Methyl Iodide (Iodomethane)

RISK CHARACTERIZATION DOCUMENT FOR INHALATION EXPOSURE

Volume IV - Part 1

Responses to OEHHA Comments

CH_3I

External Panel Review Draft

Department of Pesticide Regulation
California Environmental Protection Agency

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Office of Environmental Health Hazard Assessment

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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 <u>excess iodide</u> 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

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

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-day)$^{-1}$ and 4×10^{-3} (mg/kg-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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MEMORANDUM

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A. G. Salmon for J. P. Brown 7/21/09

DATE: July 16, 2009

SUBJECT: COMMENTS ON APPENDIX A: REVIEW OF PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL FOR HUMAN EQUIVALENT CONCENTRATION, IN APPENDICES TO VOLUME I: HEALTH RISK ASSESSMENT OF METHYL IODIDE. (Draft report from the Medical Toxicology Branch, Department of Pesticide Regulation, California Environmental Protection Agency).

This memo constitutes additional comments by the Office of Environmental Health Hazard Assessment (OEHHA) on a Department of Pesticide Regulation (DPR) review of a Physiologically Based Pharmacokinetic (PBPK) model used in a health risk assessment of methyl iodide. This memo is not an assessment of the model itself. There are several outstanding questions and uncertainties which could be resolved by augmenting the subject report appendix. We list specific details that could be supplied, and could improve the report, in our comments below.

A. Fetal Death in Rabbits

Comment 1. Page A4, Line 8. It is stated that "the same basic model structure is used for all three endpoints" except that the rat has an enhanced nose compartment. It would be helpful to provide a model diagram of the rat PBPK model.

Comment 2. Page A4, Line 42. "This section provides only a very brief description of the model." In our view this is a major deficiency of this report. The appendix on PBPK contains few details of the subject model variants; more details should be added as shown below.

Comment 3. Page A-5, Line 1. "Comparison of model output to the experimentally measured values is used to adjust input variables for model fit." How was the model validated? Were there different data sets used for model calibration and validation?

Comment 4. Page A5, Lines 5-8. This brief discussion of the origins of key model parameters is difficult to follow. It would help the reader if you could insert a table of model parameters actually used in the model and expand on their individual origin (i.e., Morris, Mileson, Sloter, or other).

Comment 5. Page A6, Fig A-1. It is not clear what the difference is between A-1a and A-1b. Figure legends should be specific as to exposure conditions and there are some misspellings that need correction.

Comment 6. Page A-7, Lines 2-3, 9-11, Table A-1. This text and table describe two ventilation rates and a table for modeled and measured results for one (12L/kg^0.75). This is confusing. The second table is not presented and should be included so the reader does not need to go to Section II C to get the comparison.

Comment 7. Page A-8, Lines 32-40, Table A-2. It would help to add the NaI data to Table A-2 even though the doses are different. The rabbit simulations seem consistent in over-predicting F/M ratios. Why wasn't this taken into account in setting the fetal influx and efflux rates in the model? The values given (some of the very few) show a rate ratio of 4.7-fold in favor of fetal uptake. This ratio is probably too high. In the human model this ratio is only 1.25.

Comment 8. Page A-11 lines 19-21. How well does the model predict fetal exposures at anticipated human exposure levels? Are there data in humans other than cord blood iodide?

Comment 9. Page A13, Lines 18-21, Fig A-3. This text and figure report model predictions of up to 513-fold fetal to maternal iodide concentration ratio in rabbit thyroid follicles following a 6 hr exposure to MeI. Were other concentrations or ventilation rates simulated? A diagram of the rabbit PBPK model would be helpful.

Comment 10. Page A15, Lines 8-9, Page A-16 Lines 1-9. The text reports predicted values of 1800-fold for fetal/maternal follicle iodide and raises concern with respect to model validation and the lack of tissue data. Gargas et al. 2005 is cited in support of the prediction but this is not published work in the available literature. Can a table be added to provide the key Gargas results "fit to human fetal thyroid iodide levels" that support the "likelihood of reality"?

Comment 11. Page A16, Lines 11-13. "The need to further investigate this issue ...." We agree that there is a need to thoroughly evaluate model parameters and structure to assure that the model predictions are reliable.

Comment 12. Page A-16, Lines 24-26. "61.1 kg and a fetal weight of 0.27 kg (i.e. a single fetus at maternal weight fraction 'VFETC' of 0.0044). The model targets the stage of fetal ontogeny...." Does the model include parameters for fetal, placental, uterine, mammary and fat growth during gestation? It seems to us that such a narrowly focused model is more likely to give erratic predictions than one covering a larger portion of the gestation period.

Comment 13. Page A-20, Lines 36-39. Notwithstanding the sharp temporality of the fetal death response during GD23-26, it makes more sense to us to adopt a not-to-exceed value at ANY point during gestation. Using a single day model metric to base the HEC may be too narrow.

Comment 14. Page A-21, Lines7-8. "Significant GSH depletion in fetal blood was detected as early as after one 6 hour 20 ppm exposure." This is unclear. Was the significant depletion seen at 6 hour or at some point after the 6 hour exposure? Please indicate the kinetics of GSH depletion (i.e., a graph).

Comment 15. Page A-21, Lines 19-21. "In summary, with insufficient support for a single MOA within the time frame of 30 or less hours, it is prudent to model the HEC at the 2 ppm NOEL based on a single day exposure for both rabbits and humans." In our view, a sound rationale for adopting a single day exposure in humans has not been established. It seems more likely that, in humans, the period of fetal vulnerability would extend well beyond a single day.

Comment 16. Page A-21, Lines 41-43. "However, the range of human F/M ratio is wide, and there are nine sets of values above 2 (range 2.08-5.4) which exceed the average F/M ratios in rabbits." This is not evident from Tables A-1 and A-2 where human F/M values are generally lower than measured or modeled rabbit values. Is there something missing from the nine sets?

Comment 17. Page A-22, Lines37-38. "In conclusion, the overall evidence presented in this and previous sections indicates that maternal iodide dose metric is most reliable for reflecting the maternal MeI exposure status on which the rabbit NOEL was based." Which maternal iodide metric is being referenced in this sentence, Cmax, C steady state, or AUC?

Comment 18. Page A-23, Lines 23-25. The discussion of rabbit and human AUCs is not clear. Generally AUCs are in units of concentration × time and usually averaged per day, e.g., mg hr/L d. Here the report is apparently equating ppm × 24 hr in rabbit with ppm × 96 hr in humans. Were regressions between ppm external and AUC established for rabbit and human exposures? This would seem to be a more rational process for extrapolating AUC rabbit to AUC human and then to HEC (i.e. ppm external for human).

Comment 19. Page A-24, Table A-4. In view of comment 18 above, it would help to show a sample calculation for AUC-derived HECs in the table. Are there any further comments on the HECs presented in the table that cover a 17-fold range? Which ones seem more reliable? Or did you pick the lowest?

Comment 20. Page A-25, Figure A-7. This figure is difficult to read. Does the inset represent the human or the main graph? The inset exposure concentrations can't be read and should be specified in the legend.

Comment 21. Page A-27, Figure 8. Is a two-day simulation sufficient to assess occupational exposure? Normally you would expect a 5 day occupational plus 2 day population exposure (168 hr). The peak concentration with 0.35 ppm × 8 hr/d has clearly not been reached. If DPR has simulations predicting a steady state Cmax, then the report should show it. Again, these are predictions subject to sufficient model validation.

B. Nasal Olfactory Epithelial Degeneration in Rats

Comment 22. Page A-28, Lines 5-6. "This section provides only a very brief description of the the Arysta mei3 model..." As noted above, a model diagram and list of parameters would greatly assist review of DPR's use of the model.

Comment 23. Page A-29, Figure A-9. Figure A-9a shows that the model overestimates the reduction in olfactory GSH concentration. ppm should be added to the inset legend. Figure A-9b shows two model simulations. What is the difference between them?

Comment 24. Page A-30, Lines 5-6. "DPR agrees with USEPA that GSH depletion at the dorsal olfactory epithelium can be the dose metric for modeling the nasal effect HECs." In view of model overestimation of this metric, which appears to increase with exposure concentration, have other model metrics been adequately evaluated? For example, the model can predict Cmax's, AUCs, and fluxes in nasal epithelium.

Comment 25. Page A-31, Figure A-10. This figure is clear and understandable. A 6 hr exposure to rats results in about a 35% reduction in GSH in the dorsal meatus region, which serves as DPR's basis for estimating an HEC.

Comment 26. Page 30, Lines 31-33. We agree that 50% GSH reduction is not a suitable benchmark for a no-effects level. Since tissues vary in GSH concentration, a single benchmark may be a flawed concept. DPR's use of 25% in relation to a nasal tissue GSH reduction threshold seems a reasonable place to start but more tissue specific data are needed to confirm this.

Comment 27. Page A-34, Lines 23-26. "Repeated exposure may result in a greater severity of cellular damage from which an HEC based on a single day exposure at 25% GSH depletion may not be adequate to protect." Agreed. That is why simulations estimating an HEC for human occupational exposure should be run for at least a week (5 × 8 hr/d plus weekend).

Comment 28. Page A-35, Lines 3-4. "The rat model uses mei3.csl and mei3cmd files submitted to DPR by Arysta (2007). Three sets of HEC simulation runs were conducted by Arysta in 2008." Does this mean that DPR didn't run any simulations with the model to confirm proposed HECs?

Comment 29. Page A-35, Lines 17-19. "..applying input parameters for children of various age (i.e., 3 month-old infants, children at 1, 5, 10, and 15 years old) did not result in different HECs than for adults." It would be useful if the report could expand on this. For example, what body weights and ventilation rates were used for infants and children?

Comment 30. Page A-35, Lines 23-29, Figure A-11. These graphs are difficult to read. Presumably they proceed from inside to outside, top to bottom. Please indicate the outermost layer in the text, gsdoe11 "The time to a less than 0.5% change in GSH level is not reached until hour 14 of exposure." What does this mean? It is not clear how this relates to the other text or Fig. A-11.

Comment 31. Page A-38 Lines 2-3, Figure A-12. "DPR's 8-hour HEC is 2.8 ppm based on DPR's default breathing rate of 833 L/hr..." It is not clear what the basis of the HEC is? Is it the average depletion of GSH in the olfactory epithelium? Please indicate clearly in the text and legend. Again the graph is difficult to read and some additional labeling would help.

C. Neurotoxicity

Comment 32. Page A-40, Lines 14-18. "...the concerns remain about the use of blood or brain MeI concentration instead of its AUC for the HEC dose metric." It seems to us that the brain AUC is the most reasonable metric for the analysis.

Comment 33. Page A-43, Lines 13-15. "Since this 8-hour HEC does not take into account the additional 16-hour exposure after work, it is realistic to set the 8-hour HEC at 3.4 ppm, the same

level for the 24-hour HEC." Is this realistic? The rationale is not clear. Why not a time weighted average, e.g., 5.5 ppm? It just seems odd that a rationale for an 8-hour value was developed and then discarded.

Comment 34. Overall the neurotoxicity section is better presented than the other endpoints.

Department of Pesticide Regulation

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MEMORANDUM

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DATE: August 10, 2009

SUBJECT: Response to Office of Environmental Health Hazard Assessment Comments on the Draft Methyl Iodide Risk Characterization Document for Inhalation Exposure Volume I and Appendices to Volume I

The following are our responses to revised comments (June 3, 2009) from the Office of Environmental Health Hazard Assessment (OEHHA) on the draft Methyl Iodide Risk Characterization Document for Inhalation Exposure Volume I and Appendices to Volume I (March 2009). The first set of comments from OEHHA was dated May 1, 2009. The revised comments contained essentially the same information but with a more complete reference citation. Responses to additional OEHHA comments (July 16, 2009) on physiologically based pharmacokinetic (PBPK) modeling review are provided in a separate memo.

OEHHA concurred with DPR's selection of the critical NOELs and the need for an additional uncertainty factor. The main comments are: genotoxicity mechanism for the oncogenicity of methyl iodide (MeI), glutathione (GSH) depletion as an adverse effect, and excess iodide discussion, and PBPK modeling.

A. Comments for Volume I:

a) Non-carcinogenic health effects

Comment #a1: 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.

DPR Response: No response needed. On GSH depletion, see response to Comment #a7.

Comment #a2: 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.

DPR Response: No response for the comment on lack of PBPK review. The basis for the comment is unclear for the comparison of NOAEL/HEC. The acute HECs are derived from PBPK modeling which is endpoint and dose-metric specific, and those for repeated exposures are from DPR default methodology with different endpoints. Current PBPK methodology is insufficient to described repeated exposures. In Table B-1 in Appendix B, the HECs for subchronic and chronic exposures based on DPR methodology and USEPA RGDR methodology, which is also followed by OEHHA, are essentially the same.

Comment #a3: 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?

DPR Response: A discussion regarding the apparent sensitivity to the developmental effects of MeI between rats and rabbits was provided in Section IV.A.1.a.(1) (page 116, lines 1 to 13). In this comparison, DPR recognizes several areas of considerations beyond comparing the NOELs between rats and rabbits. One is the severity of effects at the LOEL. The other is the possibility of different manifestation of developmental endpoints, not necessarily limited only to the prenatal fetal death.

Comment #a4: 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 <u>excess iodide</u> to support this determination?

DPR Response: The meaning of the comments is not clear. All the available data that may support this possible MOA was given in the RCD, Volume 1, section III and discussed under

IV.A.1.a.(2) Mode of Action. The toxicity of excess iodide is also discussed under V.C.1.b. Post-natal Death for the iodide discussion.

Comment #a5: 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)?

DPR Response: Using nested model to analyze developmental toxicity data was one of the first approaches DPR took to understanding the rabbit pre-natal toxicity data. However, we decided that the BMD analysis did not provide additional information that was no obvious from all aspects of data format presented in Section III.G.2 with both the initial study (Data in Table 34), the follow up study for window of susceptibility (Data in Table 35) and again in Section IV.A.1.a.(1) (Data summarized in Table 55). These include number of litter affected, total number of fetus affected, and % of fetus affected per litter.

Our initial nested analysis was aimed at modeling the level of response at 10 ppm in order to determine if the response level is of concern. In general, using the litter covariate from all dose groups gives slightly higher BMDLs than using the slightly higher covariate from the control group. The modeled extra risk response (with nested logistic model) at a BMDL of 10 ppm is 18 – 20%, a level that DPR cannot accept as equivalent to a NOEL. This conclusion is no different from the range of extra risk (10 – 30% depending on the data format) that can easily be estimated from directly from the data. Incidentally, the modeled extra risk response at BMDL of 2 ppm is 2 – 4%. Theoretically, the model can be used to establish a BMDL corresponding to any pre-determined BMR for PBPK modeling. However, modeling at BMR below 5% response is less certain due to the wide variability in these datasets. Thus, 2 ppm is the appropriate NOEL to conduct PBPK model; it is the NOEL concluded by the study author and concurred by our own review.

Comment #a6: 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.

DPR Response: The term "whole-body" will be added to the appropriate studies. DPR is well aware of the possibly significant oral component in whole-body inhalation studies and data are not available for a quantitative determination. It should be noted that a discussion for the nasal-oral component in human models is provided in Appendix A section III.C.2.

Comment #a7: 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.

DPR Response: In the RCD, the role of GSH depletion was discussed in the context of MeI toxicity. When GSH depletion was selected as the dose metric for PBPK modeling of the olfactory epithelial degeneration endpoint (Section IV.A.1.b.(2)), it was determined to protect downstream events. This effect was considered an early event because it occurred before lesions in the olfactory epithelium was detected, and the depletion of GSH due to conjugation of MeI may be a detoxification mechanism. When GSH depletion was considered as a MOA for fetal death, its involvement in disease states was included in the consideration (Section IV.A.1.a.(2)(b)).

If OEHHA's comment is to suggest a derivation of a NOEL for GSH depletion in other tissues, it would not be possible due to the lack of data. In the MeI database, GSH levels were measured in studies to examine the mechanism of toxicity or MOA for PBPK modeling (Himmelstein, 2004;

Chamberlain et al., 1998a; Sloter, 2005a; Sloter, 2005b), and limited to short-term exposures. None of them provided sufficient data to establish a dose response relationship between GSH depletion as critical toxicity endpoint from MeI exposure.

Comment #a8: 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?

DPR Response: The author of this study (Reed et al., 1995) concluded that MeI appeared to be more toxic than methyl bromide. They suggested that it may be due to the greater inherent chemical reactivity of iodide compared to bromide.

Comment #a9: 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).

DPR Response: DPR provided all the current health based standards available, including those from NAS and ATSDR which are reiterated in this comment. The presentation also contains all the qualifiers for these standards as published, and clearly showed that the ATSDR standard includes a one-day period. The use of the higher NAS's ULs rather than the ATSDR's standard to evaluate excess iodide exposure from MeI gives a larger margin to consider in a single-day exposure scenario. On the other hand, we also noted that there are other sources of iodide intake that are not accounted for in this comparison.

Please note that DPR did not compare the iodide intake standards to inhalation exposure of iodide as this comment indicated. The baseline for comparison is the body burden of iodide from MeI inhalation. As data throughout the risk assessment have shown, MeI is quickly converted to iodide upon absorption. In the revised draft, a consideration of 75% absorption/retention of MeI will be added based on the results of Morgan and Morgan (1967) who reported a range of 53% to 92% retention of MeI after inhalation exposure in adults. This study is already described in the draft RCD.

b) Genotoxicity and carcinogenic health effects

Comment #b1: 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.

DPR Response: No response is needed for the agreement.

Comment #b2: 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.

DPR Response: The RCD will be revised to discuss the oncogenicity of MeI with respect to all treatment-related tumors and its genotoxicity, as well as a discussion of the USEPA policy and the requirements for antithyroid activity.

Comment #b3: 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.

DPR Response: A discussion of genotoxicity as a mode of action will be added.

Comment #b4: 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.

DPR Response: The genotoxicity results for some studies were not definitive because they were positive only in the presence of substantial cytotoxicity as noted in the description of the studies.

Comment #b5: 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).

DPR Response: The RCD already indicated the significant trend for this dataset.

Comment #b6: 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).

DPR Response: DPR recognizes that astrocytoma is a rare tumor, and noted the finding of astrocytoma after MeI exposure in the March draft RCD even though the analysis of the overall incidences (including the interim sacrifice) showed no statistical significance. Upon reexamination of the data, DPR has revised the summary for this study with additional details. However, the data was insufficient for quantitative risk assessment since not all the animals in the low and mid-dose groups were examined.

Comment #b7: 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).

DPR Response: This set of data was already included in the weight of evidence discussion.

Comment #b8: 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} $(\text{mg/kg-day})^{-1}$ and 4×10^{-3} $(\text{mg/kg-day})^{-1}$, 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.

DPR Response: Potency factor will not be calculated for astrocytoma incidences (see Response to Comment #b6). Potency factor for thyroid tumors will be added to the revised RCD. Oncogenic risk for thyroid tumors will be estimated for both non-threshold and threshold approaches since the weight of the evidence indicated that both are possible. The exposure will be based on lifetime exposure values to be added in the document, not chronic exposure values for children as selected by OEHHA.

c) Minor comments

Comments #c 1 to 5:
Page 1, Line 10: Health should be Human.
Page 10, line 18: Resource should be Resources.
Page 10, Line35: 50% should be 75%.
Page 23, Line 39: 10-fold lower should be up to 20-fold lower.
Page 28, line 38: asparate should be aspartate.

DPR Response: These errors will be revised as suggested.

Comments #c6: 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.

DPR Response: The NOEL was established at below 30 mg/kg/day. While the incidences at 30 mg/kg/day were not statistically significant in pair-wise comparisons, they would qualitatively related to effects at higher dose levels.

Comments #c7: 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.

DPR Response: This LOEL will be noted.

Comments #c8 to 10:
Page 64, Line 8: Tables 25 and 26 should be 28 and 29.
Page 75, Lines 40-42: Tables 28 and 29 should be 31 and 32; Line 41: significant should be significantly.
Page 107, line 2: umbilicord should probably be umbilical cord.

DPR Response: These will be corrected.

Comments #c11: 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".

DPR Response: This will be corrected.

Comment #c12: 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.

DPR Response: The sentence will be reworded to reflect that human report results were used, to the extent possible, for hazard identification.

Comment #c13: Page 118, Table 56: Bottom right cell, 25% should be 40%.

DPR Response: The value should be 40% and will be corrected.

Comment #c14: 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.

DPR Response: This difference is due to the days/week factor as indicated in Table B-1 on page B-1: 34 mg/kg/day for daily dosing and 24 mg/kg/day for 5 days/week dosing.

Comment #c15: Page 148, line 17: hexokinese should be hexokinase.

DPR Response: This will be corrected.

d) Appendices to Volume I

It should be noted that comments on PBPK model review are duplicated and more extensive in OEHHA's comment on July 16, 2009. DPR responses for the same issues in the response memo by Reed (2009) will not be repeated here.

Comment #d1-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.

DPR Response: See page 1 and response to Comment 2 in Reed (2009).

Comment #d2-Appendix A: 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.

DPR Response: Basically there were two sets of figures. The discrete data points were clearly labeled in model versus measured data comparison figures in Figure A-1 for rabbit model (for deriving the first set of HEC) and Figure A-9 for the rat model (for deriving the second and third set of HEC based on effects at rat nose and brain). The remaining figures are clearly labeled as "modeled" that are provided for the corresponding discussions. Additional information are provided for these figures.

Comment #d3-Appendix A: 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.

DPR Response: See Comment 5 in Reed (2009).

Comment #d4-Appendix A: 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.

DPR Response: It is unclear whose activity levels the comment is referring to, and what type of model output is being look for. As presented in Section II.A.1. of Appendix A, the rabbit parameter is based on experimental measurements. The human QAC is consistent with DPR default values. The rationales for DPR's choice of QACs, especially when different from USEPA's, were the focus of this section. As stated, the final HECs were conducted based on DPR's choice of QACs.

The meaning of varying QAC alone for establishing HECs is unclear, as it is not a common practice unless in a probabilistic analysis. Obviously these model runs were not probabilistic, if that is what OEHHA is looking for. However, drawing conclusions based on the variability of one parameter in one species will be problematic because it will likely skewed the interpretation of the resultant HEC.

Comment #d5-Appendix B: 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.

DPR Response: The overall UF is 30, when PBPK modeling is used to derive the RfC. It is 100, when default methodology is used. This is repeatedly stated in the RCD, but will be added to the table for clarification.

Comment #d6-Appendix A: 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.

DPR Response: The choice for modeling a single day exposure is extensively discussed in Section II.B.1 in Appendix A and in Section IV.A.1.a.(2) in RCD Volume 1. The issue at hand is not whether which ways of modeling might or might not give a smaller HEC. The preponderance of data indicates that fetal death occurs within 30 hours of MeI exposure and only during a 4-day window of vulnerability. There is no support for modeling 13 days of prior exposure at which time the "steady state" for only one of the many potential dose-metric can be achieved. There is also no data to validate the model beyond 4 days of exposure. See also response to Comments 13 in Reed (2009) for related comments.

References cited in Responses:

Chamberlain, M.P., E.A. Lock, B.A. Gaskell, and C.J. Reed, 1998a. The role of glutathione S-transferase- and cytochrome P450-dependent metabolism in the olfactory toxicity of iodomethane in the rat. Arch. Toxicol. 72(7):420-428.

Himmelstein, M.W., 2004. Iodomethane: *In vivo* 2-day inhalation mechanistic toxicity study in the rat. Laboratory Project ID: DuPont-14998, E.I. du Pont de Nemours and Company, Exygen Research, and University of Massachusetts Medical School. DPR Vol. 52875-080 #216075.

Morgan, D.J. and A. Morgan, 1967. Studies on the retention and metabolism of inhaled methyl iodide-I. Retention of inhaled methyl iodide. Health Physics 13:1055-1065.

Reed, C.J., B.A. Gaskell, K.K. Banger, and E.A. Lock, 1995. Olfactory toxicity of methyl iodide in the rat. Arch. Toxicol. 70:51-56.

Reed, N.M., 2009. Response to Office of Environmental Health Hazard Assessment Comments on Appendix A: Review of physiologically based pharmacokinetic model for human equivalent concentration, in Appendices to Volume I: Health risk assessment of Methyl iodide. (Draft report from the Medical Toxicology Branch, Department of Pesticide Regulation, California Environmental Protection Agency). August 10, 2009.

Sloter, E.D., 2005a. A combined baseline/inhalation exposure study of iodomethane-related fetotoxicity in rabbits. Laboratory Study No. WIL-418031. WIL Research Laboratories, Inc., DPR Vol. 52875-085 #216254.

Sloter, E.D., 2005b. Mode of action study for iodomethane-related fetotoxicity in rabbits. Laboratory Study No. WIL-418032. WIL Research Laboratories, Inc., DPR Vol. 52875-086 #216255.

USEPA, 2007. Iodomethane: Revised HED human health risk assessment; DP Barcode: D339055, PC Code: 000011. Memorandum from Elizabeth Mendez to Mary Waller, August 23, 2007. Office of Prevention, Pesticides and Toxic Substances, US Environmental Protection Agency, Washington DC.

Department of Pesticide Regulation

Mary-Ann Warmerdam
Director

M E M O R A N D U M

Arnold Schwarzenegger
Governor

TO: Joyce Gee, Ph.D.
Senior Toxicologist
Medical Toxicology Branch

FROM: Nu-may Ruby Reed, Ph.D., D.A.B.T. *(original signed by N. Reed)*
Staff Toxicologist
(916) 324-3508

DATE: August 10, 2009

SUBJECT: Response to Office of Environmental Health Hazard Assessment Comments on *Appendix A: Review of physiologically based pharmacokinetic model for human equivalent concentration, in Appendices to Volume I: Health risk assessment of Methyl iodide. (Draft report from the Medical Toxicology Branch, Department of Pesticide Regulation, California Environmental Protection Agency).*

The following are my responses to July 16, 2009 comments from the Office of Environmental Health Hazard Assessment (OEHHA) on DPR's March 2009 draft *Appendix A: Review of physiologically based pharmacokinetic model for human equivalent concentration* received (March 2009) at DPR on July 23, 2009. This set of comments is specific to DPR's review on Arysta's PBPK model for deriving acute HECs and is an add-on to the May 1, 2009 OEHHA comments (revised on June 3, 2009).

Among the points that OEHHA agreed with DPR is the use of 25% GSH depletion as basis for nasal effect HEC and the use brain MeI AUC as dose metric for neurotoxicity HEC. However, there was no mention of agreement regarding the specific HEC levels.

A general comment was made (see Comments 2) regarding the need for more information. DPR disagrees that this constitutes a major deficiency for the document. First, this document is a part of Volume I and should be read in the context of the sizable data and discussions that were already presented in it. Much of the information requested or concepts questioned by OEHHA had been presented in Volume I, and duly referenced. Secondly, this document is a review and not a presentation of Arysta model. Sources for detail presentation of Arysta's model were cited. We pointed out the potential for future development in some areas where the model limitations were noted. Finally, at the time of this OEHHA review, the comprehensive database and the model construct, parameters, and application to MeI HEC had also been published in an entire issue of Journal of Inhalation Toxicology (2009, issue 6, volume 21). OEHHA staff is aware of them. Publications that were not available at the time of our March 2009 draft are now added to Volume I and this document. Thus, while DPR strives to provide further information in response to OEHHA's comments, it is necessary to exercise discretion of not repeating the sizable information publically available.

A. Fetal Death in Rabbits

Comment 1. Page A4, Line 8. It is stated that "the same basic model structure is used for all three endpoints" except that the rat has an enhanced nose compartment. It would be helpful to provide a model diagram of the rat PBPIC model.

DPR Response: A model diagram taken from Arysta (2007) is added.

Comment 2. Page A4, Line 42. "This section provides only a very brief description of the model." In our view this is a major deficiency of this report. The appendix on PBPK contains few details of the subject model variants; more details should be added as shown below.

DPR Response: We disagree with this view. Our key response is given in page 1 of this response. To keep this document concise, DPR carefully balanced the goal of maintaining focus on the many key issues in the review against expending the bulk by repeating detailed information available elsewhere. Ample references are given for the detailed information already presented in Volume I which had been included in Arysta model presentations, and/or given in USEPA's independent review. To facilitate comparison, major differences to USEPA's model review were also identified.

It should also be noted that prior to this July 2009 review by OEHHA, the comprehensive database and the model construct, parameters, and application to MeI HEC had also been published in an entire issue of Journal of Inhalation Toxicology (2009, issue 6, volume 21) . OEHHA was aware of their availability.

Nevertheless, DPR will add specific information requested by these OEHHA comments, to the extent of not overwhelming this review with details available in literature publications.

Comment 3. Page A-5, Line 1. "Comparison of model output to the experimentally measured values is used to adjust input variables for model fit." How was the model validated? Were there different data sets used for model calibration and validation?

DPR Response: Data used for model calibration/adjustment and model validation had been identified and presented in each respective section. In several cases, areas of lack of further data were specifically mentioned.

Comment 4. Page A5, Lines 5-8. This brief discussion of the origins of key model parameters is difficult to follow. It would help the reader if you could insert a table of model parameters

actually used in the model and expand on their individual origin (i.e., Morris, Mileson, Sloter, or other).

DPR Response: Data and description of the Morris (2004) study were in presented in Section III.J.2. of Volume I. As requested, specific reference to Table 50 is added. On the other hand, the Mileson et al 2007 was but a citation for the statement given.

A list of all input parameters for the model would have been impossible and redundant as they span a total of 10 pages in the article by Sweeney et al (2009) which is publically available.

Comment 5. Page A6, Fig A-1. It is not clear what the difference is between A- 1a and A- 1b. Figure legends should be specific as to exposure conditions and there are some misspellings that need correction.

DPR Response: No misspelling was found in Figure A-1.

Regarding the figure, an obvious difference between Figure A-1a and A-1b was in the X-axis. Figure A-1a showed the modeled versus measured data with a 24 hour period, while Figure A-1b included 4 daily MeI exposures, data ending at the termination the fourth exposure at hour 78. The measurement data were from the study of Sloter 2005a as cited. Detailed study design can be found in Section III.G.2 of Volume 1. The significance of these comparisons was presented in the corresponding text. The clarity is further enhanced to avoid further confusion.

Comment 6. Page A-7, Lines 2-3, 9-1 1, Table A-1. This text and table describe two ventilation rates and a table for modeled and measured results for one (12L/kg^0.75). This is confusing. The second table is not presented and should be included so the reader does not need to go to Section IIC to get the comparison.

DPR Response: The expectation for a “second table” is unfounded since it was not mentioned or implied. The Arysta model run submissions were iterative in response to DPR comments. In this case, once DPR had selected the proper QAC, it would not be necessary to repeat all useful model iterations prior to it.

In a review of DPR’s March 2009 draft, USEPA (Rodriguez, 2009) provided model runs demonstrating graphically the model fit at both QACs and showed no change in the F/M ratio with the higher QAC as expected. This new piece of information is added.

Comment 7. Page A-8, Lines 32-40, Table A-2. It would help to add the NaI data to Table A-2 even though the doses are different. The rabbit simulations seem consistent in over-predicting F/M ratios. Why wasn't this taken into account in setting the fetal influx and efflux rates in the model? The values given (some of the very few) show a rate ratio of 4.7-fold in favor of fetal uptake. This ratio is probably too high. In the human model this ratio is only 1.25.

DPR Response: This comment appears to reflect the lack of understanding regarding the limitation of comparability between the Morris et al (2004) and Sloter (2005b) studies with NaI versus MeI dosing. These limitations were discussed in our review. The reader should still remember in p.A-5 the modeler observation that further parameter adjustment to fit Sloter data would compromise the fit to Morris data With all things considered, DPR concluded in page A-9 that a more holistic model adjustment would be desirable.

It is unclear how OEHHA derived a ratio of 4.7. If this pertains to the rabbit, then being higher than humans in itself should not be the reason for OEHHA to conclude that the estimate is "too high".

Comment 8. Page A-11 lines 19-2 1. How well does the model predict fetal exposures at anticipated human exposure levels? Are there data in humans other than cord blood iodide?

DPR Response: As clearly presented, the apparent lack of human data was the main reason for the Rayburn et al 2007 study. It is considered by both USEPA and Arysta as the most pertinent for the MeI modeling purpose. As pointed out, this study resulted in USEPA's change of the HEC dose metric from maternal serum iodide to fetal serum iodide.

In terms of additional paired cord and maternal blood data, DPR was aware of a 1972 Cottino et al study associated with iodomethylsparteine i.v. injection during delivery, but decided that the Rayburn study was more suitable for the current discussion. However, since it was repeatedly mentioned by Arysta, the Cottino study is now added. The time between the injection and delivery ranged from 15 minutes to 48 hours, and the paired cord-to-maternal blood iodide concentration ranged from 0.5 to 3.4.

Comment 9. Page A13, Lines 18-21, Fig A-3. This text and figure report model predictions of up to 513-fold fetal to maternal iodide concentration ratio in rabbit thyroid follicles following a 6 hr exposure to MeI. Were other concentrations or ventilation rates simulated? A diagram of the rabbit PBPK model would be helpful.

DPR Response: The PBPK model diagram is added in response to comment 1.

The purpose for the additional information is amiss in this comment. Regarding the ratio of fetal to maternal iodide in rabbit thyroid follicles, model output from different sets of runs indicated that the ratio is 37 at 20 ppm MeI (maternal 0.4 mg/L, fetal 14.9 mg/L) and 68 at 10 ppm (maternal 0.14 mg/L, fetal 9.8 mg/L) MeI. Thus, these additional data did not change the pattern already described. As stated in our document, the main point was that this pattern was contrary to the lack of fetal thyroid iodide accumulation reported in the Morris study from NaI iv injection.

Comment 10. Page A15, Lines 8-9, Page A-16 Lines 1-9. The text reports predicted values of 1800-fold for fetal/maternal follicle iodide and raises concern with respect to model validation and the lack of tissue data. Gargas et al. 2005 is cited in support of the prediction but this is not published work in the available literature. Can a table be added to provide the key Gargas results "fit to human fetal thyroid iodide levels" that support the "likelihood of reality"?

DPR Response: The comment is apparently referring to the end of page A-14 (lines 22-23) and page A-15 (lines 33-41). As stated, fetal thyroid iodide is not a candidate HEC dose metric for MeI. Thus, DPR did not see the need to extend this issue beyond simply pointing out the areas that could benefit from further study, especially if this becomes a critical health concern for MeI exposure. The modelers' perspective about the lack of modeling stability was given to further support our decision for not expending on this subject.

The single Gargas et al citation was simply for documenting the source for further reading of their iodide submodel. The modelers indicated that the human pregnancy model for iodide was based on the perchlorate models by Clewell's group and others in several publications. It was built based on the fit to human fetal thyroid iodide levels. DPR opined that further model adjustment would be needed for applying this submodel from perchlorate thyroid inhibition MOA to scenarios of excess iodide from MeI exposure. The mention of the perchlorate iodide submodel is added for clarification sake.

Comment 11. Page A16, Lines 11-13. "The need to further investigate this issue . . . ." We agree that there is a need to thoroughly evaluate model parameters and structure to assure that the model predictions are reliable.

DPR Response: No response is necessary. However, we noted that the criteria for "reliable model prediction" are not specified in this comment.

Comment 12. Page A-16, Lines 24-26. "61.1 kg and a fetal weight of 0.27 kg (i.e. a single fetus at maternal weight fraction 'VFETC' of 0.0044). The model targets the stage of fetal

ontogeny…" Does the model include parameters for fetal, placental, uterine, mammary and fat growth during gestation? It seems to us that such a narrowly focused model is more likely to give erratic predictions than one covering a larger portion of the gestation period.

DPR Response: The fetal portion of the model includes tissue compartments. However, DPR did not view this aspect in itself would categorically invalidate modeling the early fetal stage without giving specific reasons. Instead, DPR's focal issues were as stated, i.e., the range of gestation stage during which fetal thyroid may remain vulnerable, and how these developmental-stage related parameters may affect the estimate of HEC.

As a comment to DPR's March 2009 draft, Arysta provided a model run showing that a 10-fold higher VFETC would result in decreased human iodide level by 12% in the maternal but 42% in the fetal serum at 0.24 ppm MeI exposure. This new information is now added. In the context of HEC derivation, we found that the new data further support DPR's choice of maternal serum iodide dose metric for HEC determination.

Comment 13. Page A-20, Lines 36-39. Notwithstanding the sharp temporality of the fetal death response during GD23-26, it makes more sense to us to adopt a not-to-exceed value at ANY point during gestation. Using a single day model metric to base the HEC may be too narrow.

DPR Response: DPR disagrees with this speculation. There is no data to support a "do-not-exceed" point "at ANY point during gestation". There was no disagreement from Arysta or USEPA regarding the narrow window of vulnerability on GD23-26. Rabbit fetal death did not occur with MeI exposure during GD6-22. On the other hand, it was repeatedly mentioned that death occurred immediately after the second 6-hour exposure within 30 hours.

Comment 14. Page A-21, Lines7-8. "Significant GSH depletion in fetal blood was detected as early as after one 6 hour 20 ppm exposure." This is unclear. Was the significant depletion seen at 6 hour or at some point after the 6 hour exposure? Please indicate the kinetics of GSH depletion (i.e., a graph).

DPR Response: As an appendix to Volume I, this document did not repeat the detailed data that had already been presented in it, but gave reference to the sections containing them. In this case, Section IV.A.I.a. of Volume I was referenced.

In fact, the available information is far more than just a summary table from two studies and a graph from one to four 6-hour of exposures. Data in the liver, kidney, and blood were also presented. The focus for what was recaptured in the discussion here was as stated; i.e., data

showed GSH depression occurring as early as after one (the first) 6-hour of exposure. And this supported DPR's decision to model the HEC based on a single day exposure.

Comment 15. Page A-2 1, Lines 1 9-2 1. "In summary, with insufficient support for a single MOA within the time frame of 30 or less hours, it is prudent to model the HEC at the 2 ppm NOEL based on a single day exposure for both rabbits and humans." In our view, a sound rationale for adopting a single day exposure in humans has not been established. It seems more likely that, in humans, the period of fetal vulnerability would extend well beyond a single day.

DPR Response: The possible MOAs were extensively covered in Volume I. While no specific argument was given for questioning the adequacy of support for DPR's single day exposure conclusion, OEHHA also did not provide any concrete alternative for modeling consideration. See also DPR's disagreement in response to Comment 13 if contains OEHHA's alternative.

In addition, it should be noted that as in all risk assessment establishing a single day HEC does not deny any vulnerability beyond a single day. Our concern for fetal thyroid vulnerability beyond this single day MeI exposure for fetal death endpoint was addressed in Volume I and in the uncertainty factor discussions therein. Again, Volume I contains crucial perspectives for selecting a single day NOEL and dose metric for the single day HEC and should be consulted.

Comment 16. Page A-21, Lines 41-43. "However, the range of human F/M ratio is wide, and there are nine sets of values above 2 (range 2.08-5.4) which exceed the average F/M ratios in rabbits." This is not evident from Tables A-1 and A-2 where human F/M values are generally lower than measured or modeled rabbit values. Is there something missing from the nine sets?

DPR Response: This comment appears to be out of context or deviating from the main point. The focal issue was about the range within the measurements in humans, not about human versus rabbits. Also, the comment looked into Table A-1 and A-2, while the text for the DPR statement referred to Table A-3.

Comment 17. Page A-22, Lines 37-38. "In conclusion, the overall evidence presented in this and previous sections indicates that maternal iodide dose metric is most reliable for reflecting the maternal Me1 exposure status on which the rabbit NOEL was based." Which maternal iodide metric is being referenced in this sentence, Cmax, C steady state, or AUC?

DPR Response: The specifically cited sentence was from a succinct conclusion referring to the general comparison between choosing the maternal versus fetal iodide dose metrics. Thus, this comment did not consider the preceding discussions about the support for using the AUC metric.

Nor did it consider the subsequent mention of the maternal serum iodide AUC as the final dose metric for HEC at the start of the next paragraph.

Comment 18. Page A-23, Lines 23-25. The discussion of rabbit and human AUCs are in units of concentration x time and usually averaged per day, e.g., mg/L d. Here the report is apparently equating ppm x 24 hr in rabbit with ppm x 96 hr in humans. Were regressions between ppm extena1 and AUC established for rabbit and human exposures? This would seem to be a more rational process for extrapolating AUC rabbit to AUC human and then to HEC (i.e. ppm external for human).

DPR Response: DPR disagrees that an empirical approach of regressions between external concentrations and AUC base on model output is more rational when the model is available to directly describe the tissue-specific level that incorporates considerations of all species-specific pharmacokinetic factors at any given external dose.

Comment 19. Page A-24, Table A-4. In view of comment 18 above, it would help to show a sample calculation for AUC-derived HECs in the table. Are there any further comments on the HECs presented in the table that cover a 17-fold range? Which ones seem more reliable? Or did you pick the lowest?

DPR Response: It is unclear what sample calculation for which OEHHA is looking. But this uncertainty regarding DPR's final HEC is surprising as no questions had been raised in our discussions leading to this conclusion. Our extensive discussions throughout this review to support our choice of a most reliable dose metric appeared unrecognized. This is serious because the choice of dose metric is essential to the application of PBPK model. The support for DPR's final choice was presented with respect to model behavior and biological and toxicological considerations and a sizable discussion on the MOAs was presented in Volume I. Many of these were again recaptured in Section II.B.2., immediately before the presentation of the HEC in Section II.C. Further discussions were also presented for the different outcome of HECs in Table A-4.

Comment 20. Page A-25, Figure A-7. This figure is difficult to read. Does the inset represent the human or the main graph? The inset exposure concentrations can't be read and should be specified in the legend.

DPR Response: The insets are re-scaled for readability.

Comment 21. Page A-27, Figure 8. Is a two-day simulation sufficient to assess occupational exposure? Normally you would expect a 5 day occupational plus 2 day population exposure (168 hr), The peak concentration with 0.35 ppm x 8 hr/d has clearly not been reached. If DPR has simulations predicting a steady state Cmax, then the report should show it. Again, these are predictions subject to sufficient model validation.

DPR Response: Again, it should be kept in mind that the HEC is for a single day based on the single day NOEL of 2 ppm. Thus, the second day simulation was not intended for addressing repeated days of exposure. As stated, its inclusion was an extra effort for illustration purposes. The rationale for not presenting data beyond day 2 was also stated, i.e., third day peak only increased by 2%.

Please also keep in mind that the HEC dose metric for this endpoint is the maternal serum iodide AUC, and not the peak concentration commented here, or the “Cmax” that was unspecified and undefined in this comment.

The risk assessment of repeated daily exposure was presented in Volume I. Based on Volume II, the exposure scenarios are: seasonal exposure of more than 1 week and up to 3 months, the annual exposure of 3 months to a year, and the lifetime exposures.

B. Nasal Olfactory Epithelial Degeneration in Rats

Comment 22. Page A-28, Lines 5-6. "This section provides only a very brief description of the Arysta mei3 model.. ." As noted above, a model diagram and list of parameters would greatly assist review of DPR's use of the model.

DPR Response: See response to Comment 1 regarding the diagram. See response to comment 4 regarding the redundancy in this model review to list the huge parameter set which is now published in the open literature.

Comment 23. Page A-29, Figure A-9. Figure A-9a shows that the model overestimates the reduction in olfactory GSH concentration. ppm should be added to the inset legend.” Figure A-9b shows two model simulations. What is the difference between them?

DPR Response: The MeI concentration (25 and 100 ppm) and the two simulations for the two olfactory regions (dorsal meatus and ethmoid) in Figure A-9a were labeled in the graph legend. It is not appropriate to edit the legend accompanying the graph since they were taken directly from Mileson et al (2007). Some requested information is now repeated in our legend to avoid further confusion.

Comment 24. Page A-30, Lines 5-6. "DPR agrees with USEPA that GSH depletion at the dorsal olfactory epithelium can be the dose metric for modeling the nasal effect HECs." In view of model overestimation of this metric, which appears to increase with exposure concentration, have other model metrics been adequately evaluated? For example, the model can predict Cmax's, AUCs, and fluxes in nasal epithelium.

DPR Response: The “Cmax, AUCs, and fluxes” in this comment lack definition for meaningful response. Again, throughout this review the crucial role of the MOA was repeatedly emphasized in this document for choosing the dose metric for the HECs. Extensive effort was devoted in Volume I for the MOA deliberation for all endpoints. The specific section for the nasal effect was cited. DPR concluded that GSH depletion was a likely early event for the nasal effect and a pertinent marker for its HEC.

Comment 25. Page A-31, Figure A-10. This figure is clear and understandable. A 6 hr exposure to rats results in about a 35% reduction in GSH in the dorsal meatus region, which serves as DPR's basis for estimating an HEC.

DPR Response: No response is needed.

Comment 26. Page 30, Lines 31-33. We agree that 50% GSH reduction is not a suitable benchmark for a no-effects level. Since tissues vary in GSH concentration, a single benchmark may be a flawed concept. DPR's use of 25% in relation to a nasal tissue GSH reduction threshold seems a reasonable place to start but more tissue specific data are needed to confirm this.

DPR Response: While the comment agrees with DPR’s 25% GSH depletion threshold, no further response can be given for the needed tissue data since they were not specified.

DPR is well aware of the possibility of a probabilistic modeling that considers the variability of key parameters. However, DPR strongly disagrees that a single benchmark of 25% GSH depletion is a flawed concept. In fact, drawing such a conclusion based on the variability of one parameter in one species is problematic because it will likely skew the interpretation of the resultant HEC.

Comment 27. Page A-34, Lines 23-26. "Repeated exposure may result in a greater severity of cellular damage from which an HEC based on a single day exposure at 25% GSH depletion may not be adequate to protect." Agreed. That is why simulations estimating an HEC for human occupational exposure should be run for at least a week (5 x 8 hr/d plus weekend).

DPR Response: DPR appreciates OEHHA's agreement on DPR's appraisal based on the lack of time for GSH recovery in a 24-hour exposure scenario. However, more important is our repeated reminder that the HEC established in this review for all three endpoints are for a single day acute exposure. In risk assessment, these HECs are applied only to a single day upper bound of MeI concentration and not an average concentration from consecutive days.

DPR disagrees that our appraisal should be the basis for OEHHA's advocating for modeling a week of exposure for workers. The worker related key considerations were presented in Section III.C.2. In terms of a 24-hour exposure for workers that include the 16-hour off work time, their 2.8 ppm HEC was discussed in the context of the 24-hr 2.2 ppm HEC for the general public.

The basis for OEHHA's concern about the "5 x 8 hr/day" is not supported in light of the Figure A-12 showed the recovery after the 8-hour exposure was near completion at the end of a 24-hour cycle.

Comment 28. Page A-35, Lines 3-4. "The rat model uses mei3.csl and mei3cmd files submitted to DPR by Arysta (2007). Three sets of HEC simulation runs were conducted by Arysta in 2008." Does this mean that DPR didn't run any simulations with the model to confirm proposed HECs?

DPR Response: DPR did not see the need to physically conduct side-by-side repeated iterations for each model run provided by Arysta. Again, please keep in mind that many of these model runs were iterative based on DPR's issues that were raised as the model review progressed. It is important to note that, in our review, care had been taken to examine all the input, output, and run files for all the model sets presented in this review. Often, analyses are additionally performed by DPR based on the information in these model files.

As a review of DPR's March 2009 document, Rodriguez (2009) from USEPA repeated the key HEC related model runs and did not uncover any additional issue that DPR had not already identified. The integrity of DPR model review is affirmed.

Comment 29. Page A-35, Lines 17-19. "..applying input parameters for children of various age (i.e., 3 month-old infants, children at 1, 5, 10, and 15 years old) did not result in different HECs than for adults." It would be useful if the report could expand on this. For example, what body weights and ventilation rates were used for infants and children?

DPR Response: The specific values for children of various ages were not given in the USEPA model review. Arysta came to the same conclusion of no age differences by assuming a constant

TVol/BWt ratio in age-specific model runs. The 2009 open literature article by Mileson et al is added for this information.

Comment 30. Page A-35, Lines 23-29, Figure A-11. These graphs are difficult to read. Presumably they proceed from inside to outside, top to bottom. Please indicate the outermost layer in the text, gsdoe11 "The time to a less than 0.5% change in GSH level is not reached until hour 14 of exposure." What does this mean? It is not clear how this relates to the other text or Fig. A-11.

DPR Response: The designation "outermost" is added for "gsdoe11" in both the text and the figure legend.

The time to the steady state GSH depletion was observed in Figure A-11. The significance for this observation is as presented; i.e., the importance of time factor in the exposure duration such that increase in exposure duration is expected to result in greater GSH depletion before the steady state depletion is reached.

Comment 31. Page A-38 Lines 2-3, Figure A- 12. "DPR's 8-hour HEC is 2.8 ppm based on DPR's default breathing rate of 833 L/hr.. ." It is not clear what the basis of the HEC is? Is it the average depletion of GSH in the olfactory epithelium? Please indicate clearly in the text and legend. Again the graph is difficult to read and some additional labeling would help.

DPR Response: It is not necessary to repeat all details in this summary section. Details for the 2.8 ppm HEC were given in the preceding section III.C.2. The use of the average GSH depletion in human olfactory region as the HEC dose metric was presented in Section III.B.1. It should be clear that the 25% GSH depletion dose metric was used for both the general public and occupational HECs.

No specific reasons were given in this comment for OEHHA's difficulties to read the graph. Suffice to add "outermost" to the gsdoe11 layer as per Comment 30.

C. Neurotoxicity

Comment 32. Page A-40, Lines 14-18. ". . .the concerns remain about the use of blood or brain Me1 concentration instead of its AUC for the HEC dose metric." It seems to us that the brain AUC is the most reasonable metric for the analysis.

DPR Response: In their review of our March 2009 draft document, USEPA (Rodriguez, 2009) also agreed with DPR that the AUC is the most reasonable dose metric for HEC.

Comment 33. Page A-43, Lines 13-15. "Since this 8-hour HEC does not take into account the additional 16-hour exposure after work, it is realistic to set the 8-hour HEC at 3.4 ppm, the same level for the 24-hour HEC." Is this realistic? The rationale is not clear. Why not a time weighted average, e.g., *5.5* ppm? It just seems odd that a rationale for an 8-hour value was developed and then discarded.

DPR Response: DPR's reasoning for the 8-hour HEC is an obvious mathematical treatment of one-third of 9.7 ppm.

DPR considers OEHHA's "time weighted average" (TWA) conceptually flawed and irrelevant for this application. Presumably, OEHHA's 5.5 ppm was derived from (9.7 ppm x 8/24) + (3.4 x 16/24). This approach cannot be applied to deriving the HEC as an upper limit of exposure.

It is important to keep in mind that the goal at hand is to find an exposure level that would not exceed a 24-hour AUC in rats at the NOEL of 27 ppm. Given that the 24-hour matched HEC is 3.4 ppm, an exposure limit for the 8 out of a 24-hour exposure would be either the same or lower if the higher breathing rate would not result in significantly higher brain MeI concentration. Thus, OEHHA's erroneous application of the TWA method can be illustrated herein. Assuming that the contribution to the total AUC due to the higher breathing rate is insignificant, had the workers been allowed an exposure at 5.5 ppm for 8 hours and additionally exposed to 3.4 ppm for the remaining 16 hours as a member of the general public, their 24-hour TWA of 4.1 ppm would have exceeded the 24-hour 3.4 ppm.

Comment 34. Overall the neurotoxicity section is better presented than the other endpoints.

DPR Response: No specific response is needed. However in all fairness it should be recognized that compared to the complexity of issues under the preceding two modeled endpoints, the neurotoxicity section is the least complicated since the available data are most limited. Thus the brief coverage might have contributed to the ease of understanding.

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Director

Department of Pesticide Regulation

Arnold Schwarzenegger
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M E M O R A N D U M

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DATE: May 29, 2009

SUBJECT: RESPONSE TO THE OFFICE ENVIRONMENTAL HEALTH HAZARD ASSESSMENT'S (OEHHA) COMMENTS ON THE EXPOSURE ASSESSMENT FOR METHYL IODIDE

The Office of Environmental Health Hazard Assessment (OEHHA) initially sent comments on the Exposure Assessment Document for Methyl Iodide (MIEAD) on May 1, 2009, and added the comment at the end of this memo on May 28, 2009. OEHHA's comments are italicized below, with the response to the comments immediately following.

OEHHA: *Table 3, presented on page 6 of the EAD, lists the general information for submitted products containing Mel as an active ingredient. The product formulations consist of iodomethane technical (99.8% Mel) and varying ratios of MeI to chloropicrin, ranging from 98% MeI/2% chloropicrin to 25% MeII75% 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% Mel 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 LCso-rat for TM-425 (99.7% MeI) at 3.9 mg/L for both males and females and for TM-42503 (25% Mel, 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 in 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.*

WH&S: DPR is also concerned with the risks associated with formulations containing more than one active ingredient. Although this exposure assessment document (EAD) only addresses human exposure to methyl iodide, estimates of chloropicrin exposure resulting from the application of chloropicrin as a warning agent, or as a co-active ingredient in different

formulations is currently being conducted. Those estimates will appear in a separate exposure assessment document for chloropicrin.

OEHHA: *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, cited in EAD) 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.*

WH&S: The respiratory rates that were used in the methyl iodide exposure assessment document are default values for individuals to be used when duration of activity and activity patterns are not specified. These values are listed in a joint policy memorandum issued by the Worker Health and Safety and Medical Toxicology branches (HSM 00010).

OEHHA: *The product label for Midas 98:2 provided in Appendix I, pages 58-67, states, "Do not apply within a quarter 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 quarter 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?*

WH&S: Both the 152 m and 402 m buffer zones are federally mandated buffer zones that appear on the labels. Label language is within the federal purview.

OEHHA: *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:

WH&S: For this assessment, DPR relied on the federally assigned protection factors for personal protective equipment that can be found in 29CFR1910.134 Subsection d3iA.

The label for Midas 98:2 (page 59) does not specify that the respirator be tested and adjusted so that it fits properly. A respirator will not provide 90% protection if it does not fit properly.

WH&S: Because the label requires a respirator to be used, the applicators must follow California regulations. These regulations specify procedures that applicators must follow to ensure that the respirators will fit properly- Title 3 CCR subsection E- fit testing.

OEHHA: *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.*

WH&S: The service life of the air-purifying cartridge, when not specified on the label, is covered under California regulations- Title 3 CCR subsection O- end of service life. Thus, the cartridge can only be used once, and then must be discarded at the end of shift.

OEHHA: *Worker compliance with this requirement* (wearing respirators) *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.*

WH&S: This EAD addresses exposures that occur from actions that are in compliance with state and federal laws. DPR is also concerned with compliance. The County Agricultural Commissioners and the Department of Pesticide Regulation have enforcement functionaries to ensure compliance with State and Federal laws. Applicator non-compliance with label requirements and/or California regulations can result in fines, loss of license, and even criminal charges.

OEHHA: *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.*

WH&S: Because the label states that applicators must wear respiratory protection, this is a baseline exposure scenario that reflects the minimum requirements as stipulated by federal and state laws. Should mitigation of exposure be necessary, then other measures to reduce exposure will be considered.

OEHHA: *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?*

WH&S: Worker Health and Safety is also concerned about the efficacy of engineering controls in reducing the air concentrations of MI. Engineering controls were present in only one of the three studies involving shank injection of MI. As noted in the text of the EAD (p 26), "Engineering controls were used in the Manteca study. According to the labels, either engineering controls or respiratory protection must be used when applying MI. It was assumed that engineering controls would produce at least a 10-fold reduction in driver exposure. The exposures of the applicators in the Manteca study were adjusted 10-fold upward to match those of the applicators in the other studies that were conducted without additional PPE." Consideration of a 90% protection factor from label-required PPE (engineering controls or respiratory protection) to those un-mitigated air concentrations of MI was made using equation 2, page 28.

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Director

Department of Pesticide Regulation

Arnold Schwarzenegger
Governor

M E M O R A N D U M

TO: Randy Segawa
Environmental Program Manager I
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FROM: Jing Tao, Ph.D. *Original signed by*
Environmental Scientist
Environmental Monitoring Branch
916-324-4201

DATE: June 29, 2009

SUBJECT: RESPONSES TO THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMEMT COMMENTS ON VOLUME III, ENVIRONMENTAL FATE OF THE METHYL IODIDE RISK CHARACTERIZATION DOCUMENT FOR INHALATION EXPOSURE

This memorandum contains the Environmental Monitoring branch responses to the Office of Environmental Health Hazard Assessment (OEHHA) comments on the environmental fate document, volume III of three volumes comprising the Department of Pesticide Regulation (DPR) Risk Characterization Document for Inhalation Exposure. Each OEHHA comment is in bold italics, followed by the Environmental Monitoring response.

1. The document does not consider the potential for MeI or its primary degradation product iodide to contaminate surface water or groundwater. …

Response: Sections pertaining to surface water and ground water have been added.

2. As a proposed alternative to methyl bromide, MeI use in California could conceivably reach several million pounds per year. If this were to 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 groundwater because the compound is readily mobile in soil. In our opinion, the potential adverse effects of iodine and MeI contamination of surface and groundwater on humans and ecological receptors should be evaluated.

Response: Sections pertaining to surface water and ground water have been added.

3. Table 2 and 3 are poorly formatted and need to be revised.

Response: Table 2 has been reformatted. Table 3 has been revised according to the comment and now is Table 4.

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, R.C. (ed.) Handbook of Chemistry and Physics. 67th ed. Boca Raton Fl: CRS Press Inc., 1986-87, p. F-63 and p. D-275]. According to Budavari, S. (The Merck Indes – An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ.: Merck and Co., Inc., 1996. p. 1039] MeI is colorless, transparent liquid which turns brown on exposure to light. According to the DPR description (first paragraph 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.

Response: The additional information was added in the Table 1 (Page 1). The text in the first paragraph about the color was revised (Page 2).

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 be updated to include the following sentence: "In October 2008, U.S. EPA extended conditional registration of MeI without specifying and time limits."

Response: A similar sentence has been added (Page 2, the third paragraph).

6. At the top of 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.

Response: The table of application rate (Table 3) was revised according to the U.S. Environmental Protection Agency label information (Page 3). As for the application acreage, it may be possible to estimate the acreage that might be fumigated with methyl iodide in California, based on the acreage treated by other fumigants. However, this estimate would have high uncertainty. In addition, the total acreage fumigated has no effect on DPR's current estimates of exposures. For these reasons, DPR prefers not to estimate the total acreage.

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

Response: This information was added in the end of the second paragraph of Use Profile (Page 3).

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 methylating agent. MeI released to air at 25 C and 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 W. Mill T, J Chem Ref Data 7: 383-415(1978)]. Volatilization from moist soil surfaces and water surfaces is an important fate process of MeI based upon this compounds' 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 [Lyman WJ et al., Washington, DC; Amer Chem Soc pp 4-9, 15-29 (1990), Zafiriou OC, J Mar Res 33: 75-81 (1975)]. In addition, the general population may be exposed to MeI through ingesting seafood (Toxnet, 2009).

Response: "The major source from marine organism" was addressed in Section C (Page 5). The temperature and vapor pressure has been added to the first paragraph of Section C. Photolysis was addressed. Volatilization of methyl iodide was addressed. The phrase "exposure through ingesting seafood" has been added in the Use Profile (Page 3).

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 M. Gao S. on the degradation of MeI in soil and the effect 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 [J Environ Qual 2009 Feb 6; 38 (2) 513-9]. 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.

Response: DPR will consider this and other mitigation measures during the risk management process.

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 DOR's document. Even though abiotic degradation (involving light, temperature, atmospheric gases, sunlight, irridation,and photohydrolysis) constitutes minor dissipation of MeI from the environment, it still would be informative to address it.

The abiotic dissipation of methyl iodide from aquatic environment and soil was addressed on Pages 3-4.

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.

Response: Glossary has been added as Section V (Page 11).

12. A mistake was made in numbering the tables.

Response: All the numbers of table have been changed.