08-063

Office of Environmental Health Hazard Assessment

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MEMORANDUM

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DATE: June 3, 2009

SUBJECT: REVISED COMMENTS ON DRAFT RISK CHARACTERIZATION DOCUMENT FOR INHALATION EXPOSURE OF METHYL IODIDE (IODOMETHANE)

Enclosed please find a copy of the Office of Environmental Health Hazard Assessment's (OEHHA) revised comments on the Department of Pesticide Regulation's (DPR) Draft Risk

Characterization Document, dated March 2009, for the active ingredient methyl iodide. The draft consists of three volumes: Volume I, Health Risk Assessment; Volume II, Exposure Assessment; and Volume III, Environmental Fate. A copy of OEHHA's comments on the draft document was submitted to DPR on May 1, 2009. The revised comments provide editorial changes and added references to the comments submitted.

Under the general authority of the Health and Safety Code, Section 59004, and the Food and Agricultural Code (FAC), Section 13129, OEHHA has the authority to provide advice, consultation, and recommendations to DPR concerning the risks to human health associated with exposure to pesticides. Pursuant to FAC Sections 14022 and 14023, OEHHA provides consultation and technical assistance to DPR on the evaluation of health effects of candidate toxic air contaminants (TAC) and prepares health-based findings.

Should you have any questions regarding OEHHA's comments on the draft Risk Characterization Document on Methyl Iodide, please contact Dr. Anna M. Fan at (510) 622-3165, Dr. Melanie Marty at (510) 622-3154, or Dr. David Ting at (510) 622-3226

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OEHHA comments on the draft Risk Characterization Document for Inhalation Exposure to Methyl Iodide (Iodomethane)

Introduction

The Office of Environmental Health Hazard Assessment (OEHHA) reviews risk assessments prepared by the Department of Pesticide Regulation (DPR) under the general authority of the Health and Safety Code, Section 59004, and also under the Food and Agricultural Code (FAC), Section 13129, in which OEHHA has the authority to provide advice, consultation, and recommendations to DPR concerning the risks to human health associated with exposure to pesticides. Pursuant to Food and Agricultural Code Sections 14022 and 14023, OEHHA provides consultation and technical assistance to DPR on the evaluation of health effects of candidate toxic air contaminants (TAC) and prepares health-based findings.

Methyl iodide (MeI) is being considered as a new pre-plant soil fumigant to be used in California. It can be used to control soil-borne pests in fields intended for crops such as strawberries and tomatoes, trees and vine re-plant, and ornamental plants. MeI is being considered to replace methyl bromide as it is not an ozone depleter.

OEHHA reviewed the draft Risk Characterization Document for Inhalation Exposure to MeI prepared by DPR (2009). The draft human health risk assessment consists of three volumes. Volume I is on Health Risk Assessment. Volume II is on Exposure Assessment. Volume III is on Environmental Fate. Volume I has three appendices: Appendix A, Review of Physiologically Based Pharmacokinetic model for Human Equivalent Concentration; Appendix B, Calculations; and Appendix C, U.S. Environmental Protection Agency risk assessment.

Comments in this document are organized by the volume of the draft risk assessment that they are addressing.

A. Comments on the Draft Risk Characterization Document (Health Risk Assessment, Volume I)

This section provides OEHHA's comments on the draft Risk Characterization Document (RCD) (Health Risk Assessment, Volume I). The comments are organized into four parts: (a) non-carcinogenic health effects, (b) genotoxicity and carcinogenic health effects, (c) minor comments on the RCD, and (d) appendices of Volume I.

a) Non-carcinogenic health effects

1. OEHHA agrees with the identification of the critical animal toxicity studies and the determination of the critical No-Observed-Adverse-Effect Levels (NOAELs) as described in Summary Table 1, except for concerns expressed in comment #7 below. Significant glutathione depletion should be considered an upstream marker for adverse effects. Further depletion of an important anti-oxidant from routine pesticide exposure should not be considered inconsequential.

2. Due to the complexity of Physiologically Based Pharmacokinetic (PBPK) models and the relatively short time OEHHA has to complete the review, an in-depth review of the modeling procedure, assumptions, and parameters was not possible. PBPK modeling was used to extrapolate from animal data to Human Equivalent Concentrations (HECs). OEHHA noticed that the ratios of NOAEL/HEC ranged from 7.5 to 9 for acute exposure and 1.2 for sub-chronic, chronic, and lifetime exposures (as shown in Summary Table 1). It would be helpful if DPR can provide an explanation for the divergence of the results.

3. On page 80, a rat developmental study showed no developmental effects were observed up to 60 ppm (81 mg/kg-day). In this study, mated female rats were exposed to MeI from Gestation Day 6 through 19 via inhalation (Nemec, 2002a). By contrast, a rabbit developmental study indicated a developmental NOAEL of 2 ppm (1.5 mg/kg-day). In this study, mated female rabbits were exposed to MeI from Gestation Day 6 through 28 via inhalation (Nemec, 2002b). Is there an explanation for the differences in developmental toxicity observed in these two species?

4. Thyroid perturbation from excess iodide is listed as a possible Mode Of Action (MOA) for the critical endpoint of fetal death in the rabbit study. Are there reproductive or developmental toxicity studies of excess iodide to support this determination?

5. The rabbit developmental toxicity study by Nemec (2002b) states, "While statistical significance was reported only for the 20-ppm group, the result for the 10-ppm group was

considered toxicologically significant because of an almost 7-fold increase [in late resorptions] from the control (1.7%)." Since the NOEL established by DPR is 2 ppm while U.S. EPA established a NOEL of 10 ppm for this endpoint and fetal death/late resorption was not statistically significant at 10 ppm, was this dataset modeled with a nested benchmark dose model to account for any intra-litter correlation (the tendency of littermates to respond similarly to one another relative to the other litters in a dose group)?

6. Some of the studies used for determining critical NOAELs used whole-body inhalation (rabbit fetal death in Nemec, 2002b, page 80; rat neurotoxicity in Schaefer, 2002, page 25) or did not specify whole-body or nose-only inhalation (rat nasal toxicity in Kirkpatrick, 2002, page 37). There is a concern that animals subjected to whole-body inhalation could have additional intake of MeI via the oral route from grooming compared to nose-only exposures, which in turn could affect the NOAEL.

7. This RCD lists glutathione (GSH) depletion as a possible mode of action and uses GSH depletion as a dose metric in PBPK modeling based on the apparent relationship between GSH depletion and cellular degeneration in the olfactory epithelium. However, there is evidence to support consideration of the use of GSH depletion as an adverse effect, or a biomarker of toxicity in a manner analogous to acetylcholinesterase inhibition. For example, GSH depletion induces mitochondrial impairment, which is an early event in the process of apoptosis (Higuchi, 2004). In the lung, GSH depletion has been associated with the increased risk of lung damage and disease (Rahman *et al.*, 1999). GSH concentrations vary throughout the respiratory tract, being lower in the nasal lining fluid than in alveolar lining fluid (Rahman and MacNee, 1999), which may contribute to the occurrence of lesions in the olfactory epithelium but not the respiratory epithelium (Chamberlain *et al.*, 1998). Furthermore, it has been hypothesized that neuronal loss may be initiated by GSH depletion, which can enhance oxidative stress and increase the levels of excitotoxic molecules, leading to the initiation of cell death in distinct neuronal populations (Bains and Shaw, 1997). Bains and Shaw (1997) present evidence for a role of oxidative stress and diminished GSH status in Lou Gehrig's disease, Parkinson's disease, and Alzheimer's disease. Additionally, GSH levels are decreased in the epithelial lining fluid of patients with idiopathic pulmonary fibrosis, acute respiratory distress syndrome, cystic fibrosis, and HIV (Rahman and MacNee, 1999). Thus, GSH depletion not only contributes to toxicity via its role in the initiation of cell death, but its dysregulation in certain disease states makes it an important factor in considering the effects of GSH-depleting chemicals on the health of susceptible individuals.

8. On page 31, lines 13-15 state, "Methyl bromide (200 ppm for 6 hours) treated rats, as the positive control, showed similar damage to the olfactory epithelium as the 100-ppm (6

hours)." Does this suggest that MeI is twice as toxic as methyl bromide for this endpoint?

9. On page 152, DPR suggested that an additional uncertainty factor of 10 is needed to account for the lack of a neurodevelopmental effects study, the severity (fetal death) of effect in the developmental rabbit study (page 80), and the excess iodide resulted from MeI exposure. OEHHA supports the use of an additional uncertainty factor of 10 to protect the workers, bystanders, and residents. However, OEHHA does not believe an acute exposure to an iodide level that is slightly higher than the Tolerable Upper Levels (ULs) would disrupt thyroid function. The Recommended Dietary Allowances (RDAs) and ULs recommended by the National Academy of Sciences are applicable to daily dietary intake level, not acute inhalation exposure. ATSDR (2004) developed a Minimal Risk Level of 0.01 mg/kg-day (approximately 600-700 µg/day) for acute-duration oral exposure (1-14 days) for iodine. OEHHA suggests the discussion of this issue be modified accordingly (pages 149 to 155 of the RCD).

b) Genotoxicity and carcinogenic health effects

1. Page 2. OEHHA agrees with DPR in identifying MeI as a carcinogen. MeI is listed under Proposition 65 as a chemical known to cause cancer. U.S. EPA determined that MeI as "Not likely to be carcinogenic to humans at doses that do not alter rat thyroid hormone homeostasis." IARC determined that MeI was not classifiable as to its carcinogenicity to humans (Group 3). However, U.S. EPA did not correctly evaluate the impact of the positive genotoxicity data and the astrocytoma data (Kirkpatrick, 2005) in the overall cancer risk assessment. Additionally, the 1986 IARC cancer evaluation did not have the Kirkpatrick (2005) rat cancer study or the Harriman (2005) mouse study available for inclusion into their document. MeI has been observed to cause thyroid follicular cell tumors in male Sprague-Dawley rats exposed by inhalation (Kirkpatrick, 2005). A positive dose-response trend was observed, and the tumor incidence in the high-dose animals (60 ppm; 58 mg/kg/day) was significantly increased compared to controls.

2. The RCD document (IV.A.4.a. Weight of Evidence) states "Methyl iodide can be considered a weak oncogen", and "MeI-induced thyroid tumor formation is likely caused by the perturbation of thyroid function" (IV.A.4.b. Mode of Action). Based on these determinations, the document proceeds to develop a cancer risk assessment based on a threshold model. OEHHA disagrees with DPR that the carcinogenic effects of MeI can be estimated using a threshold approach. This is because MeI is clearly genotoxic and

some evidence exists for MeI-induced carcinogenicity in rodents at sites other than the thyroid.

Also on page 2, the statement "Since the formation of thyroid tumors is generally considered a threshold effect" was made. This generalization does not hold when there are data to indicate otherwise, as in the case of MeI. Thyroid tumor induction may be partly or entirely due to genotoxic mechanisms. In the "Assessment of Thyroid Follicular Cell Tumors," U.S. EPA (1998) stated that in order to show the antithyroid activity of a chemical is the cause of thyroid tumors observed in rodents, it has to meet five specific requirements. OEHHA has not seen the data showing that all five requirements are met.

3. MeI is clearly genotoxic in that it causes DNA damage, gene mutations and chromosomal damage in a variety of genotoxicity test systems. MeI also induces thyroid follicular cell tumors in rats and mice, astrocytomas in rats, and benign uterine and cervical fibromas in mice. MeI is clearly capable of causing increased TSH levels, thyroid weights (relative to body weight) and thyroid hyperplasia in rats and mice. The combined MeI genotoxicity data, rat astrocytoma incidence data, and mouse uterine and cervical fibroma incidence data suggest that the rat and mouse thyroid follicular cell tumors are not solely due to thyroid function perturbation. MeI is likely to be a genotoxic carcinogen whose thyroid tumor-inducing ability is enhanced by its effects on thyroid metabolism.

4. Page 135 of the RCD (IV.A.4.a. Weight of Evidence) states "There is some evidence that MeI is genotoxic, though it is not definitive". This is not an accurate representation of the existing data. MeI has been observed to cause DNA damage in human lymphoblast cells exposed *in vitro* and in rats exposed *in vivo*. MeI has also been observed to induce gene mutations in bacteria (*Salmonella* and *E. coli*), yeast (*saccharomyces cerevisiae*) and mammalian cells (Chinese hamster ovary (CHO), mouse lymphoma L5178Y $TK^{+/-}$). Additionally, MeI causes chromosomal damage in CHO cells, and causes small colony formation in the mouse lymphoma L5178Y $TK^{+/-}$ assay; formation of small colonies in this assay is considered to be associated with chromosomal damage. OEHHA considers MeI to be clearly genotoxic because of the data indicating that MeI causes DNA damage, gene mutations and chromosomal damage in a variety of genotoxicity test systems.

5. The RCD also describes a study by Harriman (2005) in which Crl:CD-1(ICR) mice were exposed to MeI in the diet for 18 months (less than a lifetime exposure). The male mouse exposure groups (0, 8, 28 and 84 mg/kg/day) did not demonstrate significant

increases in thyroid follicular cell tumors compared to concurrent controls, but did demonstrate a significant tumor dose-response ($p < 0.05$, Cochran-Armitage trend test).

6. Some evidence exists for MeI-induced carcinogenicity in rodents at sites other than the thyroid. The RCD outlines the occurrence of astrocytomas (a glial brain tumor) in MeI-exposed animals in the study by Kirkpatrick (2005). Astrocytoma incidences (benign and malignant) for the 0, 5, 20 and 60 ppm exposure groups were 0/60, 1/27, 0/26 and 3/59 for males, and 0/60, 0/27, 0/28 and 1/60 for females, respectively (this data listing does not include the 10 animals in the 60 ppm exposure group that underwent an interim sacrifice at week 52, and only half the available animals in the 5 and 20 ppm groups were evaluated for astrocytomas). None of the exposed groups demonstrated a tumor incidence significantly greater than controls, but the tumor dose-response trend in males is statistically significant ($p < 0.05$, Cochran-Armitage trend test). It should be noted that only half of the available animals in the 5 and 20 ppm exposure groups underwent a pathological evaluation for astrocytomas, reducing the potential sensitivity of the bioassay to detect this tumor. Additionally, the astrocytoma incidence in the 60 ppm male rats is 5%. Historical control incidences for this tumor type in Sprague-Dawley rats range from 0.5% to 1.5% (Maekawa and Mitsumori, 1990; Giknis and Clifford, 2004; Brix *et al.*, 2005). Therefore, the astrocytoma incidence in the 60 ppm male rats is approximately from 3 to 10-fold greater than historical controls. The 60 ppm male rat astrocytoma incidence is significantly greater than the corresponding historical control incidence reported by Charles River Laboratories (26/2146, 1.21% incidence; $p = 0.04$, Fisher exact test).

7. The mouse oral MeI study by Harriman (2005) described above also reported an increased incidence of cervical and uterine fibromas. Individual exposure group tumor incidences were not significantly greater than controls, but a significant dose-response trend was noted for cervical fibromas and cervical and uterine fibromas combined ($p <$ 0.05 and 0.01, respectively). Additionally, the reported historical control incidence for these tumors is very low (uterine fibromas 2/3182, cervical fibromas 0/3078) (Giknis and Clifford, 2004 and 2005).

8. Benchmark dose analysis of the rat astrocytoma and thyroid follicular cell tumor incidence data using Benchmark Dose Software (BMDS) 2.0 (U.S. EPA, 2009) analysis software yields cancer potency factors of approximately 1.8×10^{-3} $(mg/kg\text{-}day)^{-1}$ and 4×10^{-3} $(mg/kg\text{-}day)^{-1}$, respectively. The 70-year lifetime cancer risk at the RCD Reference Concentration (RfC) for 24-hour infant/child chronic exposure of 2 ppb would be 6 in 1 million and 13 in 1 million for astrocytomas and thyroid tumors, respectively. OEHHA suggests that cancer potency values be calculated from the Kirkpatrick (2005) rat thyroid

follicular cell tumor incidence and astrocytoma incidence data sets using a linear non-threshold model.

c) Minor comments on the RCD

1. Page 1, Line 10: Health should be Human.
2. Page 10, line 18: Resource should be Resources.
3. Page 10, Line 35: 50% should be 75%.
4. Page 23, Line 39: 10-fold lower should be up to 20-fold lower.
5. Page 28, line 38: asparate should be aspartate.
6. Page 44 (III.C.3. Rat – Dermal) of the RCD, the document states "The NOEL for local effects was <30 mg/kg/day (lowest dose tested)." The NOEL for local effects in this case would be exactly 30 mg/kg/day.
7. Page 60, line 24: The statement that "The study NOEL was < 60 ppm (< 8 mg/kg/day in males) for decreased body weight; markedly elevated thyroid/parathyroid weights, increased colloid and cytoplasmic vacuolation in thyroid; follicular cell hyperplasia; and hyperkeratosis as evidence of upper GI tract local irritation" is somewhat confusing. The statement is true, but it should also be mentioned that the study LOEL for the endpoints mentioned above was 60 ppm.
8. Page 64, Line 8: Tables 25 and 26 should be 28 and 29.
9. Page 75, Lines 40-42: Tables 28 and 29 should be 31 and 32; Line 41: significant should be significantly.
10. Page 102, line 2: umbilicord should probably be umbilical cord.
11. Page 108 (lines 14-15): "Fetal tissues, in contrast, were inefficient (liver) or apparently incapable of metabolism (kidney), as evidenced by low Km and Vmax values" is not correct. Low Km indicates high affinity (strong binding) of the enzyme for the substrate. Higher Vmax and lower Km values result in higher catalytic efficiency. A possible

rewording of this statement would be "Fetal tissues, in contrast, were inefficient (liver) or apparently incapable of metabolism (kidney), as evidenced by low Vmax values".

12. Page 113 (lines 5-6): "Hazard identification of MeI is based on the results from laboratory animal studies because human case reports do not provide sufficient data to provide dose-response evaluations." The human case reports may not have sufficient dose-response data to be useful in quantitative risk assessment, but can still be useful in the hazard identification of MeI.

13. Page 118, Table 56: Bottom right cell, 25% should be 40%.

14. Page 132, Table 62: Rat GD 0 to 20, and LD 5 to 20 (Nemec, 2004) NOEL is 25 ppm, 34 mg/kg/day. Rat 4 weeks (Nemec, 2004) NOEL is 25 ppm, 24 mg/kd/day. Is the difference of 10 mg/kg/day a typo? If not, please explain how the same ppm value was converted to mg/kg/day to result in the different numbers.

15. Page 148, line 17: hexokinese should be hexokinase.

d) Appendices of Volume I

1. Appendix A. Information on the PBPK models used in the RCD provides no information on the actual models used except to cite a half-dozen or more contractor's reports. OEHHA suggests that Appendix A be revised to provide sufficient model details to allow the reader to check the simulation-based calculations (mainly the acute HECs). Additionally, an example of the actual model computer code for a key simulation should also be provided.

2. Many of the PBPK modeling results are presented without data. There seems to be some confusion over the difference between actual data and predictions based on model simulations. Most of the figures (e.g., Figures. A2 - A5) refer to data but show only continuous model predictions, not discrete data points.

3. Figure A-1 does show data, but aside from the time it is difficult to know what the difference is between Figures A-1a and A-1b. It would be useful if figure legends were globally made specific as to exposure conditions.

4. The authors used a couple of different alveolar ventilation rates and identified this parameter as a problem area. This suggests the need for further development of this

parameter in the context of the acute HEC with predictions for different activity level scenarios.

5. In Table B-2, the rendering where the UF-PKA subfactor of $10^{0.5}$ is broken out from the UF-PDA and UFH at the far right of the table somewhat obscures the fact that the overall UF is 100 and not 30.

6. OEHHA suggests back calculating acute HECs from the 24-hour exposure scenario but adding the contribution from internal body stores to the calculation. Figure A-7b on page A-25 of the appendices to Volume I of the RCD demonstrated how the time-course of blood iodide in rabbits was "matched" to the time course in human blood. Acute HECs were then derived by back calculating them from the appropriate blood iodide level. PBPK models were used to match the blood-iodide levels in humans at hour 24 from a 24-hour exposure to levels in rabbits, or rats at hour 24 following a 6-hour exposure. At least two options were available for deriving acute HECs. They could be derived from blood concentrations following:

    - a single-day of exposure with no previous exposure.
    - a single day of exposure following exposures over enough days for the body to reach steady state.

In the document, only the first scenario was modeled, the second was not. However, the dosing regimen described in the rabbit study is similar to the second scenario. In that animal study, blood iodide levels at a time point during the study reflect iodide from both the acute exposure plus internal releases of iodide from body stores. Therefore, back calculating from this scenario would produce a smaller HEC. It would be informative to see how the HECs differ by modeling both scenarios.

B. Review of the Draft Exposure Assessment Document (Volume II)

This section provides OEHHA's comments on the draft Exposure Assessment Document (EAD) (Volume II).

1. Table 3, presented on page 6 of the EAD, lists the general information for submitted products containing MeI as an active ingredient. The product formulations consist of iodomethane technical (99.8% MeI) and varying ratios of MeI to chloropicrin, ranging from 98% MeI:2% chloropicrin to 25% MeI:75% chloropicrin. The MeI application rates listed range from 175 lbs. of formulation per broadcast acre to 700 lbs. per broadcast acre. Since the 700 lbs. per broadcast acre application rate appears to be based on the formulation having only 25% MeI as the active ingredient, OEHHA is concerned about the increase in chloropicrin that would accompany such an application. Table 5 on page 24 of the RCD lists the acute inhalation LC_{50}-rat for TM-425 (99.7% MeI) at 3.9 mg/L for both males and females and for TM-42503 (25% MeI, 75% chloropicrin) at 0.18 mg/L (males) and 0.24 mg/L (females). The LC_{50} for the formulation containing 75% chloropicrin is over 20-fold lower than the LC_{50} for 99.7% MeI for male rats. Will the application of 700 lbs. of Midas 25:75 (25% MeI:75% chloropicrin) allow the levels of chloropicrin to exceed regulatory limits set for chloropicrin in the state of California? It should be noted that similar concerns were expressed by OEHHA on its June 30, 2003 memorandum on methyl bromide. There was a concern that the toxicity of chloropicrin, when used as a warning agent or as a co-active ingredient, was not included in the methyl bromide risk assessment.

2. The calculations for estimated absorbed dosages of MeI (Tables 15-19, pages 40-43) in the EAD apply default human inhalation rates based on data from Layton, 1993. Layton's (Layton, 1993) daily inhalation rates were estimated from the food-energy intakes for cohorts sampled in the 1977-1978 Nationwide Food Consumption Survey (NFCS). More recently, the U.S. Department of Agriculture's 1994-1995 Continuing Survey of Food Intakes by Individuals (CSFII) has demonstrated that there have been significant changes in consumption patterns in the 17 years between the NCSF and CSFII (Enns, 1997). Furthermore, U.S. EPA has recently released its finalized Child-Specific Exposure Factors Handbook (U.S. EPA, 2008). The inhalation rates recommended by this handbook are based on four studies published in 2006 and 2007, representing current exposure conditions and improvements upon the methodology used by Layton (1993). To provide values that are more representative of the current population and exposure conditions, OEHHA recommends using the inhalation rates from the 2008 Child-Specific Exposure Factors Handbook in calculating the absorbed dosages and HECs for MeI. The

1997 U.S. EPA Exposure Factors Handbook provides inhalation rates based on the Layton, 1993 study among others. An average hourly inhalation rate of 1.3 m^3/hr is recommended for outdoor workers (p. 147 of the Exposure Factors Handbook). Inhalation rates are also provided for adults under different scenarios in this handbook.

3. The product label for Midas 98:2 provided in Appendix I, pages 58-67, states, "Do not apply within ¼ mile of any occupied sensitive site such as schools, day care facilities, nursing homes, hospitals, prisons, and playgrounds." The EAD indicates the buffer zone for non-worker bystanders, which includes residents, is 152 meters. The residential population can include sensitive populations such as infants/children, the elderly, and people with susceptible medical conditions. Since 152 m is significantly less than the ¼ mile (402 m) "do not apply" zone designated on the label, wouldn't it be more consistent as well as health protective to include residences on the list of occupied sensitive sites?

4. Exposure estimates were calculated assuming that certain applicators and handlers of MeI use air-purifying respirators (APRs) equipped with 3M brand 60928 cartridge filters (activated carbon impregnated with triethylenediamine). Therefore, the exposure estimates for these workers were calculated assuming a respiratory protection factor of 0.9 (90%; see Equation 2 on page 28). We have several concerns with incorporating an assumed "protection factor" in these exposure estimates:

   - The label for Midas 98:2 (page 59) does not specify that the respirator be tested and adjusted so that is fits properly. A respirator will not provide 90% protection if it does not fit properly.
   - The product information from 3M Corporation indicates "While NIOSH does not have a test procedure to certify air purifying filters against radioiodine [tested as methyl radioiodine] or methyl bromide, this combination cartridge is recommended by 3M for use against radioiodine or methyl bromide at ambient concentrations up to 5 ppm and for not more than one shift." The label for Midas 98:2 does not appear to specify a change-out frequency for the APR cartridge.
   - Worker compliance with this requirement is likely to be less than 100%, particularly on warm humid days, and the workers are also required to wear long pants and long-sleeved shirts
   - Including a respiratory protection factor in the equation used to estimate exposure does not represent a baseline exposure scenario. Consequently, risk managers may never consider alternative exposure mitigation strategies that may be more feasible, more effective, less expensive, and/or have better worker compliance.

5. Tractor drivers and their assistants (co-pilots) are not required to wear respirators if the tractor cabin meets certain engineering standards; specifically, an air intake that is 10½ feet from the ground. Presumably, this configuration is intended to ensure that "dilution air" from ten or so feet above ground surface is sufficient to reduce the airborne concentration of MeI to a safe level. However, in two of the three studies of worker exposure, the air concentration for the tractor driver (Table 6) or the driver's assistant (Table 7) were the highest of any occupational group studied. If this is the case, what assurance is there that the "engineering controls" that are intended to minimize exposure actually work?

C. Review of the Draft Environmental Fate Document (Volume III)

This section provides OEHHA's comments on the draft Environmental Fate Document (EFD) (Volume III).

1. The document does not consider the potential for MeI or its primary degradation product iodide to contaminate surface water or groundwater. In part, this appears to be a consequence of failing to recognize that iodide is a by-product of MeI degradation. For example, in discussing the abiotic hydrolysis of ^{14}C-iodomethane at different pH levels (page 3), the report concludes "The major degradate at both temperatures was methanol." Similarly, in describing the results of a study evaluating the rate of photolysis of MeI in water, the report states "The primary photodegradates were methanol and formaldehyde." In both cases, the fact that iodide had to be produced as well was not mentioned.

2. As a proposed alternative to methyl bromide, MeI use in California could conceivably reach several million pounds per year. If this were to be the case, the potential for surface water and groundwater to become contaminated with iodide appears to be significant. Given the potential volume of use, even if 90-95% of applied MeI evaporates within a few days, the residual remaining in soil could eventually contaminate ground water because the compound is readily mobile in soil. In our opinion, the potential adverse effects of iodine and MeI contamination of surface and ground water on humans and ecological receptors should be evaluated.

3. Tables 2 and 3 are poorly formatted and need to be revised. In Table 3, the independent variables (pH and temperature) should be column and row headings, and the dependent variable (hydrolysis half-life) should be in the data cells of the table.

	Temperature (°C.)		
pH	**20°**	**25°**	**50°**
4	224	105	3.3
7	247	113	3.2
9	241	109	3

Presented this way, one can immediately conclude that pH had no effect on the rate of hydrolysis while temperature had a huge effect.

4. Page 1. We suggest including in table 1 more information on the physical and chemical properties of MeI. This would include critical temperature (254.8 °C) and critical pressure (72.7 atm) (Weast, 1987). According to Budavari (1996), MeI is a colorless, transparent liquid which turns brown on exposure to light. According to the DPR description (first paragraph on page one): "On exposure to light, discoloration (of iodomethane) occurs due to decomposition and liberation of free iodine." It would be useful to check which information is more accurate.

5. Page 2. As is indicated in the second paragraph on page two, "In October, 2007, the USEPA issued a one year Time-Limited registration of Iodomethane." OEHHA suggests that the registration status of MeI be updated to include the following sentence: "In October 2008 U.S. EPA extended conditional registration of MeI without specifying any time limits."

6. At the top of the page 3 there is a table of Iodomethane Application Rates. This table refers to Commodity/Site and Rate (pounds of MeI per acre). We understand that it is difficult to predict how many acres will be treated with MeI in California. However, DPR could provide the range of acreage that may be treated in the future. This information will also be helpful for risk assessment.

7. Page 2. Besides its future use as a soil fumigant, MeI can be formed in the environment of nuclear reactors and vented in exhaust gases. OEHHA also suggests including this information in the DPR report.

8. Page 3. OEHHA suggests including the following information in the EFD. Marine macroalgae produce MeI and the ocean is the major source of this chemical. Biogenic sources of MeI are major in comparison with the anthropogenic ones resulting from its

use as a methylating agent. MeI released to air at 25 °C and a vapor pressure of 405 mm Hg will exist as a vapor in the ambient atmosphere; it will degrade in the atmosphere primarily through photolysis (Mabey and Mill, 1978). Volatilization from moist soil surfaces and water surfaces is an important fate process of MeI based upon this compound's estimated Henry's Law constant [(0.0054 atm-m3/mol (250C)]. Estimated volatilization half-lives for a model river and model lake are 1.3 hours and 4.8 days, respectively (Zafiriou, 1975). In addition, the general population may be exposed to MeI through ingesting seafood (National Library of Medicine, 1998).

9. Page 4. Environmental factors such as soil temperature and content of organic matter in soil influence the atmospheric volatilization of MeI from soil. An interesting, recent publication by Guo and Gao (2009) on the degradation of MeI in soil and the effects of environmental factors on its dissipation showed that soil amended with cattle manure shortened the half-life of MeI in soil, causing reduction in its volatilization to atmosphere. Concerns about the environmental fate of MeI following its future soil fumigation should take into account ways of decreasing its atmospheric volatilization and minimizing groundwater contamination.

10. Page 6. Dissipation of MeI from the aquatic environment and soil is by abiotic degradation. This is not discussed in the "Environmental Fate" part of the DPR's document. Even though abiotic degradation (involving light, temperature, atmospheric gases, sunlight, irradiation, and photohydrolysis) constitutes minor dissipation of MeI from the environment, it still would be informative to address it.

11. We suggest inclusion of a list of abbreviations with definitions of scientific terms used in the EFD. It would also be advisable to give explanations of scientific terms and abbreviations under tables.

12. A mistake was made in numbering tables. A table on page three does not have a number. The number of this table should be "3". The numbers of the subsequent tables starting with the table on page four should be changed.

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