Methyl Iodide (Iodomethane)

RISK CHARACTERIZATION DOCUMENT FOR INHALATION EXPOSURE

Volume IV - Part 2

Responses to USEPA Comments (Part a)

CH_3I

External Panel Review Draft

Department of Pesticide Regulation
California Environmental Protection Agency

August 2009

ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

June 2, 2009

Marylou N. Verger-Carlos, DVM, MPVM, Associate Director
Pesticide Programs Division
Department of Pesticide Regulation
California Environmental Protection Agency
1001 I Street, P.O. Box 4015
Sacramento, CA 95812-4015

Re: U.S. EPA Comments On DPR Iodomethane Risk Characterization Documents

Dear Dr. Verder-Carlos,

The United States Environmental Protection Agency is pleased to submit its comments on the risk characterization documents completed by the Department for iodomethane that were recently provided to the Agency for review. The documents we reviewed can be identified by the following information:

- ***Risk Characterization Document For Inhalation Exposure, Volume I, Health Risk Assessment CH_3I, DPR and External Review Draft***, Authors: Lim and Reed, Medical Toxicology Branch, Department of Pesticide Regulation, California Environmental Protection Agency (March 2009).

- ***Appendices to Volume I: Health Risk Assessment of Methyl Iodide DPR and External Review Draft***, Medical Toxicology Branch, Department of Pesticide Regulation, California Environmental Protection Agency (March 2009).

- ***Risk Characterization Document For Inhalation Exposure, Volume II, Exposure Assessment CH_3I, DPR and External Review Draft***, (HS-1866), Author: Cochran, Worker Health and Safety Branch, Department of Pesticide Regulation, California Environmental Protection Agency (March 2009).

- ***Risk Characterization Document For Inhalation Exposure, Volume III, Environmental Fate CH_3I, DPR and External Review Draft***, Authors: Barry and Kollman, Environmental Monitoring Branch, Department of Pesticide Regulation, California Environmental Protection Agency (March 2009).

Attached you will find our four review documents which specifically address the hazard aspects of the assessment, the exposure assessment related elements; the environmental fate components of the assessment, and issues related to the prospective use patterns that are anticipated for iodomethane (Attachments A through D, respectively).

Our findings indicate that our agencies are essentially using the same hazard and exposure data as the basis for our individual assessments but our respective use of the information differs. These alternate approaches have resulted in different predictions of risk. The key differences between our approaches which we have identified include: use of a body burden risk estimate approach as opposed to the use of a route-specific inhalation based risk metric outlined in the Agency's peer reviewed Reference Concentration methodology; differences in endpoint selection and the use of a pharmacokinetics model for that purpose; use of a different statistical representation of the data used to calculate occupational risks; and use of a deterministic rather than distributional approach to air modeling for predicting bystander risks.

Also, note that the Iodomethane Docket at EPA-HQ-OPP-2005-0252, contains extensive materials including the Agency's Risk Assessment of Iodomethane.

It is understood that the Department will commence with an external peer review process for iodomethane in early June. It is our hope that the review documents which we have prepared will be utilized in this process. Please contact Cynthia Giles-Parker of my staff at giles-parker.cynthia@epa.gov if you have comments, questions or require further clarifications on this submission.

Sincerely,

Debra Edwards, Ph.D.
Director, Office of Pesticide Programs

Attachment A: U.S. EPA Review Comments on DPR Iodomethane Hazard Assessment

Similar to the US EPA health risk assessment, the hazard assessment and PBPK evaluation presented in the CDPR's risk characterization documents represents the culmination of years of work by dozens of scientists. More detailed comments on the PBPK modeling are provided by scientists from the US EPA's National Center for Computational Toxicology (NCCT) under a separate memorandum (attached).

General Comments:

CDPR's risk characterization documents relied primarily on the same data used by the Agency. There are, however, substantial differences in the interpretation and application of these data. Some of these differences include: (i) NOAEL established for the pre-natal developmental study in rabbits; (ii) requirement for a developmental neurotoxicity study (DNT); (iii) use of different methodology to derive human equivalent concentrations (HECs); (iv) uncertainty factors used in the risk assessment; (v) dose metrics and parameters used in the Physiologically Based Pharmacokinetic Model (PBPK) model; (vi) determination of the carcinogenic mode of action; (vii) use of data from deliberate human iodomethane exposures which possibly could not meet the Agency's requirement under the provisions of the Federal Policy for the Protection of Human Subjects of Research (the ``Common Rule"; (viii) quantitative risk assessments for oral and dermal exposures. In general, the differences in HECs derived by the Agency and CDPR reflect the changes in the methodology used to calculate HECs since for the most part both regulatory bodies selected the same studies and NOAELs/LOAELs for the risk assessment. Another difference is that CDPR calculated dose levels using a body burden approach from inhalation studies (i.e., represented in mg/kg/day). Typically, the Agency does not do that for fumigant risk assessments where adequate inhalation data are available and prefers to use an inhalation route-specific approach based on the use of HECs. In general, this extrapolation is not considered appropriate or needed since it does not take into consideration the kinetic differences inherent to different routes of exposure. More specific comments addressing the hazard characterization are included below.

Summary (pp. 2-8)

Toxicology Profile and Hazard Identification

For the acute risk assessment, CDPR selected the endpoint of fetal death from the prenatal developmental toxicity study in rabbits. For this study CDPR established a NOAEL at 2 ppm while the Agency established the NOAEL at 10 ppm. The Agency's decision to establish the NOAEL at 10 ppm is based on the observation that the incidence of fetal deaths seen at this concentration were within historical control obtained from the Middle Atlantic Reproduction and Teratology Association (MARTA), one of the world's

largest repositories of reproduction and developmental historical control data. Moreover, the standard deviation for fetal losses at this concentration was approximately 2-fold higher than the mean (0.1±0.22) thus rendering the observation indistinguishable from background. Similarly, the incidence of late resorptions at the 10 ppm could not be distinguished from background since the standard deviation was also ≈ 2-fold higher than the mean (0.9±1.60). In contrast, the effects observed at the 20 ppm concentration (the concentration used by the Agency as the LOAEL) are more robust including a 41% decrease in the number of live fetuses per doe, a 20% decrease in fetal weight, and a 1500% increase in late resorptions. In addition to selecting a different NOAEL for the study, CDPR also used a different dose metric from the Agency to calculate the HEC for this endpoint using the iodomethane PBPK model. Since perturbations of fetal thyroid function lead to the fetal losses observed in the study, the Agency used the area under the curve for fetal plasma iodide as the dose metric for calculating HECs. The Agency considers this to be an appropriate dose metric as it is more representative of the conditions leading to the effect of concern. CDPR, however, selected the maternal plasma iodide concentration (area under the curve [AUC]) as the dose metric. Further comments on this selection, by NCCT scientists evaluating CDPR's changes to the PBPK model which was used to develop the Agency's assessment is attached. These differences in the selection of NOAELs and dose metrics for the PBPK model led CDPR to select the prenatal developmental toxicity in rabbits as the critical study for the acute exposure risk assessment with an HEC of 0.22 ppm for the occupational assessment and 0.24 ppm for the bystander assessment. In contrast, the Agency selected a HEC of 5.8 ppm for the occupational assessment and 4.5 ppm for the bystander assessment based on degeneration of the olfactory epithelium observed in the subchronic inhalation toxicity study. Using the parameters selected by the Agency's pharmacokinetic experts to parameterize the PBPK model submitted to the Agency, the degeneration of the olfactory epithelium is the most sensitive endpoint and yields the lowest HEC for this duration of exposure. To provide risk managers a more comprehensive view of the acute toxicity profile for iodomethane, three potentially critical endpoints were identified: nasal histopathology in the subchronic inhalation toxicity study in rats, the fetal losses in the developmental toxicity study in rabbits, and neurotoxicity in rats. Using the RfC methodology, the HECs for fetal death and neurotoxicity were higher than those calculated for the nasal lesions.

The Agency and CDPR used a different dose metric to evaluate the risk for degeneration of the olfactory epithelium after exposure *via* the inhalation route. CDPR selected 25% GSH depletion as the dose metric in contrast to the 50% depletion selected by the Agency. Although the Agency had originally selected 25% GSH depletion as the dose metric for its risk assessment, in the most recent risk assessment, the Agency selected 50% GSH depletion as the dose metric. This change is due to the additional refinements in the PBPK model that allow Agency scientists to calculate GSH depletion in distinct layers of the olfactory epithelium thus ensuring that no single layer has more than the 50%GSH depletion commonly cited in the literature as critical for development of nasal histopathology. Moreover, the model describes GSH depletion resulting from conjugation with methyl iodide, metabolic consumption, synthesis, and degradation in each of the four top layers. It does not, however, fully account for the impact of GSH

diffusion across layers thus potentially overestimating the extent of GSH depletion in each of the top layers. It should also be noted that the emission profile of iodomethane suggests that during peak emissions GSH depletion is likely lower than 50% (*e.g.* 38%).

CDPR also altered the dose metric for the endpoint of neurotoxicity obtained from the Acute Neurotoxicity Study in rats. While the Agency used steady state to parameterize the PBPK model and calculate HECS, CDPR used brain iodomethane AUC concentrations as the dose metric. The principle of periodic steady state (*i.e.,* periodicity) is embedded in the Agency's RfC methodology which would have been used as a default to calculate HECs if a PBPK had not been available. Periodicity state is achieved if the concentrations of the inhaled compound within the animal achieved periodicity with respect to time (i .e., periodic steady state-the concentration versus time profile is the same for every time point). Practically, the conditions of periodicity should be met during "most" of the exposure duration . For example, if this condition is met for 90% of the time (e .g ., periodic during the last 90 weeks of a 100 week experiment), then estimates of average concentrations will be in error by less than 10% . Given that iodomethane reaches steady state after 30 minutes of a 6 hour exposure, the Agency is confident that the use of steady state is appropriate.

The differences in the points of departure used for the subchronic and chronic risk calculations also reflect the differences in the methodologies used by CDPR and US EPA to calculate HECs and exposures (i.e., body burden instead of a route-specific approach). While CDPR's calculations to estimate the inhalation risk to humans are based on different breathing rates for different life stages, the Agency's calculations are dependent on the regional gas dose ratio (RGDR). In the case of systemic effects, the RGDR is defined as the ratio of the blood:gas partition coefficient of the chemical for the test species to humans ($H_{b/g\ animal}/H_{b/g\ human}$). When this ratio is unknown or when the $H_{b/g\ animal} > H_{b/g\ human}$ a default value of 1.0 is used as the RGDR. This default is based on the observation that for chemicals where partition coefficient data are available in both rats and humans the RGDR value has usually been comparable or slightly higher than 1. Thus, the use of an RGDR of 1 results in a protective calculation of the inhalation risk. CDPR's methodology assumes that the more of the compound that is inhaled the more of it enters the blood stream or deposits in the respiratory tract. This does not take into account the anatomical and physiological differences between test species and humans. The RfC methodology developed by the US EPA Office of Research and Development offers a more refined methodology that, based on the PBPK ventilation-perfusion model concept (e .g., Ramsey and Andersen, 1984), use algebraic equations to relate organ and tissue compartment concentrations to exposure concentrations. The procedure assumes that the toxic effects observed are related to the arterial blood concentration (concentration leaving lung compartment in the model) of the inhaled compound and that $NOAEL_{HEC}$ should be such that the human time-integrated arterial blood concentration is less than or equal to that of the exposed laboratory animal. Given that the ability for arterial blood to carry compounds from the lung compartment does not significantly vary with age, the Agency does not calculate different HECs for different life stages but rather calculates different HECs based on duration of exposure.

The HECs selected for each of the risk assessments by the US EPA and CDPR are compared in Table 1. For subchronic/intermediate risk assessments the HECs selected by US EPA and CDPR are comparable in spite of the differences in methodology to derive the HECs. The major differences are noted in the acute risk assessments and are intrinsically related to the parameterization of the model as well as the NOAEL selection for the prenatal developmental study. As previously noted, comments on the parameterization of the model by NCCT scientists is attached as a separate memorandum. Regardless of the points of departure there are still differences in the interpretation of the data. For instance, it is unclear to the Agency CDPR's rationale for selecting the endpoints of decreased pup weight/pup weight gain and delays in sexual maturation (i.e., delayed vaginal patency acquisition) to assess risks for adults. These are clearly effects related to exposure to the young since body weight decrements were not the most sensitive endpoints in any of the adult studies and onset of sexual maturation would occur prior to adulthood.

Duration	Toxicity Endpoint	NOAEL[a]	Human Equivalent Concentrations (HECs)			
			US EPA		CDPR	
			Bystander	Occupational	Bystander	Occupational
Acute	Fetal Death in rabbits	2 ppm	N.A.[b]	N.A.	0.24 ppm (women of child-bearing age)	0.22 ppm
	Fetal Death in rabbits	10 ppm	7.4 ppm	23 ppm	N.A.	N.A.
	Degeneration olfactory epithelium	21 ppm	4.5 ppm	5.8 ppm	2.2 ppm (all ages)	2.8 ppm
	Neurotoxicity	27 ppm	10 ppm	10 ppm	3.4 ppm (all ages)	3.4 ppm
Intermediate/ Subchronic term	↓pup weight, ↓pup weight gain, ↓ thymus weight, delayed vaginal patency acquisition	5 ppm	1.25 ppm	N.A.	1.4 ppm (adult)	4.1 ppm
	Degeneration of the olfactory epithelium	21 ppm	N.A.	3.7 ppm	N.A.	N.A.
	↑ relative liver wt., ↓ body weight gain	21 ppm	N.A.	N.A.	2.4 ppm (child) 1.9 ppm (infant	N.A.
Chronic	↑ salivary gland squamous cell metaplasia	5 ppm	0.89 ppm	3.75 ppm	1.0 ppm (adult) 0.6 ppm (child) 0.5 ppm (infant)	4.1 ppm
Lifetime	Thyroid tumors	20 ppm	Not likely to be carcinogenic to humans at doses that do not alter rat thyroid hormone		3.9 ppm (adult)	16.3 ppm

homeostasis

[a] CDPR selected NOELs while USEPA routinely selects NOAELs

[b] N.A.: Not applicable; not used in the risk assessment by the regulatory body

With regards to the carcinogenic potential of iodomethane, the CDPR risk characterization documents assume that humans are more sensitive to the oncogenicity potential of iodomethane than animals. The Agency does not concur with this conclusion. Both CDPR and US EPA considered the formation of thyroid tumors as the outcome of thyroid hormone perturbations and not a mutagenic effect. Chemicals that produce thyroid follicular cell tumors in rats by prolonged TSH stimulation are not likely to be carcinogenic to humans. Humans respond as do experimental animals to disturbances in thyroid function from various antithyroid stimuli such as iodide deficiency, partial thyroidectomy and goitrogenic chemicals: when circulating thyroid hormone levels go down, the TSH level rises which in turns lead to thyroid hypertrophy and hyperplasia (goiter). Cellular and biochemical studies, however, provide **compelling evidence that rats are substantially more sensitive than humans to the development of thyroid follicular cell tumors in response to thyroid hormone imbalance** (IARC, 2001, Meek et al., 2003, EPA,1998; Dohler et al., 1979). There are a number of quantitative differences between rats and humans that explain this increased sensitivity. The rat has a much shorter thyroid hormone half-life than humans. The half-life of thyroxin (T4) is about 12 hours in rats compared to 5-9 days in humans (Dohler et al., 1979). The longer half-life in humans is likely related to the presence of a high-affinity binding globulin for thyroxin that is absent in rats. In humans this binding of thyroid hormone to this globulin accounts for slower metabolic degradation and clearance. Additionally, there is a larger thyroid hormone reserve in the human compared to the rat. Increased turnover and hepatic clearance of thyroid hormone (T3, T4) result in the thyroid gland being more active in rats than in humans. The constitutive TSH levels are approximately 25 times higher in rats than in humans, reflecting the increased activity of the thyroid-pituitary axis in rats (Dohler et al, 1979; McClain 1992). Lastly, rats appear to be very susceptible to thyroid neoplasia secondary to thyroid hormone imbalance. Modest changes in thyroid hormone homeostasis may promote tumor formation in rats. In contrast, data in humans suggest that prolonged TSH stimulation of the thyroid gland poses a negligible risk of thyroid carcinogenesis (Curran and DeGroot, 1991). Studies of individuals with hyperthyroidism (patients with Graves Disease, goiters) indicate the occurrence of thyroid cancer is rare (e.g., Mazzaferri, 2000; Gabriele et al., 2003). Also, a study of environmental and heritable causes of cancer among 9.6 million individuals using the Nationwide Swedish Family-Cancer Database found that the environment did not appear to play a principal causative role in thyroid cancer (Czene et al., 2002). The only known human thyroid carcinogen is x-irradiation.

Risk Appraisal

CDPR has concluded that the "benchmark" MOE for iodomethane should be 300 instead of the conventional 30 that is used when points of departure for inhalation risk assessments are expressed in terms of HECs. CDPR states that an additional 10X factor is needed to assess "the concerns about the serious and irreversible nature of

neurodevelopmental effects that have not been studied, the post-natal mortality from excess iodide that needs further study in the context of iodomethane exposure, and the level of excess iodide in MeI being added to the background iodide intake." Later in the report (p. 101) CDPR states that a DNT was not required by the Agency because "is not being required by the USEPA because MeI is considered a non-food use and, therefore, not subjected to Food Quality Protection Act considerations (USEPA, 2006A)." This is not an accurate representation of the Agency's rationale for not requiring a DNT. Like iodomethane, a number of pesticide chemicals have been shown to perturb thyroid hormone homeostasis via reduction of circulating thyroid hormones (Hurley *et al.,* 1998). Chemicals that perturb thyroid homeostasis and result in hypothyroidism are known to be associated with neurological disorders and alterations in neurological development, both in animals and humans (Fisher, 2000; Chan and Kilby, 2000; Morreale de Escobar *et al.*, 2000; Zoeller and Rovet, 2004; Anderson *et al.*, 2003). Thus, in the assessment of the toxic characteristics of a thyroid disrupting pesticide, determination of the potential to adversely impact thyroid hormones, thyroid structure, and/or thyroid hormone homeostasis during development is important. Normally, if a neurodevelopmental concern is raised by existing data on a pesticide, a rat developmental neurotoxicity (DNT) study is requested. However, disruption of thyroid homeostasis by thyroid disrupting pesticides is the initial, critical effect that may lead to adverse effects on the developing nervous system. Thus, *in lieu* of the rat DNT study, a study that entails a mechanistic approach to generate specific data on the thyroid (*i.e.*, the primary target of the chemical of interest) to protect the developing nervous system from thyroid hormone disrupting chemicals is typically required by the Agency. The specific purpose of this study is to generate data to establish NOAELs and LOAELs (or benchmark doses) that may be used to derive RfCs that would be protective of the ability of a chemical to disrupt thyroid function in pregnant females and in the fetus and newborn. In the case of iodomethane, a study evaluating the impact of iodomethane exposure on both pregnant females and their offspring is available in the most sensitive species – the rabbit. Thus, the need for the DNT is obviated by the availability of these data. Measures of thyroid hormone status in both the pregnant female and her offspring are known to be more sensitive than the apical measures that are evaluated in the DNT. Moreover, the DNT is conducted in the rat; a species that is not as susceptible to iodomethane exposure as the rabbit.

<u>Toxicology Profile (pp 14-110)</u>

Pharmacokinetic (p. 14-15)

CDPR used data from metabolism studies in which humans were deliberately exposed to ^{132}I-MeI by inhalation. Under the provisions of the Federal Policy for the Protection of Human Subjects of Research (the ``Common Rule"), the Agency will only consider human studies conducted prior to the Agency's final rule (2006) after conducting a comprehensive ethics review and/or is evaluated by the Human Studies Review Board (HSRB) empanelled by the Agency after enactment of the final rule. Since the study cited in this section was not subject to this process, the Agency will not consider the study.

Absorption and Distribution (pp. 15-20)

CDPR used a study intended to evaluate the disposition of MeI in rabbits after a single exposure. In this study rabbits were exposed to ^{14}C-MeI *via* subcutaneous injection. The Agency does not consider subcutaneous injection a relevant route of exposure. Since this exposure strategy would significantly impact the absorption and distribution of the test compound in an unrealistic setting, this study was not considered by the Agency because exposures in the field occur via inhalation.

CDPR also conducted an evaluation of studies in which MeI was formulated with another fumigant, chloropicrin. Though these two compounds are likely to be used in conjunction with each other under field conditions, the Agency does not as a matter of practice conduct risk assessments on mixtures. Consequently, studies with MeI/chloropicrin formulations were not considered in the Agency's assessment.

Acute Toxicity (pp. 23-33)

Rat Inhalation (pp. 25-32)

In the study conducted to generate data for the PBPK model, male Sprague Dawley rats were exposed to 0, 25, or 100 ppm iodomethane *via* the inhalation route for either one or two consecutive days. At 25 ppm, 13-44% GSH depletion was observed in the olfactory epithelium. CDPR has selected 25% GSH depletion in the olfactory epithelium to parameterize the model. Given that exposure to 21 ppm for up to 90 days did not elicit an adverse effect on the olfactory epithelium (*i.e.*, NOAEL = 21 ppm), it is unclear why a 25% dose metric was selected for the PBPK model as opposed to the 50% used by the Agency. Presumably a longer duration of exposure at a concentration comparable to what was used in this study would result in a comparable or higher level of GSH depletion yet no effects were seen after this prolongued exposure. This suggests that use of 50% GSH depletion as the dose metric for olfactory epithelium degeneration would not underestimate risks; consistent with the level of GSH depletion commonly cited in the literature as critical for development of nasal histopathology. Based on this information, it seems that the use of 25% as a dose metric is overly conservative and punitive. Other effects noted by CDPR in this study included a 19% increase in cholesterol and LDL levels. These effects were not considered sufficiently robust to be toxicologically relevant by the Agency particularly in light of the observation that they are accompanied by a 20% increase in HDL and a 30% decrease in triglycerides. It should be noted that this study was not intended to be used to establish NOAELs/LOAELs but rather to provide data for parameterization of the PBPK model.

Rat/Mouse Oral (pp. 32-33)

Although iodomethane is proposed to be used as an agricultural pesticide, it is considered a non-food use chemical since it is quickly volatilized, degraded or metabolized and subsequently incorporated into natural plant constituents. The levels of iodide released

from iodomethane degradation/metabolism are lower than those expected to cause toxic effects. Furthermore, enforcement of tolerances would not be possible since no iodide-free samples are available and residue field trials show evidence of control samples with higher iodide residues than iodomethane treated samples. Moreover, iodide is ubiquitous in the environment and a required nutrient. Finally, iodomethane residues must dissipate in the soil prior to planting. Accordingly, the Agency concluded tolerances are not required for iodomethane. As a result, only a screening level assessment of the oral toxicity studies has been completed.

Rabbit Dermal/Subcutaneous (pp. 33-36)

The Agency does not expect dermal exposure to iodomethane of any significance as described below in Attachment B. As such, a quantitative dermal exposure assessment has not been completed. With regards to the subcutaneous exposure study, the Agency does not consider a subcutaneous study to be a relevant route of exposure and therefore has not conducted this risk assessment.

Subchronic Toxicity (pp. 37-51)

Rat – Inhalation (pp. 37-40)

Both the Agency and CDPR established a NOAEL of 21 ppm for the 13-week inhalation toxicity study. However, CDPR based the NOAEL on increased relative liver weights and decreased body weight gains seen at the LOAEL (70 ppm) while the Agency based the NOAEL on port-of-entry effects (degeneration of the olfactory epithelium) and decreases in body weight, body weight gains, and food consumption. This difference in the endpoints selected to establish the NOAEL are due to the fact that the Agency does not consider relative liver weight changes in the absence of corroborative clinical chemistry changes as adverse. Instead, the Agency considers this to be an adaptive response as the liver increases its metabolic capabilities in response to the presence of a xenobiotic. Furthermore, when assessing the potential health impact of fumigant exposure, the Agency whenever possible establishes port-of-entry specific NOAELs/LOAELs since the algorithm used to calculate HECs from systemic effects and respiratory tract effects are different in the RfC methodology.

Rat/Mouse/Dog Oral (pp. 41-43 and 46-51)

Although iodomethane is proposed to be used as an agricultural pesticide, it is considered a non-food use chemical since it is quickly degraded or metabolized and subsequently incorporated into natural plant constituents. The levels of iodide released from iodomethane degradation/metabolism are lower than those expected to cause toxic effects. Furthermore, enforcement of tolerances would not be possible since no iodide-free samples are available and residue field trials show evidence of control samples with higher iodide residues than iodomethane treated samples. Moreover, iodide is ubiquitous in the environment and a required nutrient. Finally, iodomethane residues must dissipate in the soil prior to planting. Accordingly, the Agency concluded tolerances are not

required for iodomethane. As a result, only a screening level assessment of the oral toxicity studies has been completed.

Rat Dermal (pp. 43-45)

See comments on acute dermal toxicity above.

Chronic Toxicity and Oncogenicity (pp 52-67)

Rat – Inhalation (pp. 52-54)

Both the Agency and CDPR selected a NOAEL of 5 ppm for the systemic effects in this study based on an increased incidence of salivary gland squamous cell metaplasis. In addition the Agency also established a port-of-entry specific NOAEL of 20 ppm based on olfactory epithelial degeneration seen at the 60 ppm concentration. Separate NOAELs for systemic and port-of-entry effects are selected by the Agency since the algorithm used to calculate HECs from systemic effects and respiratory tract effects are different in the RfC methodology and lower HECs may be derived from higher animal NOAELs.

Mouse – Oral

Although the Agency did not conduct an oral risk assessment and a NOAEL was not established for this study, it was considered as part of the weight-of-evidence analysis during the cancer determination. Only the thyroid tumors were considered treatment-related by the Agency while the uterine and cervical were not considered related to iodomethane exposure. This is in contrast to CDPR's evaluation which considered that the cervical fibromas may be treatment-related.

Genotoxicity (pp. 68-73)

The only evidence of genotoxicity observed in the guideline studies submitted to the Agency is an induction of structural chromosome aberrations (clastogenesis).

Reproductive Toxicity (pp 74-79)

Rat – Inhalation

CDPR established a parental NOEL of 20 ppm based on decreased body weight and degeneration of the olfactory epithelium at 50 ppm. Similarly, the Agency established a parental NOAEL of 20 ppm and a LOAEL of 50 ppm but based this LOAEL on numerous endpoints including decreases in body weight/weight gains, changes in organ weights, gross pathology and histopathological findings. CDPR reproductive NOEL (20 ppm) is based on decreases in live litter size at 50 ppm. In contrast, the Agency established the reproductive NOAEL at 5 ppm with a LOAEL of 20 ppm based on delays in vaginal patency acquisition. The Agency considers delays in sexual maturation to be reproductive effects rather than developmental effects as they are effects in the

reproductive tract. CDPR used this endpoint to establish the developmental NOAEL/LOAEL (5 ppm/20 ppm). The Agency established an offspring NOAEL of 5 ppm based on decreased pup weight/weight gain, and decreases in thymus weight. It also established a port-of-entry specific NOAEL of 20 ppm based on degeneration of the olfactory epithelium at 50 ppm (LOAEL).

Developmental Toxicity (pp 80-100)

Rabbit – Inhalation

In this study CDPR selected a developmental NOEL of 2 ppm and a LOEL of 10 ppm based on decreased fetal weight and fetal viability and increases in late resorptions while the Agency established the NOAEL at 10 ppm and a LOAEL of 20 ppm. The Agency's decision to establish the NOAEL at 10 ppm is based on the observation that the incidence of fetal deaths seen at this concentration were within historical control obtained from the Middle Atlantic Reproduction and Teratology Association (MARTA), one of the world's largest repositories of reproduction and developmental historical control data. Moreover, the standard deviation for fetal losses at this concentration was approximately 2-fold higher than the mean (0.1±0.22) thus rendering the observation indistinguishable from background. Similarly, the incidence of late resorptions at the 10 ppm could not be distinguished from background since the standard deviation was also ≈ 2-fold higher than the mean (0.9±1.60). In contrast, the effects observed at the 20 ppm concentration (the concentration used by the Agency as the LOAEL) are more robust including a 41% decrease in the number of live fetuses/doe, 20% decrease in fetal weight, and a 1500% increase in late resorptions. With regards to the fetal weight, the Agency considered the fetal weight decrease at the 10 ppm concentration not sufficiently robust to establish a LOAEL given the lack of statistical significance.

Neurotoxicity (p. 101)

CDPR states that the Agency did not require a developmental neurotoxicity (DNT) study because "MeI is considered a non-food use and, therefore, not subjected to Food Quality Protection Act considerations." This does not completely reflect the Agency's rationale for not requesting a DNT. Typically, if a neurodevelopmental concern is raised by existing data on a pesticide, a rat developmental neurotoxicity (DNT) study is requested. However, disruption of thyroid homeostasis by thyroid disrupting pesticides is the initial, critical effect that may lead to adverse effects on the developing nervous system. Thus, *in lieu* of the rat DNT study, a study that entails a mechanistic approach to generate specific data on the thyroid (*i.e.*, the primary target of the chemical of interest) to protect the developing nervous system from thyroid hormone disrupting chemicals is required by the Agency. Since the iodomethane database contains numerous studies assessing the impact of iodomethane exposure on thyroid hormone homeostasis at different life stages, neither a DNT nor a special thyroid hormone study was required.

Human Toxicity Case Reports (pp. 101-103)

The Agency looked into the incident data available in the literature for exposure to iodomethane. The studies cited by CDPR were part of the Agency's review. Over the past century, only 11 incidents of iodomethane poisoning have been reported in the published literature[1]. In general, symptoms of iodomethane intoxication in humans were related to effects on the nervous system ranging from somnolence to ataxia, seizures, delirium and coma in severe cases. In some patients, cerebellar lesions and damage of the third, fourth, or sixth cranial nerve pathways as well as spinal cord lesions producing motor and sensory disturbances have been reported. Latent symptoms of iodomethane intoxication include psychological disorders such as depression. In addition to neurological effects, iodomethane exposure has also been linked to congestive changes in the lungs and oliguric renal failure. It is noteworthy, however, that in most of these incidents the precise iodomethane exposure concentration is unknown though it appears that exposure was to high levels (due in part to use of inadequate protective devices) resulting from industrial uses and far exceeding those proposed for regulatory purposes in this risk assessment or anticipated agricultural uses. For further details, please refer to additional discussion of these incidents in Attachment B

An updated literature search on May 30, 2007 for iodomethane poisoning produced only one additional case report. [Schwartz MD, et al. *Acute methyl iodine exposure with delayed neuropsychiatric sequelae: report of a case*. Am J Ind. Med. 2005 Jun; 47(6): 550-6] that found;

> "The case patient experienced a massive exposure to methyl iodide with resulting life-threatening burns. During convalescence, various cognitive and behavioral deficits became apparent."

The authors recommend that a comprehensive evaluation at an occupational toxicology clinic include sequential neuropsychometric testing, if iodomethane poisoning is suspected. This incident occurred during the manufacturing process but it is not clear if the material was destined for pesticide use. It also appears to have been caused by a breech in the protective clothing the individual was wearing.

Finally, CDPR used an intentional exposure case, where an individual intravenously (IV) injected iodomethane as part of an attempted suicide, to help test the human model in PBPK modeling of acute exposure. This study was not considered by the Agency as IV injection would have a significant impact on the adsorption, distribution, metabolism, and excretion of the compound. Given the potential impact of this unrealistic exposure scenario (for bystanders and workers) on the kinetics, the Agency does not consider this study appropriate to help test the human PBPK model.

PBPK and Mode of Action Studies

Comments on this section were provided by Agency scientists from the National Center for Computational Toxicology (NCCT) under a separate memorandum (attached).

---

[1]Hermouet, C. *et al.* "Methyl iodide poisoning: Report of two cases" *Am. J. Ind. Medicine* (1996) **30**: 759-764 & Appel, G.B. *et al.* "Methyl iodide intoxication" *Annals of Int. Med* (1975) **82**:534-536

Risk Assessment (pp 113-145)

As previously stated differences in the HECS calculated by the Agency and CDPR reflect the use of different methodologies. The CDPR uses a methodology that relies on age-related differences in breathing rates while the Agency relies on the RfC Methodology developed by the Office of Research and Development (ORD) (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=71993). It should be noted that the RfC has been the approach used by the Agency since 1994 and that this methodology has undergone several levels of peer review including an SAB review (Nov. 1998) (http://yosemite.epa.gov/sab/SABPRODUCT.NSF/60E4F6C9E3B0C36D8525718F004FFF0A/$File/ehc9902.pdf).

Acute Inhalation Toxicity

Fetal Death

Unlike the Agency which considered the fetal death endpoint to be the outcome of perturabation of fetal thyroid function, CDPR states that "convincing evidence is lacking for supporting this MOA as the sole or immediate MOA for the endpoint, and thus additional dose metrics need to be considered." The Agency does not concur with this statement. Given the remarkable concordance between the timing of fetal death, occurring only between GD 23-26, and ontogeny of fetal thyroid function (GD22), and the known impact of the Wolff-Chaikoff effect on fetal viability, it is unclear why cholesterol levels or GSH depletion would be considered as plausible MOA. Cholesterol perturbations and GSH depletion have not been demonstrated to have such a narrow window of sensitivity during development. The data accounting for the potential impact of cholesterol levels on fetal viability come from a series of studies where animals received injections of plasma triglyceride clearance blockers prior to insemination. While cholesterol levels were indeed affected by this treatment, it is unclear what other effects this treatment may have had on pregnancy outcomes

Nasal Effects

Both the Agency and CDPR considered GSH depletion as a plausible MOA for this endpoint the differences in the HECs derived by these regulatory bodies reflects the differences in the parameterization of the PBPK model. Further comments on this were submitted by NCCT scientists under a separate memorandum (attached)

Neurotoxicity Effects

CDPR used area under the curve to parameterize the PBPK model for neurotoxicity while the Agency used steady state. The principle of periodic steady state (*i.e.,* periodicity) is embedded in the Agency's RfC methodology which would have been used as a default to calculate HECs if a PBPK had not been available. Periodicity state is achieved if the concentrations of the inhaled compound within the animal achieved periodicity with

respect to time (i .e., periodic steady state-the concentration versus time profile is the same for every time point). Practically, the conditions of periodicity should be met during "most" of the exposure duration . For example, if this condition is met for 90% of the time (e .g ., periodic during the last 90 weeks of a 100 week experiment), then estimates of average concentrations will be in error by less than 10% . Given that iodomethane reaches steady state after 30 minutes of a 6 hour exposure, the Agency is confident that the use of steady state is appropriate.

Thyroid tumors

The Agency has classified iodomethane as "not likely to be carcinogenic to humans at doses that do not later rat thyroid hormone homeostasis." The CDPR risk characterization documents, however, assume that humans are more sensitive to the oncogenicity potential of iodomethane than animals. This is based on a number of studies cited by CDPR. It should be noted that the results of these studies have not been borne out by more recent cellular and biochemical studies which provide **compelling evidence that rats are substantially more sensitive than humans to the development of thyroid follicular cell tumors in response to thyroid hormone imbalance** (IARC, 2001, Meek et al., 2003, EPA,1998; Dohler et al., 1979). The interpretation used by the Agency is consistent with the interpretation used by the International Agency for Research on Cancer (IARC) [*Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis.* IARC Scientific Publications No. 147]

Risk Appraisal

Hazard Identification

CDPR states that additional data, including a DNT and studies evaluating postnatal effects of MeI on nasal tissues, are needed for iodomethane. The Agency does not share CDPR's opinion. Using the RfC methodology and the PBPK model for iodomethane, the HECs calculated and used in the Agency's risk assessment are not expected to underestimate risks to children. In fact comparison of the HEC derived for adults and children for nasal toxicity showed that levels of GSH depletion in adults and children were comparable at the same dose level, as seen below:

<u>Adult Worker</u>
PREGHUM,
WOE=0.006, WOX=0.08
CONC = 5.8
T 8.00000 GSHL 5.42681 GSHK 1.33688
CGSHDR 0.551752 CGSHEO 0.768624 CGSHDO 0.743154
CGSHWR1 0.553692 CGSHWR2 0.562702 CA_I 3.30147e+006
CA 0.117731
GSDOE11 = 0.2723 GSDOE21 = 0.3771 GSDOE31 = 0.4510 GSDOE41 = 0.4980
GSDOEX1 = 0.7689 CGSHDO2 = 0.3996
%GSH Depletion

GSDOE11 = 66 GSDOE21 = 53 GSDOE31 = 44 GSDOE41 = 38
CGSHDO2 = 50%

Child Bystander Comparisons (4.5 ppm 24 hr exposure simulations)
MALEHUM
WOE=0.006, WOX=0.05 (for 3mth, 1 & 5 yr) or WOX=0.08 (for 10 & 15 yr)
CONC=4.5

<u>3 mth child</u>

T 24 GSHL 5.1064 GSHK 1.3032
CGSHDR 0.5588 CGSHEO 0.8000 CGSHDO 0.7477
CGSHWR1 0.5593 CGSHWR2 0.5618 CA_I 9.4068e+006
CA 0.0948
GSDOE11 = 0.2876 GSDOE21 = 0.3981 GSDOE31 = 0.4791 GSDOE41 = 0.5355
GSDOEX1 = 0.7865 CGSHDO2 = 0.4251
%GSH Depletion
GSDOE11 = 64 GSDOE21 = 50 GSDOE31 = 40 GSDOE41 = 33
CGSHDO2 = 47%

<u>1 yr child</u>

T 24.0000 GSHL 5.03781 GSHK 1.31168
CGSHDR 0.557384 CGSHEO 0.799990 CGSHDO 0.747545
CGSHWR1 0.557874 CGSHWR2 0.560422 CA_I 1.16541e+007
CA 0.0979790
GSDOE11 = 0.2856 GSDOE21 = 0.3965 GSDOE31 = 0.4779 GSDOE41 = 0.5345
GSDOEX1 = 0.7864 CGSHDO2 = 0.4236
%GSH Depletion
GSDOE11 = 64 GSDOE21 = 50 GSDOE31 = 40 GSDOE41 = 33
CGSHDO2 = 47%

<u>5 yr child</u>

T 24.0000 GSHL 5.20766 GSHK 1.32843
CGSHDR 0.557270 CGSHEO 0.799993 CGSHDO 0.766938
CGSHWR1 0.557822 CGSHWR2 0.561179 CA_I 9.31576e+006
CA 0.0948048
GSDOE11 = 0.2797 GSDOE21 = 0.3851 GSDOE31 = 0.4600 GSDOE41 = 0.5088
GSDOEX1 = 0.7938 CGSHDO2 = 0.4084
GSDOE11 = 65 GSDOE21 = 52 GSDOE31 = 43 GSDOE41 = 36
CGSHDO2 = 49%

<u>10 yr child</u>

T 24.0000 GSHL 5.25861 GSHK 1.33699
CGSHDR 0.557024 CGSHEO 0.799993 CGSHDO 0.766947
CGSHWR1 0.557594 CGSHWR2 0.561161 CA_I 8.81614e+006
CA 0.0986206
GSDOE11 = 0.2799 GSDOE21 = 0.3852 GSDOE31 = 0.4601 GSDOE41 = 0.5089

GSDOEX1 = 0.7938 CGSHDO2 = 0.4085
%GSH Depletion
GSDOE11 = 65 GSDOE21 = 52 GSDOE31 = 42 GSDOE41 = 36
CGSHDO2 = 49%

15 yr child

T 24.0000 GSHL 5.39194 GSHK 1.34752
CGSHDR 0.559037 CGSHEO 0.799993 CGSHDO 0.767123
CGSHWR1 0.559618 CGSHWR2 0.563101 CA_I 6.05452e+006
CA 0.0943949
GSDOE11 = 0.2827 GSDOE21 = 0.3874 GSDOE31 = 0.4619 GSDOE41 = 0.5104
GSDOEX1 = 0.7939 CGSHDO2 = 0.4106
%GSH Depletion
GSDOE11 = 65 GSDOE21 = 52 GSDOE31 = 42 GSDOE41 = 36
CGSHDO2 = 49%

Health-based standards

CDPR expresses a concern for the addition of iodide exposure due to MeI use to the background iodide exposure levels. It should be noted that the Agency does not concur with these concerns as they are based on a point of departure lower than the one used by the Agency. Furthermore, the RfCs used to compare to the health based standards were calculated using a dose metric that is not consistent with the parameterization used by the Agency.

Additional Uncertainty Factors

The Agency does not consider that an additional uncertainty factor is warranted based on the extensive mechanistic and toxicological data available for iodomethane. The Agency is confident data available and used for the risk assessment afford an adequate level of protection.

Attachment B: U.S. EPA Review Comments on DPR Iodomethane Exposure Assessment

The exposure assessment completed by the California Department of Pesticide Regulation (DPR) was presented in two of the referenced documents including Volumes I and II described in the above letter (Lim and Reed, 2009 and Cochran 2009, respectively). The primary information is presented in Volume II (Cochran 2009). As such, the issues which were identified in this document are presented first followed by those identified associated with Volume I (Lim and Reed, 2009) since it is based on the information presented in Volume II.

EPA Review DPR Volume II (Cochran, 2009):

In this document DPR completed an exposure assessment using essentially the same sources of data as used in the U.S. EPA risk assessment. The key differences between the the DPR assessment and the EPA assessment included: (1) the choice of statistic used to represent certain exposure patterns differed (e.g., acute exposure estimates), (2) a body burden approach was used to calculate risks rather than the route-specific RfC methodology, (3) there was a slight difference in the types of scenarios considered, (4) there were major differences in endpoints including consideration of a 1 hour duration exposure to evaluate possible eye effects, (5) a deterministic air model under non-variable weather conditions was used rather than a distributional air model that accounts for weather changes over 5 year periods to calculate bystander exposures, (6) a rudimentary modeling approach was used to estimate seasonal bystander and community-based exposures, (7) more recent emissions data completed at lower application rates with barrier films that empirically illustrate dramatic reductions in iodomethane and chloropicrin emissions were not considered, and (8) annualized exposure estimates were calculated through an amortization process.

A series of more specific comments have been developed and these are summarized below with a reference to the specific page in Cochran 2009 to which they refer. [Note: There are several sections of this document which reference other elements of the overall assessment (e.g., Introduction subparts H through K, pages 10-12) which reference directly other documents referenced above in the introductory letter. These elements have not been reviewed herein because they will be addressed in the other attachments.]

Abstract: It was indicated that a buffer distance of 152 meters was used for a series of calculations but no justification was provided for this distance. Seasonal and amortized annual exposures were also estimated for individuals spending 100 percent of their time at this distance while being exposed which is also unlikely given the mobility of the vast majority of the population.

I. Introduction (Page 1): It is indicated that every scenario will not be assessed but it is not clear what scenarios lack the appropriate data. Exposure assessments have only been completed by DPR using a standard tarp which indicates that more recent emissions data completed at lower application rates with barrier films that empirically illustrate dramatic reductions in iodomethane and chloropicrin emissions were not considered.

I. Introduction (Table 1, page 2): A fumigation activity, under the "early entry handler" category, referred to as tarp removers and tarp remover drivers were included for the tarped raised bed and tarped drip irrigation scenarios. These scenarios are unlikely with this cultural practice because in the vast majority of circumstances the tarp is retained over the course of a growing season as a key element of the cultural practice.

I. Introduction (Table 2, page 3): A number of representative scenarios are presented in the table provided with 3 being defined based on the depth of injection. It is not clear that this parameter is significant with regard to altered emissions for iodomethane because it is so volatile. As such, it is not clear that scenarios should be defined primarily based on this principle.

I. Introduction/Section B. Federal Regulatory History (page 4): It is indicated a draft risk assessment was completed by the EPA in 2006 and a final assessment was completed in 2007. More accurately, the 2006 was a final risk assessment and the 2007 version was a revised risk assessment based on the availability of additional data and updated analytical methods. There is also no mention about the FIFRA Scientific Advisory Panel Review of the PERFUM air model (see http://www.epa.gov/scipoly/sap/meetings/2004/082404_mtg.htm for more details) or the evaluation of the RfC methodology.

I. Introduction/Section B. Federal Regulatory History (page 5): It is indicated that an IRED was issued for iodomethane but this is not the case because iodomethane is not a reregistration chemical.

I. Introduction/Section D. Formulations (page 6): There is a discussion of the parameters which constitute a restricted use pesticide. It should be noted that the definitions of restricted use pesticides will be altered with regard to fumigants in the upcoming 2009 decisions and that the definition will be broadened.

II. Exposure Assessment/Section A. Occupational Exposure Studies (pages 13-26): A description and summary of the study results for all of the available worker studies was included on these pages. The descriptions and summaries of the available worker exposure monitoring data are accurate. There were slight differences in how some adjustments were made based on the available quality control data.

II. Exposure Assessment/Section A. Treatment of Study Data (pages 26-28): In this section an overview of the DPR use of the data is provided. According to the document, "DPR has a policy of using an upper-bound of work-task exposure to represent potential acute exposures (Frank, 2009)." It was also indicated that results from the Manteca monitoring site were adjusted up by a factor of 10-fold because of the use of a fan by the applicators to mimic potentially higher exposures for those situations where they are not available. Workday durations were also assumed to be 8 hours which was used in the determination of body burden estimates for workers. Finally, to calculate amortized annual estimates of exposure a 3 month period of use based on methyl bromide use patterns was assumed (Figure 4, page 28). The EPA calculations of exposure differed

from those developed by DPR because instead of using a calculated upper confidence limit on an upper bound exposure (Frank, 2009) the maximum monitored concentration was used to assess acute worker risks for each task scenario considered. Also, EPA did not apply a 10 fold factor to model increased exposures, analogous to the DPR use of the Manteca monitoring data, due to a lack of a fan to reduce exposures for those applicators.

II. Exposure Assessment/Section A. Absorbed Dose (page 28): In this section, the monitored air concentrations were adjusted by application rate. In the Agency assessment the same values were not adjusted because so many factors in a fumigant application can impact potential exposures such as sealing efficacy (e.g., tarp placement and/or compaction), soil parameters (e.g., type and moisture levels) and/or optimization of application equipment for reducing emissions (e.g., shank type and orientation).

II. Exposure Assessment/Section A. Dermal Route (pages 28-29): A dermal dose was estimated and it was concluded that exposures via this route were insignificant. This is the same as the conclusion of the Agency which was developed on the use of physical-chemical properties.

II. Exposure Assessment/Section A. Absorbed Dose/Table 11 (page 31): Absorbed dose estimates for workers are presented in this table for acute, seasonal, and annual durations of exposure. These were calculated using the same ventilation rate of 833 L/hr based on Andrews and Patterson (2000). There is no discussion of the Agency's Exposure Factors Handbook on inhalation (see http://www.epa.gov/nceawww1/efh/pdfs/efh-chapter05.pdf) which can be used to obtain the latest information on human ventilation rates for individuals engaged in different levels of activities, in different settings, at varied stages of their lives. Arithmetic mean values were used to estimate seasonal doses which is a similar approach to that used by the Agency. The annual absorbed dose was calculated using a 3 month application window for all workers coupled with 9 months on no iodomethane use. The Agency did not estimate annual or chronic worker risks because it does not believe that exposures occur over the course of a year and the short-/intermediate-term endpoint used to calculate the corresponding HECs, based on the RfC methodology address such potential, but likely limited, prolonged exposure patterns. The 3 month application window was also apparently based on translation of methyl bromide use patterns to the iodomethane risk analysis but this is clearly a conservative approach because it is not clear that if iodomethane were registered in California that it would fill all use niches where methyl bromide is currently used given that much efficacy research is focused on several other chemicals as well. All dose estimates included in this table reflect the inherent use of a PF 10 air purifying respirator. The Agency presented risks both with and without such devices to allow for a more informed risk management decision. Iodomethane products which will likely be most prevalent in the marketplace contain high percentages of the companion fumigant, chloropicrin. This is recognized as a highly irritating material that has been widely used as a companion warning agent of exposure at much lower concentrations (e.g., 2% of total applied was typical) and it also has significant pesticidal properties. The Agency has opted to harness this warning agent property along with the

use of respirators in its strategy to manage worker risks that alleviates some of the physical burden of respirator use for extended periods.

II. Exposure Assessment/Section B. Bystander Exposures (pages 32-36): The same volatility data which were included in the Agency's 2007 risk assessment were used in the DPR assessment. The calculated flux values appear reasonable and appropriate for the approaches used in the assessment. It should be noted that additional field volatility data were generated under a recent Experimental Use Permit for iodomethane (i.e., EPA MRIDs 472952-02, -03, -04) that utilized higher barrier agricultural films, reduced application rates, and a patented pulse application system (i.e., Symmetry). The results of this study indicate that emissions were greatly reduced compared to the studies used by DPR and in the 2007 Agency assessment. One major difference between the Agency and DPR assessments is that DPR used a deterministic modeling approach based on the use of the ISCST3 model coupled with a static weather condition and wind vectors faced downwind 100 percent of the exposure duration. These environmental conditions are not realistic in the majority of situations. It is also highly unlikely that most impacted individuals would be at such a downwind location for extended periods of time. Conversely, the Agency used a distributional approach to air modeling based on the PERFUM model which was considered by the FIFRA Scientific Advisory Panel (see http://www.epa.gov/scipoly/sap/meetings/2004/082404_mtg.htm for more details) as described above. The Agency believes that the use of the PERFUM model, coupled with consideration of monitoring data and analysis of incident rates and the nature of incidents provides for a more informed risk management decision. PERFUM also allows for consideration of outputs which are similar in nature to those calculated using ISCST3 (i.e., maximum buffer distance outputs at higher percentiles of exposure would be analogous). In the DPR assessment 1, 8, and 24 hour time-weighted average air concentrations were calculated. The Agency does not concur with the use of the 1 hour interval based on the eye irritation endpoint, particularly since iodomethane is always co-applied with chloropicrin which is a potent warning agent that would preclude such eye effects from iodomethane.

II. Exposure Assessment/Section B. Seasonal Exposure (page 36): Seasonal exposures were calculated for repetitive exposures over longer intervals that "reflect the reality of changing wind directions." DPR estimated 2 week TWA concentrations by calculating average 24 hour flux over a 2 week period then "adjusting with a time-scaling factor" which was derived using peak to mean theory based on empirical and theoretical studies (Barry 2008b). A key assumption was that bystanders would be at the 152 meter buffer distance for the entire 2 week period. The Agency could not verify the calculations in Barry 2008b since it was not provided. Additionally, there is no discussion of the possible uncertainty associated with this overall methodology. For example, it would be highly unlikely that individuals possibly impacted by the most serious potential effects of iodomethane (i.e., fetal loss) would be at a 152m buffer distance over an entire 2 week period. Available time-location data indicate that individuals, particularly women of child bearing age where this effect would be possible, would be unlikely not to move amongst varied locations over such an extended period of time. The Agency views this approach as likely to be highly conservative for most

individuals in potentially impacted populations. The Agency did not complete such a calculation but instead considered ambient monitoring data for methyl bromide which is volatile like iodomethane and is used in a fashion which would be anticipated for iodmethane in high use areas in the season of high use as a surrogate to evaluate possible longer duration exposures.

II. Exposure Assessment/Section B. Seasonal Exposure (page 37): In Table 13 DPR presented on this page maximum single day time-weighted average air concentrations for 1, 8 and 24 hour periods to reflect the time to effect for several toxicological concerns. The Agency also used 8 and 24 hour durations as the basis for its calculations but did not include 1 hour calculations because it does not adhere to the DPR concerns over possible eye irritation effects and since iodomethane will always be used in conjunction with cholorpicrin as a warning agent which would likely preclude such effects from occurring as a result of exposure to iodomethane. Additionally, as commented on above, the Agency is not using the deterministic air modeling approach used by DPR but instead completed such calculations using the PERFUM model.

II. Exposure Assessment/Section C. Community Exposures (page 38): As described above for the section on seasonal exposure (page 36) 2 week time weighted average concentrations were calculated which were compared to the 2 week seasonal exposures calculated by Thongsinthusak and Haskell in 2002 for methyl bromide using monitoring data from the season of use in high use areas. These values varied by only 34% which is remarkable considering the uncertainties associated with the approach (i.e., 0.07μg/L calculated compared to methyl bromide monitoring value of 0.046 μg/L). DPR concluded because of these differences that "thus, ambient air concentrations do not capture the worst case scenario for seasonal exposures." The Agency does not concur with these conclusions because of the issues described for the comment pertaining to page 36 above. Additionally, the Agency believes that several other factors support the position that the use of the methyl bromide data are more appropriate for consideration for these types of exposures including methyl bromide is more volatile and is longer-lived in the environment than iodomethane and its market share is likely much greater than would be expected for iodomethane.

II. Exposure Assessment/Section D. Estimation of Absorbed Dose (pages 38-43): On these pages a series of absorbed dose estimates were presented for adults, children, and infants using varied breathing rates, durations of exposure, and body weights. The Agency does not believe that the use of a body burden approach is appropriate since Human Equivalent Concentrations (HECs) can be calculated using the available hazard information and pharmacokinetics model. Iodomethane is also highly volatile and the exposures of concern are via inhalation which have been quantified using monitoring data or empirically based modeling. Because of these factors, an inhalation route-specific calculation of risk based on comparing exposure concentrations to HECs is believed to be the most applicable metric. This is also consistent with longstanding Agency guidance for using route-specific metrics as a preferred approach (e.g., 1992 EPA Exposure Assessment Guidelines).

III. Exposure Appraisal/Section A. Physiological Assumptions (pages 43-44): A brief summary of the factors used were presented. Please refer to the response for pages 38-43 and Attachment A for further information on these issues.

III. Exposure Appraisal/Section B. Analytical Assumptions (page 44): A brief discussion was provided about general uncertainty associated with analytical measurements. Chemical specific information from available iodomethane data were not summarized within which would be a better measure of actual uncertainty for this case.

III. Exposure Appraisal/Section C. Estimation of Application Site Air Concentrations (pages 44-46): A general discussion was provided pertaining to the factors which can impact emissions and exposures. Also, a description was included describing why modeling is more appropriate for use rather than just the use of empirical monitoring data. Finally, the use of the ISCST3 model was described. The Agency agrees with many of these factors but it does not believe that the use of the ISCST3 is more appropriate than the use of the PERFUM model or other model with similar functionality. Also, as described above it would recommend that all available emissions data be considered including those where high barrier films have been used coupled with reduced application rates because they represent viable, alternative farming practices which are readily implementable. Finally, the factors which can potentially impact emissions have been examined in great detail by the Agency (see www.regulations.gov under docket EPA-HQ-OPP-2005-0123-0467). It is recommended that this document be considered in further revisions to the DPR risk characterization document.

III. Exposure Appraisal/Section D. Occupational Exposures (pages 46-47): Two key issues were discussed by DPR in this section including that the exposure data were generated in relatively small fields (e.g., 2.5 acres) when under actual commercial conditions much larger fields could possibly be treated on a daily basis. Additionally, the sporadic nature of possible fumigator exposures was considered which creates uncertainty in trying to predict possible chronic effects. The issue of extrapolation based on area treated, amount of active ingredient handled, or other exposure factor which changes due to use is a very difficult effect to quantify as discussed by the Agency before the FIFRA Scientific Advisory Panel (see the following http://www.epa.gov/scipoly/sap/meetings/2007/010907_mtg.htm for more information) and the Human Studies Review Board with regard to the statistical design goals of the Agricultural Handlers Exposure Task Force (see http://www.epa.gov/osa/hsrb/meetings.htm for more information). In typical assessments we acknowledge it as an uncertainty without being able to truly quantify it. However, it is the estimation of the Agency that this uncertainty might be more appropriately considered in assessments where a body burden is calculated similar to the DPR approach rather than the HEC approach preferred by the Agency. In this approach measured air concentrations are compared to the HEC but air concentration peak levels can be impacted by a variety of factors such as soil conditions, barrier layers, and application equipment configuration not just the amount of acres treated (see www.regulations.gov under docket EPA-HQ-OPP-2005-0123-0467). As such, the Agency does not believe

that the use of 2.5 acre fields leads to additional levels of uncertainty to the extent noted by DPR. The Agency also agrees that there can be uncertainty associated with trying to predict possible chronic effects from exposure patterns which are sporadic in nature akin to those anticipated for iodomethane fumigators. However, given the toxicokinetics of iodomethane, it is likely that chronic studies would overestimate the risks posed to iodomethane fumigators under the anticipated use pattern.

III. Exposure Appraisal/Section E. Bystander Exposures (pages 47-48): The uncertainties associated with the premise of the acute bystander exposure estimates and the estimates calculated for repetitive exposures were considered. These included consideration of time-activity patterns, the assumption that outdoor and indoor air concentrations are equivalent, and that a relatively short 2 week period was considered as the basis for calculating a seasonal exposure estimate. The Agency essentially concurs with these suppositions but it does note that there is no stated basis for the use of a 2 week period for calculating seasonal exposures. DPR notes that iodomethane treatments within a field would likely be once per year so the seasonal exposure estimate could be vastly different based on the averaging time considered. It is not clear that a time to effect for a 2 week period can be justified.

Appendix III. Occupational Exposure Estimates (pages 73-74): This section of the document provided a comparison of the Agency and DPR approaches with 6 specific items presented. These included (1) duplicate samplers on the same individuals were averaged by DPR rather than used individually as by the Agency; (2) DPR adjusted for application rates; (3) DPR adjusted the results for recovery and analytical method; (4) DPR used an upper bound, statistically derived value while the maximum monitored value was used by the Agency; (5) DPR used the arithmetic mean to estimate seasonal exposure of workers and EPA did not estimate these exposures; (6) EPA estimated the protective effect of respiratory protection on worker exposure to maximum measured air concentrations while DPR factored in the use of respirators for workers once the required PPE was on the labels.

The Agency has addressed each of these comments below. On comment (1) the Agency opted to use individual samples rather than the average values to estimate risks because of the numbers of factors which have been identified that could possibly impact peak emission levels in an attempt to capture any transient high level of exposure rather than dilution of a peak value by averaging. A dilution of peak values by averaging for acute exposure durations would be less health protective. For comment (2) the Agency did not adjust worker exposure estimates by application rates for the reasons outlined above. Even given this, it appears that both agencies reached similar conclusions pertaining to the risks for workers who are involved in iodomethane applications. For comment (3) the Agency used the values reported by the investigators as the basis for its assessments without altering the corrections applied to the results. These corrections would have minimal impacts. The Agency compared to monitored values used by DPR and its own and found very little differences. In some cases EPA estimates were slightly higher while in other cases DPR estimates were slightly higher. This leads to comment (4) because the major differences in the worker exposure results utilized by DPR compared to the

Agency are that an upper confidence limit statistic is used by DPR while the maximum monitored values were used by the Agency. These are policy-based differences developed based on the needs of each respective agency. In comment (5) DPR indicates it considered seasonal exposures to workers and that EPA did not. In fact, this is not the case, in the 2006 and 2007 risk assessments for iodomethane short-term (i.e., similar to seasonal considerations by DPR) were addressed. In the 2007 risk assessment D339055 (8/23/07, page 70) it indicates "risks from short- and intermediate-term exposures, based on average values, were calculated but not presented below because acute risks, calculated based on maximum monitored values are protective of possible exposures of this duration." For comment (6) it is not clear that there is a scientific basis which would result in different conclusions given the available approaches and the same starting exposure concentrations because both methods apply the same protection factors (e.g., 10 for an APR). It should also be noted that DPR prepared tables to compare the different results which were calculated (i.e., Tables 1 and 2 in Appendix 3). The differences could be explained given the variations in the methods used to calculate them as described above.

Appendix III. Comparison of Calculated Air Concentrations (pages 74-75): In this section DPR commented that both ISCST3 and PERFUM were used to calculate air concentrations for various field sizes, application rates, application methods and distances from the field. A comparison was provided between the EPA estimated emission ratio values and the DPR estimated emission ratio values. Minor differences were observed except for that calculated for the Oxnard California tarped raised bed study. A few comments of note are (1) that 3 additional emissions monitoring studies are available for iodomethane that were not considered (i.e., Guadalupe CA tarped raised bed application and drip irrigation application and a Camarillo CA drip irrigation application); (2) the EPA is no longer using deterministic approaches for air modeling based on ISCST3 but is using the PERFUM model which accounts for 5 years of weather data fluctuation; and (3) it appears DPR is apparently confusing modeling constructs which have been used by the Agency because it indicates "U.S. EPA used the whole field approach" which is, in fact, not true if ISCST3 is the basis for this comment because the premise of that approach is one is downwind of the worst weather condition 100 percent of the exposure duration. The "whole field" output is an aspect of the kinds of results which are available from the PERFUM model which is not referenced anywhere else in this section of the document by DPR. Finally, it should also be noted that all PERFUM outputs were considered in the ultimate decision regarding iodomethane by the Agency in order to provide for a broader consideration of the possible risks associated with its possible use. Finally, as noted above, additional data have been developed for iodomethane using reduced application rates and barrier films which greatly reduce emissions that have not been considered by DPR in their assessment that could provide additional viable agricultural production practices to growers.

Appendix III. Why DPR Does Not Use the PERFUM Model (pages 75-76): DPR acknowledges the PERFUM model in this comment but indicates its review of the code associated with this model was incomplete at the time this assessment was completed so it was not used. The Agency has considered a code level evaluation of the PERFUM

model but at this point in time has, like DPR, not completed such an effort. Over the period of the past several years the Agency has however, identified several programming errors or other fixes in PERFUM which have been presented to the developer who has subsequently modified the program and recompiled it as updated versions.

Additionally, from a theoretical context, the FIFRA SAP has acknowledged the validity of the approach. The PERFUM model provides a variety of outputs so one would expect a concurrence of the ISCST3 approach at outputs which represent the highest percentiles of exposure and this is in fact observed. This is another indication that PERFUM is adequate as a tool for calculating buffer estimates. Finally, the Agency is aware that some level of review of the PERFUM code has been completed by DPR but no acknowledgement of this process has been included in the DPR RCD even though it may be still somewhat incomplete. It would be a more balanced consideration of the modeling approaches if the preliminary results of this analysis was included in the RCD especially if no major issues were identified or, conversely, if DPR had identified substantive issues at the code level for PERFUM.

Appendix III. Buffer Zones (page 76): A discussion was provided by DPR describing how PERFUM outputs contain both whole and maximum buffer distances. The comments provided also indicate that the Agency based its determination of buffer distances solely on the whole field buffer statistics provided by PERFUM. They also present failure rates for other chemicals including methyl bromide, metam sodium, and chloropicrin but it is not clear how they were determined. In fact, the Agency did consider the whole field buffer statistic for iodomethane but other criteria were considered as well including other PERFUM outputs (i.e., maximum buffer statistic and the air concentration outputs by distance rings), incident rates for similar chemicals where the anticipated use of iodomethane might fill a niche (e.g., methyl bromide), and the available monitoring data itself. The probability of a series of sequential factors which could lead to severe deleterious health effects (e.g., possibility of fetal loss) was also considered in the determination of the ultimate buffer distances which were applied to iodomethane. The latter factor was also acknowledged by DPR in their risk characterization piece as described above. In summary, the deterministic approach for calculating buffer distances is legitimate but does not provide as broad of a information base for risk managers to consider in the formulation of their decisions as opposed to the use of PERFUM which provides a variety of outputs which can be considered by risk managers including results for the highest percentiles of exposure that emulate those calculated by DPR (e.g., maximum buffer distances at the highest percentiles of exposure).

Appendix III. Intermediate and Annual Bystander Exposure Estimates (page 76): The consideration of seasonal exposures is presented in this section. DPR indicates that U.S. EPA "did not include an estimate of potential community exposures" but that it did compare "iodomethane to the ambient air levels that were quantified for methyl bromide." DPR utilized a modeling approach instead to estimate the exposure of an individual at a 152 meter buffer zone over the course of a 2 week period. The Agency

does not concur with this approach for the reasons outlined above in responses focused on Sections II.B & II.C (pages 36 & 38 of the document).

EPA Review of Exposure Aspects of DPR Volume I (Lim & Reed, 2009):

In this document DPR completed the risk assessment (DPR Volume I/Lim & Reed, 2009) by summarizing the results of the exposure analysis (DPR Volume II/Cochran, 2009) commented upon above. Many of the comments focused on DPR Volume II (Cochran, 2009) would be repetitive to the risk assessment document as well. For clarity and brevity, such comments have not been repeated below. As such, only those Agency comments which are unique to this document, compared to DPR Volume II, are included.

It should be noted that this aspect of the Agency comments applies only to the exposure assessment related aspects of the DPR risk assessment. The Agency has also compiled a number of comments on the hazard assessment, environmental fate, and use projection aspects of the DPR analysis which are addressed in other aspects of this document (see Attachments A, C, and D).

I. Summary/Exposure Assessment (pages 4-8): The issues which were identified in this section of the DPR document have also been identified and discussed above in the review of DPR Volume II (e.g., use of body burden dose metric, use of worker exposure monitoring data, etc.).

III.I Toxicology Profile/Human Toxicity Case Reports (pages 101-103): In this section 5 incidents were discussed by DPR but each of the discussions lacked pertinent case elements. Also, in each case the incidents did not occur in an agricultural setting analogous to what would be expected with soil fumigant use and it was not possible to ascertain what, if any, appropriate risk mitigation elements were in use at the time the exposures occurred. The current iodomethane labels require extensive levels of personal protective measures and equipment. [Note: One of the 5 cases was an intentional suicide attempt where a 19 year old injected himself with iodomethane.] In the first incident (Garland and Camps, 1945) it would be highly unlikely that given the occupational health standards of the era that any comparable level of risk mitigation would have been required for the exposed individual compared to modern standards. It is clear that this individual had extremely high urinary output of iodine (i.e., 9 mg/100mL) compared to the median value reported in the NHANES 2000 of 16.1 μg/deciliter (see http://www.cdc.gov/nchs/products/pubs/pubd/hestats/iodine.htm) but it is not clear if there were other confounding health conditions which could have contributed. It is also not clear what the tasks were for this individual at the manufacturing facility or what the associated processes were that could have contributed to his exposures. Without this information, it is not clear how this case would relate to a highly prescribed use of iodomethane in agriculture given all of the inherent risk mitigation requirements such as techniques which can significantly reduce emissions (e.g., high barrier film use). The second incident (Appel et al, 1975) was a similar circumstance. A chemist was exposed while attempting to synthesize iodomethane. The same conclusions apply as described for the interpretation of the Garland and Camps (1945) case. Similarly, the third case

(Hermouet et al, 1996) involved 2 workers who were exposed during production in an industrial facility. Like the first 2 incidents noted above the results are equivocal with regard to how this provides useful information for mitigating worker risks associated with use as a fumigant. The fourth incident which was reported (Knudsen and Nielsen, 1999) involved an accidental spill by a worker onto his fingers and hands. Like the other incidents noted above, the results of this incident are equivocal when evaluating use as a fumigant except to indicate that skin effects were noted as would be expected from a direct exposure of substantive skin loading levels as noted in the current Agency assessments. For this reason, the Agency has required extensive health and safety risk management requirements when working around pressurized elements of the application systems for iodomethane in an attempt to alleviate further like exposures from occurring. In the final incident (Robertz-Vaupel et al, 1991) a 19 year old male attempted suicide via intravenous injection of iodomethane. Clearly this event does not reflect possible exposure patterns from soil fumigant use but it could possibly be used to compare effects with a dose. In fact, DPR indicated that the data from this study was used to test the Agency's PBPK modeling approach. There was no mention about possible ethical concerns with the use of this study for these purposes. The Agency was not aware of this incident and its use for this purpose by DPR. The Agency will investigate this further in its comments on the hazard assessment noted above in Attachment A.

IV.B Exposure Assessment (pages 140-145): The issues which were identified in this section of the DPR document have also been identified and discussed above in the review of DPR Volume II (e.g., use of body burden dose metric, use of worker exposure monitoring data, etc.).

V.C.3 Cumulative Toxicity (pages 149-152): DPR indicates in this section of the document that they are concerned with "an additional iodide body burden from the conversion of MeI to iodide in the body after MeI exposure." In order to demonstrate this concern a series of current health criteria (Table 70, page 150) were presented which represent different types of recommendations for daily intake of iodide in the diet and as a limit from food additives in the diet. One limit presented was the Tolerable Upper Intake Level (UL) based on a National Academy of Sciences (2000) evaluation which indicated this level is "likely to pose no risk of adverse effect to almost all individuals in the general population." DPR then compared these values to a body burden estimate of exposure which was calculated using their proposed RfC values for each endpoint of concern (i.e., developmental toxicity, neurotoxicity, and nasal lesion formation). The body burden estimates were calculated by adjusting the RfCs by standard daily breathing volumes (i.e., the 1997 U.S. EPA Exposure Factors Handbook was cited), accounting for the amount of iodide per molecule of iodomethane and the assumption that 100 percent of the iodide inhaled as iodomethane over the course of a day would be retained and absorbed. This is highly unlikely given the physical-chemical properties of iodomethane and its demonstrated pharmacokinetics. Moreover, converting RfCs to a body burden assumes the same adsorption and distribution regardless of the route of exposure. As indicated above, the Agency prefers the use of a route-specific dose metric for calculating risks when feasible, as in this case given the extensive inhalation toxicity database for iodomethane.

Attachment C: U.S. EPA Review Comments on DPR Iodomethane Environmental Fate Assessment

In general, CALDPR's environmental fate characterization was found to be consistent with EPA's risk assessment entitled, "Environmental Fate and Ecological Risk Assessment for the Registration of Iodomethane (Methyl Iodide)", dated September 2003. However, there are a few exceptions which are highlighted in comments below, which were noted from Volumes II and III. The several inconsistencies noted do not result in a conflict with the basis of the Agency's risk conclusions.

Comments for, "California Department of Pesticide Regulation 2009. Methyl Iodide (Iodomethane) – Risk Characterization Document for Inhalation Exposure. Volume II, Exposure Assessment. CALDPR, Worker Health and Safety Branch. Sacramento, CA. March 2009."

1. p. 35 (Tables 12 and 13) – Utilization of time-averaged flux, as listed in Table 12, to determine estimated exposure concentrations in air is not consistent with present EPA policy regarding risk assessments. The flux profile, measured at specific time intervals over time, is used in dispersion models to predict estimated exposure concentrations in air. Although a short-term averaging period (e.g., 4 hours) is often selected corresponding to the exposure time in an acute toxicity study in the concentration profile, the measured flux at each sampling period is compiled from the field study and matched sequentially to 5 years worth of hourly meteorological data using the PERFUM model in order to obtain estimate exposure concentrations in air. This process was established in the 2004 SAP, "Fumigant Bystander Exposure Model Review: Probabilistic Exposure and Risk model for FUMigants (PERFUM) Using Iodomethane as a Case Study". While CALDPR's approach using ISCST3 with static meteorological data provides a conservative estimated exposure concentration in air, the Office of Air Quality Planning and Standards's Guideline on Air Quality Models (Appendix W) recommends that additional refinement by the way of use of 5-years worth of meteorological in the determination of estimated exposure concentrations. Therefore, CALDPR should incorporate this type of method into the ISCST3 model and the health risk assessment.

   In the 2003 risk assessment, EPA used the same approach as the CALDPR approach. Therefore, given the toxicological data submitted, the conclusion regarding the low likelihood of risk to terrestrial organisms would not change adapting the PERFUM methodology.

Comments for, "California Department of Pesticide Regulation 2009. Methyl Iodide (Iodomethane) – Risk Characterization Document for Inhalation Exposure. Volume III, Environmental Fate."

1. p. 1 (Table 1); p. 8. (second paragraph) – CALDPR's cited ODP value of 0.0015 is an order of magnitude lower than reported in EPA's risk assessment, 0.029. EPA had consulted with Donald J. Wuebbles of the University of Illinois regarding their studies of ozone depletion potential for short-lived gases in the atmosphere. Their results indicate that the Ozone Depletion Potential of iodomethane is 0.029 assuming an equal distribution of iodomethane emissions with latitude. In addition, Zhang et al. (1998) reported that the iodomethane ODP can approach 0.1 in the tropics assuming dense iodomethane emissions at low latitudes. The research from Wuebbles, (2001) and Zhang et al., (1998) considered the ODP of the parent, not just the halogenated radical as in Solomon, 2004. Class I ozone depleting compounds possess an ODP of greater than 0.1. Therefore, the EPA and CALDPR's reported ODP values both fall below the 0.1 threshold.

2. p. 1 (Table 1) and p. 13 (first paragraph) – In table 1, CALDPR states that the atmospheric lifetime is 5.2 days which is inconsistent on p. 7 which refers to the atmospheric half-life of 2-8 days. CALDPR used atmospheric photolytic half-life and atmospheric lifetime interchangeably, which is incorrect. These terms can not be used as interchangeably. In addition, the citation of the source of this data is unclear. The EPA risk assessment reported an atmospheric lifetime value of 11.5 days per communication with D. Wuebbles from the University of Illinois.

3. p. 3 (second paragraph) and Page 5 (3rd paragraph)- CALDPR states that iodomethane is quickly biodegraded under aerobic conditions with an aerobic soil metabolism half-life under 2 hours. This is consistent with EPA's risk assessment with the exception of the caveat that volatilization also may have contributed to the short half-life as well.

4. p. 3 (second paragraph); p. 8 (third paragraph) – CALDPR states that the maximum air concentration based on field volatility studies was 0.065 ppm. However, air concentrations up to 0.99 ppm were measured 30 cm above ground level in the Manteca, CA field volatility study.

5. p. 6 (first paragraph) – The term, "inch", needs to be inserted in the sentence "Soil sample cores at Florida site were collected in 6-inch increments down to 48 *inch* increments on day 0…."

Attachment D: U.S. EPA Review Comments on DPR Iodomethane Use Pattern Projections

- Volume II, pages 5-8. The Agency agrees that the formulations and the listed uses are from the EPA label. Since Midas has not yet been registered in California, there are no usage data.

- Volume II, pages 27-28, Figure 4. The assessment does use the annual monthly use of methyl bromide as a surrogate for the seasonal use of methyl iodide. The Agency agrees that this is appropriate and the values used are reasonable.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
National Center for Computational Toxicology
Research Triangle Park, NC 27711

May 29, 2009

OFFICE OF
RESEARCH AND
DEVELOPMENT

MEMORANDUM

SUBJECT: IODOMETHANE: Review of PBPK modeling changes made by California Environmental Protection Agency Department of Pesticide Regulation

FROM: Chester Rodriguez, Ph.D.
Biologist (B205-01)

THRU: David J. Dix Ph.D.
Acting Deputy Director (B205-01)

Robert J. Kavlock, Ph.D.
Director (B205-01)

TO: Elizabeth Mendez, Ph.D.
Toxicologist, Reregistration Branch I
Health Effects Division (7509C)

This memo reviews specific changes made by the California Environmental Protection Agency Department of Pesticide Regulation (CDPR) to the US EPA physiologically based pharmacokinetic (PBPK) modeling of iodomethane/methyliodide (MeI). PBPK modeling is being used to derive inhalation human equivalent concentrations (HEC) estimates that would result in the same internal dose metrics as those associated with animal toxicity endpoints [1]. This memo is not intended to be a review of the PBPK model for MeI (for a review see [2]), but an evaluation of the changes reported by CDPR for their impact on the final HEC estimates. The PBPK modeling of MeI is based on three No-Observed-Adverse-Effect Levels (NOAEL) values from acute exposure animal toxicity studies. The toxicity endpoints are as follows:

- Fetal death in rabbits resulting from maternal exposure
- Nasal olfactory epithelial degeneration in rats

- Neurotoxicity in rats

The same basic PBPK model structure was used for all three endpoints. However, in the case of the nasal olfactory epithelial degeneration, the model contains an enhanced nose compartment used for simulating the HEC that would result in an internal dose associated with nasal olfactory epithelial degeneration in the rat. This version of the model is referred to as "full model." A version of the model which simulates alveolar gas exchange directly is referred to as "simplified model." Both versions of the model reportedly give similar results [1]. The approach undertaken for this analysis is based on: (1) reproducing the modeling (and associated HEC estimates) previously reported in Barton 2007 [1] and (2) evaluating the changes reported by CDPR for their impact on final HEC estimates.

(I). SUMMARY OF FINDINGS:

CDPR made parameter/simulation changes for all three animal toxicity endpoints being used to derive HEC estimates. These changes are summarized in Table 1. The most changes are associated with the rabbit fetal death endpoint and consists of (1) using a 1.7-fold higher alveolar ventilation rate for simulating serum iodide in the rabbit; (2) selecting maternal versus serum iodide as rabbit dose metric; (3) selecting 2 versus 10 ppm NOAEL as point of departure; (4) using a 1.5-fold higher breathing rate for estimating an 8-h occupational HEC; and (5) selecting a 24 versus 96-h time window for deriving their 8-h occupational HEC estimate. The 1.5-fold higher breathing rate was applied to all three 8-h occupational HEC estimates. The results of this analysis indicate that while the 24-h HEC estimate of 0.24 ppm MeI based on rabbit fetal death was confirmed as reported by CDPR, the 8-h occupational HEC of 0.22 ppm MeI was not and probably involved mistakenly using minute versus alveolar ventilation rate. The changes associated with the rat olfactory epithelial degeneration as reported by CDPR are based on a 25 versus 50% GSH depletion benchmark and were confirmed in this analysis. The changes reported for the rat neurotoxicity endpoint are based on (1) selecting brain MeI AUC instead of steady state levels as dose metric; and (2) setting the 8-h occupational HEC estimate to the same value as the 24-h HEC estimate for not accounting for the additional 16-h exposure after work as bystander. These changes

were confirmed except for a 40% oronasal breathing assumed but not reported by CDPR for deriving their 8-h occupational HEC estimate. The impact of this unreported change, however, is deemed small given that the 8-h HEC estimate was set to the same value as the 24-h HEC.

TABLE 1: SUMMARY OF US EPA 2007 and CDPR 2009 HEC ESTIMATES

Toxicity Endpoint	US EPA 2007				CDPR			EVALUATION			
	NOAEL (ppm)	PBPK Dose Metric	HEC (ppm)		NOAEL (ppm)	PBPK Dose Metric	Parameter/Simulation Changes	HEC (ppm)			
			24-h	8-h				24-h		8-h	
Rabbit Fetal Death	10	AUC for Fetal Serum Iodide	7.4	23	2	AUC for Maternal Serum Iodide	- Rabbit: increased QAC from 12 to 20 L/h*kg$^{0.75}$ - Human: used a 1.47-fold higher - ventilation rate for occupational HEC - Human: selected 24 versus 96-h for estimating occupational HEC	0.24	✓	0.22[a]	✗ (0.5)[b]
Rat Olfactory Epithelial Degeneration	21	GSH Depletion (50%benchmark)	4.5	5.8	Same	GSH Depletion (25% benchmark)	- Human: used a 1.5-fold higher ventilation rate for occupational HEC	2.2	✓	2.8	✓
Rat Neurotoxicity	27	Steady State Mel Brain Levels	10	10	Same	AUC for Mel Brain Levels	- Human: used a 1.5-fold higher ventilation rate for occupational HEC - Human: set occupational HEC equal to general population HEC	3.4	✗ (2.8)[c]	3.4[d]	✗ (7.5)[e]

✓ Indicates that the HEC estimate was confirmed after incorporating changes reported by CDPR

✗ Indicates that a different HEC was obtained after incorporating the changes reported by CDPR; the value in parenthesis indicates the HEC that should have been obtained given the reported changes.

[a] Probably obtained by mistakenly using minute instead of alveolar ventilation rate in addition to the proposed 1.47-fold increase and 24-h time window.

[b] Obtained by incorporating the proposed 1.47-fold higher alveolar ventilation rate, but modeling a single 8-h exposure for a period of 96-h time as reported in Barton 2007.

[c] A higher AUC value was obtained but not addressed by CDPR, resulting in the higher HEC estimate

[d] Set equal to the 24-h HEC estimate for being approximately 3x higher and not accounting for the additional 16-h exposure after work. The original 8-h estimate was 9.7 ppm was likely obtained assuming a 40% of air inhaled orally not reported by CDPR.

[e] Obtained by incorporating the proposed 1.47-fold higher alveolar ventilation rate and a 40% fraction of air inhaled orally. The difference from 9.7 ppm is due to an unaddressed higher AUC value obtained by CDPR for the same rat NOAEL of 27 ppm Mel

(I). HEC ESTIMATES BASED ON FETAL DEATH IN RABBITS

The changes reported by CDPR for deriving inhalation HEC estimates based on fetal death in rabbits resulting from maternal exposure can be briefly summarized as follows:

(A). Rabbit simulation: use of a 1.7-fold higher alveolar ventilation rate (QAC) for simulating serum iodide levels.

(B). Rabbit simulation: selection of maternal versus fetal serum iodide as dose metric for estimating a HEC.

(C). Rabbit simulation: selection of 2 versus 10 ppm NOAEL as point of departure.

(D). Human simulation: use of a 1.5-fold higher breathing rate for estimating an 8-h occupational HEC.

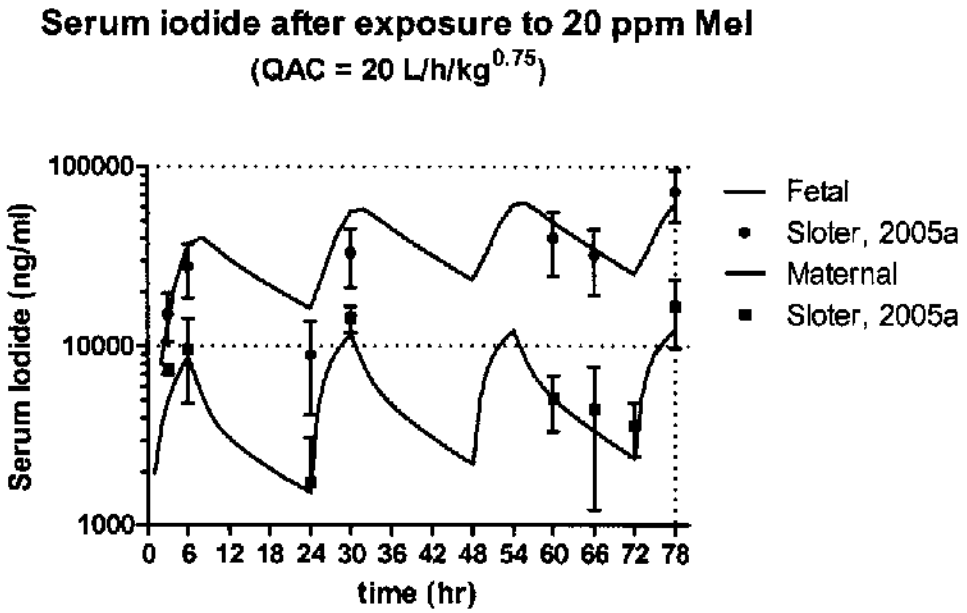
(E). Human simulation: selection of 24 versus 96-h time window for estimating an 8-h occupational HEC.

(A). Rabbit simulation: use of a 1.7-fold higher QAC for simulating serum iodide levels.

CDPR raised the issue that a QAC of 12 L/h*kg$^{3/4}$ was used in Barton 2007 [1] for simulating the area under fetal serum iodide concentration-time curve (AUCCAF_I) associated with the NOAEL of 10 ppm MeI, whereas a higher QAC of 20 L/h*kg$^{3/4}$ was used to evaluate the model performance against experimental data from Sloter et al. 2005a,b [3, 4]. A QAC of 12 L/h*kg$^{3/4}$ is reportedly only about 70% of the value measured by DeLorme et al. 2004 [5] for non-pregnant females during an exposure to 18.5 ppm MeI, and supposedly results in greater deviation of model predictions from the experimental measurements of Sloter et al. 2005a,b [3, 4]. Figure A-1 of appendix A provided by CDPR shows the supposedly "superior" performance of the model in predicting data from Sloter et al. 2005a using a QAC value of 20 L/h*kg$^{3/4}$. The greater deviation resulting from using a QAC of 12 L/h*kg$^{3/4}$ is depicted only numerically by CDPR in Table A1 by comparing predicted serum iodide concentrations and fetal-to-maternal (F/M) ratios to those empirically determined [3, 4]. In an effort to address the impact of using a QAC of 20 versus 12 L/h*kg$^{3/4}$, simulations of maternal and fetal serum iodide levels from 6-h daily inhalation exposures to 20 ppm MeI were carried out against the experimental measurements of Slotter et al. 2005a,b [3, 4] using both QAC

values. The simulations are shown in Figure 1. In addition, the predicted values along with F/M ratios using both QAC values are compared to those empirically determined in Table 2. Serum values are reported in the same units as DPR to facilitate comparison.

The results show that using a QAC of 12 $L/h*kg^{3/4}$ can yield predictions for maternal serum iodide that deviate from measurements from -68.2 to -37.6 %, whereas deviations can range from -9.0 to 37.6 % using a QAC of 20 $L/h*kg^{3/4}$. On the other hand, predictions of fetal serum iodide levels can deviate from measurements from -51.9 to 0.7% using a QAC of 12 $L/h*kg^{3/4}$, and from -14.2 to 81.3% with a QAC of 20 $L/h*kg^{3/4}$. Therefore, while simulations with a QAC of 20 $L/h*kg^{3/4}$ may better in predicting maternal serum iodide levels, a QAC of 12 $L/h*kg^{3/4}$ is more consistent for predicting fetal serum iodide levels. DPR presented higher predicted F/M ratios in Table A-1 (Page A-7, Appendix A) as evidence for the greater deviation of model predictions with a QAC of 12 $L/h*kg^{3/4}$. However, this analysis indicates that both QAC values result in very comparable higher F/M ratios relative to experimental measurements (Table 2). CDPR adopted a QAC of 20 $L/h*kg^{3/4}$ for subsequent simulations of fetal death in rabbit.



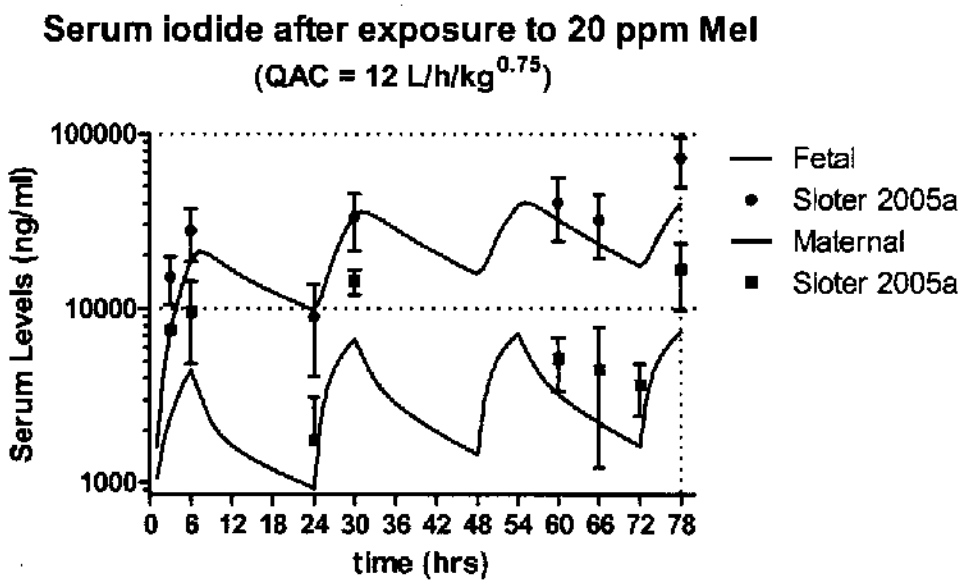


Figure 1: Simulation of fetal and maternal serum iodide in the rabbit after 6-h daily exposures to 20 ppm MeI using an alveolar ventilation rate (QAC) of 20 (top plot) and 12 L/h*kg$^{0.75}$ (bottom plot)

Table 2: Measured versus simulated values of maternal and fetal serum iodide at different alveolar ventilation rates (QAC) after 6-h daily exposures to 20 ppm MeI

				QAC = 12 L/hr*kg$^{0.75}$						QAC = 20 L/hr*kg$^{0.75}$					
Measured values				Simulated values						Simulated values					
time (hr)	Maternal (mg/L)	Fetal (mg/L)	F/M	time (hr)	Maternal (mg/L)	% Dev.	Fetal (mg/L)	% Dev.	F/M	time (hr)	Maternal (mg/L)	% Dev.	Fetal (mg/L)	% Dev.	F/M
3	7.50 ± 0.49	15.10 ± 4.62	2	3	2.39	-68.2	7.26	-51.9	3.0	3	5.01	-33.2	14.30	-5.3	2.9
6	9.57 ± 4.75	27.80 ± 9.25	2.9	6	4.42	-52.7	18.54	-33.3	4.2	6	8.69	-9.0	36.50	31.3	4.2
24	1.74 ± 1.34	8.96 ± 4.83	5.2	24	0.92	-47.0	9.76	8.9	10.6	24	1.52	-12.4	16.25	81.3	10.7
30	14.30 ± 2.36	33.20 ± 11.90	2.3	30	6.56	-54.1	33.43	0.7	5.1	30	11.54	-19.3	56.14	69.1	4.9
60	5.11 ± 1.76	40.10 ± 15.70	7.9	60	3.19	-37.6	32.08	-20.0	10.0	60	5.09	-37.6	48.91	22.0	9.6
66	4.47 ± 3.25	32.00 ± 11.90	7.2	66	2.19	-51.0	23.33	-27.1	10.7	66	3.35	-25.0	34.62	8.2	10.3
72	3.61 ± 1.20	-	-	72	1.61	-55.4	17.47		10.9	72	2.36	-34.5	25.18		10.7
78	16.60 ± 6.80	72.60 ± 23.20	4.4	78	7.28	-56.1	39.75	-45.2	5.5	78	12.30	-25.9	62.29	-14.2	5.1

% Dev. refers to percent deviation calculated by the following formula: ((predicted – measured) / measured)*100

In an effort to evaluate the impact of using a QAC of 20 versus 12 L/h*kg$^{0.75}$ on the HEC estimates reported in Barton 2007 [1], the 24-h AUC for fetal serum iodide corresponding to the 10 ppm NOAEL was first simulated using a QAC of 12 L/h*kg$^{0.75}$. As shown in Figure 2, the 24-h AUC for fetal serum iodide of 1.18 x 10^{+8} ng/L*hr matches the value reported in Barton 2007 [1].The profile of maternal and fetal serum iodide associated with the equivalent inhalation HEC of 7.4 ppm MeI that matches the AUCCAF_I of 1.18 x 10^{+8} ng/L*hr is shown in Figures 3A-B. Figure 3A shows the maternal and fetal serum iodide time profiles from a 24-h exposure to 7.4 ppm MeI. The difference in time scale (24 versus 96 hrs) reflects difference in iodide clearance between rabbits and humans. Figure 3B shows the AUC profiles for maternal and fetal serum iodide and the equivalent AUCCAF_I of 1.18 x 10^{+8} ng/L*hr achieved at 96-h. Figure 3A matches Figure 2 reported in Barton 2007 [1].

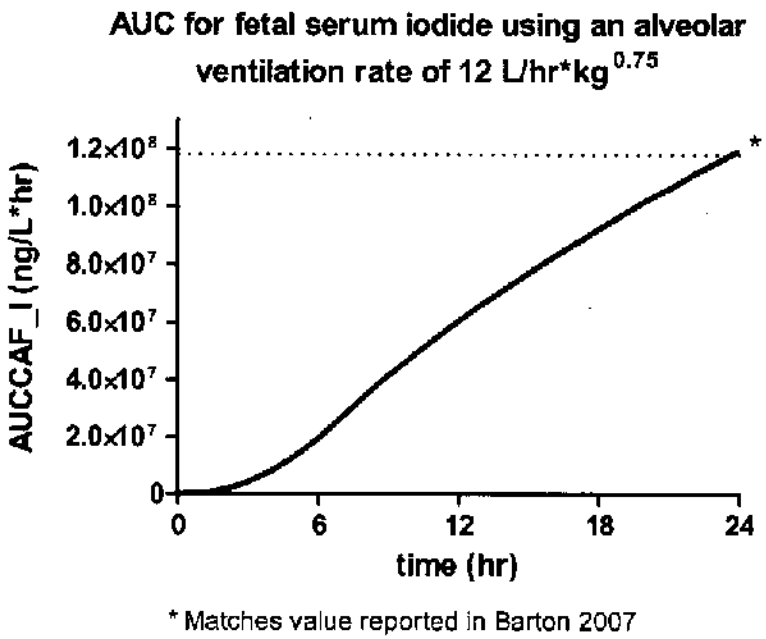


Figure 2: Predicted AUC for fetal serum iodide at the NOAEL of 10 ppm. The dashed line represents the value of 1.18 x 10^{8} ng/L also reported in Barton 2007 [1].

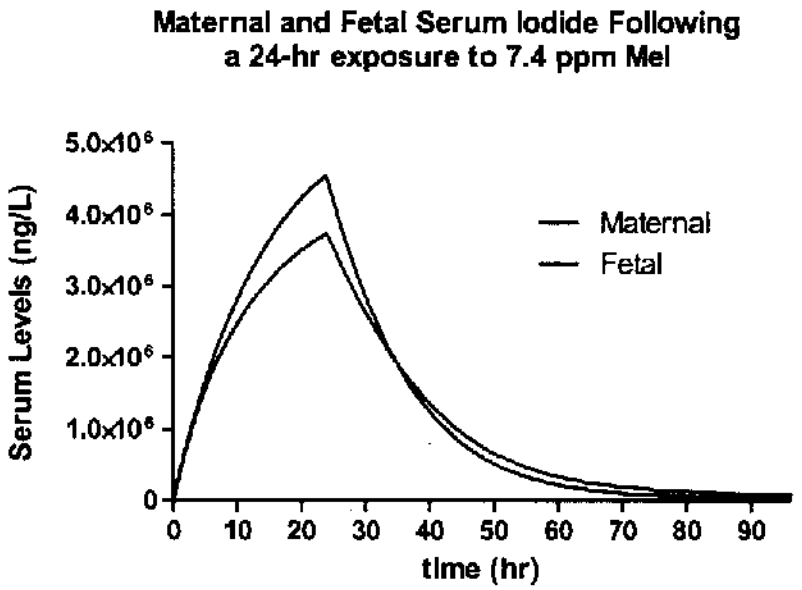


Figure 3A: Predicted human serum iodide profile following a 24-h exposure to 7.4 ppm MeI. Simulation matches Figure 2 in Barton 2007 [1].

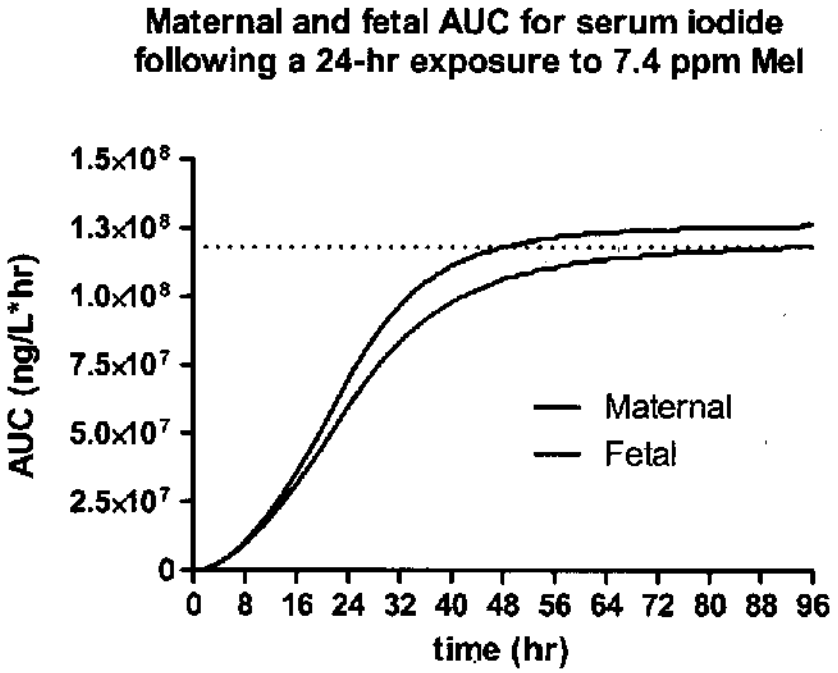


Figure 3B: The AUC profile for maternal and fetal serum iodide simulated from a 24-h exposure to a HEC of 7.4 ppm MeI. The dashed line represents the AUC of 1.18 x 10^{+8} ng/L*hr predicted for the 10 ppm NOAEL in the rabbit.

(B). Rabbit simulation: selection of maternal versus fetal serum iodide as dose metric for estimating the HEC.

CDPR prefers maternal over fetal serum iodide as a dose metric for estimating a HEC. The basis for selecting maternal serum as reported by CDPR can be briefly summarized as follows:

(1) the overestimation of F/M ratios as compared to experimental measurements (Table A1, Appendix A) introduces significant uncertainty in the fetal compartment. The overestimation of F/M ratios may be in part due to adjustments for model fit against experimental measurements (model calibration);

(2) the serum iodide measurements used for model validation are from fetuses that survived the Mel exposure, a different outcome than the endpoint being targeted for modeling (i.e., fetal death resulting from maternal exposure); and

(3) no mechanism of action (MOA) has been firmly supported for Mel. Therefore, the use of maternal serum iodide is described by CDPR as a way to focus on total internal dose and a more reliable dose metric for interspecies comparisons.

(C). Rabbit simulation: selection of 2 versus 10 ppm NOAEL as point of departure

In contrast to the 10 ppm NOAEL used in Barton 2007 [1], CDPR derived HEC estimates based on the 2 ppm NOAEL. Figure 4A shows the simulation of maternal and fetal serum iodide profiles at the 2 ppm Mel NOAEL using a QAC of 20 L/h*kg$^{3/4}$. As described previously, the coverage is 24 h for rabbits and 96 h in humans to account for interspecies difference in clearance. The predicted maternal peak serum iodide concentration of 0.33 mg/L at 6 h in Figure 4A is comparable the value of 0.31 mg/L reported by CDPR (page A-24, Appendix A). Figure 4B shows the corresponding AUC profiles. The predicted AUC value of 3.72 mg/L*hr at 24 h for maternal serum iodide matches the value reported by CDPR (Page A-24, Appendix A). The profile of the HEC of 0.24 ppm reported by CDPR (Table A-4, page A-24, Appendix A) that would result in an equivalent maternal serum iodide AUC is shown in Figure 5A-B. Figure 5A shows the maternal serum iodide time course following the 24-h exposure to 0.24 ppm Mel simulated to 96-h. The peak maternal serum iodide concentration of 0.13 mg/L is

consistent with the simulation reported by CDPR in Figure A-7 (Page A-25, Appendix A). Figure 5B shows the AUC for maternal serum iodide. The predicted AUC value of 3.68 mg/L*h at 96-h is comparable to 3.72 mg/L*h reported by CDPR (page A-24, Appendix A).

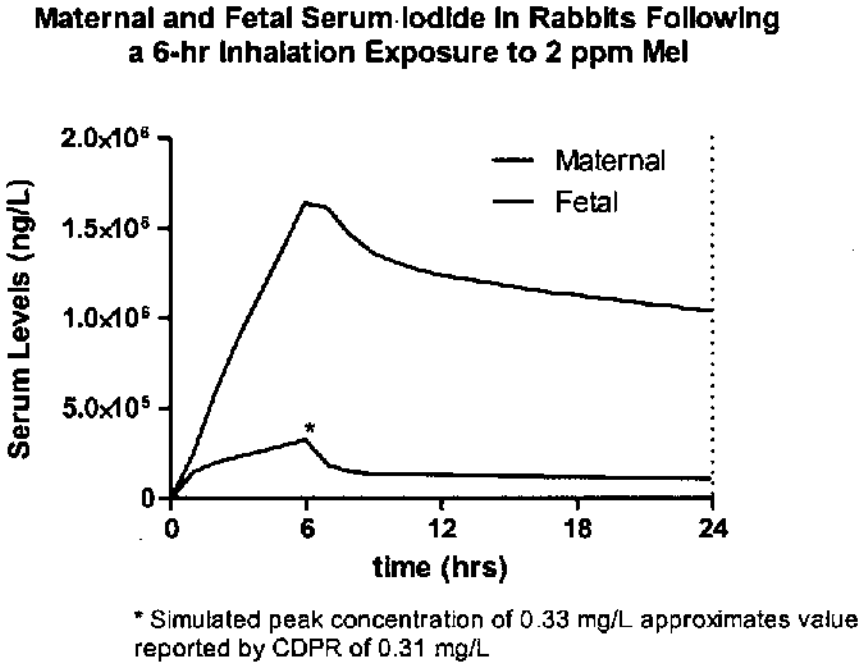


Figure 4A: Simulation of maternal and fetal serum iodide in rabbits from a 6-h inhalation exposure to 2 ppm MeI. The predicted peak maternal serum iodide concentration of $3.3 \times 10^{+5}$ ng/L is comparable to 0.31 mg/L reported by CDPR (Page 24, Appendix A).

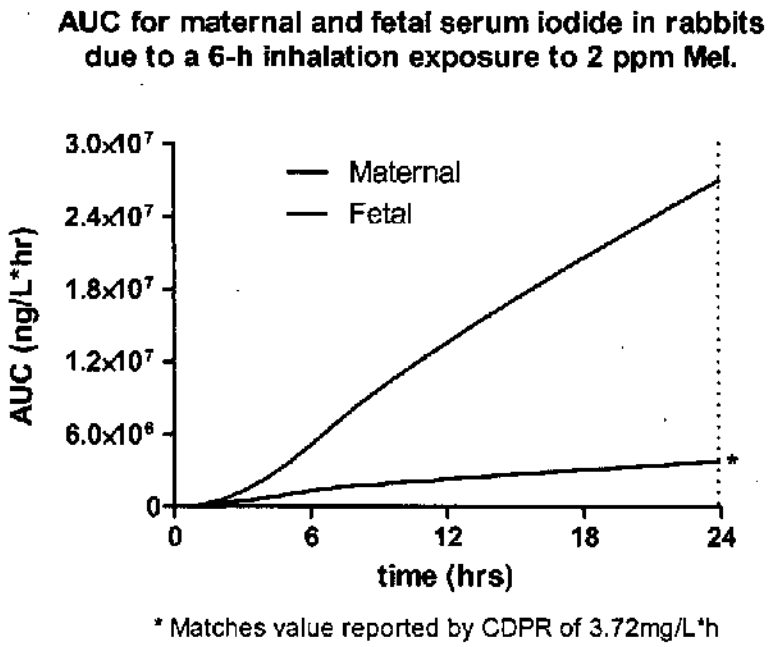


Figure 4B: Predicted AUC for maternal and fetal serum iodide in rabbits due to a 6-h inhalation exposure to 2 ppm MeI. The predicted value of 3.72 x 10^{+6} ng/L*h matches 3.72 mg/L*h reported by CDPR (Appendix A, page A-24).

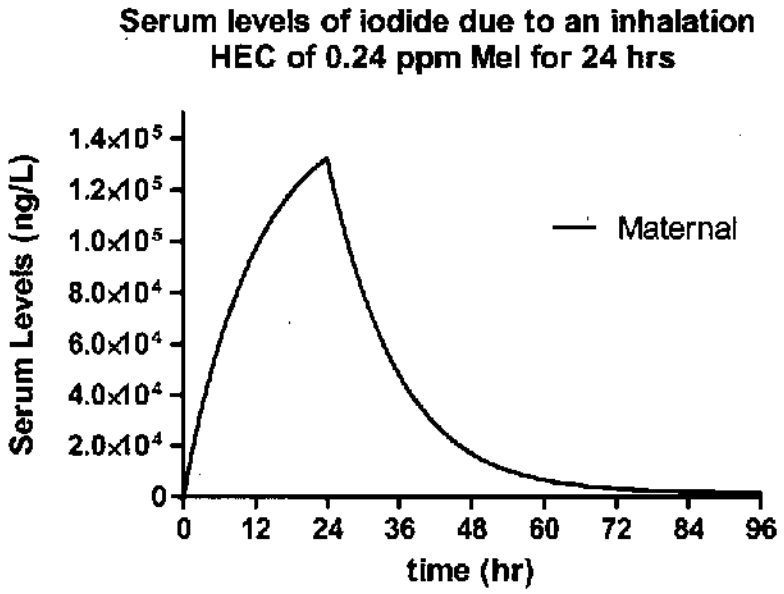
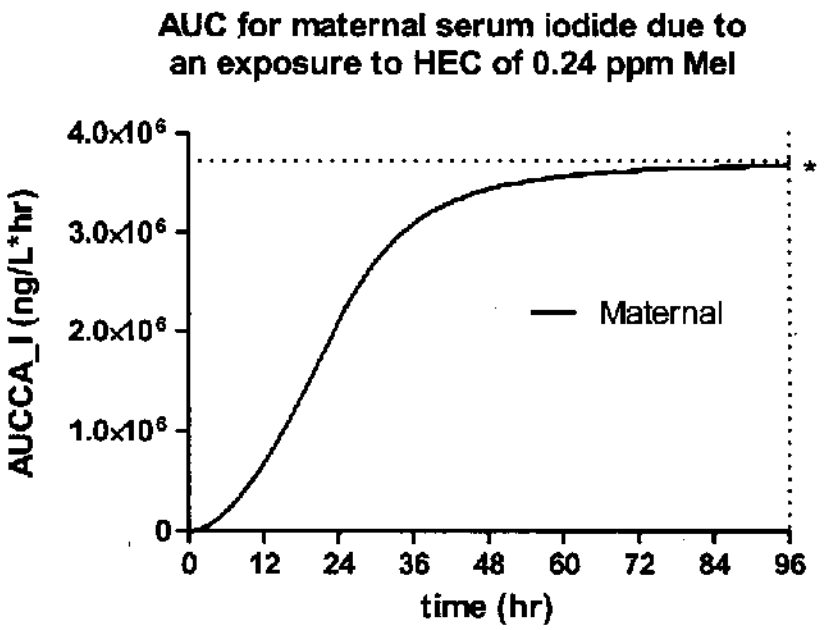


Figure 5A: Simulation of maternal serum iodide profile from a 24-h HEC of 0.24 ppm MeI. The peak concentration is predicted to be 0.13 mg/L.



* Predicted value of 3.68 x 10^{+6} ng/L*h is comparable to the value of 3.72 mg/L*h reported by CDPR

Figure 5B: Predicted AUC for maternal serum iodide from a 24-h HEC of 0.24 ppm Mel. The predicted value of 3.68 mg/L*h is comparable to the value reported by CDPR of 3.72 mg/L*hr (dashed line) (Appendix A, page A-24).

Evaluating the Impact of Changes in QAC and NOAEL on HEC Estimates

The impact of the changes in QAC and NOAEL reported by CDPR on the AUC for fetal serum iodide can be illustrated in Table 3. The AUC of 1.18 x 10^{+8} ng/L*h predicted for the 10 ppm NOAEL and corresponding HEC estimate of 7.4 ppm confirm the findings reported in Barton 2007 [1] using a QAC of 12 L/h*$kg^{3/4}$. The use of a QAC of 20 L/h*$kg^{3/4}$ would result in a two-fold increase in AUC to a value of 2.37 x 10^{+8} ng/L*h and a corresponding HEC estimate of 15 ppm. Selecting 2 ppm as the point of departure but keeping QAC at 12 L/h*$kg^{0.75}$ would result in a seven-fold lower AUC of 1.68 x 10^{7} ng/L*h and a corresponding HEC of 0.94 ppm (i.e., a nearly 8-fold decrease). Implementing the higher QAC of 20 L/h*$kg^{3/4}$ as suggested by CDPR would result in a HEC estimate of 1.5 ppm Mel.

Table 3: Evaluation of a higher alveolar ventilation rate of 20 L/h*kg$^{0.75}$ and 2 ppm NOAEL on HEC estimates based on fetal serum iodide AUC

NOAEL (ppm)	QAC (L/h*kg$^{0.75}$)	Fetal serum iodide 24-h AUC (ng/L*h)	HEC Estimate (ppm)
2	12	1.68×10^7	0.94 [a]
2	20	2.70×10^7	1.5 [b]
10	12	1.18×10^8 [c]	7.4 [c]
10	20	2.37×10^8	15

[a] Comparable to the value of 0.78 reported by CDPR (Table A-4, page A-24, Appendix A)
[b] Comparable to value of 1.3 ppm reported by CDPR (Table A-4, page A-24, Appendix A)
[c] Reported in Barton 2007

Table 4 shows the impact of the same changes in QAC and NOAEL but using the AUC for maternal serum iodide. HEC estimates based on maternal serum iodide AUC values at the NOAEL of 2 ppm using QAC of 12 and 20 L/h*kg$^{0.75}$ were reported by CDPR in Table A-4 (page A-24, Appendix A) and matched in this analysis. If HEC estimates were to be based on the 10 ppm NOAEL, then the impact of using a QAC value of 20 versus 12 L/h*kg$^{0.75}$ would be an approximate increase of 2-fold in the maternal serum iodide AUC and HEC estimates, i.e., from 1.62×10^7 to 2.24×10^7 ng/L*h, and from 1.0 to 2.1 ppm, respectively (Table 4).

Table 4: Evaluation of a higher alveolar ventilation rate of 20 L/h*kg$^{0.75}$ and 2 ppm NOAEL on HEC estimates based on maternal serum iodide AUC

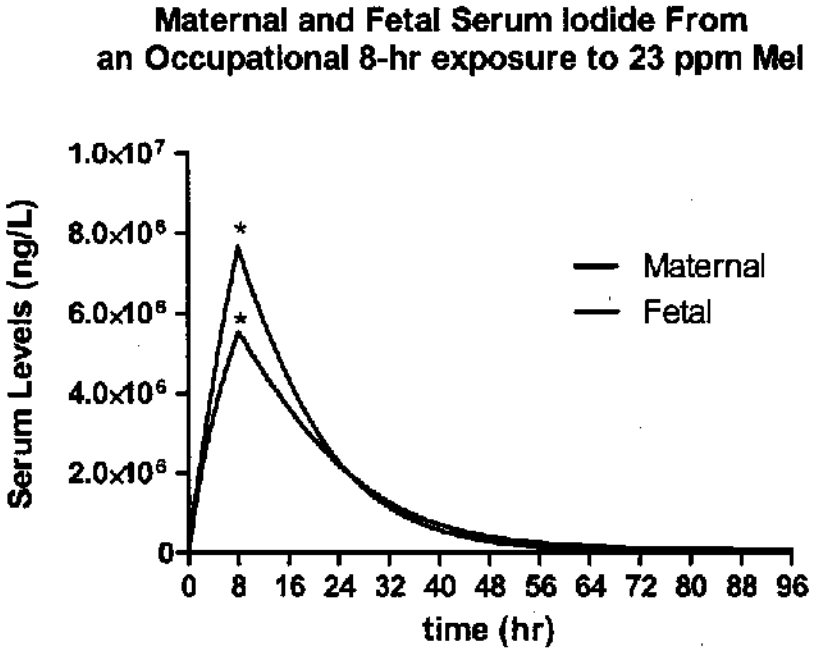
NOAEL (ppm)	QAC (L/h*kg$^{0.75}$)	Maternal serum iodide 24-h AUC (ng/L*h)	HEC Estimate (ppm)
2	12	2.24×10^6	0.15 [a]
2	20	3.72×10^6	0.24 [a]
10	12	1.62×10^7	1.1
10	20	3.29×10^7	2.1

[a] Matches value reported by CDPR (Table A-4, page A-24, Appendix A).

(D). Human simulation: use of a 1.5-fold higher breathing rate for estimating the occupational HEC.

CDPR estimated an occupational HEC based on higher breathing rate than that used in Barton 2007 [1]. A minute ventilation rate of 567 L/h (tidal volume of 630 ml and breathing frequency of 15 breaths/minute) is supposedly more consistent with short term sedentary activities as described in the US EPA Exposure Factors Handbook

(EFH) [6]. CDPR adopted a breathing rate of 833 L/h which is supposedly still lower than the 1000 L/h recommended in EFH for light activities, but more suitable for simulating occupational exposures. In an initial effort to evaluate the impact of a higher ventilation rate, simulations were first carried out to confirm the occupational HEC of 23 ppm MeI reported in Barton 2007 [1] using a QAC of 16.4 L/h*kg$^{0.75}$ (mistakenly listed by CDPR as 16.5 L/h*kg$^{0.75}$). The occupational exposure is based on a pregnant female being exposed for 8 hours. Figure 6A shows the maternal and fetal serum iodide profiles following the 8-h inhalation exposure to 23 ppm MeI. The predicted peak maternal and fetal serum iodide levels of 7.67 x 10^6 ng/L and 5.54 x 10^6 ng/L, respectively, match those reported in Barton 2007 [1]. Figure 6B shows the corresponding AUC profiles and the matching value of 1.18 x 10 ng/L*hr at 96-h to the 10 ppm NOAEL in the rabbit study described above.



* Match values reported in Barton 2007

Figure 6A: Maternal and feral serum iodide profiles from an 8-h occupational exposure of 23 ppm MeI. The predicted peak serum iodide concentrations match those reported in Barton 2007.

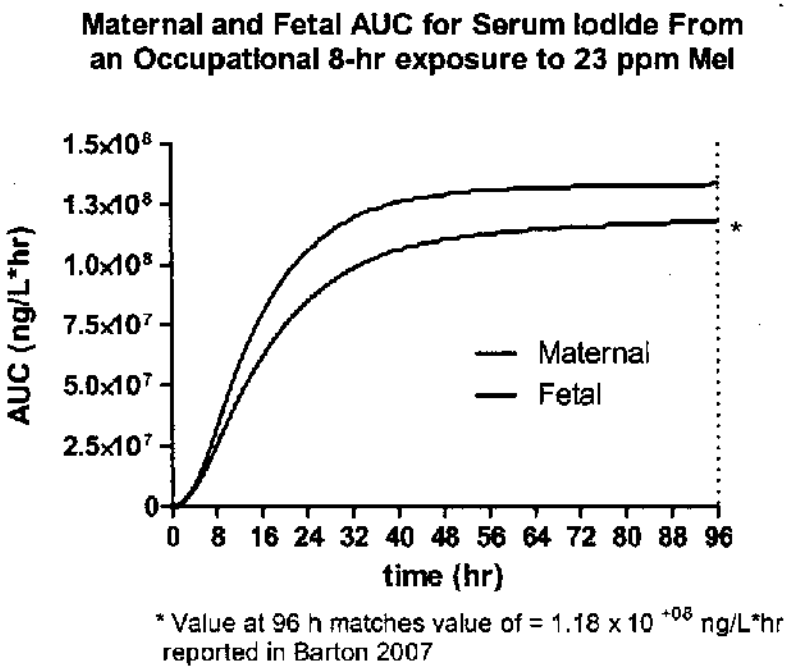


Figure 6B: AUC profiles for maternal and fetal serum iodide from an 8-h occupational exposure of 23 ppm MeI. The predicted fetal AUC at 96 h matches the value obtained for fetal death in the rabbit at the NOAEL of 10 ppm MeI.

In an effort to evaluate the impact of 1.47-fold increase in ventilation rate, QAC was increased from 16.4 to 24.1 L/h*kg$^{0.75}$ in the simplified model. As shown in Figure 7, the resulting simulation does not match that reported by CDPR in Figure A-8a (Page A-27, Appendix A). At the end of the first 8 h exposure, the maternal serum iodide AUC reported by CDPR approaches a value of about 0.8 mg/L*h (Figure A-8a), whereas only about half that value is reached in this analysis (Green line, Figure 7).

(E). Human simulation: selection of 24 versus 96-h time window for estimating an 8-h occupational HEC

In a somewhat different approach adopted by CDPR, a second daily exposure was simulated to illustrate the point that the occupational HEC curves approaches the general population HEC shortly after 24 hours. Therefore, CDPR is using a 24-h time window for their estimation of an 8-h occupational exposure which contrasts the 96-h time window used in Barton 2007 [1] (Figure 6B). Furthermore, the resulting AUC at 24-h is significantly lower than the targeted 3.72 mg/L*h value; only a value of about 2.2

mg/L*h is reached (Figure A-8a, Appendix A). Following the second 8-h exposure, the maternal serum iodide AUC reported by CDPR reaches 5 mg/L*h at 48-h, whereas it does not even reach 3 mg/L*h in this analysis (Figure 7, green line). For comparison with Figure A-7a provided by CDPR, the AUC curve associated with the rabbit 2 ppm NOAEL (black line, Figure 7) is also plotted along with the estimated 24-h HEC of 0.24 ppm (red line, Figure 7). In contrast to the occupational HEC simulation provided by CDPR, these two simulations match those of Figure A-8a (page A-27, Appendix A).

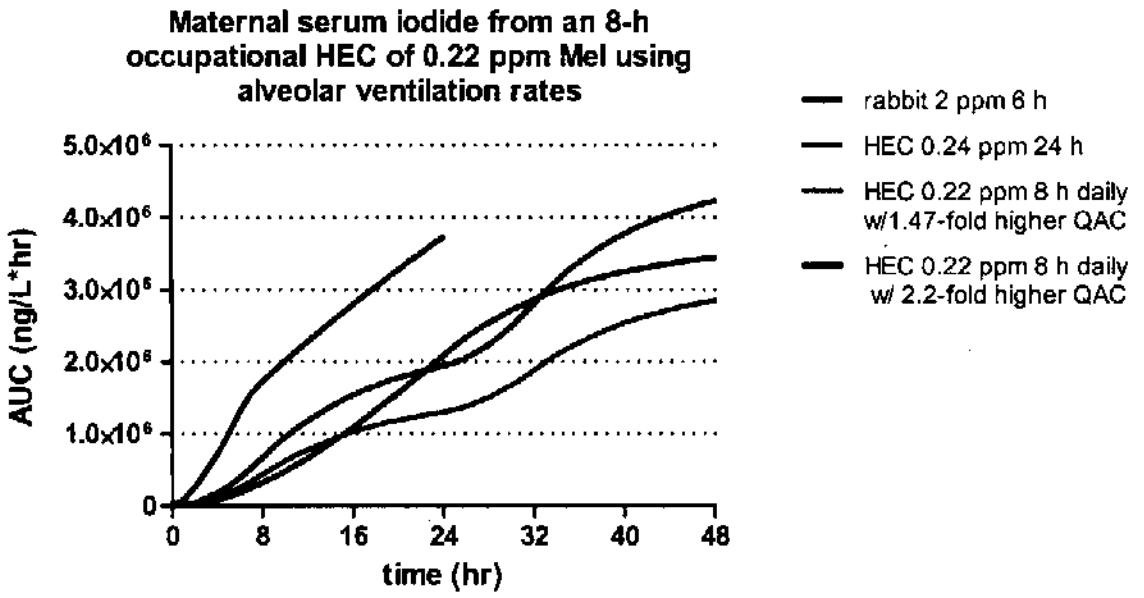


Figure 7: AUC profiles for maternal serum iodide at different alveolar ventilation rates following an 8-h occupational exposure of 0.22 ppm MeI. The predicted AUC profile approximates the 24-h HEC curve at 24-h only using a 2.2-fold higher alveolar ventilation rate.

It is unclear why the simulation of the occupational HEC in this analysis differs from that reported by CDPR. One likely explanation though is that minute instead of alveolar ventilation rate was used by CDPR for estimating an 8-h occupational HEC. Minute ventilation (VE) and alveolar ventilation (QAC) differ in that VE includes the anatomical dead-space (approximated at 33% of the tidal volume) and thus it is greater than QA which is recommended for estimating internal dose [6]. VE and QA can be calculated as follows:

VE = tidal volume x breaths/min

QA = (tidal volume-dead space) x breaths/min

Using the tidal volume of 630 ml/breath and breathing frequency of 15 breaths/minute listed in Barton 2007 [1] and reiterated by CDPR (page A-8, Appendix A), VE equals 567 L/hr (VE = 0.630L/breaths * 15 breaths/min * 60 min/1 hr) which is consistent with the value reported by CDPR (page A-8, Appendix A). However, it is QAC that should be used in estimating internal dose. The corresponding QAC value would be 67% of VE, that is approximately 380 L/h (QA = 0.67*0.630L/breaths * 15 breaths/min * 60 min/1 hr). Assuming that CDPR used VE instead of QAC for estimating their occupational HEC, the impact would be a 1.5-fold increase in ventilation rate followed by the CDPR's proposed 1.47-fold increase for occupational exposures. Thus, QAC would increase to 36 $L/h*kg^{0.75}$ from the original value of 16.4 $L/h*kg^{0.75}$. Indeed, a QAC of 36 $L/h*kg^{0.75}$ results in a occupational AUC profile that is more consistent with that reported by CDPR in Figure A-8a, especially in the 8-h HEC curve approximating the 24-h HEC curve near the 24 h mark (See blue and red lines in Figure 7).

In an attempt to match the AUC of 3.72 mg/L*h for the 2 ppm NOAEL proposed by CDPR using a 1.47-fold higher QAC, i.e., 24.1 $L/h*kg^{0.75}$, a simulation was carried to estimate an occupational HEC using the same approach used in Barton 2007 [1] (i.e., a single 8-h exposure and a 96-h time window). As shown in Figure 8, a HEC of approximately 0.5 ppm results in a maternal AUC that is more consistent with 3.72 mg/L*h (dashed line in Figure 7).

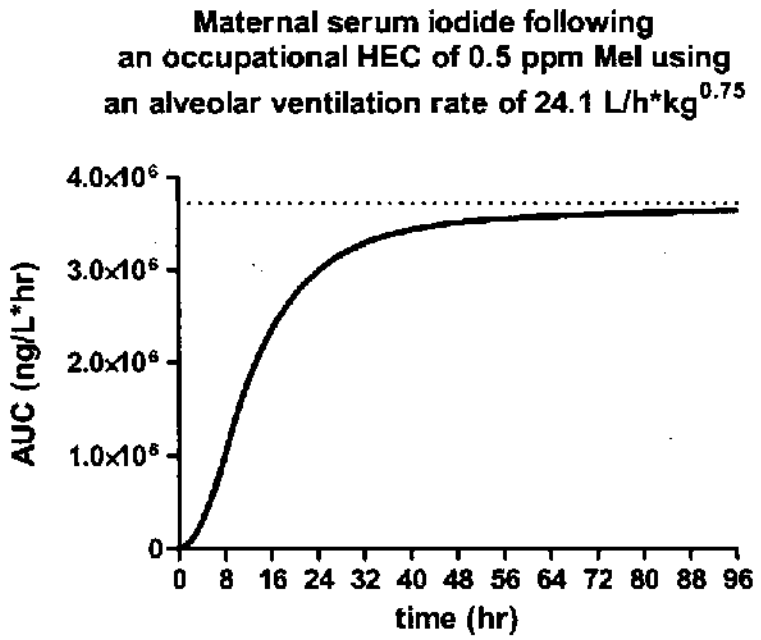


Figure 8: Maternal AUC profile following an occupational 8-h exposure to 0.5 ppm MeI. The dashed line represents the target AUC reported for the 2 ppm NOAEL in the rabbit study.

(II). HEC ESTIMATES BASED ON NASAL OLFACTORY EPITHELIAL DEGENERATION IN RATS

The changes reported by CDPR for deriving inhalation HEC estimates based on nasal olfactory epithelial degeneration in rats can be briefly summarized as follows:

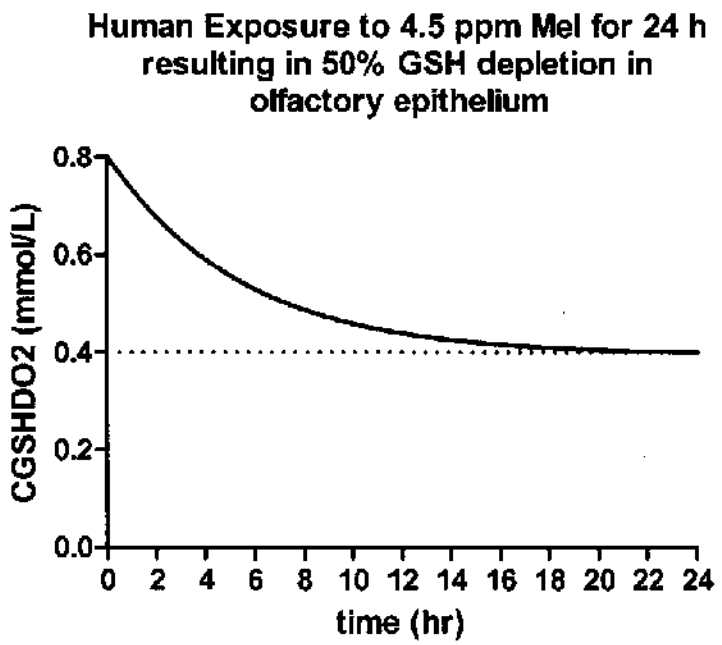
(A). Human simulation: selection of 25% versus 50% glutathione (GSH) depletion as bench mark.

(B). Human simulation: use of a 1.5-fold higher breathing rate for estimating an 8-h occupational HEC.

(A). Human simulation: selection of 25% versus 50% glutathione (GSH) depletion as bench mark.

The full model implements a complex description of the nose to describe degeneration of the olfactory epithelium resulting from MeI exposure. Based on the relationship between GSH depletion and epithelium degeneration, preventing excessive

GSH depletion would be consistent with protecting the olfactory epithelium. Therefore, one dose metric that is calculated by the model is the average GSH concentration in the olfactory epithelial tissue (denoted in the model as CGSHDO2). A 24-h HEC of 4.5 ppm MeI was estimated in Barton 2007 [1] and reproduced in this analysis based on a 50% GSH depletion benchmark (Figure 9A). Most of the GSH depletion occurs during the first 8 h while near steady state is achieved by 24 h. An 8-h occupational HEC of 5.8 ppm was similarly estimated to result in 50% GSH depletion [1]. Figure 9B reproduces the 8-h occupational HEC estimated in Barton 2007 [1]. In contrast to the 24-h HEC, significant recovery is predicted to take place following cessation of the 8-h MeI exposure. It is important to note that rats are obligate nose breathers, whereas humans can also breathe orally depending on activity and personal habits. The model parameter "ORAL" describes the fraction of air assumed to be inhaled orally in humans. All of the HEC estimates from Barton 2007 were obtained assuming 100% nasal contribution (i.e., oral=0).



* matches Figure 3 reported in Barton 2007

Figure 9A: Glutathione depletion in the olfactory epithelium from a 24-h HEC of 4.5 ppm MeI. The simulation matches Figure 3 reported in Barton 2007.

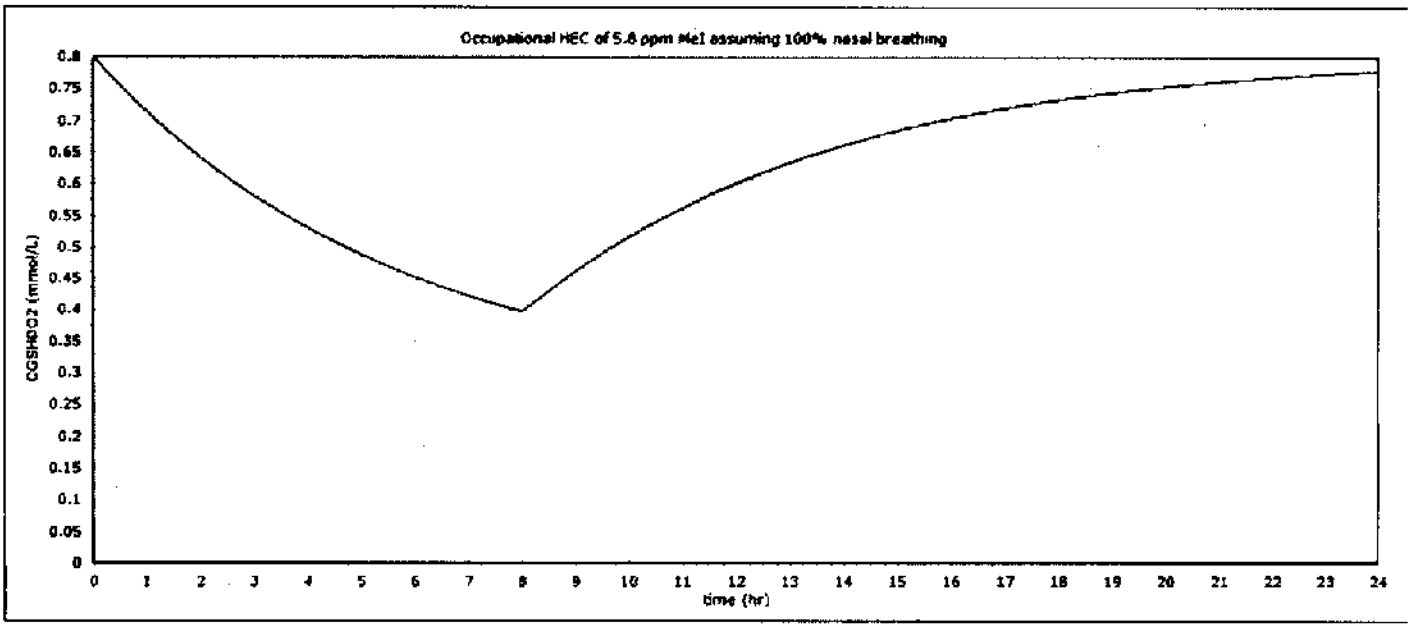
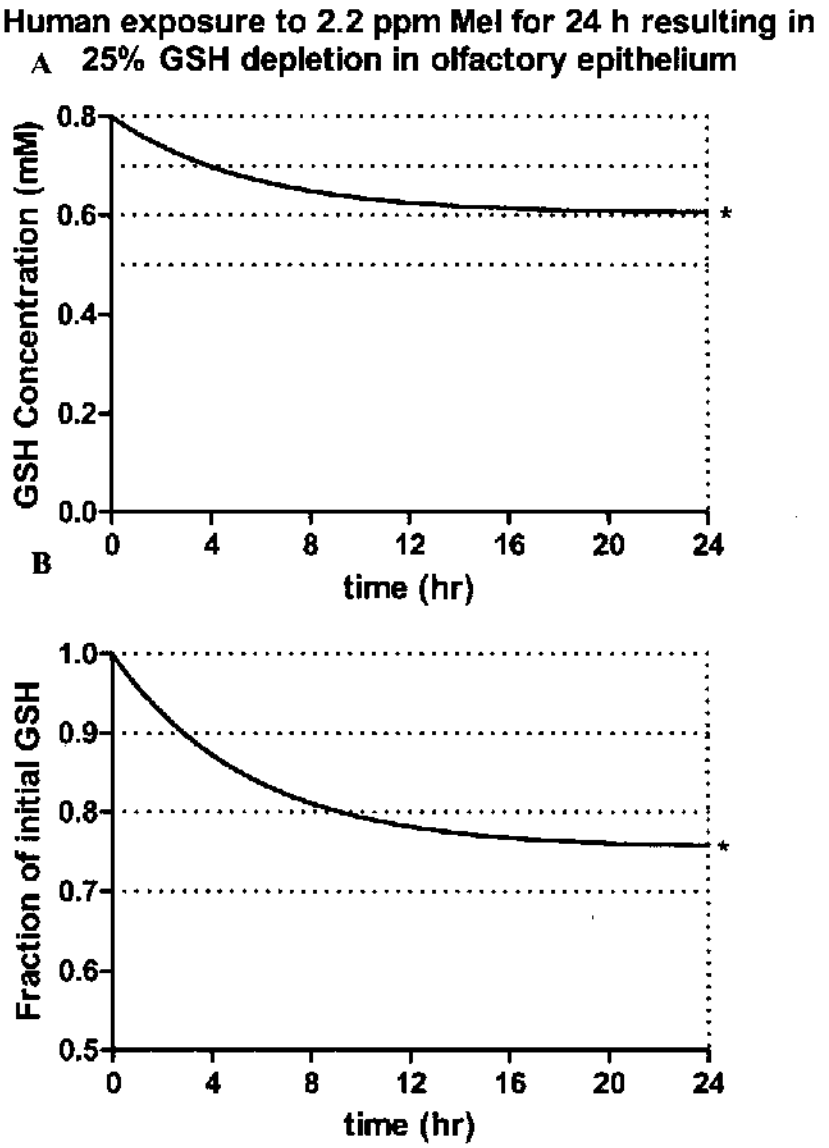


Figure 9B: Glutathione depletion in the olfactory epithelium from an 8-h occupational HEC of 5.8 ppm. The simulation matches the results reported in Barton 2007.

CDPR agrees with the selection of CGSHDO2 as an appropriate dose metric for olfactory epithelium degeneration, but disagrees with the 50% depletion benchmark. Among the main arguments raised by CDPR against the 50% GSH depletion is a wide diurnal variation of GSH levels in some tissues which can be as much as 50% (page A-32, Appendix A). Therefore, CDPR prefers a more conservative 25% GSH depletion benchmark that is more likely to be associated with no effects. Figures 10 A-B match the simulation labeled "avg gsdoe1" in Figure A-11 reported by CDPR (Page A-36, Appendix A) for a HEC of 2.2 ppm MeI that would result in 25% GSH depletion. Figure 10A simulates the time course of GSH concentrations whereas Figure 10B shows the fraction of GSH remaining during the 2.2 ppm MeI exposure to match Figure A-11 reported by CDPR.

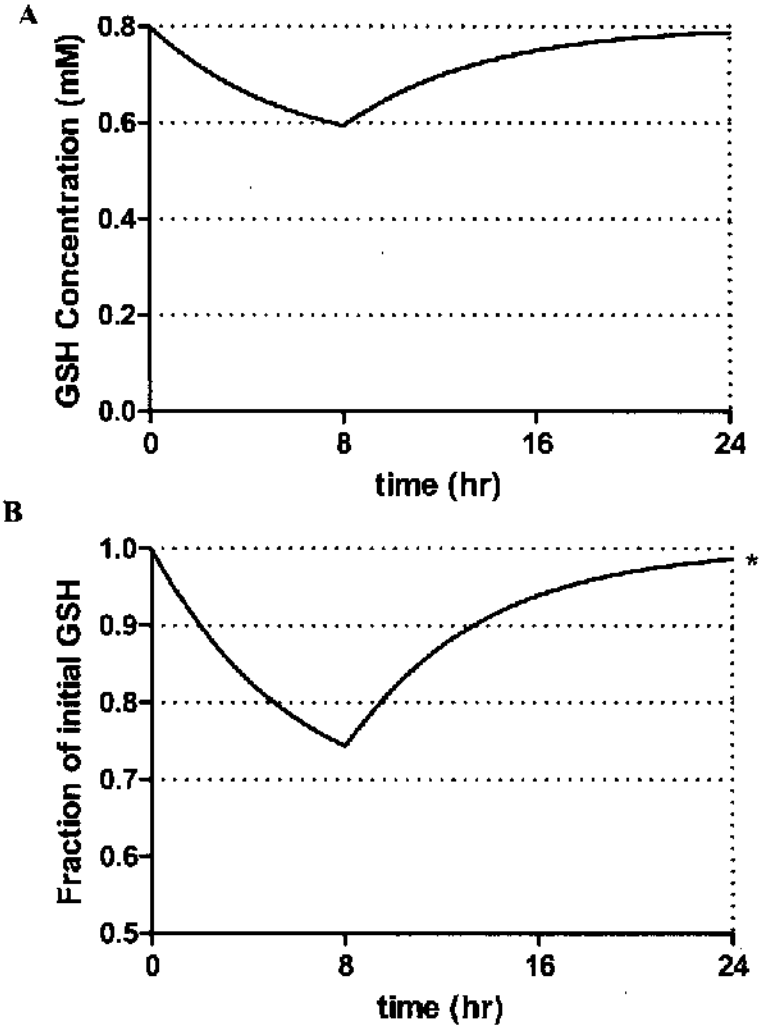


Figures 10A-B: Simulation of glutathione depletion during a 24-h exposure to a HEC of 2.2 ppm MeI. Simulations are consistent with those reported by CDPR for "ave gsdoe1" in Figure A-11 (page A-36, Appendix A).

(B). Human simulation: use of a 1.5-fold higher breathing rate for estimating an 8-h occupational HEC.

The 8-h occupational HEC that would result in 25% GSH depletion is simulated in Figure 11A-B. As with the rabbit study, CDPR prefers a 1.5-fold higher ventilation for estimating an occupational 8-h HEC. The 1.5-fold higher ventilation rate suggested by CDPR was incorporated in the model by increasing the tidal volume from 630 to 925 ml and using the same breathing frequency of 15 breaths/minute. All of the HEC estimates reported by CDPR assume100% nasal contribution. Figures 11A-B confirm the 8-h occupational HEC of 2.8 ppm MeI that would result in 25 % GSH depletion in the olfactory epithelium.

Human occupational exposure to 2.8 ppm MeI for 8 h resulting in 25% GSH depletion in olfactory epithelium



* Match simulation of avg gsdoe1reported by CDPR in Figure A-12, Appendix A

Figures 11A-B: Simulation of glutathione depletion during an 8-h occupational exposure to a HEC of 2.8 ppm MeI. Simulations are consistent with those reported by CDPR in Figure A-12 for "ave gsdoe1" (page A-38, Appendix A).

(III). HEC ESTIMATES BASED ON NEUROTOXICITY IN RATS

The changes reported by CDPR for deriving inhalation HEC estimates based on neurotoxicity in rats can be briefly summarized as follows:

(A). Rat simulation: selection of the area under the brain MeI concentration-time curve versus steady state MeI brain levels for deriving HEC estimates.

(B). Human simulation: use of a 1.5-fold higher breathing rate for estimating an 8-h occupational HEC.

(C). Human simulation: set 8-h occupational HEC to same value as 24-h HEC for not accounting for the additional 16-h exposure after work.

(A). Rat simulation: selection of area under the brain MeI concentration-time curve (AUCCBR) versus steady state MeI brain levels as dose metric for estimating HEC.

The phenotypic neurotoxicity observed in rats was reportedly in the form of decreased body temperature and motor activity after a 6-h inhalation exposure to MeI. The results were evaluated in Barton 2007 [1] based on the predicted steady state brain concentrations (CBRss) of MeI from the 6-h exposure at the NOAEL of 27 ppm MeI. The basis for selecting brain levels is based on the assumption that the induced neurotoxicity by MeI is similar to the sedative effects of volatile organic compounds. Figure 12A reproduces the results from Barton 2007 [1]. CBRss levels of about 0.1 mg/L MeI are quickly reached after about 30 minutes of exposure to 27 ppm MeI. For comparison, simulations were also carried out the LOAEL of 93 ppm MeI (Figure 12B). CBRss levels at this concentration of MeI are predicted to be about 0.38 mg/L MeI. Thus, a nearly linear relationship exists between exposure and predicted steady state brain levels, as reported in Barton 2007 [1]. The HEC of 10 ppm MeI that would result in steady state brain levels of about 0.1 mg/L MeI from a 24-h exposure is shown in Figure 13. Note that the same HEC of 10 ppm MeI is predicted for an 8-h occupational exposure since steady state is reached within 8 hours of exposure (Barton 2007) [1].

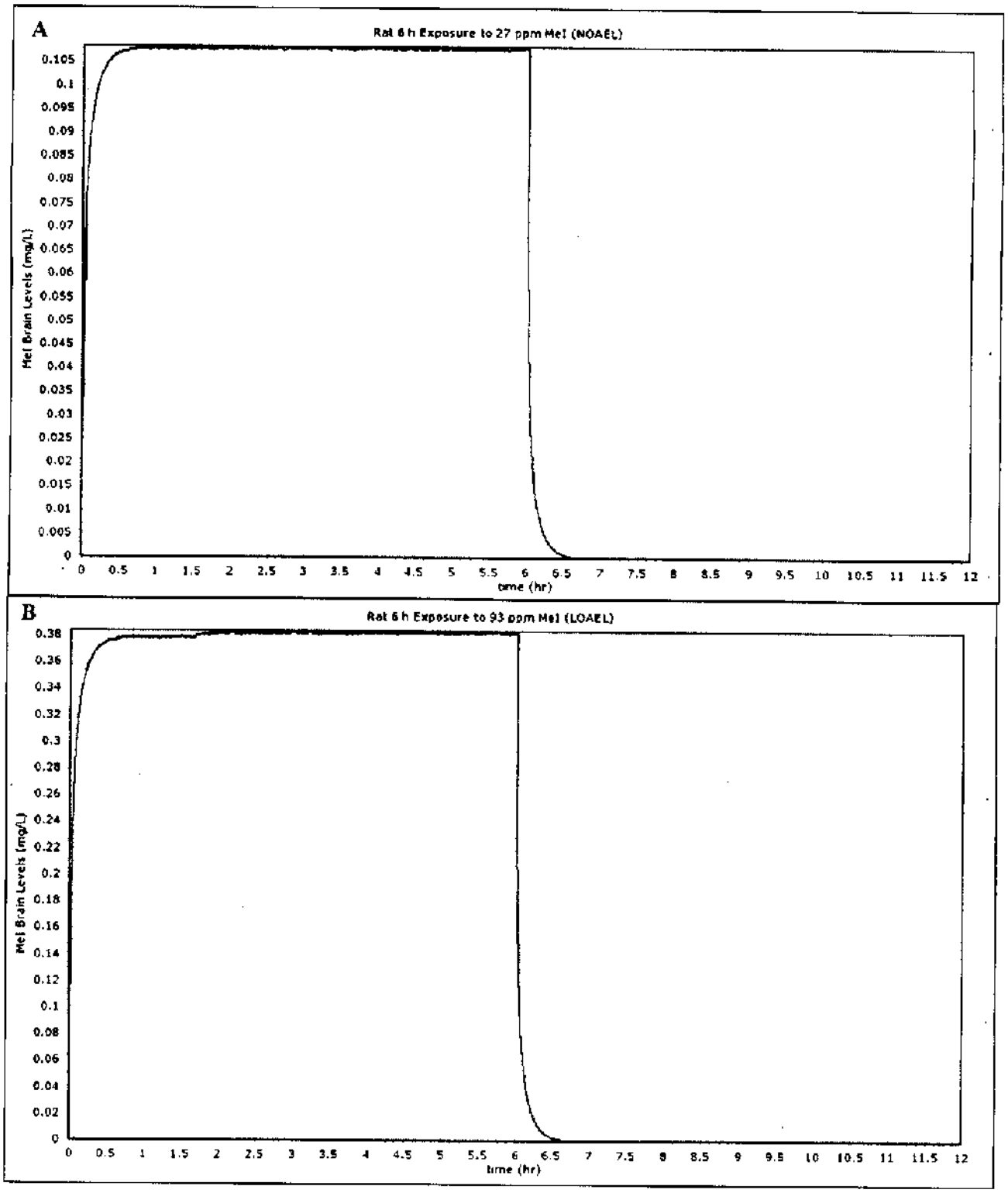


Figure 12A-B: Predicted steady state brain levels of MeI in the rat from a 6-h exposure at the NOAEL of 27 ppm (A) and LOAEL of 93 ppm (B). The simulations match those reported in Barton 2007 [1].

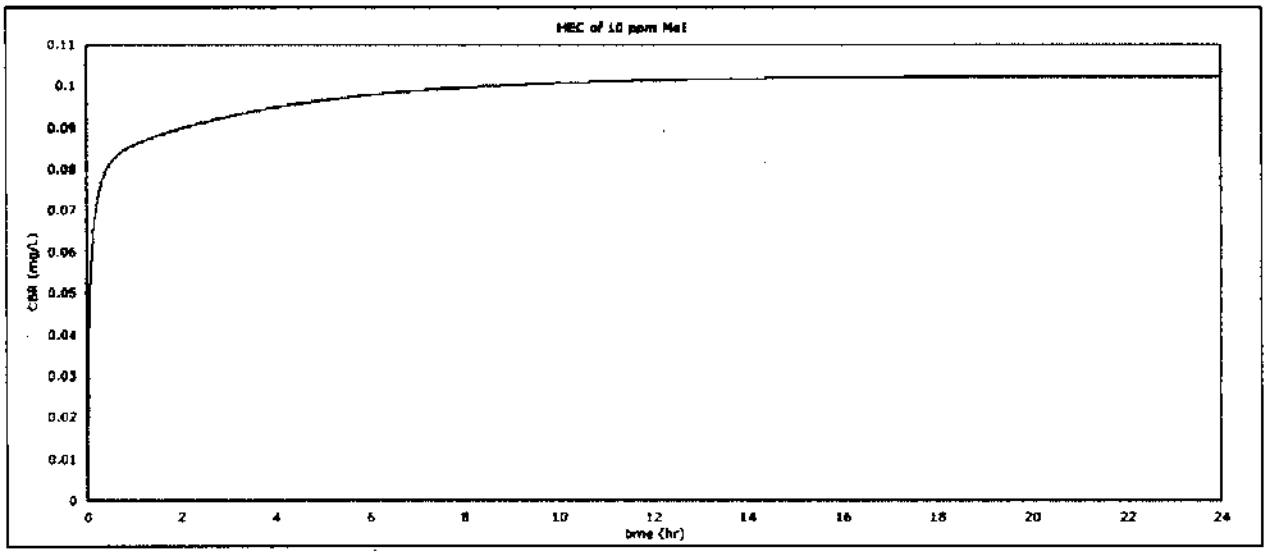


Figure 13: Predicted steady state brain levels of MeI following a 24-h exposure to the HEC of 10 ppm. The simulation matches the results in Barton 2007 [1].

CDPR agrees with the selection of brain levels as an appropriate dose metric for estimating a HEC, but disagrees with using CBRss. Instead, CDPR prefers AUCCBR supposedly as a way to account for the duration of sustained MeI levels in the brain. CDPR describes the brain levels simulated in Barton 2007 [1] as "peak" levels to presumably reflect their transient nature. It should be noted, however, that it was steady state brain levels which were used. At a constant exposure, peak levels and steady state levels will be the same but the latter is reflective of more sustained exposure. Moreover, both CBRss and AUCCBR at steady state account for duration. In fact, CBRss at steady state is simply the average daily AUCCBR divided by 24 h, so there is no additional information provided by AUCCBR as compared to CBR at steady state. Perhaps, the choice of AUCCBR by CDPR is based on the time of about 30 minutes in rats and about 10 hours in humans that it takes to reach steady state. Since clearance following cessation of exposure is very fast (i.e., takes less than1-h for most of the chemical to be cleared at the NOAEL, Figure 12A), and neurological measurements were likely performed several hours after the cessation of exposure, the use of AUC may be more appropriate.

Figure 14 shows the corresponding AUCCBR time course associated with the rat NOAEL of 27 ppm Mel. The predicted steady state AUCCBR value to be matched in the estimation of a HE is 0.647 mg/L*h. It should be noted that CDPR reported a value of 0.794 mg/L*h (Table A-6, Page A-41, Appendix A) and "peak" brain levels of 0.133 mg/L for the same rat NOAEL 0f 27 ppm Mel. This discrepancy was mentioned but not addressed by CDPR. HEC estimates of 2.6 and 3.0 ppm Mel yield AUCCBR values of 0.613 and 0.708 mg/L*h. Linear interpolation to match 0.647 mg/L*h yields a HEC of 2.76 ppm Mel that is about 20% lower than the value of 3.4 ppm reported by CDPR (page A-41, Appendix A). The difference is likely due to the higher AUCCBR obtained by CDPR for the same rat NOAEL of 27 ppm Mel. Figure 15 shows the resulting brain AUC profile for a HEC of 2.76 ppm Mel.

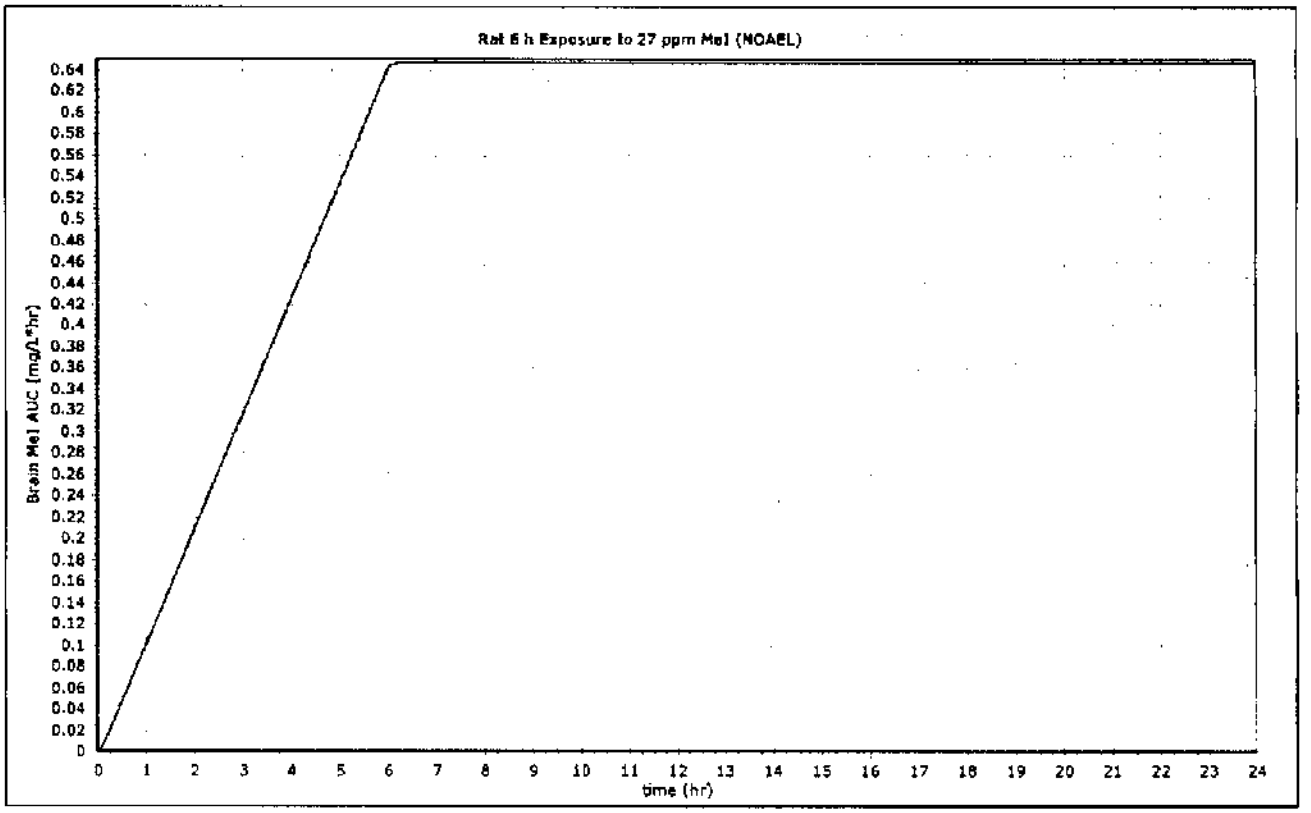


Figure 14: Brain Mel AUC profile in the rat from an exposure to Mel at the NOAEL of 27 ppm.

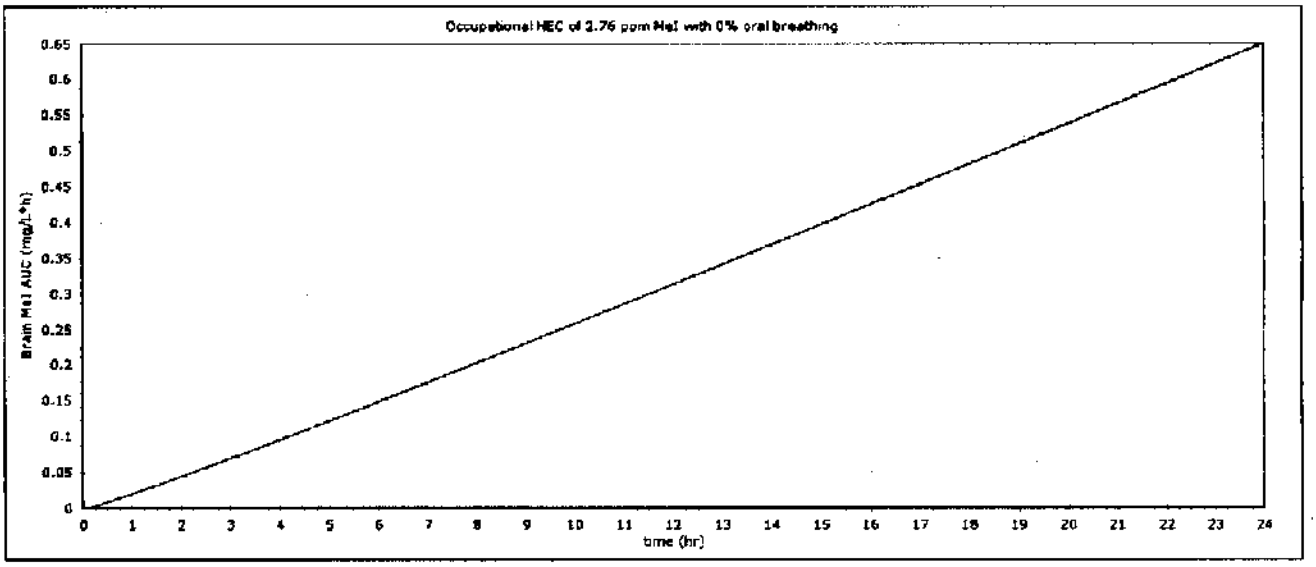


Figure 15: Brain Mel AUC profile following a 24-h exposure to the HEC of 2.76 ppm. The AUC at 24-h matches the AUC obtained for the rat at the NOAEL of 27 ppm Mel.

(B). Human simulation: use of a 1.5-fold higher breathing rate for estimating an occupational HEC.

CDPR estimated an occupational 8-h HEC based on a 1.5-fold higher ventilation rate as mentioned for the two other toxicity endpoints. This increase in ventilation rate was achieved as described previously by increasing the tidal volume from 630 to 925 ml in the full model. In an initial attempt to confirm the changes reported by CDPR, a simulation of a HEC of 9.7 ppm was first carried out to match one of the reported simulations in Figure A-14a (Page A-44, Appendix A). A match to Figure A-14a required the fraction of air inhaled orally to be set to 0.4 (i.e., ORAL=0.4) (Figure 16). CDPR did not inform of any changes associated with the parameter ORAL. Oronasal breathing acts to lower the ventilation rate and thus resulting in a lower internal dose. Assuming the same 40% fraction of air inhaled orally, HEC estimates of 2.76 and 9.7 ppm Mel yield AUCCBR values of 0.238 and 0.838 mg/L*h. Linear interpolation to match 0.647 yields a HEC of 7.5 ppm Mel. Figure 17 shows the simulation of a HEC of 7.5 ppm Mel assuming 0% (top plot) and 40% (bottom plot) oral breathing. Assuming 0% oral breathing would result in an AUC of 1.76 mg/L*h, 2.7-fold higher than the

estimated value of 0.647 mg/L*h obtained for the rat at the NOAEL of 27 ppm MeI (Figure 14).

The HEC estimate of 7.5 ppm is 23% lower than the estimate of 9.7 ppm MeI reported by CDPR (Page A-43, Appendix A). The difference may be again reflective of the higher AUCCBR obtained but not addressed by CDPR for the rat NOAEL of 27 ppm as described above.

(C). Human simulation: set 8-h occupational HEC to same value as the 24-h HEC estimate for not accounting for the additional 16-h exposure after work.

CDPR prefers to set the estimated 8-h occupational HEC to the same value as their estimated 24-h HEC of 3.4 ppm (i.e., 2.76 ppm in this analysis). Their reported rationale is based on the 8-h HEC not accounting for the additional 16-h exposure after work. Therefore, the scenario simulated by CDPR is of a worker getting exposed to an 8-h occupational exposure of MeI and then becoming a bystander for the subsequent 16-h. Such approach differs from that used in Barton 2007 [1] where the worker would not be exposed to MeI following the 8-h period.

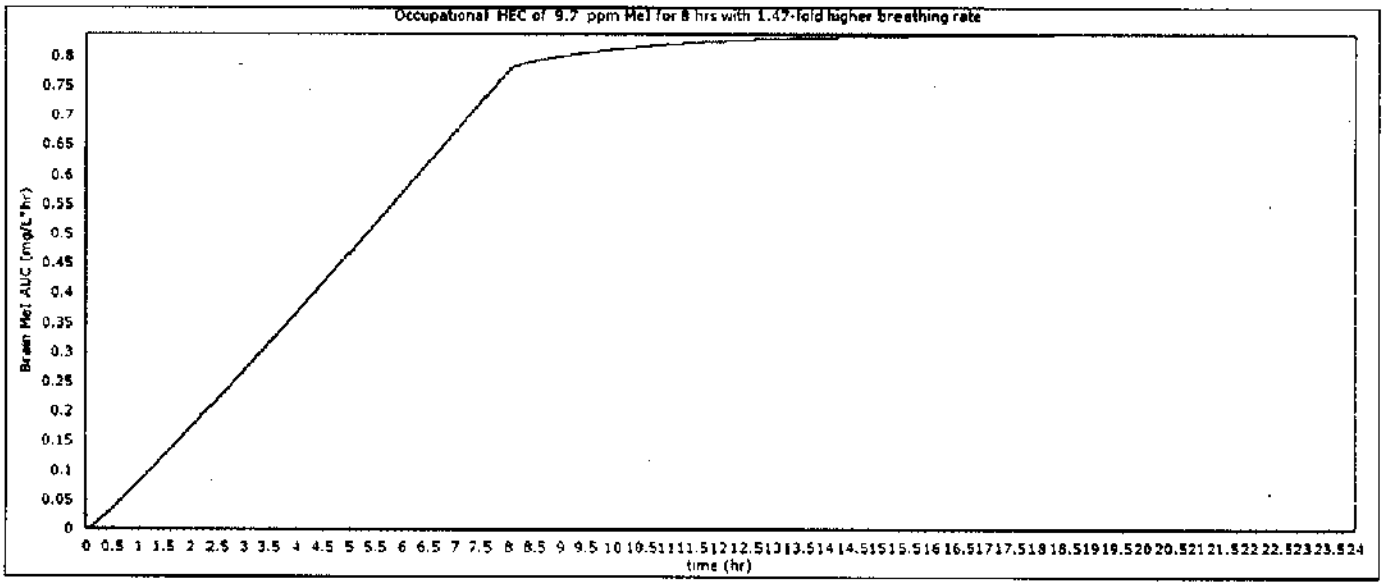


Figure 16: Simulation brain MeI AUC for a HEC of 9.7 ppm MeI with a 1.47-fold higher ventilation rate and assuming 40% of air inhaled orally.

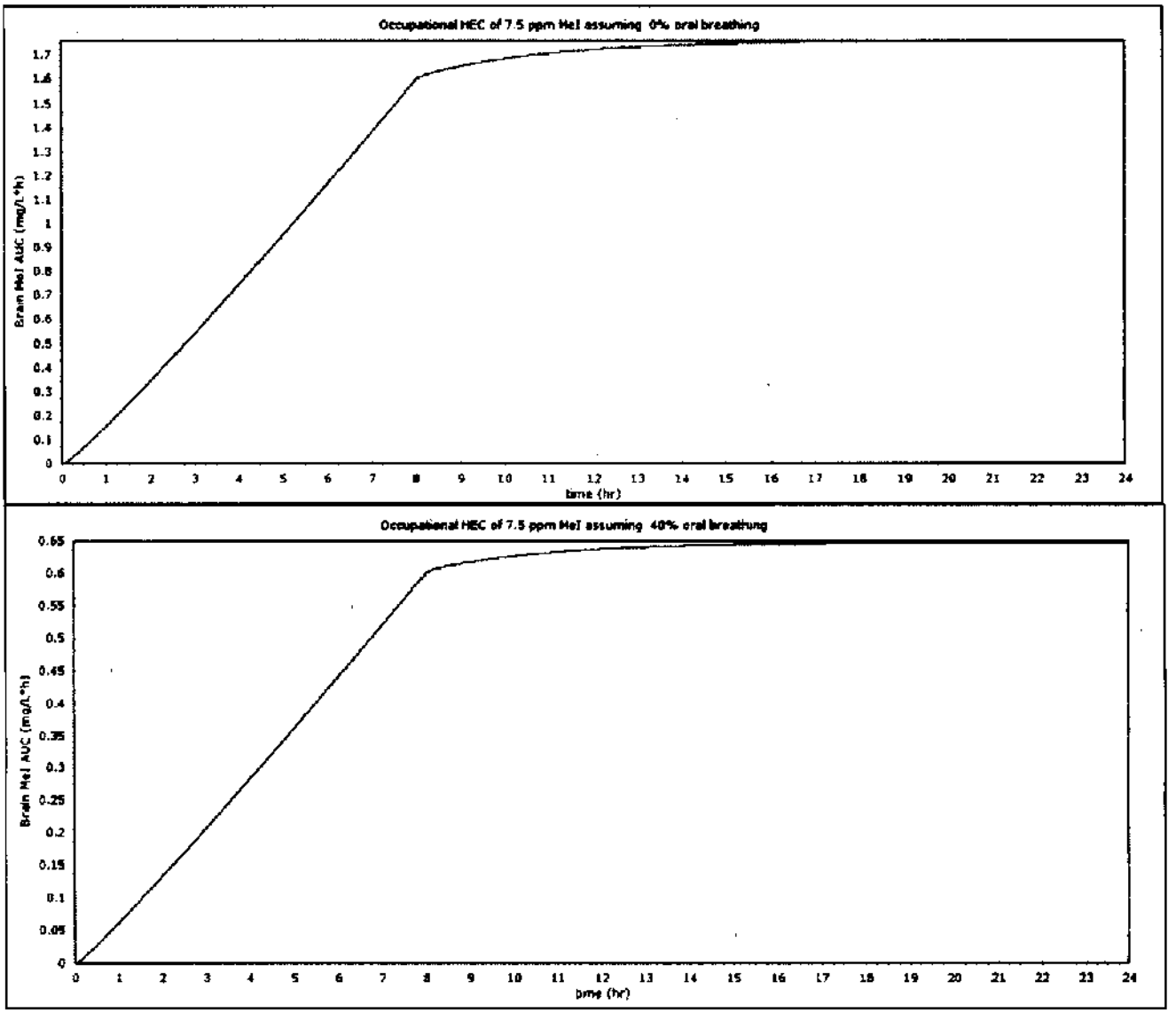


Figure 17: Simulation of brain MeI AUC for a HEC of 7.5 ppm with a 1.47-fold higher ventilation rate and assuming100% nasal breathing (top plot) and 40% oral breathing (bottom panel). The bottom panel is consistent with the HEC estimate reported by CDPR.

REFERENCES

1. Barton H. Memorandum from Hugh Barton to Elizabeth Mendez. TXR #: 0054604. 2007;06/14/07.
2. Barton H, Schlosser P. Memorandum from Hugh Barton and Paul Schlosser to Elizabeth Mendez. TXR #: 0053105. 2005;11/22/05.
3. Sloter ED. A combined baseline/inhalation exposure study of iodomethane-related fetotoxicity in rabbits. Laboratory Study No WIL-418031 WIL Research Laboratories, Inc. 2005a;DPR Vol. 52875-085(#216254).
4. Sloter ED. Mode of action study for iodomethane-related fetotoxicity in rabbits. . Laboratory Study No WIL-418032 WIL Research Laboratories, Inc. 2005b;DPR Vol. 52875-086(#216255.).
5. DeLorme, M.P. Iodomethane: Pulmonary function study in the rabbit. Laboratory Project ID: DuPont-15453, Exygen Research and EI du Pont de Nemours and Company. 2004;52875-079(#216074).
6. USEPA. Exposure Factors Handbook. 1997.

Department of Pesticide Regulation

Mary-Ann Warmerdam
Director

Arnold Schwarzenegger
Governor

MEMORANDUM

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

FROM: Lori O. Lim, Ph.D., D.A.B.T. *(original signed by L. Lim)*
Staff Toxicologist
(916) 324-3515

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: Responses to U.S. Environmental Protection Agency Comments on the Draft Methyl Iodide Risk Characterization Document for Inhalation Exposure Volume I

The following are our responses to comments from the U.S. Environmental Protection Agency (USEPA; June 2, 2009) on the draft Methyl Iodide Risk Characterization Document (Volume I) for Inhalation Exposure Volume I (March 2009).

Comments on the same subject or issue appear in multiple places in the USEPA comment document. For a more clear presentation of the responses, they are grouped together based on subject/issue with a single response. For cross reference with the Volume I, the subjects/issues with sections and page numbers from the March 2009 Volume I are given in italics. They are presented in the general order in which they are discussed in the Volume I.

Comment #1. NOAEL established for the pre-natal developmental study in rabbits

Pages 3-4 under *Summary-Toxicology Profile and Hazard Identification (p.2)*:
For the acute risk assessment, CDPR selected the endpoint of fetal death from the prenatal developmental toxicity study in rabbits. For this study CDPR established a NOAEL of 2 ppm while the Agency established the NOAEL at 10 ppm. The Agency's decision to establish the NOAEL at 10 ppm is based on the observation that the incidence of fetal deaths seen at this concentration were within historical control obtained from the Middle Atlantic Reproduction and Teratology Association (MARTA), one of the world's largest repositories of reproduction and developmental historical control data. Moreover, the standard deviation for fetal losses at this concentration was approximately 2-fold higher than the mean (0.1±0.22) thus rendering the observation indistinguishable from background. Similarly, the incidence of late resorptions at the 10 ppm could not be distinguished from background since the standard deviation was also ≈ 2-fold higher than the mean (0.9±1.60). In contrast, the effects observed at the 20 ppm concentration (the concentration used by the Agency as the LOAEL) are more robust including a

41% decrease in the number of live fetuses per doe, a 20% decrease in fetal weight, and a 1500% increase in late resorption.

Page 12 under *Toxicology Profile- Developmental Toxicity (p. 80-81)*:
In this study CDPR selected a developmental NOEL of 2 ppm and a LOEL of 10 ppm based on decreased fetal weight and fetal viability and increases in late resorptions while the Agency established the NOAEL at 10 ppm and a LOAEL of 20 ppm. The Agency's decision to establish the NOAEL at 10 ppm is based on the observation that the incidence of fetal deaths seen at this concentration were within historical control obtained from the Middle Atlantic Reproduction and Teratology Association (MARTA), one of the world's largest repositories of reproduction and developmental historical control data. Moreover, the standard deviation for fetal losses at this concentration was approximately 2-fold higher than the mean (0.1±0.22) thus rendering the observation indistinguishable from background. Similarly, the incidence of late resorptions at the 10 ppm could not be distinguished from background since the standard deviation was also ≈2-fold higher than the mean (0.9±1.60). In contrast, the effects observed at the 20 ppm concentration (the concentration used by the Agency as the LOAEL) are more robust including a 41 % decrease in the number of live fetuses/doe, 20% decrease in fetal weight, and a 1500% increase in late resorptions. With regards to the fetal weight, the Agency considered the fetal weight decrease at the 10 ppm concentration not sufficiently robust to establish a LOAEL given the lack of statistical significance.

DPR Response: As stated in the Volume I, the DPR's view is that toxicity determination should not rely solely on statistical indications without considering the magnitude of response. The magnitude of greater than 6-fold increase at 10 ppm for fetal death (Table 34) is important, especially when the variability is high for the index. In this case, the large variability is partly due to the varying number of implantation sites per litter, ranging from 1 to 11. It is noteworthy that the increase in late resorption at 10 ppm is higher than the maximum mean value[1] in the historical control data from the conducting laboratory (Nemec, 2002d; WIL Research Laboratories, 2006). There is also a greater than 3-fold increase in the number of litters with dead fetuses at 10 ppm (6/20 versus 2/22 in the controls). The trend of increase is significant ($p<0.05$) over the dose range of the study (Table 55 in the March draft Volume I). Furthermore, the ratio of total dead fetuses to the total number of fetuses per treatment group at 10 ppm was 8-fold higher than the controls (17% versus 2% in the controls), and was statistically significant ($p<0.01$). DPR's analysis using nested logistic model (USEPA Bench Mark Dose Software 2.0) showed the extra risk response at 10 ppm of 18 – 20%, a level that cannot be accepted as equivalent to a NOEL.

[1] The average historical data for late resorption per litter from 36 studies by the conducting laboratory (WIL lab) during 1999-2004 is 1.1±1.0%, with the range of 0 - 3.7% (WIL Research Laboratories, 2006).

In terms of historical database, DPR considered it more appropriate to compare data from the conducting laboratory around the same time as when the Nemec study was conducted.

Comment #2. Quantitative risk assessments for oral and dermal exposures

Page 9 under *Toxicology Profile -Absorption and Distribution (p. 19):*
CDPR used a study intended to evaluate the disposition of Me1 in rabbits after a single exposure. In this study rabbits were exposed to ^{14}C-MeI via subcutaneous injection. The Agency does not consider subcutaneous injection a relevant route of exposure. Since this exposure strategy would significantly impact the absorption and distribution of the test compound in an unrealistic setting, this study was not considered by the Agency because exposures in the field occur via inhalation.

CDPR also conducted an evaluation of studies in which Me1 was formulated with another fumigant, chloropicrin. Though these two compounds are likely to be used in conjunction with each other under field conditions, the Agency does not as a matter of practice conduct risk assessments on mixtures. Consequently, studies with MeI/chloropicrin formulations were not considered in the Agency's assessment.

Pages 9-10 under *Toxicology Profile-Rat/Mouse Oral (p. 32-33)*:
Although iodomethane is proposed to be used as an agricultural pesticide, it is considered a non-food use chemical since it is quickly volatilized, degraded or metabolized and subsequently incorporated into natural plant constituents. The levels of iodide released from iodomethane degradation/metabolism are lower than those expected to cause toxic effects. Furthermore, enforcement of tolerances would not be possible since no iodide-free samples are available and residue field trials show evidence of control samples with higher iodide residues than iodomethane treated samples. Moreover, iodide is ubiquitous in the environment and a required nutrient. Finally, iodomethane residues must dissipate in the soil prior to planting. Accordingly, the Agency concluded tolerances are not required for iodomethane. As a result, only a screening level assessment of the oral toxicity studies has been completed.

Page 10 under *Toxicology Profile-Rabbit Dermal/Subcutaneous (p. 33-36)*:
The Agency does not expect dermal exposure to iodomethane of any significance as described below in Attachment B. As such, a quantitative dermal exposure assessment has not been completed. With regards to the subcutaneous exposure study, the Agency does not consider a subcutaneous study to be a relevant route of exposure and therefore has not conducted this risk assessment.

Pages 10-11 under *Toxicology* Profile *Rat/Mouse/Dog Oral (p.41-43 and 46-51)*:
Although iodomethane is proposed to be used as an agricultural pesticide, it is considered

a non-food use chemical since it is quickly degraded or metabolized and subsequently incorporated into natural plant constituents. The levels of iodide released from iodomethane degradation/metabolism are lower than those expected to cause toxic effects. Furthermore, enforcement of tolerances would not be possible since no iodide-free samples are available and residue field trials show evidence of control samples with higher iodide residues than iodomethane treated samples. Moreover, iodide is ubiquitous in the environment and a required nutrient. Finally, iodomethane residues must dissipate in the soil prior to planting. Accordingly, the Agency concluded tolerances are not required for iodomethane. As a result, only a screening level assessment of the oral toxicity studies has been completed.

DPR Response: These comments refer to the inclusion of all available toxicity studies in the Toxicology Profile section. As stated in the introduction of this section, the purpose was to describe the entire toxicological database of MeI, which consists of pharmacokinetic and toxicity studies submitted to DPR and those published in scientific journals. The DPR risk assessment on MeI was conducted using only inhalation toxicity studies.

<u>Comment #3. Use of data from deliberate human iodomethane exposures</u>

Page 8 under *Toxicology Profile - Pharmacokinetic (p. 14-15)*:
CDPR used data from metabolism studies in which humans were deliberately exposed to ^{132}I-MeI by inhalation. Under the provisions of the Federal Policy for the Protection of Human Subjects of Research (the "Common Rule"), the Agency will only consider human studies conducted prior to the Agency's final rule (2006) after conducting a comprehensive ethics review and/or is evaluated by the Human Studies Review Board (HSRB) empanelled by the Agency after enactment of the final rule. Since the study cited in this section was not subject to this process, the Agency will not consider the study.

Pages 12-13 under *Human Toxicity Case Reports (p. 101-103)*:
The Agency looked into the incident data available in the literature for exposure to iodomethane. The studies cited by CDPR were part of the Agency's review. Over the past century, only 11 incidents of iodomethane poisoning have been reported in the published literature[2]. In general, symptoms of iodomethane intoxication in humans were related to effects on the nervous system ranging from somnolence to ataxia, seizures, delirium and coma in severe cases. In some patients, cerebellar lesions and damage of

[2] Hermouet, C. et al. "Methyl iodide poisoning: Report of two cases" Am. J. Ind. Medicine (1996) 30: 759-764 & Appel, G.B. et al. "Methyl iodide intoxication" Annals of Int. Med (1975) 82:534-536

the third, fourth, or sixth cranial nerve pathways as well as spinal cord lesions producing motor and sensory disturbances have been reported. Latent symptoms of iodomethane intoxication include psychological disorders such as depression. In addition to neurological effects, iodomethane exposure has also been linked to congestive changes in the lungs and oliguric renal failure. It is noteworthy, however, that in most of these incidents the precise iodomethane exposure concentration is unknown though it appears that exposure was to high levels (due in part to use of inadequate protective devices) resulting from industrial uses and far exceeding those proposed for regulatory purposes in this risk assessment or anticipated agricultural uses. For further details, please refer to additional discussion of these incidents in Attachment B.

An updated literature search on May 30, 2007 for iodomethane poisoning produced only one additional case report. [Schwartz MD, et al. Acute methyl iodine exposure with delayed neuropsychiatric sequelae: report of a case. Am J Ind. Med. 2005 Jun; 47(6): 550-61 that found: "The case patient experienced a massive exposure to methyl iodide with resulting life-threatening burns. During convalescence, various cognitive and behavioral deficits became apparent."

The authors recommend that a comprehensive evaluation at an occupational toxicology clinic include sequential neuropsychometric testing, if iodomethane poisoning is suspected. This incident occurred during the manufacturing process but it is not clear if the material was destined for pesticide use. It also appears to have been caused by a breech in the protective clothing the individual was wearing.

Pages 27-28 under *Human Toxicity Case Reports (p. 101-103)*:
In this section 5 incidents were discussed by DPR but each of the discussions lacked pertinent case elements. Also, in each case the incidents did not occur in an agricultural setting analogous to what would be expected with soil fumigant use and it was not possible to ascertain what, if any, appropriate risk mitigation elements were in use at the time the exposures occurred. The current iodomethane labels require extensive levels of personal protective measures and equipment. [Note: One of the 5 cases was an intentional suicide attempt where a 19 year old injected himself with iodomethane.] In the first incident (Garland and Camps, 1945) it would be highly unlikely that given the occupational health standards of the era that any comparable level of risk mitigation would have been required for the exposed individual compared to modern standards. It is clear that this individual had extremely high urinary output of iodine (i.e., 9 mg/100mL) compared to the median value reported in the NHANES 2000 of 16.1 μg/deciliter (see http://www.cdc.gov/nchs/products/pubs/pubd/hestats/iodine.htm) but it is not clear if there were other confounding health conditions which could have contributed. It is also not clear what the tasks were for this individual at the manufacturing facility or what the associated processes were that could have contributed to his exposures. Without this

information, it is not clear how this case would relate to a highly prescribed use of iodomethane in agriculture given all of the inherent risk mitigation requirements such as techniques which can significantly reduce emissions (e.g., high barrier film use), The second incident (Appel et al, 1975) was a similar circumstance. A chemist was exposed while attempting to synthesize iodomethane. The same conclusions apply as described for the interpretation of the Garland and Camps (1 945) case. Similarly, the third case (Hermouet et al, 1996) involved 2 workers who were exposed during production in an industrial facility. Like the first 2 incidents noted above the results are equivocal with regard to how this provides useful information for mitigating worker risks associated with use as a fumigant. The fourth incident which was reported (Knudsen and Nielsen, 1999) involved an accidental spill by a worker onto his fingers and hands. Like the other incidents noted above, the results of this incident are equivocal when evaluating use as a fumigant except to indicate that skin effects were noted as would be expected from a direct exposure of substantive skin loading levels as noted in the current Agency assessments. For this reason, the Agency has required extensive health and safety risk management requirements when working around pressurized elements of the application systems for iodomethane in an attempt to alleviate further like exposures from occurring.

DPR Response: These comments refer to the presentation of human studies in the Toxicology Profile section which included studies conducted using laboratory animals and humans. As stated in the introduction of this section, the purpose was to describe the entire toxicological database of MeI. While these studies may not be appropriate for setting regulatory limits, they provide information for hazard identification.

<u>Comment #4. Genotoxicity</u>

Page 11 under *Genotoxicity (p. 68-73)*
The only evidence of genotoxicity observed in the guideline studies submitted to the Agency is an induction of structural chromosome aberrations (clastogenesis).

DPR Response: From all available genotoxicity studies, DPR concluded that there was positive evidence for genotoxicity based not only from chromosomal aberration, but also increased gene mutation and DNA alkylation. This conclusion is consistent with the statement in the USEPA Cancer Assessment Review Committee report, which states that "...iodomethane has been shown to be mutagenic primarily in *in vitro* studies and produced DNA adducts in one study in rats..." (page 4; USEPA, 2005d).

Comment #5. Human Toxicity Case Report for PBPK Modeling

Pages 12-13 under *Human Toxicity Case Reports (p. 101-103)*:
Finally, CDPR used an intentional exposure case, where an individual intravenously (IV) injected iodomethane as part of an attempted suicide, to help test the human model in PBPK modeling of acute exposure. This study was not considered by the Agency as IV injection would have a significant impact on the adsorption, distribution, metabolism, and excretion of the compound. Given the potential impact of this unrealistic exposure scenario (for bystanders and workers) on the kinetics, the Agency does not consider this study appropriate to help test the human PBPK model.

Pages 27-28 under *Human Toxicity Case Reports (p. 101-103)*:
In the final incident (Robertz-Vaupel et al, 1991) a 19 year old male attempted suicide via intravenous injection of iodomethane. Clearly this event does not reflect possible exposure patterns from soil fumigant use but it could possibly be used to compare effects with a dose. In fact, DPR indicated that the data from this study was used to test the Agency's PBPK modeling approach. There was no mention about possible ethical concerns with the use of this study for these purposes. The Agency was not aware of this incident and its use for this purpose by DPR. The Agency will investigate this further in its comments on the hazard assessment noted above in Attachment A.

DPR Response: DPR did not use this study to test the Arysta's or USEPA's (as noted in this comment) PBPK modeling approach. This study was used by Arysta scientists to test the PBPK model (Sweeney et al., 2009).

Comment #6. Use of different methodology to derive human equivalent concentrations

Page 5 under *Summary p. 2-8*:
The differences in the points of departure used for the subchronic and chronic risk calculations also reflect the differences in the methodologies used by CDPR and USEPA to calculate HECs and exposures (i.e., body burden instead of a route-specific approach). While CDPR's calculations to estimate the inhalation risk to humans are based on different breathing rates for different life stages, the Agency's calculations are dependent on the regional gas dose ratio (RGDR). In the case of systemic effects, the RGDR is defined as the ratio of the b1ood:gas partition coefficient of the chemical for the test species to humans ($H_{b/g\ animal}/H_{b/g\ human}$). When this ratio is unknown or when the $H_{b/g\ animal} > H_{b/g\ human}$ a default value of 1.0 is used as the RGDR. This default is based on the observation that for chemicals where partition coefficient data are available in both rats and humans the RGDR value has usually been comparable or slightly higher than 1. Thus, the use of an RGDR of 1 results in a protective calculation of the inhalation risk. CDPR's methodology assumes that the more of the compound

that is inhaled the more of it enters the blood stream or deposits in the respiratory tract. This does not take into account the anatomical and physiological differences between test species and humans. The RfC methodology developed by the US EPA Office of Research and Development offers a more refined methodology that, based on the PBPK ventilation-perfusion model concept (e.g., Ramsey and Andersen, 1984), use algebraic equations to relate organ and tissue compartment concentrations to exposure concentrations. The procedure assumes that the toxic effects observed are related to the arterial blood concentration (concentration leaving lung compartment in the model) of the inhaled compound and that $NOAEL_{HEC}$ should be such that the human time-integrated arterial blood concentration is less than or equal to that of the exposed laboratory animal. Given that the ability for arterial blood to carry compounds from the lung compartment does not significantly vary with age, the Agency does not calculate different HECs for different life stages but rather calculates different HECs based on duration of exposure.

DPR Response: The differences between USEPA and DPR RfC methodology are already discussed in Appendix C of the Volume I. There are assumptions and uncertainties associated with both methodologies.

<u>Comment #7. Use of absorbed dose to calculate risk</u>

Page 3 under General Comments:
Another difference is that CDPR calculated dose levels using a body burden approach from inhalation studies (i.e., represented in mg/kg/day). Typically, the Agency does not do that for fumigant risk assessments where adequate inhalation data are available and prefers to use an inhalation route-specific approach based on the use of HECs. In general, this extrapolation is not considered appropriate or needed since it does not take into consideration the kinetic differences inherent to different routes of exposure.

Page 22 under *Vol II. Exposure Assessment/Section D. Estimation of Absorbed Dose (p. 38-43)*:
On these pages a series of absorbed dose estimates were presented for adults, children, and infants using varied breathing rates, durations of exposure, and body weights. The Agency does not believe that the use of a body burden approach is appropriate since Human Equivalent Concentrations (HECs) can be calculated using the available hazard information and pharmacokinetics model. Iodomethane is also highly volatile and the exposures of concern are via inhalation which have been quantified using monitoring data or empirically based modeling. Because of these factors, an inhalation route-specific calculation of risk based on comparing exposure concentrations to HECs is believed to be the most applicable metric. This is also consistent with longstanding Agency guidance for using route-specific metrics as a preferred approach (e.g., 1992 EPA Exposure Assessment Guidelines).

DPR Response: In the DPR exposure assessment (Volume II), human exposures are expressed both in term of air concentration and absorbed dose. The risk assessor determines the appropriate term to use. For MeI, the DPR non-cancer risk calculations are all based on air concentrations, not absorbed doses.

Comment #8. Fetal Death - Dose metrics and parameters used in PBPK model for Acute Toxicity

Page 4 under *Summary (p. 2-8)*:
In addition to selecting...CDPR also used a different dose metric from the Agency to calculate the HEC for this endpoint using the iodomethane PBPK model. Since the perturbations of fetal thyroid function lead to the fetal losses observed in the study, the Agency used the area under the curve for fetal plasma iodide as the dose metric for calculating HECs. The Agency considers this to be an appropriate dose metric as it is more representative of the conditions leading to the effect of concern. CDPR, however, selected the maternal plasma iodide concentration (area under the curve [AUC]) as the dose metric.

Page 9 under *Rat Inhalation (p. 28-30; Himmelstein, 2004)*
In the study conducted to generate data for the PBPK model, male Sprague Dawley rats were exposed to 0, 25, or 100 ppm iodomethane via the inhalation route for either one or two consecutive days... Other effects noted by CDPR in this study included a 19% increase in cholesterol and LDL levels. These effects were not considered sufficiently robust to be toxicologically relevant by the Agency particularly in light of the observation that they are accompanied by a 20% increase in HDL and a 30% decrease in triglycerides. It should be noted that this study was not intended to be used to establish NOAELs/LOAELs but rather to provide data for parameterization of the PBPK model.

Page 14 under *Risk Assessment-Acute Inhalation Toxicity-Fetal Death (p. 114-117)*:
Unlike the Agency which considered the fetal death endpoint to be the outcome of perturbation of fetal thyroid function, CDPR states that "convincing evidence is lacking for supporting this MOA as the sole or immediate MOA for the endpoint, and thus additional dose metrics need to be considered." The Agency does not concur with this statement. Given the remarkable concordance between the timing of fetal death, occurring only between GD 23-26, and ontogeny of fetal thyroid function (GD22), and the known impact of the Wolff-Chaikoff effect on fetal viability, it is unclear why cholesterol levels or GSH depletion would be considered as plausible MOA. Cholesterol perturbations and GSH depletion have not been demonstrated to have such a narrow window of sensitivity during development. The data accounting for the potential impact of cholesterol levels on fetal viability come from a series of studies where animals

received injections of plasma triglyceride clearance blockers prior to insemination. While cholesterol levels were indeed affected by this treatment, it is unclear what other effects this treatment may have had on pregnancy outcomes.

DPR Response: This comment noted the difference between USEPA and DPR on the MOA for fetal death. USEPA considered perturbation of fetal thyroid function by iodide as the only MOA while DPR considered other possible MOAs as stated in the draft Volume I.

Comment #9. Nasal Effect - Dose metrics and parameters used in PBPK model for Acute Toxicity

Pages 4-5 under *Summary- Toxicology Profile and Hazard Identification (p. 2-8)*
Although the Agency had originally selected 25% GSH depletion as the dose metric for its risk assessment, in the most recent risk assessment, the Agency selected 50% GSH depletion as the dose metric. This change is due to the additional refinement in the PBPK model which allow Agency scientists to calculate GSH depletion in distinct layers of the olfactory epithelium thus ensuring that no single layer has more than 50% GSH depletion commonly cited in the literature as critical for development of nasal histopathology. Moreover, the model describes GSH depletion resulting from conjugation of iodomethane, metabolic consumption, synthesis, and degradation in each of the four top layers. It does not, however, fully account for the impact of GSH diffusion across layers thus potentially overestimating the extent of GSH depletion in each of the top layers. It should be noted that the emission profile of iodomethane suggests that during peak emission GSH depletion is likely lower than 50% (e.g. 38%).

Page 9 under *Rat Inhalation (p. 28-30; Himmelstein, 2004)*
In the study conducted to generate data for the PBPK model, male Sprague Dawley rats were exposed to 0, 25, or 100 ppm iodomethane via the inhalation route for either one or two consecutive days. At 25 ppm, 13-44% GSH depletion was observed in the olfactory epithelium. CDPR has selected 25% GSH depletion in the olfactory epithelium to parameterize the model. Given that exposure to 21 ppm for up to 90 days did not elicit an adverse effect on the olfactory epithelium (i.e., NOAEL = 21 ppm), it is unclear why a 25% dose metric was selected for the PBPK model as opposed to the 50% used by the Agency. Presumably a longer duration of exposure at a concentration comparable to what was used in this study would result in a comparable or higher level of GSH depletion yet no effects were seen after this prolonged exposure. This suggests that use of 50% GSH depletion as the dose metric for olfactory epithelium degeneration would not underestimate risks; consistent with the level of GSH depletion commonly cited in the literature as critical for development of nasal histopathology. Based on this information, it seems that the use of 25% as a dose metric is overly conservative and punitive.

Page 14 under *Risk Assessment – Acute Inhalation Toxicity- Nasal Effects (p. 128-130)*:
Both the Agency and CDPR considered GSH depletion as a plausible MOA for this endpoint the differences in the HECs derived by these regulatory bodies reflects the differences in the parameterization of the PBPK model.

DPR Response: It should be noted that the Himmelstein study (2004) did not include a histological examination of the nasal tissues. Thus, as stated in the Volume I (p. 130 of March draft), three MeI datasets were used to bridge the observation of histopathological tissue damage at 100 ppm and GSH depletion (Reed *et al.*, 1995; Chamberlain *et al*., 1998a; and Himmelstein, 2004). At the NOEL of 21 ppm, the estimated GSH depletion is less than 35%, with 25% as a reasonable limit to be associated with no effects after MeI exposure.

The comments regarding repeated versus single exposure is moot since the model demonstrated GSH recovery before the next day's 6-hour exposure in rats. Thus, the GSH depletion threshold should not be increased to accommodate the frequency of exposure.

<u>Comment #10. Neurotoxicity - Dose metrics and parameters used in PBPK model for Acute Toxicity</u>

Page 5 under *Summary-Toxicology Profile and Hazard Identification (p. 2)*:
While the Agency used steady state to parameterize the PBPK model and calculate HECS, the CDPR used brain iodomethane AUC concentrations as the dose metric. The principle of periodic steady state (i.e., periodicity) is embedded in the Agency's RfC methodology which would have been used as a default to calculate HECs if a PBPK had not been available. Periodicity state is achieved if the concentrations of the inhaled compound within the animal achieved periodicity with respect to time (i.e., periodic steady state-the concentration versus time profile is the same for every time point). Practically, the conditions of periodicity should be met during "most" of the exposure duration. For example, if this condition is met for 90% of the time (e.g., periodic during the last 90 weeks of a 100 week experiment), then estimates of average concentrations will be in error by less than 10% . Given that iodomethane reaches steady state after 30 minutes of a 6 hour exposure, the Agency is confident that the use of steady state is appropriate.

Page 14 under *Risk Assessment-Acute Inhalation Toxicity- Neurotoxicity Effects (p.13)*:
CDPR used area under the curve to parameterize the PBPK model for neurotoxicity while the Agency used steady state. The principle of periodic steady state (i.e., periodicity) is embedded in the Agency's RfC methodology which would have been used as a default to calculate HECs if a PBPK had not been available. Periodicity state is achieved if the concentrations of the inhaled compound within the animal achieved periodicity with respect to time (i.e., periodic steady state-the concentration versus time profile is the

same for every time point). Practically, the conditions of periodicity should be met during "most" of the exposure duration. For example, if this condition is met for 90% of the time (e.g., periodic during the last 90 weeks of a 100 week experiment), then estimates of average concentrations will be in error by less than 10% . Given that iodomethane reaches steady state after 30 minutes of a 6 hour exposure, the Agency is confident that the use of steady state is appropriate.

DPR Response: The USEPA NCCT scientist, who performed the review of the DPR analysis of PBPK modeling, concurred with DPR's use of AUC to parameterize the PBPK model for neurotoxicity (Rodriguez, 2009).

Comment #11. Subchronic toxicity endpoint for risk characterization

Page 6 under *Summary- Toxicology Profile and Hazard Identification (p.3, Summary Table 1)*:
It is unclear to the Agency CDPR's rationale for selecting the endpoints of decreased pup weight/pup weight gain and delays in sexual maturation (i.e., delayed vaginal patency acquisition) to assess risks for adults. These are clearly effects related to exposure to the young since body weight decrements were not the most sensitive endpoints in any of the adult studies and onset of sexual maturation would occur prior to adulthood.

Page 11 under *Reproductive Toxicity- Rat – Inhalation (p. 75- 79; Nemec, 2002a)*:
CDPR established a parental NOEL of 20 ppm based on decreased body weight and degeneration of the olfactory epithelium at 50 ppm. Similarly, the Agency established a parental NOAEL of 20 ppm and a LOAEL of 50 ppm but based this LOAEL on numerous endpoints including decreases in body weigh/weight gains, changes in organ weights, gross pathology and histopathological findings. CDPR reproductive NOEL (20 ppm) is based on decreases in live litter size at 50 ppm. In contrast, the Agency established the reproductive NOAEL at 5 ppm with a LOAEL of 20 ppm based on delays in vaginal patency acquisition. The Agency considers delays in sexual maturation to be reproductive effects rather than developmental effects as they are effects in the reproductive tract. CDPR used this endpoint to establish the developmental NOAEL/LOAEL (5 ppm/20 ppm). The Agency established an offspring NOAEL of 5 ppm based on decreased pup weight/weight gain, and decreases in thymus weight. It also established a port-of-entry specific NOAEL of 20 ppm based on degeneration of the olfactory epithelium at 50 ppm (LOAEL).

DPR Response: These comments are concerned with the designation of reduced pup body weight and delays in sexual maturation, as a developmental, reproductive, or offspring effect. The USEPA apparently does not consider these endpoints as a result of adult exposure to MeI,

and thus are not applicable for the evaluation of adult risks. DPR believes otherwise because the pups were exposed to MeI in utero and as well as during lactation. Regulatory limits set for adult exposure would protect the pups against these effects. This approach is similar to that used to address developmental toxicity.

Comment #12. Determination of the carcinogenic mode of action

Page 7 under *Summary-Toxicology Profile and Hazard Identification (p. 2-3)*:
With regards to the carcinogenic potential of iodomethane, the CDPR risk characterization documents assume that humans are more sensitive to the oncogenicity potential of iodomethane than animals. The Agency does not concur with this conclusion. Both CDPR and US EPA considered the formation of thyroid tumors as the outcome of thyroid hormone perturbations and not a mutagenic effect. Chemicals that produce thyroid follicular cell tumors in rats by prolonged TSH stimulation are not likely to be carcinogenic to humans. Humans respond as do experimental animals to disturbances in thyroid function from various antithyroid stimuli such as iodide deficiency, partial thyroidectomy and goitrogenic chemicals: when circulating thyroid hormone levels go down, the TSH level rises which in turns lead to thyroid hypertrophy and hyperplasia (goiter). Cellular and biochemical studies, however, provide compelling evidence that **rats are substantially more sensitive than human to the development of thyroid follicular cell tumors in response to thyroid hormone imbalance** (IARC, 2001, Meek et al,, 2003, EPA, 1998; Dohler et al, 1979). There are a number of quantitative differences between rats and humans that explain this increased sensitivity. The rat has a much shorter thyroid hormone half-life than humans. The half-life of thyroxin (T4) is about 12 hours in rats compared to 5-9 days in human (Dohler et al., 1979). The longer half-life in humans is likely related to the presence of a high-affinity binding globulin for thyroxin that is absent in rats. In humans this binding of thyroid hormone to this globulin accounts for slower metabolic degradation and clearance, Additionally, there is a larger thyroid hormone reserve in the human compared to the rat. Increased turnover and hepatic clearance of thyroid hormone (T3, T4) result in the thyroid gland being more active in rats than in humans. The constitutive TSH levels are approximately 25 times higher in rats than in humans, reflecting the increased activity of the thyroid-pituitary axis in rats (Dohler et al, 1979 ; McClain 1992). Lastly, rats appear to be very susceptible to thyroid neoplasia secondary to thyroid hormone imbalance. Modest changes in thyroid hormone homeostasis may promote tumor formation in rats. In contrast, data in humans suggest that prolonged TSH stimulation of the thyroid gland poses a negligible risk of thyroid carcinogenesis [Curran and DeGroot, 1991). Studies of individuals with hyperthyroidism (patients with Graves Disease, goiters) indicate the occurrence of thyroid caner is rare [e.g,, Mazzaferri, 2000; Gabriele et al., 2003). Also, a study of environmental and heritable causes of cancer among 9.6 million individuals using the

Nationwide Swedish Family-Cancer Database found that the environment did not appear to play a principal causative role in thyroid cancers (Czene et al., 2002). The only known human thyroid carcinogen is x-irradiation.

Page 11 under *Toxicology Profile - Mouse – Oral (p. 59-63)*:
Although the Agency did not conduct an oral risk assessment and a NOAEL was not established for this study, it was considered as part of the weight-of-evidence analysis during the cancer determination. Only the thyroid tumors were considered treatment related by the Agency while the uterine and cervical were not considered related to iodomethane exposure. This is in contrast to CDPR's evaluation which considered that the cervical fibromas may be treatment-related.

Page 15 under *Risk Assessment- Thyroid tumors (p. 134)*:
The Agency has classified iodomethane as "not likely to be carcinogenic to humans at doses that do not later rat thyroid hormone homeostasis." The CDPR risk characterization documents, however, assume that humans are more sensitive to the oncogenicity potential of iodomethane than animals. This is based on a number of studies cited by CDPR. It should be noted that the results of these studies have not been borne out by more recent cellular and biochemical studies which provide **compelling evidence that rats are substantially more sensitive than humans to the development of thyroid follicular cell tumors in response to thyroid hormone imbalance** (IARC, 2001, Meek et al., 2003, EPA,1998; Dohler et al., 1979). The interpretation used by the Agency is consistent with the interpretation used by the International Agency for Research on Cancer (IARC) [*Species Differences in Thyroid Kidney and Urinary Bladder Carcinogenesis*. IARC Scientific Publications No. 147]

DPR Response: DPR did not make a determination of whether mutagenicity was involved in the March 2009 draft. In the revised Volume I, DPR considered the oncogenic risk by non-mutagenic and mutagenic MOAs.

As for species difference, it would have been helpful if USEPA explained how the studies cited by DPR were not “borne out” by more recent cellular and biochemical studies for which USEPA cited reviews essentially based on the data of Dohler et al., 1979. It is unclear how, in the context of species comparison, the cited epidemiological reports can be useful to resolve the issue at hand.

<u>Comment #13. Requirement for a developmental neurotoxicity study</u>

Page 8 under *Summary Risk Appraisal (p. 6-7)*:
CDPR (on page 101) states that a DNT was not required by the Agency because "is not

being required by the USEPA because Me1 is considered a non-food use and, therefore, not subjected to Food Quality Protection Act considerations (USEPA, 2006A)." This is not an accurate representation of the Agency's rationale for not requiring a DNT. Like iodomethane, a number of pesticide chemicals have been shown to perturb thyroid hormone homeostasis via reduction of circulating thyroid hormones (Hurley et al., 1998). Chemicals that perturb thyroid homeostasis and result in hypothyroidism are known to be associated with neurological disorders and alterations in neurological development, both in animals and humans (Fisher, 2000; Chan and Kilby, 2000; Morreale de Escobar et al., 2000; Zoeller and Rovet, 2004; Anderson et al., 2003). Thus, in the assessment of the toxic characteristics of a thyroid disrupting pesticide, determination of the potential to adversely impact thyroid hormones, thyroid structure, and/or thyroid hormone homeostasis during development is important. Normally, if a neurodevelopmental concern is raised by existing data on a pesticide, a rat developmental neurotoxicity (DNT) study is requested. However, disruption of thyroid homeostasis by thyroid disrupting pesticides is the initial, critical effect that may lead to adverse effects on the developing nervous system. Thus, in lieu of the rat DNT study, a study that entails a mechanistic approach to generate specific data on the thyroid (i. e., the primary target of the chemical of interest) to protect the developing nervous system from thyroid hormone disrupting chemicals is typically required by the Agency. The specific purpose of this study is to generate data to establish NOAELs and LOAELs (or benchmark doses) that may be used to derive RfCs that would be protective of the ability of a chemical to disrupt thyroid function in pregnant females and in the fetus and newborn. In the case of iodomethane, a study evaluating the impact of iodomethane exposure on both pregnant females and their offspring is available in the most sensitive species - the rabbit. Thus, the need for the DNT is obviated by the availability of these data. Measures of thyroid hormone status in both the pregnant female and her offspring are known to be more sensitive than the apical measures that are evaluated in the DNT. Moreover, the DNT is conducted in the rat; a species that is not as susceptible to iodomethane exposure as the rabbit.

Page 12 under *Neurotoxicity (p. 101)*:
CDPR states that the Agency did not require a developmental neurotoxicity (DNT) study because "MeI is considered a non-food use and, therefore, not subjected to Food Quality Protection Act considerations." This does not completely reflect the Agency's rationale for not requesting a DNT. Typically, if a neurodevelopmental concern is raised by existing data on a pesticide, a rat developmental neurotoxicity (DNT) study is requested. However, disruption of thyroid homeostasis by thyroid disrupting pesticides is the initial, critical effect that may lead to adverse effects on the developing nervous system. Thus, in lieu of the rat DNT study, a study that entails a mechanistic approach to generate specific data on the thyroid (i.e., the primary target of the chemical of interest) to protect the developing nervous system from thyroid hormone disrupting chemicals is required by the Agency. Since the iodomethane database contains numerous studies assessing the impact of iodomethane exposure on thyroid hormone

homeostasis at different life stages, neither a DNT nor a special thyroid hormone study was required.

DPR Response: The quoted statement about DNT study requirement was the DPR interpretation of the USEPA position that MeI is not subject to the amendments to the Federal Food, Drug, and Cosmetic Act (FFDCA) promulgated under the Food Quality Protection Act (FQPA) of 1996 (USEPA, 2006a and 2007). This statement will be revised to indicate that a DNT study is not available and was not part of the registration database submitted to USEPA. DPR considers the current database insufficient to provide a thorough examination of developmental neurotoxcity as discussed in the draft Volume I. Since the rabbit developmental toxicity study terminated on GD29, the question regarding the neurodevelopmental health of the surviving fetuses after exposure to MeI, a known antithyroid compound, is of great concern.

Comment #14. Postnatal effect on nasal tissue

Pages 15-17 under *Risk Appraisal - Hazard Identification (p.146)*:
CDPR states that additional data, including a DNT and studies evaluating postnatal effects of Me1 on nasal tissues, are needed for iodomethane. The Agency does not share CDPR's opinion. Using the RfC methodology and the PBPK model for iodomethane, the HECs calculated and used in the Agency's risk assessment are not expected to underestimate risks to children. In fact comparison of the HEC derived for adults and children for nasal toxicity showed that levels of GSH depletion in adults and children were comparable at the same dose level, as seen below:

Adult Worker
PREGHUM,
WOE=O.OOB, WOX=0,08
CONC = 5.8
T 8.00000 GSHL 5.42681 GSHK 1.33688
CGSHDR 0.551752 CGSHEO 0.768624 CGSHDO 0.743 1 54
CGSHWRl 0.553692 CGSHWW 0.562702 CA_I 3.30147e+006
CA 0.117731
GSDOE11 = 0.2723 GSDOE21 = 0.3771 GSDOE3 1 = 0.45 10 GSDOE41 = 0.4980
GSDOEXl = 0.7689 CGSHD02 = 0.3996
%GSH Depletion
GSDOE11 = 66 GSDOE21 = 53 GSDOE31 = 44 GSDOE41 = 38
CGSHDO2 = 50%

Child Bystander Comparisons (4.5 ppm 24 hr exposure simulations)
MALEHUM

WOE=0.006, WOX=0.05 (for 3mth, 1 & 5 yr) or WOX=0.08 (for 10 & 15 yr)
CONC=4.5

<u>3 mth child</u>
T 24 GSHL 5.1064 GSHK 1.3032
CGSHDR 0.5588 CGSHEO 0.8000 CGSHDO 0.7477
CGSHWRl 0.5593 CGSHWR2 0.56 18 CA_I 9.4068+006
CA 0.0948
GSDOE1 I = 0.2876 GSDOE21= 0.3981 GSDOE31= 0.4791 GSDOE41 = 0.5355
GSDOEXl = 0.7865 CGSHD02 = 0.4251
%GSH Depletion
GSDOEll= 64 GSDOE21= 50 GSDOE3 1 = 40 GSDOE41= 33
CGSHD02 = 47%

<u>1 yr child</u>
T 24.0000 GSHL 5.03781 GSHK 1.31168
CGSHDR 0.557384 CGSHEO 0.799990 CGSHDO 0.747545
CGSHWRl 0.557874 CGSHWR2 0.560422 CA_I 1.16541e+007
CA 0.0979790
GSDOE11 = 0.2856 GSDOE21 = 0.3965 GSDOE3 1 = 0.4779 GSDOE4 1 = 0.5345
GSDOEXl = 0.7864 CGSHD02 = 0.4236
%GSH Depletion
GSDOEl 1 = 64 GSDOE21= 50 GSDOE31= 40 GSDOWl= 33
CGSHD02 = 47%

<u>5 vr child</u>
T 24.0000 GSHL 5.20766 GSHK 1.32843
CGSHDR 0.557270 CGSHEO 0.799993 CGSHDO 0.76693 8
CGSHWRl 0.557822 CGSHWR2 0.561 179 CA_I 9.3 1576e+006
CA 0.0948048
GSDOE 1 1 = 0.2797 GSDOE21= 0.385 1 GSDOE3 1 = 0.4600 GSDOE41 = 0.5088
GSDOEXI = 0.793 8 CGSHD02 = 0.4084
GSDOEll= 65 GSDOE21= 52 GSDOE3 1 = 43 GSDOE41= 36
CGSHD02 = 49%

10 yr child
T 24.0000 GSHL 5.25861 GSHK 1.33699
CGSHDR 0.557024 CGSHEO 0.799993 CGSHDO 0.766947
CGSHWRl 0.557594 CGSHWR2 0.561 161 CA_I 8.81614e+006
CA 0.0986206
GSDOE11 = 0.2799 GSDOE2 1 = 0.3 852 GSDOE3 1 = 0.4601 GSDOE41= 0.5089

GSDOEX1 = 0.7938 CGSHD02 = 0.4085
%GSH Depletion
GSDOEl 1 = 65 GSDOE2 1 = 52 GSDOE3 1 = 42 GSDOE41= 36
CGSHDQ2 = 49%

15 yr child
T 24.0000 GSHL 5.39194 GSHK 1.34752
CGSHDR 0.559037 CGSHEO 0.799993 CGSHDO 0.767123
CGSHWRl 0.559618 CGSHWR2 0.563101 CA_I 6.05452e+006
CA 0.0943949
GSDOE11= 0.2827 GSDOE21= 0.3874 GSDOE31= 0.4619 GSDOE41 = 0.5104
GSDOEXl = 0.7939 CGSHD02 = 0.4106
%GSH Depletion
GSDOEl 1 = 65 GSDOE21= 52 GSDOE31= 42 GSDQE41= 36
CGSHD02 = 49%

DPR Response: The cited statements will exclude the concern about postnatal nasal effect.

<u>Comment #15. Uncertainty factors used in risk assessment</u>

Pages 7-8 under *Summary- Risk Appraisal (p. 6-7)*:
CDPR has concluded that the "benchmark"' MOE for iodomethane should be 300 instead of the conventional 30 that is used when points of departure for inhalation risk assessments are expressed in terms of HECs. CDPR states that an additional 10X factor is needed to assess "the concerns about the serious and irreversible nature of neurodevelopmental effects that have not been studied, the post-natal mortality from excess iodide that needs further study in the context of iodomethane exposure, and the level of excess iodide in Me1 being added to the background iodide intake."

Page 17 under *Risk Appraisal- Additional Uncertainty Factor (p. 152)*:
The Agency does not consider that an additional uncertainty factor is warranted based on the extensive mechanistic and toxicological data available for iodomethane. The Agency is confident data available and used for the risk assessment afford an adequate level of protection.

DPR Response: As stated in the Volume I, DPR does not believe that the existing database provides sufficient information regarding the cited concerns.

<u>Comment #16. Excess iodide</u>

Page 17 under *Risk Appraisal- Health-based standards (p. 149)*:
CDPR expresses a concern for the addition of iodide exposure due to Me1 use to the background iodide exposure levels. It should be noted that the Agency does not concur with these concerns as they are based on a point of departure lower than the one used by the Agency. Furthermore, the RfCs used to compare to the health based standards were calculated using a dose metric that is not consistent with the parameterization used by the Agency.

Page 28 under *V.C.3 Cumulative Toxicity (p. 149-152)*:
DPR indicates in this section of the document that they are concerned with "an additional iodide body burden from the conversion of Me1 to iodide in the body after Me1 exposure." In order to demonstrate this concern a series of current health criteria (Table 70, page 150) were presented which represent different types of recommendations for daily intake of iodide in the diet and as a limit from food additives in the diet. One limit presented was the Tolerable Upper Intake Level (UL) based on a National Academy of Sciences (2000) evaluation which indicated this level is "likely to pose no risk of adverse effect to almost all individuals in the general population." DPR then compared these values to a body burden estimate of exposure which was calculated using their proposed RfC values for each endpoint of concern (i.e., developmental toxicity, neurotoxicity, and nasal lesion formation). The body burden estimates were calculated by adjusting the RfCs by standard daily breathing volumes (i.e., the 1997 U.S. EPA Exposure Factors Handbook was cited), accounting for the amount of iodide per molecule of iodomethane and the assumption that 100 percent of the iodide inhaled as iodomethane over the course of a day would be retained and absorbed. This is highly unlikely given the physical-chemical properties of iodomethane and its demonstrated pharmacokinetics.

DPR Response: The revised draft will add the consideration of iodide intake from 75% of absorption and retention from MeI inhalation exposure. Morgan and Morgan (1967) calculated a range of 53 to 92% retention of inhaled MeI in adults. There is no information for children.

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.

Nemec, M.D., 2002d. An inhalation prenatal developmental toxicity study of iodomethane in rabbits. Study No. WIL-418002, WIL Research Laboratories. DPR Vol. 52875-018 #185693.

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.

Rodriguez, C., 2009. Memorandum to E. Mendez on "Iodomethane: Review of PBPK modeling changes made by California Environmental Protection Agency Department of Pesticide Regulation." United State Environmental Protection Agency, National Center for Computational Toxicology. Research Triangle Park, NC. May 29, 2009.

Sweeney, L.M., C.R. Kirman, S.A. Gannon, K.D. Thrall, M.L. Gargas, and J.H. Kinzell, 2009. Development of a physiologically based pharmacokinetic (PBPK) model for methyl iodide in rats, rabbits, and humans. Inhal. Toxicol. 21(6):552-582.

USEPA, 2005d. Iodomethane: Report of the Cancer Assessment Review Committee PC Code:000011. Memorandum from Jessica Kidwell to Elizabeth Mendez, November 10, 2005. Office of Prevention, Pesticides, and Toxic Substances. US Environmental Protection Agency, Washington DC.

Department of Pesticide Regulation

Mary-Ann Warmerdam
Director

Arnold Schwarzenegger
Governor

MEMORANDUM

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: Responses to U.S. Environmental Protection Agency Comments on "IODOMETHANE: Review of PBPK modeling changes made by California Environmental Protection Agency Department of Pesticide Regulation"

Below are my responses to comments from the U.S. Environmental Protection Agency (USEPA; May 29, 2009) on *IODOMETHANE: Review of PBPK modeling changes made by California Environmental Protection Agency Department of Pesticide Regulation.*

DPR appreciates USEPA's effort in the side-by-side and additional model iterations. In many ways, these model runs strengthened DPR's model review, parameter choices, and HEC determinations.

I. HEC for rabbit fetal death endpoint

The USEPA simulations that demonstrated the closer fit to the maternal serum iodide profile with DPR's choice of 20 L-hr/kg$^{3/4}$ strengthened and confirmed DPR's 24-hr HEC at 0.24 ppm.

The simulation at 20 L-hr/kg$^{3/4}$ QAC was helpful for DPR's F/M discussion. Similar data were provided by Arysta in response to DPR's March 2009 review. Both confirmed DPR's view that model calibration for a better fit was beyond the change of QAC, even with DPR's effort to apply correct physiological considerations that resulted in a better model fit for the maternal serum iodide dose metric used for DPR's HEC.

The USEPA's side-by-side simulations based on fetal serum iodide dose metric resulted in a slightly higher HEC than provided by Arysta (1.5 versus 1.3 ppm). This comparison was useful but did not impact DPR's final HEC because this dose metric was not used as the basis for our HEC.

The issue of which model parameter should be used to account for worker's higher breathing rate was interesting. While Arysta's adjustment was made through increasing the TVol parameter, USEPA indicated that the adjustment should be made on QAC. Unfortunately, no further discussion on this issue was given for reconciling the difference.

The side-by-side simulation using Arysta's adjusted TVol but extended over 96 hours was very useful for completing the modeling presentation and the resultant 8-hr HEC was added to DPR's review. However, since it did not include the additional 16-hour exposure as a general public for workers during the "off work" hours, this HEC is not used to modify DPR's worker HEC.

Incidentally, the comments mentioned that the human resting 16.4 L-hr/kg$^{3/4}$ QAC was erroneously cited by DPR as 16.5 L-hr/kg$^{3/4}$. However, DPR correctly reported this value from the model files provided by Arysta. Apparently the source of difference resided in the model input between USEPA and Arysta, not a mistake by DPR.

II. HEC for rat nasal endpoint

USEPA did not find any issue of difference in their side-by-side simulation of HECs based on DPR's 25% GSH depletion and DPR's presentation of Arysta's results. This affirmed DPR's modeled HECs.

III. HEC for neurotoxicity endpoint

DPR appreciates USEPA's affirmation of DPR's choice of dose metric; i.e., the AUC instead of peak MeI in the brain. This resulted in an approximately 3-fold lower HEC compared to USEPA's HEC.

DPR appreciates the analysis that confirmed our observation regarding the higher model output of rat brain MeI by Arysta than by USEPA. The USEPA's simulated 24-hour HEC of 2.8 ppm was added to the DPR's revised document. However, since the reason for the difference remained unidentified, and the limited difference, DPR's HEC of 3.4 ppm was not modified. This affirmed DPR's approach to interpolate model output when simulation was not provided by Arysta.

The USEPA simulation that showed a lower brain MeI concentration than the model output from Arysta is appreciated for completing the modeling picture. The contrasting 8-hour HEC of 7.5 ppm to the Arysta's HEC of 9.7 ppm was added to DPR's review. However, since the USEPA HEC did not include the additional 16-hour exposure as a general public for workers during the "off work" hours, this HEC is not used to modify DPR's worker HEC.

Mary-Ann Warmerdam
Director

Department of Pesticide Regulation

Arnold Schwarzenegger
Governor

M E M O R A N D U M

TO: Joseph P. Frank, DSc
Senior Toxicologist
Worker Health and Safety Branch
(916) 324-3517

FROM: Roger C. Cochran, PhD, D.A.B.T. *(original signed by R. Cochran)*
Staff Toxicologist (Specialist)
(916) 324-3516

DATE: August 3, 2009

SUBJECT: RESPONSE TO U.S. ENVIRONMENTAL PROTECTION AGENCY'S COMMENTS OF THE EXPOSURE ASSESSMENT DOCUMENT FOR METHYL IODIDE (HS 1866)

The U.S. Environmental Protection Agency (U.S. EPA) sent comments on the Methyl Iodide (MeI) Exposure Assessment Document (EAD) on June 4, 2009. U.S. EPA's comments are given first in darker print, with the response to the comments immediately following.

U.S. EPA: It was indicated that a buffer distance of 152 meters was used for a series of calculations but no justification was provided for this distance. Seasonal and amortized annual exposures were also estimated for individuals spending 100 percent of their time at this distance while being exposed which is also unlikely given the mobility of the vast majority of the population.

Worker Health and Safety Branch (WHS): As explained in the Abstract, the buffer zone (152 meters) is a requirement stated on the U.S. EPA-approved label. Department of Pesticide Regulation (DPR) calculates exposure based on the requirements on the U.S. EPA-approved label.

A more complete explanation of the rationale for estimating seasonal and annual exposures is given in the body of the document. *"As methyl iodide is not registered in California, no ambient air monitoring for methyl iodide has been conducted. Nonetheless, it is likely that the use of methyl iodide as a pre-plant, soil fumigant will lead to community-wide exposures. Such exposures are likely to eventually emulate those of the current pre-plant, soil fumigant, methyl bromide. However, application site exposures of residents to fumigants near treated fields, acute and repetitive, are expected to be higher than those experienced by people living in nearby communities.*

The estimated seasonal application site air concentration of methyl iodide, as stated earlier, was 0.07 µg/L. Ambient air data on methyl bromide [MeBr]concentrations was derived from Air Resources Board (ARB) monitoring studies conducted in 2000 (Thongsinthusak and Haskell, 2002). The highest ARB-measured community air concentration for a single day was 0.17 µg/L

of methyl bromide. The highest measured community 2-week average air concentration (seasonal) was 0.046 µg/L MeBr."

DPR recognized the likelihood of such repetitive exposures occurring at the edge of the buffer zone, and considered them representative, with further explanation in the Exposure Appraisal section (pp 47-48). As noted there, measurable air concentrations of MeI used in the 2-week average are only present for about 4 days. Seasonal exposure (assumed to be 3 months duration based on the methyl bromide experience) was amortized (3/12) over the full year. At the request of Medical Toxicology (MT) Branch, a lifetime average daily dose for applicators and bystanders has been added to the exposure assessment document. The uncertainties associated with a lifetime exposure have been commented on in the Appraisal section as well (p48).

U.S. EPA: Introduction (Page 1): It is indicated that every scenario will not be assessed but it is not clear what scenarios lack the appropriate data. Exposure assessments have only been completed by DPR using a standard tarp which indicates that more recent emissions data completed at lower application rates with barrier films that empirically illustrate dramatic reductions in iodomethane and chloropicrin emissions were not considered.

WHS: The activities listed in Table 1 were derived from DPR's experience with the application of methyl bromide as a pre-plant field fumigant. Table 2 lists the representative scenarios that are expected to have the same or greater exposures than other scenarios in the same categories. We have provided a better description of what Table 2 represents in the text leading up to that table.

Although U.S EPA includes mitigation measures during the process of the development of a Registration Eligibility Document (RED), DPR does not consider mitigation measures until the Risk Assessment process has been completed, and a potential need for mitigation has been shown. Thus, in California, the two processes are separate. As the current U.S. EPA-registered labels only require only a generic tarp to be used, the emissions reductions by specialized tarps (not required by the label), or reduced application rates (also not required by the label) were not considered in generating the California exposure assessment.

U.S. EPA: Introduction (Table 1, page 2): A fumigation activity, under the "early entry handler" category, referred to as tarp removers and tarp remover drivers were included for the tarped raised bed and tarped drip irrigation scenarios. These scenarios are unlikely with this cultural practice because in the vast majority of circumstances the tarp is retained over the course of a growing season as a key element of the cultural practice.

WHS: We agree with U.S. EPA that tarp-removal from raised beds is an unlikely scenario as it is contrary to current agricultural practices. As noted above, the activities listed in Table 1 were derived from DPR's experience with the application of methyl bromide as a pre-plant field fumigant. These activities constitute the possible scenarios associated with preplant field

fumigation. Although tarp removal is usually not done following pre-plant field fumigation of raised beds, the MeBr experience indicated it did occur infrequently. Table 2 lists the representative scenarios that are expected to have the same or greater exposures than other scenarios in the same categories that are listed in Table 1. Tarp removal activities associated with flat field fumigant applications are expected to result in exposures equal to, or greater than any exposures associated with tarp removal from raised beds.

U.S. EPA: Introduction (Table 2, page 3): A number of representative scenarios are presented in the table provided with 3 being defined based on the depth of injection. It is not clear that this parameter is significant with regard to altered emissions for iodomethane because it is so volatile. As such, it is not clear that scenarios should be defined primarily based on this principle.

WHS: Only one scenario for shank-injection of MeI is presented in Table 2 as representative for all shank injections. There were no studies submitted involving deep-shank injection of MeI. As DPR is trying to capture the greatest, legally permissible exposures associated with the cultural practices used in pre-plant field fumigation, the experience with applicator exposures from deep and shallow-shank applications of MeBr was used as an indicator. It was stated in the text of the EAD (p 1), "Thus, the occupational exposures from shallow-shank injection of MeI will likely be at least as great, if not greater than, those for deep shank injection. Consequently, activities involving broadcast shallow shank injection will be used as representative of all shank injection activities." DPR is not using depth of injection as a significant parameter of exposure; rather it is an application method that we use to help define exposure scenarios. DPR attempts to define all possible exposure scenarios (Table 1), then based on a number of factors narrow that down to a few scenarios to calculate exposure.

U.S. EPA: Introduction/Section B. Federal Regulatory History (page 4): It is indicated a draft risk assessment was completed by the EPA in 2006 and a final assessment was completed in 2007. More accurately, the 2006 was a final risk assessment and the 2007 version was a revised risk assessment based on the availability of additional data and updated analytical methods. There is also no mention about the FIFRA Scientific Advisory Panel Review of the PERFUM air model (see http://www.epa.gov/scipoly/sap/meetings/2004/082404 mtg.htm for more details) or the evaluation of the RfC methodology.

WHS: The text of the EAD has been modified to make the references to U.S. EPA documents more accurate. The review of the PERFUM air model by the Science Advisory Panel is mentioned in Appendix III (p 74). The RfC methodology will be addressed by Medical Toxicology.

U.S. EPA: Introduction/Section B. Federal Regulatory History (page 5): It is indicated that an IRED was issued for iodomethane but this is not the case because iodomethane is not a

reregistration chemical.

WHS: The text of the EAD has been modified to make the references to U.S. EPA documents more accurate.

U.S. EPA: Introduction/Section D. Formulations (page 6): There is a discussion of the parameters which constitute a restricted use pesticide. It should be noted that the definitions of restricted use pesticides will be altered with regard to fumigants in the upcoming 2009 decisions and that the definition will be broadened.

WHS: Thank you for the information. When the new definitions have been published, they will be included and the references cited.

U.S. EPA: Exposure Assessment/Section A. Occupational Exposure Studies (pages 13-26): A description and summary of the study results for all of the available worker studies was included on these pages. The descriptions and summaries of the available worker exposure monitoring data are accurate. There were slight differences in how some adjustments were made based on the available quality control data.

WHS: It is DPR's policy to adjust exposure based on quality control data.

U.S. EPA: Exposure Assessment/Section A. Treatment of Study Data (pages 26-28): In this section an overview of the DPR use of the data is provided. According to the document, "'DPR has a policy of using an upper-bound of work-task exposure to represent potential acute exposures (Frank, 2009)." It was also indicated that results from the Manteca monitoring site were adjusted up by a factor of IO-fold because of the use of a fan by the applicators to mimic potentially higher exposures for those situations where they are not available. Workday durations were also assumed to be 8 hours which was used in the determination of body burden estimates for workers. Finally, to calculate amortized annual estimates of exposure a 3 month period of use based on methyl bromide use patterns was assumed (Figure 4, page 28). The EPA calculations of exposure differed from those developed by DPR because instead of using a calculated upper confidence limit on an upper bound exposure (Frank, 2009) the maximum monitored concentration was used to assess acute worker risks for each task scenario considered. Also, EPA did not apply a 10 fold factor to model increased exposures, analogous to the DPR use of the Manteca monitoring data, due to a lack of a fan to reduce exposures for those applicators.

WHS: First, engineering controls were used in the Manteca study. According to the U.S. EPA-approved labels, either engineering controls or respiratory protection must be used when applying MeI. 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 personal protection equipment. Then, in the calculation of the upper-bound exposure for applicators, the expected 10-fold respiratory protection factor (mandated by the label) was included in the formula (Equation 2, page 28).

Second, DPR tries to generate estimates that are likely to reflect the pesticide exposures that workers will encounter when following label-approved requirements. The category "workers" includes not just the individuals involved in the submitted studies, but the population of workers who will be involved in those label-approved activities throughout the State of California. A population exposure estimate necessarily involves some form of statistical calculation. The most recent policy document (noted by U.S. EPA) was generated in response to continuing questions as to why DPR uses an upper-bound estimate for acute exposures. That policy document (http://www.cdpr.ca.gov/docs/whs/memo/hsm09004.pdf) provides a more complete, detailed explanation and rationale of DPR's policy on the use of upper-bound exposure estimates for acute exposures.

U.S. EPA: Exposure Assessment/Section A. Absorbed Dose (page 28): In this section, the monitored air concentrations were adjusted by application rate. In the Agency assessment the same values were not adjusted because so many factors in a fumigant application can impact potential exposures such as sealing efficacy (e.g., tarp placement and/or compaction), soil parameters (e.g., type and moisture levels) and/or optimization of application equipment for reducing emissions (e.g., shank type and orientation).

WHS: As noted above, DPR separates risk assessment from risk mitigation. Since the applicator exposures were generated from studies that were conducted at application rates different from the maximum label-approved rate, those exposure values were adjusted (assuming a direct relationship between application rate and exposure) to match what the label allows. The various factors indicated by U.S. EPA (sealing efficacy, tarp placement, compaction, moisture levels, shank type and orientation) may prove useful in the mitigation process, if mitigation is required.

U.S. EPA: Exposure Assessment/Section A. Dermal Route (pages 28-29): A dermal dose was estimated and it was concluded that exposures via this route were insignificant. This is the same as the conclusion of the Agency which was developed on the use of physical/chemical properties.

WHS: DPR attempts to make the process of developing an exposure assessment transparent. Consequently, even though dermal exposure was believed to be inconsequential, an attempt was made to derive an estimate of exposure through the dermal route so that it could be compared with the dose through the inhalation route. Such a comparison tended to confirm the initial impression of insignificant dermal exposure. DPR believes the chemical/physical properties of this chemical may not be good prognosticators for various aspects of exposure (see further explanation below).

U.S. EPA: Exposure Assessment/Section A. Absorbed Dose/Table II (page 31): Absorbed dose estimates for workers are presented in this table for acute, seasonal, and annual durations of exposure. These were calculated using the same ventilation rate of 833 L/hr based on Andrews and Patterson (2000). There is no discussion of the Agency's Exposure Factors Handbook on inhalation (see hnp:/Iwww.epa.gov/nceawwwl/efhlpdfs/eth-chapter05.pdf) which can be used to obtain the latest information on human ventilation rates for individuals engaged in different levels of activities, in different settings, at varied stages of their lives. Arithmetic mean values were used to estimate seasonal doses which is a similar approach to that used by the Agency. The annual absorbed dose was calculated using a 3 month application window for all workers coupled with 9 months on no iodomethane use. The Agency did not estimate annual or chronic worker risks because it does not believe that exposures occur over the course of a year and the short-/intermediate-term endpoint used to calculate the corresponding HECs, based on the RfC methodology address such potential, but likely limited, prolonged exposure patterns. The 3 month application window was also apparently based on translation of methyl bromide use patterns to the iodomethane risk analysis but this is clearly a conservative approach because it is not clear that if iodomethane were registered in California that it would fill all use niches where methyl bromide is currently used given that much efficacy research is focused on several other chemicals as well. All dose estimates included in this table reflect the inherent use of a PF 10 air purifying respirator. The Agency presented risks both with and without such devices to allow for a more informed risk management decision. lodomethane products which will likely be most prevalent in the marketplace contain high percentages of the companion fumigant, chloropicrin. This is recognized as a highly irritating material that has been widely used as a companion warning agent of exposure at much lower concentrations (e.g., 2% of total applied was typical) and it also has significant pesticidal properties. The Agency has opted to harness this warning agent property along with the use of respirators in its strategy to manage worker risks that alleviates some of the physical burden of respirator use for extended periods.

WHS: The respiratory rates that were used in the MeI EAD are default values for individuals to be used when duration of activity and activity patterns are not specified. Inhalation values from the Exposure Factors Handbook and more current information were considered. DPR scientists have also researched ventilation rates which resulted in the policy noted by U.S. EPA.

MeI is one of the chemicals slated to replace MeBr in pre-plant field fumigation. U.S. EPA terms the DPR assumption that the use pattern for methyl iodide will mimic that of MeBr bromide as “clearly a conservative approach because it is not clear that if iodomethane were registered in California that it would fill all use niches where methyl bromide is currently used…”. DPR does not believe that it is overly conservative. Given that the only limitations on the use of MeI (once registered) would be the current agricultural practices in California, it seems logical to utilize the same exposure parameters experienced with MeBr use.

As the U.S. EPA-approved label for all of the formulations of MeI require applicators to use respiratory protection, DPR considers unprotected applicator exposure to be unlawful. Thus, such applicator exposures were not examined.

Assessment of the risks of chloropicrin exposure, either as a warning agent, or a co-active ingredient, will be addressed in a separate risk assessment specifically for that chemical.

U.S. EPA: II. Exposure Assessment/Section B. Bystander Exposures (pages 32-36): The same volatility data which were included in the Agency's 2007 risk assessment were used in the DPR assessment. The calculated flux values appear reasonable and appropriate for the approaches used in the assessment. It should be noted that additional field volatility data were generated under a recent Experimental Use Permit for iodomethane (i.e., EPA MRIDs 472952-02, -03, -04) that utilized higher harrier agricultural films, reduced application rates, and a patented pulse application system (i.e., Symmetry). The results of this study indicate that emissions were greatly reduced compared to the studies used by DPR and in the 2007 Agency assessment.

WHS: As indicated above, DPR does not combine risk assessment with risk mitigation as U.S. EPA does. Because the label only requires a generic tarp be used, the emissions reductions that may be engendered by specialized tarps (not required by the label) were not considered in generating the exposure assessment. Likewise, specific shank injection machinery is not required by the label, so standard equipment was used as the basis for generating exposure estimates associated with the technique.

U.S. EPA: One major difference between the Agency and DPR assessments is that DPR used a deterministic modeling approach based on the use of the ISCST3 model coupled with a static weather condition and wind vectors faced downwind 100 percent of the exposure duration. These environmental conditions are not realistic in the majority of situations. It is also highly unlikely that most impacted individuals would be at such a downwind location for extended periods of time. Conversely, the Agency used a distributional approach to air modeling based on the PERFUM model which was considered by the FIFRA Scientific Advisory Panel (see http://www.epa.gov/scipoly/sap/meetings/2004/082404 mtg.htm for more details) as described above. The Agency believes that the use of the PERFUM model, coupled with consideration of monitoring data and analysis of incident rates and the nature of incidents provides for a more informed risk management decision. PERFUM also allows for consideration of outputs which are similar in nature to those calculated using ISCST3 (i.e., maximum buffer distance outputs at higher percentiles of exposure would be analogous),

WHS: Environmental Monitoring (EM) Branch will respond to comments concerning air modeling.

U.S. EPA: In the DPR assessment 1, 8, and 24 hour time-weighted average air concentrations were calculated. The Agency does not concur with the use of the 1 hour interval based on the eye irritation endpoint, particularly since iodomethane is always co-applied with chloropicrin which is a potent warning agent that would preclude such eye effects from iodomethane.

WHS: Due to the structure of the sampling intervals, we agree that estimation of a 1-hr flux for 40 acres is problematic. We also concur that this exposure situation is unlikely. Consequently, we have eliminated the 1-hour estimates of flux and exposure from the EAD.

U.S. EPA: Exposure Assessment/Section B. Seasonal Exposure (page 36): Seasonal exposures were calculated for repetitive exposures over longer intervals that "reflect the reality of changing wind directions," DPR estimated 2 week TWA concentrations by calculating average 24 hour flux over a 2 week period then "adjusting with a time-scaling factor" which was derived using peak to mean theory based on empirical and theoretical studies (Barry 2008b).

WHS: EM Branch will respond to comments concerning air modeling.

U.S. EPA: A key assumption was that bystanders would be at the 152 meter buffer distance for the entire 2 week period. The Agency could not verify the calculations in Barry 2008b since it was not provided. Additionally, there is no discussion of the possible uncertainty associated with this overall methodology. For example, it would be highly unlikely that individuals possibly impacted by the most serious potential effects of iodomethane (i.e., fetal loss) would be at a 152 m buffer distance over an entire 2 week period. Available time-location data indicate that individuals, particularly women of child bearing age where this effect would be possible, would be unlikely not to move amongst varied locations over such an extended period of time. The Agency views this approach as likely to be highly conservative for most individuals in potentially impacted populations. The Agency did not complete such a calculation but instead considered ambient monitoring data for methyl bromide which is volatile like iodomethane and is used in a fashion which would be anticipated for iodomethane in high use areas in the season of high use as a surrogate to evaluate possible longer duration exposures.

WHS: The factors that U.S. EPA points out which would cause people to move from a location with the estimated air concentrations of MeI either acutely, or longer term, are discussed in the Exposure Appraisal section (pp 47-48). DPR uses the Exposure Appraisal section to discuss the uncertainties in the data. However, at the present time there are no acceptable, quantitative methods to reduce the estimated bystander exposures. With regards to repetitive exposures, as stated in the Appraisal section, "…virtually all of the MeI is gone from treated fields by day four, and the 2-week average air concentration of MeI represents averaging the initial few days of high concentrations with the remaining days of non-detectable levels of MeI." Consequently, it is not surprising that the 2-week average application site air concentration of MeI was approximately

the same as the highest 2-week average community-wide air concentration of MeBr measured by the California Air Resources Board. Community exposures are expected to be equal to, or less than the representative, seasonal, application-site exposures.

U.S. EPA: Exposure Assessment/Section B. Seasonal Exposure (page 37): In Table 13 DPR presented on this page maximum single day time-weighted average air concentrations for 1, 8 and 24 hour periods to reflect the time to effect for several toxicological concerns. The Agency also used 8 and 24 hour durations as the basis for its calculations but did not include 1 hour calculations because it does not adhere to the DPR concerns over possible eye irritation effects and since iodomethane will always be used in conjunction with chloropicrin as a warning agent which would likely preclude such effects from occurring as a result of exposure to iodomethane. Additionally, as commented on above, the Agency is not using the deterministic air modeling approach used by DPR but instead completed such calculations using the PERFUM model.

WHS: Comments concerning air modeling will be addressed by EM Branch. As noted above, the 1 hour exposure estimates have been deleted from the document.

U.S. EPA: Exposure Assessment/Section C. Community Exposures (page 38): As described above for the section on seasonal exposure (page 36) 2 week time weighted average concentrations were calculated which were compared to the 2 week seasonal exposures calculated by Thongsinthusak and Haskell in 2002 for methyl bromide using monitoring data from the season of use in high use areas. These values varied by only 34% which is remarkable considering the uncertainties associated with the approach (i.e., 0.071µg/L calculated compared to methyl bromide monitoring value of 0.046 µg/L). DPR concluded because of these differences that "thus, ambient air concentrations do not capture the worst case scenario for seasonal exposures." The Agency does not concur with these conclusions because of the issues described for the comment pertaining to page 36 above. Additionally, the Agency believes that several other factors support the position that the use of the methyl bromide data are more appropriate for consideration for these types of exposures including methyl bromide is more volatile and is longer lived in the environment than iodomethane and its market share is likely much greater than would be expected for iodomethane.

WHS: DPR believes it is reasonable to assume that where MeI used as a pre-plant field fumigant there would be community wide exposure to MeI. The magnitude of that possible exposure to ambient air concentrations of MeI is unlikely to exceed that of MeBr, but there are no chemical specific data. Consequently, DPR uses MeBr as a surrogate chemical.

The California Scientific Review Panel, which is charged to review potential toxic air contaminants, has long contended that people living adjacent to fields treated with pesticides experience a greater repetitive exposure to airborne pesticides than people living in nearby

communities. Consequently, by way of comparison, it was shown that 2-week air concentrations of MeI adjacent to an application site were not very different from 2-week ambient air concentrations of MeBr that had been measured in communities near pre-plant field fumigation activities. Thus, it may be possible that communities would experience even lower ambient air concentrations of MeI than the seasonal application site air concentrations. The text of the EAD has been modified to make this latter point clear (p 38).

U.S. EPA cites chemical/physical parameters of MeI that predict limited ambient air levels of MeI compared to MeBr. However, chemical/physical parameters of MeI predicted less flux from field applications than MeBr. In actuality, the flux of MeI from fields was greater than that of MeBr. So relying solely on the chemical/physical parameters of MeI as completely accurate prognosticators of the environmental fate of MeI would seem to be inappropriate.

U.S. EPA: Exposure Assessment/Section D. Estimation of Absorbed Dose (pages 38-43): On these pages a series of absorbed dose estimates were presented for adults, children, and infants using varied breathing rates, durations of exposure, and body weights. The Agency does not believe that the use of a body burden approach is appropriate since Human Equivalent Concentrations (HECs) can be calculated using the available hazard information and pharmacokinetics model. Iodomethane is also highly volatile and the exposures of concern are via inhalation which have been quantified using monitoring data or empirically based modeling. Because of these factors, an inhalation route-specific calculation of risk based on comparing exposure concentrations to HECs is believed to be the most applicable metric. This is also consistent with longstanding Agency guidance for using route-specific metrics as a preferred approach (e.g., 1992 EPA Exposure Assessment Guidelines).

WHS: Exposure estimates are developed within the WHS Branch. The MT Branch evaluates the toxicological/pharmacokinetic studies, generates HECs, and estimates the risks from exposures to pesticides.

U.S. EPA: Exposure Appraisal Section A. Physiological Assumptions (pages 43-44): A brief summary of the factors used were presented. Please refer to the response for pages 38-43 and Attachment A for further information on these issues.

WHS: See responses above.

U.S. EPA: Exposure Appraisal Section B. Analytical Assumptions (page 44): A brief discussion was provided about general uncertainty associated with analytical measurements. Chemical specific information from available iodomethane data were not summarized within which would be a better measure of actual uncertainty for this case.

WHS: The chemical-specific information, based on current approved practice, assumed that the percent-recoveries and assay variabilities of field spikes were the same as test samples collected at the same time. Such assumptions were not required in the cited cases because internal recovery standards were used from start to finish. Thus, although the cited chemicals were not treated in the same fashion, the basis for making a generalized statement on uncertainty associated with measuring field samples was better.

U.S. EPA: Exposure Appraisal Section C. Estimation of Application Site Air Concentrations (pages 44-46): A general discussion was provided pertaining to the factors which can impact emissions and exposures. Also, a description was included describing why modeling is more appropriate for use rather than just the use of empirical monitoring data. Finally, the use of the ISCST3 model was described. The Agency agrees with many of these factors but it does not believe that the use of the ISCST3 is more appropriate than the use of the PERFUM model or other model with similar functionality. Also, as described above it would recommend that all available emissions data be considered including those where high barrier films have been used coupled with reduced application rates because they represent viable, alternative farming practices which are readily implementable. Finally, the factors which can potentially impact emissions have been examined in great detail by the Agency (see www.regulations.gov under docket EPA-HQ-OPP-200S·0123-0467). It is recommended that this document be considered in further revisions to the DPR risk characterization document.

WHS: EM Branch will respond to the comments on air modeling. DPR conducts the risk assessment, based on label requirements. Once that is complete, risk mitigation is considered for exposures of concern; it a separate process at DPR. If it is found that mitigation is required, the use of alternative farming practices and other types of air modeling can be explored to reduce potential exposures to MeI.

USEPA: Exposure Appraisal Section D. Occupational Exposures (pages 46-47): Two key issues were discussed by DPR in this section including that the exposure data were generated in relatively small fields (e.g., *2.5* acres) when under actual commercial conditions much larger fields could possibly be treated on a daily basis. Additionally, the sporadic nature of possible fumigator exposures was considered which creates uncertainty in trying to predict possible chronic effects. The issue of extrapolation based on area treated, amount of active ingredient handled, or other exposure factor which changes due to use is a very difficult effect to quantify as discussed by the Agency before the FIFRA Scientific Advisory Panel (see the following http://www.epa.gov/scipoly/sap/meetings/2007/01 0907 mtg.htm for more information) and the Human Studies Review Board with regard to the statistical design goals of the Agricultural Handlers Exposure Task Force (see http://www.epa.gov/osa/hsrb/meetings.htm for more information). In typical assessments we acknowledge it as an uncertainty without being able to truly quantify it. However, it is

the estimation of the Agency that this uncertainty might be more appropriately considered in assessments where a body burden is calculated similar to the DPR approach rather than the HEC approach preferred by the Agency. In this approach measured air concentrations are compared to the HEC but air concentration peak levels can be impacted by a variety of factors such as soil conditions, barrier layers, and application equipment configuration not just the amount of acres treated (see www.regulations.gov under docket EPA-HQ-OPP-2005-0123-0467). As such, the Agency does not believe that the use of 2.5 acre fields leads to additional levels of uncertainty to the extent noted by DPR. The Agency also agrees that there can be uncertainty associated with trying to predict possible chronic effects from exposure patterns which are sporadic in nature akin to those anticipated for iodomethane fumigators. However, given the toxicokinetics of iodomethane, it is likely that chronic studies would overestimate the risks posed to iodomethane fumigators under the anticipated use pattern.

WHS: MT Branch will respond to the comments on PBPK modeling and development of HECs. EM Branch will respond to the comments on air modeling.

U.S. EPA: Exposure Appraisal/Section E. Bystander Exposures (pages 47-48): The uncertainties associated with the premise of the acute bystander exposure estimates and the estimates calculated [or repetitive exposures were considered. These included consideration of time-activity patterns, the assumption that outdoor and indoor air concentrations are equivalent, and that a relatively short 2 week period was considered as the basis for calculating a seasonal exposure estimate. The Agency essentially concurs with these suppositions but it does note that there is no stated basis for the use of a 2 week period for calculating seasonal exposures. DPR notes that iodomethane treatments within a field would likely be once per year so the seasonal exposure estimate could be vastly different based on the averaging time considered. It is not clear that a time to effect for a 2 week period can be justified.

WHS: DPR believes it is reasonable to assume that where MeI is used as a pre-plant field fumigant there would be community wide exposure to MeI. The California Air Resources Board conducts 2-week seasonal monitoring studies; this is the basis for our 2-week seasonal exposure estimate. With regards to other fumigants, DPR has received the criticism that seasonal community-wide exposures to fumigants would not be as great as seasonal exposure of resident bystanders to application-site air concentrations of those same fumigants.

Consequently, by way of comparison, it was shown that air concentrations of MeI (based on average 2-week flux) adjacent to an application site were not very different from 2-week ambient air concentrations of MeBr measured in communities. Thus, it is likely that communities would experience even lower ambient air concentrations of MeI than they now currently receive of MeBr. The text has been modified to make this latter point clear (p 38).

U.S. EPA: Occupational Exposure Estimates (pages 73-74): This section of the document provided a comparison of the Agency and DPR approaches with 6 specific items presented. These included (I) duplicate samplers on the same individuals were averaged by DPR rather than used individually as by the Agency; (2) DPR adjusted for application rates; (3) DPR adjusted the results for recovery and analytical method; (4) DPR used an upper bound, statistically derived value while the maximum monitored value was used by the Agency; (5) DPR used the arithmetic mean to estimate seasonal exposure of workers and EPA did not estimate these exposures; (6) EPA estimated the protective effect of respiratory protection on worker exposure to maximum measured air concentrations while DPR factored in the use of respirators for workers once the required PPE was on the labels. The Agency has addressed each of these comments below. On comment (1) the Agency opted to use individual samples rather than the average values to estimate risks because of the numbers of factors which have been identified that could possibly impact peak emission levels in an attempt to capture any transient high level of exposure rather than dilution of a peak value by averaging. A dilution of peak values by averaging for acute exposure durations would be less health protective.

WHS: DPR generates estimates that are likely to reflect the highest, yet reasonable pesticide exposures that workers will encounter when following label-approved requirements. The category "workers" includes not just the individuals involved in the submitted studies, but the population of workers who will be involved in those label-approved activities throughout the State of California.

U.S. EPA: For comment (2) the Agency did not adjust worker exposure estimates by application rates for the reasons outlined above. Even given this, it appears that both agencies reached similar conclusions pertaining to the risks for workers who are involved in iodomethane applications.

WHS: No response needed.

U.S. EPA: For comment (3) the Agency used the values reported by the investigators as the basis for its assessments without altering the corrections applied to the results. These corrections would have minimal impacts. The Agency compared to monitored values used by DPR and its own and found very little differences. In some cases EPA estimates were slightly higher while in other cases DPR estimates were slightly higher.

WHS: WHS used the following rationale in calculating recoveries: 1) In any procedure involving sample collection, sample processing, and sample analysis a certain amount of the sample will be lost. 2) The amount of sample lost will tend to be a higher percentage of the lowest concentration samples, and a lower percentage of the highest concentration samples. 3) The worker samples should be matched up with the closest (in concentration) field spike samples (not laboratory samples) to deal with losses at each step along the way.

U.S. EPA: (4) because the major differences in the worker exposure results utilized by DPR compared to the Agency are that an upper confidence limit statistic is used by DPR while the maximum monitored values were used by the Agency. These are policy-based differences developed based on the needs of each respective agency.

WHS: DPR agrees.

U.S. EPA: (5) DPR indicates it considered seasonal exposures to workers and that EPA did not. In fact, this is not the case, in the 2006 and 2007 risk assessments for iodomethane short-term (i.e., similar to seasonal considerations by DPR) were addressed. In the 2007 risk assessment 0339055 (8/23/07, page 70) it indicates "risks from short- and intermediate-term exposures, based on average values, were calculated but not presented below because acute risks, calculated based on maximum monitored values are protective of possible exposures of this duration."

WHS: We apologize for the oversight, and the text has been modified to indicate that "intermediate-term exposures, based on average values, were calculated but not presented"(Appendix III, p72).

U.S. EPA: (6) it is not clear that there is a scientific basis which would result in different conclusions given the available approaches and the same starting exposure concentrations because both methods apply the same protection factors (e.g., 10 for an APR). It should also be noted that DPR prepared tables to compare the different results which were calculated (i.e., Tables I and 2 in Appendix 3). The differences could be explained given the variations in the methods used to calculate them as described above.

WHS: DPR agrees.

U.S. EPA: Comparison of Calculated Air Concentrations (pages 74-75): In this section DPR commented that both ISCST3 and PERFUM were used to calculate air concentrations for various field sizes, application rates, application methods and distances from the field. A comparison was provided between the EPA estimated emission ratio values and the DPR estimated emission ratio values. Minor differences were observed except for that calculated for the Oxnard California tarped raised bed study. A few comments of note are (I) that 3 additional emissions monitoring of the worst weather condition 100 percent of the exposure duration. The "whole field" output is an aspect of the kinds of results which are available from the PERFUM model which is not referenced anywhere else in this section of the document by DPR. Finally, it should also be noted that all PERFUM outputs were considered in the ultimate decision regarding iodomethane by the Agency in order to provide for a broader consideration of the possible risks associated with its possible use. Finally, as noted above, additional data have been developed for iodomethane using reduced application rates and barrier films which greatly reduce

emissions that have not been considered by DPR in their assessment that could provide additional viable agricultural production practices to growers studies are available for iodomethane that were not considered (i.e., Guadalupe CA tarped raised bed application and drip irrigation application and a Camarillo CA drip irrigation application); (2) the EPA is no longer using deterministic approaches for air modeling based on ISCST3 but is using the PERFUM model which accounts for 5 years of weather data fluctuation; and (3) it appears DPR is apparently confusing modeling constructs which have been used by the Agency because it indicates "U.S. EPA used the whole field approach" which is, in fact, not true if ISCST3 is the basis for this comment because the premise of that approach is one is downwind.

WHS: The comments on air modeling will be addressed by EM Branch.

U.S. EPA: Why DPR Does Not Use the PERFUM Model (pages 75-76): DPR acknowledges the PERFUM model in this comment but indicates its review of the code associated with this model was incomplete at the time this assessment was completed so it was not used. The Agency has considered a code level evaluation of the PERFUM model but at this point in time has, like DPR, not completed such an effort. Over the period of the past several years the Agency has however, identified several programming errors or other fixes in PERFUM which have been presented to the developer who has subsequently modified the program and recompiled it as updated versions. Additionally, from a theoretical context, the FIFRA SAP has acknowledged the validity of the approach. The PERFUM model provides a variety of outputs so one would expect a concurrence of the ISCST3 approach at outputs which represent the highest percentiles of exposure and this is in fact observed. This is another indication that PERFUM is adequate as a tool for calculating buffer estimates. Finally, the Agency is aware that some level of review of the PERFUM code has been completed by DPR but no acknowledgement of this process has been included in the DPR RCD even though it may be still somewhat incomplete. It would be a more balanced consideration of the modeling approaches if the preliminary results of this analysis was included in the RCD especially if no major issues were identified or, conversely, if DPR had identified substantive issues at the code level for PERFUM.

WHS: The comments on air modeling will be addressed by EM Branch.

U.S. EPA: Buffer Zones (page 76): A discussion was provided by DPR describing how PERFUM outputs contain both whole and maximum buffer distances. The comments provided also indicate that the Agency based its determination of buffer distances solely on the whole field buffer statistics provided by PERFUM. They also present failure rates for other chemicals including methyl bromide, metam sodium, and chloropicrin but it is not clear how they were determined. In fact, the Agency did consider the whole field buffer statistic for iodomethane but other criteria were considered as well including other PERFUM outputs (i.e., maximum buffer statistic and the air concentration outputs by

distance rings), incident rates for similar chemicals where the anticipated use of iodomethane might fill a niche (e.g., methyl bromide), and the available monitoring data itself. The probability of a series of sequential factors which could lead to severe deleterious health effects (e.g., possibility of fetal loss) was also considered in the determination of the ultimate buffer distances which were applied to iodomethane. The latter factor was also acknowledged by DPR in their risk characterization piece as described above. In summary, the deterministic approach for calculating buffer distances is legitimate but does not provide as broad of a information base for risk managers to consider in the formulation of their decisions as opposed to the use of PERFUM which provides a variety of outputs which can be considered by risk managers including results for the highest percentiles of exposure that emulate those calculated by DPR (e.g., maximum buffer distances at the highest percentiles of exposure).

WHS: EM Branch will address the comments on air modeling.

U.S. EPA: Intermediate and Annual Bystander Exposure Estimates (page 76): The consideration of seasonal exposures is presented in this section. DPR indicates that U.S. EPA "did not include an estimate of potential community exposures" but that it did compare "iodomethane to the ambient air levels that were quantified for methyl bromide." DPR utilized a modeling approach instead to estimate the exposure of an individual at a 152 meter buffer zone over the course of a 2 week period. The Agency does not concur with this approach for the reasons outlined above in responses focused on Sections II.B & II.C (pages 36 & 38 of the document).

WHS: EM Branch will address the comments concerning modeling for a seasonal exposure estimate. As noted previously, the seasonal exposure was based on an average 2-week flux that involved 3-4 days of measurable air concentrations of MeI. The uncertainties associated with estimating exposures from air concentrations associated with a single location are addressed in the Exposure Appraisal section (pp 47-48).

cc: Susan Edmiston, Chief, WHS Branch
Marylou Verder-Carlos, Assistant Director, Pesticides Program Division
Gary Patterson, Chief, MT Branch
John Sanders, Chief, EM Branch
Joyce Gee, Senior Toxicologist, MT Branch
Randy Segawa, Agriculture Program Supervisor IV (Pest Management), EM Branch
Anne Downs, Program Specialist (Pest Management), Director’s Office