: One mil high density tarpaulin.

Application method: Each plot of soil in a greenhouse to be treated with MB measured 20 feet wide by 150 feet in length. The applicator brought the fumigation trailer, which was used for heating the gas, to the east opening in the building. After all workers had cleared the area, the gas tank was connected to the heater coils that were heated by a propane burner. From the heater coils another hose was connected to the main PVC plastic pipe feeder. Hot MB was released through the plastic pipe manifold to which were attached a series of perforated plastic hoses. These hoses ran along the surface of the soil under preplaced tarpaulin.

Three days after the completion of fumigation, the tarp was cut open by hand using knives with elongated handles. The strips of the tarp were pulled apart and the greenhouse was allowed to vent for 48 hours. At the end of the venting period, the tarp was pulled and disposed.

Air monitoring study

Work tasks (monitoring time, replicates): Applicator (1.17-1.73 hrs, n=2), tarpaulin venter (0.35-0.65 hrs, n=4), tarp remover (1.03-1.37 hrs, n=4).

Exposure monitoring equipment: The exposure was measured by collecting air samples from the workers' breathing zone using charcoal sampling tubes (400/200 mg charcoal) connected to a personal air sampling pump. The flow rate was approximately 20 mL/min.

Recovery: The average recovery was 69%.

Exposures of tarp venters (must wear a SCBA) and tarp removers are included in this exposure assessment document because the aeration method was done in compliance with the permit conditions. Air concentrations of MB were adjusted using the average recovery of 69%. However, the air concentrations were readjusted by DPR to reflect a recovery of 50% (Biermann and Barry, 1999; Helliker, 1999). MB concentrations were further adjusted by DPR for an application rate of 6 Lbs MB/1,000 ft³. Results are shown in Tables B.14. Acute and nonacute exposure estimates are shown in Table 11.

Table B.14. Exposure of tarp venters and removers to methyl bromide (MB) during soil fumigations in greenhouses

Work task	Lbs MB /A	Monitoring time (hrs)	MB conc. ppm, v/v*	MB conc.** ppb, v/v	24-hr TWA (ppb)		
					Acute	Subchr.***	Chr.***
Tarp venter 1	447.75	0.4	5.766	0.800	0.03332	n/a	n/a
Tarp venter 2	447.75	0.35	0.229	0.032	0.00132	n/a	n/a
Tarp venter 3	447.75	0.6	0.01	0.001	0.00006	n/a	n/a
Tarp venter 4	447.75	0.65	0.461	0.064	0.00266	n/a	n/a
				Average	0.00934	n/a	n/a
				STDEV	0.01602	n/a	n/a
Tarp remover 1	447.75	1.03	0.038	52.704	2.20	n/a	n/a
Tarp remover 2	447.75	1.03	0.017	23.578	0.98	n/a	n/a
Tarp remover 3	447.75	1.37	0.004	5.548	0.23	n/a	n/a
Tarp remover 4	447.75	1.32	0.007	9.709	0.40	n/a	n/a
				Average	0.95	n/a	n/a
				STDEV	0.89	n/a	n/a

Lbs MB/A is Lbs active ingredient/A; TWA is time-weighted average; STDEV is standard deviation.

* Adjusted by the study director for an average recovery of 69%.

** Adjusted by DPR to reflect an application rate of 450 lbs MB/A, 50% recovery (Biermann and Barry, 1999; Helliker, 1999), and a protection factor of 10,000 for SCBA (NIOSH, 1987) worn by tarp venter.

*** subchr. (subchronic) and chr. (chronic) were used for the calculation of subchronic and chronic exposures shown in Table 11; hours/workday and workdays for subchronic and chronic exposures are shown in Appendix A.

3. MB monitoring: The Grain Product Group (Hosoda, 1992)

Exposure study assessment

Exposure data from this study, except exposure of aerators and forklift drivers, are not included in this exposure assessment document because the application of MB was not conducted according to current permit conditions/regulations. An example:

- a) No information on leak checking of all fittings, connections, and valves of the introduction plumbing.

Details of the study are as follows:

Report No. (status): Not assigned (Final report).

Study Director (company): Ed Hosoda (Cal Ag-Industrial Supply, Inc.).

Compliance with GLP standards: There was no information to determine whether the study was conducted in compliance with GLP standards.

Application information

Formulation: Methyl Bromide 100.

Application rate: 1.5-2 Lbs a.i./1,000 ft³.

Date of application: May to August, 1992.

Locations: West Sacramento, Modesto, and Maxwell.

Use of tarpaulin: 6 mil polyethylene tarpaulin, if used.

Application method:

- a) Fumigation applicators: MB was introduced from a cylinder into sea containers through ¼" polyethylene tubing. The application rate was 2 Lbs MB/1,000 ft³.
- b) Worker at initiation of aeration of sea containers/truck trailers: The workers opened both doors of the container and placed an insect screen to exclude reentry of flying insects. Eighteen-inch, 10,000 cfm "Patton" fans were left running for the entire aeration period of 24 hours.
- c) Forklift drivers emptying sea containers/truck trailers: Each container had been previously aerated for approximately 24 hours, and had no detectable amount of MB when using a Draeger MB 5/b tube. A forklift operator took about 15 minutes to unload each container contents and place produce inside the warehouse.
- d) Workers at initiation of aeration of tarpaulin fumigation: A tarp-covered stack of 1,000 ft³ of blackeye beans was fumigated with 1.5 Lbs MB. The worker removed bags of beans from the outside edge of the tarps, then lifted the edges of the tarps and removed them from the entire stack.
- e) Forklift drivers emptying noncertified fumigation chambers: Two noncertified chambers with 2,500 ft³ capacities were used in this study. Each chamber held a variety of rice products, with varying types of packaging. These chambers were aerated until air concentration of MB was below 5 ppm as measured with Draeger MB 5/b tube. Then the forklift operators were allowed to enter the chamber.

Air monitoring study

Work tasks (monitoring time, replicates): Applicators (19.5-34 min, n=3), workers at initiation of aeration of sea containers/truck trailers (3.5-8.5 min, n=3), workers at initiation of aeration of tarpaulin fumigation (4-7 min, n=3), forklift drivers emptying sea containers/truck trailers (22-41 min, n=3), forklift drivers emptying noncertified fumigation chambers (17-32.5 min, n=3).

Exposure monitoring equipment: The exposure was measured by collecting air samples from the workers' breathing zone using charcoal sampling tubes (400/200 mg charcoal) connected to a personal air sampling pump. The monitoring method followed was that recommended in "Cal/EPA, DPR Methodology for Measuring MB Exposure to Workers" (Ross and Gibbons, 1992). The two charcoal tubes can handle the maximum air volume of 11 liters.

Recovery: The average recovery was 69%.

Exposures of aerators (must wear a SCBA) and forklift drivers are included in this exposure assessment document because the aeration method was done in compliance with the permit conditions. Air concentrations of MB were adjusted using the average recovery of 69%. However, the air concentrations were readjusted by DPR to reflect a recovery of 50% (Biermann and Barry, 1999; Helliker, 1999). MB concentrations were further adjusted by DPR for an application rate of 6 Lbs MB/1,000 ft³. Results are shown in Tables B.15. Acute and nonacute exposure estimates are shown in Table 11.

Table B.15. Exposure of workers to methyl bromide (MB) during and after fumigation of grain products.

Work task	Lbs MB/ 1,000 ft3	Monitoring time (min)	MB conc.* ppm, v/v	MB conc.** ppm, v/v	24-hr TWA (ppb)		
					Acute	Subchr.***	Chr.***
Workers at initiation of aeration of sea containers/truck trailers							
Aerator 1	2	6	1.303	0.0005	0.13	0.15	0.11
Aerator 2	2	3.5	8.028	0.0033	0.83	0.90	0.69
Aerator 3	2	8.5	8.172	0.0034	0.85	0.92	0.70
				Average	0.60	0.65	0.50
				STDEV	0.41	0.44	0.34
Workers at initiation of aeration of tarpaulin fumigation							
Aerator 1	1.5	4	ND	0.00001	0.001	0.001	0.001
Aerator 2	1.5	7	0.526	0.00029	0.073	0.079	0.060
Aerator 3	1.5	7	ND	0.00001	0.001	0.001	0.001
				Average	0.025	0.027	0.021
				STDEV	0.041	0.045	0.034
Forklift drivers emptying sea containers/truck trailers							
Driver 1	2	22	ND	0.04	2	1	1
Driver 2	2	41	0.25	1.04	43	22	22
Driver 3	2	25	0.01	0.04	2	1	1
				Average	16	8	8
				STDEV	24	12	12
Forklift drivers emptying non-certifying fumigation chambers							
Driver 1	2	17	0.041	0.17	7	4	4
Driver 2	2	30	0.044	0.18	8	4	4
Driver 3	2	32.5	0.025	0.10	4	2	2
				Average	6	3	3
				STDEV	2	1	1

Lbs MB/1,000 ft3 is Lbs active ingredient/1,000 ft3; TWA is time-weighted average; STDEV is standard deviation.

* Adjusted by the study director for an average recovery of 69%.

** Adjusted by DPR to reflect an application rate of 6 lbs MB/1,000 ft3, 50% recovery (Biermann and Barry, 1999; Helliker, 1999), and a protection factors of 10,000 for SCBA (NIOSH, 1987) worn by aerators.

One-half of MDL (0.01 ppm) was used for nondetects.

*** subchr. (subchronic) and chr. (chronic) were used for the calculation of subchronic and chronic exposures shown in Table 11; hours/workday and workdays for subchronic and chronic exposures are shown in Appendix A.

4. Determination of MB exposure during dried fruit and tree nut fumigation practice (Radian Corporation, 1992)

Exposure study assessment

Exposure data from this study, except fumigation of chambers (raisins), are not included in this exposure assessment document, because of the following reasons:

Sea van. The application of MB was not conducted according to current permit conditions/regulations. Examples:

- No information on leak checking of all fittings, connections, and valves of the introduction plumbing.
- Buffer zone was not in place.

Chamber (dried prunes). The application of MB was not conducted according to current permit conditions/regulations. Examples:

- a) No information on leak checking of all fittings, connections, and valves of the introduction plumbing.
- b) Leakage of chamber.
- c) Buffer zone was not in place.

Big chamber fumigation (raisins). The application of MB was not conducted according to current permit conditions/regulations. Examples:

- a) No information on leak checking of all fittings, connections, and valves of the introduction plumbing.
- b) No stack for aeration.
- c) Buffer zone was not in place.

Chamber (raisins): The exposure data are included in this exposure assessment document because of low leakage of the chamber. Data are shown in Table B.16.

Fumigation of two noncertified chambers (walnut, shelled and in-shell). The application of MB was not conducted according to current permit conditions/regulations. Examples:

- a) No criteria for integrity of chambers.
- b) No information on leak checking of all fittings, connections, and valves of the introduction plumbing.
- c) No minimum aeration time.
- d) Buffer zone was not in place at that time.
- e) No cap of total MB can be used.
- f) Fumigation where people were present.

Sea van aeration (dried unpackaged prunes). The reason for deletion is: Data represent area sampling only.

Details of the study for chamber (raisins) are as follows:

Report No. (status): RCN 256-254-04-01 (final report)

Study Director (company): Radian Corporation

Compliance with GLP standards: The study was not conducted in compliance with GLP standards.

Application information

Formulation: Not reported.

Application rate: 0.8-3.0 Lbs a.i./1,000 ft³.

Date of application: August to October, 1992.

Area treated: Sea/land containers, chambers.

Use of tarpaulin: No.

Application method:

Chamber (contained raisins): Volume of two chambers were 45,000 and 55,000 ft³.

Application rate = 1 lb MB/1,000 ft³. Hot MB was injected into the chambers from an outside source. The fumigation time was 24 hours. The chambers were aerated for 24

hours after the completion of fumigation. The fumigated products were removed by forklift to the production line for processing.

Air monitoring study

Chamber (raisins): Fumigators, aerators, chamber worker, stem pickers, forklift driver, hopper operator, and areas. Sampling times ranged from 5 to 536 minutes. During the fumigation period, area samples were located at both sides of the chamber and attached directly to the cage. Leak check samples were collected at locations approximately 1 foot from the edge of the door. There was no information with respect to the time of collection and the distance of samples from the MB source for aeration and clearing samples.

Exposure monitoring equipment: The exposure was measured by collecting air samples from the workers' breathing zone (20 cm radius circle from the worker's nose and mouth) and work areas using charcoal sampling tubes (400/200 mg charcoal) connected to a personal air sampling pump.

Analysis: The contents of the sampling tube was emptied into a glass headspace vial. Benzyl alcohol was added and the vial was thermostated at 110 °C. The headspace gas was sampled and analyzed by a gas chromatograph equipped with an electron capture detector. A recovery study was not conducted.

Table B.16. Exposure of workers to methyl bromide (MB) during and after fumigation of dried fruit and tree nut products.

Work task	Lbs MB /1,000 ft3	Monitoring time (min)	MB conc.* ppm, v/v	MB conc.** ppm, v/v	24-hr TWA (ppb)		
					Acute	Subchr.***	Chr.***
Chamber (raisins):							
Fumigator 1	1	41	0.57	1.71	107	107	71
Fumigator 2	1	40	0.1	0.30	19	19	13
				Average	63	63	42
Aerator 1	1	3	0.34	1.02	64	64	43
Aerator 2	1	3	0.16	0.48	30	30	20
				Average	47	47	31
Clear chamber 1	1	9	7.5	22.50	1,406	1,406	938
Clear chamber 2	1	10	7.8	23.40	1,463	1,463	975
				Average	1,434	1,434	956
Stem picker 1	1	488	0.026	0.08	26	26	26
Stem picker 2	1	486	0.03	0.09	30	30	30
				Average	28	28	28
Forklift driver	1	536	0.02	0.06	3	3	1.0
Hopper operator	1	490	0.019	0.06	19	19	19
Area sampling							
Fumigation chambers	1	33	0.47	1.41	88	88	59
Fumigation cage	1	35	0.29	0.87	54	54	36
Leak check-chamber 4	1	30	0.094	0.28	6	n/a	n/a
Leak check-chamber 5	1	29	0.024	0.07	2	n/a	n/a
				Average	4	n/a	n/a
Aeration-chamber 4	1	8	0.99	2.97	186	186	124
Aeration-chamber 5	1	9	0.25	0.75	47	47	31
				Average	116	116	78
Clearing-chamber 4	1	20	0.14	0.42	26	26	18
Clearing-chamber 5	1	19	0.35	1.05	66	66	44
				Average	46	46	31
Hopper area	1	498	0.002	0.01	2	2	2
Hopper area, duplicate	1	498	0.013	0.04	13	13	13
				Average	8	8	8
Stem picker	1	479	0.029	0.09	29	29	29
Stem picker, duplicate	1	479	0.03	0.09	30	30	30
Stem picker	1	486	0.024	0.07	24	24	24
Stem picker	1	475	0.024	0.07	24	24	24
				Average	27	27	27
				STDEV	3	3	3

Lbs MB/1,000 ft3 is Lbs active ingredient/1,000 ft3; TWA is time-weighted average; STDEV is standard deviation.

*There was no indication in the report if air concentrations were adjusted for a recovery.

**Adjusted by DPR based on rates shown in Appendix A and 50% recovery (Biermann and Barry, 1999; Helliker, 1999).

***Subchr. (subchronic) and chr. (chronic) were used for the calculation of subchronic and chronic exposures shown in Table 11; hours/workday and workdays for subchronic and chronic exposures are shown in Appendix A.

5. MB: Measurement of exposure to the fumigators, forklift drivers, cherry sorters, and other workers (Stegmiller and Lee, 1992)

Exposure study assessment

Exposure data from this study are not included in this exposure assessment document because the application of MB was not conducted according to current permit conditions/regulations.

Examples:

- a) Did not purge lines between cylinders.
- b) Control room storage.
- c) Leakage of chamber.
- d) Vent to control room.
- e) Aeration time was about 3 hours (PCs require a minimum aeration time of 4 hours by active aeration).

6. Worker exposure and on-site air monitoring studies at a walnut processing facility (Air Toxics LTD, 1995).

Exposure study assessment

Some MB air concentrations from this report are not included in this exposure assessment document because the application of MB was not conducted according to current permit conditions/regulations. Examples:

- a) Worker exposure studies. The 1993 studies were conducted before DPR issued permit conditions. The 1994 study is used, except data obtained from a study at Dock 5 (leakage of MB to occupied area. The chamber was inside another building, and there was no retention test).
- b) Area sampling. Not for worker exposure assessment. Retain only exposure of sorters.
- c) On-site ambient air monitoring. Not for worker exposure assessment.
- d) Compliance monitoring. This exposure assessment document includes exposure of workers in processing areas. The study was conducted after DPR issued the permit conditions.

Details of the study are as follows:

Report No. (status): Not assigned (Final report).

Study Directors (company): Eric D. Winegar, David B. Curtis, Marie J. Yates (Air Toxics Limited).

Compliance with GLP standards: The study was not conducted in compliance with GLP standards.

Application information

Formulation: Not mentioned.

Application rate: Not mentioned.

Date of studies: 1993 (October 27 and 28; December 20 and 21), and 1994 (March 17 and 18; October 11 and 12).

Location: A walnut processing facility in Stockton.

Application method: The report indicated that methyl bromide was injected into Butler- or Polygon-type chambers. At the end of the fumigation period, chambers were aerated. The Butler chambers had a stack of sorts where the emission point was actually below the apex of the chamber. The Butler chambers were vented by a large fan system at the base of the chambers. The Polygon had no stack, only the openings at the top of the conical rooftop. These chambers were vented by a portable fan system that was inserted into an opening at the base of the chamber.

Air monitoring study

Worker exposure and area monitoring: Exposure of workers performing duties in different work areas and area air concentrations are shown in Table B.17.

Exposure monitoring equipment: For worker exposure monitoring studies - Two or three tubes of petroleum charcoal sorbent (2 of 200 mg, or 1 of 200 mg and 2 of 100 mg) and personal air sampling pumps were used. The flow rate was 30-40 mL/min. For area and on-site ambient air monitoring studies, identical sampling and analytical methods as that in the worker exposure monitoring studies were used. In addition, a few samples were collected into stainless steel canisters and analyzed using the U.S. EPA Compendium method TO-14 (cryofocus GC/MS), which afforded a lower detection limits for those samples. The distance for area and on-site monitoring studies with respect to the source of MB could not be determined from the maps, which were included in the submitted report. The fumigation of walnuts during the peak of the season was continuous. The source of MB could be from the fumigation during the study or off-gassing from previously fumigated walnuts.

Air concentrations of MB from worker exposure and area monitoring studies were calculated and reported as the 24-hour TWA; monitoring times for replicates were not mentioned in the report. On-site ambient air concentrations of MB were reported as ppb; collection times for day- and night-monitoring periods were generally long.

Recovery: Recoveries ranged from 74 to 125%. There was no information to indicate that the exposures were adjusted for the recovery. However, the air concentrations were adjusted by DPR to reflect a recovery of 50% (Biermann and Barry, 1999; Helliker, 1999).

Compliance monitoring study conducted by WH&S

On October 19, 1995, staff of the Worker Health and Safety Branch, DPR, conducted a full-shift monitoring study to determine the air concentration of MB at the four selected work stations at the Diamond Walnut facilities in Stockton (Gibbons, 1995). At each work station, three locations were chosen for the monitoring equipment. All samples were obtained as area samples and no personal samples were obtained. At all but one work station, the samplers were placed to sample air believed to be representative MB concentrations to which workers were being exposed. A representative of Air Toxics Limited also collected air samples from the same work stations. Results of this study were included in Table B.17 for comparison with those obtained from a study previously performed by Air Toxics Limited.

Table B.17. Methyl bromide (MB) air concentrations obtained from worker exposure studies, and area and on-site air monitoring studies at a walnut processing plant in Stockton.

	Work area	24-hour TWA (ppb)			
		10/1994*	Acute**	Subchr.**	Chr.**
a) Worker exposure studies	Bulk packaging	22	44		
		12	24		
		Average	34	34	n/a
	Cleaning plant	57	114		
		175	350		
		0.5	1		
		167	334		
		202	404		
		17	34		
		158	316		
		85	170		
		31	62		
		174	348		
		10	20		
		170	340		
		Average	208	208	n/a
		STDEV	155	155	n/a
	Fumigatorium	53	106		
		52	104		
		25	50		
		Average	87	63	39
		STDEV	32	23	14
	Packaging	22	44		
	Vacuum chamber	46	92		
		233	466		
		79	158		
		Average	239	239	n/a
		STDEV	200	200	n/a
	Sorting	10	20		
		27	54		
		23	46		
		7	14		
		12	24		
		16	32		
		Average	32	32	n/a
	Special cracking	STDEV	16	16	n/a
		17	34		
		16	32		
		17	34		
		8	16		
	Average ('93- Average		29	29	n/a
	STDEV ('93- STDEV		9	9	n/a

TWA is time-weighted average; STDEV is standard deviation.

Table B.17 (cont.). Methyl bromide (MB) air concentrations obtained from worker exposure studies, and area and on-site air monitoring studies at a walnut processing plant in Stockton.

Work area	24-hour TWA (ppb)			
	10/1994*	Acute**	Subchr.**	Chr.**
b) Area monitoring study				
Sorting line	40	80		
	43	86		
Average		83	n/a	n/a
c) Compliance monitoring (Gibbons, 1995) (10/19/95).				
Sorting line in cleaning plant (12-hr shift)				
Nut exit - sorting line #1	287	287		
Nut exit - sorting line #2	324	324		
Nut entrance manifold, line #2	343	343		
Average		318	318	n/a
STDEV		28	28	n/a
Cello packaging of in-shell walnuts in main building (9-hr shift)				
Packing machine #11 - power box	485	364		
Packing machine #9 - power box	435	326		
Column by boxing person near #9	500	375		
Average		355	355	n/a
STDEV		26	26	n/a
Bulk packaging of in-shell walnuts in main building (11-hr shift)				
Column by stitching station	264	242		
Control panel - bag filling	267	245		
On stitching machine	void	-		
Average		243	n/a	n/a

TWA is time-weighted average; STDEV is standard deviation.

* as shown in the submitted report. It was assumed that air concentrations were adjusted using the mid-point recovery (99.5%) of a recovery range of 74-125%.

** The calculation procedure for daily nonacute exposures are as follows:

Daily subchronic MB conc. = (Daily acute MB conc. x daily subchronic exposure time (hrs)/daily acute exposure time (hours). The same method was used for the calculation of daily chronic exposures.

Acute, subchronic and chronic exposures were adjusted for 50% recovery.

7. Space-type fumigation: Potential worker exposure to MB at a brewery facility (Gibbons, 1994).

Exposure study assessment

DPR conducted the monitoring study designed to gather data on potential worker exposure associated with the space-type fumigation at a brewery facility and during the aeration on the following day. Results are shown in Table B.18. The air concentrations shown are potential exposure and not actual exposure. Acute and nonacute exposure estimates are shown in Table 11.

Details of the study are as follows:

Application information

Formulation: Not mentioned

Application rate: Not mentioned

Date of application: November 26, 1992

Location (area treated): Fairfield (area was not known)

Use of tarpaulin: No

Application method: During the application of fumigation, two applicators wearing Self-Contained Breathing Apparatus (SCBA) made repeated entries into the grain storage and processing areas to open pre-placed small MB canisters and large cylinders. The canisters were used to treat the inside of numerous enclosed pipes and other equipment, which were used for transferring the grain. The large cylinders were used to treat the enclosed air spaces surrounding the equipment. After the fumigation was done, the fumigated area was left undisturbed for 24 hours. During the aeration phase, two workers wearing SCBA made two entries into the space to initiate the aeration. Work tasks during application and aeration are listed in Table B.18.

Air monitoring study

Work tasks (monitoring time, replicates): Applicators (5-36 min, n=4), aerators (6-24 min, n=4).

Exposure monitoring equipment: Not reported

Recovery: Not reported

Table B.18. Monitoring of methyl bromide during space fumigation and aeration at a brewery facility.*

Activity	Monit. time (minutes)	MB conc. (ppm)	Protection factor-PF**	Estimated exposure (ppb)	Estimated exposure, ppb*** (24-hr TWA)
a) Applicator (one applicator, 4 samples (s))					
Appl. 1, s 1- entry to open canisters	14	298	10,000	29.8	
Appl. 1, s 2 - reentry to open canisters	36	3624	10,000	362.4	28.9
Appl. 1, s 3 - reentry to open canisters	11	3871	10,000	387.1	
Appl. 1, s 4 - reentry to open large cylinders	5	6117	10,000	611.7	
Area sample (door to buffer zone)	1530	635	10,000	63.5	42
b) Aerator (two aerators, 4 samples)					
Aerator 1, s 1	24	7016	10,000	701.6	24
Aerator 1, s 2	20	169	10,000	16.9	
Aerator 2, s 1	19	9546	10,000	954.6	25
Aerator 2, s 2	6	11.4	10,000	1.14	
				Average	25
Area sample (left of entrance door)****	70	0.26	n/a	260	173
Area sample (on applicator's truck)****	55	0.15	n/a	150	100

TWA is time-weighted average; n/a is not applicable.

* Workers wore a SCBA during the application and aeration processes.

** A protection factor (PF) (NIOSH, 1987) was used to derive estimated exposure.

*** Calculated based on serial sampling for an applicator and two aerators. It was assumed that the indicated monitoring times were similar to actual exposure times. Exposures were adjusted by DPR for 50% recovery (Biermann and Barry, 1999; Helliker, 1999).

**** Assumed workers may work in areas where samples were collected. Typically, these workers do not use a SCBA.

8. Grouping of MB acute exposure estimates of handlers during soil fumigation.

There are several worker exposure studies during soil fumigation as shown in Tables B.1 to B.13. Some of these studies have a limited number of replicates that cannot be used to generalize the magnitude of worker exposure. Grouping of these air concentrations is an exercise to evaluate the distribution of these data if they are normally or lognormally distributed. Thereafter, the range, mean and 95th percentile are calculated for the grouped data. Mitigation measures may not be developed based on these data because the measures are based on specific fumigation methods.

Acute MB air concentrations calculated as the 24-hour TWA are grouped as follows:

- 8.a) Air concentrations obtained from nonbedded and bedded fumigation
- 8.b) Air concentrations obtained from nonbedded soil fumigation
- 8.c) Air concentrations obtained from bedded soil fumigation
- 8.d) Air concentrations obtained from commodity, greenhouse, and space-type fumigations

a) Air concentrations obtained from nonbedded and bedded fumigation

The following air concentrations were used for this grouping:

- 1). Shallow shank-tarped soil injection fumigation (Table B.1). Applicators: Noble plow shanks
- 2). Shallow shank-tarped soil injection fumigation (Table B.2). Co-pilots: Noble plow shanks
- 3). Shallow shank-tarped soil injection fumigation (Table B.3). Shovelmen: Noble plow shanks (by growers).
- 4). Deep shank injection fumigation (Table B.6). Applicators, co-pilots, cultipackers.
- 5). Deep shank injection fumigation (improved) (Table B.6). Applicators, cultipackers.
- 6). Deep shank injection fumigation (Table B.7). Applicators, disc drivers, supervisor, cultipacker tractor drivers.
- 7). Deep shank injection fumigation (Table B.8). Applicator, cultipacker tractor driver.
- 8). Shallow shank-tarped bed fumigation (Table B.9). Applicators, co-pilots.
- 9). Shallow shank-tarped bed fumigation (Table B.10). Applicators, co-pilots, tractor drivers, tape layers.
- 10). Shallow shank, tarped-bed fumigation (Table B.11). Applicators, co-pilots, shovelmen.

Results:

- a) The tests of normality and lognormality indicated that both normality and lognormality are rejected. That is neither one fits.
- b) The range of the MB concentrations (n = 57): 1-518 ppb
- c) The arithmetic mean \pm STDEV = 123 ± 120 ppb
- d) 95th percentile = Arithmetic mean + 1.671 (STDEV) = 324 ppb

b) Air concentrations obtained from nonbedded soil fumigation

- 1). Shallow shank-tarped soil injection fumigation (Table B.1). Applicators: Noble plow shanks
- 2). Shallow shank-tarped soil injection fumigation (Table B.2). Co-pilots: Noble plow shanks

- 3). Shallow shank-tarped soil injection fumigation (Table B.3). Shovelmen: Noble plow shanks (by growers).
- 4). Deep shank injection fumigation (Table B.6). Applicators, co-pilots, cultipackers.
- 5). Deep shank injection fumigation (improved) (Table B.6). Applicators, cultipackers.
- 6). Deep shank injection fumigation (Table B.7). Applicators, disc drivers, supervisor, cultipacker tractor drivers.
- 7). Deep shank injection fumigation (Table B.8). Applicator, cultipacker tractor driver.

Results:

- a) The tests of normality and lognormality indicated that both normality and lognormality are rejected. That is neither one fits.
- b) The range of the MB concentrations (n = 40): 3-518 ppb
- c) The arithmetic mean \pm STDEV = 136 ± 131 ppb
- d) 95th percentile = Arithmetic mean + 1.684 (STDEV) = 356 ppb

c) Air concentrations obtained from bedded soil fumigation

- 1). Shallow shank-tarped bed fumigation (Table B.9). Applicators, co-pilots.
- 2). Shallow shank-tarped bed fumigation (Table B.10). Applicators, co-pilots, tractor drivers, tape layers.
- 3). Shallow shank, tarped-bed fumigation (Table B.11). Applicators, co-pilots, shovelmen.

Results:

- a) The tests of normality and lognormality indicated that both normality and lognormality are rejected. That is neither one fits.
- b) The range of the MB concentrations (n = 57): 1-334 ppb
- c) The arithmetic mean \pm STDEV = 93 ± 87 ppb
- d) 95th percentile = Arithmetic mean + 1.740 (STDEV) = 245 ppb

d) Air concentrations obtained from commodity, greenhouse and space-type fumigations.

- 1) Commodity: handlers.
Exposure during dried fruit and tree nut fumigation practice (Table B.14). Fumigators, aerators.
Exposure during fumigation of grain products - sea container/truck trailer, noncertified chambers (Table B.15). Aerators.
Worker exposure and on-site air monitoring studies at a walnut processing facility (Table B.17). Fumigators.
Results:
 - a) The range of the MB concentrations (n = 15): 0.001-186 ppb.
 - b) The arithmetic mean \pm STDEV = 47.7 ± 56.2 ppb.
 - c) 95th percentile = Mean + 1.761 (STDEV) = 146 ppb.
- 2) Commodity: other workers.
Exposure during dried fruit and tree nut fumigation practice (Table B.14). Stem pickers and other area workers.

Worker exposure and on-site air monitoring studies at a walnut processing facility (Table B.17). Sorters and other area workers.

Exposure during fumigation of grain products - sea container/truck trailer, noncertified chamber (Table B.15). Drivers.

Results:

- a) The range of the MB concentrations (n = 52): 1-466 ppb.
- b) The arithmetic mean \pm STDEV = 83 ± 119 ppb.
- c) 95th percentile = Mean + 1.678 (STDEV) = 283 ppb.

3) Greenhouse:

Exposure of workers to MB during soil fumigation in greenhouse (Table B.14). Tarp venters.

Results:

- a) The range of the MB concentrations (n = 4): 0.0001-0.03 ppb.
- b) The arithmetic mean \pm STDEV = 0.009 ± 0.016 ppb.
- c) 95th percentile = Mean + 2.353 (STDEV) = 0.047 ppb.

4) Greenhouse:

Exposure of workers to MB during soil fumigation in greenhouse (Table B.14). Tarp removers.

Results:

- a) The range of the MB concentrations (n = 4): 0.4-2.2 ppb.
- b) The arithmetic mean \pm STDEV = 1.0 ± 0.9 ppb.
- c) 95th percentile = Mean + 2.353 (STDEV) = 3.1 ppb.

5) Brewery facility: Handlers.

Exposure replicates are not sufficient for grouping purposes.

Table B.19. Grouping of acute methyl bromide (MB) exposure estimates for workers during fumigations of soil, commodity and brewery facility^a.

Types of fumigation	MB concentration (ppb)			
	Replicate	Mean \pm STDEV	Range	95 th percentile
Soil: Nonbedded & Bedded ^b	57	123 ± 120	1 - 518	324
Soil: Nonbedded ^b	40	136 ± 131	3 - 515	356
Soil: Bedded ^b	17	93 ± 87	1 - 334	245
Commodity: Handlers	15	48 ± 56	0.001 - 186	146
Commodity: Other workers	52	83 ± 119	1 - 404	283
Greenhouse: Tarp venters	4	0.01 - 0.02	0.0001 – 0.03	0.05
Greenhouse: Tarp removers	4	1.0 ± 0.9	0.4 – 2.2	3.1
Brewery facility ^c	Exposure replicates are not sufficient for grouping purposes			

STDEV is standard deviation.

^a exposure estimates were grouped according to types of fumigations.

^b exposure of handlers.

^c was not grouped because there are only 1 to 2 replicates for each exposure scenario.

Appendix C

Residential Exposure Studies

DowElanco submitted a study conducted by the University of Florida in support of sulfuryl fluoride registration (Bloomcamp *et al.*, 1991). The same report also contained data on MB indoor air concentrations after subsequent aeration of 10 fumigated homes. These homes were fumigated with MB at a rate of 16 g/m³ and thereafter aerated to 5 ppm according to U. S. EPA-approved procedures. However, the air concentration substantially increased (19.2 ± 10.9 ppm) after the doors and windows were closed for two hours. Homes were aerated and closed again. During the second 2-hour closure, MB concentration increased above 5 ppm in four homes (18.6 ± 5.4 ppm). This study was conducted to better characterize the fate of indoor air concentrations of the fumigant following aeration.

A second submitted report related to indoor fumigation was conducted because of a request to modify a method to release MB into the fumigated structure (Soil Chemicals Corp., 1980). Results from three tests indicated that equilibrium of the fumigant can be best achieved by shooting gas into the attic. Data indicated that the gas initially tends to move in a downward direction. When the gas was shot into the living space, the attic was the last area to reach equilibrium. This report did not provide appropriate indoor air concentration to estimate exposure of residents.

1. Residential exposure studies.

- a) Residents/bystanders (outdoor and indoor air concentrations of MB near fumigated single-family houses (Gibbons *et al.*, 1996a).

Exposure study assessment

Exposure data from this study are not included in this exposure assessment document because the application of MB was not conducted according to current regulations (CCR, 2000). Example:

- a) The distance of air sampling stations is no longer valid based on current regulations.

- b) Residents/bystanders (downwind outdoor and indoor air concentrations of MB during aeration of fumigated single-family houses (Gibbons *et al.*, 1996b).

Exposure study assessment

Exposure data from this study are not included in this exposure assessment document because the application of MB was not conducted according to current regulations (CCR, 2000). An example:

- a) The aeration method used in the study is no longer valid based upon the new regulations for MB structural fumigation.

2. Exposure of residents to methyl bromide during reentry into fumigated houses (Gibbons, 1992).

Residents can be exposed to airborne MB after reentry into their fumigated houses following aeration. MB product labels require a minimum active aeration period (e.g., using fans) of 72

hours and the level of MB must be less than 3 ppm measured in the ground receptacle of an interior electrical outlet or other enclosed space within the wall or an interior and a perimeter wall. The aeration period must last for a minimum of 7 days if nonmechanical or natural ventilation is used. This exposure monitoring study of fumigated houses used only 24-hour aeration period.

Exposure study assessment

Exposure data from this study are not included in this exposure assessment document because the application of MB was not conducted according to current regulations (CCR, 2000) and product labels. An example:

- a) The active aeration time was only 24 hours. Current product labels require a 72-hour active aeration period.

3. Exposure of residents to methyl bromide from living near commodity fumigation facility.

During commodity fumigation and aeration periods, leaks and off gassing with subsequent dilution can aid in dispersion of MB vapor into the surrounding areas. Residents who live at or beyond an established buffer zone may be exposed to airborne MB. The following assumptions were used to estimate exposure of residents to airborne residues of MB from commodity fumigation.

- a) Residents live at an established buffer zone. We did not attempt to estimate exposure of residents beyond the buffer zone.
- b) The wind blows continually from the fumigation areas toward residential areas in the same direction. This represents an extreme exposure scenario.
- c) Residents are assumed to be exposed to MB at the target level of 210 ppb calculated as the 24-hour TWA (Nelson, 1992).
- d) The housing structure does not provide protection from inhalation exposure to MB.
- e) There are intermittent fumigations of chambers in those areas contributing to exposure days of more than approximately 33% of days in a 7-day, 90-day or 365-day period. These exposures constitute subacute, subchronic and chronic exposures, respectively (Sanders, 1998). Likewise, if exposure days are less than the specified exposure frequency, there will be no subacute, subchronic and chronic exposures. Also, more frequent MB fumigations in those areas will result in maintaining the target exposure level at or close to the target level of 210 ppb.

The low and high ranges of exposure days for workers during commodity fumigations were adopted from Haskell (1998a, 1998b) for use in the estimation of residential exposure. Subacute, subchronic and chronic exposures are shown in Table C.1.

Table C.1. Exposure of residents to airborne methyl bromide during commodity fumigation^a.

Range of exposure	Subacute exposure		Subchronic exposure		Chronic exposure	
	/7days	MB (ppb)	/90 days	MB (ppb)	/365 days	MB (ppb)
Low ^b	3	90	30	70	150	86
High ^b	6	180	75	175	185	106

^a assumed residents are exposed to the target level of 210 ppb (24-hour TWA).

^b exposure days were based on Haskell, 1998a and 1998b. The low and high exposures represent the low and high exposure days for subacute, subchronic and chronic exposures.

4. Exposure of residents to MB from living at the buffer zone distance.

Methyl bromide air concentrations at the buffer zone distance are needed for the determination of exposure of residents and workers, who live or work at the buffer zone distance. The air concentrations must reflect different field sizes, recommended application methods, and the maximum allowed application rates because the emission rates are varied based on these conditions. Hence, MB air concentrations based upon these conditions are not the same. Currently, there is no exposure study to measure MB concentrations at the buffer zones to reflect these conditions. MB concentrations at the buffer zones were generated by simulation technique.

Johnson (2001) provided detailed explanation as to how MB air concentrations at the buffer zone distance were estimated. The simulation consisted of daily (24-hour) simulations using the Industrial Source Complex-Short Term model 3 (ISCST3) version 99155. The simulations were designed to cover the proposed buffer zones for 1 to 40-acre fields with emission rates ranging from 30 to 225 lbs/acre-day. For the actual simulation, the emission rate of 225 lbs/acre-day was used. To obtain simulation results at lower emission rates, a post-processing computer program scaled the concentrations down proportionally, assuming emission and concentrations are proportional. The post-processing program with the construction of transects enable the estimation of proposed (daily) buffer zones (Johnson, 2001). The maximum MB concentrations at the buffer zone distances were determined for different emission rates and field sizes. The maximum MB concentrations ($\mu\text{g}/\text{m}^3$) determined from the program for key percentiles are shown in the nonshaded (nonboxed) areas of Table C.2. MB air concentrations in the shaded (boxed) areas were interpolated to reflect other emission rates (100, 150, 160, 200 and 320 lbs/acre-day).

The column headings indicate emission rates, ranging from 30 to 320 lbs/acre-day. Methyl bromide concentrations ($\mu\text{g}/\text{m}^3$) are shown in columns under emission rates. These concentrations are grouped according to the field sizes (1, 10, 20, 30, and 40 acres) and reflect different cumulative probability (0.1 to 0.999). The regulatory MB concentration level for acute exposure is 210 ppb, which is equivalent to $815 \mu\text{g}/\text{m}^3$. The highest air concentrations at the 95th percentile, which represent a range of emission rates in Table C.2 for 1, 10, 20, 30, and 40 acres were used to estimate the exposures. The method used to determine the highest MB concentration is given in the subsequent sections.

Table C.2. Interpolated methyl bromide air concentrations (ug/m3, shaded or boxed areas) based on different emission rates and field sizes.*

Emission **		30	80	100	130	150	160	180	200	225	320
Cum. Prob.***		Methyl bromide concentration (ug/m3)									
1 acre	0.1	95	240	238	234	229	227	222	220	217	206
	0.2	109	278	277	275	270	267	262	260	257	246
	0.3	122	310	309	308	302	300	294	292	290	282
	0.4	133	339	339	340	334	332	326	323	320	307
	0.5	144	369	371	373	367	365	359	357	354	343
	0.6	157	401	404	408	404	402	398	394	390	373
	0.7	172	439	445	454	448	446	440	437	433	418
	0.8	189	486	494	507	502	500	495	492	489	476
	0.85	200	515	527	546	540	537	531	529	527	519
	0.9	217	558	572	592	590	590	588	586	584	576
	0.925	228	585	602	628	626	625	623	623	622	620
	0.95	243	625	645	675	676	677	678	677	676	672
	0.96	251	646	669	704	703	702	701	703	705	713
	0.97	263	679	706	746	744	744	742	744	747	758
	0.98	283	734	763	806	807	808	809	810	811	815
	0.99	316	820	860	919	925	928	934	936	938	946
	0.999	449	1166	1226	1317	1351	1367	1401	1419	1442	1529
10 acres	0.1	231	285	271	251	248	247	244	236	226	188
	0.2	271	337	322	299	296	295	292	283	271	227
	0.3	303	381	363	337	335	333	331	320	306	253
	0.4	333	420	402	374	371	369	366	355	341	288
	0.5	361	463	443	413	411	409	407	394	378	317
	0.6	392	508	488	457	455	453	451	436	418	348
	0.7	426	564	543	511	508	506	503	487	466	388
	0.8	469	633	610	576	573	572	569	551	529	445
	0.85	496	678	655	621	619	618	616	598	575	488
	0.9	533	739	717	684	683	682	681	661	635	538
	0.925	557	777	757	726	726	727	727	707	681	584
	0.95	588	835	816	788	790	790	792	769	741	633
	0.96	611	875	852	818	818	819	819	800	777	688
	0.97	642	918	900	874	873	873	872	851	824	723
	0.98	681	1003	984	955	955	954	954	926	890	755
	0.99	760	1129	1120	1107	1104	1102	1099	1073	1041	919
	0.999	1123	1538	1531	1521	1562	1582	1623	1597	1564	1439

Emission **		30	80	100	130	150	160	180	200	225	320
Cum. Prob.***		Methyl bromide concentration (ug/m3)									
20 acres	0.1	286	291	281	267	259	255	247	244	241	228
	0.2	336	347	335	317	309	305	297	294	290	275
	0.3	377	392	379	360	350	346	336	333	329	314
	0.4	416	434	420	399	388	383	372	369	366	353
	0.5	450	480	465	442	431	426	415	410	404	381
	0.6	489	526	511	489	477	472	460	455	449	426
	0.7	529	586	571	548	534	528	514	508	501	474
	0.8	580	659	643	619	604	597	582	576	569	542
	0.85	612	705	689	666	651	644	629	625	619	598
	0.9	657	772	756	733	718	710	695	691	686	667
	0.925	686	813	799	779	766	759	746	740	733	706
	0.95	719	874	863	847	833	825	811	807	802	783
	0.96	746	919	902	877	863	855	841	841	841	841
	0.97	780	964	952	935	920	912	897	894	890	875
	0.98	835	1053	1042	1025	1007	998	980	972	963	927
	0.99	927	1182	1186	1191	1167	1155	1131	1128	1125	1112
	0.999	1338	1629	1635	1644	1656	1662	1674	1679	1685	1708
30 acres	0.1	333	297	281	256	253	252	249	248	247	243
	0.2	389	353	334	306	304	302	300	300	300	300
	0.3	437	400	379	347	344	342	339	340	341	345
	0.4	478	444	420	385	382	381	378	378	379	381
	0.5	519	490	465	428	424	423	419	419	420	422
	0.6	564	539	513	474	471	469	466	466	465	463
	0.7	608	600	572	530	526	524	520	520	519	517
	0.8	664	676	646	600	596	593	589	590	592	598
	0.85	700	723	693	647	645	643	641	641	641	641
	0.9	749	793	761	713	711	710	708	710	713	724
	0.925	781	833	803	758	758	759	759	761	763	771
	0.95	821	895	868	827	827	827	827	830	834	849
	0.96	845	945	909	856	857	858	859	866	875	909
	0.97	886	992	960	913	914	914	915	919	924	943
	0.98	939	1079	1045	994	994	995	995	1001	1008	1035
	0.99	1044	1215	1195	1166	1162	1159	1155	1162	1170	1202
	0.999	1506	1679	1653	1614	1651	1670	1707	1732	1764	1884

Emission **		30	80	100	130	150	160	180	200	225	320
Cum. Prob.***		Methyl bromide concentration (ug/m3)									
40 acres	0.1	367	304	291	271	265	262	256	256	256	256
	0.2	429	363	347	324	318	314	308	309	311	317
	0.3	482	412	394	367	359	356	348	350	353	364
	0.4	530	457	437	407	400	396	389	391	393	401
	0.5	573	505	485	454	445	441	432	433	435	441
	0.6	624	555	534	502	493	489	480	481	482	486
	0.7	672	617	595	562	552	546	536	537	539	545
	0.8	733	694	671	637	625	619	607	611	615	632
	0.85	772	743	721	687	677	672	662	664	667	678
	0.9	825	815	792	757	747	741	731	735	741	762
	0.925	860	856	836	805	796	792	783	787	793	814
	0.95	906	918	901	875	867	863	855	860	866	889
	0.96	933	970	945	908	900	896	888	897	908	950
	0.97	973	1022	1001	970	960	956	946	953	961	993
	0.98	1035	1107	1086	1054	1044	1039	1029	1037	1046	1082
	0.99	1148	1249	1246	1241	1223	1213	1195	1204	1216	1260
	0.999	1658	1724	1721	1716	1734	1744	1762	1798	1842	2011

* Emission (flux) rate (lbs MB/acre-day) = Maximum application rate (lbs/acre) x emission ratio. MB concentrations (ug/m3) (non-shaded columns) were generated using the air dispersion model, ISCST3, by the use of flux and 5-year weather data from the 4 highest MB use counties (Merced, Ventura, Monterey, and Fresno Counties) (Johnson, 2000a). MB concentrations in the shaded columns were linear interpolated from simulated MB concentrations (non-shaded areas).

** Emission rates (lbs MB/acre-day) in non-shaded columns were used in the simulation; those in the shaded columns were derived to represent flux rates for different soil application methods and maximum application rates as described in 3CCR 6450.3(a).

*** cum. prob. is cumulative probability (e.g. cum. prob. of 0.95 is the 95th percentile).

It is necessary to calculate emission rates, which will be used to determine MB air concentrations from data in Table C.2. Emission rates for MB fumigation are calculated using the following equation:

$$\text{Emission rate (lbs MB/acre-day)} = \text{Emission ratio (ER)} \times \text{maximum application rate (lbs/acre)}$$

An emission ratio is a fraction of the total applied MB that volatilizes during the 24 hours showing the highest air concentrations. An emission ratio of 0.30 means 30 percent of the total applied MB volatilizes under that specified conditions. Emission ratios of some different soil injection methods are not the same. The emission ratios shown in Table C.3 for different fumigation methods were those recommended by DPR (2001).

The fumigation methods and the maximum application rates are those listed in the current methyl bromide regulations in California Code of Regulations (CCR, 2001). The estimated emission rates for the recommended fumigation methods and the maximum application rates are shown in Table C.3.

Table C.3. Emission rates for different application methods when using maximum application rates.

Maximum MB application rate, (lbs/acre) (Application method)	Emission ratio	Emission rate (lbs MB/acre-day)
200 (Nontarp/shallow/bed)	0.4	80
400 (Tarp/deep/broadcast)	0.4	160
400 (Nontarp/deep/broadcast)	0.4	160
250 (Tarp/shallow/bed)	0.8	200
225 (Drip system-hot gas)	1.0	225
400 (Tarp/shallow/broadcast)	0.8	320

The 95th percentile MB concentrations ($\mu\text{g}/\text{cm}^2$ and ppb) at the buffer zone distance were determined from Table C.2 based on these emission rates for field sizes of 1, 10, 20, 30 and 40 acres. These MB concentrations, representing acute exposures, are shown in Tables C.4. The buffer distances for different field sizes and emission rates (DPR 2001) are also shown in Table C.4. The 95th percentile MB concentrations should be used in the risk assessment because the exposure at this percentile is generally considered health protective. MB concentrations in Table C.4 are not appropriate for use in the determination of subchronic exposure because exposure days for persons at the buffer zone distance of a particular field will not be lengthy enough to be considered a subchronic exposure. Ambient air concentrations shown in Appendix D (Table D.1) should be considered for a subchronic exposure.

Table C.4. Acute methyl bromide (MB) exposures (95th percentile) of persons at the buffer zone distance following field fumigation.

Field	1 acre					10 acres					20 acres					30 acres					40 acres				
Emission rate*	80	160	200	225	320	80	160	200	225	320	80	160	200	225	320	80	160	200	225	320	80	160	200	225	320
Buffer zone (ft)	110	290	380	420	580	410	1100	1400	1600	2100	610	1600	2000	2300	3100	770	2000	2600	2900	3900	900	2400	3000	3400	4600
MB (ug/m3)	625	677	677	676	672	835	790	769	741	633	874	825	807	802	783	895	827	830	834	849	918	863	860	866	889
MB (ppb)	163	176	176	176	175	217	205	200	193	165	227	215	210	209	204	233	215	216	217	221	239	224	224	225	231

* Notes on emission rates:

1 ppb = 0.26 x ug/m3

The emission rate of 80 lbs MB/acre-day was determined for nontarp/shallow/bed fumigation method.

The emission rate of 160 lbs MB/acre-day was determined for tarp/deep/broadcast fumigation method.

The emission rate of 160 lbs MB/acre-day was determined for nontarp/deep/broadcast fumigation method.

The emission rate of 200 lbs MB/acre-day was determined for tarp/shallow/bed fumigation method.

The emission rate of 225 lbs MB/acre-day was determined for drip system-hot gas fumigation method.

The emission rate of 320 lbs MB/acre-day was determined for tarp/shallow/broadcast fumigation method.

Appendix D

Exposure of Persons to Ambient Methyl Bromide in the High Use Counties

At the request of DPR, ARB conducted MB ambient air monitoring studies in Monterey, Santa Cruz and Kern Counties in 2000. The study periods and sites were selected based upon the historical trends in MB use from 1996 to 1998 (Sanders, 2000). Sanders suggested that monitoring studies should occur over a two-month period during July and August in Kern County, and September and October in Monterey or Santa Cruz County.

1. Ambient MB monitoring study in Monterey and Santa Cruz Counties.

ARB conducted MB ambient air monitoring in Monterey and Santa Cruz Counties from September 11, 2000 through November 3, 2000 (ARB, 2001). This monitoring period coincided with the use of MB prior to planting of a variety of crops. The sampling site selection specifically focused on areas of historical use of MB prior to planting strawberries.

Ambient air samples were collected at four sites in Monterey County and one site in Santa Cruz County. At each location, 24-hour samples were collected four days per week for eight weeks. Additional samples were collected for quality control. Air samples for MB (and 1,3-dichloropropene) were collected using evacuated 6 liter Silicosteel[®] canisters. Each canister sample was analyzed for both compounds. Sampling for MB was also conducted for one week using charcoal tubes. The samplers were placed approximately 5½ feet above the building rooftops for the ambient monitoring. The height of samplers for all sampling sites ranged from 17 to 23 feet above the ground level. The air flow rate for the canisters was 3 standard cubic centimeters per minute (sccpm). MB in canisters was analyzed using gas chromatography equipped with a mass selective detector. MB in charcoal tubes was analyzed using gas chromatography equipped with an electron capture detector.

ARB conducted a field spike recovery study during the sampling period. A small volume (100 mL) of a gas standard, with a certified concentration of MB, was added to an evacuated canister. The field spikes were collected by sampling ambient air into the previously spiked canisters and were collocated with an ambient sample (same location, flow rate and sampling time). The collocated (unspiked) sample result is subtracted from the field spike sample result before calculation of percent recovery of the analysis. A similar field spike recovery study was also conducted for charcoal tubes. A small volume (20 µL) of a solvent standard with a known amount of MB was added to the charcoal cartridges. The average recoveries for MB field spikes were 58% for charcoal tubes and -5% for canisters. The negative recovery for canisters resulted because the ambient air concentration of MB was much higher than the spiked amount. The average MB recoveries for laboratory and trip spikes were 101 and 101%, respectively.

2. Ambient MB monitoring study in Kern County.

ARB conducted an ambient air monitoring study in Kern County from July 19, 2000 through September 1, 2000 (ARB, 2000). This study period coincided with the use of MB prior to planting of a variety of crops. The sampling site selection specifically focused on the use of 1,3-dichloropropene prior to planting carrots. In one case, Cotton Research Station (CRS) was selected for monitoring based on its proximity to the use of MB on roses. The sample collection

method, MB analysis and field spike were similar to those employed in the study in Monterey and Santa Cruz Counties. At each location, 24-hour samples were collected four days per week for seven weeks. Additional samples were collected for quality control. The average field spike recovery of MB using canisters was 102%. A field spike recovery of MB was not performed for charcoal tubes.

3. Calculations of MB air concentrations.

Powell (2001) summarized air concentrations of MB obtained from the studies in Monterey, Santa Cruz and Kern Counties. MB in charcoal tubes for Monterey and Santa Cruz Counties were not used because the identities of some of collected samples were lost (mis-labeled). Only thirteen samples from six sites were analyzed and the results were indicated "nondetectable." The MB air concentrations from the canisters are grouped into 24-hour (daily), 7-day (weekly) and 7 or 8-week concentrations (Table D.1). MB concentrations from the studies were not adjusted for field spike recoveries because the average recovery was approximately 100%. Powell (2001) indicated that before calculating the exposures, one-half the detection limit was substituted for two Kern County samples that were below the detection limit. (No samples in Monterey/Santa Cruz were below the quantitation limit.). The detection limit for methyl bromide was 7.1 ng/m³ (0.00182 ppb). Further, where there were pairs of collocated samples for the same day, the two values were averaged. The 95th percentile values were calculated using the following equations:

24-hour exposure:

$$95^{\text{th}} \text{ \%ile} = \exp\{\text{arithmetic mean of log concentrations} + t_{(.95; n-1)} \times (\text{standard deviation of logs})\}$$

7-day exposure:

$$95^{\text{th}} \text{ \%ile} = \text{arithmetic mean of week means} + t_{(.95; n-1)} \times (\text{standard deviation of week means}).$$

7- or 8-week exposure:

For each monitoring site separately, 7- or 8-week exposure is the mean concentration over the monitoring period. It is calculated as the arithmetic mean of the 8 (7 in Kern County) weekly means calculated as above for 7-day exposure.

It is important to note that these ambient air concentrations were obtained from sampling stations that were not necessarily located at the buffer zone distance like those derived from the model shown in Section 4 of Appendix C (Exposure of residents to MB from living at the buffer zone distance). The daily MB exposure obtained from the model and that from the ambient monitoring studies may be used in risk assessment under different exposure scenarios. Persons (such as residents, school children, and bystanders) would be more likely to be exposed to ambient MB than they would be exposed to MB at the buffer zone distance. Ambient MB from the studies represents a realistic exposure scenario during the peak use period, whereas the latter was obtained from the model, which may not represent a realistic exposure situation.

Table D.1. Methyl bromide concentrations (ppb) based on the Air Resources Board 2000 monitoring studies in Monterey, Santa Cruz and Kern Counties.^a

		Daily		Weekly		7 or 8-week
Site ^b	Monitoring days	Maximum 24-hour	95 th percentile 24-hour	Maximum weekly mean	95 th percentile weekly mean	Mean of weekly means
Monterey and Santa Cruz Counties (8 monitoring weeks, September 11 – November 3, 2000)						
		-----ppb-----				
CHU	31	2.41	2.26	1.61	1.63	0.644
LJE	30	24.0	18.5	10.5	11.1	3.79
OAS	31	1.84	1.21	1.01	0.918	0.387
PMS	31	30.8	30.2	15.5	17.1	7.68
SAL	31	7.91	6.17	3.01	3.14	1.29
SES	31	16.4	12.2	8.30	7.45	2.60
Kern County (7 monitoring weeks, July 19 – September 1, 2000)						
		-----ppb-----				
ARB	25	0.996	0.556	0.507	0.507	0.189
CRS	24	14.2	25.4	4.59	5.54	2.16
MET	26	0.224	0.239	0.145	0.163	0.084
MVS	26	0.487	0.262	0.201	0.195	0.092
SHA	26	3.52	3.98	1.77	2.05	0.792
VSD	26	0.347	0.292	0.175	0.181	0.099

^a Methods and equations used to derive different categories of air concentrations are shown in Appendix D, section 3 - Calculations of MB air concentrations.

^b Names of ambient sampling sites (Monterey and Santa Cruz): Chualar School (CHU), La Jolla Elementary School (LJE), Oak Avenue School (OAS), Pajaro Middle School (PMS), MBUAPCD Ambient Monitoring Station, Salinas (SAL), Salsepuedes Elementary School (SES); (Kern): ARB Ambient Monitoring Station (ARB), Cotton Research Station (CRS), Mettler-Fire Station (MET), Mountain View School (MVS), Shafter-Walker Ambient Monitoring Station (SHA), Vineland School District-Sunset School (VSD).

Appendix E

Adjusted Acute and Nonacute Exposure Estimates of Persons in California to Methyl Bromide

Previously, acute and nonacute (subacute, subchronic, and chronic) MB exposures (Table 11) were calculated for persons during soil, commodity, and structural (brewery facility) fumigations by using work hours obtained from a survey (Appendix A). Current MB regulations for soil fumigation or permit conditions for greenhouse, potting soil, and commodity fumigations specify daily work hours for persons, who may be exposed to MB. Consequently, the exposure estimates were recalculated based upon work hours indicated in the regulations or permit conditions. The recalculation did not include exposures of residents to MB during commodity fumigation, from living at the buffer zone distance, or to ambient MB in the high use counties because the MB concentration used in the calculation was either a default value, determined from a mathematical model or obtained from sampling of ambient air.

In cases where the same study shows exposure for growers and PCOs (Table 11), only the exposure for PCOs is used in Appendix E. Basically, adjusted average acute exposures for growers and PCOs are the same because the current regulations and permit conditions do not separate work hours for growers and PCOs. However, if a study shows exposure for growers only, the exposure is used in Appendix E.

Nonacute exposures are normalized (amortized) by employing adjusted acute exposure estimates and workdays (exposure days) for each of these three groups of exposure. Adjusted exposures are calculated as follows:

Adjusted average acute exposure =
$$\frac{\text{Average acute exposure (Table 11)} \times \text{work hours (allowed)}}{\text{work hours (previously used)}}$$

Adjusted average subchronic exposure =
$$\frac{\text{Adjusted average acute exposure} \times \text{workdays in 90 days}}{90 \text{ days}}$$

Adjusted average chronic exposure =
$$\frac{\text{Adjusted average acute exposure} \times \text{workdays per year}}{365 \text{ days}}$$

The upper bound exposure estimate for the adjusted average acute exposure was also calculated by using the following equation:

Adjusted upper bound acute exposure =
$$(\text{Adjusted average acute exposure} + (1.645 \times \text{Adjusted standard deviation for acute exposure}))$$

Adjusted acute and nonacute exposure, and upper bound acute exposure estimates are shown in Appendix E.

Appendix E
Adjusted Acute and Nonacute Exposure Estimates of Persons in California to Methyl Bromide(a)

Number/ Type of application (Data from Table)	Acute exposure (ppb)(b)					Subacute exp. (ppb)		Subchronic exp. (ppb)		Chronic exp. (ppb)	
	Work hour(c)		Adjusted average(d)		Upper	77-day period		790-day period		7365-day period	
	Avg.	Used	Allowed	Avg.		Days	Adj. Avg.(e)	Days	Adj. avg.(f)	Days	Adj. avg.(g)
a) Shallow shank-tarped soil injection fumigation (Table B.1) Applicators: Noble plow shanks	111	5.8	4	77	188	6	66	40	34	n/a	n/a
a) Shallow shank-tarped soil injection fumigation (Table B.2) Co-pilots: Noble plow shanks	224	5.8	3	116	245	6	99	40	51	n/a	n/a
a) Shallow shank-tarped soil injection fumigation (Table B.3) Shovelmen: Noble plow shanks	147	5.8	3	76	191	3	33	n/a	n/a	n/a	n/a
a) Shallow shank-tarped soil injection fumigation Tarp removers (Table B.4)(h)	835	6	7	974	2118	5	696	55	595	n/a	n/a
b) Nontarp deep shank injection fumigation (Table B.6) Applicators	154	5.8	4	106	281	6	91	40	47	n/a	n/a
Co-pilots	49	5.8	4	34	89	6	29	40	15	n/a	n/a
Cultipacker	99	5.8	4	68	181	6	59	n/a	n/a	n/a	n/a
b) Nontarp deep shank injection fumigation (improved) (Table B.6) Applicator	57	5.8	4	39	104	6	34	40	17	n/a	n/a
Cultipacker	70	5.8	4	48	128	6	41	n/a	n/a	n/a	n/a
c) Nontarp deep shank injection fumigation (Table B.7) Applicator: Basic + a second tractor with a disc	88	5.8	4	61	161	6	52	40	27	n/a	n/a
Disc driver: Basic + a second tractor with a disc	512	5.8	4	353	934	6	303	40	157	n/a	n/a
Applicator: Basic + a cultipacker	94	5.8	4	65	171	6	56	40	29	n/a	n/a
Supervisor: Basic + a cultipacker	67	5.8	4	46	122	6	40	40	21	n/a	n/a
Cultipacker: Basic + a cultipacker	34	5.8	4	23	62	6	20	n/a	n/a	n/a	n/a
d) Nontarp deep shank injection fumigation (Table B.8) Applicator: With 4 forward curved shanks	7	5.8	4	5	13	6	4	40	2	n/a	n/a
Cultipacker: 4 forward curved shanks	7	5.8	4	5	13	6	4	n/a	n/a	n/a	n/a

(a) MB exposure estimates shown in Table 11 were adjusted for work hours allowed by current regulations or permit conditions for acute exposures.

(b) acute exposure is the exposure that occurs daily or within 24 hours; subacute exposure is the exposure that occurs in a seven-day period; subchronic exposure is the exposure where days of exposure is 30 days or longer in a 90-day period; chronic exposure is the exposure where days of exposure is 120 days or longer in a 365-day period.

(c) hour (used): Previously used in the calculation of exposure estimates; hour (allowed): based on the current MB regulations or permit conditions.

(d) adjusted upper bound MB concentrations = (average+(1.645 x STDEV)) x hours allowed/hours used. When there is one or two data points, the STDEV is assumed to be equal to that data point or the average of two data points.

(e) average subacute exposure = average acute exposure x workday per week/7 days.

(f) average subchronic exposure = average acute exposure x workdays in 90 days/90 days.

(g) average chronic exposure = average acute exposure x workdays in 365 days/365 days.

(h) tarp removers removed tarp the same day the tarp was cut. This tarp cutting practice was not in compliance with the current regulations.

(i) MB concentrations in work areas must be monitored and the work hours adjusted accordingly so that the daily exposure will not exceed the target level. The maximum exposure estimate is assumed to be 210 ppb. MB concentration of 210 ppb was used to calculate subacute, subchronic and chronic exposures when estimated MB air concentration is greater than 210 ppb. Otherwise, the average acute exposure was used for the calculation.

Abbreviations: exp. is exposure; PCO is pest control operator; Avg. is average; inj. = injection; n/a = not applicable.

Appendix E (continued 1)
Adjusted Acute and Nonacute Exposure Estimates of Persons in California to Methyl Bromide(a)

Number/ Type of application (Data from Table)	Acute exposure (ppb)(b)					Subacute exp. (ppb)		Subchronic exp. (ppb)		Chronic exp. (ppb)	
	Work hour(c)		Adjusted average(d)		Upper	77-day period		790-day period		7365-day period	
	Avg.	Used	Allowed	Avg.		Days	Adj. Avg.(e)	Days	Adj. avg.(f)	Days	Adj. avg.(g)
e) Shallow shank-tarped bed fumigation (Table B.9)											
Applicator: Conventional+raised platform&inj. 8"	80	5.8	4	55	146	6	47	40	25	n/a	n/a
Co-pilots: Conventional+raised platform&inj. 8"	104	5.8	4	72	190	6	61	40	32	n/a	n/a
Applicators: Conventional+closing shoes	44	5.8	4	30	80	6	26	40	13	n/a	n/a
Co-pilots: Conventional+closing shoes	167	5.8	4	115	305	6	99	40	51	n/a	n/a
f). Shallow shank-tarped bed fumigation (Table B.10)											
Driver: Tractor was equipped for fumigation	28	5.8	4	19	51	6	17	40	9	n/a	n/a
Applicator: Tractor was equipped for fumigation	45	5.8	4	31	82	6	27	40	14	n/a	n/a
Tape layer: Tractor was equipped for fumigation	65	5.8	4	45	119	3	19	n/a	n/a	n/a	n/a
Driver: Tractor was equipped for laying tarp	4	5.8	4	3	7	6	2	40	1	n/a	n/a
Co-pilot: Tractor was equipped for laying tarp	34	5.8	4	23	62	6	20	40	10	n/a	n/a
g). Shallow shank, tarped-bed fumigation (Table B.11)											
Applicator	2	5.8	4	1	4	6	1	40	1	n/a	n/a
Co-pilot	32	5.8	4	22	58	6	19	40	10	n/a	n/a
Shovelman	0.6	5.8	4	0.4	1	3	0.2	n/a	n/a	n/a	n/a
h). Tarp shallow with Noble plow shanks (Table B.12)											
Cutter: From broadcast application	82	6	4	55	202	5	39	30	18	n/a	n/a
Puller: From broadcast application	33	6	7	39	215	5	28	30	13	n/a	n/a
i). Tarp shallow with Noble plow shanks (Table B.13)											
From use of high barrier (HB) tarp											
Cutter	78	6	4	52	138	5	37	30	17	n/a	n/a
Remover: Tractor driver	343	6	7	400	1058	5	286	30	133	n/a	n/a
Remover: Basketman	325	6	7	379	1003	5	271	30	126	n/a	n/a
Remover: End puller	7	6	7	8	22	5	6	30	3	n/a	n/a
2.a. Worker exposure assessment during potting soil fumigation (no usable data)											
2.b. Greenhouse soil fumigation (Table B.14)											
Tarp venters(i)	0.009	1	varied	0.01	210	1	0.001	n/a	n/a	n/a	n/a
Tarp removers(i)	0.95	1	varied	0.95	210	1	0.14	n/a	n/a	n/a	n/a
3. Fumigation of grain products (chambers, sea containers) (T. B.15)											
Initiation of aeration of sea containers/truck trailers											
Aerator(i)	0.6	6	varied	0.6	210	5	0.43	45	0.30	180	0.30
Initiation of aeration of tarpaulin fumigation											
Aerator(i)	0.025	6	varied	0.03	210	5	0.02	45	0.01	180	0.01
Emptying sea containers/truck trailers											
Forklift driver(i)	16	1	varied	16	210	5	11	45	8	180	8
Emptying non-certifying fumigation chambers											
Forklift driver(i)	6	1	varied	6	210	5	4	45	3	180	3

Appendix E (continued 2)
Adjusted Acute and Nonacute Exposure Estimates of Persons in California to Methyl Bromide(a)

Number/ Type of application (Data from Table)	Acute exposure (ppb)(b)					Subacute exp. (ppb)		Subchronic exp. (ppb)		Chronic exp. (ppb)	
		Work hour(c)		Adjusted average(d)		77-day period		790-day period		7365-day period	
	Avg.	Used	Allowed	Avg.	Upper	Days	Adj. Avg.(e)	Days	Adj. avg.(f)	Days	Adj. avg.(g)
4. Fumigation of dried fruit and tree nut products (Table B.16)(h)											
Chamber (raisins):											
Fumigators(i)	63	1.5	varied	63	210	6	54	63	44	150	26
Aerators(i)	47	1.5	varied	47	210	6	40	63	33	150	19
Clear chambers 1-2(i)	1434	1.5	varied	210	210	6	180	63	147	150	86
Stem pickers(i)	28	8	varied	28	210	6	24	63	20	150	12
Forklift driver(i)	3	1	varied	3	210	6	3	63	2	150	1
Hopper operator(i)	19	8	varied	19	210	6	16	63	13	150	8
Area sampling:											
Fumigation chambers(i)	88	1.5	varied	88	210	6	75	63	62	150	36
Fumigation cage(i)	54	1.5	varied	54	210	6	46	63	38	150	22
Leak checkers-chambers 4-5(i)	4	0.5	varied	4	210	n/a	n/a	n/a	n/a	n/a	n/a
Aeration-chambers 4-5(i)	116	1.5	varied	116	210	6	99	63	81	150	48
Clearing-chambers 4-5(i)	46	1.5	varied	46	210	6	39	63	32	150	19
Hopper areas(i)	8	8	varied	8	210	6	7	63	6	150	3
Stem picker(i)	27	8	varied	27	210	6	23	63	19	150	11
5. Measurement of MB exposure to the fumigators, forklift drivers, cherry sorters and other workers (no usable data)											
6. Methyl bromide air monitoring studies at a walnut processing facility (Table B.17)											
a) Worker exposure studies:											
Bulk packaging(i)	34	8	varied	34	210	6	29	75	28	n/a	n/a
Cleaning plant(i)	208	8	varied	208	210	6	178	75	173	n/a	n/a
Fumigatorium(i)	87	5.5	varied	87	210	6	75	75	73	180	43
Packaging(i)	44	8	varied	44	210	6	38	75	37	n/a	n/a
Vacuum chamber(i)	239	8	varied	210	210	6	180	75	175	n/a	n/a
Sorting(i)	32	8	varied	32	210	6	27	75	27	n/a	n/a
Special cracking(i)	29	8	varied	29	210	6	25	75	24	n/a	n/a
b) Area samples:											
Sorting line(i)	83	8	varied	83	210	2	24	n/a	n/a	n/a	n/a
d) Compliance monitoring:											
Sorting line in cleaning plant(i)	318	8	varied	210	210	6	180	75	175	n/a	n/a
Cello packaging of in-shell walnuts in main bldg.(i)	355	8	varied	210	210	6	180	75	175	n/a	n/a
Bulk packaging of in-shell walnuts in main bldg.(i)	243	8	varied	210	210	6	180	75	175	n/a	n/a
7. Fumigation and aeration at a brewery facility (Table B.18)											
a) Applicators											
Entry and reentry to open canisters/cylinders(i)	28.9	1.1	varied	29	210	2	8	n/a	n/a	n/a	n/a
Area sample (door to buffer zone)(i)	42	8	varied	42	210	2	12	n/a	n/a	n/a	n/a
b) Aerators											
Aerators(i)	25	0.6	varied	25	210	2	7	n/a	n/a	n/a	n/a
Area sample (left of entrance door)(i)	173	8	varied	173	210	2	49	n/a	n/a	n/a	n/a
Area sample (on applicator's truck)(i)	100	8	varied	100	210	2	29	n/a	n/a	n/a	n/a

Attachment G.**Calculation Equations:****1. Human equivalent methyl bromide concentration:**

$$ppm \text{ (human)} = ppm \text{ (animal)} \times \frac{\text{animal respiration rate}}{\text{human respiration rate}} \times \frac{\text{hours exposed}}{24 \text{ hrs}} \times \frac{\text{days exposed per week}}{7 \text{ days}}$$

The term for number of days exposed per week/7 days is used in the calculation only for studies when the animals were dosed for 5 or more days. The dose was not corrected for absorption (absorption factor, AF) since the absorption rates of methyl bromide in humans (52-55%) were similar to those for experimental animals, beagle dogs 40%, and rats 27% to 48%.

The default respiration rates used are: 0.46 m³/kg/day for children, 0.26 m³/kg/day for human adults³, 0.96 m³/kg/day for rats, 0.54 m³/kg/day for rabbits, 0.45 m³/kg/day for guinea pigs, 0.39 m³/kg/day for dog, and 1.80 m³/kg/day for mouse (Zielhuis and van der Kreek, 1979); and 0.43 m³/kg/day for monkey based on body weight of 3.5 kg, if actual body weight was not given in the study (U.S. EPA, 1988).

2. Human equivalent NOEL calculation for acute exposure based on a NOEL of 40 ppm (developmental toxicity study in rabbits; Breslin *et al.*, 1990) for adults:

$$40 \text{ ppm} \times \frac{0.54 \text{ m}^3/\text{kg-day}}{0.26 \text{ m}^3/\text{kg-day}} \times \frac{6 \text{ hours}}{24 \text{ hours}} = 21 \text{ ppm}$$

3. Human equivalent NOEL calculation for short-term (1-week) exposure based on a NOEL of 20 ppm (neurotoxicity in rabbits; Sikov *et al.*, 1981) for children:

$$20 \text{ ppm} \times \frac{0.54 \text{ m}^3/\text{kg-day}}{0.46 \text{ m}^3/\text{kg-day}} \times \frac{7 \text{ hours}}{24 \text{ hours}} = 7 \text{ ppm}$$

a In the draft Technical Support Document for Exposure Assessment and Stochastic Analysis, OEHHA determined mean breathing rates of 0.24±0.07 and 0.45±0.07 m³/kg/day for adults and children, respectively (OEHHA, 1996; Marty *et al.*, 1997).

4. Human equivalent NOEL calculation for subchronic (seasonal) exposure based on an ENEL of 0.5 ppm (neurotoxicity in dogs; Newton, 1994b) for children:

$$0.5 \text{ ppm} \times \frac{0.39 \text{ m}^3/\text{kg-day}}{0.46 \text{ m}^3/\text{kg-day}} \times \frac{7 \text{ hours}}{24 \text{ hours}} \times \frac{5 \text{ days}}{7 \text{ days}} = 0.1 \text{ ppm}$$

5. Human equivalent NOEL calculation for chronic exposure based on an ENEL of 0.3 ppm (nasal epithelial hyperplasia/degeneration in rats; Reuzel et al., 1987) for children:

$$0.3 \text{ ppm} \times \frac{0.96 \text{ m}^3/\text{kg-day}}{0.46 \text{ m}^3/\text{kg-day}} \times \frac{6 \text{ hours}}{24 \text{ hours}} \times \frac{5 \text{ days}}{7 \text{ days}} = 0.1 \text{ ppm}$$

6. Margin of Exposure:

$$\text{Margin of Exposure} = \frac{\text{Human equivalent NOEL}}{\text{Exposure Level}}$$

7. Calculation of Reference Concentration:

$$\text{Reference Concentration} = \frac{\text{Human equivalent NOEL}}{100}$$

For acute exposure:

$$\frac{21 \text{ ppm}}{100} = 210 \text{ ppb}$$

Attachment H.1 to H.4.

Beginning in 1992, DPR, methyl bromide registrants, and academic researchers began more comprehensive monitoring of field and commodity fumigations.

Attachment H.1. Field Fumigation

Methyl bromide flux was measured in several studies. The flux of methyl bromide from tarped field ranged from 22% in 5 days (Majewski *et al.*, 1995), 34% in 7 days (Yagi *et al.*, 1995), to 61% after 5.6 days (Yates *et al.*, 1996a and b) depending on the experimental conditions. The loss of applied methyl bromide in a tarped field was 4 times less than that from a nontarped field (Majewski *et al.*, 1995). The highest rate of loss was during the day when the temperature was high and the atmosphere was unstable. The remainder of the applied methyl bromide was adsorbed to the soil or degraded.

DPR used the initial studies to develop mitigation measures (permit conditions, including buffer zones), and later studies to check the effectiveness of the mitigation measures. Several different field fumigation methods were monitored (Table H1). In these studies, air monitoring was conducted using personal air sampling pumps equipped with activated charcoal tubes. The samplers were set up around the field at a distance of 30 feet from the edge of field and at the permit condition buffer zone determined for the application. Sampling was initiated at the start of the application and continued for one to seven days, with each sampling interval 6 - 12 hours. The air flow rate for all samplers was calibrated to approximately 15 mL/min. Wind speed, wind direction, air temperature, and relative humidity were recorded every five minutes with a Met-1[®] meteorological station.

A summary of the monitoring results from 39 field fumigations is shown in Table H1. Initial monitoring in 1992 showed air concentrations as high as 1.8 ppm (24-hour time-weighted average). The highest concentrations were detected at downwind locations closest to the treated area and declined with distance. Initial monitoring data indicated that methyl bromide air concentrations varied with application rate, acreage treated, and method of application. DPR used the Industrial Source Complex-Short Term computer model to assist in the data evaluation. This model was used to normalize for field-to-field differences such as application rate, acreage treated, field dimensions, and weather. After accounting for field-to-field differences, the monitoring data indicated that tarpaulin applications had lower air concentrations than nontarpaulin applications. Deep injections (20 inches or more) showed lower air concentrations than shallow injections (12 inches or less). However, deep injections continued to off-gas for a longer period of time. Based on the initial monitoring data, DPR recommended buffer zones so that air concentrations are not likely to exceed a target level at the specified distance. The target level currently used for the buffer zones is 0.21 ppm (24-hour time-weighted average), identified in the Preliminary Risk Assessment (Attachment A). Buffer zones varied in size with application rate, acreage, and application method.

Table H1. Maximum methyl bromide air concentration from different application methods at buffer zones specified by Department of Pesticide Regulation permit conditions.

Application Monitored and Study ID	Permit Condition Application Method	Date Applied	County	Applic Rate (lb/ac)	Acres	24-hr Max Conc @ Buffer (ppm) ^a	Perm Cond Buffer (ft) ^b
1: Hicks, 1992b	1-nontarp shallow	8/19/92	Monterey	186	19	0.042@300ft	390
2: Hicks, 1992b	1-nontarp shallow	9/24/92	Monterey	180	15	0.26@300ft	330
3: Hicks, 1992b/Ross, 1996	1-nontarp shallow	10/27/92	Monterey	180	15	0.55@50ft	330
4: Wofford and Segawa, 1998e	1.1-nontarp shallow (wing chisel)	3/12/98	Merced	150	7.5	0.15	200
5: Hicks, 1992a	2-nontarp deep	7/28/92	Kern	350	17	0.70@600ft	1060
6: Hicks, 1992a	2-nontarp deep	10/21/92	Kern	396	15	0.61@600ft	1170
7: Wofford and Segawa, 1998a	2-nontarp deep	1/22/98	Madera	348	33	0.11	510
8: Hicks, 1993a	3-nontarp deep (implements)	3/8/93	Fresno	396	40	0.56@200ft	2010
9: Hicks, 1993b	3-nontarp deep (implements)	3/13/93	Madera	400	20	0.34@200ft	940
10: Hicks, 1996	3-nontarp deep (implements)	10/31/95	San Joaquin	450	7	0.11@80ft	780
11: Siemer, 1992	4/5-tarp shallow	6/30/92	Kern	396	20	0.07@600ft	590
12: Ross, 1996	4/5-tarp shallow	10/26/92	Monterey	235	10	0.15@30ft	90
13: Sanders, 1997a	4/5-tarp shallow	2/13/97	SLO	200	10	0.082	30
14: DPR, 1997 a & b	4/5-tarp shallow	8/21/97	Ventura	180	9	0.069	30
15: Wofford and Segawa, 1998b	4/5-tarp shallow	11/1/97	Monterey	205	12	0.13	70

Table H1. (continued)

Application Monitored and Study ID	Permit Condition Application Method	Date Applied	County	Applic Rate (lb/ac)	Acres	24-hr Max Conc @ Buffer (ppm) ^a	Perm Cond Buffer (ft) ^b
16: Kim and Segawa, 1998b	4/5-tarp shallow	6/5/98	Orange	231	1	0.069@30ft	100
17: “	normal	“	“	234	“	0.060@30ft	“
18: “	edge panels	6/7/98	“	231	“	0.053@30ft	“
19: “	normal	“	“	226	“	0.046@30ft	“
	edge panels						
20: Gillis, 1998a	4/5-tarp shallow	7/25/98	Monterey	216	5	0.043	100
21: Gillis, 1998b	4/5-tarp shallow	8/7/98	Ventura	206	4	0.029	100
22: Gillis and Becker, 1993	8.1-tarp shallow Very High Barrier	10/19/93	Monterey	392	7	0.13	30
23: Sanders, 1997a	8.1-tarp shallow Very High Barrier	2/6/97	Madera	350	19	0.99	30
24: Sanders, 1997b	8.1-tarp shallow Very High Barrier	7/28/97	Monterey	240	12	0.23@25ft	200/30
25: “		8/1/97			10	0.44@60ft	200/30
26: Segawa and Sanders, 1997	8.1-tarp shallow Very High Barrier	9/25/97	Santa Cruz	210	10	0.054	60
“	tarp removal	10/25/97	“	“	8	0.042@30ft	50
27: Hicks, 1993c	9-tarp bed	7/13/93	SLO	256	9	0.092@30ft	110
28: Wofford and Segawa, 1998c	9.1-tarp bed (Colby)	9/8/97	Orange	160	4	0.17@20ft	30
29: Sanders, 1997a	10-tarp bed (Kenco)	12/12/96	Riverside	200	20	0.57	470

30: Wofford and Segawa, 1998d 10-tarp bed (Kenco) 12/17/97 Riverside 196 16 0.59@625ft 420

Table H1. (continued)

Application Monitored and Study ID	Permit Condition Application Method	Date Applied	County	Applic Rate (lb/ac)	Acres	24-hr Max Conc @ Buffer (ppm) ^a	Perm Cond Buffer (ft) ^b
31: Gillis, 1992	11-tarp deep	11/9/92	Merced	405	7	0.06@300ft	300
32: Sanders, 1997a	12-tarp bed (hot gas)	12/11/96	Riverside	200	25	1.7@330ft	550
33: Sanders, 1997a	12-tarp bed (hot gas)	1/20/97	Kern	200	14	0.16	360
34: Sanders, 1997a	12-tarp bed (hot gas)	1/27/97	Imperial	200	14	0.55	360
35: Kim and Segawa, 1998a	Virtually Impermeable-method 5	5/2/98	Orange	235	11	0.16@60ft	200
36: Kim and Segawa, 1998b	Virtually Impermeable-method 5 edge panels	6/5/98	Orange	234	1	0.066@30ft	100
37: “	normal	“	“	233	“	0.072@30ft	“
38: “	edge panels	6/7/98	“	220	“	0.065@30ft	“
39: “	normal	“	“	238	“	0.042@30ft	“

a/ Highest measured concentration at the buffer zone distance (some samplers not at buffer distance, as noted). Values as reported from the laboratory; S and TC studies are adjusted for lab recovery, EH studies are not adjusted for recovery.

b/ Buffer zone size required by permit conditions at the time of the monitoring. Some buffer zones were subsequently revised.

Additional monitoring conducted since 1996 indicated that air concentrations may also vary with other factors. However, there were insufficient data to show clear correlations. Of the 39 applications monitored, seven exceeded the 0.21 ppm target level at the buffer zone distance (Table H1, applications 23, 24, 25, 29, 30, 32, 34).¹ Tarpaulin-bedded applications and applications using “very high barrier” tarpaulins appeared to have higher air concentrations than originally assumed in the permit conditions. Of the seven tarpaulin-bedded applications monitored, four exceeded the 0.21 ppm target level at the original buffer zone distance. Of the five very high barrier tarpaulin applications monitored, three exceeded the target level at the original buffer zone distance. None of the other application methods exceeded the target level at the buffer zone distance. Applications monitored in inland areas of California exceeded the target level at the original buffer zone distance more frequently (5 of 15 applications), compared to coastal areas (2 of 24 applications). Applications monitored during winter months exceeded the target level more frequently (5 of 8 applications), compared to other seasons (2 of 31 applications). It is unclear if method of application, geographic area, or season exerts the greater influence on air concentrations.

The monitoring data indicated that while tarped applications had lower air concentrations than untarped applications, tarpaulin permeability (as measured in the laboratory) had little influence on air concentrations detected in the field. Five applications were monitored using “very high barrier” tarpaulins, with methyl bromide permeability approximately one-half the standard tarpaulin. Three of these exceeded the target concentration at the buffer zone distance (Table H1, applications 23 to 25). In addition, a series of field tests with a “virtually impermeable film” showed no difference in air concentrations between the virtually impermeable film and a standard tarpaulin (Table H1, applications 16 to 19, 35 to 39). Other factors measured during the monitoring such as soil texture, soil moisture content, and air temperature did not show any correlations with air concentrations, or the correlations are masked by other factors.

Attachment H.2. Commodity Fumigation

DPR and commodity groups have also conducted air monitoring for post-harvest commodity fumigations. These types of fumigations are very different from field fumigations (see section **II.D. USAGE**) and methods of application vary widely, both in the types of enclosures used to contain the methyl bromide and in the methods of aerating the enclosures. Examples of enclosures used for fumigation include dedicated fumigation chambers, large food processing plants, wood bins covered with tarpaulins, and transportation containers. Examples of aeration methods include forced air exhaust stacks, opening doors, and removing tarpaulins. The amount of methyl bromide used for a single fumigation ranges from one pound to several thousand pounds. Air concentrations vary widely because of the variation in the methods of application and amounts of methyl bromide. Most of the monitoring was conducted for fumigations using larger amounts of methyl bromide (Table H2).

The most complete off-site air concentration data came from chamber fumigations which are forcibly exhausted through stacks (Table H2). Off-site concentrations of methyl

¹ DPR revised the buffer zones in 1997 and 1998 to provide a higher margin of safety. Under the revised buffer zones, none of the 39 fields monitored exceed 0.21 ppm at the buffer zone distance.

bromide during commodity fumigations depended on various conditions of the treatment and aeration. Off-site concentrations during a treatment in a sealed chamber were usually low, although at one site a 2-hour concentration of 1.8 ppm was detected 2 meters from a chamber (Radian Corp., 1992), indicating a leaky seal. Another study measured a maximum 12-hour concentration of 0.228 ppm 12 meters from a chamber during treatment. The highest concentrations were usually found during aeration, and is dependent on stack height, fan velocity and meteorological conditions during exhaust. During aeration, downwind concentrations were detected up to 250 meters away and a concentration of 6.8 ppm was measured 116 meters away in a 5 minute sample (Segawa *et al.*, 1992). Downwind concentrations from commodity fumigations seemed to decrease rapidly over time and crosswind distance. Concentrations away from the downwind plume decreased rapidly, but with a direct wind the plume could extend for several hundred meters.

Attachment H.3. Warehouse (Building) Fumigation

Very large warehouses and processing plants are fumigated using thousands of pounds of methyl bromide during each treatment (Segawa *et al.*, 1994a, Segawa *et al.*, 1994b and Segawa *et al.*, 1995). Several types of buildings were monitored, such as large cement-wall food processing plants, warehouses, mills, and corrugated metal buildings (Table H2). The construction of the building being fumigated made a large difference in the ability to contain the methyl bromide. As much as 70% of the applied methyl bromide leaked out of one metal building monitored during the first 24 hour of fumigation (Segawa *et al.*, 1994c) where a 20-hour concentration of 0.131 ppm was measured 152 meters from the building. Measurements of air concentration in a cement-wall warehouse indicated that at least 59% of the applied methyl bromide was retained during a 23-hour treatment period (Segawa *et al.*, 1994b). Increased retention during treatment normally caused higher concentrations of methyl bromide during aeration. Concentrations as high as 6.44 ppm were measured during the first hour of aeration 9.1 meters from one building. During aeration, concentrations exceeding the 0.21 ppm exposure level were detected as far as 262 meters from another warehouse.

Attachment H.4. Other Commodity Fumigations

Tarpaulin-covered commodities retained approximately 77% of the injected methyl bromide before aeration (Air Toxics Limited, 1993). Stacks attached to the tarped commodities assist in aeration, which showed a 64% loss over the first 2 hours. Measurable concentrations of methyl bromide were detected 1248 meters downwind from the application area. Containers used to ship products by truck, ship, or railroad are also used for methyl bromide fumigation. The transportation containers are usually aerated passively by opening the doors. During both applications monitored, measurable concentrations were still detected 15 meters downwind from the containers an hour after the doors were open (Radian Corp., 1992).

Table H2. Maximum methyl bromide air concentration from various commodity fumigations.

Type	Study ID	Date	Volume (ft ³)	Aeration method	Total MeBr (lbs)	Max conc. and distance from source (ppm) ^a	Furthest measured conc. (ppm)
Chamber	Segawa et al, 1992	5/21/92	21,280	Stack	64	0.235 for 30 min at 108m	same
Chamber	Segawa et al, 1992	6/1/92	16,000	Stack	50	1.005 for 5 min at 75m	0.031 for 5 min at 125m
Chamber	Segawa et al, 1992	6/5/92	14,000	Stack	30	0.786 for 5 min at 52m	0.11 for 5 min at 250m
Chamber	Segawa et al, 1992	6/23/92	16,000	Stack	50	0.012 for 5 min at 152m	same
Chamber	Segawa et al, 1992	6/25/92	18,000	Stack	45	6.79 for 5 min at 116m	0.375 for 5 min at 152m
Chamber	Radian Corp., 1992	8/11/92 8/17/92	15,000	Stack	12	1.8 for 120 min at 2m (fumigation)	0.10 for 15 min 50m
Chamber (2)	Wofford and Segawa, 1997	10/23/96	11,000 11,970	Stack	22 32	0.228 for 12 hr at 12m (fumigation)	0.009 for 12 hr at 22m (fumigation)
Warehouse	Wofford and Bennett, 1993	4/6/93	144,000	Doors	108	0.30 for 24 hr at 9.1m	same
Warehouse	Segawa et al, 1994a	10/15/93	6,800,000	Doors w/floor fans	7,350	5.522 for 2.3 hr at 104m	0.889 for 2.3 hr at 284m
Warehouse	Segawa et al, 1994a	10/20/93	3,100,000	Doors w/4 roof vents	2,975	3.17 for 2 hr at 100m	0.528 for 2 hr at 314m
Processing plant	Segawa et al, 1994b	4/8/93	1,450,000	Doors w/3 roof vents	2,175	14.98 for 15 min at 9.1m	12.93 for 15 min at 30m
Processing plant	Segawa et al, 1994c	5/28/93	320,000	Doors	700	1.041 for 7 hrs at 9.1m (fumigation)	0.301 for 7 hrs at 152m fumigation)

Table H2. Maximum methyl bromide air concentration from various commodity fumigations (cont.).

Type	Study ID	Date	Volume (ft ³)	Aeration method	Total MeBr (lbs)	Max conc. and distance from source (ppm) ^a	Furthest measured conc. (ppm)
Processing plant	Segawa et al, 1995	6/5/93	2,600,000	Roof fans	5,325	0.575 for 2.7 hr at 9.1m	0.107 for 2.7 hr at 116m
Processing plant	Segawa et al, 1995	6/12/93	2,160,000	Roof fans	4,320	1.403 for 12 hr at 9.1m (fumigation)	0.008 for 9 hrs at 52m (fumigation)
Tarped commodity	Air Toxics Limited, 1993	4/13/93	5(53,975) 1(46,750)	Stack	1,262	5.4 for 30 min at 15m	0.0015 for 2 hr at 1248m
Transport containers	Radian Corp., 1992	8/6/92	2,200	Doors	5	1.2 for 2 min at 15m	same
Transport containers	Radian Corp., 1992	10/1/92	2,200	Doors	6	0.84 for 16 min at 18m	same

a/ All concentrations measured during aeration period unless otherwise noted.



Paul E. Helliker
Director

Department of Pesticide Regulation



Gray Davis
Governor

Winston H. Hickox
Secretary, California
Environmental
Protection Agency

March 30, 2001

TO: Interested Parties

SUBJECT: SUMMARY OF AMBIENT AIR MONITORING FOR METHYL BROMIDE

At the request of the Department of Pesticide Regulation (DPR), the Air Resources Board (ARB) monitored for methyl bromide in two areas of the state between July and November 2000. DPR has evaluated ARB's data by comparing the measured air concentrations to target concentrations. DPR's goal is to regulate methyl bromide use so that the target concentrations are not exceeded. As described in the attached document, air concentrations for all one-day and one-week periods were below the target concentrations, but air concentrations for an eight-week period were above the target concentration.

DPR is analyzing the monitoring data as well as pesticide use patterns and weather data to determine the major factors causing the high air concentrations. Based on this analysis, DPR will develop mitigation measures to reduce air concentrations to acceptable levels. Some of the mitigation measures that DPR is investigating are limits on the amount of methyl bromide that can be applied in a given area, increasing the time or distance between methyl bromide fumigations, and increasing the size of buffer zones. We expect to discuss the options with you over the next few months. If additional mitigation measures are needed, we plan on implementing them prior to July 2001, the start of the peak use period.

DPR has requested ARB conduct additional monitoring later this year to determine the effectiveness of the mitigation measures. In addition, the monitoring will help determine if the regulations implemented in January 2001 have had any effect on methyl bromide levels in air.

For additional information concerning this monitoring or other methyl bromide issues please feel free to contact Mr. Randy Segawa, of my staff, at (916) 324-4137, rsegawa@cdpr.ca.gov, or DPR's web site, www.cdpr.ca.gov.

Sincerely,

John S. Sanders, Ph.D.
Environmental Monitoring Branch
(916) 324-4100

FLEX YOUR POWER! *The energy challenge facing California is real. Every Californian needs to take immediate action to reduce energy consumption. For a list of simple ways you can reduce demand and cut your energy costs, see our Web page at www.cdpr.ca.gov.*

Summary of Ambient Air Monitoring for Methyl Bromide March 28, 2001

BACKGROUND

Methyl bromide is one of the most widely used pesticides in California, with approximately 15 million pounds applied annually in the state. Methyl bromide is a gaseous fumigant that kills insects, mites, rodents, nematodes, termites, weeds, and organisms that cause plant diseases. Because it is a colorless, odorless gas, methyl bromide is normally mixed with chloropicrin, a tear gas with a noticeable odor.

Farmers use methyl bromide to treat soil before planting vegetable, fruit and nut crops, and flower and forest nurseries. Depending on the crop, field applications may occur annually, or once every several years. Methyl bromide is injected into the soil with specialized application equipment. After harvest, methyl bromide fumigation protects crops from pest damage during storage and transportation. The fumigant is also used for termite eradication in homes and other structures, and to control insects in mills, ships, railroad cars and other transportation vehicles.

The Department of Pesticide Regulation (DPR) and the county agricultural commissioners have implemented extensive restrictions on the use of methyl bromide, such as buffer zones surrounding treated fields, equipment and procedures for application, worker safety requirements, and notification to people near fumigated fields.

As required by state law, DPR evaluates, identifies, and controls pesticides as toxic air contaminants. Under this program, methyl bromide was identified as a toxic air contaminant in 1996. As part of the toxic air contaminant program, the Air Resources Board (ARB) monitors for pesticides under the direction of DPR. ARB conducted ambient air monitoring for methyl bromide in 2000. DPR requested this monitoring as part of an ongoing effort to evaluate seasonal exposures to methyl bromide and determine if current restrictions provide adequate safety for people who live and work in areas where fumigations occur to multiple fields. This document summarizes the monitoring results and preliminary risk evaluation.

SAMPLING PLAN

Monitoring was conducted within the areas and periods of most use. ARB monitored six locations in Kern County from July 19 to September 1, 2000 (Figure 1). At each location, 1-day samples were collected four days per week for seven weeks. ARB monitored six locations in the Monterey and Santa Cruz area from September 11 to November 3, 2000 (Figure 2). At each location, 24-hour samples were collected four days per week for eight weeks. Additional samples were collected for quality control.

RESULTS

The results are summarized in Table 1, and the complete results are given in Appendix A. All but one of the 320 samples contained a detectable and quantifiable amount of methyl bromide (detection limit 0.002 parts per billion [ppb], quantitation limit 0.01 ppb). *See Appendix B for an explanation of terminology, such as detection limit and parts per billion.* The highest 1-day concentration detected was 30.8 ppb. The highest 1-week average concentration was 15.5 ppb. The highest average concentration for the study period (7 or 8 weeks) was 7.7 ppb.

EVALUATION OF HEALTH RISKS

Methyl bromide causes a variety of health effects in experimental animals and humans. To evaluate health risks, DPR has calculated target concentrations or goals based on the toxic properties of methyl bromide, and compared the target concentrations to the monitoring data. These target concentrations are generally 100 times lower than doses that do not cause adverse effects, or the no-observed effect level (NOEL) in animal studies, adjusting for breathing rate differences between animals and humans. The 100-fold factor accounts for variation in sensitivity between individuals and assumes that people are more sensitive than experimental animals to the effects of methyl bromide. For a 1-day average exposure, the target concentration is 250 ppb for children and 210 ppb for adults (the target concentration for a child is higher than an adult in this case). For a 1-week average exposure, the target concentration is 70 ppb for children and 120 ppb for adults. For an 8-week average exposure, the target concentration is 1 ppb for children and 2 ppb for adults.

DPR's goal is to regulate methyl bromide use so that the target concentrations are not exceeded. The air concentrations for all 1-day and 1-week periods were lower than the target concentrations, but air concentrations exceeded the target concentration over a 7 to 8-week period (Table 1). For the location with the highest concentration, the 8-week exposure was almost eight times the target level.

While the 8-week target concentration was exceeded in several locations, illnesses would not be expected to occur because the target concentration incorporates a 100-fold safety factor.

PRELIMINARY CONCLUSIONS

Monitoring was conducted during the high methyl bromide use period of July 19 to September 1 in Kern county, and September 11 to November 3 in Monterey and Santa Cruz counties.

Monitoring was conducted in two areas of the highest methyl bromide use.

The 1-day air concentrations of methyl bromide met DPR's goal (i.e., lower than the 1-day target concentration) at all locations.

The 1-week air concentrations of methyl bromide met DPR's goal (i.e., lower than the 1-week target concentration) at all locations.

The average air concentrations of methyl bromide for the 7 to 8-week study period did not meet DPR's goal (i.e., greater than the 8-week target concentration) at one of the six monitoring locations in Kern County and at four of the six monitoring locations in the Monterey/Santa Cruz area.

FUTURE ACTIVITIES

DPR is currently analyzing the data to determine whether application patterns, weather, or other factors played a role in ambient air levels. DPR expects to finalize its analysis this spring, and if additional restrictions are deemed necessary, DPR intends to take action before the high-use season begins.

DPR has requested that ARB conduct additional ambient air monitoring for methyl bromide in these same areas in 2001 since it can be accomplished simultaneously with other planned monitoring. Additionally, the monitoring will show the change in air concentrations due to new methyl bromide regulations implemented in January 2001.

ADDITIONAL INFORMATION

This summary is based on the following documents.

ARB, 2000. Final Report for the 2000 Methyl Bromide and 1,3-Dichloropropene Air Monitoring in Kern County. California Air Resources Board, Sacramento, CA.

ARB, 2001. Final Report for the 2000 Methyl Bromide and 1,3-Dichloropropene Air Monitoring in Monterey and Santa Cruz Counties. California Air Resources Board, Sacramento, CA.

DPR, 1999. Methyl Bromide Risk Characterization Document for Inhalation Exposure (DRAFT RCD 99-02). California Department of Pesticide Regulation, Sacramento, CA.

Lim, 2001. Evaluation of Ambient Air Concentration of Methyl Bromide in Monterey, Santa Cruz, and Kern Counties. Memorandum from Lori Lim to Gary Patterson, Medical Toxicology Branch, February 15, 2001. California Department of Pesticide Regulation, Sacramento, CA.

Powell, 2001. Exposures to methyl bromide based on ARB 2000 monitoring in Monterey/Santa Cruz and Kern Counties. Memorandum from Sally Powell to Joe Frank, Worker Health and Safety Branch, February 9, 2001. California Department of Pesticide Regulation, Sacramento, CA.

Figure 1.

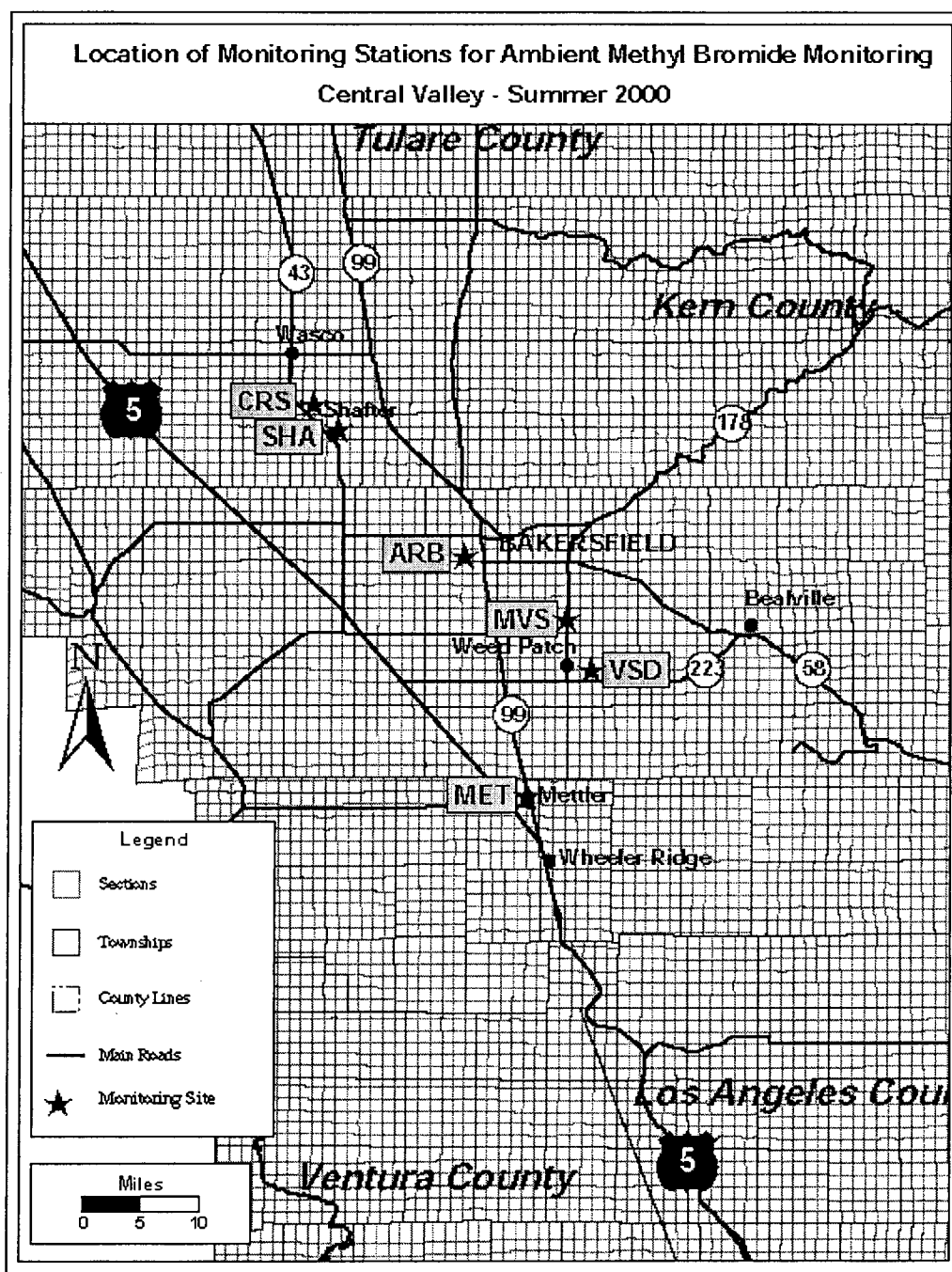


Figure 2.

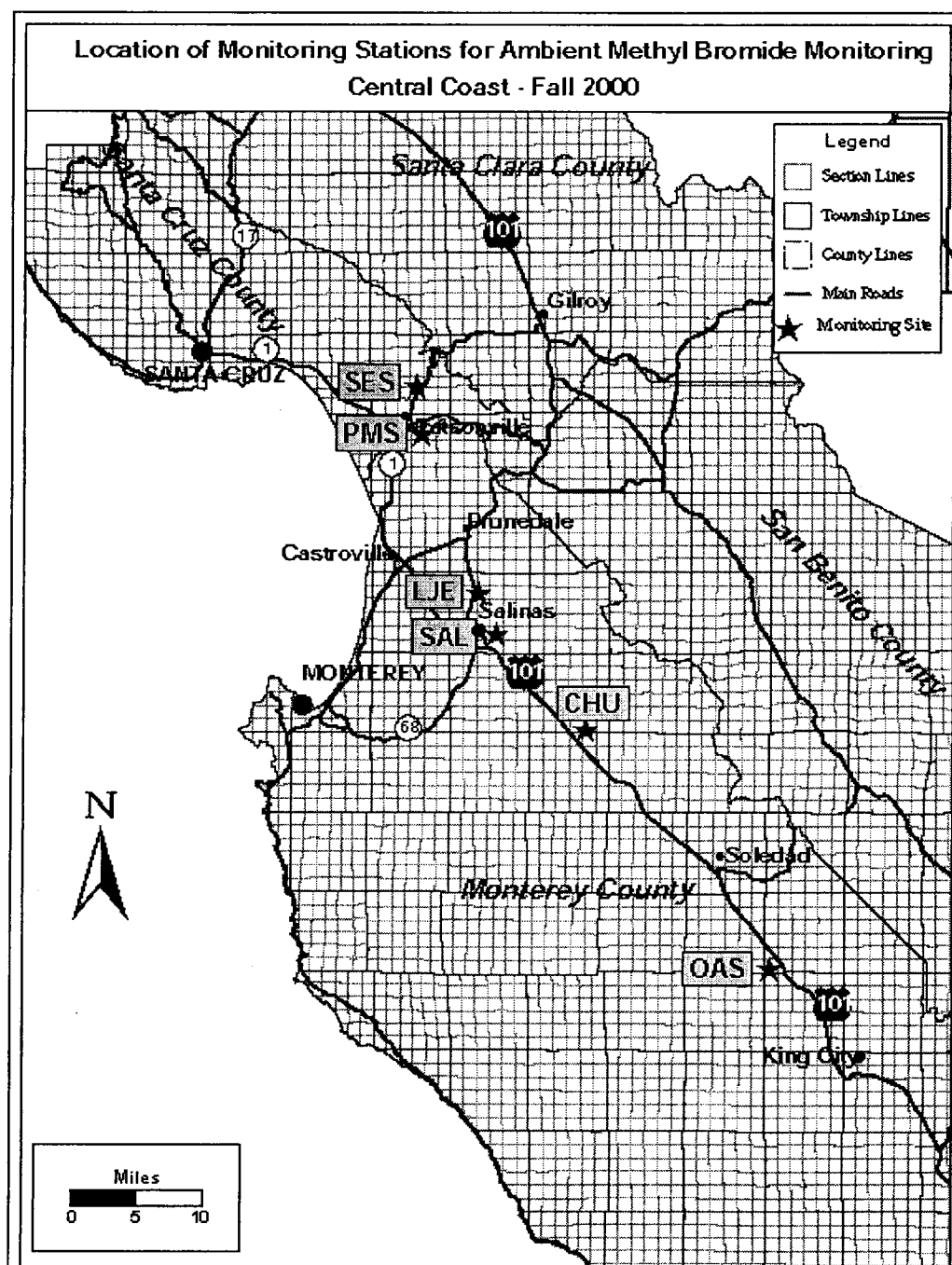


Table 1. Summary of methyl bromide air monitoring results.

Location	Highest 1-Day Concentration (ppb)	Highest 1-Week Concentration (ppb)	Average Concentration for Study Period (ppb)
Monterey and Santa Cruz Counties, Sep 11 - Nov 3, 2000			
CHU Chualar School, Chualar, CA	2.4	1.6	0.6
LJE La Joya Elementary School, Salinas, CA	24.0	11.1	3.8
OAS Oak Avenue School, Greenfield, CA	1.8	1.0	0.4
PMS Pajaro Middle School, Watsonville, CA	30.8	15.5	7.7
SAL Ambient Monitoring Station, Salinas, CA	7.9	3.0	1.3
SES Salsepuedes Elementary School, Watsonville, CA	16.4	8.3	2.6
Kern County, Jul 19 - Sep 1, 2000			
ARB Ambient Monitoring Station, Bakersfield, CA	1.0	0.5	0.2
CRS Cotton Research Station, Shafter, CA	14.2	4.6	2.2
MET Mettler-Fire Station, Mettler, CA	0.2	0.1	0.08
MVS Mountain View School, Lamont, CA	0.5	0.2	0.09
SHA Shafter-Walker Ambient Monitoring Station, Shafter, CA	3.5	1.8	0.8
VSD Vineland School District, Bakersfield, CA	0.3	0.2	0.1
Target Concentrations^a			
<i>Child</i>	<i>250</i>	<i>70</i>	<i>1</i>
<i>Adult</i>	<i>210</i>	<i>120</i>	<i>2</i>

^a DPR uses target concentrations as benchmarks for its regulatory program. DPR establishes and modifies its restrictions so that the target concentrations should not be exceeded. Target concentrations are based on no-observed-effect levels established from animal tests of various exposure periods with a safety factor of 100x.

APPENDIX A RESULTS OF EACH SAMPLE

Table 2. Methyl bromide results from Kern County (ppb)

Sample Start Date	Monitoring Locations ¹					
	ARB	CRS	MET	MVS	SHA	VSD
07/19/00	0.02	ND ²	0.02	0.02	0.02	0.02
07/19/00	0.02	ND	0.11	0.02	0.03	0.02
07/20/00	1.00	5.66	0.11	0.10	3.53	0.21
07/24/00	0.18	3.11**	0.08	0.05**	0.63	0.06
07/25/00	0.34	0.89	0.03**	0.05**	0.36	0.04**
07/26/00	0.05**	1.43	0.11	0.08**	0.67	0.06
07/26/00	0.07**	1.45	0.21	0.07	0.66	0.06**
07/27/00	0.18	9.14	0.22	0.21	1.17	0.23
07/31/00	0.06**	1.61	0.19**	0.07	0.81	0.12**
08/01/00	0.93	1.72	0.12	0.08	1.15	0.12
08/02/00	0.11	0.86**	0.08**	0.06**	0.63	0.07**
08/02/00	0.11	0.85	0.08	0.06	0.62	0.07
08/03/00	0.07	14.18	0.06**	0.05	0.66	0.06
08/07/00	0.22	0.60	0.04	0.03	0.16	0.03
08/08/00	0.10	0.24	0.05	0.09	0.19**	0.09
08/09/00	0.10	0.09	0.05	0.05	0.09	0.07
08/09/00	0.10	0.09	0.05	0.05**	0.08	0.07
08/10/00	0.19	0.91	0.14	0.21	0.90	0.23
08/14/00	0.03	0.06	0.03	0.03	0.06	0.03
08/15/00	0.08	0.24**	0.04	0.05	0.06	0.05
08/16/00	0.01	NS ³	0.01**	0.01	0.02**	0.01
08/16/00	0.02	NS	0.02	0.02**	0.02	0.01
08/17/00	0.04	NS	0.03	0.04	0.04	0.04
08/21/00	0.03	0.05	0.03	0.03	0.46	0.03
08/22/00	0.03	0.07	0.05	0.03	0.07	0.04
08/23/00	0.11	1.38	0.07	0.07	0.35	0.07
08/23/00	0.11	1.32	0.03**	0.07**	0.38	0.07
08/24/00	NA	1.07	0.09	0.24	0.49	0.19
08/28/00	0.31	2.69	0.19	0.49	2.83	0.35
08/29/00	0.10	4.88	0.09	0.09	1.02	0.10
08/30/00	0.26	2.59	0.22	0.16	1.84	0.18
08/30/00	0.25	2.66	0.22**	0.16**	1.86	0.18
08/31/00	0.09	0.94	0.07	0.07	0.42	0.06

¹ See Table 1 for description of monitoring locations

² None Detected, detection limit 0.002 ppb

³ No Sample

**Sample air flow rate deviation was >25%, not used to calculate averages

Table 3. Methyl bromide results (ppb) from Monterey and Santa Cruz Counties

Sample Start Date	Monitoring Locations ¹					
	CHU	LJE	OAS	PMS	SAL	SES
09/11/00	0.67	5.57	0.31	5.08	1.98	9.46
09/12/00	0.81	24.03	0.70	10.10	2.14	16.43
09/12/00	NS ²	NS	0.28	NS	NS	NS
09/13/00	0.94	7.32	0.68	1.11	1.50	2.62**
09/13/00	0.88	8.41	NS	1.12	1.46	NS
09/14/00	0.50	4.52	0.22	4.39	0.97	4.54
09/14/00	NS	NS	NS	NS	NS	4.86
09/18/00	0.58	11.08	0.42	11.22	1.45	3.93**
09/19/00	2.16	11.85	0.65	15.46	3.50	7.22
09/20/00	0.71	1.57	0.63	1.99	1.77	0.16
09/20/00	1.63**	2.48	0.54	1.30	1.49	0.14
09/21/00	0.84	NS	0.06	3.88	2.74	0.21
09/25/00	0.12	0.30	0.12**	1.24	0.15	1.22
09/26/00	0.32	0.60	0.15	2.73	0.26	0.82
09/26/00	0.33**	0.79**	0.16	3.57	NS	0.80
09/27/00	0.23	0.27	0.25	13.29	0.08	1.69
09/28/00	0.68	3.71	0.16	21.48	2.58	4.12
10/02/00	0.37	0.20	0.29	0.78	0.19	0.97
10/03/00	0.31	0.13	0.42	1.14	0.09	0.48
10/03/00	0.31	0.12	NS	0.91	0.09	0.48
10/04/00	0.61	4.26	0.34	1.26	1.08	0.44
10/04/00	NS	NS	0.34	NS	NS	NS
10/05/00	0.31	0.81	0.55	1.90	0.65	2.29
10/10/00	0.07	0.69	0.12**	5.45	0.06**	0.96
10/10/00	NS	NS	NS	NS	NS	1.07
10/11/00	0.38	0.62	0.33	13.12	0.38	0.52
10/11/00	0.05**	0.25**	NS	12.54**	0.39	NS
10/12/00	0.33	1.20	0.28	28.18	1.65	0.92
10/12/00	NS	1.13	0.29	NS	NS	NS
10/16/00	2.41	10.75	0.90	22.27	7.91	3.24**
10/16/00	NS	13.16	0.94	23.03**	NS	3.28
10/17/00	NA	2.13	0.70	3.94	1.21	2.95
10/17/00	1.29	NS	NS	NS	NS	NS
10/18/00	1.21	3.53	0.70	6.86	0.78	4.76
10/18/00	NS	NS	NS	NS	0.81	NS
10/19/00	1.54	3.69	1.84	4.15	2.12	3.53
10/23/00	1.14	7.04	0.62	30.77	2.38	3.28
10/24/00	0.57	1.25**	0.59	8.45	1.23	1.20
10/25/00	0.30	0.77	0.22	3.06	0.64	2.11
10/25/00	0.30	0.79	0.23	2.89	0.65	2.23
10/26/00	0.34	1.26	0.12	2.55	0.55	1.32
10/30/00	0.11	0.20	0.07	0.54	0.10	0.08
10/31/00	0.11	0.31	0.10	1.78	0.13	0.27
11/01/00	0.09	0.20	0.07	1.71	0.14	0.16
11/01/00	0.08	0.20	0.06	1.74	0.14	0.16
11/02/00	0.11	0.30	0.08	0.38	0.19	0.36

¹ See Table 1 for description of monitoring locations² No Sample

**Sample air flow rate deviation was >25%, not used to calculate averages

APPENDIX B

EXPLANATION OF TERMINOLOGY

Concentration: The amount of a chemical in air is normally expressed as a concentration, the amount of the chemical in a given amount of air. Concentrations in air can be expressed in many different units, the same way that distance can be expressed as inches, feet, meters, or miles. Concentrations in air can be expressed in units of volume or weight. One common unit is percent volume. For example, air contains 21 percent oxygen. This means in 100 cubic meters of air, 21 cubic meters is comprised of oxygen.

Concentration Units and Conversion Factors: DPR often expresses methyl bromide air concentrations in parts per billion (ppb). Similar units are parts per million (ppm) and percent (percent is synonymous with parts per hundred). These units are all ratios or proportions and refer to the volume of a chemical in a volume of air. For example, 1,000 ppb means that 1,000 cubic meters of methyl bromide is contained in 1 billion cubic meters of air. While it may seem counterintuitive because a billion is more than a million, 1 ppm is a concentration 1000 times greater than 1 ppb.

ARB's report expresses the methyl bromide air concentrations as nanograms per cubic meter (ng/m³). This refers to the amount (weight) of methyl bromide in a volume of air. For example, 1,000 ng/m³ means 1,000 nanograms of methyl bromide is contained in one cubic meter of air.

The conversion factor from nanograms per cubic meter to parts per billion is not straightforward because it is usually different from chemical to chemical. For methyl bromide, the concentration in nanograms per cubic meter should be divided by 3,880 to convert to parts per billion. For example, 388,000 ng/m³ divided by 3,880 equals 100 ppb. The following table summarizes these conversion factors.

<u>Change From</u>	<u>To</u>	
ng/m ³	ppb	divide by 3,880
ppb	ng/m ³	multiply by 3,880
ppb	ppm	divide by 1,000
ppm	ppb	multiply by 1,000

Detection Limit: The detection limit is the smallest amount of the chemical that can be identified in a sample with the method employed. For example, a detection limit of 0.002 ppb for methyl bromide means that a sample can be identified as containing methyl bromide if the concentration is at least 0.002 ppb. If the sample contains no methyl bromide, or methyl bromide at a concentration less than 0.002 ppb, the sample is designated as containing no detectable amount. When calculating average concentrations or other statistics, samples with no detectable amount are normally assumed to have a concentration of one-half the detection limit. For example, if the detection limit is 0.002 ppb, samples with no detectable amount are assumed to have 0.001 ppb. The detection limit is a characteristic of both the method and the chemical. Different methods can have different detection limits for the same chemical. The same method can have different detection limits for different chemicals. See also quantitation limit.

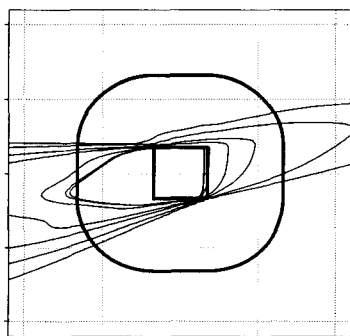
No-Observed-Effect Level, NOEL: The NOEL is the lowest experimental concentration for which no adverse health effects were documented in a toxicology test. For example, a NOEL of 2000 ppb means that test subjects (usually animals) exposed to 2000 ppb had no adverse health effects for the duration of the test. Adverse effects occurred at the next highest dose of the test. The health or toxic effects of a chemical are related to the amount of chemical absorbed by the body. The more chemical absorbed by the body the greater the toxic effects. Scientists often say that the dose makes the poison, or stated another way, there are no poisons only poisonous doses. The NOEL is usually different for each chemical. Also, the NOEL is usually different for different exposure periods. Normally, the longer the exposure period, the lower the NOEL. In other words, it takes less chemical to produce an adverse effect if exposure occurs for one year, than if exposure occurs for one day.

Parts Per Billion, ppb: See Concentration Units and Conversion Factors.

Quantitation Limit: Similar to detection limit, the quantitation limit is the smallest amount of the chemical that can be measured. For example, a quantitation limit of 0.01 ppb for methyl bromide means that the concentration can be measured if the sample contains at least 0.01 ppb of methyl bromide. Samples with concentrations less than the quantitation limit, but more than detection limit can be identified as containing methyl bromide, but the concentration cannot be measured reliably with the method employed. For example, if the detection limit is 0.002 ppb and the quantitation limit is 0.01 ppb, samples with concentrations at least 0.01 ppb can be measured, samples with concentrations between 0.002 and 0.01 ppb contain an unmeasurable concentration between 0.002 and 0.01 ppb, and samples with concentrations less than 0.002 ppb are designated as containing no detectable amount. When calculating average concentrations or other statistics, samples with an unmeasurable concentration are normally assumed to have a concentration of the midpoint between the detection limit and the quantitation limit. For example, if the detection limit is 0.002 ppb and the quantitation limit is 0.01 ppb, samples with an unmeasurable amount are assumed to have 0.006 ppb. As with the detection limit, the quantitation limit is a characteristic of both the method and the chemical. Different methods can have different quantitation limits for the same chemical. The same method can have different quantitation limits for different chemicals.

Target Concentration: The target concentration is the benchmark or goal that DPR does not want to exceed. The target concentration is not a legal standard, but a goal for DPR's regulatory program. For example, if the target concentration for methyl bromide is 2 ppb, DPR implements restrictions on the use of methyl bromide (examples: buffer zones or acreage limitations) so that people's exposure should not exceed 2 ppb. The target concentration is based on the no-observed effect level and incorporates a safety factor. Scientists often refer to this target concentration as the reference concentration.

Evaluating the Effectiveness of Methyl Bromide Soil Buffer Zones in Maintaining Acute Exposures Below a Reference Air Concentration



Bruce Johnson

April 2001



**STATE OF CALIFORNIA
Environmental Protection Agency
Department of Pesticide Regulation
Environmental Monitoring Branch
Environmental Hazards Assessment Program
1001 I Street
Sacramento, California 95812**

EH 00-10

**EXECUTIVE SUMMARY
OF REPORT EH 00-10
EVALUATING THE EFFECTIVENESS OF METHYL BROMIDE
SOIL BUFFER ZONES IN MAINTAINING ACUTE EXPOSURES
BELOW A REFERENCE AIR CONCENTRATION**

**Environmental Monitoring Branch
Department of Pesticide Regulation
April, 2001**

Background

Methyl bromide is one of the mostly widely used pesticides in California—about 15 million pounds are applied annually in the State. It is a gaseous fumigant that is used for soil fumigation to control insects, mites, rodents, nematodes, termites, weeds, and organisms that cause plant diseases. It is used prior to planting a variety of fruit, nut, vegetable, and ornamental crops.

Methyl bromide is injected into the soil with specialized application equipment a few weeks prior to planting. Tarpaulins are often used to cover the treated area and contain the gas until the fumigation is complete. Depending upon the crop, field applications may occur annually, or once every several years.

Because methyl bromide has the potential to produce harmful human health effects when inhaled, the Department of Pesticide Regulation (DPR) and the county agricultural commissioners have implemented extensive use restrictions designed to ensure that workers and the general public will not be exposed to unacceptable levels. For the purposes of DPR's regulatory program, an unacceptable level is any detected concentration that exceeds DPR's "reference concentration" of 210 parts per billion (ppb) (815 ug/m^3). The term reference concentration refers to the exposure level that DPR believes represents an acceptable level of risk. Reference concentrations are typically 100 times lower than doses that do not cause adverse effects—or the no-observed-effect level [NOEL]—identified in animal studies. The 100-fold factor accounts for variation in sensitivity between individuals and assumes that people are more sensitive than experimental animals to the effects of methyl bromide.

A key approach used to implement the methyl bromide use restrictions is the establishment of a "buffer zone" around a fumigated field. The buffer zone is an area that surrounds a fumigated field. Within this area, activities are restricted to protect human health and safety.

Purpose:

This study was conducted to evaluate the effectiveness of the methyl bromide buffer zones established by DPR in 2001. To calculate the size of buffer zones, DPR adapted the U.S. EPA Industrial Source Complex-Short Term 3 (ISCST3) model, commonly used for predicting emissions of industrial air pollution. The ISCST3 model predicts air concentrations based on the magnitude of emissions during a period of time (flux), weather conditions at the time of emission

(e.g., wind speed, wind direction, atmospheric stability), and terrain over the downwind area (elevation, urban or rural geography). DPR inputted into the ISCST3 model the following data: 1) a flux value (an estimate of the amount of methyl bromide gas rising from a field over time following a fumigation); 2) the number of acres treated; 3) a standardized set of weather conditions. The calculation resulted in a prescribed buffer zone for specific combinations of field sizes and flux magnitudes. Prescribed buffer zone sizes range from 30 to 3400 feet measured from the edge of the fumigated field, depending on field size and flux (which is related to the amount of methyl bromide used and the method of application).

The intent of the buffer zone is to prevent unacceptable exposures under a wide range of weather conditions. The prescribed buffer zone must take into account these factors by establishing a distance that is protective under different scenarios. For instance, the amount of methyl bromide gas rising from a field declines from time of application, and but the rate of decline can be influenced by such factors as application depth, tarpaulin permeability, and soil moisture, texture, and density. In addition, identical applications may show variations at different times of the year due to differences in meteorological conditions. To calculate buffer zone sizes adequate for most agricultural applications, varying field sizes and methyl bromide flux rates were inputted in all computer simulations with a standard meteorological condition, which approached, but did not represent the worst-case situation.

Within this current study, DPR took two approaches to test the effectiveness of the prescribed methyl bromide buffer zones around a treated field. One method evaluated how often the reference concentration of 210 ppb was exceeded at the outer edge of the prescribed buffer zone. A second method evaluated the effectiveness of the buffer zone distances in maintaining acute exposures below the 210 ppb level. This report also responds to comments made by a National Academy of Sciences panel during its peer review of DPR's methyl bromide risk assessment.

Study Methods

Meteorological data were obtained from the California Irrigation Management Information System weather station network for the five counties with the highest methyl bromide soil application use as documented by California's pesticide use report. The data were screened using U.S. EPA methodology to produce four data sets, each consisting of five years of daily meteorological data for Fresno, Merced, Monterey, and Ventura counties. When combined, the entire data set provided 20 years of daily meteorological data.

Model simulations—the generation of hypothetical data values based upon specific flux, acreage, and historical weather conditions—consisted of daily (24 hour) simulations using the ISCST3 version 99155 model. Simulations covered five field sizes (1, 10, 20, 30 and 40 acres) and five flux values (30, 80, 130, 180 and 225 pounds per acre-day [lbs/acre-day]) to yield 25 combinations of acreage and flux. For each of the 25 acreage/flux combinations, 20 years of daily meteorological data were applied to generate 7,166 data points. Each day of calculation produced either distances to the 210 ppb (815 ug/m^3) reference concentration or air concentrations calculated at the buffer zone distance.

Two cumulative frequency distributions were calculated for distances and air concentrations. One was the cumulative frequency distribution for the maximum air concentration or maximum distance to the reference concentration for each of the field size, flux, and meteorologically defined day combination. This represented a worst-case scenario at each of the simulated field size, flux, and meteorologically defined day combinations.

A second, more comprehensive cumulative frequency distribution was calculated for all distances to the reference concentration, or all concentrations at the buffer zone distance at each of the simulated field size, flux, and meteorologically defined day combinations using all directional vectors surrounding the field size. In other words, these comprehensive cumulative frequency distributions are representative of every direction around a 360 degree arc surrounding every field size. They include values representing all wind directions during the meteorological conditions defining that specific day.

Results

The methyl bromide buffer zones were effective in capturing air concentrations greater than the reference concentration of 210 ppb (815 ug/m^3) for fields ranging from 1 to 40 acres in size using the tested range of flux rates. The level of effectiveness ranged from 100% to 89.2% under the worst case maximum daily distance scenario, and from 100% to 98.6% when the cumulative frequency distribution for distances radiating in all directions from a field was evaluated. The lowest efficiencies were observed in the 40-acre field x 30 lbs/acre-day combination under both testing scenarios when the efficiencies were 89.2% for maximum daily distance and 98.6% for the all directions case, respectively.

The second method of evaluating the effectiveness of the methyl bromide buffer zones using cumulative frequency distributions of the maximum air concentrations at the buffer zones, and air concentrations at the buffer zone distances radiating in all directions from the field produced identical results. In the context of evaluating buffer zone adequacy, air concentration and distance are surrogates for each other due to the unique ISCST3 solution for any given daily meteorological parameter set.

This exercise provided an independent quantitative validation of the prescribed methyl bromide buffer zones, developed using the DPR standard meteorological condition. Buffer zones were effective in including at least 89.2% of air concentrations exceeding 210 ppb (815 ug/m^3) under a worst case scenario where only maximum value of distance and/or air concentrations exceeding the reference concentration when all distances and/or air concentrations were considered.

Outliers

Outlier values most often resulted from meteorological data that were acquired on days that were colder, winter days with stable conditions and lower wind speeds and a higher number of calm hours.

Verification of Model Results

The program-estimated daily required buffer zones closely matched manually derived required buffer zones. Similarly, the comparison between the maximum concentration along the buffer zone and manually derived values was also very close.

Conclusion

This study indicates that the proposed buffer zones achieve the desired result—protection of the public from exposure to unacceptable levels of methyl bromide for most applications. In a small number of applications, the 100-fold safety margin would be reduced. However, it should be noted that although the four counties whose meteorology was used in this study are among the areas of heaviest methyl bromide use, a significant portion of the methyl bromide use in the state (62 percent) occurs in the State's other 54 counties. The four counties used in this study (two coastal and two inland valley) represent varying meteorological conditions, but it is possible that they may not accurately represent statewide conditions and that regional variations may produce differing results.

Another reasonable question is whether there are meteorological conditions that are not captured by the methodology in this study that could lead to high methyl bromide concentrations. For instance, calm meteorological conditions are not simulated by the ISCST3 model (or its replacement model, AERMOD), and yet calm conditions could conceivably lead to high methyl bromide concentrations.

ATTACHMENT I
COMMENTS AND RESPONSE

Office of Environmental Health Hazard Assessment



Winston H. Hickox
Secretary for
Environmental
Protection

Joan E. Denton, Ph.D., Director
Headquarters • 301 Capitol Mall, Rm. 205 • Sacramento, California 95814-4308
Oakland Office • Mailing Address: 1515 Clay Street, 16th Floor • Oakland, California 94612



Gray Davis
Governor

MEMORANDUM

TO: Gary T. Patterson, Ph.D., Chief
Medical Toxicology Branch
Department of Pesticide Regulation
830 K Street
Sacramento, California 95614-3510

FROM: Anna M. Fan, Ph.D., Chief *AMF for AMF*
Pesticide and Environmental Toxicology Section

DATE: September 1, 1999

SUBJECT: COMMENTS ON THE DEPARTMENT OF PESTICIDE REGULATION'S
DRAFT RISK CHARACTERIZATION DOCUMENT FOR INHALATION
EXPOSURE TO THE ACTIVE INGREDIENT METHYL BROMIDE

We have completed our review of the draft risk characterization document (RCD) for methyl bromide prepared by the Department of Pesticide Regulation (DPR). Methyl bromide is a soil, structural, and commodity fumigant used for the control of insects, rodents, nematodes, weeds, and other organisms. From 1991 to 1997, an average of 15 to 19 million pounds of methyl bromide was used per year in California. The majority of use was for soil fumigation (96%), with lesser amounts used for structural (3%), and commodity and nursery fumigation (1%). Methyl bromide is a class one ozone depleter and its use is regulated by the U.S. Clean Air Act and the United Nations Montreal Protocol. In California, it is regulated under the Health and Safety Code Sections 39650 to 39670 (Toxic Air Contaminants, AB 1807), the Food and Agriculture Code Section 13134 (Dietary Risk Assessment, AB 2161), the Birth Defect Prevention Act of 1984 (SB 950), and for structural use only, the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65).

The package submitted to the Office of Environmental Health Hazard Assessment (OEHHA) for review consists of the draft RCD (March 1, 1999) and various appendices (A through I). These appendices include, among other documentation, a summary of toxicology data for methyl bromide (March 5, 1999) and an exposure assessment dated January 11, 1999, prepared by the Worker Health and Safety Branch. Furthermore, on July 14, 1999, staff of DPR and OEHHA met at U.C. Davis to discuss the draft RCD and technical issues identified by OEHHA.

California Environmental Protection Agency



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The draft RCD is one of the more comprehensive and well-written characterizations prepared by DPR under SB 950 to date. However, based on our review of the draft RCD and the July 14 discussion, we still feel that the document needs significant revision before finalization. Our major technical comments are as follows. More detailed comments are provided in the attachment.

1. The draft RCD addresses only inhalation exposures to methyl bromide and states that the potential risk from dietary exposure to methyl bromide residues in food will be addressed in a separate document. This underestimates the potential risk posed by methyl bromide use. A more complete risk assessment would include characterization of oral and dermal exposures in addition to inhalation for methyl bromide. This is especially important for those scenarios in which dermal contact is the primary source of exposure. However, OEHHA concurs with the use of inhalation exposure alone for now, in order to expedite actions to protect public health against the identified hazards of methyl bromide.
2. Application of an additional uncertainty factor to protect infants and children appears to be warranted based on the acute neurotoxic effects of methyl bromide and the data gap for a developmental neurotoxicity study under Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).
3. The methyl bromide RCD does not include adequate information on chloropicrin toxicity, exposure, and interaction with methyl bromide to address the risk of the formulations containing methyl bromide and chloropicrin. This is especially important for those formulations that contain a large proportion of chloropicrin (up to 1:1 with methyl bromide in some cases). Because chloropicrin is much more acutely toxic than methyl bromide (up to about 50 times more potent as an irritant), the acute hazard from the use of some mixtures will be dominated by the effects of chloropicrin. Without this information, the development of mitigation measures might be based on an insufficient analysis of the toxicity of the formulated products. However, the calculated margins of exposure based on methyl bromide alone are so small that any further delay to address the chloropicrin toxicity issues would be counterproductive.
4. Concerns regarding the reliability of the recovery calculations add significant uncertainty to the exposure calculations. Based on information presented at a symposium in June, methyl bromide exposure levels using the results of past ambient air sampling appear to be at least 40% greater than presented in the draft RCD, with correspondingly lower margins of exposure (MOEs).
5. The inclusion of "reference exposure levels" (RELs) with observed exposure levels would be appropriate in order to compare health-based exposure levels with measured air levels. Some

Gary T. Patterson, Ph.D., Chief
September 1, 1999
Page 3

discussion of these limitations is needed in the technical summary and risk appraisal sections. When possible, additional analysis (such as for a characterization of dermal exposures) would be helpful. Inclusion of a summary of chloropicrin toxicity would be important in order to provide an adequate characterization of the risks posed by the use of methyl bromide-containing products in California.

Most of the MOEs for worker exposure scenarios presented in the draft RCD are less than 100, and some are below 1.0, especially for acute exposures (Tables 21 to 24). Assuming that the document was revised to address our technical concerns, these MOEs would be even lower. Given the very low MOEs, it is not clear how the use and exposure pattern could be changed to protect workers. We request an opportunity to comment on the draft mitigation proposals for methyl bromide before they are finalized.

Thank you for the opportunity to comment on the draft RCD for methyl bromide. If you have any questions about our comments, please contact Dr. Michael J. DiBartolomeis or me at (510) 622-3170.

Attachment

cc: Joan E. Denton, Ph.D., Director, OEHHA
Val F. Siebal, Chief Deputy Director, OEHHA
George V. Alexeeff, Ph.D., DABT, Deputy Director for Scientific Affairs, OEHHA
Michael J. DiBartolomeis, Ph.D., PETS/OEHHA

Attachment

Comments on the Draft Toxic Air Contaminant Document for Methyl Bromide

General Comments

The draft risk characterization document (RCD) for methyl bromide is one of the more comprehensive and well-written risk characterizations prepared by DPR under SB 950 to date. We agree with the selection of critical studies and their respective lowest-observed-adverse-effect-levels (LOAELs) or no-observable-adverse-effect-levels (NOAELs). We also acknowledge that the developmental effects of methyl bromide have been discussed extensively. The citation and incorporation of relevant information from the published literature is much more comprehensive than in earlier documents. However, a few other articles may be worth noting, as listed at the end of these comments.

The draft RCD addresses only inhalation exposures to methyl bromide and this is appropriately reflected in the title of the document. The rationale that the Department of Pesticide Regulation (DPR) provides for only considering inhalation exposures in this document is that the majority of exposures to methyl bromide are via inhalation and other exposures such as from dietary residues would be relatively small. We have been informed that a dietary risk characterization is under preparation. Nevertheless, a complete assessment of the risk of methyl bromide from airborne exposures would include characterization of at least dermal exposures to methyl bromide. This is especially important for those scenarios in which dermal contact is the primary source of exposure, such as for workers who wear respirators in areas with relatively high concentrations of methyl bromide (see specific comments).

The application of an additional uncertainty factor to protect infants and children appears to be warranted based on the acute neurotoxic effects of methyl bromide. Neurotoxicity is a major effect of methyl bromide in critical acute, short-term, and subchronic toxicity studies. There is evidence suggesting that children may be more sensitive to these effects than adults. There is also a lack of appropriate neurotoxicity studies to assess the risks of methyl bromide exposure to infants and children. Under the Federal Insecticide, Fungicide and Rodenticide Act, there is a data gap for a developmental neurotoxicity study. We agree with the conclusions in the draft RCD that the calculated margins of exposure (MOEs) categories of workers are extremely low and present a potential health hazard to workers. However, we conclude that the benchmark of 100 for an MOE, which is stated in the draft RCD, is not adequate for short-term exposures of methyl bromide to infants and children. Therefore, we recommend the use of an additional uncertainty factor for potential developmental neurotoxicity, where appropriate.

Recent information presented by DPR staff at a symposium on June 29, 1999 indicated that methyl bromide exposures using ambient air sampling are likely to be underestimated because the

analyses utilized inaccurate recovery estimates. We interpret these findings to mean that actual exposures are at least 40% greater than estimated in the draft RCD, with correspondingly lower MOEs (see specific comments). We recommend that these recent results on air monitoring be described in the RCD.

Chloropicrin is used with methyl bromide in various products at ratios varying from approximately 1:400 to 1:1. Because chloropicrin is much more acutely toxic than methyl bromide (up to about 50 times more potent as an irritant), the acute hazard from the use of some mixtures will be dominated by the effects of chloropicrin. Additive or even synergistic effects are possible, but are not adequately discussed in the draft RCD (mentioned only in Table 7, Appendix E). The minimal discussion of this co-active ingredient in methyl bromide formulations leaves a major gap in the characterization of the toxic potential resulting from use of methyl bromide products. However, because of the magnitude of the hazard as described, we do not recommend delays in completion of this document to address the additional concerns about combined exposures.

An MOE of 100 based on the use of animal studies is generally considered to be a "benchmark MOE" and adequately health-protective by DPR. However, during our joint meeting on July 14, 1999 in Davis, we agreed that an MOE of 100 is not adequately health-protective in all situations for all persons. Therefore, we recommended that in addition to MOE calculations, the RCD include reference exposure levels (RELs) which include appropriate uncertainty factors to protect the health of the most susceptible individuals. When measured or estimated exposure levels are compared to RELs, it is easier to determine by how much an actual or estimated exposure is above or below a health-protective exposure level. The inclusion of RELs should give a more complete characterization of risk than the inclusion of MOEs alone.

While not a part of this draft RCD, we reviewed the document entitled "Toxicological Endpoint Evaluation and Exposure Assessment for Methyl Bromide" prepared by the Methyl Bromide Industry Panel (MBIP) of the Chemical Manufacturer's Association. We also read DPR's memorandum (dated September 25, 1998) containing comments on MBIP's document. We agree with DPR's evaluation of MBIP's document.

Specific Comments

We found the organization of the draft RCD, particularly in the appendix section, to be confusing. For example, duplication of appendices with the same letters (appendices to the draft RCD and sub-appendices to Appendix E) presented some difficulty. This problem is only partially solved by the page numbering (E1, E2, etc.), and the double numbering of many pages lends additional confusion. We recommend using two independent systems for identifying the respective appendices, such as A, B, C and I, II, III.

A discussion of the potentially increased sensitivity of the more susceptible subpopulations, as provided on page 124, should be added to the technical summary on page 7.

We note that 2.8 million pounds of chloropicrin were used in 1997, compared to 15.7 million pounds of methyl bromide (Pesticide Use Report, DPR, 1997). This is particularly relevant in applications to strawberries, for which methyl bromide use in 1997 was 4.1 million pounds, and chloropicrin use was 1.9 million pounds (presumably applied together). Because the volatility and evaporation rate of chloropicrin is lower than that of methyl bromide, it is likely that chloropicrin persists longer in the environment. Therefore, measured levels of methyl bromide in ambient air would not accurately predict chloropicrin levels based on the initial mixture ratio. For example, the observed methyl bromide to chloropicrin ratio after soil fumigation was 1.66 ($1133/681 = 1.66$) and 37.8 ($900/23.8 = 37.8$) in the field and 20 yards away from the field, respectively (page 17, first paragraph, last line). Therefore, it appears that the longer-duration inhalation exposures from use of the combined products could be essentially chloropicrin exposure. Due to the low margins of exposure calculated for the inhalation exposure alone, any further delay to address methyl bromide and chloropicrin co-exposure would be inappropriate. However, these issues could be addressed in the RCD dealing with exposures to methyl bromide in food.

III.D.1. Inhalation - rat

There are some discrepancies between the description given in the toxicology summary for the inhalation toxicity study in rats and in the discussion in the text of the draft RCD. For example, there is no discussion of granular cell myoblastoma at the 30 ppm dose level in the draft RCD as indicated in the toxicology summary.

III E.4. In vitro and in vivo human studies

The draft RCD provides a discussion of the polymorphism of glutathione-S-transferase and its effects on methyl bromide toxicity and mutagenicity. Since glutathione also activates chloropicrin (Schneider et al., 1999), an overall discussion of these two chemicals and the effects of glutathione-S-transferase polymorphism would have been appropriate in this section. We acknowledge, as discussed at the July 14 workshop in Davis, that the effect of this polymorphism on human sensitivity cannot be determined at this time. Nevertheless, we still recommend that additional discussion in the document, such as what was presented by the primary author of the draft RCD at the workshop, would be useful.

III F. & G. Reproductive and developmental studies

It would be worth noting and citing the other rat and rabbit developmental toxicity studies for which data have been submitted to DPR (Appendix D). At least two of these data sets have also been reported in the published literature (Kaneda et al., 1993, 1998).

IV.B. Exposure assessment

Risk evaluations in the draft RCD are based on the inhalation route and occupational exposures only, and do not account for other routes and aggregate exposures. It is possible that a soil fumigant worker could live in a nearby home and have additional residential exposures to methyl bromide. This could be discussed in the context of number of days exposed in the exposure assessment.

Information presented by DPR staff at a methyl bromide symposium on June 29, 1999 indicated that methyl bromide exposures using ambient air sampling with charcoal tubes are likely to be underestimated because the analyses utilized inaccurate recovery estimates. One of the authors of the report entitled "Evaluation of charcoal tube and SUMMA canister recoveries for methyl bromide air sampling" (DPR, EH 99-02) raised the issue that due to the inaccurate recovery estimates, actual exposures may be at least 40% greater than earlier estimates (as presented in the draft RCD). This was based on a mean methyl bromide recovery from field spikes using charcoal tubes of 49%, compared to the previously used values of 69% to 88% (pages E51 to E95). Data from one six-hour day time collection (EH 99-02, Table 6) showed average recoveries of only 23%. The authors conclude "To account for these differences, DPR will review air concentrations listed in past studies and make appropriate adjustments, and will review the methyl bromide sampling methodology used in future studies." The authors also state, "The fact that 6-hour sampling with charcoal tubes during the day recovered less methyl bromide than 12-hour sampling with charcoal tubes at night needs further study" (EH 99-02, page 5). We agree with these conclusions and recommend that the exposure calculations presented in the draft RCD be re-evaluated based on the new recovery data. Based on the discussion at the symposium, the MOEs for methyl bromide that rely on the results of the ambient air monitoring are likely to be significantly lower than those presented in the draft RCD.

We cannot comment much on the quantitative significance of dermal exposure to methyl bromide and the potential risks of consuming treated produce because these analyses were outside the scope of the draft RCD. Some discussion of these additional exposure routes and mechanisms would be useful in the document.

For example, the draft RCD assumed a personal protection factor of 10,000 (based on the NIOSH guidelines for self-contained breathing apparatus) used during space fumigation at a brewery (page E92, Table 32). This appears to be the protection factor for respiratory hazard only, which would not incorporate the potential for dermal exposures. However, methyl bromide can be absorbed through skin and high concentrations have been noted to cause dermal toxicity (page 15, paragraph four). Chloropicrin also has a high skin hazard rating. Assuming under the conditions of space fumigation that dermal exposure would provide about 1 to 5% of the unprotected inhalation dose, dermal exposure would be 100 to 500 times greater than that received by inhalation during this task assuming the mask truly provides a 10,000-fold inhalation protection factor. Therefore, the acute MOEs for the brewery activities would be in the range of about 1 to 10, rather than 241 to 1,458, as stated in the draft RCD. Failure to address the potential hazard from dermal exposures when working in a high-concentration environment, wearing respiratory protection, is a significant limitation of the RCD. This specific analysis should be included

regardless of the extent of the general discussion on dermal exposure that is added based on our previous comments.

IV.C. Risk characterization

MOEs for approximately 25% of the acute, 26% of the short-term, and 50% of the seasonal exposure estimates are below 100 (Tables 21 to 24). Most of these MOEs are in the range of 1 to 50 and some are even less than 1.0, especially for the seasonal exposure scenarios. Actual exposures will vary widely from the mean values given, and are likely to be underestimated because of the apparently erroneous methyl bromide analytical recovery values used for these calculations in the draft RCD. This suggests an ongoing hazard to workers from the use of this pesticide.

Limitations and uncertainties of the exposure assessment are presented in Appendix E (Exposure Appraisal, page E35). For example, the use of repeated estimates from one location, lack of recovery study and standards, missing application rates, and limited data on frequency and duration of exposures might affect the MOEs. While this is a useful qualitative discussion, it could be improved by adding a more quantitative discussion of the variability of the exposure estimates (i.e., the distribution of potential acute, short-term, and seasonal exposures).

In several instances a default exposure estimate of 210 ppb has been used in the exposure assessment calculation (see page E103, Table 37) because of its designation as a "regulatory limit under permit conditions" (page 13, paragraph four). The calculated MOEs should be based on actual or estimated exposures, not on a "regulatory limit" that might not be solely health-based. We recommend that risk estimates calculated based on the "regulatory limit" of 210 ppb also be calculated based on actual or estimated exposures, providing a range of values in the RCD if necessary.

V. Risk appraisal

The risk appraisal is well written and comprehensive for inhalation exposures. As already noted the need for further incorporation of other exposure routes (especially dermal exposures), and combined exposures with chloropicrin should be acknowledged in the risk characterization and Executive Summary.

References

De Vreede et al. (1998). Exposure to methyl bromide during greenhouse fumigation on Crete, Greece. *Arch Environ Contam Toxicol* 35(3):539-547.

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Goldman et al. (1987). Acute symptoms in persons residing near fields treated with the soil fumigant methyl bromide and chloropicrin. *West J Med* 147(1):95-98.

Horowitz et al. (1998). An unusual exposure to methyl bromide leading to fatality. *J Toxicol Clin Toxicol* 36(4):353-357.

Kaneda et al. (1993). A two generation reproduction study in rats with methyl bromide fumigated diet. *Food Chem Toxic* 31:533-542.

Kaneda et al. (1998). Oral teratogenicity studies of methyl bromide in rats and rabbits. *Food Chem Toxicol* 36(5):421-427.

Schneider et al. (1999). Glutathione activation of chloropicrin in the *Salmonella* mutagenicity test. *Mut Res* 439:233-238.

Wilson et al. (1998). Methyl bromide: 1-year dietary study in dogs. *Food Chem Toxicol* 36(7):575-584.

Wong et al. (1984). Mortality of workers potentially exposed to organic and inorganic brominated chemicals, DBCP, TRIS, PBB, and DDT. *Brit J Indust Med* 41:15-24.



Winston H. Hickox
Secretary for
Environmental
Protection

Department of Pesticide Regulation

Paul E. Helliker, Director
830 K Street • Sacramento, California 95814-3510 • www.cdpr.ca.gov



Gray Davis
Governor

MEMORANDUM

TO: Joyce Gee, Acting Branch Chief

FROM: Lori O. Lim, Staff Toxicologist

Lori O. Lim

DATE: September 16, 1999

SUBJECT: Methyl Bromide

The following is my response to the comments provide by the Office of Environmental Health Hazard Assessment (September 1, 1999) on the draft risk characterization document on Methyl Bromide for Inhalation (March 1, 1999). Comments on the occupational and residential exposure assessment will have to be addressed by the Worker Health and Safety Branch.

Major Technical Comments:

p. 2, item#2: Application of an additional uncertainty factor to protect infants and children appears to be warranted.

Response: The need to consider such a factor is discussed in the document. The application of the factor is a risk management decision.

p. 2, item #3: The RCD should include adequate information on chloropicrin toxicity.

Response: The use of chloropicrin alone and in the conjunction with methyl bromide is a health concern. However, as indicated by OEHHA's comments, the time it takes to provide an adequate coverage of chloropicrin in this RCD would result in the delay of mitigation measures for methyl bromide. Therefore, only a summary of the use and toxicity of chloropicrin will be provide in an Appendix in the revised RCD (Attachment 1 of this memo). A risk characterization document for chloropicrin is currently underway.

p.2, item #5. "Reference exposure levels" (RELs) should be included.

Response: As agreed at the July 14, 1999 meeting, reference concentrations will be added to the table with the critical NOELs.

General Comments from the Attachment

(same as those above for the Major Technical Comments)

Specific Comments

Attachment p.2, 4th ¶: Duplication of appendices with the same letters are confusing.

Response: Since some of appendices were written by other Branches and they are stand-alone documents, the numbering system is therefore not consistent.

Attachment p.2, 5th ¶: Potential increased sensitivity of susceptible subpopulations should be added to the technical summary.

Response: This will be mentioned in the technical summary.

Attachment p.3, III.D.1: Granular cell myoblastoma needs to be added to the text for the study.

Response: This will be added to the text for the study.

Attachment p.3, III.E.4.: Additional discussion, as presented at the July 14 meeting, on the polymorphism of glutathione-S-transferase is needed.

Response: Additional discussion will be added to the Risk Appraisal section (Attachment 2 of this memo).

Attachment p.3, III.F. & G.: The rat and rabbit developmental toxicity studies (Kaneda et al. 1998) and the rat reproductive toxicity study (Kaneda et al. 1993) should be included.

Response: These studies will be included in revised RCD (Attachment 3 of this memo). The results from these studies do not change the critical NOELs used to calculate the MOEs for inhalation exposure.

cc. Keith Pfeifer
Gary Patterson



CHLOROPICRIN



1. Introduction

This appendix contains general information on chloropicrin which is used as a warning agent in some of the methyl bromide products. A comprehensive review will be conducted in the Risk Characterization Document for chloropicrin as an active ingredient.

Chloropicrin (trichloronitromethane, nitrochlorform, nitrotrichloromethane) is a colorless, slightly oily, heavy liquid with an intense irritating tear gas odor (The Merck Index, 1989; Farm Chemicals Handbook, 1998). In a mixture with methyl bromide, it volatilizes readily when released from the tanks (Extoxnet, 1999). Chloropicrin has been used as an insecticide since 1917 and as a soil fumigant since 1920 (Extonet, 1999). As a pesticide for space and soil fumigation, it controls nematodes, bacteria, fungi, insects, and weeds. In 1999, there are 44 active registered products with chloropicrin in California. The registrants for these products are: Ameribrom, Inc.; Great Lakes Chemical Corp.; Soil Chemicals Corp.; Niklor Chemical Co.; Holtrachem Manufacturing Co.; Trical, Trinity Manufacturing, Inc.; Osmose Wood Preserving, Inc.; and Shadow Mountain Products Corp. Twenty-six of the products are in combination with methyl bromide, while 8 of the products are in combination with 1,3-dichloropropene (telone).

From 1993 to 1997, the use of chloropicrin increased from 2.1 million pounds in 1993 to 2.8 million pounds in 1995, 1996 and 1997. The majority of the total use (>67%) is for strawberry fields in efforts to decrease the amount of methyl bromide applied. The use of methyl bromide for all uses are under strict use permit conditions requiring a minimum buffer zone of 100 feet for residents and 30 feet for workers.

From 1982 to 1996, there were a total of 363 cases with health effects "definitely", "probably", or "possibly" related to chloropicrin exposure reported in the California Pesticide Illness Surveillance Program (Mehler, 1999). Systemic effects as well as local effects to the eye and skin were reported. Some of the reported cases were due to drift from application sites. The highest number of cases was reported in 1987 where 71 residents in a nearby labor camp were exposed to chloropicrin being applied to a 9- acre field. Fumes were detected and the residents showed symptoms of exposure.

As a warning agent, the odor threshold is 1.1 ppm while 0.3 to 0.37 ppm results in painful irritation to the eyes in 3-30 seconds (ACGIH, 1997). For occupational exposure, the American Conference of Governmental Industrial Hygienists (ACGIH) has recommended a Threshold Limit Value (TLV^R) of below 0.1 ppm for occupational exposure and measured as an 8-hour time-weighted average air concentration. This level would protect for eye irritation. This level has been adopted as the Permissible Exposure Limit (PEL) by the Occupational Safety and Health Administration and the

California Occupational Safety and Health Administration. Respiratory protection for workers is required if the air level exceeds 0.1 ppm. National Institute of Occupational Safety and Health has established 2 ppm as the Immediately Dangerous to Life and Health (IDLH) level. In California, the Reference Exposure Levels are 4.4 ppb and 13 ppb for mild and severe effects, respectively (OEHHA, 1999).

2. Toxicology

2.a. Acute Toxicity

Because of its acute toxicity, chloropicrin is in toxicity category I, under FIFRA toxicity classification, and is a restricted use pesticide. It is a severe irritant to the eye, skin, and upper respiratory tract. The dose response for chloropicrin is considered steep. In humans, the no observable effect is 100 ppb (ACGIH, 1997). At 300 ppb, cough, nausea, and vomiting occur. Direct skin contact results in severe skin irritation. A summary of concentration for lethality and acute effect is presented in Table E1.

2.b. Other Toxicity Studies

Toxicity studies submitted for the fulfillment of SB 950 data requirement and reviewed under FIFRA guidelines are summarized in Table E2.

Table E1. Acute toxicity of chloropicrin in experimental animals and human.

Species	Inhalation LC 50	Inhalation (non lethal effects)	Oral LD50	Dermal LD50	Reference
Human	2000 ppm (10 min) as lethal dose		5 to 50 mg/kg as lethal dose		HSDB, 1994
Human	200 ppm (10 min) as lethal dose				Prentiss, 1937
Rat	25.5 ppm (1 hr) ^a		37.5 mg/kg ^a	100 mg/kg ^a	U.S. Testing Co. Inc., 1976
Rat	11.9 ppm (4 hr) ^b				Yoshida <i>et al.</i> , 1987a
Mouse		8-9 ppm ^c			Kane et al., 1979
Mouse	9.9 ppm (4 hr)				HSDB, 1994
Dog	134 ppm (30 min) "majority" dead				Lambert and Jackson, 1920
Cat	120 ppm (20 min)				HSDB, 1994
Guinea Pigs	120 ppm (20 min)				HSDB, 1994

a/ Lethal doses were based on deaths within 14 days.

b/ Rats were exposed to chloropicrin (0, 8.8 to 16 ppm) for 4 hours. Necropsy showed lung lesions (edema, emphysema) and gastric distension. All animals showed reduced body weights.

c/ RD50= dose which caused 50% decrease in the respiration rate.

Table E2. Summary of findings from toxicity studies in the SB 950 database.

Species /Route (Dose)	NOEL	Effects	Ref
Subchronic Toxicity			
Rat / inhalation (0, 0.37, 0.67, 1.58, or 2.93 ppm)	0.67 ppm	↓ body weights, food consumption and food efficiency; ↑ lung weights; ↑ epithelial hypertrophy of bronchus and bronchiole	1
Chronic Toxicity			
Rat / oral gavage (0, 0.1, 1.0, or 10 mg/kg/day for 2 years)	<0.1mg/kg/day	Periportal vacuolization of hepatocytes	2*
Dog / oral capsule (0, 0.1, 1.0, or 5.0 mg/kg/day for 1 year)	1.0 mg/kg/day	↓ body weight (male), MCV, MCH, total protein and albumin	3*
Mouse/ inhalation (0, 0.1, 0.5, or 1.0 ppm for at least 78 weeks)	0.1 ppm	↓ body weight and body weight gain (both sexes), food consumption (females); ↑ lung weights; and lung and kidney lesions	4*
Oncogenicity			
Rat / oral gavage (0, 0.1, 1.0, or 10 mg/kg/day for 2 years)	NA	stomach papilloma (1 male), ↑ mammary fibroadenomas in 10 mg/kg females	2*
Mouse / inhalation (0, 0.1, 0.5, or 1.0 ppm for 78 weeks)	NA	No oncogenic effects	4*
Reproductive Toxicity			
Rat / inhalation (0, 0.5, 1.0, or 1.5 ppm for 2 generations)	Systemic effects 0.5 ppm	↓ body weight, and macro, microscopic lung lesions (F0 females) No pup or reproductive effects	5*
Developmental Toxicity			
Rat / inhalation (0, 0.4, 1.2, or 3.5 ppm on gestation day 6 to 15)	Maternal 1.2ppm	↓ body weight, body weight gain, and food consumption;↑ clinical sign	6*
	Fetal 0.4 ppm	↑ skeletal variations	
Rabbit / inhalation (0, 0.4, 1.2, or 2.0 ppm on gestation day 7 to 20)	Maternal 0.4 ppm	↑ clinical signs, abortions, and mortality	7*
	Fetal 1.2 ppm	↑ skeletal variations	
Genotoxicity			
Mouse lymphoma cells	NA	No increase in forward mutation frequency	8*
<i>S. typhimurium</i> 5 strains	NA	↑ revertant colonies ± rat liver S9	9*
Chinese hamster ovary cells	NA	↑ chromosomal aberrations	10*
Rat primary hepatocytes	NA	No effect on unscheduled DNA synthesis	11*

a/ * Studies were considered acceptable under FIFRA guidelines. Reference: 1. Yoshida *et al.*, 1987b; 2. Slaughter, 1995; 3. Wisler, 1994; 4. Burleigh-Flayer *et al.*, 1995; 5. Schardein, 1994; 6. Schardein, 1993; 7. York, 1993; 8. San *et al.*, 1990a; 9. San *et al.*, 1990b; 10. Putman and Morris, 1990; and 11. Curren, 1990. NA= not applicable.

V.D.2. Intraspecies Extrapolation

For intraspecies variation in the response to methyl bromide, the default uncertainty factor of 10 was used because human illness/poisoning reports did not provide sufficient information to derive another factor. In these reports (discussed in **III.H. Neurotoxicity**), some individuals showed more severe symptoms than others. However, this difference in response was not quantified, and may only be quantified in well-conducted experimental studies.

Studies on the role of glutathione-S-transferase (GST) in methyl bromide metabolism and toxicity also provided evidence for variations in human response to methyl bromide. The glutathione-S-transferases are a multi-gene family of enzymes involved in the metabolism (activation and detoxification) of a wide variety of chemicals (Eaton and Bammler, 1999). They catalyze the general reaction: $\text{GSH} + \text{R-X} \rightarrow \text{GSR} + \text{HX}$. The mammalian soluble GSTs are divided into 4 main classes, alpha (A), mu (M), pi (P), and theta (T). The role of these enzymes in individual susceptibility to chemical exposure and toxicity is difficult to determine because of the large number of isozymes in the body. Second, GST expression varies among tissues. Not all isoforms are found in every tissue or all species. One important example, with respect to methyl bromide, is GSTT which is found in the human erythrocytes but not in rodent erythrocytes. Third, GSTs have been found to be polymorphic in the human population. There are individuals who do not have the gene for certain GSTs. It has been determined that 50% of the Caucasian population do not have GSTM1, and 16% do not have GSTM3. GSTT has been found to be variable among different ethnic groups. The percentages of the population without the GSTT gene ranged from 9.7 % (Mexican-Americans) to 64.6 % (Chinese-Americans), as cited by Garnier *et al.* (1996). With GSTP, the different variants of the enzyme are due to the transition mutation of a codon (s) such that other amino acids are expressed.

Methyl bromide has been identified as a substrate for GSTT (Eaton and Bammler, 1999). In 1990, Hallier *et al.* (1990) showed that when human erythrocyte cytoplasm was incubated with methyl bromide, there was a loss of methyl bromide in the gas phase with the formation of S-methylglutathione via an enzymatic reaction. Individuals which showed this activity were designated as "conjugators" while those with activity level comparable to boiled erythrocyte cytoplasm were "non-conjugators".



This interaction of methyl bromide with sulfhydryl groups has been used in the study of methyl bromide workers. Iwasaki *et al.* (1989) and Goergens *et al.*, (1994) showed methylcysteine levels in hemoglobin proteins were higher in some methyl bromide workers compared to controls (Details of these studies are in **III.E.4.**). However, a quantitative relationship between adduct level and exposure was not determined.

There is evidence which shows conjugators, i.e., individuals with GSTT, may be more protected than non-conjugators from the genotoxicity of methyl bromide. In the study by Hallier *et al.*, (1993), methyl bromide was incubated with whole blood from conjugators and non-conjugators. Lymphocytes from conjugators had lower number (range of 6.51 to 7.95) of sister chromatid exchanges per cell than non-conjugators (range of 10.19 to 13.97) for the non-conjugators. The lower level of SCEs in the conjugators, compared to the non-conjugators, was

attributed to the reduced amount of methyl bromide available to interact with lymphocyte DNA because of reaction with erythrocyte proteins mediated by GSTT.

On the other hand, there is evidence that shows methyl bromide reaction with GST may be involved in the manifestation of neurotoxicity. In Davenport *et al.*, (1992), GST activity was inhibited in the brain of rats exposed to methyl bromide (details in **III.B.1.**). The GST activity was protected when the rats were either pre- or post-treated with an inhibitor of monohalomethane toxicity. In a report of poisoning of two workers, the non-conjugator had fewer neurotoxic effects when compared to the conjugator (Garnier *et al.*, 1996) (details in **III.H.1. Occupational Exposure**). The formation of S-methylglutathione, via conjugation of methyl bromide with GSH, in the brain of the conjugator was hypothesized to be involved in the neurotoxicity. The non-conjugator also had 2-fold higher concentrations of S-methylcysteine adduct in the erythrocytes; but the reaction was considered non-enzymatic.

In conclusion, the data shows that the interaction of methyl bromide and GST is complex. While the polymorphism of GSTT in the human population is important to consider, it is not possible to determine whether or not this variation is sufficiently addressed within the 10-fold default intra-individual factor.

Attachment 3: Addition of studies by Kaneda et al on developmental and reproductive toxicity.

III.F.2. Oral - Rat

In a published study to investigate the effects of methyl-bromide fumigated feeds, Crj:CD (SD) rats (24/sex/group) were given either basal diet or fumigated feed (80 ppm, 200 ppm, or 500 ppm total bromine) for 18 weeks for each generation (Kaneda *et al.*, 1993). Methyl bromide concentration was reported as < 20 ppb but analytic data were not given. Using the average consumption rates provided in the report, the exposure in terms of methyl bromide was approximately 200 ng/kg/day (average body weights of 0.35 kg and 0.25 kg for males and females, respectively, and consumption rates of 25 g/week and 20 g/week for males and females, respectively). The significant effects were reduced food consumption in the 500 ppm total bromide F1 parental females during the weeks 9 and 10 of the premating period and on days 0 to 21 of lactation (87-93% of controls), and lowered body weights throughout the lactation period of 500 ppm total bromide F2 female pups (91-95% of controls). Since the actual methyl bromide concentration in each dose is not known, it is not possible to determine whether the effects were due to bromine itself or methyl bromide.

III.G.3. Oral - Rat

Pregnant rats (Crj:CD (SD), 23-24 rats/dose) were given methyl bromide (purity 99.5%; 0, 3, 10, or 30 mg/kg) dissolved in corn oil by gavage on gestation days 6-15 and sacrificed on day 20 (Kaneda *et al.*, 1998). No clinical signs were observed. Food consumption and weight gain were reduced in the dam of the 30 mg/kg group. Food consumption was also reduced in the control group given corn oil; this suggested that the effect may be related to large volume of corn oil used (10 mL/kg) or the method of administration. At necropsy, all dams in the 30 mg/kg group showed erosion and thickening of the wall in the nonglandular part of the stomach and adhesions between the stomach and the spleen, liver or diaphragm. In the fetuses from the 30 mg/kg dams, there were increased incidences of microphthalmia in 2 fetuses (two litters, 8% incidence), and having 25 (not 26) presacral vertebrae count in 5 fetuses (two litters, 8% incidence). While neither effect was statistically significant, no cases were observed in the control group. This study was considered supplemental information by DPR.

III.G.4. Oral - Rabbit

Pregnant rabbits (Kbl:JW, 15-18 rabbits/dose) were given methyl bromide (purity 99.5%; 0, 1, 3, or 10 mg/kg) dissolved in corn oil by gavage on gestation days 6-18 and sacrificed on day 27 (Kaneda *et al.*, 1998). No clinical signs were observed. Food consumption and weight gain were reduced in the 10 mg/kg does. In fetuses, total litter resorption occurred with 2 high-dose does and one control doe; the number of resorptions involved were not indicated. Skeletal malformations involving 2-3 litters in at least one methyl bromide-treated group included: splitting of the nasal/frontal/parietal bones; hemivertebra; fusion of the ribs/sternbrae; and absence of the metacarpal and phalangeal bones. While the number of fetuses with malformation were higher in the treated groups than the control groups; the increase was neither statistically significant at the litter level nor related to the dose. This study was considered supplemental information by DPR.



Winston H. Hickox
Secretary for
Environmental
Protection

Department of Pesticide Regulation

Paul E. Helliker, Director
830 K Street • Sacramento, California 95814-3510 • www.cdpr.ca.gov



Gray Davis
Governor

MEMORANDUM

TO: Chuck Andrews, Branch Chief
Worker Health and Safety Branch

HSM-99017

FROM: Tom Thongsinthusak, Staff Toxicologist
Worker Health and Safety Branch
(916) 445-4267

Tom Thongsinthusak

DATE: September 15, 1999

SUBJECT: METHYL BROMIDE: RESPONSES TO COMMENTS FROM OEHHHA

The following are my responses to comments from the Office of Environmental Health Hazard Assessment (OEHHHA) concerning the methyl bromide (MB) exposure assessment document dated January 11, 1999. OEHHHA sent Gary Patterson a draft memorandum dated August 24, 1999 and a final memorandum dated September 1, 1999. On July 14, 1999, staff of the Worker Health and Safety Branch responded to some of those comments at the meeting at U.C. Davis.

1. OEHHHA contended that dermal exposure is important for those scenarios in which dermal contact is the primary source of exposure, such as for workers who wear respirators in areas with relatively high concentrations of MB (Memorandum page 2 (paragraph 2); attachment pages 1 (paragraph 2) and 4 (paragraph 4)).

Based upon illness reports in the literature, there is the potential for significant dermal exposure of workers who wear self-contained-breathing apparatus (SCBA) in high MB concentration environment and work in the area for extended periods. Zwaveling *et al.* (1987) and Hezemans-Boer (1988) reported skin lesions in six workers eight hours after exposure for 40 minutes to high concentration of MB of approximately 40 g/m³ or 10,000 ppm during the fumigation of an enclosed building. These workers wore coveralls on top of normal daily clothing, PVC gloves, and work shoes. During the actual fumigation, these workers breathed pressurized air from a portable container through a tight fitting facemask. The skin lesions consisted of sharply demarcated erythema with multiple vesicles and large bullae. The lesions were limited to parts of the skin that were relatively moist and/or subjected to mechanical stress such as the armpits, the groin, the labia, the vulva, the penis, the scrotum, the rima ani, the navel, and the skin under the waistbelt. The mean plasma bromide concentration for samples collected immediately after the exposure and 12 hours after the exposure were 95 ± 15 and 72 ± 24 µmol/L, respectively. It is possible that MB absorption is increased in this partly lipophilic (sebaceous glands) and partly hydrophilic (sweat glands) environment (Zwaveling *et al.*, 1987). The percentage of dermal absorption could not be determined. Healing of the skin lesions of these workers occurred in 2 weeks. Deschamps and Turpin (1996) reported illnesses of two experienced fumigators who wore a cartridge respirator with activated charcoal. They entered a building where the concentration of MB was 17g/m³.



09/15/99

Under the very high MB concentration environment, it is likely that the respirator was rapidly saturated with MB. It is for this reason that NIOSH does not recommend any air-purifying respirator for MB.

Dermal absorption of vapors of chemicals other than MB was studied. Four human volunteers (naked excepted shorts) were exposed to styrene vapors in the air within the concentration range of 1,300 to 3,200 mg/m³ for 2 hours (Wieczorek, 1985). These volunteers (3 men and 1 woman aged 25-35) breathed pure air from outside through a respirator. The results showed that dermal absorption of the styrene vapors contributed about 5% to the amount absorbed in the respiratory tract under the same conditions when the subjects did not wear a respirator. Riihimaki and Pfaffli (1978) studied percutaneous absorption of xylene, styrene, toluene, 1,1,1-trichloroethane, and tetrachloroethane vapors employing restricted numbers of human volunteers (n = 2-3 for each kind of vapor). The percutaneous absorption when the volunteers were exposed to moderate air concentrations of 300 and 600 ppm for 3.5 hours were about 0.1 to 2% of the amount estimated to be absorbed from the unprotected respiratory tract.

McDougal *et al.* (1985) studied dermal absorption of dibromomethane (DBM, 500 to 10,000 ppm) and bromochloromethane (BCM, 2,500 to 40,000 ppm) vapors in rats. The percentage of body burden, which was due to penetration of the skin, would be 5.8% for DBM and 4.2% for BCM. The observed permeability constants in rats for styrene, xylene, toluene, perchloroethylene, benzene, halothane, hexane, and isoflurane were estimated to be two to four times greater than the human permeability constants calculated from the available literature data (McDougal *et al.*, 1990). Based upon the difference in absorption of various chemical vapors in rats and humans, the percentage of body burden in humans was assumed to be 1.5 to 2.9% for DBM and 1.1 to 2.1% for BCM.

In conclusion, the dermal absorption of MB can be significant based upon reported illnesses of individuals with SCBA exposed to high concentration of MB for extended periods. Dermal exposures of other gases in humans such as styrene, xylene, styrene, toluene, 1,1,1-trichloroethane, tetrachloroethane, dibromomethane, and bromochloromethane can be in the range of 0.1-5% of the unprotected respiratory exposure. However, there is no chemical-specific dermal absorption study for MB; we cannot meaningfully estimate dermal exposure at this time.

2. Chloropicrin exposure assessment (Memorandum page 2 (paragraph 4); attachment page 2 (paragraph 2)).

Currently, chloropicrin exposure assessment has not been initiated. This chemical has been placed in a high priority list under the Birth Defect Prevention Act of 1984 (SB 950). I assume that the exposure assessment may be initiated depending on the priority of the Department's risk assessment.

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3. Adjustment of MB exposure estimates for recovery deficiencies (Memorandum page 2 (paragraph 5); attachment page 4 (paragraph 2)).

Most estimates in the MB exposure document (January 11, 1999) were adjusted for the percentages of recoveries of 69% (majority), 71.4%, 88%, and 74-125%. I did not adjust the exposure estimates obtained from two studies – fumigation of dried fruits and tree nuts, and a brewery facility because the submitted reports did not provide information on the recovery study.

Based upon a recent public notice from Paul Helliker, the Director of the Department of Pesticide Regulation (DPR), I will assume that I have to adjust the air monitoring data to reflect the percentage recovery of 50%. This percentage recovery was obtained from a recovery study conducted by Biermann and Barry (1999).

4. In several instances a default estimate of 210 ppb has been used in the exposure assessment calculation because of its designation as a "regulatory limit under permit conditions." OEHHA recommended that risk estimates should also be calculated based on actual or estimated exposure (Attachment page 5 (paragraph 4)).

There was no actual measurement for MB acute exposure on day one after a 72-hour active aeration period for fumigated houses. Residents were assumed to be exposed to a target level of 210 ppb (24-h TWA). This is a conservative exposure level because MB air concentrations of fumigated houses are likely to be lower than 210 ppb according to the following calculation.

Human exposure potential to MB in recently fumigated houses:

Ideal gas law $C_1 V_1 = C_2 V_2$ or $C_2 = (V_1/V_2) C_1$

Active ventilation (e.g., 3,000 ft³/min) period = 3 days

MB levels in wall voids (V_1) (e.g., electrical sockets) = 3 ppm (C_1)

Exposure potential to reoccupants (C_2) in fumigated houses (V_2):

$$\begin{aligned} \text{WV/DV (or } V_1/V_2) &= 0.056 \pm 0.004 \text{ (Johnson, 1992)} \\ C_2 &= 0.056 \times 3,000 \text{ ppb} \\ &= \underline{168 \text{ ppb}} \end{aligned}$$

(WV, wall volume; DV, dwelling volume)

The same default of 210 ppb was also used for exposure of residents who live near fumigated fields and commodity fumigation facilities. Therefore, MOEs for acute exposure cannot be calculated based on actual or estimated exposure for residents.

5. A quantitative discussion of the variability should be provided in the exposure appraisal section (Attachment page 5 (paragraph 3)).

Information on some of the variables, such as the use of repeated estimates from one location, lack of recovery study and standards, missing application rates, or limited data on frequency and duration of exposure, is intended to be qualitative in nature. It is difficult to judge quantitatively how these variables might affect MOE. For example, if the application rate was not mentioned, the rate could be at the maximum application rate. Hence, this variable would have no effect on MOE. Furthermore, we do not know if more data on frequency and duration of exposure would

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affect MOE and to what extent. I think that we do not have sufficient background information to assign numbers to those variables. If we do so, it will cause some uncertainty concerning those assigned numbers.

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cc: Gary Patterson
Sue Edmiston

(MB-MSW/HS-99017)