

APPENDIX L

**COMMENTS FROM THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT
AND RESPONSES TO COMMENTS**

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 *MMQ 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
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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.
- Dimitriou and Tsoukali (1998). Personal and environmental air sampling of methyl bromide during experimental greenhouse fumigation. *J Environ Health B* 33(3):267-277.
- Garry et al. (1990). Preparation for human study of pesticide applicators: sister chromatid exchanges and chromosome aberrations in cultured human lymphocytes exposed to selected fumigants. *Teratogen Carcinogen Mutagen* 10(1):21-29.
- 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, nitrochloroform, 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 (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 <i>et al.</i> , 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*

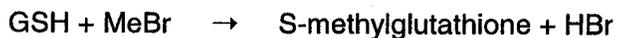
a/ * Studies were considered acceptable under FIFRA guidelines. Reference: 1. Yoshida *et al.*, 1987b; 2. Slauter, 1995; 3. Wisler, 1994; 4. Burleigh-Flayer *et al.*, 1995; 5. Schardein, 1994; 6. Schardein, 1993; 7. York, 1993; 8. San *et al.*, 1990a; 9. San *et al.*, 1990b; 10. Putman and Morris, 1990; 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: $GSH + R-X \rightarrow GSR + HX$. 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 pre-mating 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/sternae; 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 Tom Thongsinthusak
(916) 445-4267

DATE: September 15, 1999

SUBJECT: METHYL BROMIDE: RESPONSES TO COMMENTS FROM OEHHA

The following are my responses to comments from the Office of Environmental Health Hazard Assessment (OEHHA) concerning the methyl bromide (MB) exposure assessment document dated January 11, 1999. OEHHA 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. OEHHA 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/m^3 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 $72 \pm 24 \text{ } \mu\text{mol/L}$, 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 17 g/m^3 .

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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.

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 $C_1V_1 = C_2V_2$ 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)