Methyl Iodide (Iodomethane)

RISK CHARACTERIZATION DOCUMENT FOR INHALATION EXPOSURE

Volume IV - Part 3

Responses to Arysta Comments

CH_3I

External Panel Review Draft

Department of Pesticide Regulation
California Environmental Protection Agency

August 2009

April 30, 2009

Ms. Anne Downs
Program Specialist
Department of Pesticide Regulation
Pesticide Registration Branch
1001 I Street, P.O. Box 4015
Sacramento, CA 95814-4015

Dear Ms. Downs:

SUBJECT: RESPONSE BY ARYSTA LIFESCIENCE NA TO CALIFORNIA DEPARTMENT OF PESTICIDE REGULATION'S RISK CHARACTERIZATION DOCUMENT FOR IODOMETHANE

Attached is a document which provides comments by Arysta LifeScience NA to the California Department of Pesticide Regulation, in response to the Medical Toxicology Branch Risk Characterization Document (RCD) for Iodomethane dated March 9, 2009.

Arysta is providing comments primarily related to Volume I (Health Risk Assessment) and Volume II (Bystander and Occupational Exposure Assessment) of the iodomethane Risk Characterization Document. Please forward these responses to the appropriate scientists in the Medical Toxicology and Worker Health and Safety Branches for their review and comments. Arysta wishes to reserve its right to provide further comment during the public comment period.

Should the Department have any questions concerning the responses submitted, please contact Becky Rhodes at becky.rhodes@arystalifescience.com or at 865-850-3824, or Arysta Regulatory Consultant, Robert Ehn at robertehn@sbcglobal.net or 559-297-9322. We look forward to a response from Medical Toxicology and Worker Health and Safety scientists.

Sincerely,

Robert C. Ehn
Regulatory Agent/Consultant for Arysta LifeScience North America

Enclosure (s)
cc: Becky Rhodes, Head of Regulatory, Arysta LifeScience North America
Marylou N. Verder-Carlos, D.V.M., M.P.V.M., Assistant Director, Department of Pesticide Regulation, Pesticide Programs Division

Iodomethane: Arysta Life Science NA Response to the Medical Toxicology Branch's Methyl Iodide (Iodomethane) Risk Characterization Document for Inhalation Exposure

Volume I Health Risk Assessment and Volume II Exposure Assessment

Issued March 13 2009

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Iodomethane: Arysta Life Science NA Response to the Medical Tocicology Branch's Methyl Iodide (Iodomethane) Risk Characterization Document for Inhalation Exposure

Volume I

Health Risk Assessment

The purpose of this document is to provide Arysta LifeScience North America's (Arysta's) comments to the California Department of Pesticide Regulation's (DPR) Risk Characterization for iodomethane. We have commented on Volume I and II. We reserve the right to comment further on Volumes I, II, and III during the public comment period.

Volume I

III.A. Pharmacokinetics
III.A.1. Absorption and Distribution Page 15

DPR Comment

With oral exposure for both doses, the maximal concentration in the blood was achieved between 4 to 6 hours.

Arysta Response

Throughout this section there are statements that speculate about what may (or may not) have occurred between measurements. The statements must be limited to the data available, for example by stating that the maximum observed concentration occurred at a given time point.

III.A.2. Metabolism and Excretion Page 20

DPR Comment

…the conjugation of MeI with GSH as a metabolic pathway was studied in female white rats (Porton strain) given a single oral dose of MeI (0, 50, 75, and 100 mg/kg) (Johnson, 1966). Liver non-protein thiols (predominantly 2 GSH) were depleted at all doses tested;

Arysta Response

The time of the GSH measurements in Johnson (1966) should be specified.

III.B. Acute Toxicity Page 23

DPR Comment

lethal dose at 50% death

Arysta Response

The more traditional and clear language is: "dose that produces lethality in 50% of the population."

III.B.2. Rat – Inhalation Page 28

DPR Comment

From 1 to 48 hours after the initiation of the first exposure, GSH and iodide were measured in the serum, liver, kidneys, and nasal olfactory and nasal respiratory epithelium.

Arysta Response

Iodide was only measured in serum; GSH was measured in blood and tissues.

DPR Comment

At 25 ppm MeI, maximal GSH depletion (40 to 50% of control) was measured in the nasal epithelium, and about 30% in the other tissues, 3 to 6 hours after exposure (Table 8).

Arysta Response
3 to 6 hrs after exposure" should be corrected to "3 to 6 hours after initiation of exposure."

DPR Comment

The increase in depletion was only about 10% for the other tissues. (lines 29-30)

Arysta Response
It is not clear to what tissues and data DPR is referring.

III.B.2. Rat – Inhalation Page 31

DPR Comment

The GSH depletion was more gradual in the liver and brain (cerebellum and forebrain), and was 40% and 70-80% of control, respectively.

Arysta Response

The percentages in this statement are reversed. The GSH levels remaining were 40% and 70-80% respectively, meaning that the depletion was 60% and 20-30% of control, respectively.

III.G.2. Rabbit – Inhalation Page 80

General Comment from Arysta for this section:

The litter is generally considered the proper unit for evaluation of reproductive and developmental effects rather than the fetus.

DPR Comment

The calculated exposure concentrations were 0.011, 0.057, and 0.113 mg/L, respectively. The equivalent dosages were 1.5, 8, and 16 mg/kg/day.

Arysta Response

DPR used a default rabbit breathing rate to identify dosages of 1.5, 8, and 16 mg/kg/day iodomethane, which is inconsistent with the breathing rate used in the PBPK model. The rabbit PBPK modeling uses an alveolar ventilation rate of approximately 317 L/kg bw/day, which is lower than the DPR default rate of 540 L/kg bw/day. This becomes important when dose comparisons between studies are made.

DPR Comment

A statistically significant reduction (47%) in body weight gain was recorded for GD 6 through 29 at 20 ppm (Table 34). This was primarily due to a body weight loss of 12 grams on GD 24 to 25.

Arysta Response

The only statistically significant 2-day reduction in body weight the does exposed to 20 ppm iodomethane in this study experienced was a 22 g decrease on GD 28-29. This 22 g

body weight decrease that would appear to be the primary cause of the significant reduction in body weight recorded for GD 6 through 29, not the 12 gram decrease recorded on GD 24-25.
-25.

III.G.2. Rabbit – Inhalation Page 90

DPR Comment

Tables 39 and 40, Mean serum iodide and thyroid hormone concentrations in pregnant and fetal rabbits exposed to MeI (25 ppm) by inhalation during gestation.

Arysta Response

Sampling times should be included in the tables.

III.G.2. Rabbit – Inhalation Page 97

DPR Comment

Table 45 Maternal and fetal TSH, T3, and T4 in rabbits exposed to MeI (20 ppm) by inhalation or sodium iodide by intravenous injection.

Arysta Response

It is clear from the data presented in this table that the effects of iodomethane and NaI on the fetal thyroid are much more profound and sustained than the effects on the maternal thyroid. This fact is obscured later in the document by selective inclusion of data in Table 57 (p. 119).

III.J.1 PBPK and Mode of Action Studies
III.J.3. Glutathione and MeI Toxicity Page 103

DPR Comment

This section describes additional studies which had been conducted for PBPK modeling and Toxicity of MeI.

Page 108

DPR Comment

Glutathione and MeI Toxicity

Arysta Response

This section describes studies which evaluated glutathione levels in various tissues including nasal epithelium. In their discussion DPR failed to include other relevant studies of naphthalene vapor exposure which elucidated the relationship between glutathione (GSH) depletion in target nasal tissue and the susceptibility of those tissues to damage from chemical exposure. These studies show that a substantial depletion in GSH in respiratory tissue is necessary for toxicity to occur.

The primary target cells for rodent naphthalene toxicity are the Clara cells in the distal airways of the lung, and injury may extend into the proximal airways as the dose increases. This difference in relative sensitivity of cells in different airway levels of the mouse was exploited in a study by Plopper and coworkers to show that Clara cells exposed to naphthalene that maintained at least 50% of the control levels of GSH did not exhibit changes in organelles indicative of toxicity (Plopper *et al*, 2001). Clara cells that did not maintain GSH levels of 50% of control levels were susceptible to naphthalene-induced injury.

Gentner (2004) linked rat nasal damage from naphthalene exposure to olfactory mucosal bioactivation of naphthalene by cytochromes P450 (CYPs) 2A3 and 2f2 which formed reactive species that depleted glutathione.

In a more recent study on naphthalene, mice were exposed to 15 ppm naphthalene and GSH levels were measured and correlated with histological analyses (Phimister *et al*., 2004). A 2-hour exposure to 15 ppm napthalene resulted in a 90% loss of GSH in the distal airways, but after 24-hours, no signs of cellular injury were observed. Conversely a 4-hour exposure to 15 ppm naphthalene did cause the Clara cells in the distal airways to be swollen and vacuolated. Thus the Clara cells of the distal airways could survive a 2-hour, 90% depletion of GSH without alterations in cellular organelles, but a longer severe depletion in GSH resulted in toxicity.

In 2005 Phimister, *et al*, showed that glutathione depletion in respiratory cells of mice associated positively with naphthalene cytotoxicity and that the cytotoxicity could be prevented by maintaining cellular glutathione levels. (2005 a and b).

Lee, *et al*, in 2005 showed that region-specific injury to rat nasal mucosa occurred following naphthalene exposure and that the pattern of injury correlated with regional

metabolic capability for naphthalene. Similar finding are now being described for nonhuman primates (Lin, 2006).

These investigations establish the importance of GSH depletion in the mode-of-action of naphthalene nasal cavity cytotoxicity. DPR should consider the weight-of-evidence imposed by this data set in its evaluation of the relationship between iodomethane and nasal cavity injury in the rat. The information developed on naphthalene supports arguments not only for GSH depletion but also for oxidative stress in general as a component of iodomethane cytotoxicity.

DPR Comment

Table 52. Metabolic rate constants for MeI in tissues in vitro.

Arysta Response

Data should be reported with standard deviations (rat, rabbit, and fetal rabbit) or individual data (human). At a minimum, the subject number for the human values should be reported.

IV RISK ASSESSMENT
IV.A.1.a. Fetal Death
IV.A.1.a.(1) Critical NOEL Page 114

DPR Comment

The critical NOEL for acute MeI toxicity established by DPR is 2 ppm based on rabbit fetal death during late gestation period at the LOEL of 10 ppm (Table 34; Nemec, 2002d). Fetal body weight was also significantly lower at this LOEL. Based on the same endpoints as described for DPR's NOEL determination, the study author also concluded that the NOEL for pre-natal developmental toxicity is 2 ppm (Nemec, 2002d).

Arysta Response

Arysta believes the content of this paragraph is in error and the phrasing is misleading. The wording in the quoted paragraph should be modified to accurately reflect the results from the Nemec (2002d) study. The first sentence should state that the increase in fetal deaths were not statistically significant. In the second sentence the word "also" before the words "significantly lower," should be removed, the fact that only the female fetuses were reduced significantly in body weight at 10 ppm should be included, and the statement that the study author NOEL determination was based on the same endpoints as DPR's should be removed. The study author's stated conclusion regarding fetal body

weight changes in the 10 ppm group was "the effect at 10 ppm was considered to be treatment-related, but of equivocal toxicological significance" (Nemec, 2002d).

IV.A.1.a.(1) Critical NOEL Page 115

DPR Comment

Fetal death in rabbits as a consequence of - MeI exposure was also reported in a subsequent study by Nemec (2003) that was conducted to determine the window of vulnerability for fetal death.

Arysta Response

The topic of this section of the document is the critical NOEL, and the focus of the previous paragraph is a 2 ppm exposure. It would be helpful for the paragraph cited above to make it clear that the Nemec (2003) study evaluated fetal effects from exposure to 20 ppm iodomethane. The quoted sentence could be changed to "Fetal death in rabbits as a consequence of 20 ppm iodomethane exposure was reported in a subsequent study…"

DPR Comment

One clarification should be made about "late resorption" as an endpoint. This term was used in the submitted toxicity and pharmacokinetic studies of MeI in rabbits. One companion observation in these reports was "dead fetus". However, none of these reports clearly describe how "dead fetus" is different than "late resorption".

Arysta Response

Arysta contacted WIL laboratory staff who categorized the effects in the rabbit studies to obtain clarification of the difference between "late resorptions" and "dead fetus" as identified at necropsy. Arysta provided this information to DPR in 2006 (Arysta, 2006). Briefly, the manager of necropsy at WIL Laboratories stated that the criteria for identification of late resorptions and fetal deaths follow an internal Standard Operating Procedure. Late resorptions are identified based on the placentae having a mottled appearance and the presence of autolysis. Late-stage resorptions are considered to have died before the scheduled laparohysterectomy. Dead fetuses are presumed to have died at or near the time of the scheduled laparohysterectomy. The placentae of fetuses determined as dead do not have a mottled appearance and autolysis is absent.

DPR Comment

As noted in Table 55, one fetus per 10 and 20 ppm dose groups in the Nemec study (2002d) was found dead at sacrifice on GD 29. No dead fetus was found in the subsequent study by Nemec (2003). In this document, fetuses from late resorption are generally referred to as "dead", and the endpoint is collectively referred to as fetal death.

Arysta Response

The manager of necropsy at WIL Laboratories stated that the criteria for identification of late resorptions as separate from dead fetuses had not changed over the years (Arysta, 2006). If DPR wants to combine incidences of late resorptions and dead fetuses they should develop an argument that does not insinuate that the laboratory categorized late resorptions and dead fetuses inconsistently among studies performed on iodomethane.

IV.A.1.a.(1) Critical NOEL Page 116

DPR Comment

The acute critical NOEL established by USEPA is 10 ppm, also based on the Nemec study (2002d), 5-fold higher than that by DPR and the study investigator. The USEPA basis was a lack of statistical significance of fetal death at 10 ppm when data are expressed as percentage of fetal resorption per litter (i.e., group average of 11.1% versus 1.8% in the controls, Table 55).

Arysta Response

Arysta supports the EPA determination that the appropriate NOAEL for developmental toxicity in the rabbit is 10 ppm based on the following:

1) the percentage of fetal resorptions per litter was not significantly different from the concurrent control group value.

2) this increase in mean percent late fetal resorptions at 10 ppm was insufficient to affect fetal viability (mean live litter sizes and mean percent live fetuses was not significantly different from the concurrent control group values and were within the historical control ranges of the testing facility).

3) all other measures of fetal viability at the 10 ppm level were within the historical control ranges and also were not significantly different from the concurrent control group values. These included litter means for percent early resorptions and percent

postimplantation loss, as well as the percentages of does with postimplantation loss, early resorptions, late resorptions or dead fetuses.

IV.A.1.a.(2) Mode of Action

Page 116 - 117

DPR Comment

The four respective possible MOAs explored in this section are: fetal thyroid perturbation from excess iodide, GSH depletion, direct alkylation, and altered cholesterol homeostasis. The observations can be part of key events with more than one MOA leading to fetal death. In contrast, USEPA considered thyroid perturbation as the sole MOA and did not consider other possibilities (USEPA, 2007).

Arysta Response

The risk assessment presented by the USEPA (2007) is a summary of an extensive evaluation that **did** include consideration of alternate modes of action for the fetal loss in rabbits exposed to iodomethane.

DPR Comment

Due to data limitations and gaps, it was not possible to completely organize the data according to the International Programme on Chemical Safety (IPCS) framework for MOA evaluation of non-cancer effects for human relevance involving 1) key events, 2) concordance of dose-response relationship, 3) temporal association, 4) strength, consistency, and specificity of association of toxicological response with key events, and 5) biological plausibility and coherence (Boobis et al, 2008).

Arysta Response

Critical effects of iodomethane observed in animal studies can be organized in a way that meets the requirements of the Mode-of-Action Human Relevance Framework as described by Boobis, *et al*, 2008. The weight-of-evidence establishing causality for fetal toxicity, neurotoxicity and nasal epithelial cell damage, critical endpoints identified by CDPR for human risk characterization of iodomethane is sufficient for the appropriate life stage consideration and satisfies the Modified Hill Criteria. Key events critical to the induction of toxicity have been measured for each acute endpoint of concern. These events, listed briefly below, support a Mode-of-Action (MOA) for the effects. Details of the support for the MOA are presented by Kirman, *et al* (2009).

For fetal loss in rabbits following iodomethane administration, evidence exists suggesting that at least four MOA's are plausible. The MOA supported by the strongest evidence is thyroid hormone modulation by excess iodide during fetal development. The key events associated with this MOA are:

1) an increase in fetal iodide
2) loss of colloid in fetal thyroid.

Experimental support for the key events comes from observations of ancillary thyroid effects such as decrease in circulating T3/T4 and an increase in TSH. Kirman, *et al*, cite supporting evidence to describe a pathway for the decrease in thyroid hormone following iodide administration. Concordance for iodide effects can be seen across three species (rabbits, rats and hamsters but apparently not pigs). Kirman, *et al*, cite work indicating that fetal rabbits concentrate iodide relative to the doe and that fetal rabbits lack autoregulatory capacity for limiting excess iodide, suggesting a rationale for iodide sensitivity in the fetal rabbit. These key events have plausibility for human relevance based on human experience with thyroid perturbation during pregnancy, though humans do not concentrate iodide in the fetus as rabbits do (Rayburn *et al*, 2008, Cottino, 1972). The temporal relationship of observed thyroid effects in the fetal rabbit and exposure to iodomethane during gestation is solidly established at gestation days 23-26. It is during this gestational period that critical events occur in development of the rabbit thyroid and it is during this gestational time that iodomethane produces thyroid effects in the rabbit fetus as noted above (Sloter, *et al*, 2005).

Kirman, *et al*, also present evidence for a MOA for neurological and nasal epithelial cell effects of iodomethane in rats. In each case causality was established which satisfies the Hill criteria. The weight-of-evidence is sufficient to establish a MOA for the effect in animals. Human relevance of the MOA could not be excluded on the basis of significant qualitative differences in key events or significant quantitative kinetic or dynamic differences in key events between humans and test animals.

Accordingly, the statements appearing on pages 116-117 of Volume I of the draft DPR Health Risk Assessment for iodomethane should be modified to acknowledge that adequate information does exists to permit an analysis and presentation of iodomethane toxicology according to the International Programme on Chemical Safety (IPCS) framework for MOA evaluation of non-cancer effects for human relevance. DPR's draft report contains nearly 12 pages of text, tables, and figures (pages 116-128) on the MOA for developmental effects, as well as additional sections for nasal and neurological effects supporting this. Furthermore, additional data are available for the effects of excess iodide that are relevant to iodomethane, but were not considered by DPR. For these reasons, there appears to be sufficient information available to support the use of the MOA framework, as was presented by Kirman *et al*., and DPR should perform such an analysis.

IV.A.1.a.(2) Mode of Action, Page 117

DPR Comment

Studies designed for PBPK modeling used high concentrations of MeI (20 and 25 ppm) that may or may not inform the pharmacokinetics at the 2 ppm NOEL.

Arysta Response

Analyses of the 20 and 25 ppm data and 2 ppm PBPK simulations suggest that the iodide kinetics are approximately linear with exposure concentration.

DPR Comment

Since all fetal data are collected from fetuses that survived to GD 29, relating these data to dead fetuses requires an assumption that they are representative of the latter,…"

Arysta Response

The DPR statement is not correct. The fetal kinetic data were all collected prior to GD 29 and much of the Sloter (2005a, b) data were collected prior to GD 29. Data from rabbit fetuses were collected in the Sloter 2005b study throughout the window of sensitivity to iodomethane exposure, on gestation days: 24, 25, 26 as well as GD 29. Data from rabbit fetuses were collected in the Sloter 2005a study on gestation days: 21, 22, 23, 24, 25, 26, and 27.

DPR Comment

Elevated iodide levels were measured in the serum and tissues after MeI exposure.

Arysta Response

Iodide has been measured in serum after iodomethane exposure, but has not been measured in tissues after iodomethane exposure.

IV.A.1.a.(2)(a) Fetal Thyroid Perturbation from Excess Iodide, Page 117

DPR Comment

The issue is whether the death of rabbit fetuses is through the MOA of excess iodide specifically to the fetus, or related and influenced by maternal toxicity. If the fetal thyroid effect is the direct cause of fetal death, fetal serum iodide is an appropriate dose metric for PBPK modeling, as is presented in the USEPA risk assessment (USEPA, 2007).

However, it is DPR's position 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.

Arysta Response

Use of maternal iodide as a dose measure is not well supported by the available data, and does not take into consideration several biological factors that contribute to the unique sensitivity of the rabbit fetus to the effects of iodide, which include:

(1) the fetal rabbit lacks the autoregulatory capacity to limit the effects of excess iodide (Price and Sherwin, 1986).

(2) the fetal rabbits concentrate iodide relative to the doe (Logothetopoulos and Scott, 1956; Sloter, 2005b);.

IV.A.1.a. (2) (a) Fetal Thyroid Perturbation from Excess Iodide Page 121

DPR Comment

Comparison of maternal and fetal TSH data after MeI exposure shows greater consistency in maternal than in fetal TSH patterns after 2 days of MeI exposure, suggesting a role for maternal effects in the MOA. The maternal TSH level is significantly increased, as early as after 2 days of exposure (GD23 to GD24) - the first time point of evaluation (Tables 56 and 57). Its persistence onto day 4 (from GD23 to GD26) of exposure was observed only with MeI at 25 ppm (Table 56). On the other hand, the average TSH levels in the fetuses are somewhat lower than the controls during GD23-24, but greatly increased in the GD23-26 groups.

Arysta Response

There is no support for the DPR position that greater consistency in maternal than in fetal TSH patterns after 2 days of iodomethane exposure suggests a role for maternal effects in the MOA for fetal loss. The data available support a role for fetal effects in the MOA for fetal loss. DPR notes that the increase in maternal TSH after two days of iodomethane exposure on GD 23-24 is maintained after 4 days of exposure only in does exposed to 25 ppm iodomethane, not in does exposed to 20 ppm iodomethane. In Nemec (2003) it was demonstrated that effects of iodomethane exposure on rabbit fetuses are increased dramatically when exposure occurs over the 4 days of GD 23 to 26 (16.3% late resorptions) compared to 2 days of exposure on GDs 23 to 24 (5.3% late resorptions). Fetal TSH level increased with increasing days of 20 ppm iodomethane exposure over gestation days 23, 24, 25 and 26, reaching statistical significance from control on

gestation days 25 through 29 (Sloter, 2005b). The increase in late resorptions after4 days of exposure on GDs 23-26 correlates with the greater effect on TSH levels in fetal rabbit plasma than in maternal rabbit plasma after exposure to iodomethane on GDs 23 to 26. Thus, consistency in maternal TSH patterns after 2 days of iodomethane exposure does not correlate with fetal loss, but increased fetal TSH levels after 4 days of exposure GDs 23-26 does correlate with fetal loss, supporting a causal role for fetal effects in the MOA for fetal loss.

DPR Comment

There is a lack of causal relationship between fetal thyroid perturbation and fetal death, within the GD 23 to 24 period, after MeI exposure, to support this MOA. Histopathology in the fetal thyroid included decreased colloid, follicular epithelial vacuolation and follicular hypertrophy (Tables 56 and 57). In Sloter (2005a) at 25 ppm MeI, higher incidences were reported in the 4-day than the 2-day exposure groups, yet the "% fetus/litter" of late resorption immediately after the end of MeI exposure were the same at these corresponding time points (i.e., 5.7% after 2 days and 5.2% after 4 days of MeI exposure) (Table 56).

Arysta Response

DPR states that there is a lack of a causal relationship between fetal thyroid perturbation and fetal death within the 23 to 24 day period, Arysta disagrees. The discussion presented and the data available *do* support a causal association between fetal thyroid perturbation by iodide and fetal death. As noted by DPR, histopathologic findings included follicular cell hypertrophy in 37% of fetal rabbits exposed to 25 ppm iodomethane on GDs 23-24 and in 94% of those exposed on GDs 23-26, and colloid depletion in 14% of fetal rabbits exposed to 25 ppm iodomethane on GDs 23-24 and in 89% of those exposed on GDs 23-26. DPR maintains there is no concordance between thyroid histopathology and adverse outcome because the percent resorptions identified immediately after exposure were virtually the same in both groups. The fallacy in this argument is that adverse effects from altered fetal thyroid function are not necessarily immediately fatal. DPR has presented no data or rationale to support the implied contention that follicular cell hypertrophy and colloid depletion in fetal rabbits would be immediately fatal. An increase in late resorptions after 20 ppm iodomethane exposure was observed 3 days after exposure on GDs 23-26, but not immediately after exposure, and this is shown in Table 47 of the RCD. Data in Table 47 indicate that 4% late resorptions were observed on GD 26 after exposure on GD 23-26, and 50.4% late resorptions were observed on GD 29 after an identical exposure pattern. The fetal rabbit group that had the higher incidences of hypertrophy and colloid depletion after iodomethane exposure on GD 23-26 ultimately had higher incidences of late resorptions on GD 29, thus there is concordance of histopathologic effects in the thyroid and fetal resorptions.

DPR Comment

Furthermore, comparison of data from MeI and NaI treatment indicates that fetal thyroid perturbation through excess iodide is not the sole MOA for fetal death. Effects of high fetal serum iodide on fetal thyroid may be second in sequence, after an initial MOA that causes fetal death from MeI. In Sloter (2005b), the estimated iodide dose for MeI (13.4 mg/kg/day) is 6-fold higher than that for NaI (2.58 mg/kg/day) exposure, assuming 100% uptake and rapid and complete breakdown. Yet, both treatments resulted in comparable effects on fetal thyroid histopathology (Table 57, more detailed in Table 48) and TSH profile during treatment from GD23 to GD26 (Figure 2, hours 23 to 72). With the higher iodide exposure in the MeI group, significantly increased fetal late resorption and reduced fetal viability was seen only in the MeI group, but not with NaI (Table 57).

Arysta Response

The total iodomethane dose calculated using DPR's default breathing rate exceeds the intake calculated using the alveolar ventilation rate used in the PBPK modeling (540 L/kg/d, vs 317 L/kg/d), distorting the comparisons among dosing regimens (i.e., iodomethane vs. NaI). The more detailed data presented in Table 48 show a greater incidence and severity of histopathology in the fetal thyroids of rabbits on GD 29 in those exposed to iodomethane compared to NaI.

IV.A.1.a. (2) (a) Fetal Thyroid Perturbation from Excess Iodide Page 122

DPR Comment

At both NaI treatment levels, the highest maternal iodide concentration is in the thyroid (Figures 4a and 4b). The pattern of iodide distribution to the thyroid is different between the does and the fetuses. The maternal and fetal thyroid iodide both reached approximately the same level within 2 hours, and remain more or less steady until 6 hours. Thereafter, the maternal thyroid continues to accumulate iodide but not the fetal thyroid. At the end of 24 hours, the concentration in the maternal thyroid was higher than the blood by 20-fold with 0.75 mg NaI/kg treatment and 270-fold with 10 mg NaI/kg treatment. The high maternal thyroid iodide pattern on GD25 appears to correspond to the TSH profile shown in Table 57 for NaI and MeI exposures by Sloter (2005b), i.e., increased maternal TSH at the earliest measurement, i.e., immediately after the second of a 2-day NaI exposure on GD23-24. However, fetal TSH did not change during this time. Contrary to the pattern of maternal iodide distribution, the highest fetal iodide concentration is in the stomach contents and the lowest in the blood, with the levels at other measured sites (trachea, thyroid+trachea, amniotic fluid) all higher than in the blood. The higher iodide in tissues raises a concern for potential damage from excess

iodide in tissues besides thyroid and may contribute toward MeI fetal death immediately after the second 6-hr MeI exposure.

Arysta Response

Relative concentrations of iodide in maternal and fetal thyroid do not take account of the following aspects of iodide reaction in maternal and fetal rabbits. First, despite the higher apparent concentrations of iodide in the maternal thyroid, the toxic effects of treatment (colloid depletion, hypertrophy of follicular epithelium) are much less severe in maternal thyroid when compared to the dramatic effects observed in fetal thyroid. The difference in effects, particularly severity of effects, identifies the fetus as the more sensitive target for iodide toxicity. Because of this, the appropriate metric for iodide effects for this endpoint is the fetal plasma iodide level.

Second, the DPR does not take into consideration either the treatment effects of iodomethane on the thyroid or the developmental changes to the fetal thyroid for iodide tissue distribution. Lower measured concentrations of iodide in fetal thyroid relative to maternal thyroid can be counterintuitive given that blood levels are higher in the fetus (Table 58). However, further consideration of fetal rabbit ontogeny provides an explanation of the apparent contradiction.

Because the fetal rabbit thyroid lacks the ability to autoregulate iodide uptake in the presence of excess iodide (Price and Sherwin, 1986), tissue iodide concentrations may not consistently parallel blood iodide concentrations. More importantly, the apparent difference in maternal vs. fetal thyroid iodide levels likely reflects the fact that fetal thyroid is relatively devoid of colloid, the normal storage depot for iodide. The presence of elevated concentrations of iodide in the fetal alimentary canal is not surprising because the colloid (and associated iodide) released by the fetal thyroid is most likely distributed to the fetal gastrointestinal tract via the thyroglossal duct, an embryological anatomical structure forming an open connection between the initial area of development (oropharynx) of the thyroid gland and its final position. This duct normally atrophies and closes off before birth. This mechanism for fetal iodide distribution would explain the high concentrations in the trachea, stomach, and amniotic fluid (subsequent elimination from the gastrointestinal tract) that are of concern to DPR. Because the elevated levels of iodide in these tissues most likely reflect iodide that was once associated with fetal thyroid, the fetal thyroid is much more highly exposed to iodide than is apparent by the thyroid tissue concentrations. Under these conditions, fetal plasma iodide levels are the most reliable metric for fetal iodomethane toxicity, the most sensitive effect following iodomethane administration to pregnant rabbits, e.g., the most sensitive species evaluated. The most sensitive effect is the effect that if prevented will protect against all other adverse effects. If the public health goal is to establish effect levels based on the most sensitive indicator of toxicity, then rabbit fetal plasma levels of iodide are the most sensitive indicator of that effect.

IV.A.1.a.(2)(b) GSH Depletion Page 126

DPR Comment

The aforementioned GSH database may suggest two possible implications with regard to MeI fetal toxicity in rabbits. First, compared to the adult brain, death of neural cells in the fetal brain can be more detrimental and possibly contribute to fetal death.

Arysta Response

It is a big leap to go from cell death in rat neuronal cell cultures to fetal rabbit death in vivo. It should be recalled that in Nemec (2002), the brain from each rabbit fetus was examined by a mid-coronal slice, and no abnormalities were noted.

IV.A.1.c. Neurotoxicity
IV.A.1.c.(2) Mode of Action Page 130

DPR Comment

One possibility is via GSH depletion in the brain. In a rat study by Chamberlain et al. (1998a), a 20-30% decrease in brain NP-SH was reported at the end of a 6 hour exposure to 100 ppm MeI with slightly greater decrease in the forebrain than in cerebellum. The information from in vitro investigation showed that GSH depletion by MeI results in cytotoxicity in cultured neural cells. Cell death became more evident long after the recovery of GSH level (Davenport et al, 1992; Bonnefoi, 1992; Chamberlain et al, 1999).

Arysta Response

A cytotoxic mode of action mediated by GSH depletion is contraindicated by the transient nature of the clinical signs (generally resolved by the following day), and the absence of any neuropathological effects associated with cell death. Consideration should be given to a general mode of action by the parent chemical via modification of ion currents in neurons as is typically observed with solvents at high concentrations (see Kirman *et al*, 2009).

IV.A.I.c.(3) Human Equivalent Concentration, Page 131

DPR Comment

Since the 8-hour HEC does not take into account the additional 16-hour exposure after work, it is considered not sufficiently protective. Therefore, the 3.4 ppm from the 24-hour/day exposure value is to be used for both durations.

Arysta Response

The PBPK model developed for iodomethane can be used to estimate area under the concentration curve (AUC) values for both 8-hour exposures (which can include internal exposures that continue after external exposure ceases) and 24-hour time exposures. The use of a single human equivalent concentration for both time periods is not justified.

V. RISK APPRAISAL

V.A. Hazard Identification Page 146

DPR Comment

The main uncertainty in hazard identification is the lack of data to address potential toxicity in the young, since all the studies were conducted with adult animals. NOELs generated from observations of adult animals may not be sufficiently protective.

Arysta Response

It is not true that all the studies on iodomethane were conducted with adult animals. Arysta has conducted and submitted two guideline developmental toxicity studies to characterize the potential effects of iodomethane exposure in young rats and young rabbits, and one guideline two-generation study in rats to characterize the potential effects on rats through two generations. In the 2-generation rat study, offspring were exposed via lactation beginning 5 days after birth, and were exposed directly to iodomethane beginning on postnatal day 28. Three additional non-guideline studies were performed and submitted to further characterize the effects of iodomethane on developing rabbits (Nemec, 2003, Sloter, 2005a and 2005b).

DPR Comment

Studies on developmental neurotoxicity for animals exposed during in utero, as well as those examining the postnatal effects of MeI on nasal tissues and the nervous system of young animals are needed. The absence of such studies can lead to the underestimation of the toxicity based on the current database.

Arysta Response

The F1 generation rats exposed to iodomethane in the 2-generation study by lactation beginning on postnatal day (PND) 5 and directly via inhalation on PND 28 were evaluated for effects on the nasal olfactory epithelium. The NOAEL for effects on the nasal epithelium was identical to the adult NOEL, 20 ppm, indicating no difference in sensitivity of young rats compared to adult rats for this endpoint.

Sufficient data are available to determine that a developmental neurotoxicity study is not necessary. Alterations in thyroid and pituitary function, as can occur following exposure to high levels of iodomethane, can impact brain development. Exposure to lower levels of iodomethane that do not cause alterations in thyroid and pituitary function would not be expected to impact neurological development. Data are available to demonstrate that repeated exposure of female rats to 20 ppm iodomethane 5 days/week for 26 weeks does not alter T3, T4, reverse T3 or TSH (Kirkpatrick, 2005). TSH levels were increased in female rats exposed to 60 ppm iodomethane for 26 weeks, but all other parameters were similar to control females in the 60 ppm group. The 20 ppm NOAEL for pituitary and thyroid hormone effects in female rats will protect developing fetuses from potential developmental neurotoxicity resulting from altered thyroid function. The US EPA and OECD have designed guidelines to evaluate potential developmental neurotoxicity in rats but not rabbits (EPA OPPTS 870.6300, OECD 426).

V.C. Risk Characterization age 146-147

DPR Comment

When the HEC is used in the MOE calculation, a benchmark MOE of 30 is considered health protective such that any exposure with a MOE ≥ 30 would not be of significant health concern. In the risk characterization for MeI, this benchmark of 30 may be insufficient because of the following:

(1) The lack of data for potential neurodevelopmental effects, in the presence of evidence for MeI perturbation of maternal and fetal thyroid functions.
(2) The substantial post-natal death in neonates of rats and rabbits associated with pre12 and post- natal exposure to NaI and KI.

(3) The high iodide levels from exposure to MeI at the reference concentration (RfC), when compared with current health-based limits of iodide intake.

Arysta Response

Arysta believes data are available to support the MOE of 30, and the potential insufficiencies identified by DPR are addressed briefly below:

1) A NOAEL for alteration of thyroid and pituitary hormone levels is available and this endpoint is protective of neurodevelopmental effects that could result from thyroid perturbation.

2) Substantial data and a PBPK model are available to determine an HEC for iodide level with reasonable certainty.

3) The acceptable level for an acute duration exposure to iodomethane should not be confused with the acceptable daily upper limit of dietary iodide intake.

V.C.1.a. Thyroid Perturbation and Developmental Effects Page 147

DPR Comment

There is a concern for potential developmental toxicity from MeI exposure because neurodevelopmental effects associated with thyroid toxicity is well documented (Howdeshell, 26 2002; Zoeller et al, 2002; Zoeller, 2003). Thyroid hormone dysfunction affects many fetal organs, e.g., heart, liver, muscle, and development…..

Arysta Response

Protection against effects on pituitary and thyroid hormones will protect against any potential effects on neurological development that could result from "thyroid hormone dysfunction." The NOAEL for effects on thyroid and pituitary hormones in rats exposed to iodomethane is 20 ppm with a LOAEL of 60 ppm (Kirkpatrick 2005).

DPR Comment

Neurobehavioral effects may be the result of excess iodide. PBPK modeling for MeI predicted an extraordinarily high accumulation of iodide in the fetal thyroid (Appendix A). In the study with KI by Vorhees et al (1984), Sprague-Dawley rats were fed diets containing 0.025, 0.05, or 0.1% KI 14 days before mating and during mating….

Arysta Response

The paragraph partially excerpted above discusses neurobehavioral effects identified in rats fed diets containing high levels of iodide. This paragraph is not related to iodomethane exposure and does not inform potential effects from iodomethane exposure and should be deleted. The dose of iodide in the diet is not related to iodomethane exposure, and the only sentence in the paragraph that relates to iodomethane states that the PBPK model projects high levels of iodide may accumulate in the thyroid. The neurobehavioral information from the dietary iodide studies would be useful only if the internal iodide doses in the dietary and the rat inhalation exposure studies were presented.

V.C.1.b. Post-natal Death Page 148

DPR Comment

Published literature suggests that post-natal death in rabbits from MeI exposure should also be of concern. Marked reduction in the survival of neonates associated with pre- and post natal iodide exposure was reported by Ammerman et al (1964) and Arrington et al. (1965). From the data for post-natal survival, Arrington et al. (1965) reported a 30% survival of 3 days old rabbit pups from does that received the lowest tested level of 250 ppm iodide in the diet (9 mg iodide/kg/day) for 2 days before parturition (i.e., equivalent to GD29-30), while the pup survival in the control group was 91%. This iodide level in the diet is comparable to the total iodide at the MeI LOEL of 10 ppm (7.6 MeI /kg/day, or 6.8 mg iodide/kg/day).

Arysta Response

The published literature referred to by DPR evaluated dietary iodide intake in experimental animals, not iodomethane exposure. The estimated amount of iodide received by pregnant rabbits exposed to 10 ppm iodomethane for 6 hours per day depends upon the inhalation rate used in the calculation. Total iodide of 6.8 mg/kg/day was estimated using the DPR default breathing rate of 540L/kg/day (RCD Table B-1), but the estimated iodide amount from iodomethane exposure would be lower if the more accurate breathing rate of approximately 317 L/kg/day used by DPR in the PBPK modeling were used in the calculation. Thus the iodide dose comparisons between studies are not accurate.

V.C.3.b. Additional Iodide from MeI; Page 150

DPR Comment

As shown in Table 71, the estimated additional iodide intake from MeI at the hypothetical RfCs, without any consideration for background iodide exposure, exceeds the tolerable ULs in most cases.

Arysta Response

DPR has taken the National Academy of Sciences (NAS) Dietary Reference Intakes for iodide and applied these acceptable upper limits for daily dietary exposure to acute (single day) exposure to iodomethane.

Iodine is an essential dietary element required for synthesis of thyroid hormones. Iodine deficiency results in hypothyroidism, goiter, and severe developmental abnormalities. The human health impacts of iodine deficiency, and iodine excess, are well established and documented (FAO, 2001; NAS, 2002; ATSDR, 2004). It is generally believed, and described in these documents, that more people are at risk for low iodine intake than for excess intake. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) assessed the human data on iodine intake and established a maximum tolerated daily intake level (WHO, 1989). The JECFA report noted that the majority of cases in the literature of adverse effects from excess iodine exposure stem from the use of iodine-containing pharmaceuticals, such as drugs and antiseptics. The Committee concluded that most people are tolerant of excess iodine and that the maximum tolerable level of iodine for the general population is likely to be higher than 1,000 micrograms per day (i.e., 0.017 mg/kg body weight per day).

A more recent report by the FAO/WHO reviewed the mineral requirements for humans (FAO, 2001). Based primarily on recent studies conducted in Belgium, the FAO committee proposed revised iodine intake recommendations for different age groups. The recommended iodine intakes proposed by FAO are comparable to the NAS (2002) recommendations, but include a new category for premature infants (Table 1). Premature infants have an immature thyroid gland which has a reduced ability to take-up plasma iodine relative to a more mature infant (FAO, 2001). Thus, the upper limit of a premature infant (100 microgram/kg/d) is lower than full term infants (150 micrograms/kg/d), but these intakes are still 2- to 3-times higher than an upper limit for adults (50 micrograms/kg/d). The FAO upper limit of iodine intake values (levels deemed likely to be safe) are higher than the NAS upper limit values, indicating that the new Belgium cohort data suggest that higher intakes of iodine are not likely to cause adverse health effects.

Table 1. WHO/FAO Recommended Dietary Intake of Iodine and Probable Safe Upper Limits (FAO, 2001).

Group	Recommended μg/kg/d (μg/d)	Upper limit μg/kg/d (μg/d)
Premature infants	30	100
Infants 0-6 mo	15	150
Infants 7-12 mo	15 (90)	140 (840)
Children 1-6 yr	6 (90)	50 (750)
Children 7-12 yr	4 (120)	50 (1,500)
Adolescents and adults (>12 yr)	2 (150)	30 (2,250)
Pregnancy and lactation	3.5 (200)	40 (2,286)

These upper limit iodine intakes are daily intakes which appear not to impair thyroid function that are based on loading studies performed in adults in the United States and infants studied in Europe.

The weight of the evidence indicates that DPR has selected a particularly conservative measure of acceptable daily iodide intake via the diet and applied this to risk assessment from acute exposure to iodomethane. Arysta suggests that a more appropriate single day acceptable iodide exposure level be identified and compared to the single day iodide intake from iodomethane exposure in the acute exposure iodomethane risk assessment.

V.D. Additional Uncertainty Factor Page 152

DPR Comment

An additional uncertainty factor is considered for MeI for young children because of 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 MeI exposure, and the level of excess iodide in MeI being added to the background iodide intake.

Arysta Response

An additional uncertainty factor is not warranted for any of the reasons mentioned because:1) potential neurodevelopmental effects described throughout this document are prevented by prevention of alterations in thyroid hormone levels, which occurs at the rat NOAEL of 20 ppm; 2) potential postnatal mortality has been studied and characterized in the guideline 2-generation rat study that was performed and submitted as required; and 3) iodide is an essential element that has been widely studied and DPR should make use of

data that provide acceptable short-term exposures to iodide for comparison to short term exposure to iodomethane.
used in the calculation. Thus the iodide dose comparisons between studies are not accurate.

Appendix A. Review of Physiologically Based Pharmacokinetic Model for Human Equivalent Concentration

Section II. Fetal Death in Rabbit Page A-4

DPR Comment

A key issue in selecting the dose metric for the HEC is the exposure duration and frequency associated with the NOEL.

Arysta Response

The use of NOELs rather than NOAELs is a fundamental problem with the assessment, particularly as it pertains to the developmental endpoint, where the NOEL of 2 ppm rather than the NOAEL of 10 ppm (Nemec, 2002; Mileson *et al*, 2009

Section II.A.1. Alveolar Ventilation Rate (QAC), Rabbit simulation Page A-5

DPR Comment

The illustration of the model fit to the data from the Sloter studies are provided by Mileson et al (2007) and given in Figure A-1a and A-1b (taken from Figures 4a, b in Mileson et al, 2007). The model showed reasonable fit to the 3 data points for fetal serum levels within 24 hours, but underestimated the maternal data, especially at hour 3. The fit for both maternal and fetal data became poorer as time progressed (Figure A-1b). No experimental data are available for model validation beyond a few days. The poor model fit in time indicates increasing uncertainty for extending the model beyond 24 hours, especially for accommodating the assumption by Mileson et al (2007) that the NOEL should represent a single day incremental exposure after the steady state of fetal blood iodide is reached on day 13. This issue on defining a single day HEC corresponding to the NOEL is discussed in Section II.B.1.

Arysta Response

The DPR evaluation of the model fit to iodide data from the Sloter studies (2005a, 2005b) was incomplete and not consistent with the standard practices of PBPK model evaluation (e.g., Chiu *et al*, 2007, USEPA, 2000). The comparisons of model predictions to experimental data were limited to data from the 20 ppm final study (Sloter 2005b), and did not include data from the 25 ppm preliminary study (Sloter 2005a). DPR notes that the model "underestimated the maternal data, especially at hour 3" and that the "fit for both maternal and fetal data became poorer as time progressed." It is important to note that the deviation of the fit of the model from the experimental data is in the health-protective (conservative) direction and, overall, the fit is very good based on recognized methods for PBPK model evaluation (Chiu *et al*, 2007). Assessment of the quality of fit (e.g., excellent, good, fair, poor) of PBPK models to experimental data has typically been subjective, based on visual inspection rather than rigorous statistical comparisons (Chiu *et al*, 2007). However, an example of a quantitative benchmark is the U.S. EPA's designation that a PBPK model would be acceptable for use in route-to-route extrapolation under an Enforceable Consent Agreement if the deviation of the model predictions from the experimental data did not exceed, on average, a factor of 2 (U.S. EPA, 2000).

A quantitative evaluation of the model fit to the experimental data demonstrates that the average difference in plasma iodide prediction compared to measured levels through 4 days of iodomethane exposure is only 24 and 28 percent for fetal and maternal levels respectively. For the quantitative method, the modeled value (m) is compared to the mean experimental value (e), and the maximum of m/e or e/m is used, such that the discrepancy between the model and mean experimental value is always expressed as a value greater than 1 (or equal to one if the prediction exactly matches the mean experimental value).

Of the 10 maternal iodide measurements at 20 or 25 ppm, only once did the model underpredict the maternal iodide concentration. In this case a model/experiment ratio of 1.03 resulted, indicating a 3% underprediction of maternal plasma iodide at 60 hrs—6 hrs after the end of exposure on day 3—for exposure to 20 ppm Iodomethane. Likewise, maximum fetal iodide underprediction was 14% (at the end of the second day of exposure). The maximum discrepancy between the modeled and average experimental values was a ratio of 1.80 for the fetal iodide at t=78 hrs (end of the 4th day of exposure) in rabbits exposed to 20 ppm iodomethane. The geometric mean for all comparisons of modeled maternal iodide and mean experimental values was 1.28, with ratios of 1.20 for the 3 through 24 hr data and 1.32 for the 30 through 78 hr data. The geometric mean for all comparisons of modeled fetal iodide and mean experimental values was 1.24, with ratios of 1.11 for the 3 through 24 hr data and 1.32 for the 30 through 78 hr data. It is inappropriate for DPR to criticize the slightly poorer fit of the model to the later data when DRP omitted some of the data from their analysis. The fit of the model to the later

data is still very good, with an average error of only 32 percent for both maternal and fetal iodide. (U.S. EPA, 2000). Clearly, the model more than meets the standard identified by the U.S. EPA which states that a PBPK model would be acceptable for use in route-to-route extrapolation if the deviation of the model predictions from the experimental data did not exceed, on average, a factor of 2 (U.S. EPA, 2000). This model meets this standard of acceptability.

Section II.A.1. Alveolar Ventilation Rate (QAC), Rabbit simulation , Page A-7

DPR Comment

The model output at 20 ppm Iodomethane exposure but using the non-pregnant 12 L-hr/kg3/4 QAC is presented in Table A-1. As expected, the lower QAC results in further deviation from the experimental measurements. The lack of model fit is also evident in the deviation from the experimental data regarding fetal-to-maternal iodide ratio, discussed in the next section. The use of lower QAC is troubling also regarding its biological implication, given that the window of vulnerability for fetal death in rabbits is during GD23-26.

Arysta Response

In this section DPR provides a comparison of modeling to experimental data using an alveolar ventilation rate (QAC) of 12 L-hr/kg$^{0.75}$, even though the comparisons of the model to the experimental data is most appropriately done using the higher QAC of 20 L-hr/kg$^{0.75}$ due to the period of gestation in which these exposures occurred (appropriate comparisons are shown in Figure A-1),. Therefore there is no value in making comparisons between model predictions using QAC of 12 L-hr/kg$^{0.75}$ to experimental values for any metrics derived from these studies—either the serum iodide concentrations or any ratios derived from these concentrations. We also are unclear why the use of the lower rabbit QAC of 12 L-hr/kg$^{0.75}$ in the assessments but Arysta (Arysta 2008 a, b) would be "troubling… given that the window of vulnerability for fetal death in rabbits is during GD23-26." The values derived from this value are simply more conservative. Given DPR's decision to use the simulations with the higher QAC value (Arysta, 2008e), DPR should revise Appendix A, eliminating/replacing any calculations and comparisons made using the QAC of 12 L-hr/kg$^{0.75}$ simulations.

The utility of evaluating the model predictions of ratios to the ratios of experimental values is questionable. The maternal/fetal plasma iodide ratios are not metrics used in the risk assessment per se. It is appropriate to consider the accuracy of the fetal predictions, if fetal metrics are considered for use in risk assessment, and likewise for maternal predictions; however evaluations of the ratios are not valuable in and of themselves.

DPR Comment

Table A-1: Modeled versus measured rabbit serum iodide concentrations after repeated 20 ppm Iodomethane (6 hour/day) exposure.

Arysta Response

The model output and the measured iodide concentrations in Table A-1 are not comparable and the table should be deleted or revised to include the appropriate model output as described below. Arysta will be happy to provide such a table at DPRs request. DPR has misused simulations intended to demonstrate HEC derivations (model application that includes a conservative assumption for breathing rate) and apparently is using these simulations as a check on the model development/validation. Actual model development and validation preceded the HEC derivations. The proper simulations for model validation are the QAC = 20 L-hr/kg$^{0.75}$ simulations of figure A-1b and simulations of the 25 ppm exposure (Sloter, 2005a). In DPR's table (A-1), the measured maternal iodide concentrations generally exceed the modeled values by about a factor of 2, whereas in the Arysta model validation simulations, the model never exceeded the experimental value by more than 3%. In DPR's table A-1, the modeled F/M ratios consistently exceed the experimentally measured ratios. In Arysta's simulations, (reproduced in Figure A-1b), the geometric mean of the ratio of modeled F/M value to the experimental F/M value was 0.94.

II.A.2. Maternal and Fetal Iodide Transfer

Rabbit Simulation Page A-8

DPR Comment

The resultant fetal-to-maternal serum iodide ratios (F/M) are compared to the two sets of experimental data.

Arysta Response

We wish to reiterate our criticism of the use of maternal/fetal ratios for comparing model simulations to experimental data. Comparisons of maternal simulations to data are appropriate, and comparisons of fetal simulations to fetal data are appropriate, but comparisons of ratios have no utility in and of themselves.

DPR Comment

The ratios from model output during the similar period are 3.1-8.2 at 2 ppm Iodomethane and 3.4-10.0 at 10 ppm Iodomethane exposure (Table A-2).

Arysta Response

Values in Table 2 based on modeling with QAC = 12 L-hr/kg$^{0.75}$ should be removed or replaced with the appropriate values from modeling with QAC =20 L-hr/kg$^{0.75}$.

II.A.2. Maternal and Fetal Iodide Transfer Rabbit Simulation, Page A-9

DPR Comment

No other experimental data are available for similar validation comparisons.

Arysta Response

Again, Arysta does not think it is valuable to make comparisons of ratios, when the serum concentrations per se are what is relevant for risk assessment. However, we must reiterate that DPR has not considered the serum iodide measurements from the 25 ppm iodomethane exposures (Sloter, 2005a).

DPR Comment

The extent of contribution by the lower QAC input parameter to this discrepancy is unknown.

Arysta Response

Comparisons of model simulations at QAC = 12 L-hr/kg$^{0.75}$ throughout Appendix. A should be replaced with the outcomes from the 20 L-hr/kg$^{0.75}$ simulations, and comparisons of the ratios are not valuable for risk assessment. We have found that the F/M ratios are more accurately predicted when QAC = 20 L-hr/kg$^{0.75}$, is used the value used in model development, as described above (Page A-5, Lines 33-43). Since DPR does not use any simulations of 10 ppm rabbit exposures to develop HECs and there are no 10 ppm data available for comparison, there is no value in presenting the 10 ppm simulations. For the 2 ppm simulations, DPR has only considered a single-day exposure (no preceding exposure), so there is no value to presenting 2 ppm rabbit simulations beyond 24 hrs. The correctly simulated 2 ppm rabbit concentrations and ratios are provided below, and were previously provided to DPR.

Hour	Fetal serum iodide (mg/L)	Maternal serum iodide (mg/L)	F/M ratio
3	0.23	0.74	3.2
6	0.33	1.4	0.42
24	0.11	0.87	7.8

II.A.2. Maternal and Fetal Iodide Transfer, Human Simulation, Page A-10

DPR Comment

The cord-to-maternal blood iodide ratio of 1.2 was used to adjust the CLTRANS1C (placenta to fetus) and CLTRANS2C (fetus to placenta) parameters to 0.15 and 0.12 L/hr-kg$^{0.75}$ respectively (Mileson et al, 2007; Barton, 2007).

Arysta Response

In should be noted that the CLTRANS1C and CLTRANS2C values produce a cord/maternal blood iodide ratio of 1.2 for **long-term, low level, constant** exposure. As DPR has noted in its analyses, the modeled human fetal/maternal serum iodide ratio is dynamic with short-term, discontinuous exposures.

DPR Comment

"However, even if this early stage is the only target period for fetal death concern, data are unavailable for determining how well iodide levels collected from deliveries during gestation week 29-36 may represent the neonatal stage at the end-of-first-trimester."

Arysta Response

We assume that DPR meant "prenatal" or "fetal" rather than "neonatal." DPR provides no rationale to support an assertion that the fetal/maternal iodide ratio might be different at the end of the first trimester compared to week 29. This sentence also suggests that the Rayburn *et al* 2008 data regarding iodide levels measured in maternal blood and cord blood during gestation weeks 29-36 might not be representative of the blood iodide levels during the target period of concern, the end of the first trimester (around gestation week 12). It is true that no data on cord iodide levels have been collected that early in human pregnancy, but Liberman *et al* 1998 reported that the average serum iodide concentrations in maternal blood during human pregnancy are 1.6 ± 0.2, 1.8 ± 0.2, and 1.8 ± 0.2 ug/dL in the first, second and third trimesters, respectively. This indicates that at least for the mother, the iodide concentrations in blood remain constant throughout pregnancy. In addition, in the Rayburn *et al* 2008 study a plot of the cord iodide concentrations vs. gestation week (see Fig 1 in Rayburn *et al*, 2008) showed a downward trend in cord iodide concentrations from late to early in pregnancy with a regression that

almost reached significance. This implies that the cord iodide levels might be expected to decrease or stay the same at earlier times during pregnancy, such as back to the first trimester. While these findings are not definitive, they do indicate that the cord iodide concentrations from gestation weeks 29-36 could very likely be representative of the cord iodide concentrations present at the end of the first trimester as well.

II.A.2. Maternal and Fetal Iodide Transfer, Human Simulaiton,Page A-11

DPR Comment

Another important issue regarding the maternal to fetal iodide transfer is that the F/M ratio is dynamic, not a fixed constant.

Arysta Response

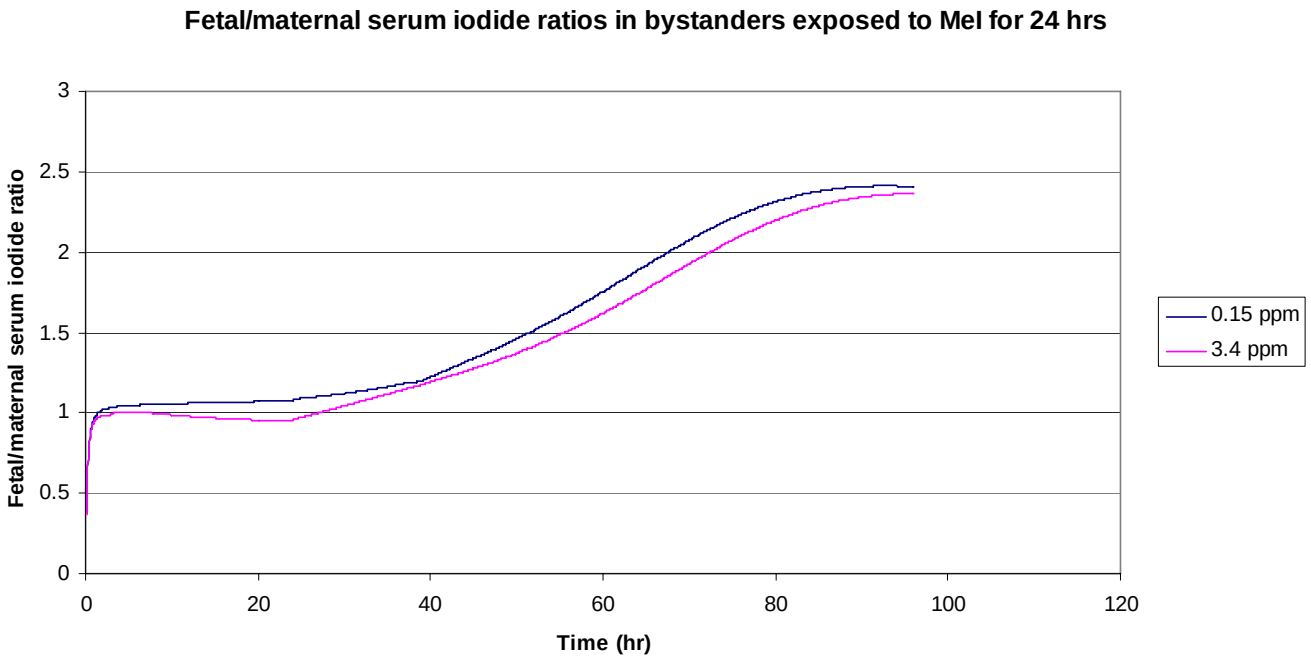
Again, we assert that the ratios of the model predictions should not be a focus of the model evaluation since this ratio is not a metric used in the risk assessment.

DPR Comment

While the fetal iodide concentration is consistently higher than the maternal level at 0.15 ppm Iodomethane exposure, this relationship is reversed near the peak concentration at 3.4 ppm Iodomethane.

Arysta Response

While changes in the predicted fetal/maternal iodide ratio with time and dose can be inferred from the plots, if DPR wishes to persist in analyzing this ratio, it would be much simpler to use the data from the spreadsheets to calculate the ratios, plot them over time, and combine the comparisons for the 0.15 and 3.4 ppm simulations into a single plot as provided below. The ratio profiles are very similar for the two concentrations. We speculate that the decline in the fetal/maternal ratio near the end of exposure at 3.4 ppm, but not 0.15 ppm, may be due to saturation of placental uptake. Overall, the time-dependence of the modeled fetal/maternal ratio does not appear to be very sensitive to iodomethane concentration in this 20-fold Iodomethane concentration range and thus the ratio is not sensitive to serum I- concentration.



DPR Comment

The F/M ratio gradually increases with decreasing serum iodide level after the end of 24 hours of exposure; from 1.0 within hour 24 to 2.1 - 2.4 by hour 78 - 96.

Arysta Response

The increases in fetal/maternal serum iodide ratio are clearly related to the change from I- accumulation to I- elimination in the modeled compartments, not the absolute value of the iodide concentration. For example, the fetal iodide concentration at the end of the 3.4 ppm simulation (Figure A-2, lower panel) is similar to the fetal iodide concentration at ~6 hrs exposure to 0.15 ppm iodide (Figure A-2, upper panel), but the fetal/maternal iodide ratios are ~2.4 and 1, respectively.

DPR Comment

Overall, data both in rabbits and humans indicate greater uncertainty at the fetal compartment level.

Arysta Response

We disagree. As noted in the response to Page A-5, Lines 33-43, the geometric mean model discrepancies for fetal and maternal rabbit iodide were 24 and 28%, respectively, so, if anything, fetal iodide is the more certain metric. The discrepancies do not increase

meaningfully with increased exposure duration. Also, DPR has not provided separate evaluations of the model's ability to predict human maternal vs. human fetal iodide levels, focusing instead on fetal/maternal ratios, so their analyses do not provide information on which metric (maternal or fetal iodide) is simulated with greater certainty.

DPR Comment

In the human model, it is uncertain how well data from the Rayburn study can adequately represent the modeled Iodomethane exposure scenarios; specifically regarding the unmatched gestation stage (i.e., applying data from beyond gestation week 29 to model the end of the first trimester stage) and the iodide exposure status (i.e., applying data from non-iodide exposure conditions to substantially high excess iodide exposure scenarios).

Arysta Response

These sentences also refer to whether the results from Rayburn *et al* 2008 for gestation weeks 29-36 are representative of the end of the first trimester. We refer to our comment concerning page A-10, L 13-15 earlier in the doucment. DPR's concern about whether the fetal/maternal iodide blood ratios are consistent between unexposed (e.g. the Rayburn study) and humans that might be more highly exposed to iodide, has been addressed in a report sent to DPR by Arysta LifeScience North America entitled, " Iodomethane: Arysta Responses to Toxicology Questions Discussed with Department of Pesticide Regulation", dated March 19, 2008 (DPR ID No.: CRR 192894N). A short summary of that report follows. Briefly, a study by Cottino *et al*, (1972) evaluated subjects who received a therapeutic injection of an iodated oxytocic preparation during labor to characterize placental iodine transfer and storage. The dynamics of mother-fetus iodine exchange was studied following administration of iodomethylspartein to parturient women. Cottino *et al* measured serum iodide levels in maternal and cord (fetal) plasma samples at birth, and birth occurred between 15 minutes and 48 hours after injection. Paired maternal and fetal serum iodide data from the Cottino study showed that iodine in soluble compounds rapidly cross the placenta and reach approximately the same levels in the fetus as in the mother. The return from the fetus to the mother appeared to be equally rapid as the maternal levels decreased as iodide was eliminated via the kidney. These data demonstrate that the fetal:maternal iodide ratio does not change when pregnant women are challenged by exposure to increased iodide.

The iodide concentrations reported by Cottino *et al*. were quite high (compared to the cord and maternal blood levels reported in Rayburn *et al* (in the 1 to 2 ug/100 mL range). Therefore, DPR's concern about using iodide ratios in unexposed people for estimating the ratios in exposed people are unfounded.

Section II.A.3. Fetal Thyroid Iodide Levels Page A-13

DPR Comment

Data from the Morris et al. (2004) rabbit study with NaI were used as starting points for modeling iodide disposition variables. The stated model assumption was that when blood kinetics are accurately predicted, tissue-specific parameters are sufficiently accurate without needing further adjustment (Mileson et al., 2007).

Arysta Response

The model developers recommended the use of fetal plasma iodide levels rather than a thyroid iodide dose metric in their assessment because the model does not predict tissue iodide levels with sufficient accuracy (Sweeney *et al*., 2009). The available data on rabbit tissue levels of iodide (Morris *et al*., 2004) after IV administration of iodide were used to develop approximations of parameters that determine the tissue levels of iodide. A major limitation of these data with respect to modeling was that the iodide measurements at the last three time points (6, 12, and 24 hrs after injection) were very similar in most tissues and higher in maternal thyroid at 24 hrs than at 12 hrs after injection. Thus the clearance phase of plasma and tissue iodide disposition could not be well-characterized from these data. When the values derived from the iodide iv study were used in simulations to predict serum iodide levels in rabbits repeatedly exposed to iodomethane (Sloter *et al*., 2005 a and b), parameters had to be adjusted to match the observations. The final iodide parameters do not adequately simulating the iv study (Sweeney *et al*., 2009). Thus with the current parameterization, the fit of the final model to the plasma and tissue data in the iodide iv study was sacrificed in order to fit the plasma iodide data in the iodomethane inhalation studies. The resulting rabbit plasma iodide dose metrics should therefore be considered the only valid iodide metrics available from the model for making predictions of iodide in iodomethane-exposed rabbits.

DPR Comment

The Morris study showed that within 24 hours of NaI injection on GD25, fetal thyroid did not accumulate iodide as compared to levels in fetal trachea.

Arysta Response

A closer review of the Morris study data indicates that fetal thyroid does accumulate iodide. The fetal thyroid iodide levels 24 hrs after the injection of the low dose, ranged from 1.88 to3.40 ug/g, for an average ± standard deviation of 2.92 ± 0.48 ug/g. The iodide levels in the fetal trachea were highly variable at all time points in the low dose study, with coefficients of variation (CVs) ranging from 0.65 at 1 hr after dosing to 1.3 at 24 hrs after dosing. The low dose, 24-hr levels of iodide measured in the trachea were

0.414, 0.8182, 0.8332, 0.8899, 0.9546, 1.77, 2.319, 3.429, and 10.22 ug/g, a 25-fold range, with an average ± standard deviation of 2.4 ± 3.08. If only the highest measured trachea iodide concentration is excluded, the average drops to 1.43 ±1.01. When the highest measured trachea iodide concentration is excluded, the ratio of the average thyroid concentration to the average trachea concentration is greater than 2 and using the median values, a thyroid/trachea ratio of 3 is computed. These data support the position that the fetal rabbit thyroid accumulates iodide.

DPR Comment

Thus, it is surprising that the model predicted a 4.2 mg/L peak fetal thyroid iodide level at the end of the 6 hour Iodomethane exposure, a level that is 217-fold higher than the maternal level at 0.02 mg/L (Figure A-3).

Arysta Response

The Morris data represent whole-thyroid concentrations of iodide, whereas the thyroid iodide predictions shown in DPR's Figure A-3 are for follicles only. Iodide preferentially partitions into the colloid of the follicle (7:1) and adults have a higher fraction of the thyroid volume as colloid than the fetuses (0.45 vs. 0.183). Thus it is to be expected that the whole tissue fetal thyroid/whole tissue maternal thyroid iodide ratio will be smaller than the ratio for follicles alone.

Section II.A.4. Human Neonatal Stage Page A-16

DPR Comment

Assuming the applicability of the low normalized sensitivity coefficient1 for VFETC (given as "<0.05" in Table 11 of Mileson et al., 2007) in this case, a 5- to 10-fold higher value for the VFETC (from 0.27 kg, or 0.6 pounds, to 3 to 6 pound fetuses) for later gestation period may still be significant.

Arysta Response

DPR suggests that changes in human fetal body weight (VFETC) may have a significant impact on risk, assuming the applicability of information in Table 11 of Mileson *et al.* (2007). DPR (inappropriately) uses information from a sensitivity analysis of the rabbit model rather than conduct a sensitivity analysis of the human model. Arysta , at DPR's request, is happy to provide either a human sensitivity analysis or greater precision in the rabbit sensitivity coefficients. The normalized sensitivity coefficient for rabbit maternal serum iodide AUC is 0.02 at 10 ppm and 0.01 at 2 ppm, and the normalized sensitivity coefficient for fetal serum iodide AUC at 2 ppm was 0.02. A normalized sensitivity

coefficient of 0.02 means that even with a 10-fold increase in the input parameter, the output is expected to increase by only 20 percent. Therefore any uncertainty about the relevant rabbit fetal stage has minimal contribution to uncertainty in the rabbit dose metric. This variability/uncertainty is more than adequately accounted for with DPR's uncertainty factors. We conducted human simulations at DPR's HEC of 0.24 ppm with the baseline human VFETC value (0.0044) and a value that is10-fold higher. At the higher VFETC, both maternal and fetal serum iodide AUC were decreased (maternal AUC decreased to 88% of baseline value, fetal value decreased to 58% of the baseline value), in demonstrating that the use of an early stage of human development is health-protective with respect to the HEC derivation.

II.A.5. Time Course Profile Page A-17

DPR Comment

Comparison of maternal and fetal parameters in rabbits (i.e., comparing blood to blood, thyroid to thyroid) shows that the maternal parameter is higher for the Iodomethane profiles whereas the fetal is higher for the iodide profiles.

Arysta Response

It is confusing when DPR uses the term "parameters" to refer to the model outputs. In PBPK modeling, the term parameters is usually reserved for the model inputs (flow rates, partition coefficients, metabolic rate constants), not the outputs. The maternal/fetal comparisons are not meaningful. The fetal/maternal ratios of various dose metrics in humans have no implications for risk if the same ratios are observed in the test species, so no useful generalizations can be drawn from these observations. The figures to which DPR refers should be replaced with figures generated using the model parameter values used in the HEC derivations (i.e., QAC = 20 L-hr/kg$^{0.75}$).

II.A.6. Summary Page A-17

DPR Comment

Available data for adjusting the input variables are limited, with experimental data only at 10-fold above the modeled 2 ppm and with high variability.

Arysta Response

DPR has neglected to consider the 25 ppm data set. The variability in the 20 and 25 ppm data is not extensive as demonstrated by an average discrepancy between the model and

experimental data of 28 percent (maternal) and 24 percent (fetal) calculated above in Arysta's Response to II.A.1

DPR Comment

The fundamental issue concerning modeling fetal death based on surviving fetal data remains unresolved.

Arysta Response

See comment below for Page A-21, Lines 30-35.

DPR Comment

"…the model shows some discrepancy within the first 24 hours of exposure and to a greater extent beyond the one day period."

Arysta Response

DPR apparently arrived at this conclusion without, reviewing all of the serum iodide data for iodomethane exposed rabbits. When the data for both 20 and 25 ppm are considered, it is clear that the discrepancy between the model and the experimental data is modest and not substantially different beyond 24 hours than within the first 24 hours.

DPR Comment

In general, the model output shows greater iodide in rabbit fetal serum relative to the maternal level than experimentally reported.

Arysta Response

DPR arrived at this conclusion by not consulting the applicable model simulations (i.e., they used model simulations with a lower estimated alveolar ventilation rate). The analysis should be re-done based on the applicable data. DPR also invested a great deal of effort in evaluating a model metric (fetal/maternal ratio) which is not a metric proposed for use in risk assessment. It would have been more appropriate for DPR to focus on the ability of the model to predict fetal serum iodide and/or maternal serum iodide, but not the ratio of the two.

DPR Comment

This may indicate a greater uncertainty for using rabbit fetal serum iodide as a dose metric for HECs.

Arysta Response

As noted above, the model predictions for fetal rabbit serum iodide are actually slightly more accurate than the predictions for maternal rabbit serum iodide (24 vs. 28 percent error), when experimental data from both 20 and 25 ppm exposures are considered.

DPR Comment

Questions remain for some biological input parameters (e.g., fetal stages) and simulation outcomes (e.g., extremely high fetal thyroid level).

Arysta Response

The sensitivity analyses do not indicate a significant impact for changes in fetal body weight on iodide AUCs. It is our opinion that thyroid simulations should not be used in the assessment because of insufficient data to confidently identify clearance of iodide from the rabbit thyroid.

II.B. Dose Metric Page A-20

DPR Comment

Thus, there is no support for modeling HEC based on 14 days of Iodomethane exposure (i.e., rabbit [$AUC_{day14} - AUC_{day13}$]).

Arysta Response

DPR mischaracterizes the approach used by Mileson *et al*. (2007). Mileson *et al*. (2007) model the HEC based **one** day of iodomethane exposure, not 14. The HEC developed and presented in Mileson *et al*. (2007) was derived on the basis of the fetal serum iodide AUC on one day, a day that was preceded by several previous days of iodomethane exposure. DPR recognizes that when rabbit iodomethane exposures do not include GD 23-26, no fetal death occurs. However that does not mean that the exposures on earlier days do not contribute to the toxicity observed in Nemec (2002). The exposure on days prior to GD 23 contributes to the body burden of iodide already present when exposures start on GD 23, enhancing the susceptibility to the GD 23-26 exposures." The pharmacokinetic simulations of the key study should describe the experiment as it was

conducted, rather than relying on an untested scenario. In the key study, the pharmacokinetics in the window of exposure are appropriately described when the contribution of previous days' iodide load is accounted for through PBPK modeling.

DPR Comment

It has also been demonstrated that during GD23-26, fetal death is evident at hour 30, immediately after the second 6-hour daily exposure to 20 - 25 ppm Iodomethane (Tables 55, 56, and 57 in Volume I). Thus, it is reasonable to model the HEC based on a single day exposure.

Arysta Response

Only Table 56 of Volume I includes results of exposures wherein fetal death was identified at hour 30, so references to tables 55 and 57 should be removed. This finding was not statistically significant.

II.B. Dose Metric, Page A-21

DPR Comment

Given the lack of data, DPR follows the conventional default for assessing developmental effects

Arysta Response

We disagree with DPR's statement that there is a "lack of data."

DPR Comment

…and assumes that these effects can occur as a result of a single exposure event within a specific window of vulnerability corresponding to a specific vulnerable developmental stage (USEPA, 1991).

Arysta Response

The approach used by Mileson *et al*. (2007) is consistent with the assumption that "a single exposure event within a specific window of vulnerability" can produce developmental toxicity. The data supports the kinetic modeling assumption that, in the study for which dose response data are available, the key exposure event occurs after previous days of exposure that did not contribute to toxicity. The way DPR has modeled the key study is only consistent with the hypothesis that the exposure on GD6 in Nemec

(2002) was responsible for the toxicity observed at higher exposure concentrations, a hypothesis incompatible with the data of Nemec (2003).

DPR Comment

Significant GSH depletion in fetal blood was detected as early as after one 6 hour 20 ppm exposure.

Arysta Response

DPR's arguments that fetal blood GSH decreases provide support for fetal death related to oxidative stress and cell death are very weak compared to the arguments previously developed for a mode of action related to increased fetal iodide. Even at 20 ppm, the LOAEL for fetal death, and 25 ppm, fetal GSH declines in blood are modest, and GSH levels in liver did not show statistically significant declines. The 20 and 25 ppm exposures on GD 23-24 show a reverse dose response with respect to blood GSH depletion (i.e., at 20 ppm, blood GSH was 55% of control, but a lesser decline, to 72% of control was observed at 25 ppm). Thus a dose-response concordance is lacking. A mode of action related to such a generic process as cell death would be expected to be operative throughout gestation, rather than being limited to such a narrow window of susceptibility.

DPR Comment

Fetal circulating iodide is a pertinent dose metric because experimental data in rabbits are available. However, the use of this dose metric should be viewed with caution for several reasons. First, all the experimental measurements used for model validation are from fetuses that survived the iodomethane exposure, a direct opposite outcome to the endpoint targeted for modeling.

Arysta Response

We agree that fetal circulating iodide is a pertinent, and we believe, the most pertinent, dose metric for this endpoint. The data used for model validation of the fetal plasma concentrations were time-course measurements taken in does and fetuses after 6 hour inhalation exposures to iodomethane during GD 23, 24, 25 and 26 (see Sloter *et al*. 2009), the window of susceptibility for fetal rabbit death. Based on the data from Nemec *et al*. 2009, some of the rabbit fetuses from which blood samples were collected during GD 23 through GD 26 would have died by GD 29. Therefore, the plasma iodide levels measured in the Nemec *et al*. 2009 experiments would have included surviving fetuses, as well as fetuses that were going to die by GD 29. It is unlikely that the reason some fetuses die and some live is due to pharmacokinetic differences (e.g. possibly higher iodide levels) as the DPR seems to imply, but is more likely due to pharmacodynamic reasons (e.g. differences in susceptibility), something seen quite frequently in other toxicity

experiments (the same internal doses lead to affects in some animals, but not others). Since we are of the opinion that fetal plasma iodide concentrations are the appropriate dose metric for the fetal death endpoint, then if the susceptible fetuses actually did have higher plasma iodides than those that survived (although we do not believe that is the case), the use of our dose metric should be considered conservative as the lower plasma iodides from surviving fetuses would have diluted the higher levels from fetuses that would have died (the plasma iodides were averaged for all fetuses in a timed group). In any event, the model is ultimately used to simulate the kinetics at the NOEL, a scenario for which, by definition, there is no toxic outcome. We do not believe that caution in using this dose metric is warranted based on this reason stated by DPR.

DPR Comment

…the model predicted iodide F/M (fetal-to-maternal) ratios are generally higher than experimentally measured in rabbits (Section II.A.4).

Arysta Response

We have previously commented on DPR's use of model simulations that are not applicable to the model validation, as discussed in our comments on Section II.A.4. These comparisons were not made appropriately. Furthermore, what is important is the model's fidelity to each independently, experimentally measured metric that is relevant to validation, not to relationships among these metrics.

DPR Comment

DPR: "The proportionately higher distribution to the rabbit fetal compartment…"

Arysta Response

The appropriateness of the fetal model predictions should be based on comparisons of fetal data to fetal simulations, not fetal/maternal ratios, and the model does an excellent job of predicting the available fetal and maternal data.

DPR Comment

the range of human F/M ratio is wide and there are 9 sets of values above 2 (2.08 – 5.4).

Arysta Response

The number of sets should be put in the context of the size of the study, which consisted of an n of 121. There are a number of reasons why the fetal/iodide ratio may be variable. One possibility is the administration of IV fluids diluting maternal blood. As noted from

the iodomethane modeling, the fetal/maternal iodide ratio appears to increase after iodide delivery stops. Food is typically withheld from women in labor, which could interrupt the maternal iodide supply, producing an imbalance in which fetal iodide temporarily exceeds maternal iodide.

Page A-22

DPR Comment

The use of the maternal iodomethane or iodide dose metric has the advantage of focusing more on the total internal dose of exposure without the additional uncertainty of further modeling to the fetal distribution level.

Arysta Response

DPR falsely asserts that there is more certainty regarding the maternal iodide than fetal iodide. Clearly, the modeling of serum iodide in maternal and fetal rabbits have equivalent certainty.

DPR Comment

"They [maternal Iodomethane and iodide] are more suitable dose metrics when no single MOA can be supported."

Arysta Response
We strongly disagree. For any compound displaying **selective** developmental toxicity, fetal dose metrics are much more suitable than maternal dose metrics.

DPR Comment

The 6- versus 24-hour Iodomethane exposure durations between rabbits and humans can be accounted for by the AUC dose metric but not by the peak concentration…

Arysta Response

DPR asserts that the 6 hr exposure in the rabbit study vs. the 24 hr exposure of humans cannot be accounted for by peak concentration. We do not understand why a model deemed to acceptably compute AUCs for a given exposure scenario cannot acceptably account for peak concentrations as well. In section II.C of appendix A, DPR used model-derived peak concentrations.

DPR Comment

…maternal iodide dose metric is most reliable for reflecting the maternal Iodomethane exposure

Arysta Response

DPR asserts that maternal iodide is the most "reliable" dose metric for reflecting maternal iodomethane exposure. A fundamental flaw in DPR's assessment is the failure to separate model validation from model application in dose-response (HEC assessment). Indeed, the iodide measurements reliably indicate how much free iodide was generated from iodomethane metabolism. But just because a dose measure is a "reliable" indicator of *exposure*, doesn't make it an **appropriate** metric for *toxicity*. The appropriate dose metric should be related to the mode of action.

Section II C. HECs Page A-23

DPR Comment

HECs based on all 8 dose metrics (i.e., permutation of peak concentration or AUC of Iodomethane or iodide in maternal or fetal blood) are presented below for demonstrating their overall impact to the HEC.

Arysta Response

Potential MOAs associated with each of the 8 dose metrics should be presented. If no justifiable MOA can be developed, the dose metric should be eliminated from consideration. Even if no MOA data were available, the preferred dose metric for a selective developmental toxicant should be fetal dose metrics rather than maternal dose metrics.

DPR Comment

When the dose metric is based on the peak concentrations, it is taken from immediately after the cessation of exposure (i.e., hour 6 for rabbits, hour 24 for humans), since the concentration declines thereafter (Figure A-5 and A-6).

Arysta Response

We have noted that the peak iodide concentrations in the simulations are typically observed shortly after the end of exposure.

DPR Comment

The lower sensitivity of Iodomethane parameters is likely due to its rapid transformation into iodide.

Arysta Response

Please note that, as commonly used in PBPK modeling, these iodomethane-related dose metrics should not be referred to as "parameters." Their lack of sensitivity to QAC is independent of the metabolism rate of iodomethane, but it due to rapid equilibration with tissues.

Page A-24

DPR Comment

Table A-4 shows that within the same parameters (i.e., serum Iodomethane or iodide), the HECs…

Arysta Response

DPR's use of "parameters" is inconsistent with the usage of this term in the PBPK modeling community, and therefore potentially confusing.

DPR Comment

The higher rabbit fetal iodide partitioning parameter contributes significantly to this overall 4- to 5-fold higher HEC.

Arysta Response

There is no "rabbit fetal iodide partioning parameter". There are parameters that describe the transport to and from the fetus, and within the fetus there are multiple iodide partition coefficients that describe the equilibrium partitioning of between serum and tissues.

DPR Comment

Iodomethane at 0.24 ppm represents the HEC at the most pertinent dose metric and is the final 24-hour HEC for assessing the risk of the general public.

Arysta Response

We disagree with DPR's statement that maternal iodide AUC is the "most pertinent" dose metric. We believe that the most pertinent dose metric is fetal iodide. If DPR is truly convinced that there is insufficient data to identify an adequately supported MOA, fetal rabbit Iodomethane should be used as the dose metric.

DPR Comment

An ideal portrayal of the total amount of maternal exposure to Iodomethane would include also the portion of Iodomethane that is not yet converted to iodide.

Arysta Response

Based on the simulations conducted, the portion of iodomethane that is not yet converted to iodide would not be sufficient to generate enough additional iodide to substantially increase the AUC. As noted by DPR, this amount of iodide is insignificant.

Section II.C.2. Occupational HEC Page A-26

DPR Comment

Paragraphs 1-3

Arysta Response

The HEC modeling simulations for worker exposures included the assumption that respiration was increased to 833L/hour during the 8-hour workday and decreased to resting (567 L/hour) the remaining 16 hours per day. For the developmental endpoint, worker exposure was assumed to occur for 8 hours per day, seven days per week and the iodide dose metrics were derived for day 7 of the exposure. The HEC was designed to protect the worker from increased plasma iodide for all days including the seventh day of exposure when iodide levels could have built up from the prior day exposures.

Iodomethane: Arysta Life Science NA Response to the Medical Tocicology Branch's Methyl Iodide (Iodomethane) Risk Characterization Document for Inhalation Exposure

Volume II

Exposure Assessment

Volume II

Appendix III Comparison of DPR's Exposure Estimates with the Exposure Estimates in US EPA's Registration Eligibility Documents, Occupational Exposure Estimates

Page 73

DPR Comment

DPR used the field spikes to make its own adjustment for recovery and analytical technique. U.S. EPA used the registrant's calculated field spike adjustments

Arysta Response

It is Arysta's view that the study director is highly valuable in determining appropriate recovery values in an exposure assessment. DPR has calculated its own values based on the field spikes. The apparent difference between the DPR and study director recovery estimates is that the study director considered the subset of trapping efficiency tests conducted with higher concentrations more reliable.

For example, in the Oxnard study (Baker *et al*., 2003e), the trapping efficiency was measured as 53%, 81%, and 79% for fortification levels of 0.4 ppb, 43 ppb, 422 ppb, respectively. The study director used a value of 80% to adjust all of the samples in the study based on the average of the two trapping efficiency measurements above the limit of quantification (LOQ) (43 and 422 ppb). By contrast, DPR apparently attempted to match the measured concentrations in the study to the closest field spike to adjust for recovery, which resulted in the use of 53% recovery for hole punchers and planters and 81% for tractor drivers, shovelers, and tarp monitors. However, the measured iodomethane concentrations for hole punchers was 10 ppb and the measured iodomethane concentration for planters was 5 ppb (identical measurement for two replicates). The hole puncher concentration of 10 ppb is closest in magnitude[1] to the 43 ppb trapping efficiency value and the 5 ppb concentration for the planters is roughly between the 0.4 and 43 ppb trapping efficiency values.

Furthermore, the trapping efficiencies measured at higher concentrations are more accurate because there is less analytical error in these measurements compared to the measurement of concentrations below the LOQ (the LOQ is 17 ppb compared to the low field fortification level of 0.4 ppb).

For these reasons, Arysta requests that DPR use the most reliable data to estimate field recovery, which includes trapping efficiency tests with concentrations greater than the LOQ only. Also,

[1] Because the concentrations in the trapping efficiency measurements differ by orders of magnitude, the appropriate base of comparison is on a logarithmic scale which compares the relative orders of magnitude of the values.

Arysta requests an explanation from DPR about the methodology it used to estimate recovery values and why it selected not to use the laboratory values.

II A. EXPOSURE ASSESSMENT, Occupational Exposure Studies Treatment of Study Data Page 27

DPR Comment

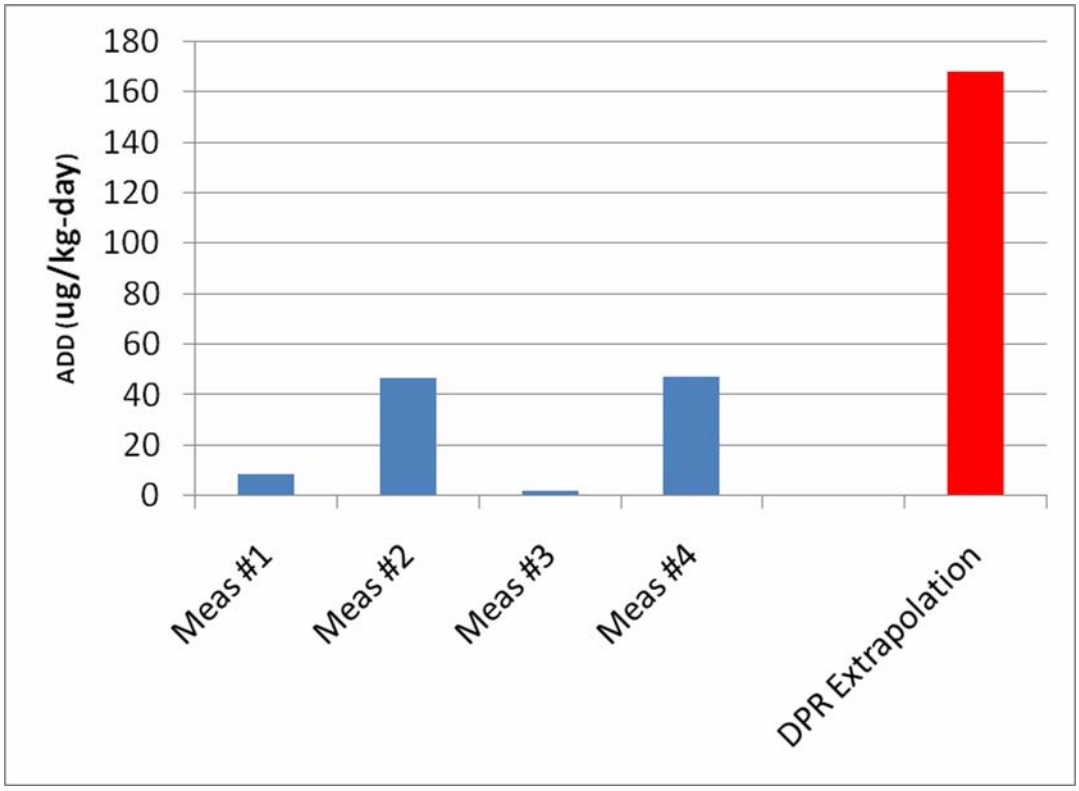
In calculating acute exposures, DPR uses an upper-bound estimate of the measured air concentrations (Frank, 2009). By convention, the upper-bound used is a point estimate of the 95th percentile of a lognormal distribution of MI concentrations

Arysta Response

DPR applied an overly conservative methodology to estimate exposures for workers applying iodomethane. Arysta has provided six occupational exposure field studies with multiple measurements of worker tasks in each study. The U.S. EPA estimated occupational risks with the average and maximum value for each of the worker tasks. Instead of applying this reasonable methodology, DPR developed an extrapolation method based on a lognormal distribution in ~~to~~ an attempt to estimate a 95th percentile value. Given that there are less than 20 measurements for the occupational exposure scenarios, DPR's exposure estimates are higher than the maximum measured value in every case, sometimes by more than a factor of three.

For example, for drivers and applicators for the shallow-shank, tarped-bed injection studies, the four measured values from the occupational exposure studies were 8.7, 46.9, 2.1, and 47.3 µg/kg-day. DPR applied its extrapolation procedure to these four data points to estimate a 95th percentile value, which resulted in 168 µg/kg-day. These values are summarized in Table 1. Thus, in this case, the value DPR used~~s~~ for risk assessment is 3.6 times higher than any measured value.

Figure 1. Measured and extrapolated absorbed daily dose values for drivers and applicators for tarped bed applications



DPR applied this methodology based on a policy memorandum that was issued in the last few months[2]. In fact, this memorandum appears to have been written while this assessment was in progress. Arysta requests a list of recent occupational assessments performed by DPR utilizing this methodology so that we can further evaluate its reliability.

The DPR policy memo provides no explanation regarding why DPR assumed a lognormal distribution for the data. DPR must have a lot of occupational exposure data in its possession, including for fumigants, and could have performed an analysis of these data to justify this assumption rather than assuming a statistical distribution with a large uncertainty at the upper percentiles DPR indicates "any discrepancy from the lognormal distribution will be greatest at the upper extremes"

[2] Frank, J.P. Method for calculating short-term exposure estimates. California Department of Pesticide Regulation. HSM-09004.

II A. Exposure Assessment, Occupational Exposure Studies, Treatment of Study Data Page 27

DPR Comment

The arithmetic mean, 8-hour air concentrations of MI for each of the task categories was used to represent seasonal exposures for these workers.

Arysta Response

Arysta is pleased that DPR used an average value to estimate exposures for durations longer than a day. However, DPR assumed that a worker will be involved in iodomethane applications for every day for three months, including weekends. This is clearly an unreasonable assumption. Applicators typically apply different fumigants over the course of the growing season, so there is no reason to believe that they will apply iodomethane every day. Furthermore, most commercial applicators work normal 5 day/week schedules, except in unusual circumstances. Arysta recommends that DPR consider a more typical application regime of no more than three applications of iodomethane per week. Thus, the seasonal and annual exposure estimates should be adjusted by 3/7.

Additionally, the overestimation with this methodology is compounded by assuming that the worker is exposed for 8 hours each and every day of exposure. In the occupational exposure studies submitted by Arysta, the exposure durations were typically 5 hours. In reality, the exposure duration will be determined by the size of the field, the type of application, and the amount of preparation required before applying the fumigant. Also, it is typical for workers to take occasional breaks, including a half-hour or hour lunch break. For this reason, many air pollution studies have utilized 6.6 hour daily exposure duration protocols, as acknowledged by the California Office of Environmental Health Hazard Assessment (OEHHA)[3].

I INTRODUCTION

J Inhalation Uptake/Dermal Absorption Page 11

DPR Comment

The arithmetic mean, 8-hour air concentrations of MI for each of the task categories was used to represent seasonal exposures for these workers. Thus, the percent

[3] Recommendation for an Ambient Air Quality Standard for Ozone, http://www.oehha.ca.gov/air/criteria_pollutants/pdf/ozonerec1.pdf

retention/absorption of methyl iodide for individuals at rest or at work can vary widely. As a consequence, a default factor of 100% retention/absorption will be used (Frank, 2008)

Arysta Response

The PBPK model can be used to accurately estimate inhalation absorption. DPR has used the PBPK model to develop HECs for this assessment, so it's not clear to us why DPR did not use it for this purpose as well.

II. B Exposure Assessment (Application Site Air Monitoring Studies) Page 34

DPR Comment

The time-weighted-average (TWA) of maximum estimated methyl iodide soil flux densities at 1 hour, 8 hours, and 24 hours are shown in Table 12, along with the application rates (for a full description of the technique see Barry, 2008a).

Arysta Response

For the Oxnard shank, raised bed study (DPR Data Volume 52875-046), the "maximum" 1-hour flux rate refers to the period just after the application and the flux rate was calculated only assuming the portion of the field that was treated during the measurement period. For the first period after the application, the flux rate was calculated assuming only 28% of the field was applied, and for the second period, the flux rate was calculated assuming only 55% of the field was applied. DPR applies this flux value over an entire 40 acre field for their modeling calculations. By doing so, DPR's calculation includes more mass emissions than actually occurred in the field study, resulting in an overestimation of the concentration.

According to Arysta's calculations, the flux rates for the Oxnard shank, raised bed study, adjusted for a 40 acre field, should be as follows:

- 1-hr: The flux rate should be 151 $\mu g/m^2/sec$ instead of 535 $\mu g/m^2/sec$ as DPR has calculated.
- 8-hr: The flux rate should be 134 $\mu g/m^2/sec$ instead of 266 $\mu g/m^2/sec$ as DPR has calculated.
- 24-hr: The flux rate should be 131 $\mu g/m^2/sec$ instead of 187 $\mu g/m^2/sec$ as DPR has calculated.

This should result in lower concentration estimates for the raised bed, shank injection results in Table 13.

It would be helpful to Arysta if DPR tabulated the exact flux rates it used for the calculations in Table 13. These rates were apparently adjusted from the flux rates summarized in Table 12 to account for the maximum application rate and the portion of the field treated for raised bed and drip applications. Having the exact flux rates would be useful for further review.

DPR Comment

The meteorological conditions used for each averaging time were: 1 m/s wind speed and D stability (maximum daytime atmospheric stability) at both 1 and 8 hours; and 1.44 m/s and C stability (DPR 24-hr screening meteorological conditions) at 24 hours (Segawa, 1997).

Arysta Response

There are a number of advanced probabilistic modeling tools available to estimate concentrations downwind of fumigant applications. Most notably, the PERFUM model, sponsored by Arysta, has the capability of estimating buffer distances and air concentrations following fumigant applications. The user has the capability to employ historical meteorological datasets from weather stations to simulate actual meteorological conditions at any site of interest. In Arysta's discussions with DPR, the department indicated that one of the reasons that it did not use PERFUM was that the model does not provide air concentration estimates, but instead only estimates buffer zone distances. PERFUM was modified about two years ago, and now includes the capability to estimate air concentrations at different downwind distances. Further, if DPR needs estimates for a downwind distance that is not currently included in the PERFUM model, Arysta is willing to work with DPR to provide a customized version.

DPR has chosen to estimate downwind concentrations of iodomethane using an extremely simple and crude modeling methodology that doesn't account for real meteorological conditions. Specifically, DPR made the following assumptions:

- 1-hr and 8-hr peak concentrations: wind speed of 1 m/sec, "D" class atmospheric stability, and a constant wind direction
- 24-hr concentration: wind speed of 1.4 m/sec, "C" class atmospheric stability, and a constant wind direction.

The assumption of a constant wind direction over 24 hours, or for that matter 8 hours, is particularly unrealistic. Furthermore, the wind speed assumption is at the extreme low-

end of the distribution of wind speeds in the environment. In fact, the dispersion model used by DPR will not even accept a smaller wind speed than 1 m/sec.

The illogical nature of DPR's calculations can be observed by comparing the concentration estimates averaged over 8-hour and 24-hours in Table 13. These concentrations are intended to be "maximum" concentrations at different distances from the edge of the field and refer to the concentrations at 152 meters from the edge of a 40-acre field where iodomethane was applied at the maximum usage rate. For a given "maximum" 8-hour average concentration, the corresponding "maximum" 24-hour average concentration should not be less than one-third of the "maximum" 8-hour average concentration. Even if the concentration over the other 16 hours of the day was zero, the "maximum" 24-hour average concentration would be one-third of the "maximum" 8-hour average concentration. However, in a number of cases, the "maximum" 24-hour concentration is less than one-third of the "maximum" 8-hour concentration. For example, for the drip irrigation estimate at 152 meters in Table 13, the "maximum" 8-hour concentration is 9.5 µg/L, while the "maximum" 24-hour concentration is 1.7 µg/L. Even if the concentration were zero for the other 16 hours of the day, given a concentration of 9.5 µg/L for the first 8 hours, the "maximum" 24-hour concentration would be 3.2 µg/L.

Arysta does not point out this inconsistency to argue that one or the other of DPR's concentration estimates are the correct one. Neither is correct. Instead, this comparison shows that DPR's use of artificial meteorological scenarios lead to results that are not even consistent with one another.

II. B. Exposure Assessment, Bystander Exposures (Application Site Air Monitoring Studies) Page 35

<u>DPR Comment</u>

The greatest, estimated, adjusted time-weighted average air concentrations of methyl iodide associated with different application techniques in a 40-acre field were generated from the flux estimates shown in Table 12.

<u>Arysta Response</u>

DPR estimates MOEs for worker bystanders using the 8-hour exposure estimate at the edge of the buffer zone (152 meters) and MOEs for other bystanders using the exposure estimate for 24-hours at the edge of the buffer zone. Logically, one would assume that the risk is higher for being at the edge of the buffer zone for 24-hours compared to 8-hours. However, the MOEs are less (higher risk) for the 8-hour exposure. DPR derived the HEC of 0.22 ppm used for worker bystanders by assuming 7 days of consecutive exposure for 8 hours per day and basing the HEC on iodide level at 7 days. This

assumption is unreasonable for a worker bystander as DPR's calculation assumes the peak flux rates immediately after the application, but the flux rate declines substantially over the first 7 days. DPR does not account for the decrease in flux rates

DPR also provides estimates for concentrations at closer distances to the field than 152 meters, but does not provide MOEs at these distances. Providing MOEs for the smaller distances would add perspective to the risk assessment.

II. B. Exposure Assessment, Bystander Exposures (Application Site Air Monitoring Studies), Seasonal Exposure Page 36

DPR Comment

Barry (2008b) estimated 2-week TWA concentrations to be used for estimating repetitive bystander exposures, by first calculating an average 24-hour flux over a 2 week period, then adjusting the flux with a time-scaling factor. The time-scaling factor is derived using peak-to-mean theory, based on both empirical and theoretical studies (Barry, 2008b). As bystanders can be no closer than 152 m for the first 48 hours, it was assumed that bystanders who may reside next to the treated field would be at 152 m 100% of the time for the entire 2-week period.

Arysta Response

DPR estimated "seasonal" exposure by calculating a 2-week average concentration for someone continually living at 152 meters from the edge of the treated field following an application. This assumption seems particularly unlikely. Over the course of a 2-week period, even someone that by chance lives right at 152 meters from the edge of the field will go other places, such as work or school or to other places for recreation or to run errands. Furthermore, DPR's methodology for estimating the 2-week average concentration is based on something DPR calls "peak-to-mean" theory, which is described in a memorandum that is not available to us. The most appropriate way to estimate a long-term average concentration is to use a dispersion model with historical meteorological data. This would allow one to account for changing wind directions and wind speed instead of just assuming low wind speed and a constant wind direction.

II. C. Exposure Assessment, Community Exposures (Ambinent Air Concentrations) Page 38

DPR Comment

For the purposes of comparison between application site versus community repetitive exposures to ambient air concentrations of fumigants, methyl bromide could be

considered a surrogate chemical for two reasons. First, methyl bromide and methyl iodide are similar chemically. Second, the measured air concentrations of the two chemicals from application site monitoring (24-hour TWA) and worker activities indicated comparability.

Arysta Response

Arysta has supplied a complete data set to DPR including 11 flux studies. DPR should be using the iodomethane data set in this risk assessment rather than using methyl bromide, or any other fumigant as a surrogate. DPR makes an inappropriate comparison of iodomethane to methyl bromide in this discussion saying that "methyl bromide could be considered a surrogate chemical" for iodomethane because they are "similar chemically" and "measured air concentrations of the two chemicals from application site monitoring" are similar.

Iodomethane degrades in the atmosphere with a half-life of 5.2 days (as noted in the risk assessment). Methyl bromide is far more persistent with a half-life of about 1.5-2 years[4]. This is why methyl bromide makes its way up to the stratosphere and depletes the ozone layer. The fast atmospheric degradation rate of iodomethane results in a substantially smaller probability of significant community exposure, compared to the very persistent methyl bromide.

DPR tries to justify its approach by stating that its modeling estimate of the 2-week concentration for iodomethane is similar to the community exposures measured for methyl bromide. However, the similarity of the values of 0.07 µg/L for iodomethane; and 0.046 µg/L for methyl bromide is fortuitous. There is no validation of DPR's modeling approach for iodomethane for a 2-week exposure which results in the 0.046 µg/L estimate. Additionally, given that DPR assumes a constant wind direction over the entire period, the methodology overstates the true concentration. Furthermore, DPR's community monitoring was not intended to measure the concentration at the edge of a buffer zone. -The air monitors yielding the results of 0.07 µg/L for methyl bromide were not that close to the downwind edge of any field. DPR needs to reconsider the reasoning it has used to equate methyl bromide and iodomethane and needs to develop a more realistic modeling methodology for seasonal exposures. The SOFEA model developed by Dow was designed for this purpose and DPR has successfully used the SOFEA model for Telone. DPR should either use the SOFEA model to estimate two week average concentration or work with Arysta to modify PERFUM to perform these calculations

Another limitation with DPR's comparison of its modeling estimate to the measured methyl bromide concentrations is that the modeling estimate is based on the absolute

[4] http://www.ars.usda.gov/is/np/mba/april96/sims.htm

worst-case scenario, which includes a 40 acre field at the maximum application rate of 175 lbs/acre and the maximum flux rates across the studies conducted by Arysta.

III C Exposure Appraisal Estimation of Application Site Air Concentrations Page 46

DPR Comment

However, looping of the plume (atmospheric waves of different contaminant concentrations) under these conditions can result in high local air concentrations (Stull, 1988).

Arysta Response

This is actually highly unlikely to happen for an area source such as a fumigant application where the emission is spread over a large area and emitted from the ground. This point is accurate for any of the possible acreages for fumigant applications (e.g., 1-40 acres). The reference cited by DPR likely refers to a plume emitted from an elevated stack into a highly unstable atmosphere

Appendix III Comparison of DPR's Exposure Estimates with the Exposure Estimates in US EPA's Registration Eligibility Documents Page 75

DPR Comment

Although the ISCST3 model has been thoroughly evaluated at DPR, the PERFUM components had not at the time this exposure assessment was completed. Therefore, only screening level air concentration estimates have been used for the DPR methyl iodide exposure assessment.

Arysta Response

Firstly, this position is inconsistent with DPR's use of the PERFUM model for the development of mitigation measures for another fumigant, metam sodium (Barry, 2007[5]). DPR demonstrated no reservation in this instance to using PERFUM for developing buffer zones for another fumigant.

[5] Barry (2007) Development of additional isothiocyanate buffer zones for the metam sodium mitigation proposal. Internal DPR memo to Charles Andrews from Terrell Barry via Randy Segawa.

Secondly, PERFUM has been widely used for more than 5 years by the EPA and has undergone significant scrutiny over that period and has remained intact with only a few very minor bug fixes required. EPA has thoroughly evaluated the model and successfully used it for all soil fumigants. National buffer zone requirements included in the draft Reregistration Eligibility Documents issued in July, 2008; and expected to be implemented by EPA are largely based on the PERFUM model. It is concerning for DPR to eschew use of the model with such a casual statement.

Thirdly, use of the PERFUM model provides regulators with substantially more information about potential risks given that it provides probabilistic estimates using two different types of distributions, including the maximum concentration distribution which considers only the downwind distances with the highest concentration and the "whole field" approach which considers all downwind distances. The information available to regulators is substantially more robust with PERFUM compared to DPR's deterministic approach.

Fourthly, PERFUM allows the use of actual meteorological data providing a more credible result in order to base important regulatory decisions, instead of relying on only crude generalizations of meteorology data as DPR has done.

Appendix III. Comparison of DPR's Exposure Estimates with the Exposure Estimates in US EPA's Registration Eligibility Documents, Buffer Zones Page 76

DPR Comment

In a second iteration of a draft risk assessment for MI (USEPA, 2007), U.S. EPA estimated whole field" buffer zone distances near 40-acre fields using the PERFUM model and "target concentrations" derived from various acute toxicological endpoints … The whole field buffer zone method does not control the per application buffer zone failure rate.

Arysta Response

The "whole field" buffer zone approach is perfectly reasonable. In contrast to DPR's default approach, the "whole field" approach considers the entire area around a treated field to better approximate the true probability of an exposure. Specifically, locations around the whole circumference of the field are included in the concentration distribution. The approach recognizes that there is not necessarily a bystander in every direction around a treated field, particularly in rural agricultural areas, and that the wind direction is constantly changing so that a person at the maximum concentration location one hour may not even be exposed the next hour. Therefore, any methodology that is limited to considering only the direction around a field where the maximum concentration occurs

will significantly overestimate the true probability of there being an exceedance of the target concentration.

When DPR calculates a worker exposure for an applicator, DRP knows that this activity will actually happen for a given application. For bystanders, it is actually unlikely that any person will be at the edge of the buffer zone in the location with the maximum concentration for the entire 24 hours following an application. Yet, this is what the "maximum concentration" approach employed by DPR assumes. The "whole field" approach merely acknowledges that the probability of someone being at the point of maximum concentration for an entire exposure period is small. Therefore, the "whole field" approach allows a buffer zone to be estimated by more closely approximating a true probability of someone actually being exposed.

EPA has found this approach to be reasonable and conservative. Arysta agrees with EPA's position and requests that DPR reconsider use of the "whole field" approach.

References

Ammerman, C. B., L. R. Arrington, A. C. Warnick, J. L. Edwards, R. L. Shirley and G. K. Davis, 1964. Reproduction and lactation in rats fed excessive iodine. J. Nutrition 85:107-112.

Arrington, L. R., R. N. Taylor, Jr., C. B. Ammerman and R. L. Shirley, 1965. Effects of excess dietary iodine upon rabbits, hamsters, rats and swine. J. Nutrition 86:394-398.

Arysta (Arysta LifeScience North America Corporation). 2006. Iodomethane: Arysta responses to toxicology issues raised by Department of Pesticide Regulation. Submitted to DPR through Technology Sciences Group Inc., Sacramento. April 14, 2006

Barry, T. 2007. Development of additional isothiocyanate buffer zones for the metam sodium proposal. Memorandum to C. Andrews. Environmental Monitoring Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA.

Barry, T., 2008a. Screening level air concentration estimates for Worker Health and Safety Exposure Appraisals. Memorandum to Randy Segawa dated August 21, 2008. Environmental Monitoring Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA.

Barry, T., 2008b. Development of sub-chronic air concentration estimates associated with a single fumigant application. Sacramento, CA: Environmental Monitoring, Department of Pesticide Regulation, California Environmental Protection Agency.

Boobis, A. R., J. E. Doe, B. Heinrich-Hirsch, M. E. Meek, S. Munn, M. Ruchirawat, J. Schlatter, J. Seed and C. Vickers, 2008. IPCS Framework for Analyzing the Relevance of a Noncancer Mode of Action for Humans. Crit. Rev. Toxicol 38(2):87-96.

Chiu, W.A., H. A. Barton, R. S. DeWoskin, P. Schlosser, C. M. Thompson, B. Sonawane, J. C. Lipscomb and K. Krishnan, 2007. Evaluation of physiologically based pharmacokinetic models for use in risk assessment. J Appl Toxicol. 27:218-37.

Genter, M., 2004. Olfactory Mucosal Metabolic Enzymes: Modulation of Toxic Endpoints Based on Distribution, Induction, and Age-and Species Variables. The Toxicologist, (1-S), 193.

Howdeshell, K. L., 2002. A Model of the Development of the Brain as a Construct of the Thyroid System. Environ. Health Perspect. 110 (Suppl. 3):337-348.

Kirkpatrick, D. T., 2005. A 24-month inhalation combined chronic toxicity/carcinogenicity study 18 of iodomethane in rats. Project no. WIL-418019, WIL Research Laboratories. DPR Vol. 52875-094 #217697.

Kirman, C. R., L. M. Sweeney, M. L. Gargas and J. H. Kinzell. 2009. in press. Evaluation of possible modes of action for acute effects of methyl iodide in laboratory animals. Inhal. Toxicol. (in press).

Lee, M. *et al*., 2005. In Situ Naphthalene Bioactivation and Nasal Airflow Cause Region-Specific Injury Patterns in the Nasal Mucosa of Rats Exposed to Naphthalene by Inhalation. J. of Pharmacol. and Exper. Theurapeutics,314, 103-110.

Lin, C., *et al*, 2006. Identification of Proteins Adducted by Reactive Metabolites of Naphthalene and 1-Nitronaphthalene in Dissected Airways of Rhesus Macaques. Proteomics, 6, 972-982.

Logothetopoulos, J. and Scott, R. F. (1956) Active iodide transport across the placenta of the guinea pig, rabbit and rat. J. Physiol. 132:365-371

Nemec, M.D., 2003. A phased-exposure prenatal developmental toxicity study of iodomethane in rabbits. Study No. WIL-418023, WIL Research Laboratories. DPR Vol. 52875-045 #202641.

Phimister, A. J. *et al*, 2004. Glutathione Depletion is a Major Determinant of Inhaled Naphthalene Respiratory Toxicity and Naphthalene Metabolism in Mice. Toxic. Sci. 82, 268-278.

Phimister, A. J., *et al*, 2005a. Prevention of Naphthalene-Induced Pulmonary Toxicity by Glutathione Prodrugs: Roles for Glutathione depletion in Adduct Formation and Cell Injury. J. Biochem. Molecular Toxicology, 19: 1, 42-51.

Phimister, A. J., *et al*, 2005b. Consequences of abrupt Glutatione Depletion in Murine Clara Cells: Ultrastructural and Biochemical Investigations into the Role of Glutathione Loss in Naphthalene Toxicity. J. of Pharmacol. and Exper. Theurapeutics, 314, 506-513.

Plopper C., *et al*, 2001. Early Events in Naphthalene-Induced Acute Clara Cell Toxicity Comparison of Glutathione Depletion and Histopathology by Airway Location. Am.J. Respir. Cell Mol. Biol. 24, 272-281.

Price D. J. and J. R. Sherwin, 1986. Autoregulation of Iodide Transport in the Rabbit: Absence of Autoregulation in Fetal Tissue and Comparison of Maternal and Fetal Thyroid Iodination Products. Endocrinology 119(6): 2547-2552

Segawa, R., 1997. Description of computer modeling procedures for methyl bromide. Memorandum to J. Sanders, Environmental Monitoring and Pest Management Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA, dated September 4, 1997.

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

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

Stull, R. B., Ed., 1988. *An Introduction to Boundary Layer Meterorology*. 5th ed. The Netherlands: Kluwer Academic Publishers, p 666.

USEPA, 2000. 1,1,2-Trichloroethane (TCE); Final Enforceable Consent Agreement and Testing Consent Order. Federal Register 65, No. 116, pp 37550-37553, June 15, 2000.

USEPA, 2007. Iodomethane: Revised HED human health risk assessment which incorporates results of human iodine monitoring. *Health Effects Division (7509P), Office of Pesticide Programs*. (August 23, 2007).

Vorhees, C. V., R. E. Butcher, and R. L. Brunner, 1984. Developmental toxicity and psychotoxicity of potassium iodide in rats: A case for the inclusion of behaviour in toxicological assessment. Food Chem. Toxic. 22(12):963-970.

Zoeller, R. T., A. L. S. Dowling, C. T. A. Herzig, E. A. Iannacone, K. J. Gauger, and R. Bansal, 2002. Thyroid hormone brain development, and the environment. Health Perspect. 110 (Suppl.3): 355-361.

Zoeller, R. T., 2003. Challenges confronting risk analysis of potential thyroid toxicants. Risk Anal. 23(1):143-162.

Attachments

Genter, M., 2004. Olfactory Mucosal Metabolic Enzymes: Modulation of Toxic Endpoints Based on Distribution, Induction, and Age-and Species Variables. The Toxicologist, (1-S), 193.

Kirman, C. R., L. M. Sweeney, M. L. Gargas and J. H. Kinzell. 2009. in press. Evaluation of possible modes of action for acute effects of methyl iodide in laboratory animals. Inhal. Toxicol. (in press).

Lee, M. *et al*., 2005. In Situ Naphthalene Bioactivation and Nasal Airflow Cause Region-Specific Injury Patterns in the Nasal Mucosa of Rats Exposed to Naphthalene by Inhalation. J. of Pharmacol. and Exper. Theurapeutics,314, 103-110.

Lin, C., *et al*, 2006. Identification of Proteins Adducted by Reactive Metabolites of Naphthalene and 1-Nitronaphthalene in Dissected Airways of Rhesus Macaques. Proteomics, 6, 972-982.

Logothetopoulos, J. and Scott, R. F. (1956) Active iodide transport across the placenta of the guinea pig, rabbit and rat. J. Physiol. 132:365-371

Phimister, A. J. *et al*, 2004. Glutathione Depletion is a Major Determinant of Inhaled Naphthalene Respiratory Toxicity and Naphthalene Metabolism in Mice. Toxic. Sci. 82, 268-278.

Phimister, A. J., *et al*, 2005a. Prevention of Naphthalene-Induced Pulmonary Toxicity by Glutathione Prodrugs: Roles for Glutathione depletion in Adduct Formation and Cell Injury. J. Biochem. Molecular Toxicology, 19: 1, 42-51.

Phimister, A. J., *et al*, 2005b. Consequences of abrupt Glutatione Depletion in Murine Clara Cells: Ultrastructural and Biochemical Investigations into the Role of Glutathione Loss in Naphthalene Toxicity. J. of Pharmacol. and Exper. Theurapeutics, 314, 506-513.

Plopper C., *et al*, 2001. Early Events in Naphthalene-Induced Acute Clara Cell Toxicity Comparison of Glutathione Depletion and Histopathology by Airway Location. Am.J. Respir. Cell Mol. Biol. 24, 272-281.

Price D. J. and J. R. Sherwin, 1986. Autoregulation of Iodide Transport in the Rabbit: Absence of Autoregulation in Fetal Tissue and Comparison of Maternal and Fetal Thyroid Iodination Products. Endocrinology 119(6): 2547-2552

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DATE: August 10, 2009

SUBJECT: Responses to Arysta LifeScience Corporation Comments on the Draft Methyl Iodide Risk Characterization Document for Inhalation Exposure Volume I and Appendices to Volume I

The following are our responses to comments from Arysta LifeScience Corporation (Arysta) on Volume I and Appendices to Volume I of draft Methyl Iodide Risk Characterization Document (RCD) for Inhalation Exposure (March 2009). In this response, the comments are in numerical order for ease of cross reference. The italicized text is a direct quote from Volume I as cited in Arysta's comments.

Arysta supported their submitted comments with recently published papers, which were not available to DPR when the draft Volume I was completed. Some of the published papers are based on the reports already submitted to DPR; these will be indicated in Volume I. The discussions from Kirman et al. (2009), Mileson et al. (2009), and Sweeney et al. (2009) useful for enhancing the clarity of model description and risk assessment, are incorporated into the revised version of Volume I.

Responses to Comments on Volume I

Comment #1 p.15, lines 15 to p.16, line 3; lines 43-44: *With oral exposure for both doses, the maximal concentration in the blood was achieved between 4 to 6 hours.*

Arysta Comment: Throughout this section there are statements that speculate about what may (or may not) have occurred between measurements. The statements must be limited to the data available, for example by stating that the maximum observed concentration occurred at a given time point.

DPR Response: This section provides a general summary of the results and is not intended to speculate.

Comment #2 p. 20, line 46: *…the conjugation of MeI with GSH as a metabolic pathway was studied in female white rats (Porton strain) given a single oral dose of MeI (0, 50, 75, and 100 mg/kg) (Johnson, 1966). Liver non-protein thiols (predominantly 2 GSH) were depleted at all doses tested;*

Arysta Comment: The time of the GSH measurements in Johnson (1966) should be specified.

DPR Response: The time of measurement will be added.

Comment # 3 p.23, line 7: *lethal dose at 50% death*

Arysta Comment: The more traditional and clear language is: "dose that produces lethality in 50% of the population."

DPR Response: This will be revised.

Comment #4 p.28, line 20: *From 1 to 48 hours after the initiation of the first exposure, GSH and iodide were measured in the serum, liver, kidneys, and nasal olfactory and nasal respiratory epithelium.*

Arysta Comment: Iodide was only measured in serum; GSH was measured in blood and tissues.

DPR Response: This will be revised.

Comment #5 p.28, line 26: *At 25 ppm MeI, maximal GSH depletion (40 to 50% of control) was measured in the nasal epithelium, and about 30% in the other tissues, 3 to 6 hours after exposure (Table 8).*

Arysta Comment: 3 to 6 hrs after exposure" should be corrected to "3 to 6 hours after initiation of exposure."

DPR Response: This will be revised.

<u>Comment #6 p.28, lines 29-30</u>: *The increase in depletion was only about 10% for the other tissues.*

Arysta Comment: It is not clear to what tissues and data DPR is referring.

DPR Response: This will be clarified.

<u>Comment #7 p.31 line 28</u>: *The GSH depletion was more gradual in the liver and brain (cerebellum and forebrain), and was 40% and 70-80% of control, respectively.*

Arysta Comment: The percentages in this statement are reversed. The GSH levels remaining were 40% and 70-80% respectively, meaning that the depletion was 60% and 20-30% of control, respectively.

DPR Response: This will be revised accordingly.

<u>Comment #8 p.80:</u>

Arysta Comment for this section: The litter is generally considered the proper unit for evaluation of reproductive and developmental effects rather than the fetus.

DPR Response: DPR is fully aware that the litter is generally the unit for evaluation, and has included the data expressed in the litter term in the tables. However, this should not preclude additional data analysis that allows a more holistic support for establishing the critical NOEL.

<u>Comment #9 p.80, line 36</u>: *The calculated exposure concentrations were 0.011, 0.057, and 0.113 mg/L, respectively. The equivalent dosages were 1.5, 8, and 16 mg/kg/day.*

Arysta Comment: DPR used a default rabbit breathing rate to identify dosages of 1.5, 8, and 16 mg/kg/day iodomethane, which is inconsistent with the breathing rate used in the PBPK model. The rabbit PBPK modeling uses an alveolar ventilation rate of approximately 317 L/kg bw/day, which is lower than the DPR default rate of 540 L/kg bw/day. This becomes important when dose comparisons between studies are made.

DPR Response: The model input QAC is scaled by body weight to a three fourth power. The DPR 540 L/kg/day default value is for all dose groups of rabbits at different body weights. As a

model input, the QAC value is selected pertinent to the gestation period and window of vulnerability and this is discussed extensively in the Appendix A to Volume I (section II.A.1.)

Comment #10 p.80, lines 37-40: *A statistically significant reduction (47%) in body weight gain was recorded for GD 6 through 29 at 20 ppm (Table 34). This was primarily due to a body weight loss of 12 grams on GD 24 to 25.*

Arysta Comment: The only statistically significant 2-day reduction in body weight the does exposed to 20 ppm iodomethane in this study experienced was a 22 g decrease on GD 28-29. This 22 g body weight decrease that would appear to be the primary cause of the significant reduction in body weight recorded for GD 6 through 29, not the 12 gram decrease recorded on GD 24-25.

DPR Response: This will be revised accordingly.

Comment #11 p.90: *Tables 39 and 40, Mean serum iodide and thyroid hormone concentrations in pregnant and fetal rabbits exposed to MeI (25 ppm) by inhalation during gestation.*

Arysta Comment: Sampling times should be included in the tables.

DPR Response: This will be added to the study description.

Comment #12 p.97: *Table 45 Maternal and fetal TSH, T3, and T4 in rabbits exposed to MeI (20 ppm) by inhalation or sodium iodide by intravenous injection.*

Arysta Comment: It is clear from the data presented in this table that the effects of iodomethane and NaI on the fetal thyroid are much more profound and sustained than the effects on the maternal thyroid. This fact is obscured later in the document by selective inclusion of data in Table 57 (p. 119).

DPR Response: The selected datasets shown in Table 57 are the only ones which allow side-by-side comparison of both fetal and maternal parameters. Data from other time points are incomplete.

Comment #13 p.108: *This section describes studies which evaluated glutathione levels in various tissues including nasal epithelium.*

Arysta Comment: This section describes studies which evaluated glutathione levels in various tissues including nasal epithelium. In their discussion DPR failed to include other relevant studies of naphthalene vapor exposure which elucidated the relationship between glutathione (GSH) depletion in target nasal tissue and the susceptibility of those tissues to damage from chemical exposure. These studies show that a substantial depletion in GSH in respiratory tissue is necessary for toxicity to occur.

The primary target cells for rodent naphthalene toxicity are the Clara cells in the distal airways of the lung, and injury may extend into the proximal airways as the dose increases. This difference in relative sensitivity of cells in different airway levels of the mouse was exploited in a study by Plopper and coworkers to show that Clara cells exposed to naphthalene that maintained at least 50% of the control levels of GSH did not exhibit changes in organelles indicative of toxicity (Plopper *et al*, 2001). Clara cells that did not maintain GSH levels of 50% of control levels were susceptible to naphthalene-induced injury. Gentner (2004) linked rat nasal damage from naphthalene exposure to olfactory mucosal bioactivation of naphthalene by cytochromes P450 (CYPs) 2A3 and 2f2 which formed reactive species that depleted glutathione.

In a more recent study on naphthalene, mice were exposed to 15 ppm naphthalene and GSH levels were measured and correlated with histological analyses (Phimister *et al*., 2004). A 2-hour exposure to 15 ppm napthalene resulted in a 90% loss of GSH in the distal airways, but after 24-hours, no signs of cellular injury were observed. Conversely a 4-hour exposure to 15 ppm naphthalene did cause the Clara cells in the distal airways to be swollen and vacuolated. Thus the Clara cells of the distal airways could survive a 2-hour, 90% depletion of GSH without alterations in cellular organelles, but a longer severe depletion in GSH resulted in toxicity.

In 2005 Phimister, *et al*, showed that glutathione depletion in respiratory cells of mice associated positively with naphthalene cytotoxicity and that the cytotoxicity could be prevented by maintaining cellular glutathione levels. (2005 a and b).

Lee, *et al*, in 2005 showed that region-specific injury to rat nasal mucosa occurred following naphthalene exposure and that the pattern of injury correlated with regional metabolic capability for naphthalene. Similar finding are now being described for nonhuman primates (Lin, 2006).

These investigations establish the importance of GSH depletion in the mode-of-action of naphthalene nasal cavity cytotoxicity. DPR should consider the weight-of-evidence imposed by this data set in its evaluation of the relationship between iodomethane and nasal cavity injury in the rat. The information developed on naphthalene supports arguments not only for GSH depletion but also for oxidative stress in general as a component of iodomethane cytotoxicity.

DPR Response: As stated in Volume I., this section (III.J.) discussed only data for MeI for PBPK modeling. Pertinent studies for other chemicals relating to the nasal effect are discussed

in Appendix A of Volume I (III.B.2.). DPR concluded that the most relevant data to determine the dose metric should be from within the MeI database (page A-32).

Comment #14 p.108: *Table 52. Metabolic rate constants for MeI in tissues in vitro.*

Arysta Comment: Data should be reported with standard deviations (rat, rabbit, and fetal rabbit) or individual data (human). At a minimum, the subject number for the human values should be reported.

DPR Response: The number of samples will be added. For simplicity of presentation, the standard deviations were not included.

Comment #15 p.114, lines 15-19: *The critical NOEL for acute MeI toxicity established by DPR is 2 ppm based on rabbit fetal death during late gestation period at the LOEL of 10 ppm (Table 34; Nemec, 2002d). Fetal body weight was also significantly lower at this LOEL. Based on the same endpoints as described for DPR's NOEL determination, the study author also concluded that the NOEL for pre-natal developmental toxicity is 2 ppm (Nemec, 2002d).*

Arysta Comment: Arysta believes the content of this paragraph is in error and the phrasing is misleading. The wording in the quoted paragraph should be modified to accurately reflect the results from the Nemec (2002d) study. The first sentence should state that the increase in fetal deaths were not statistically significant. In the second sentence the word "also" before the words "significantly lower," should be removed, the fact that only the female fetuses were reduced significantly in body weight at 10 ppm should be included, and the statement that the study author NOEL determination was based on the same endpoints as DPR's should be removed. The study author's stated conclusion regarding fetal body weight changes in the 10 ppm group was "the effect at 10 ppm was considered to be treatment-related, but of equivocal toxicological significance" (Nemec, 2002d).

DPR Response: The cited statements were in the Hazard Identification section, and were intended as a summary of the endpoints for the basis of the NOEL. Mere emphasis on statistical significance diminishes the toxicological significance of the findings. The only revision is to remove the word "also." It should be noted that the study investigator (Nemec, 2002d) stated that "the prenatal developmental toxicity was expressed at exposure levels of 10 and 20 ppm by increases in postimplantation losses (primarily late resorptions), reduced mean numbers of viable fetuses and/or reduced mean fetal body weights. Based on the results of this study, the NOAEL for ...prenatal developmental toxicity was considered to be 2 ppm."

<u>Comment #16 p.115, lines 1-3</u>: *Fetal death in rabbits as a consequence of MeI exposure was also reported in a subsequent study by Nemec (2003) that was conducted to determine the window of vulnerability for fetal death.*

Arysta Comment: The topic of this section of the document is the critical NOEL, and the focus of the previous paragraph is a 2 ppm exposure. It would be helpful for the paragraph cited above to make it clear that the Nemec (2003) study evaluated fetal effects from exposure to 20 ppm iodomethane. The quoted sentence could be changed to "Fetal death in rabbits as a consequence of 20 ppm iodomethane exposure was reported in a subsequent study…"

DPR Response: This will be revised to indicate 20 ppm was the only dose studied.

<u>Comment #17 p.115, lines 22-25</u>: *One clarification should be made about "late resorption" as an endpoint. This term was used in the submitted toxicity and pharmacokinetic studies of MeI in rabbits. One companion observation in these reports was "dead fetus". However, none of these reports clearly describe how "dead fetus" is different than "late resorption".*

Arysta Comment: Arysta contacted WIL laboratory staff who categorized the effects in the rabbit studies to obtain clarification of the difference between "late resorptions" and "dead fetus" as identified at necropsy. Arysta provided this information to DPR in 2006 (Arysta, 2006). Briefly, the manager of necropsy at WIL Laboratories stated that the criteria for identification of late resorptions and fetal deaths follow an internal Standard Operating Procedure. Late resorptions are identified based on the placentae having a mottled appearance and the presence of autolysis. Late-stage resorptions are considered to have died before the scheduled laparohysterectomy. Dead fetuses are presumed to have died at or near the time of the scheduled laparohysterectomy. The placentae of fetuses determined as dead do not have a mottled appearance and autolysis is absent.

DPR Response: This sentence "However, none of these reports clearly describe how "dead fetus" is different than "late resorption" will be deleted.

<u>Comment #18 p.115, lines 25-29</u>: *As noted in Table 55, one fetus per 10 and 20 ppm dose groups in the Nemec study (2002d) was found dead at sacrifice on GD 29. No dead fetus was found in the subsequent study by Nemec (2003). In this document, fetuses from late resorption are generally referred to as "dead", and the endpoint is collectively referred to as fetal death.*

Arysta Comment: The manager of necropsy at WIL Laboratories stated that the criteria for identification of late resorptions as separate from dead fetuses had not changed over the years (Arysta, 2006). If DPR wants to combine incidences of late resorptions and dead fetuses they

should develop an argument that does not insinuate that the laboratory categorized late resorptions and dead fetuses inconsistently among studies performed on iodomethane.

DPR Response: No insinuation was intended by DPR. Data are presented as given in the reports.

Comment #19 p. 116, lines 16-19: *The acute critical NOEL established by USEPA is 10 ppm, also based on the Nemec study (2002d), 5-fold higher than that by DPR and the study investigator. The USEPA basis was a lack of statistical significance of fetal death at 10 ppm when data are expressed as percentage of fetal resorption per litter (i.e., group average of 11.1% versus 1.8% in the controls, Table 55).*

Arysta Comment: Arysta supports the EPA determination that the appropriate NOAEL for developmental toxicity in the rabbit is 10 ppm based on the following:

1) the percentage of fetal resorptions per litter was not significantly different from the concurrent control group value.

2) this increase in mean percent late fetal resorptions at 10 ppm was insufficient to affect fetal viability (mean live litter sizes and mean percent live fetuses was not significantly different from the concurrent control group values and were within the historical control ranges of the testing facility).

3) all other measures of fetal viability at the 10 ppm level were within the historical control ranges and also were not significantly different from the concurrent control group values. These included litter means for percent early resorptions and percent postimplantation loss, as well as the percentages of does with postimplantation loss, early resorptions, late resorptions or dead fetuses.

DPR Response: We disagree. The basis for the NOEL is as stated in this section of Volume I.

Comment #20 p.116, lines 36-40: *The four respective possible MOAs explored in this section are: fetal thyroid perturbation from excess iodide, GSH depletion, direct alkylation, and altered cholesterol homeostasis. The observations can be part of key events with more than one MOA leading to fetal death. In contrast, USEPA considered thyroid perturbation as the sole MOA and did not consider other possibilities (USEPA, 2007).*

Arysta Comment: The risk assessment presented by the USEPA (2007) is a summary of an extensive evaluation that **did** include consideration of alternate modes of action for the fetal loss in rabbits exposed to iodomethane.

DPR Response: As stated in the Arysta comment, the USEPA risk assessment has a summary of the evaluation. Consideration of alternative MOA was not included there or any document available to the public.

Comment #21 p. 116, lines 42-44, p.117, lines 1-3: *Due to data limitations and gaps, it was not possible to completely organize the data according to the International Programme on Chemical Safety (IPCS) framework for MOA evaluation of non-cancer effects for human relevance involving 1) key events, 2) concordance of dose-response relationship, 3) temporal association, 4) strength, consistency, and specificity of association of toxicological response with key events, and 5) biological plausibility and coherence (Boobis et al, 2008).*

Arysta Comment: Critical effects of iodomethane observed in animal studies can be organized in a way that meets the requirements of the Mode-of-Action Human Relevance Framework as described by Boobis, *et al*, 2008. The weight-of-evidence establishing causality for fetal toxicity, neurotoxicity and nasal epithelial cell damage, critical endpoints identified by CDPR for human risk characterization of iodomethane is sufficient for the appropriate life stage consideration and satisfies the Modified Hill Criteria. Key events critical to the induction of toxicity have been measured for each acute endpoint of concern. These events, listed briefly below, support a Mode-of-Action (MOA) for the effects. Details of the support for the MOA are presented by Kirman, *et al* (2009).

For fetal loss in rabbits following iodomethane administration, evidence exists suggesting that at least four MOA's are plausible. The MOA supported by the strongest evidence is thyroid hormone modulation by excess iodide during fetal development. The key events associated with this MOA are:

1) an increase in fetal iodide
2) loss of colloid in fetal thyroid.

Experimental support for the key events comes from observations of ancillary thyroid effects such as decrease in circulating T3/T4 and an increase in TSH. Kirman, *et al*, cite supporting evidence to describe a pathway for the decrease in thyroid hormone following iodide administration. Concordance for iodide effects can be seen across three species (rabbits, rats and hamsters but apparently not pigs). Kirman, *et al*, cite work indicating that fetal rabbits concentrate iodide relative to the doe and that fetal rabbits lack autoregulatory capacity for limiting excess iodide, suggesting a rationale for iodide sensitivity in the fetal rabbit. These key

events have plausibility for human relevance based on human experience with thyroid perturbation during pregnancy, though humans do not concentrate iodide in the fetus as rabbits do (Rayburn *et al*, 2008, Cottino, 1972). The temporal relationship of observed thyroid effects in the fetal rabbit and exposure to iodomethane during gestation is solidly established at gestation days 23-26. It is during this gestational period that critical events occur in development of the rabbit thyroid and it is during this gestational time that iodomethane produces thyroid effects in the rabbit fetus as noted above (Sloter, *et al*, 2005).

Kirman, *et al*, also present evidence for a MOA for neurological and nasal epithelial cell effects of iodomethane in rats. In each case causality was established which satisfies the Hill criteria. The weight-of-evidence is sufficient to establish a MOA for the effect in animals. Human relevance of the MOA could not be excluded on the basis of significant qualitative differences in key events or significant quantitative kinetic or dynamic differences in key events between humans and test animals.

Accordingly, the statements appearing on pages 116-117 of Volume I of the draft DPR Health Risk Assessment for iodomethane should be modified to acknowledge that adequate information does exists to permit an analysis and presentation of iodomethane toxicology according to the International Programme on Chemical Safety (IPCS) framework for MOA evaluation of non-cancer effects for human relevance. DPR's draft report contains nearly 12 pages of text, tables, and figures (pages 116-128) on the MOA for developmental effects, as well as additional sections for nasal and neurological effects supporting this. Furthermore, additional data are available for the effects of excess iodide that are relevant to iodomethane, but were not considered by DPR. For these reasons, there appears to be sufficient information available to support the use of the MOA framework, as was presented by Kirman *et al*., and DPR should perform such an analysis.

DPR Response: This comment reflects differences in opinion on the sufficiency of the data to establish a single MOA for each toxicity endpoint. Arysta is in error to imply that DPR had not conducted a MOA analysis. It was after such an analysis that DPR concluded that it was not possible to <u>completely</u> organize the data for MOA framework evaluation due to data limitations and gaps, and suggested that more than one MOA, in particular for fetal death, may be involved. Since the analysis was lengthy, an abridged form was presented in the 12 pages of MOA discussion as noted by Arysta. The significant data limitations, as discussed in the cited section, included wide variability, small sample size, limited MeI concentrations, and no data for dead fetuses. On the other hand, Arysta had not acknowledged these problems with the database for MOA determination. Instead, Arysta considered the weight-of-evidence establishing causality for fetal toxicity, neurotoxicity and nasal epithelial cell damage as sufficient for the appropriate life stage consideration and satisfied the Modified Hill Criteria. In this comment, Arysta further concluded that "key events critical to the induction of toxicity had been measured for each acute

endpoint of concern," which is not accurate. In the revised Volume I, the MOA discussion will be expanded.

The comment that DPR had not considered data on excess iodide is incorrect. If the referred data were those from Ammerman et al. (1964) and Arrington et al. (1965), they were discussed under the section specific associated with potential post-natal death from excess iodide (**V.C. Risk Characterization,** page 148 of March draft of Volume I).

Comment #22 p.117, lines 7-9: *Studies designed for PBPK modeling used high concentrations of MeI (20 and 25 ppm) that may or may not inform the pharmacokinetics at the 2 ppm NOEL.*

Arysta Comment: Analyses of the 20 and 25 ppm data and 2 ppm PBPK simulations suggest that the iodide kinetics are approximately linear with exposure concentration.

DPR Response: The point at issue remains that no measured data are available to validate the simulation at 2 ppm.

Comment #23 p.117, lines 10-12: *Since all fetal data are collected from fetuses that survived to GD 29, relating these data to dead fetuses requires an assumption that they are representative of the latter,…"*

Arysta Comment: The DPR statement is not correct. The fetal kinetic data were all collected prior to GD 29 and much of the Sloter (2005a, b) data were collected prior to GD 29. Data from rabbit fetuses were collected in the Sloter 2005b study throughout the window of sensitivity to iodomethane exposure, on gestation days: 24, 25, 26 as well as GD 29. Data from rabbit fetuses were collected in the Sloter 2005a study on gestation days: 21, 22, 23, 24, 25, 26, and 27.

DPR Response: The point was that data are available only for live fetuses, not dead ones. It was not about when the data were collected. The text will clarify that it was up to GD 29.

Comment #24 p.117, lines 29-30: *Elevated iodide levels were measured in the serum and tissues after MeI exposure.*

Arysta Comment: Iodide has been measured in serum after iodomethane exposure, but has not been measured in tissues after iodomethane exposure.

DPR Response: This will be revised.

<u>Comment #25 p.117, lines 33-38</u>:
The issue is whether the death of rabbit fetuses is through the MOA of excess iodide specifically to the fetus, or related and influenced by maternal toxicity. If the fetal thyroid effect is the direct cause of fetal death, fetal serum iodide is an appropriate dose metric for PBPK modeling, as is presented in the USEPA risk assessment (USEPA, 2007). However, it is DPR's position 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.

Arysta Comment: Use of maternal iodide as a dose measure is not well supported by the available data, and does not take into consideration several biological factors that contribute to the unique sensitivity of the rabbit fetus to the effects of iodide, which include:

(1) the fetal rabbit lacks the autoregulatory capacity to limit the effects of excess iodide (Price and Sherwin, 1986).

(2) the fetal rabbits concentrate iodide relative to the doe (Logothetopoulos and Scott, 1956; Sloter, 2005b);.

DPR Response: DPR will add a new section on species specificity and discuss these studies. There is no change in DPR's position.

<u>Comment #26 p.121, lines 1-7</u>: *Comparison of maternal and fetal TSH data after MeI exposure shows greater consistency in maternal than in fetal TSH patterns after 2 days of MeI exposure, suggesting a role for maternal effects in the MOA. The maternal TSH level is significantly increased, as early as after 2 days of exposure (GD23 to GD24) - the first time point of evaluation (Tables 56 and 57). Its persistence onto day 4 (from GD23 to GD26) of exposure was observed only with MeI at 25 ppm (Table 56). On the other hand, the average TSH levels in the fetuses are somewhat lower than the controls during GD23-24, but greatly increased in the GD23-26 groups.*

Arysta Comment: There is no support for the DPR position that greater consistency in maternal than in fetal TSH patterns after 2 days of iodomethane exposure suggests a role for maternal effects in the MOA for fetal loss. The data available support a role for <u>fetal</u> effects in the MOA for fetal loss. DPR notes that the increase in maternal TSH after two days of iodomethane exposure on GD 23-24 is maintained after 4 days of exposure only in does exposed to 25 ppm iodomethane, not in does exposed to 20 ppm iodomethane. In Nemec (2003) it was demonstrated that effects of iodomethane exposure on rabbit fetuses are increased dramatically when exposure occurs over the 4 days of GD 23 to 26 (16.3% late resorptions) compared to 2 days of exposure on GDs 23 to 24 (5.3% late resorptions). Fetal TSH level increased with increasing days of 20

ppm iodomethane exposure over gestation days 23, 24, 25 and 26, reaching statistical significance from control on gestation days 25 through 29 (Sloter, 2005b). The increase in late resorptions after4 days of exposure on GDs 23-26 correlates with the greater effect on TSH levels in fetal rabbit plasma than in maternal rabbit plasma after exposure to iodomethane on GDs 23 to 26. Thus, consistency in maternal TSH patterns after 2 days of iodomethane exposure does not correlate with fetal loss, but increased fetal TSH levels after 4 days of exposure GDs 23-26 does correlate with fetal loss, supporting a causal role for fetal effects in the MOA for fetal loss.

DPR Response: DPR was concerned about fetal death after 2 days (GD 23-24, within 30 hours of start of exposure) and after 4 days (GD 23-26). Thus, comparisons between maternal and fetal results were made for both durations. As stated on page 121 (lines 23-25), effect of high fetal serum iodide on fetal thyroid may be second in sequence, and there may be other MOA that causes more immediate fetal death from MeI.

Comment #27 p.121, lines 14-20: *There is a lack of causal relationship between fetal thyroid perturbation and fetal death, within the GD 23 to 24 period, after MeI exposure, to support this MOA. Histopathology in the fetal thyroid included decreased colloid, follicular epithelial vacuolation and follicular hypertrophy (Tables 56 and 57). In Sloter (2005a) at 25 ppm MeI, higher incidences were reported in the 4-day than the 2-day exposure groups, yet the "% fetus/litter" of late resorption immediately after the end of MeI exposure were the same at these corresponding time points (i.e., 5.7% after 2 days and 5.2% after 4 days of MeI exposure) (Table 56).*

Arysta Comment: DPR states that there is a lack of a causal relationship between fetal thyroid perturbation and fetal death within the 23 to 24 day period, Arysta disagrees. The discussion presented and the data available *do* support a causal association between fetal thyroid perturbation by iodide and fetal death. As noted by DPR, histopathologic findings included follicular cell hypertrophy in 37% of fetal rabbits exposed to 25 ppm iodomethane on GDs 23-24 and in 94% of those exposed on GDs 23-26, and colloid depletion in 14% of fetal rabbits exposed to 25 ppm iodomethane on GDs 23-24 and in 89% of those exposed on GDs 23-26. DPR maintains there is no concordance between thyroid histopathology and adverse outcome because the percent resorptions identified immediately after exposure were virtually the same in both groups. The fallacy in this argument is that adverse effects from altered fetal thyroid function are not necessarily immediately fatal. DPR has presented no data or rationale to support the implied contention that follicular cell hypertrophy and colloid depletion in fetal rabbits would be immediately fatal. An increase in late resorptions after 20 ppm iodomethane exposure was observed 3 days after exposure on GDs 23-26, but not immediately after exposure, and this is shown in Table 47 of the Volume I. Data in Table 47 indicate that 4% late resorptions were observed on GD 26 after exposure on GD 23-26, and 50.4% late resorptions were observed on

GD 29 after an identical exposure pattern. The fetal rabbit group that had the higher incidences of hypertrophy and colloid depletion after iodomethane exposure on GD 23-26 ultimately had higher incidences of late resorptions on GD 29, thus there is concordance of histopathologic effects in the thyroid and fetal resorptions.

DPR Response: DPR is glad that the comments agree with our observation that there is no rationale to support the causality of fetal thyroid pathology to the immediate fetal death. It should also be noted that the histopathologic findings are from fetuses that survived to a given examination time point when death to some fetuses had already occurred.

There should not be any dispute about the detrimental consequence of such severe fetal thyroid damage from MeI exposure. However, the mechanism that results in the immediate death is the focus for modeling a single day HEC.

Comment #28 p.121, lines 22-31: *Furthermore, comparison of data from MeI and NaI treatment indicates that fetal thyroid perturbation through excess iodide is not the sole MOA for fetal death. Effects of high fetal serum iodide on fetal thyroid may be second in sequence, after an initial MOA that causes fetal death from MeI. In Sloter (2005b), the estimated iodide dose for MeI (13.4 mg/kg/day) is 6-fold higher than that for NaI (2.58 mg/kg/day) exposure, assuming 100% uptake and rapid and complete breakdown. Yet, both treatments resulted in comparable effects on fetal thyroid histopathology (Table 57, more detailed in Table 48) and TSH profile during treatment from GD23 to GD26 (Figure 2, hours 23 to 72). With the higher iodide exposure in the MeI group, significantly increased fetal late resorption and reduced fetal viability was seen only in the MeI group, but not with NaI (Table 57).*

Arysta Comment: The total iodomethane dose calculated using DPR's default breathing rate exceeds the intake calculated using the alveolar ventilation rate used in the PBPK modeling (540 L/kg/d, vs 317 L/kg/d), distorting the comparisons among dosing regimens (i.e., iodomethane vs. NaI). The more detailed data presented in Table 48 show a greater incidence and severity of histopathology in the fetal thyroids of rabbits on GD 29 in those exposed to iodomethane compared to NaI.

DPR Response: See response to Comment #9.

Comment #29 p.122, lines 14-29: *At both NaI treatment levels, the highest maternal iodide concentration is in the thyroid (Figures 4a and 4b). The pattern of iodide distribution to the thyroid is different between the does and the fetuses. The maternal and fetal thyroid iodide both reached approximately the same level within 2 hours, and remain more or less steady until 6 hours. Thereafter, the maternal thyroid continues to accumulate iodide but not the fetal thyroid.*

At the end of 24 hours, the concentration in the maternal thyroid was higher than the blood by 20-fold with 0.75 mg NaI/kg treatment and 270-fold with 10 mg NaI/kg treatment. The high maternal thyroid iodide pattern on GD25 appears to correspond to the TSH profile shown in Table 57 for NaI and MeI exposures by Sloter (2005b), i.e., increased maternal TSH at the earliest measurement, i.e., immediately after the second of a 2-day NaI exposure on GD23-24. However, fetal TSH did not change during this time. Contrary to the pattern of maternal iodide distribution, the highest fetal iodide concentration is in the stomach contents and the lowest in the blood, with the levels at other measured sites (trachea, thyroid+trachea, amniotic fluid) all higher than in the blood. The higher iodide in tissues raises a concern for potential damage from excess iodide in tissues besides thyroid and may contribute toward MeI fetal death immediately after the second 6-hr MeI exposure.

Arysta Comment: Relative concentrations of iodide in maternal and fetal thyroid do not take account of the following aspects of iodide reaction in maternal and fetal rabbits. First, despite the higher apparent concentrations of iodide in the maternal thyroid, the toxic effects of treatment (colloid depletion, hypertrophy of follicular epithelium) are much less severe in maternal thyroid when compared to the dramatic effects observed in fetal thyroid. The difference in effects, particularly severity of effects, identifies the fetus as the more sensitive target for iodide toxicity. Because of this, the appropriate metric for iodide effects for this endpoint is the fetal plasma iodide level.

Second, the DPR does not take into consideration either the treatment effects of iodomethane on the thyroid or the developmental changes to the fetal thyroid for iodide tissue distribution. Lower measured concentrations of iodide in fetal thyroid relative to maternal thyroid can be counterintuitive given that blood levels are higher in the fetus (Table 58). However, further consideration of fetal rabbit ontogeny provides an explanation of the apparent contradiction.

Because the fetal rabbit thyroid lacks the ability to autoregulate iodide uptake in the presence of excess iodide (Price and Sherwin, 1986), tissue iodide concentrations may not consistently parallel blood iodide concentrations. More importantly, the apparent difference in maternal vs. fetal thyroid iodide levels likely reflects the fact that fetal thyroid is relatively devoid of colloid, the normal storage depot for iodide. The presence of elevated concentrations of iodide in the fetal alimentary canal is not surprising because the colloid (and associated iodide) released by the fetal thyroid is most likely distributed to the fetal gastrointestinal tract via the thyroglossal duct, an embryological anatomical structure forming an open connection between the initial area of development (oropharynx) of the thyroid gland and its final position. This duct normally atrophies and closes off before birth. This mechanism for fetal iodide distribution would explain the high concentrations in the trachea, stomach, and amniotic fluid (subsequent elimination from the gastrointestinal tract) that are of concern to DPR. Because the elevated levels of iodide in these tissues most likely reflect iodide that was once associated with fetal thyroid, the fetal thyroid is much more highly exposed to iodide than is apparent by the thyroid tissue

concentrations. Under these conditions, fetal plasma iodide levels are the most reliable metric for fetal iodomethane toxicity, the most sensitive effect following iodomethane administration to pregnant rabbits, e.g., the most sensitive species evaluated. The most sensitive effect is the effect that if prevented will protect against all other adverse effects. If the public health goal is to establish effect levels based on the most sensitive indicator of toxicity, then rabbit fetal plasma levels of iodide are the most sensitive indicator of that effect.

DPR Response: No response is needed. The cited paragraph is simply a description of the data from the study. Further discussion about the Morris data and the implication on model prediction is in the response to Comment #57.

In terms of "rabbit fetal plasma level of iodide" as the most sensitive indicator, DPR would refer to Table A-4 showing a 4-fold higher HEC based on this than on the maternal plasma iodide as the dose metric, and the DPR response to Comment #54 regarding the relatively greater modeling confidence in the latter.

Comment #30 p.126, lines 1-3: *The aforementioned GSH database may suggest two possible implications with regard to MeI fetal toxicity in rabbits. First, compared to the adult brain, death of neural cells in the fetal brain can be more detrimental and possibly contribute to fetal death.*

Arysta Comment: It is a big leap to go from cell death in rat neuronal cell cultures to fetal rabbit death in vivo. It should be recalled that in Nemec (2002), the brain from each rabbit fetus was examined by a mid-coronal slice, and no abnormalities were noted.

DPR Response: This section discusses the implications of the available data, which is limited. The Nemec 2002d study stated that the rabbit fetal brain was examined by the mid-coronal slice, but there was no information in the report about the result or sensitivity of the examination to detect cell death. And since the examination was likely to be performed on live fetuses, it is questionable how such data would apply toward dead or dying fetuses. Even if assuming no "abnormalities" in live fetuses, the possibility of "abnormalities" as a cause of fetal death cannot be excluded.

Comment #31 p.130, lines 39-45: *One possibility is via GSH depletion in the brain. In a rat study by Chamberlain et al. (1998a), a 20-30% decrease in brain NP-SH was reported at the end of a 6 hour exposure to 100 ppm MeI with slightly greater decrease in the forebrain than in cerebellum. The information from in vitro investigation showed that GSH depletion by MeI results in cytotoxicity in cultured neural cells. Cell death became more evident long after the recovery of GSH level (Davenport et al, 1992; Bonnefoi, 1992; Chamberlain et al, 1999).*

Arysta Comment: A cytotoxic mode of action mediated by GSH depletion is contraindicated by the transient nature of the clinical signs (generally resolved by the following day), and the absence of any neuropathological effects associated with cell death. Consideration should be given to a general mode of action by the parent chemical via modification of ion currents in neurons as is typically observed with solvents at high concentrations (see Kirman *et al*, 2009).

DPR Response: No data have been submitted on the potential effects of MeI on ion currents in neurons. The illogical attempt to extend any absence of neuropathology in live fetuses to imply no such effect for the dead fetuses was addressed in Comment #30.

Comment #32 p.131, lines 6-9: *Since the 8-hour HEC does not take into account the additional 16-hour exposure after work, it is considered not sufficiently protective. Therefore, the 3.4 ppm from the 24-hour/day exposure value is to be used for both durations.*

Arysta Comment: The PBPK model developed for iodomethane can be used to estimate area under the concentration curve (AUC) values for both 8-hour exposures (which can include internal exposures that continue after external exposure ceases) and 24-hour time exposures. The use of a single human equivalent concentration for both time periods is not justified.

DPR Response: Please note that the "8-hour" refers to the time during occupational exposure and not the only duration of daily exposure for workers. It is unreasonable to assume that workers will be at MeI-free zone after work and not be exposed to MeI as members of the general public.

It stands to reason that the higher 8-hr exposure at work would have contributed to a higher 24-hr total AUC and therefore resulting in the need for a HEC lower than 3.4 ppm for workers. To avoid any further misunderstanding, a caution for the inadequate protection in the use of the 3.4 ppm HEC for workers is added to the Volume I HEC discussion.

Comment #33 p.146, lines 15-17: *The main uncertainty in hazard identification is the lack of data to address potential toxicity in the young, since all the studies were conducted with adult animals. NOELs generated from observations of adult animals may not be sufficiently protective.*

Arysta Comment: It is not true that all the studies on iodomethane were conducted with adult animals. Arysta has conducted and submitted two guideline developmental toxicity studies to characterize the potential effects of iodomethane exposure in young rats and young rabbits, and one guideline two-generation study in rats to characterize the potential effects on rats through two generations. In the 2-generation rat study, offspring were exposed via lactation beginning 5 days after birth, and were exposed directly to iodomethane beginning on postnatal day 28.

Three additional non-guideline studies were performed and submitted to further characterize the effects of iodomethane on developing rabbits (Nemec, 2003, Sloter, 2005a and 2005b).

DPR Response: This comment is taken out of context from the discussion of need to study developmental neurotoxicity. DPR is concerned about postnatal developmental effect in the young that includes pre- and post-natal exposures in the most sensitive species for such effects.

Comment #34 p.146, lines 17-21: *Studies on developmental neurotoxicity for animals exposed during in utero, as well as those examining the postnatal effects of MeI on nasal tissues and the nervous system of young animals are needed. The absence of such studies can lead to the underestimation of the toxicity based on the current database.*

Arysta Comment: The F1 generation rats exposed to iodomethane in the 2-generation study by lactation beginning on postnatal day (PND) 5 and directly via inhalation on PND 28 were evaluated for effects on the nasal olfactory epithelium. The NOAEL for effects on the nasal epithelium was identical to the adult NOEL, 20 ppm, indicating no difference in sensitivity of young rats compared to adult rats for this endpoint.

Sufficient data are available to determine that a developmental neurotoxicity study is not necessary. Alterations in thyroid and pituitary function, as can occur following exposure to high levels of iodomethane, can impact brain development. Exposure to lower levels of iodomethane that do not cause alterations in thyroid and pituitary function would not be expected to impact neurological development. Data are available to demonstrate that repeated exposure of female rats to 20 ppm iodomethane 5 days/week for 26 weeks does not alter T3, T4, reverse T3 or TSH (Kirkpatrick, 2005). TSH levels were increased in female rats exposed to 60 ppm iodomethane for 26 weeks, but all other parameters were similar to control females in the 60 ppm group. The 20 ppm NOAEL for pituitary and thyroid hormone effects in female rats will protect developing fetuses from potential developmental neurotoxicity resulting from altered thyroid function. The US EPA and OECD have designed guidelines to evaluate potential developmental neurotoxicity in rats but not rabbits (EPA OPPTS 870.6300, OECD 426).

DPR Response: It is well recognized that conventional chronic and reproductive toxicity studies are not designed to sufficiently evaluate pre- or post-natal developmental toxicity.

Comment #35 p.146, lines 45-46, p.147, lines 1 to 14): *When the HEC is used in the MOE calculation, a benchmark MOE of 30 is considered health protective such that any exposure with a MOE ≥ 30 would not be of significant health concern. In the risk characterization for MeI, this benchmark of 30 may be insufficient because of the following:*

(1) The lack of data for potential neurodevelopmental effects, in the presence of evidence for MeI perturbation of maternal and fetal thyroid functions.
(2) The substantial post-natal death in neonates of rats and rabbits associated with pre12 and post- natal exposure to NaI and KI
(3) The high iodide levels from exposure to MeI at the reference concentration (RfC), when compared with current health-based limits of iodide intake.

Arysta Comment: Arysta believes data are available to support the MOE of 30, and the potential insufficiencies identified by DPR are addressed briefly below:

1) A NOAEL for alteration of thyroid and pituitary hormone levels is available and this endpoint is protective of neurodevelopmental effects that could result from thyroid perturbation.

2) Substantial data and a PBPK model are available to determine an HEC for iodide level with reasonable certainty.

3) The acceptable level for an acute duration exposure to iodomethane should not be confused with the acceptable daily upper limit of dietary iodide intake.

DPR Response: For (1), see response to Comment #34. For (2), PBPK model only addresses the pre-natal death. For (3), as stated in the Volume I, DPR utilized available iodide values and there is no established acute inhalation reference concentration. See response to Comment #39.

Comment #36 p.147, lines 24-37: *There is a concern for potential developmental toxicity from MeI exposure because neurodevelopmental effects associated with thyroid toxicity is well documented (Howdeshell, 26 2002; Zoeller et al, 2002; Zoeller, 2003). Thyroid hormone dysfunction affects many fetal organs, e.g., heart, liver, muscle, and development…..*

Arysta Comment: Protection against effects on pituitary and thyroid hormones will protect against any potential effects on neurological development that could result from "thyroid hormone dysfunction." The NOAEL for effects on thyroid and pituitary hormones in rats exposed to iodomethane is 20 ppm with a LOAEL of 60 ppm (Kirkpatrick 2005).

DPR Response: DPR is concerned by the repeated implication that the chronic toxicity study by Kirkpatrick (2005) in adult rat is sufficient to address the potential neurodevelopmental toxicity in young animals.

Comment #37 p.147, lines 39-42: *Neurobehavioral effects may be the result of excess iodide. PBPK modeling for MeI predicted an extraordinarily high accumulation of iodide in the fetal*

thyroid (Appendix A). In the study with KI by Vorhees et al (1984), Sprague-Dawley rats were fed diets containing 0.025, 0.05, or 0.1% KI 14 days before mating and during mating….

Arysta Comment: The paragraph partially excerpted above discusses neurobehavioral effects identified in rats fed diets containing high levels of iodide. This paragraph is not related to iodomethane exposure and does not inform potential effects from iodomethane exposure and should be deleted. The dose of iodide in the diet is not related to iodomethane exposure, and the only sentence in the paragraph that relates to iodomethane states that the PBPK model projects high levels of iodide may accumulate in the thyroid. The neurobehavioral information from the dietary iodide studies would be useful only if the internal iodide doses in the dietary and the rat inhalation exposure studies were presented.

DPR Response: The first sentence will be revised. The risk assessment considers all pertinent data as they are available.

Comment #38 p.148, lines 24-31: *Published literature suggests that post-natal death in rabbits from MeI exposure should also be of concern. Marked reduction in the survival of neonates associated with pre- and post natal iodide exposure was reported by Ammerman et al (1964) and Arrington et al. (1965). From the data for post-natal survival, Arrington et al. (1965) reported a 30% survival of 3 days old rabbit pups from does that received the lowest tested level of 250 ppm iodide in the diet (9 mg iodide/kg/day) for 2 days before parturition (i.e., equivalent to GD29-30), while the pup survival in the control group was 91%. This iodide level in the diet is comparable to the total iodide at the MeI LOEL of 10 ppm (7.6 MeI /kg/day, or 6.8 mg iodide/kg/day).*

Arysta Comment: The published literature referred to by DPR evaluated dietary iodide intake in experimental animals, not iodomethane exposure. The estimated amount of iodide received by pregnant rabbits exposed to 10 ppm iodomethane for 6 hours per day depends upon the inhalation rate used in the calculation. Total iodide of 6.8 mg/kg/day was estimated using the DPR default breathing rate of 540L/kg/day (Volume I, Table B-1), but the estimated iodide amount from iodomethane exposure would be lower if the more accurate breathing rate of approximately 317 L/kg/day used by DPR in the PBPK modeling were used in the calculation. Thus the iodide dose comparisons between studies are not accurate.

DPR Response: The cited literature publications were indeed identified as iodide exposure studies. In fact, these two studies were brought to our attention because they were cited by Arysta (2006) to support their view on species sensitivity of excess iodide from MeI. Our detailed evaluation of these studies not only disagreed with Arysta's conclusion but also uncovered additional concerns for post-natal death that have not been studied within the MeI database.

<u>Comment #39 p.150, lines 27-29</u>: *As shown in Table 71, the estimated additional iodide intake from MeI at the hypothetical RfCs, without any consideration for background iodide exposure, exceeds the tolerable ULs in most cases.*

Arysta Comment: DPR has taken the National Academy of Sciences (NAS) Dietary Reference Intakes for iodide and applied these acceptable upper limits for daily dietary exposure to acute (single day) exposure to iodomethane.

Iodine is an essential dietary element required for synthesis of thyroid hormones. Iodine deficiency results in hypothyroidism, goiter, and severe developmental abnormalities. The human health impacts of iodine deficiency, and iodine excess, are well established and documented (FAO, 2001; NAS, 2002; ATSDR, 2004). It is generally believed, and described in these documents, that more people are at risk for low iodine intake than for excess intake. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) assessed the human data on iodine intake and established a maximum tolerated daily intake level (WHO, 1989). The JECFA report noted that the majority of cases in the literature of adverse effects from excess iodine exposure stem from the use of iodine-containing pharmaceuticals, such as drugs and antiseptics. The Committee concluded that most people are tolerant of excess iodine and that the maximum tolerable level of iodine for the general population is likely to be higher than 1,000 micrograms per day (i.e., 0.017 mg/kg body weight per day).

A more recent report by the FAO/WHO reviewed the mineral requirements for humans (FAO, 2001). Based primarily on recent studies conducted in Belgium, the FAO committee proposed revised iodine intake recommendations for different age groups. The recommended iodine intakes proposed by FAO are comparable to the NAS (2002) recommendations, but include a new category for premature infants (Table 1). Premature infants have an immature thyroid gland which has a reduced ability to take-up plasma iodine relative to a more mature infant (FAO, 2001). Thus, the upper limit of a premature infant (100 microgram/kg/d) is lower than full term infants (150 micrograms/kg/d), but these intakes are still 2- to 3-times higher than an upper limit for adults (50 micrograms/kg/d). The FAO upper limit of iodine intake values (levels deemed likely to be safe) are higher than the NAS upper limit values, indicating that the new Belgium cohort data suggest that higher intakes of iodine are not likely to cause adverse health effects.

Table 1. WHO/FAO Recommended Dietary Intake of Iodine and Probable Safe Upper Limits (FAO, 2001).

Group	Recommended μg/kg/d (μg/d)	Upper limit μg/kg/d (μg/d)
Premature infants	30	100
Infants 0-6 mo	15	150
Infants 7-12 mo	15 (90)	140 (840)
Children 1-6 yr	6 (90)	50 (750)
Children 7-12 yr	4 (120)	50 (1,500)
Adolescents and adults (>12 yr)	2 (150)	30 (2,250)
Pregnancy and lactation	3.5 (200)	40 (2,286)

These upper limit iodine intakes are daily intakes which appear not to impair thyroid function that are based on loading studies performed in adults in the United States and infants studied in Europe.

The weight of the evidence indicates that DPR has selected a particularly conservative measure of acceptable daily iodide intake via the diet and applied this to risk assessment from acute exposure to iodomethane. Arysta suggests that a more appropriate single day acceptable iodide exposure level be identified and compared to the single day iodide intake from iodomethane exposure in the acute exposure iodomethane risk assessment.

DPR Response: DPR have provided all the current health based standards available, including the Delange (2007) report of proposing updates of WHO standards. Our presentation also contains all the qualifiers for these standards, and clearly showed that the ATSDR standard includes a one-day period (ATSDR, 2004). We chose to compare the excess iodide exposure from MeI to the higher NAS's ULs (NAS, 2000) rather than the lower ATSDR's standard, which is applicable for acute (1-14 days) and chronic exposures (see Table 70 of Volume 1) in order to give as much allowance as possible for a single day exposure scenarios. On the other hand, we cautioned that there are other sources of iodide intake that are not accounted for in this comparison. In addition, we also noted that this comparison may not afford protection for sensitive individuals.

It is important to view the upper limits of the FAO/WHO values provided by Arysta in context. Please note the accompanying qualifier for these values is "appear not to impair thyroid function" and "probably safe" limits. Instead, a level deemed <u>likely</u> to be safe should be the public health protection goal against additional iodide exposure from MeI.

Note also that Arysta has not submitted to DPR the studies which formed the basis used in the table presented by Arysta from this FAO/WHO chapter. In a previous discussion on the values

for pregnant women, Arysta has not been able to provide DPR with the requested supporting data.

Comment #40 p.152, lines 17-20: *An additional uncertainty factor is considered for MeI for young children because of 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 MeI exposure, and the level of excess iodide in MeI being added to the background iodide intake.*

Arysta Comment: An additional uncertainty factor is not warranted for any of the reasons mentioned because:1) potential neurodevelopmental effects described throughout this document are prevented by prevention of alterations in thyroid hormone levels, which occurs at the rat NOAEL of 20 ppm; 2) potential postnatal mortality has been studied and characterized in the guideline 2-generation rat study that was performed and submitted as required; and 3) iodide is an essential element that has been widely studied and DPR should make use of data that provide acceptable short-term exposures to iodide for comparison to short term exposure to iodomethane. used in the calculation. Thus the iodide dose comparisons between studies are not accurate.

DPR Response: No response is needed because no new issue is raised in this comment.

Responses to Comments on Volume I Appendix A.

Comment #41 p.A-4, lines 34-35: *A key issue in selecting the dose metric for the HEC is the exposure duration and frequency associated with the NOEL.*

Arysta Comment: The use of NOELs rather than NOAELs is a fundamental problem with the assessment, particularly as it pertains to the developmental endpoint, where the NOEL of 2 ppm rather than the NOAEL of 10 ppm (Nemec, 2002; Mileson *et al*, 2009)

DPR Response: As indicated in Volume I, the NOEL includes the consideration of adversity as in the term "NOAEL." No fundamental problem should exist that the "NOEL" here is the "NOAEL" when death is the endpoint. Note that Nemec (2002d) designated 2 ppm as a NOAEL for the study.

Comment #42 p.A-5, lines 33-43: *The illustration of the model fit to the data from the Sloter studies are provided by Mileson et al (2007) and given in Figure A-1a and A-1b (taken from Figures 4a, b in Mileson et al, 2007). The model showed reasonable fit to the 3 data points for fetal serum levels within 24 hours, but underestimated the maternal data, especially at hour 3. The fit for both maternal and fetal data became poorer as time progressed (Figure A-1b). No experimental data are available for model validation beyond a few days. The poor model fit in time indicates increasing uncertainty for extending the model beyond 24 hours, especially for accommodating the assumption by Mileson et al (2007) that the NOEL should represent a single day incremental exposure after the steady state of fetal blood iodide is reached on day 13. This issue on defining a single day HEC corresponding to the NOEL is discussed in Section II.B.1.*

Arysta Comment: The DPR evaluation of the model fit to iodide data from the Sloter studies (2005a, 2005b) was incomplete and not consistent with the standard practices of PBPK model evaluation (e.g., Chiu *et al*, 2007, USEPA, 2000). The comparisons of model predictions to experimental data were limited to data from the 20 ppm final study (Sloter 2005b), and did not include data from the 25 ppm preliminary study (Sloter 2005a). DPR notes that the model "underestimated the maternal data, especially at hour 3" and that the "fit for both maternal and fetal data became poorer as time progressed." It is important to note that the deviation of the fit of the model from the experimental data is in the health-protective (conservative) direction and, overall, the fit is very good based on recognized methods for PBPK model evaluation (Chiu *et al*, 2007). Assessment of the quality of fit (e.g., excellent, good, fair, poor) of PBPK models to experimental data has typically been subjective, based on visual inspection rather than rigorous statistical comparisons (Chiu *et al*, 2007). However, an example of a quantitative benchmark is the U.S. EPA's designation that a PBPK model would be acceptable for use in route-to-route

extrapolation under an Enforceable Consent Agreement if the deviation of the model predictions from the experimental data did not exceed, on average, a factor of 2 (U.S. EPA, 2000).
A quantitative evaluation of the model fit to the experimental data demonstrates that the average difference in plasma iodide prediction compared to measured levels through 4 days of iodomethane exposure is only 24 and 28 percent for fetal and maternal levels respectively. For the quantitative method, the modeled value (m) is compared to the mean experimental value (e), and the maximum of m/e or e/m is used, such that the discrepancy between the model and mean experimental value is always expressed as a value greater than 1 (or equal to one if the prediction exactly matches the mean experimental value).

Of the 10 maternal iodide measurements at 20 or 25 ppm, only once did the model underpredict the maternal iodide concentration. In this case a model/experiment ratio of 1.03 resulted, indicating a 3% underprediction of maternal plasma iodide at 60 hrs—6 hrs after the end of exposure on day 3—for exposure to 20 ppm Iodomethane. Likewise, maximum fetal iodide underprediction was 14% (at the end of the second day of exposure). The maximum discrepancy between the modeled and average experimental values was a ratio of 1.80 for the fetal iodide at t=78 hrs (end of the 4th day of exposure) in rabbits exposed to 20 ppm iodomethane. The geometric mean for all comparisons of modeled maternal iodide and mean experimental values was 1.28, with ratios of 1.20 for the 3 through 24 hr data and 1.32 for the 30 through 78 hr data. The geometric mean for all comparisons of modeled fetal iodide and mean experimental values was 1.24, with ratios of 1.11 for the 3 through 24 hr data and 1.32 for the 30 through 78 hr data. It is inappropriate for DPR to criticize the slightly poorer fit of the model to the later data when DRP omitted some of the data from their analysis. The fit of the model to the later data is still very good, with an average error of only 32 percent for both maternal and fetal iodide. (U.S. EPA, 2000). Clearly, the model more than meets the standard identified by the U.S. EPA which states that a PBPK model would be acceptable for use in route-to-route extrapolation if the deviation of the model predictions from the experimental data did not exceed, on average, a factor of 2 (U.S. EPA, 2000). This model meets this standard of acceptability.

DPR Response: DPR acknowledges that some measure of relativity and subjectivity is unavoidable in assessing the quality of model fit. This is especially true when a seemingly "small" difference may have significant impact to the HEC determination. Suffice to say that DPR's conclusion is the same as Arysta's and USEPA's in that the current PBPK modeling is a valid tool that allows for deviation from the current default methodology.

<u>Comment #43 p. A-7, lines 2 to 7</u>: *The model output at 20 ppm MeI exposure but using the non-pregnant 12 L-hr/kg3/4 QAC is presented in Table A-1. As expected, the lower QAC results in further deviation from the experimental measurements. The lack of model fit is also evident in the deviation from the experimental data regarding fetal-to-maternal iodide ratio, discussed in the*

next section. The use of lower QAC is troubling also regarding its biological implication, given that the window of vulnerability for fetal death in rabbits is during GD23-26.

Arysta Comment: In this section DPR provides a comparison of modeling to experimental data using an alveolar ventilation rate (QAC) of 12 L-hr/kg$^{0.75}$, even though the comparisons of the model to the experimental data is most appropriately done using the higher QAC of 20 L-hr/kg$^{0.75}$ due to the period of gestation in which these exposures occurred (appropriate comparisons are shown in Figure A-1). Therefore there is no value in making comparisons between model predictions using QAC of 12 L-hr/kg$^{0.75}$ to experimental values for any metrics derived from these studies-either the serum iodide concentrations or any ratios derived from these concentrations. We also are unclear why the use of the lower rabbit QAC of 12 L-hr/kg$^{0.75}$ in the assessments but Arysta (Arysta 2008 a, b) would be "troubling… given that the window of vulnerability for fetal death in rabbits is during GD23-26." The values derived from this value are simply more conservative. Given DPR's decision to use the simulations with the higher QAC value (Arysta, 2008e), DPR should revise Appendix A, eliminating/replacing any calculations and comparisons made using the QAC of 12 L-hr/kg$^{0.75}$ simulations.

The utility of evaluating the model predictions of ratios to the ratios of experimental values is questionable. The maternal/fetal plasma iodide ratios are not metrics used in the risk assessment per se. It is appropriate to consider the accuracy of the fetal predictions, if fetal metrics are considered for use in risk assessment, and likewise for maternal predictions; however evaluations of the ratios are not valuable in and of themselves.

DPR Response: It is worth repeating that a conscious effort to steer toward being more conservative at the expense of pertinent data has not been DPR's mode of operation for reviewing Arysta's PBPK model. In this case, DPR did not accept Arysta's initial PBPK runs simply because the lower QAC was not physiologically based. Nevertheless, these model outputs remain to be of value since the lower QAC was used by USEPA.

Model output from Arysta using the DPR preferred QAC came when our draft review was near completion and the majority of model presentations from the lower QAC runs was already in place. For the purpose of illustrating model behavior, DPR did not consider it necessary to delay the review process by requesting further model runs from Arysta (i.e., at 20 ppm) or invest substantial resources to re-do a different set of model behavior illustrations thereafter. The value of QAC is clearly labeled for all data presented in this review.

The significance of validating the fetal-to-maternal iodide ratio is presented in section II.A.2. Due diligence was carried out in comparing model output to as many measured data as possible, especially for areas that could have major impact on the HEC determination.

<u>Comment #44 p. A-7</u>: Table A-1: Modeled versus measured rabbit serum iodide concentrations after repeated 20 ppm MeI (6 hour/day) exposure.

Arysta Comment: The model output and the measured iodide concentrations in Table A-1 are not comparable and the table should be deleted or revised to include the appropriate model output as described below. Arysta will be happy to provide such a table at DPRs request. DPR has misused simulations intended to demonstrate HEC derivations (model application that includes a conservative assumption for breathing rate) and apparently is using these simulations as a check on the model development/validation. Actual model development and validation preceded the HEC derivations. The proper simulations for model validation are the QAC = 20 L-hr/kg$^{0.75}$ simulations of figure A-1b and simulations of the 25 ppm exposure (Sloter, 2005a). In DPR's table (A-1), the measured maternal iodide concentrations generally exceed the modeled values by about a factor of 2, whereas in the Arysta model validation simulations, the model never exceeded the experimental value by more than 3%. In DPR's table A-1, the modeled F/M ratios consistently exceed the experimentally measured ratios. In Arysta's simulations, (reproduced in Figure A-1b), the geometric mean of the ratio of modeled F/M value to the experimental F/M value was 0.94.

DPR Response: DPR believes that Arysta misunderstood the purpose for Table A-1. A part of the argument Arysta is making in this comment is exactly how we attempted to show the troubling results from the use of lower QAC. We were puzzled by Arysta's initial choice of a higher QAC for model validation, then switched to a lower QAC for HEC simulation. DPR could not accept Arysta's argument for using the lower QAC just because it produced a more "conservative" output. It became clear in subsequent discussions with Arysta that the lower QAC was most likely a "left-over" from Arysta's initial modeling in an attempt to represent the MeI exposure starting on GD6. However, since the window of vulnerability is on GD23-26, DPR decided that the use of the lower QAC should be corrected for HEC simulations.

<u>Comment #45 p.A-8, lines 25-26</u>: *The resultant fetal-to-maternal serum iodide ratios (F/M) are compared to the two sets of experimental data.*

Arysta Comment: We wish to reiterate our criticism of the use of maternal/fetal ratios for comparing model simulations to experimental data. Comparisons of maternal simulations to data are appropriate, and comparisons of fetal simulations to fetal data are appropriate, but comparisons of ratios have no utility in and of themselves.

DPR Response: Please see our response on Comment #43 for the reiterated criticism.

<u>Comment #46 p.A-8, 37-39</u>: *The ratios from model output during the similar period are 3.1-8.2 at 2 ppm MeI and 3.4-10.0 at 10 ppm MeI exposure (Table A-2).*

Arysta Comment: Values in Table 2 based on modeling with QAC = 12 L-hr/kg$^{0.75}$ should be removed or replaced with the appropriate values from modeling with QAC =20 L-hr/kg$^{0.75}$.

DPR Response: Please see our response on Comment #43 about the timeline of data submission with respect to DPR review process. Together with Table A-1, Table A-2 serves its purpose for illustrating the issue at hand.

<u>Comment #47 p.A-9, line 2</u>: *No other experimental data are available for similar validation comparisons.*

Arysta Comment: Again, Arysta does not think it is valuable to make comparisons of ratios, when the serum concentrations per se are what is relevant for risk assessment. However, we must reiterate that DPR has not considered the serum iodide measurements from the 25 ppm iodomethane exposures (Sloter, 2005a).

DPR Response: The focus of comparison is the time course which is not available in the Sloter 2005a study. Even if the F/M ratio from Sloter 2005a study is pooled into the comparison, it would not have provided additional information; i.e., F/M ratio was 2.2 after either 2 or 4 MeI exposures.

<u>Comment #48 p.A-9, lines 2-3</u>: *The extent of contribution by the lower QAC input parameter to this discrepancy is unknown.*

Arysta Comment: Comparisons of model simulations at QAC = 12 L-hr/kg$^{0.75}$ throughout Appendix. A should be replaced with the outcomes from the 20 L-hr/kg$^{0.75}$ simulations, and comparisons of the ratios are not valuable for risk assessment. We have found that the F/M ratios are more accurately predicted when QAC = 20 L-hr/kg$^{0.75}$, is used the value used in model development, as described above (Page A-5, Lines 33-43). Since DPR does not use any simulations of 10 ppm rabbit exposures to develop HECs and there are no 10 ppm data available for comparison, there is no value in presenting the 10 ppm simulations. For the 2 ppm simulations, DPR has only considered a single-day exposure (no preceding exposure), so there is no value to presenting 2 ppm rabbit simulations beyond 24 hrs. The correctly simulated 2 ppm rabbit concentrations and ratios are provided below, and were previously provided to DPR.

Hour	Fetal serum iodide (mg/L)	Maternal serum iodide (mg/L)	F/M ratio
3	0.23	0.74	3.2
6	0.33	1.4	0.42
24	0.11	0.87	7.8

DPR Response: Although the 10 ppm scenario was not used by DPR, it is pertinent because it was used by USEPA.

Again, the time points beyond 24 hours are included because of the focus on time course, showing increasing modeled F/M ratio in time.

It is not clear how the F/M ratio provided by Arysta would have made any difference to the issue at hand (i.e., resulting in similar F/M ratio as given in Table A-2). In fact, the ratios in this comment help to demonstrate why DPR did not consider it necessary to re-do our model illustrations after receiving the correct model re-run from Arysta at a late stage of our review process. Nor does DPR consider it justifiable to further delay model review by requesting for more iterations of model runs, e.g., at 20 ppm with the high QAC.

Please note the apparent error of the "0.42" in the table from this Arysta comment.

<u>Comment #49 p.A-10, lines 6-8</u>: *The cord-to-maternal blood iodide ratio of 1.2 was used to adjust the CLTRANS1C (placenta to fetus) and CLTRANS2C (fetus to placenta) parameters to 0.15 and 0.12 L/hr-kg$^{0.75}$ respectively (Mileson et al, 2007; Barton, 2007).*

Arysta Comment: In should be noted that the CLTRANS1C and CLTRANS2C values produce a cord/maternal blood iodide ratio of 1.2 for **long-term, low level, constant** exposure. As DPR has noted in its analyses, the modeled human fetal/maternal serum iodide ratio is dynamic with short-term, discontinuous exposures.

DPR Response: No response is necessary, unless Arysta is intimating that the data from Rayburn et al. (2007) is only pertinent to long-term exposures and not suitable to guide the modeling of acute HECs.

<u>Comment #50 p.A-10, lines 12-15</u>: *"However, even if this early stage is the only target period for fetal death concern, data are unavailable for determining how well iodide levels collected*

from deliveries during gestation week 29-36 may represent the neonatal stage at the end-of-first-trimester."

Arysta Comment: We assume that DPR meant "prenatal" or "fetal" rather than "neonatal." DPR provides no rationale to support an assertion that the fetal/maternal iodide ratio might be different at the end of the first trimester compared to week 29. This sentence also suggests that the Rayburn *et al* 2008 data regarding iodide levels measured in maternal blood and cord blood during gestation weeks 29-36 might not be representative of the blood iodide levels during the target period of concern, the end of the first trimester (around gestation week 12). It is true that no data on cord iodide levels have been collected that early in human pregnancy, but Liberman *et al* 1998 reported that the average serum iodide concentrations in maternal blood during human pregnancy are 1.6 ± 0.2, 1.8 ± 0.2, and 1.8 ± 0.2 ug/dL in the first, second and third trimesters, respectively. This indicates that at least for the mother, the iodide concentrations in blood remain constant throughout pregnancy. In addition, in the Rayburn *et al* 2008 study a plot of the cord iodide concentrations vs. gestation week (see Fig 1 in Rayburn *et al*, 2008) showed a downward trend in cord iodide concentrations from late to early in pregnancy with a regression that almost reached significance. This implies that the cord iodide levels might be expected to decrease or stay the same at earlier times during pregnancy, such as back to the first trimester. While these findings are not definitive, they do indicate that the cord iodide concentrations from gestation weeks 29-36 could very likely be representative of the cord iodide concentrations present at the end of the first trimester as well.

DPR Response: The word "neonatal" is deleted.
Regarding the iodide levels, DPR did not speculate beyond the data cited as Arysta did in this comments. Nevertheless, DPR is pleased to have Arysta's agreement that the data did not provide definitive determination of cord iodide level at the end of first trimester.

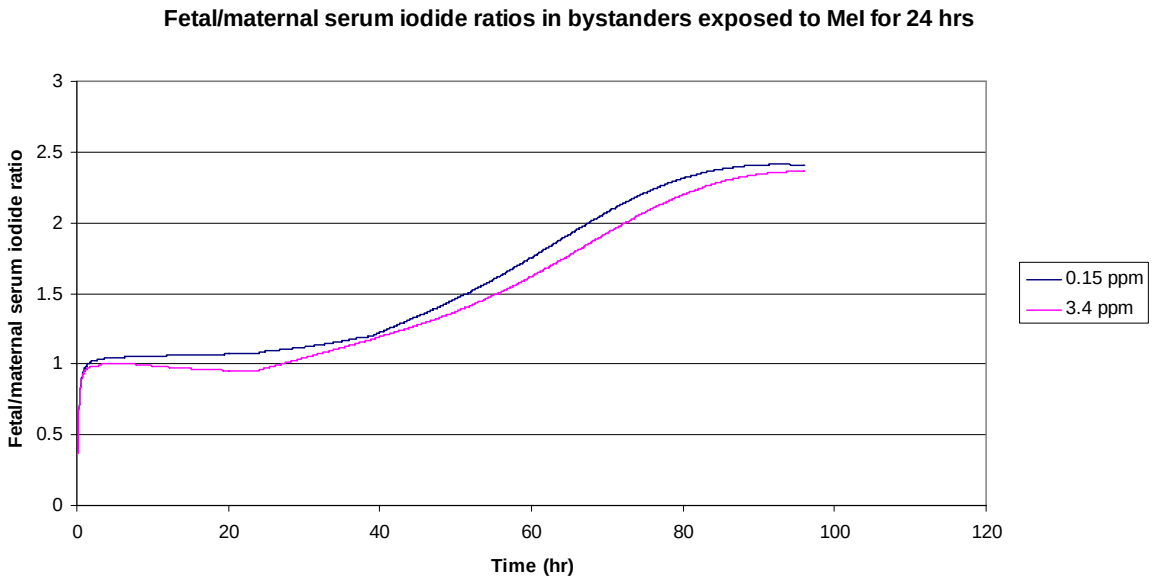
Comment #51 p.A-11, lines 1-2: *Another important issue regarding the maternal to fetal iodide transfer is that the F/M ratio is dynamic, not a fixed constant.*

Arysta Comment: Again, we assert that the ratios of the model predictions should not be a focus of the model evaluation since this ratio is not a metric used in the risk assessment.

DPR Response: No additional response is necessary.

Comment #52 p.A-11, lines 6-8: *While the fetal iodide concentration is consistently higher than the maternal level at 0.15 ppm MeI exposure, this relationship is reversed near the peak concentration at 3.4 ppm MeI.*

Arysta Comment: While changes in the predicted fetal/maternal iodide ratio with time and dose can be inferred from the plots, if DPR wishes to persist in analyzing this ratio, it would be much simpler to use the data from the spreadsheets to calculate the ratios, plot them over time, and combine the comparisons for the 0.15 and 3.4 ppm simulations into a single plot as provided below. The ratio profiles are very similar for the two concentrations. We speculate that the decline in the fetal/maternal ratio near the end of exposure at 3.4 ppm, but not 0.15 ppm, may be due to saturation of placental uptake. Overall, the time-dependence of the modeled fetal/maternal ratio does not appear to be very sensitive to iodomethane concentration in this 20-fold Iodomethane concentration range and thus the ratio is not sensitive to serum I- concentration.



DPR Response: DPR considers the extent of analysis already performed is sufficient to illustrate the dynamic nature of the F/M ratio and did not see the value of persisting further analysis as provided in the comments. Nevertheless, Arysta's speculation on model behavior in the comments is appreciated.

<u>Comment #53 p.A-11, lines 11-12</u>: *The F/M ratio gradually increases with decreasing serum iodide level after the end of 24 hours of exposure; from 1.0 within hour 24 to 2.1 - 2.4 by hour 78 - 96.*

Arysta Comment: The increases in fetal/maternal serum iodide ratio are clearly related to the change from I- accumulation to I- elimination in the modeled compartments, not the absolute

value of the iodide concentration. For example, the fetal iodide concentration at the end of the 3.4 ppm simulation (Figure A-2, lower panel) is similar to the fetal iodide concentration at ~6 hrs exposure to 0.15 ppm iodide (Figure A-2, upper panel), but the fetal/maternal iodide ratios are ~2.4 and 1, respectively.

DPR Response: No further response is necessary.

Comment #54 p.A-11, lines 19-20: Overall, data both in rabbits and humans indicate greater uncertainty at the fetal compartment level.

Arysta Comment: We disagree. As noted in the response to Page A-5, Lines 33-43, the geometric mean model discrepancies for fetal and maternal rabbit iodide were 24 and 28%, respectively, so, if anything, fetal iodide is the more certain metric. The discrepancies do not increase meaningfully with increased exposure duration. Also, DPR has not provided separate evaluations of the model's ability to predict human maternal vs. human fetal iodide levels, focusing instead on fetal/maternal ratios, so their analyses do not provide information on which metric (maternal or fetal iodide) is simulated with greater certainty.

DPR Response: Aside from the details in DPR's evaluation, suffice to say that the DPR conclusion is consistent with those presented by the model authors in their recent publication. Regarding the comparative sense of uncertainty at the fetal compartment level, it was stated that "Accordingly, confidence in the PBPK model predictions for the reproductive/development effects of iodide in rabbits is considered moderate using fetal iodide and high using maternal iodide..." (Sweeney et al., 2009).

Comment #55 p.A-11, lines 22-27: *In the human model, it is uncertain how well data from the Rayburn study can adequately represent the modeled MeI exposure scenarios; specifically regarding the unmatched gestation stage (i.e., applying data from beyond gestation week 29 to model the end of the first trimester stage) and the iodide exposure status (i.e., applying data from non-iodide exposure conditions to substantially high excess iodide exposure scenarios).*

Arysta Comment: These sentences also refer to whether the results from Rayburn *et al* 2008 for gestation weeks 29-36 are representative of the end of the first trimester. We refer to our comment concerning page A-10, L 13-15 earlier in the document. DPR's concern about whether the fetal/maternal iodide blood ratios are consistent between unexposed (e.g. the Rayburn study) and humans that might be more highly exposed to iodide, has been addressed in a report sent to DPR by Arysta LifeScience North America entitled, " MeI: Arysta Responses to Toxicology Questions Discussed with Department of Pesticide Regulation", dated March 19, 2008 (DPR ID No.: CRR 192894N). A short summary of that report follows. Briefly, a study by Cottino *et al*,

(1972) evaluated subjects who received a therapeutic injection of an iodated oxytocic preparation during labor to characterize placental iodine transfer and storage. The dynamics of mother-fetus iodine exchange was studied following administration of iodomethylspartein to parturient women. Cottino *et al* measured serum iodide levels in maternal and cord (fetal) plasma samples at birth, and birth occurred between 15 minutes and 48 hours after injection. Paired maternal and fetal serum iodide data from the Cottino study showed that iodine in soluble compounds rapidly cross the placenta and reach approximately the same levels in the fetus as in the mother. The return from the fetus to the mother appeared to be equally rapid as the maternal levels decreased as iodide was eliminated via the kidney. These data demonstrate that the fetal:maternal iodide ratio does not change when pregnant women are challenged by exposure to increased iodide.

The iodide concentrations reported by Cottino *et al*. were quite high (compared to the cord and maternal blood levels reported in Rayburn *et al* (in the 1 to 2 ug/100 mL range). Therefore, DPR's concern about using iodide ratios in unexposed people for estimating the ratios in exposed people are unfounded.

DPR Response: The Cottino et al. (1972) study does not provide additional information for the issue at hand. Within the 18 pairs of measurements, the cord-to-maternal iodide ratio ranged 0.5 - 3.4. Moreover, these data could not convey the pattern of F/M ratio during the end of first trimester at which the HEC was modeled, especially when Arysta assumed that this was the critical window of human fetal vulnerability. However, because of this comment, data from Cottino study will be added to strengthen DPR's concern for the wide range of human cord-to-maternal iodide ratio.

Comment #56 p.A-13, lines 3-6: *Data from the Morris et al. (2004) rabbit study with NaI were used as starting points for modeling iodide disposition variables. The stated model assumption was that when blood kinetics are accurately predicted, tissue-specific parameters are sufficiently accurate without needing further adjustment (Mileson et al., 2007).*

Arysta Comment: The model developers recommended the use of fetal plasma iodide levels rather than a thyroid iodide dose metric in their assessment because the model does not predict tissue iodide levels with sufficient accuracy (Sweeney *et al*., 2009). The available data on rabbit tissue levels of iodide (Morris *et al*., 2004) after IV administration of iodide were used to develop approximations of parameters that determine the tissue levels of iodide. A major limitation of these data with respect to modeling was that the iodide measurements at the last three time points (6, 12, and 24 hrs after injection) were very similar in most tissues and higher in maternal thyroid at 24 hrs than at 12 hrs after injection. Thus the clearance phase of plasma and tissue iodide disposition could not be well-characterized from these data. When the values derived from the iodide iv study were used in simulations to predict serum iodide levels in rabbits repeatedly exposed to iodomethane (Sloter *et al*., 2005 a and b), parameters had to be

adjusted to match the observations. The final iodide parameters do not adequately simulating the iv study (Sweeney *et al*., 2009). Thus with the current parameterization, the fit of the final model to the plasma and tissue data in the iodide iv study was sacrificed in order to fit the plasma iodide data in the iodomethane inhalation studies. The resulting rabbit plasma iodide dose metrics should therefore be considered the only valid iodide metrics available from the model for making predictions of iodide in iodomethane-exposed rabbits.

DPR Response: This comment limited the model reliability to only plasma iodide dose metric, even though tissue- and sub-tissue- specific supporting data were gathered, generated, applied, and discussed in the model description, and the model output reviewed by DPR and commented by Arysta herein. Nevertheless, serum iodide dose metric is the basis for DPR derived HECs for fetal death endpoint. However, the implication of lack of reliability for model output other than serum iodide levels does diminish the confidence in using brain level MeI for neurotoxicity HEC.

Comment #57 p.A-13, lines 15-16: *The Morris study showed that within 24 hours of NaI injection on GD25, fetal thyroid did not accumulate iodide as compared to levels in fetal trachea.*

Arysta Comment: A closer review of the Morris study data indicates that fetal thyroid does accumulate iodide. The fetal thyroid iodide levels 24 hrs after the injection of the low dose, ranged from 1.88 to3.40 ug/g, for an average ± standard deviation of 2.92 ± 0.48 ug/g. The iodide levels in the fetal trachea were highly variable at all time points in the low dose study, with coefficients of variation (CVs) ranging from 0.65 at 1 hr after dosing to 1.3 at 24 hrs after dosing. The low dose, 24-hr levels of iodide measured in the trachea were 0.414, 0.8182, 0.8332, 0.8899, 0.9546, 1.77, 2.319, 3.429, and 10.22 ug/g, a 25-fold range, with an average ± standard deviation of 2.4 ± 3.08. If only the highest measured trachea iodide concentration is excluded, the average drops to 1.43 ±1.01. When the highest measured trachea iodide concentration is excluded, the ratio of the average thyroid concentration to the average trachea concentration is greater than 2 and using the median values, a thyroid/trachea ratio of 3 is computed. These data support the position that the fetal rabbit thyroid accumulates iodide.

DPR Response: As stated in DPR review, the study "… showed that within 24 hours of NaI injection on GD25, fetal thyroid did not accumulate iodide as compared to the levels in fetal trachea." The same conclusion was reached by the same author group in the published version of the study stating in a conclusion that "There was no evidence for preferential accumulation of radioiodide in fetal thyroid tissues" (Thrall et al., 2009).

<u>Comment #58 p.A-13, lines 18-20</u>: *Thus, it is surprising that the model predicted a 4.2 mg/L peak fetal thyroid iodide level at the end of the 6 hour MeI exposure, a level that is 217-fold higher than the maternal level at 0.02 mg/L (Figure A-3).*

Arysta Comment: The Morris data represent whole-thyroid concentrations of iodide, whereas the thyroid iodide predictions shown in DPR's Figure A-3 are for follicles only. Iodide preferentially partitions into the colloid of the follicle (7:1) and adults have a higher fraction of the thyroid volume as colloid than the fetuses (0.45 vs. 0.183). Thus it is to be expected that the whole tissue fetal thyroid/whole tissue maternal thyroid iodide ratio will be smaller than the ratio for follicles alone.

DPR Response: The word "follicle" as specified in Figure A-3 will be added to the text.

<u>Comment #59 p.A-16, lines 25-28</u>: *Assuming the applicability of the low normalized sensitivity coefficient1 for VFETC (given as "<0.05" in Table 11 of Mileson et al., 2007) in this case, a 5- to 10-fold higher value for the VFETC (from 0.27 kg, or 0.6 pounds, to 3 to 6 pound fetuses) for later gestation period may still be significant.*

Arysta Comment: DPR suggests that changes in human fetal body weight (VFETC) may have a significant impact on risk, assuming the applicability of information in Table 11 of Mileson *et al*. (2007). DPR (inappropriately) uses information from a sensitivity analysis of the rabbit model rather than conduct a sensitivity analysis of the human model. Arysta, at DPR's request, is happy to provide either a human sensitivity analysis or greater precision in the rabbit sensitivity coefficients. The normalized sensitivity coefficient for rabbit maternal serum iodide AUC is 0.02 at 10 ppm and 0.01 at 2 ppm, and the normalized sensitivity coefficient for fetal serum iodide AUC at 2 ppm was 0.02. A normalized sensitivity coefficient of 0.02 means that even with a 10-fold increase in the input parameter, the output is expected to increase by only 20 percent. Therefore any uncertainty about the relevant rabbit fetal stage has minimal contribution to uncertainty in the rabbit dose metric. This variability/uncertainty is more than adequately accounted for with DPR's uncertainty factors. We conducted human simulations at DPR's HEC of 0.24 ppm with the baseline human VFETC value (0.0044) and a value that is10-fold higher. At the higher VFETC, both maternal and fetal serum iodide AUC were decreased (maternal AUC decreased to 88% of baseline value, fetal value decreased to 58% of the baseline value), in demonstrating that the use of an early stage of human development is health-protective with respect to the HEC derivation.

DPR Response: DPR appreciates the greater precision of sensitivity, from <0.05 to 0.02. The implication of a 12% and 42% reduction is not trivial. The new information will be considered.

<u>Comment #60 p.A-17, lines 10-13</u>: *Comparison of maternal and fetal parameters in rabbits (i.e., comparing blood to blood, thyroid to thyroid) shows that the maternal parameter is higher for the MeI profiles whereas the fetal is higher for the iodide profiles.*

Arysta Comment: It is confusing when DPR uses the term "parameters" to refer to the model outputs. In PBPK modeling, the term parameters is usually reserved for the model inputs (flow rates, partition coefficients, metabolic rate constants), not the outputs. The maternal/fetal comparisons are not meaningful. The fetal/maternal ratios of various dose metrics in humans have no implications for risk if the same ratios are observed in the test species, so no useful generalizations can be drawn from these observations. The figures to which DPR refers should be replaced with figures generated using the model parameter values used in the HEC derivations (i.e., QAC = 20 L-hr/kg$^{0.75}$).

DPR Response: It is curious how this confusion for "parameter" would suddenly appear so far down this document. "Parameter" was used in this review as a general term to express model related entities as in "input parameter" and "output parameter". Nevertheless, to honor Arysta's convention, wording will be changed to the very few undesignated "parameter" in this document in order to avoid unnecessary confusion.

No further response is necessary regarding the fetal/maternal comparison or model output from the lower QAC.

<u>Comment #61 p.A-17, lines 17-18</u>: *Available data for adjusting the input variables are limited, with experimental data only at 10-fold above the modeled 2 ppm and with high variability.*

Arysta Comment: DPR has neglected to consider the 25 ppm data set. The variability in the 20 and 25 ppm data is not extensive as demonstrated by an average discrepancy between the model and experimental data of 28 percent (maternal) and 24 percent (fetal) calculated above in Arysta's Response to II.A.1

DPR Response: As stated in the comments, data between 20 and 25 ppm are not very different. Thus, DPR generally referred to them as one group of concentration that is 10-fold above 2 ppm. The word "approximately" will be added.

<u>Comment #62 p.A-17, lines 18-19</u>: *The fundamental issue concerning modeling fetal death based on surviving fetal data remains unresolved.*

Arysta Comment: See comment below for Page A-21, Lines 30-35.

DPR Response: This comment will be address under Comment #72.

Comment #63 p.A-17, lines 20-21: *"…the model shows some discrepancy within the first 24 hours of exposure and to a greater extent beyond the one day period."*

Arysta Comment: DPR apparently arrived at this conclusion without, reviewing all of the serum iodide data for iodomethane exposed rabbits. When the data for both 20 and 25 ppm are considered, it is clear that the discrepancy between the model and the experimental data is modest and not substantially different beyond 24 hours than within the first 24 hours.

DPR Response: No further response is necessary (see: response to Comment #42)

Comment #64 p.A-17, lines 22-23: *In general, the model output shows greater iodide in rabbit fetal serum relative to the maternal level than experimentally reported.*

Arysta Comment: DPR arrived at this conclusion by not consulting the applicable model simulations (i.e., they used model simulations with a lower estimated alveolar ventilation rate). The analysis should be re-done based on the applicable data. DPR also invested a great deal of effort in evaluating a model metric (fetal/maternal ratio) which is not a metric proposed for use in risk assessment. It would have been more appropriate for DPR to focus on the ability of the model to predict fetal serum iodide and/or maternal serum iodide, but not the ratio of the two.

DPR Response: No response to this summary statement is necessary. Nevertheless, Arysta is in error. The issue of fetal versus maternal serum iodide still stands regardless if the lower or the most appropriate QAC was used. Please see the data provided by Arysta in Comment #48.

Comment #65 p.A-17, lines 23-24: *This may indicate a greater uncertainty for using rabbit fetal serum iodide as a dose metric for HECs.*

Arysta Comment: As noted above, the model predictions for fetal rabbit serum iodide are actually slightly more accurate than the predictions for maternal rabbit serum iodide (24 vs. 28 percent error), when experimental data from both 20 and 25 ppm exposures are considered.

DPR Response: No response to this summary statement is necessary.

Comment #66 p.A-17, lines 24-26: *Questions remain for some biological input parameters (e.g., fetal stages) and simulation outcomes (e.g., extremely high fetal thyroid level).*

Arysta Comment: The sensitivity analyses do not indicate a significant impact for changes in fetal body weight on iodide AUCs. It is our opinion that thyroid simulations should not be used in the assessment because of insufficient data to confidently identify clearance of iodide from the rabbit thyroid.

DPR Response: No response to this summary statement is necessary. Nevertheless, this comment contradicts with the additional analysis provided in Arysta's Comment #59 showing substantial impact especially with human fetal serum iodide dose metric.

Comment #67 p.A-20, lines 34-36: *Thus, there is no support for modeling HEC based on 14 days of MeI exposure (i.e., rabbit [$AUC_{day14} - AUC_{day13}$]).*

Arysta Comment: DPR mischaracterizes the approach used by Mileson *et al*. (2007). Mileson *et al*. (2007) model the HEC based **one** day of MeI exposure, not 14. The HEC developed and presented in Mileson *et al*. (2007) was derived on the basis of the fetal serum iodide AUC on one day, a day that was preceded by several previous days of MeI exposure. DPR recognizes that when rabbit MeI exposures do not include GD 23-26, no fetal death occurs. However that does not mean that the exposures on earlier days do not contribute to the toxicity observed in Nemec (2002). The exposure on days prior to GD 23 contributes to the body burden of iodide already present when exposures start on GD 23, enhancing the susceptibility to the GD 23-26 exposures." The pharmacokinetic simulations of the key study should describe the experiment as it was conducted, rather than relying on an untested scenario. In the key study, the pharmacokinetics in the window of exposure are appropriately described when the contribution of previous days' iodide load is accounted for through PBPK modeling.

DPR Response: DPR is well aware of Arysta's arguments and did not mischaracterize Arysta's approach. It is obvious that in order to model the one day incremental iodide level, the simulation had to be carried out to day 14. However, the model cannot be validated beyond day 4, and already showed duration-related increase in deviation from measured data within this period.

As to the need for MeI exposure prior to the GD23-26 window of vulnerability, data from Arysta showed that fetal death occurred with only exposure within this vulnerability period.

Considerations for these and other aspects of dose metric selection are provided in Section II.B. of Appendix A.

<u>Comment #68 p.A-20, lines 36-39</u>: *It has also been demonstrated that during GD23-26, fetal death is evident at hour 30, immediately after the second 6-hour daily exposure to 20 - 25 ppm MeI (Tables 55, 56, and 57 in Volume I). Thus, it is reasonable to model the HEC based on a single day exposure.*

Arysta Comment: Only Table 56 of Volume I includes results of exposures wherein fetal death was identified at hour 30, so references to tables 55 and 57 should be removed. This finding was not statistically significant.

DPR Response: It is not clear why data from Tables 55 and 57 should be excluded as they all contain fetal death data within the window of vulnerability for a more complete picture.

DPR will not belabor the general problem of dismissing a toxicologically significant endpoint by relying solely on statistical significance criteria (see DPR's response to Comment #15 and #19). Nevertheless, specific to the dataset of Arysta's choice in Table 56, the small sample size should be considered such that Arysta would not be advocating that the general public should accept the outcome of a 17 - 25% excess risk of litter affected by fetal death just because these are not statistically significant among 10 litters or to ignore the marked increase of the percentage of fetus per litter that died.

All arguments aside, the inconsistency of using statistical criterion alone for determining the occurrence of biological is obvious here. While Arysta emphasized "not statistically significant" findings here was recognized by Arysta and study authors as unequivocally significant for identifying the window of susceptibility.

<u>Comment #69 p.A-21, line 2</u>: *Given the lack of data, DPR follows the conventional default for assessing developmental effects*

Arysta Comment: We disagree with DPR's statement that there is a "lack of data."

DPR Response: No response is necessary. Arysta has taken this phrase out of context.

<u>Comment #70 p.A-21, lines 3-5</u>: *…and assumes that these effects can occur as a result of a single exposure event within a specific window of vulnerability corresponding to a specific vulnerable developmental stage (USEPA, 1991).*

Arysta Comment: The approach used by Mileson *et al*. (2007) is consistent with the assumption that "a single exposure event within a specific window of vulnerability" can produce developmental toxicity. The data supports the kinetic modeling assumption that, in the study for which dose response data are available, the key exposure event occurs after previous days of

exposure that did not contribute to toxicity. The way DPR has modeled the key study is only consistent with the hypothesis that the exposure on GD6 in Nemec (2002) was responsible for the toxicity observed at higher exposure concentrations, a hypothesis incompatible with the data of Nemec (2003).

DPR Response: DPR is puzzled by Arysta's attributing the hypothesis to DPR that the exposure on GD6 was responsible for fetal death. This notion is far from DPR's understanding. We agree with Arysta that it is incompatible with the available data. Could it be that this comment somehow missed the crucial concept about the "window of vulnerability"?

Moreover, DPR is puzzled by this comment that disagrees with DPR's application of USEPA's 1991 guideline when the same approach was used in Arysta's risk assessment as presented in Mileson et al (2009).

Comment #71 p.A-21, lines 8-9: *Significant GSH depletion in fetal blood was detected as early as after one 6 hour 20 ppm exposure.*

Arysta Comment: DPR's arguments that fetal blood GSH decreases provide support for fetal death related to oxidative stress and cell death are very weak compared to the arguments previously developed for a mode of action related to increased fetal iodide. Even at 20 ppm, the LOAEL for fetal death, and 25 ppm, fetal GSH declines in blood are modest, and GSH levels in liver did not show statistically significant declines. The 20 and 25 ppm exposures on GD 23-24 show a reverse dose response with respect to blood GSH depletion (i.e., at 20 ppm, blood GSH was 55% of control, but a lesser decline, to 72% of control was observed at 25 ppm). Thus a dose-response concordance is lacking. A mode of action related to such a generic process as cell death would be expected to be operative throughout gestation, rather than being limited to such a narrow window of susceptibility.

DPR Response: GSH depletion was one of the MOA explored and the final dose metric was not based on GSH depletion.

Comment #72 p.A-21, lines 31-36: *Fetal circulating iodide is a pertinent dose metric because experimental data in rabbits are available. However, the use of this dose metric should be viewed with caution for several reasons. First, all the experimental measurements used for model validation are from fetuses that survived the MeI exposure, a direct opposite outcome to the endpoint targeted for modeling.*

Arysta Comment: We agree that fetal circulating iodide is a pertinent, and we believe, the most pertinent, dose metric for this endpoint. The data used for model validation of the fetal plasma concentrations were time-course measurements taken in does and fetuses after 6 hour inhalation

exposures to MeI during GD 23, 24, 25 and 26 (see Sloter *et al*. 2009), the window of susceptibility for fetal rabbit death. Based on the data from Nemec *et al*. 2009, some of the rabbit fetuses from which blood samples were collected during GD 23 through GD 26 would have died by GD 29. Therefore, the plasma iodide levels measured in the Nemec *et al*. 2009 experiments would have included surviving fetuses, as well as fetuses that were going to die by GD 29. It is unlikely that the reason some fetuses die and some live is due to pharmacokinetic differences (e.g. possibly higher iodide levels) as the DPR seems to imply, but is more likely due to pharmacodynamic reasons (e.g. differences in susceptibility), something seen quite frequently in other toxicity experiments (the same internal doses lead to affects in some animals, but not others). Since we are of the opinion that fetal plasma iodide concentrations are the appropriate dose metric for the fetal death endpoint, then if the susceptible fetuses actually did have higher plasma iodides than those that survived (although we do not believe that is the case), the use of our dose metric should be considered conservative as the lower plasma iodides from surviving fetuses would have diluted the higher levels from fetuses that would have died (the plasma iodides were averaged for all fetuses in a timed group). In any event, the model is ultimately used to simulate the kinetics at the NOEL, a scenario for which, by definition, there is no toxic outcome. We do not believe that caution in using this dose metric is warranted based on this reason stated by DPR.

DPR Response: DPR respects Arysta's line of reason. However, the deliberation should be taken in its entirety as presented in the Volume I. DPR included HECs for all 8 possible scenarios to show the substantial impact on the HEC based on different dose metrics.

Again, it is important not to lose sight of the overall picture in the final analysis. Arysta's conclusion "...confidence in the PBPK model predictions for the reproductive/developmental effects of iodide in rabbits is considered moderate using fetal iodide and high using maternal iodide..." (Sweeney et al., 2009) should add further justification for DPR's choice of maternal instead of fetal serum iodide dose metric.

Comment #73 p.A-21, lines 36-37: …the model predicted iodide F/M (fetal-to-maternal) ratios are generally higher than experimentally measured in rabbits (Section II.A.4).

Arysta Comment: We have previously commented on DPR's use of model simulations that are not applicable to the model validation, as discussed in our comments on Section II.A.4. These comparisons were not made appropriately. Furthermore, what is important is the model's fidelity to each independently, experimentally measured metric that is relevant to validation, not to relationships among these metrics.

DPR Response: No further response is necessary as these comments have previously been made.

<u>Comment #74 p.A-21, lines 37-40</u>: DPR: "The proportionately higher distribution to the rabbit fetal compartment…"

Arysta Comment: The appropriateness of the fetal model predictions should be based on comparisons of fetal data to fetal simulations, not fetal/maternal ratios, and the model does an excellent job of predicting the available fetal and maternal data.

DPR Response: No further response is necessary as these same issues were previously raised.

<u>Comment #75 p.A-21, lines 42-44</u>: the range of human F/M ratio is wide and there are 9 sets of values above 2 (2.08 – 5.4).

Arysta Comment: The number of sets should be put in the context of the size of the study, which consisted of an n of 121. There are a number of reasons why the fetal/iodide ratio may be variable. One possibility is the administration of IV fluids diluting maternal blood. As noted from the MeI modeling, the fetal/maternal iodide ratio appears to increase after iodide delivery stops. Food is typically withheld from women in labor, which could interrupt the maternal iodide supply, producing an imbalance in which fetal iodide temporarily exceeds maternal iodide.

DPR Response: It is well understood that the biological system is not uniform. However, this should not be the reason to take lightly these higher values, especially without clear reasons to exclude them. The document will be revised to show that it is in fact 12 out of 121 sets that has cord-to-maternal ratio of 2 and above.

<u>Comment #76 p.A-22, lines 11-13</u>: *The use of the maternal MeI or iodide dose metric has the advantage of focusing more on the total internal dose of exposure without the additional uncertainty of further modeling to the fetal distribution level.*

Arysta Comment: DPR falsely asserts that there is more certainty regarding the maternal iodide than fetal iodide. Clearly, the modeling of serum iodide in maternal and fetal rabbits have equivalent certainty.

DPR Response: This comment about equivalent certainty is in contradiction to the conclusion by the modelers (see: DPR response to Comments #54 and #65). A lower level of confidence based on fetal serum iodide dose metric was stated in the literature publication by Sweeney et al (2009).

<u>Comment #77 p.A-22, lines 13-14</u>: "They [maternal MeI and iodide] are more suitable dose metrics when no single MOA can be supported."

Arysta Comment: We strongly disagree. For any compound displaying **selective** developmental toxicity, fetal dose metrics are much more suitable than maternal dose metrics.

DPR Response: No further response is necessary as this issue was previously addressed repeatedly.

<u>Comment #78 p.A-22, lines 33-36</u>: *The 6- versus 24-hour MeI exposure durations between rabbits and humans can be accounted for by the AUC dose metric but not by the peak concentration…*

Arysta Comment: DPR asserts that the 6 hr exposure in the rabbit study vs. the 24 hr exposure of humans cannot be accounted for by peak concentration. We do not understand why a model deemed to acceptably compute AUCs for a given exposure scenario cannot acceptably account for peak concentrations as well. In section II.C of appendix A, DPR used model-derived peak concentrations.

DPR Response: Different dose metric addresses different concerns. This is not about what model can or cannot do. Perhaps the missing piece for Arysta's misunderstanding is that the context of this discussion is on the factor of cumulative dose over time which AUC can address but not the peak. This is not about what a model can or cannot do.

<u>Comment #79 p.A-22, lines 39-40</u>: *…maternal iodide dose metric is most reliable for reflecting the maternal MeI exposure*

Arysta Comment: DPR asserts that maternal iodide is the most "reliable" dose metric for reflecting maternal MeI exposure. A fundamental flaw in DPR's assessment is the failure to separate model validation from model application in dose-response (HEC assessment). Indeed, the iodide measurements reliably indicate how much free iodide was generated from MeI metabolism. But just because a dose measure is a "reliable" indicator of *exposure*, doesn't make it an **appropriate** metric for *toxicity*. The appropriate dose metric should be related to the mode of action.

DPR Response: No further response is necessary as the lack of convincing support for Arysta's MOA has been extensively discussed. Other factors of considerations were also presented or added based on various comments that we received. Moreover, Arysta's literature publication

agreed with DPR regarding the greater confidence of HEC based on maternal instead of fetal serum iodide dose metric.

Comment #80 p.A-23, lines 16-18: *HECs based on all 8 dose metrics (i.e., permutation of peak concentration or AUC of MeI or iodide in maternal or fetal blood) are presented below for demonstrating their overall impact to the HEC.*

Arysta Comment: Potential MOAs associated with each of the 8 dose metrics should be presented. If no justifiable MOA can be developed, the dose metric should be eliminated from consideration. Even if no MOA data were available, the preferred dose metric for a selective developmental toxicant should be fetal dose metrics rather than maternal dose metrics.

DPR Response: No further response is necessary.

Comment #81 p.A-23, lines 23-25: *When the dose metric is based on the peak concentrations, it is taken from immediately after the cessation of exposure (i.e., hour 6 for rabbits, hour 24 for humans), since the concentration declines thereafter (Figure A-5 and A-6).*

Arysta Comment: We have noted that the peak iodide concentrations in the simulations are typically observed shortly after the end of exposure.

DPR Response: A quick examination of Figure A- 5 and A-6 as cited shows the highest maternal serum iodide concentration is indeed at hour 6.0, not hour 5.9 nor hour 6.1. For the human model, the highest maternal serum iodide concentration is at hour 24, and the levels at 23.9 and 24.1 are usually within 99% of the hour 24 peak. It is possible that Arysta may be referring to fetal iodide profile. More importantly, it is recognized that both "immediately" and "shortly after" connote a relatively short time frame and should not be a point of discussion without revealing the purpose for such comments.

Comment #82 p.A-23, lines 40-41: *The lower sensitivity of MeI parameters is likely due to its rapid transformation into iodide.*

Arysta Comment: Please note that, as commonly used in PBPK modeling, these MeI-related dose metrics should not be referred to as "parameters." Their lack of sensitivity to QAC is independent of the metabolism rate of MeI, but it due to rapid equilibration with tissues.

DPR Response: This information is added.

<u>Comment #83 p.A-24, lines 1-2</u>: *Table A-4 shows that within the same parameters (i.e., serum MeI or iodide), the HECs…*

Arysta Comment: DPR's use of "parameters" is inconsistent with the usage of this term in the PBPK modeling community, and therefore potentially confusing.

DPR Response: See response to Comment #60.

<u>Comment #84 p.A-24, lines 3-4</u>: *The higher rabbit fetal iodide partitioning parameter contributes significantly to this overall 4- to 5-fold higher HEC.*

Arysta Comment: There is no "rabbit fetal iodide partioning parameter". There are parameters that describe the transport to and from the fetus, and within the fetus there are multiple iodide partition coefficients that describe the equilibrium partitioning of between serum and tissues.

DPR Response: The text is revised.

<u>Comment #85 p.A-24, lines 34-35</u>: *MeI at 0.24 ppm represents the HEC at the most pertinent dose metric and is the final 24-hour HEC for assessing the risk of the general public.*
Arysta Comment: We disagree with DPR's statement that maternal iodide AUC is the "most pertinent" dose metric. We believe that the most pertinent dose metric is fetal iodide. If DPR is truly convinced that there is insufficient data to identify an adequately supported MOA, fetal rabbit MeI should be used as the dose metric.

DPR Response: No further response is necessary as the issue has been previously addressed.

<u>Comment #86 p.A-24, lines 35-37</u>: *An ideal portrayal of the total amount of maternal exposure to MeI would include also the portion of MeI that is not yet converted to iodide.*

Arysta Comment: Based on the simulations conducted, the portion of MeI that is not yet converted to iodide would not be sufficient to generate enough additional iodide to substantially increase the AUC. As noted by DPR, this amount of iodide is insignificant.

DPR Response: No response is necessary because this comment is merely finishing up what was included in the DPR document.

<u>Comment #87 p.A-26, lines 3 to 25</u>: *Paragraphs 1-3*

Arysta Comment: The HEC modeling simulations for worker exposures included the assumption that respiration was increased to 833L/hour during the 8-hour workday and decreased to resting (567 L/hour) the remaining 16 hours per day. For the developmental endpoint, worker exposure was assumed to occur for 8 hours per day, seven days per week and the iodide dose metrics were derived for day 7 of the exposure. The HEC was designed to protect the worker from increased plasma iodide for all days including the seventh day of exposure when iodide levels could have built up from the prior day exposures.

DPR Response: No response is necessary for the additional description.

References cited in responses:

Ammerman, C.B., L.R. Arrington, A.C. Warnick, J.L. Edwards, R.L. Shirley and G.K. Davis, 1964. Reproduction and lactation in rats fed excessive iodine. J. Nutrition 85:107-112.

Arrington, L.R., R.N. Taylor, Jr., C.B. Ammerman and R.L. Shirley, 1965. Effects of excess dietary iodine upon rabbits, hamsters, rats and swine. J. Nutrition 86:394-398.

Arysta (Arysta LifeScience North America Corporation), 2006. Iodomethane: Arysta responses to toxicology issues raised by Department of Pesticide Regulation. April 14, 2006. DPR Vol. 52875-109, #224248.

ATSDR, 2004. Toxicological profile for iodine. http://www.atsdr.cdc.gov/toxprofiles/tp158.html

Cottino, F., G. Zoppetti, A. Favero, M. Lombardi, G. Cenderelli, and A. Costa, 1972. Placental tissue and maternal and cord serum iodine following pharmacological loading. Folia. Endocrinol. 25(4):278-285.

Delange, F., 2007. Iodine requirements during pregnancy, lactation and the neonatal period and indicators of optimal iodide nutrition. Public Health Nutr. 10(12A):1571-1580.

Kirkpatrick, D.T., 2005. A 24-month inhalation combined chronic toxicity/carcinogenicity study of iodomethane in rats. Project no. WIL-418019, WIL Research Laboratories. DPR Vol. 52875-094 #217697.

Kirman, C.R., L.M. Sweeney, M.L. Gargas, and J.H. Kinzell, 2009. Evaluation of possible modes of action for acute effects of methyl iodide in laboratory animals. Inhal. Toxicol. 21(6) (in press, DOI:10.1080/08958370802601510).

Logothetopoulos, J. and R. F. Scott, 1956. Active iodide transport across the placenta of the guinea-pig, rabbit and rat. J. Physiol. 132:365-371.

Mileson, B.E., L.M. Sweeney, M.L. Gargas, and J. Kinzell, 2009. Iodomethane human health risk characterization. Inhal. Toxicol. 21(6):583-605.

Morris, J.E., L.B. Sasser, J.A. Creim, K.D. Thrall, and R.A. Corley, 2004. Studies supporting the development of a PBPK model for methyl iodide: The pharmacokinetics of sodium iodide (NaI) in pregnant rabbits. Project No. 47542, Battelle, Pacific Northwest Division. DPR Vol. 52875-070 #215234.

NAS, 2000. Dietary reference intakes for Vitamin A, Vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. National Academy of Sciences.

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.

Price, D.J., and J.R. Sherwin, 1986. Autoregulation of iodide transport in the rabbit: Absence of autoregulation in fetal tissue and comparison of maternal and fetal thyroid iodination products. Endocrinology 119(6): 2547-2552.

Rayburn, W.F., A. Robinson, L.E. Braverman, X. He, S. Pino, M.L. Gargas, L.M. Sweeney, and B.E. Mileson, 2007. Iodide concentrations in matched maternal plasma, cord plasma, and amniotic fluid from term and pre-term human pregnancies. Laboratory Project ID: 06-240. DPR Vol. 52875-0118 #230153.

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

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.

Thrall, K.D., J.E. Morris, L.B. Sasser, J.A. Creim, M.L. Gargas, J.H. Kinzell, and R.A. Corley, 2009. Studies supporting the development of a PBPK model for methyl iodide: the pharmacokinetics of sodium iodide (NaI) in pregnant rabbits. Inhal. Toxicol. 21(6) (in press, DOI: 10.1080/08958370802598286).

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DATE: August 3, 2009

SUBJECT: RESPONSE TO ARYSTA'S COMMENTS OF THE EXPOSURE ASSESSMENT DOCUMENT FOR METHYL IODIDE (HS 1866)

The Registrant, Arysta, sent comments on the Exposure Assessment Document (EAD) for Methyl Iodide (MeI) on May 5, 2009. Arysta's comments are italicized below, with the response to the comments immediately following.

Arysta: *It is Arysta's view that the study director is highly valuable in determining appropriate recovery values in an exposure assessment. DPR has calculated its own values based on the field spikes. The apparent difference between the DPR and study director recovery estimates is that the study director considered the subset of trapping efficiency tests conducted with higher concentrations more reliable.*

For example, in the Oxnard study (Baker et al., 2003e), the trapping efficiency was measured as 53%, 81%, and 79% for fortification levels of 0.4 ppb, 43 ppb, 422 ppb, respectively. The study director used a value of 80% to adjust all of the samples in the study based on the average of the two trapping efficiency measurements above the limit of quantification (LOQ) (43 and 422 ppb). By contrast, DPR apparently attempted to match the measured concentrations in the study to the closest field spike to adjust for recovery, which resulted in the use of 53% recovery for hole punchers and planters and 81% for tractor drivers, shovelers, and tarp monitors. However, the measured iodomethane concentrations for hole punchers was 10 ppb and the measured iodomethane concentration for planters was 5 ppb (identical measurement for two replicates). The hole puncher concentration of 10 ppb is closest in magnitude to the 43 ppb trapping efficiency value and the 5 ppb concentration for the planters is roughly between the 0.4 and 43 ppb trapping efficiency values. (Footnote: Because the concentrations in the trapping efficiency measurements differ by orders of magnitude, the appropriate base of comparison is on a logarithmic scale which compares the relative orders of magnitude of the values.)

Furthermore, the trapping efficiencies measured at higher concentrations are more accurate because there is less analytical error in these measurements compared to the measurement of concentrations below the LOQ (the LOQ is 17 ppb compared to the low field fortification level of 0.4 ppb).

For these reasons, Arysta requests that DPR use the most reliable data to estimate field recovery, which includes trapping efficiency tests with concentrations greater than the LOQ only. Also, Arysta requests an explanation from DPR about the methodology it used to estimate recovery values and why it selected not to use the laboratory values.

Worker Health and Safety (WHS): The rationale that WHS used in calculating recoveries is this: 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.

Both the 5 and 10 ppb samples were closer in concentration to the 0.4 ppb field spike than either the 43 ppb, or 422 ppb field spikes that the Study Director averaged together.

Arysta: *DPR applied an overly conservative methodology to estimate exposures for workers applying iodomethane. Arysta has provided six occupational exposure field studies with multiple measurements of worker tasks in each study. The U.S. EPA estimated occupational risks with the average and maximum value for each of the worker tasks. Instead of applying this reasonable methodology, DPR developed an extrapolation method based on a lognormal distribution in ~~to~~ an attempt to estimate a 95th percentile value. Given that there are less than 20 measurements for the occupational exposure scenarios, DPR's exposure estimates are higher than the maximum measured value in every case, sometimes by more than a factor of three.*

For example, for drivers and applicators for the shallow-shank, tarped-bed injection studies, the four measured values from the occupational exposure studies were 8.7, 46.9, 2.1, and 47.3 µg/kg-day. DPR applied its extrapolation procedure to these four data points to estimate a 95th percentile value, which resulted in 168 µg/kg-day. These values are summarized in Table 1. Thus, in this case, the value DPR used for risk assessment is 3.6 times higher than any measured value.

DPR applied this methodology based on a policy memorandum that was issued in the last few months (Frank, J.P. Method for calculating short-term exposure estimates. California Department of Pesticide Regulation. HSM-09004). In fact, this memorandum appears to have been written while this assessment was in progress. Arysta requests a list of recent occupational assessments performed by DPR utilizing this methodology so that we can further evaluate its reliability.

The DPR policy memo provides no explanation regarding why DPR assumed a lognormal distribution for the data. DPR must have a lot of occupational exposure data in its possession, including for fumigants, and could have performed an analysis of these data to justify this

assumption rather than assuming a statistical distribution with a large uncertainty at the upper percentiles DPR indicates "any discrepancy from the lognormal distribution will be greatest at the upper extremes".

WHS: The first Department of Pesticide (DPR) risk assessment that utilized an upper-bound acute exposure estimate for workers was for hydrogen cyanamide (Dormex), completed on December 3, 1993. All DPR risk assessments since that time have used upper-bound acute exposure estimates. These risk assessments are posted on DPR's external website. The rationale for using the upper-bound of a log-normal distribution is detailed in Frank, 2007 [http://www.cdpr.ca.gov/docs/whs/memo/hsm07005.pdf].

DPR is responsible for insuring worker safety in the application of pesticides. In order to do this, DPR needs to generate estimates that are likely to reflect the pesticide exposures that workers may encounter when following label-approved activities. 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. In the example of driver and co-pilot exposure that Arysta presented in their comments, the number of individuals engaged in the activities was small. In one study, there was an equipment malfunction that resulted in a much larger exposure for one individual than any of the other co-pilot/drivers received. Although equipment problems are not a routine occurrence, they do happen. Some malfunctions may be more extensive or frequent than the one in the submitted study. Consequently, that individuals' exposure was included with the other individual exposures. The combination of a small "n", and the single high exposure value resulted in an upper-bound estimate above the highest measured value.

The most recent policy document (noted by Arysta) was generated in response to continuing questions as to why DPR uses an upper-bound estimate for acute exposures. That policy document (HSM-09004; 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. Virtually all of the environmental exposure data indicates a lognormal distribution.

In the course of reviewing Arysta's comments on the use of the upper-bound estimate of exposure, we determined that the **sample** standard deviation had been used in the calculation of the upper-bound values. Numerical computation has shown that maximum likelihood estimates should be used for all practical purposes because they are easier to calculate than the uniformly minimum variance unbiased estimate. Consequently, the **population** standard deviation should have been used (Shimizu, 1988). As a result, the upper-bound acute exposures of the applicators have been re-calculated. Although the upper-bound estimates of worker exposure are somewhat lower, they are still in excess of the highest measured values for the studies.

Arysta: *Arysta is pleased that DPR used an average value to estimate exposures for durations longer than a day. However, DPR assumed that a worker will be involved in iodomethane applications for every day for three months, including weekends. This is clearly an unreasonable assumption. Applicators typically apply different fumigants over the course of the growing season, so there is no reason to believe that they will apply iodomethane every day. Furthermore, most commercial applicators work normal 5 day/week schedules, except in unusual circumstances. Arysta recommends that DPR consider a more typical application regime of no more than three applications of iodomethane per week. Thus, the seasonal and annual exposure estimates should be adjusted by 3/7.*

Additionally, the overestimation with this methodology is compounded by assuming that the worker is exposed for 8 hours each and every day of exposure. In the occupational exposure studies submitted by Arysta, the exposure durations were typically 5 hours. In reality, the exposure duration will be determined by the size of the field, the type of application, and the amount of preparation required before applying the fumigant. Also, it is typical for workers to take occasional breaks, including a half-hour or hour lunch break. For this reason, many air pollution studies have utilized 6.6 hour daily exposure duration protocols, as acknowledged by the California Office of Environmental Health Hazard Assessment (OEHHA).

WHS: There is no assumption on the number of workdays in a week in the estimate of seasonal exposure to MeI. It is assumed that workers will average working 8 hours/day at the average air concentration of MeI. If Arysta has studies indicating that applicators involved in pre-plant field fumigation typically work for less than 8 hours/day, WHS would be willing to evaluate the data.

The occupational exposure studies submitted by Arysta involved fumigating fields of minimum size compared to what the label allows. Consequently, the length of time that the applicators worked in that small sample set is not compelling evidence for a shorter workday. Although workers probably take a break, eat lunch, etc., it is unlikely that they go far from the field under fumigation, and thus receive bystander exposures to MeI escaping from the soil. Quantitatively, the bystander exposure they would receive would probably be less than what they received during application activities, but without data, the exposure numbers cannot be adjusted.

Arysta: *The PBPK model can be used to accurately estimate inhalation absorption. DPR has used the PBPK model to develop HECs for this assessment, so it's not clear to us why DPR did not use it for this purpose as well.*

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

Arysta: *For the Oxnard shank, raised bed study (DPR Data Volume 52875-046), the "maximum" 1-hour flux rate refers to the period just after the application and the flux rate was calculated only assuming the portion of the field that was treated during the measurement period. For the first period after the application, the flux rate was calculated assuming only 28% of the field was applied, and for the second period, the flux rate was calculated assuming only 55% of the field was applied. DPR applies this flux value over an entire 40 acre field for their modeling calculations. By doing so, DPR's calculation includes more mass emissions than actually occurred in the field study, resulting in an overestimation of the concentration.*

According to Arysta's calculations, the flux rates for the Oxnard shank, raised bed study, adjusted for a 40 acre field, should be as follows:

- *1-hr: The flux rate should be 151 µg/m^2/sec instead of 535 µg/m^2/sec as DPR has calculated.*
- *8-hr: The flux rate should be 134 µg/m^2/sec instead of 266 µg/m^2/sec as DPR has calculated.*
- *24-hr: The flux rate should be 131 µg/m^2/sec instead of 187 µg/m^2/sec as DPR has calculated.*

This should result in lower concentration estimates for the raised bed, shank injection results in Table 13.

It would be helpful to Arysta if DPR tabulated the exact flux rates it used for the calculations in Table 13. These rates were apparently adjusted from the flux rates summarized in Table 12 to account for the maximum application rate and the portion of the field treated for raised bed and drip applications. Having the exact flux rates would be useful for further review.

WHS: Staff has been aware that the first three sampling intervals of the Oxnard study monitored partial areas as the application progressed. Due to the structure of the sampling intervals, estimation of a 1-hr flux for 40 acres base on this study is problematic. Consequently, DPR has eliminated the 1-hour estimates of flux and exposure from the EAD.

Environmental Monitoring (EM) Branch will respond to questions regarding air modeling.

Arysta: *There are a number of advanced probabilistic modeling tools available to estimate concentrations downwind of fumigant applications. Most notably, the PERFUM model, sponsored by Arysta, has the capability of estimating buffer distances and air concentrations following fumigant applications. The user has the capability to employ historical meteorological datasets from weather stations to simulate actual meteorological conditions at any site of interest. In Arysta's discussions with DPR, the department indicated that one of the reasons that*

it did not use PERFUM was that the model does not provide air concentration estimates, but instead only estimates buffer zone distances. PERFUM was modified about two years ago, and now includes the capability to estimate air concentrations at different downwind distances. Further, if DPR needs estimates for a downwind distance that is not currently included in the PERFUM model, Arysta is willing to work with DPR to provide a customized version.

DPR has chosen to estimate downwind concentrations of iodomethane using an extremely simple and crude modeling methodology that doesn't account for real meteorological conditions. Specifically, DPR made the following assumptions:

- *1-hr and 8-hr peak concentrations: wind speed of 1 m/sec, "D" class atmospheric stability, and a constant wind direction*
- *24-hr concentration: wind speed of 1.4 m/sec, "C" class atmospheric stability, and a constant wind direction.*

WHS: EM Branch will respond to questions regarding air modeling.

Arysta: *The assumption of a constant wind direction over 24 hours, or for that matter 8 hours, is particularly unrealistic. Furthermore, the wind speed assumption is at the extreme low-end of the distribution of wind speeds in the environment. In fact, the dispersion model used by DPR will not even accept a smaller wind speed than 1 m/sec.*

WHS: EM Branch will respond to questions regarding air modeling.

Arysta: *The illogical nature of DPR's calculations can be observed by comparing the concentration estimates averaged over 8-hour and 24-hours in Table 13. These concentrations are intended to be "maximum" concentrations at different distances from the edge of the field and refer to the concentrations at 152 meters from the edge of a 40-acre field where iodomethane was applied at the maximum usage rate. For a given "maximum" 8-hour average concentration, the corresponding "maximum" 24-hour average concentration should not be less than one-third of the "maximum" 8-hour average concentration. Even if the concentration over the other 16 hours of the day was zero, the "maximum" 24-hour average concentration would be one-third of the "maximum" 8-hour average concentration. However, in a number of cases, the "maximum" 24-hour concentration is less than one-third of the "maximum" 8-hour concentration. For example, for the drip irrigation estimate at 152 meters in Table 13, the "maximum" 8-hour concentration is 9.5 µg/L, while the "maximum" 24-hour concentration is 1.7 µg/L. Even if the concentration were zero for the other 16 hours of the day, given a concentration of 9.5 µg/L for the first 8 hours, the "maximum" 24-hour concentration would be 3.2 µg/L.*

Arysta does not point out this inconsistency to argue that one or the other of DPR's concentration estimates are the correct one. Neither is correct. Instead, this comparison shows that DPR's use of artificial meteorological scenarios lead to results that are not even consistent with one another.

WHS: EM Branch will respond to questions regarding air modeling.

Arysta: *DPR estimates MOEs for worker bystanders using the 8-hour exposure estimate at the edge of the buffer zone (152 meters) and MOEs for other bystanders using the exposure estimate for 24-hours at the edge of the buffer zone. Logically, one would assume that the risk is higher for being at the edge of the buffer zone for 24-hours compared to 8-hours. However, the MOEs are less (higher risk) for the 8-hour exposure. DPR derived the HEC of 0.22 ppm used for worker bystanders by assuming 7 days of consecutive exposure for 8 hours per day and basing the HEC on iodide level at 7 days. This assumption is unreasonable for a worker bystander as DPR's calculation assumes the peak flux rates immediately after the application, but the flux rate declines substantially over the first 7 days. DPR does not account for the decrease in flux rates*

DPR also provides estimates for concentrations at closer distances to the field than 152 meters, but does not provide MOEs at these distances. Providing MOEs for the smaller distances would add perspective to the risk assessment.

WHS: These questions will be addressed by MT Branch.

Arysta: *DPR estimated "seasonal" exposure by calculating a 2-week average concentration for someone continually living at 152 meters from the edge of the treated field following an application. This assumption seems particularly unlikely. Over the course of a 2-week period, even someone that by chance lives right at 152 meters from the edge of the field will go other places, such as work or school or to other places for recreation or to run errands. Furthermore, DPR's methodology for estimating the 2-week average concentration is based on something DPR calls "peak-to-mean" theory, which is described in a memorandum that is not available to us. The most appropriate way to estimate a long-term average concentration is to use a dispersion model with historical meteorological data. This would allow one to account for changing wind directions and wind speed instead of just assuming low wind speed and a constant wind direction.*

WHS: The bystander exposures adjacent to application sites are considered representative, estimating bystander exposures equal to, or greater than those of individuals residing in nearby communities. The factors that Arysta points out that 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. However, at the present time there is no acceptable, quantitative method 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 methyl bromide (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. Environmental Monitoring will respond to questions regarding air modeling.

Arysta: *Arysta has supplied a complete data set to DPR including 11 flux studies. DPR should be using the iodomethane data set in this risk assessment rather than using methyl bromide, or any other fumigant as a surrogate. DPR makes an inappropriate comparison of iodomethane to methyl bromide in this discussion saying that "methyl bromide could be considered a surrogate chemical" for iodomethane because they are "similar chemically" and "measured air concentrations of the two chemicals from application site monitoring" are similar.*

Iodomethane degrades in the atmosphere with a half-life of 5.2 days (as noted in the risk assessment). Methyl bromide is far more persistent with a half-life of about 1.5-2 years[1]. This is why methyl bromide makes its way up to the stratosphere and depletes the ozone layer. The fast atmospheric degradation rate of iodomethane results in a substantially smaller probability of significant community exposure, compared to the very persistent methyl bromide.

DPR tries to justify its approach by stating that its modeling estimate of the 2-week concentration for iodomethane is similar to the community exposures measured for methyl bromide. However, the similarity of the values of 0.07 µg/L for iodomethane; and 0.046 µg/L for methyl bromide is fortuitous. There is no validation of DPR's modeling approach for iodomethane for a 2-week exposure which results in the 0.046 µg/L estimate. Additionally, given that DPR assumes a constant wind direction over the entire period, the methodology overstates the true concentration. Furthermore, DPR's community monitoring was not intended to measure the concentration at the edge of a buffer zone. -The air monitors yielding the results of 0.07 µg/L for methyl bromide were not that close to the downwind edge of any field. DPR needs to reconsider the reasoning it has used to equate methyl bromide and iodomethane and needs to develop a more realistic modeling methodology for seasonal exposures. The SOFEA model developed by Dow was designed for this purpose and DPR has successfully used the SOFEA model for Telone. DPR should either use the SOFEA model to estimate two week average concentration or work with Arysta to modify PERFUM to perform these calculations

[1] http://www.ars.usda.gov/is/np/mba/april96/sims.htm

Another limitation with DPR's comparison of its modeling estimate to the measured methyl bromide concentrations is that the modeling estimate is based on the absolute worst-case scenario, which includes a 40 acre field at the maximum application rate of 175 lbs/acre and the maximum flux rates across the studies conducted by Arysta.

WHS: We believe it is reasonable to assume that where MeI is used as a pre-plant field fumigant there would be community wide exposure to MeI. At the same time, 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 2-week air concentrations of MeI adjacent to an application site (a worst case situation) 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.

Arysta 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 chemical/physical parameters as prognosticators would be inappropriate.

There are several technical problems in adapting SOFEA for use with methyl iodide or pesticides other than 1,3-dichloropropene: (1) The buffer zone regimes would be different. In the case of MeI, buffer zones are complex, based on method and rates. SOFEA would have to be reprogrammed in order to accommodate label-mandated buffer zones for MeI. (2) SOFEA currently only allows representation of two flux functions. MeI has more than two fumigation methods and flux profiles. (3) SOFEA requires the input of historical use data classified by application method, but these data are not available for MeI.

Arysta: *This (*looping of the plume*) is actually highly unlikely to happen for an area source such as a fumigant application where the emission is spread over a large area and emitted from the ground. This point is accurate for any of the possible acreages for fumigant applications (e.g., 1-40 acres). The reference cited by DPR likely refers to a plume emitted from an elevated stack into a highly unstable atmosphere*

WHS: The discussion in the Appraisal section was provided to indicate various uncertainties associated with estimating air concentrations of MeI. DPR staff are aware that looping plumes are associated with elevated stacks spewing contaminants into a highly unstable atmosphere. This concept was not used to develop any of the estimated air concentrations. To avoid any confusion, the sentence has been removed from the Appraisal section.

Arysta: *Firstly, this position* ("Although the ISCST3 model has been thoroughly evaluated at DPR, the PERFUM components had not at the time this exposure assessment was completed. Therefore, only screening level air concentration estimates have been used for the DPR methyl iodide exposure assessment.") *is inconsistent with DPR's use of the PERFUM model for the development of mitigation measures for another fumigant, metam sodium (Barry, 2007). DPR demonstrated no reservation in this instance to using PERFUM for developing buffer zones for another fumigant.*

WHS: EM Branch will respond to questions regarding air modeling.

Arysta: *Secondly, PERFUM has been widely used for more than 5 years by the EPA and has undergone significant scrutiny over that period and has remained intact with only a few very minor bug fixes required. EPA has thoroughly evaluated the model and successfully used it for all soil fumigants. National buffer zone requirements included in the draft Reregistration Eligibility Documents issued in July, 2008; and expected to be implemented by EPA are largely based on the PERFUM model. It is concerning for DPR to eschew use of the model with such a casual statement.*

WHS: EM Branch will answer questions regarding air modeling.

Arysta: *Thirdly, use of the PERFUM model provides regulators with substantially more information about potential risks given that it provides probabilistic estimates using two different types of distributions, including the maximum concentration distribution which considers only the downwind distances with the highest concentration and the "whole field" approach which considers all downwind distances. The information available to regulators is substantially more robust with PERFUM compared to DPR's deterministic approach.*

WHS: As noted above, unlike U.S. Environmental Protection Agency (U.S. EPA), DPR separates the risk assessment process from the risk mitigation process. The function of a risk characterization document is to identify exposures with unacceptable risk levels. DPR believes that the additional information obtainable with the use of PERFUM is more appropriately implemented during the mitigation phase.

Arysta*: Fourthly, PERFUM allows the use of actual meteorological data providing a more credible result in order to base important regulatory decisions, instead of relying on only crude generalizations of meteorology data as DPR has done.*

WHS: EM Branch will address questions regarding air modeling.

Arysta: *The "whole field" buffer zone approach is perfectly reasonable. In contrast to DPR's default approach, the "whole field" approach considers the entire area around a treated field to*

better approximate the true probability of an exposure. Specifically, locations around the whole circumference of the field are included in the concentration distribution. The approach recognizes that there is not necessarily a bystander in every direction around a treated field, particularly in rural agricultural areas, and that the wind direction is constantly changing so that a person at the maximum concentration location one hour may not even be exposed the next hour. Therefore, any methodology that is limited to considering only the direction around a field where the maximum concentration occurs will significantly overestimate the true probability of there being an exceedance of the target concentration.

When DPR calculates a worker exposure for an applicator, DRP knows that this activity will actually happen for a given application. For bystanders, it is actually unlikely that any person will be at the edge of the buffer zone in the location with the maximum concentration for the entire 24 hours following an application. Yet, this is what the "maximum concentration" approach employed by DPR assumes. The "whole field" approach merely acknowledges that the probability of someone being at the point of maximum concentration for an entire exposure period is small. Therefore, the "whole field" approach allows a buffer zone to be estimated by more closely approximating a true probability of someone actually being exposed.

EPA has found this approach to be reasonable and conservative. Arysta agrees with EPA's position and requests that DPR reconsider use of the "whole field" approach.

WHS: A comparison of U.S. EPA's approach with DPR's approach to estimating bystander exposure was presented in Appendix III. In addition, several accessible memoranda that go into a more detailed examination of the two approaches, including the pros and cons, were cited. As noted above, in the process of generating a Registration Eligibility Document, U.S. EPA combines both risk assessment and risk mitigation. DPR treats the two processes separately, first assessing the risks, then determining how to mitigate those risks if need be.

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M E M O R A N D U M

TO: Randy Segawa
Environmental Program Manager I
Environmental Monitoring Branch

FROM: Terrell Barry, Ph.D., Research Scientist III *Original signed by*
Environmental Monitoring Branch
916-324-4140

DATE: June 17, 2009

SUBJECT: RESPONSES TO ARYSTA COMMENTS ON THE AIR DISPERSION MODELING SECTIONS OF THE METHYL IODIDE EXPOSURE APPRAISAL DOCUMENT (VOLUME II)

This memorandum contains the Environmental Monitoring (EM) branch responses to the Arysta comments on air dispersion modeling sections of the methyl iodide exposure appraisal document, volume II of three volumes comprising the Department of Pesticide Regulation (DPR) Risk Characterization Document. Each Arysta comment is in bold italics, followed by the EM response.

Arysta: ***For the Oxnard shank, raised bed study (DPR Data Volume 52875-046), the "maximum" 1-hour flux rate refers to the period just after the application and the flux rate was calculated only assuming the portion of the field that was treated during the measurement period. For the first period after the application, the flux rate was calculated assuming only 28% of the field was applied, and for the second period, the flux rate was calculated assuming only 55% of the field was applied. DPR applies this flux value over an entire 40 acre field for their modeling calculations. By doing so, DPR's calculation includes more mass emissions than actually occurred in the field study, resulting in an overestimation of the concentration.***

According to Arysta's calculations, the flux rates for the Oxnard shank, raised bed study, adjusted for a 40 acre field, should be as follows:

- ***<u>1-hr</u>: The flux rate should be 151 µg/m^2/sec instead of as DPR has calculated.***
- ***<u>8-hr</u>: The flux rate should be 134 µg/m^2/sec instead of 266 µg/m^2/sec as DPR has calculated.***
- ***<u>24-hr</u>: The flux rate should be 131 µg/m^2/sec instead of 187 µg/m^2/sec as DPR has calculated.***

This should result in lower concentration estimates for the raised bed, shank injection results in Table 13.

It would be helpful to Arysta if DPR tabulated the exact flux rates it used for the calculations in Table 13. These rates were apparently adjusted from the flux rates summarized in Table 12 to account for the maximum application rate and the portion of the field treated for raised bed and drip applications. Having the exact flux rates would be useful for further review.

EM: DPR staff was aware that the first three sampling intervals of the Oxnard study monitored partial areas as the application progressed.

Due to the structure of the sampling intervals, estimation of a 1-hr flux for 40 acres base on this study is problematic. It was decided to use the 535 $\mu g/m^2/sec$ directly for the maximum one hour flux since, clearly, the loss in the first few hours is high and this application proceeded unusually slowly. It is highly likely that commercial applications will be made more quickly. That said, we agree that it may be most reasonable to eliminate the 40 acre 1-hr estimate for this application method. However, for smaller application sizes the 535 $\mu g/m^2/sec$ 1-hr flux estimate is certainly reasonable. We do not agree that 535*0.28 = 151$\mu g/m^2/sec$ is the "correct" 1-hr flux estimate. This Arysta proposed calculation in effect spreads the mass loss from a smaller area over the entire field. The loss from the actual treated area of 11 acres (28% of 40 acres) results in 535 $\mu g/m^2/sec$. That is a large flux that must be accounted for if an estimate is provided. It is clear from the 535$\mu g/m^2/sec$ estimate that the initial mass loss in the first few hours can be substantial. This study used a single rig moving very slowly for a small application. Multiple rigs can be used for applications to larger fields. Thus, substantially more initial acreage than applied in this study could be applied within 2 hours. It can be assumed that the area treated by each rig would show the same high loss in the first few hours. At Worker Health and Safety Branch request, air concentrations for either a smaller application or multiple rig scenario could be provided.

DPR staff does not agree with the Arysta proposed 8-hr flux. DPR believes an application of 40 acres can be completed within 8 hours.

DPR staff does not agree with the Arysta proposed 24-hr flux. The DPR calculated 24-hr time weighted average flux accounts for the higher losses during the initial application phase. In addition, the substantial drop in flux following the application is the most heavily weighted component of the flux calculation.

Two memoranda (attached) describe in more detail the methods used to derive the air concentration estimates. Table 12 lists results using flux estimates taken directly from the Arysta data volumes. The 8-hr and 24-hr flux estimates are time weighted averages according to the sampling intervals shown it the Arysta data volumes. The Arysta studies were not conducted using a uniform application rate and flux is assumed to be proportional to application rate. Thus, the flux estimates in Table 12 cannot be cross-compared without first being adjusted to a common application rate. The air concentration estimates produced for the exposure appraisal were standardized to an effective broadcast application rate of 175 lb/acre. The air concentration

estimates shown in Table 13 are on a standard basis of 175 lb/acre. The adjustment factors for each study to achieve the 175 lb/acre basis are shown in Table 1 of the attached memorandum by T. Barry dated August 21, 2008.

Arysta: ***There are a number of advanced probabilistic modeling tools available to estimate concentrations downwind of fumigant applications. Most notably, the PERFUM model, sponsored by Arysta, has the capability of estimating buffer distances and air concentrations following fumigant applications. The user has the capability to employ historical meteorological datasets from weather stations to simulate actual meteorological conditions at any site of interest. In Arysta's discussions with DPR, the department indicated that one of the reasons that it did not use PERFUM was that the model does not provide air concentration estimates, but instead only estimates buffer zone distances. PERFUM was modified about two years ago, and now includes the capability to estimate air concentrations at different downwind distances. Further, if DPR needs estimates for a downwind distance that is not currently included in the PERFUM model, Arysta is willing to work with DPR to provide a customized version.***

DPR has chosen to estimate downwind concentrations of iodomethane using an extremely simple and crude modeling methodology that doesn't account for real meteorological conditions. Specifically, DPR made the following assumptions:

- ***<u>1-hr and 8-hr peak concentrations</u>: wind speed of 1 m/sec, "D" class atmospheric stability, and a constant wind direction***
- ***<u>24-hr concentration</u>: wind speed of 1.4 m/sec, "C" class atmospheric stability, and a constant wind direction.***

EM: Screening methods are acceptable and appropriate to produce air concentration estimates. DPR has used this approach since 1992 when mitigation measures in the form of buffer zones were developed for methyl bromide. Because of the long history of use, screening methods used at DPR are well understood and characterized. In fact, the document "Screening Procedures for Estimating the Air Quality Impact of Stationary Sources, Revised (EPA-454/R-92-019)" is currently on the U.S. Environmental Protection Agency (EPA) Support Center for Regulatory Atmospheric Modeling Web site at: <http://www.epa.gov/scram001/guidance_permit.htm>. This document includes methods for estimating screening level air concentrations for area sources and has an update that specifically applied to screening estimates for area sources at: <http://www.epa.gov/scram001/guidance/guide/scrupd.pdf>. Thus, it is still a U.S. EPA accepted method. Screening methods are reasonable worst-case estimates.

The U.S. EPA Screening Procedures document states: "The simple screening procedure (Phase 1) is applied to determine if the source poses a potential threat to air quality. The purpose of first applying a simple screening procedure is to conserve resources by eliminating from further analysis those sources that clearly will not cause or contribute to ambient concentrations in excess of short-term air quality standards or allowable concentration increments. A relatively large degree of "conservatism" is incorporated in that screening procedure to provide reasonable assurance that maximum concentrations will not be underestimated."

This is exactly the stage that DPR is at with Iodomethane. DPR chose to use the screening method at this stage of evaluation.

Arysta: ***The assumption of a constant wind direction over 24 hours, or for that matter 8 hours, is particularly unrealistic. Furthermore, the wind speed assumption is at the extreme low-end of the distribution of wind speeds in the environment. In fact, the dispersion model used by DPR will not even accept a smaller wind speed than 1 m/sec.***

This is a misunderstanding of the screening level meteorological conditions. The estimated air concentration is tied directly to the flux averaging time, not the "apparent" time step of the model. In the context of a 24-hr screening air concentration estimate based on a 24-hr time weighted average flux, the wind direction for the weather is interpreted as a predominant (or average) direction.

Arysta: ***The illogical nature of DPR's calculations can be observed by comparing the concentration estimates averaged over 8-hour and 24-hours in Table 13. These concentrations are intended to be "maximum" concentrations at different distances from the edge of the field and refer to the concentrations at 152 meters from the edge of a 40-acre field where iodomethane was applied at the maximum usage rate. For a given "maximum" 8-hour average concentration, the corresponding "maximum" 24-hour average concentration should not be less than one-third of the "maximum" 8-hour average concentration. Even if the concentration over the other 16 hours of the day was zero, the "maximum" 24-hour average concentration would be one-third of the "maximum" 8-hour average concentration. However, in a number of cases, the "maximum" 24-hour concentration is less than one-third of the "maximum" 8-hour concentration. For example, for the drip irrigation estimate at 152 meters in Table 13, the "maximum" 8-hour concentration is 9.5 µg/L, while the "maximum" 24-hour concentration is 1.7 µg/L. Even if the concentration were zero for the other 16 hours of the day, given a concentration of 9.5 µg/L for the first 8 hours, the "maximum" 24-hour concentration would be 3.2 µg/L.***

Arysta does not point out this inconsistency to argue that one or the other of DPR's concentration estimates are the correct one. Neither is correct. Instead, this comparison shows that DPR's use of artificial meteorological scenarios lead to results that are not even consistent with one another.

Arysta states: ***"The assumption of a constant wind direction over 24 hours, or for that matter 8 hours, is particularly unrealistic. Furthermore, the wind speed assumption is at the extreme low-end of the distribution of wind speeds in the environment. In fact, the dispersion model used by DPR will not even accept a smaller wind speed than 1 m/sec."***

Air concentration produced using screening methods are not "incorrect." As discussed above, the document "Screening Procedures for Estimating the Air Quality Impact of Stationary Sources, Revised (EPA-454/R-92-019)" is currently on the U.S. EPA Support Center for Regulatory Atmospheric Modeling Web site. The meteorological conditions used to product the air concentrations are not "artificial." They are screening meteorological scenarios that can, and do, occur.

Arysta states: ***"The illogical nature of DPR's calculations can be observed by comparing the concentration estimates averaged over 8-hour and 24-hours in Table 13."***

There are several interacting and confounding factors that make the Arysta comparisons inappropriate: (1) the maximum 8-hr flux was chosen using a rolling average. This highest average flux was then paired with the reasonable worst-case meteorological conditions for the 8-hr scenario. This estimate is totally independent of the 24-hr scenario and should be interpreted as such, (2) The meteorological scenarios are different for the 8-hr versus the 24-hr averaging times. The 8-hr case uses D stability, the 24-hr case uses C stability. Even if all other factors were held constant (which they are not since the flux estimates are specific to the averaging time), the difference in stability class produces significant nonlinear changes in air concentrations between averaging times. Thus, the 8-hr air concentration is expected to be substantially higher than the 24-hr air concentration because it was derived independently using maximum 8-hr flux and more stable atmospheric conditions. The example calculation Arysta presents, ***"Even if the concentration were zero for the other 16 hours of the day, given a concentration of 9.5 µg/L for the first 8 hours, the "maximum" 24-hour concentration would be 3.2 µg/L,"*** is not valid because of this difference in atmospheric stability, and (3) The effect of scaling on averaging times is not proportional. For example, the maximum continuous 8-hr concentration during a continuous 24-hr monitoring period will be in the neighborhood of twice the 24-hr concentration. This effect is documented in air dispersion theory literature.

Thus, it is inappropriate to make the direct comparison and calculations such as those made by Arysta. With respect to the DPR air concentration estimates, it is not possible to make simple statements such as "***For a given "maximum" 8-hour average concentration, the corresponding***

"maximum" 24-hour average concentration should not be less than one-third of the "maximum" 8-hour average concentration."

Arysta: ***DPR estimated "seasonal" exposure by calculating a 2-week average concentration for someone continually living at 152 meters from the edge of the treated field following an application. This assumption seems particularly unlikely. Over the course of a 2-week period, even someone that by chance lives right at 152 meters from the edge of the field will go other places, such as work or school or to other places for recreation or to run errands. Furthermore, DPR's methodology for estimating the 2-week average concentration is based on something DPR calls "peak-to-mean" theory, which is described in a memorandum that is not available to us. The most appropriate way to estimate a long-term average concentration is to use a dispersion model with historical meteorological data. This would allow one to account for changing wind directions and wind speed instead of just assuming low wind speed and a constant wind direction.***

EM: The two-week average is for a receptor at a particular location. The two-week air concentration incorporates expected fluctuations in plume location and atmospheric conditions over that averaging time.

Arysta states: ***"DPR's methodology for estimating the 2-week average concentration is based on something DPR calls "peak-to-mean" theory…"*** Peak-to-mean theory is not something that DPR named. The technique is commonly used in the air pollution regulatory community. The memorandum cited (Barry, 2000) is available for reference at: <http://www.cdpr.ca.gov/docs/emon/pubs/ehapreps/analysis_memos/2000_segawa.pdf>. The theoretical foundation of "peak-to-mean" methods dates back to 1921 in the work of G.I. Taylor's concepts of diffusion by continuous motion. The first major paper addressing the peak-to-mean concept was published in 1959 by Gifford. The method was further developed by Hino in 1968 and is referenced specifically by Turner in his 1994 text entitled "Workbook of atmospheric dispersion estimates. Furthermore, the peak-to-mean adjustment concept is used by U.S.EPA in the 1992 document Screening Procedures for Estimating the Air Quality Impact of Stationary Sources, Revised (EPA-454/R-92-019) in the same manner as applied by DPR. This method has been used routinely to obtain long-term averages from shorter averaging time air concentrations.

Arysta: ***This (*looping of the plume*) is actually highly unlikely to happen for an area source such as a fumigant application where the emission is spread over a large area and emitted from the ground. This point is accurate for any of the possible acreages for fumigant applications (e.g., 1-40 acres). The reference cited by DPR likely refers to a plume emitted from an elevated stack into a highly unstable atmosphere***

EM: DPR staff is aware that looping plumes are associated with elevated stacks into a highly unstable atmosphere. This concept was not used to develop any of the estimated air

concentrations. This discussion was initially provided solely to provide general background the reader unfamiliar with the general concepts used in air dispersion modeling. It appears to have caused confusion, thus it will be deleted.

Arysta: **(**In response to the DPR text: "Although the ISCST3 model has been thoroughly evaluated at DPR, the PERFUM components had not at the time this exposure assessment was completed. Therefore, only screening level air concentration estimates have been used for the DPR methyl iodide exposure assessment.") ***Firstly, this position is inconsistent with DPR's use of the PERFUM model for the development of mitigation measures for another fumigant, metam sodium (Barry, 2007). DPR demonstrated no reservation in this instance to using PERFUM for developing buffer zones for another fumigant.***

Secondly, PERFUM has been widely used for more than 5 years by the EPA and has undergone significant scrutiny over that period and has remained intacwith only a few very minor bug fixes required. EPA has thoroughly evaluated the model and successfully used it for all soil fumigants. National buffer zone requirements included in the draft Reregistration Eligibility Documents issued in July, 2008; and expected to be implemented by EPA are largely based on the PERFUM model. It is concerning for DPR to eschew use of the model with such a casual statement.

Thirdly, use of the PERFUM model provides regulators with substantially more information about potential risks given that it provides probabilistic estimates using two different types of distributions, including the maximum concentration distribution which considers only the downwind distances with the highest concentration and the "whole field" approach which considers all downwind distances. The information available to regulators is substantially more robust with PERFUM compared to DPR's deterministic approach.

Fourthly, PERFUM allows the use of actual meteorological data providing a more credible result in order to base important regulatory decisions, instead of relying on only crude generalizations of meteorology data as DPR has done.

EM: (1) The use of PERFUM and FEMS for metam sodium was in the context of mitigation. Methyl Iodide is in the risk assessment stage of evaluation. DPR has decided to use the screening methods for reasons stated in responses above.

(2) While U.S. EPA extensively used the PERFUM model for the fumigant reregistration eligibility decisions, no document was issued by EPA presenting a through quantitative evaluation. The PERFUM model concepts and basic framework was evaluated by the Scientific Advisory Panel (SAP) and found to be "scientifically sound." See <http://www.epa.gov/scipoly/SAP/meetings/2004/august1/august2425minutes.pdf> for minutes of that meeting. However, the SAP did not put the model through a detailed quantitative verification.

DPR staff, during review of the methyl bromide commodity modeling discovered a significant error in the structure of the PERFUM input code related to stack releases (Barry, 2006). Although this portion of the model is not related to soil fumigation, it does illustrate the importance of thoroughly evaluating models before use.

DPR staff has performed a thorough evaluation of the soil fumigant 24-hour averaging time on an older version of the PERFUM model (Barry and Johnson, 2005). No other averaging times were evaluated and DPR staff has not evaluated the air concentration distribution generation portion of the model.

(3) The risk characterization document objective is to identify unacceptable risks. DPR believes that the additional information obtainable with the use of PERFUM is more appropriately implemented at the mitigation phase.

(4). DPR is interested in model results from reasonable worst case meteorological conditions. The set of screening meteorological conditions DPR has used are included in the matrix of combinations recommended in the SCREEN3 model User's Guide at: <http://www.epa.gov/scram001/userg/screen/screen3d.pdf>. Although DPR did not use SCREEN3, because it is the screening version of the ISC model, the results would have been identical. See also the responses related to earlier Arysta comments on the screen level meteorology.

Arysta: ***The "whole field" buffer zone approach is perfectly reasonable. In contrast to DPR's default approach, the "whole field" approach considers the entire area around a treated field to better approximate the true probability of an exposure. Specifically, locations around the whole circumference of the field are included in the concentration distribution. The approach recognizes that there is not necessarily a bystander in every direction around a treated field, particularly in rural agricultural areas, and that the wind direction is constantly changing so that a person at the maximum concentration location one hour may not even be exposed the next hour. Therefore, any methodology that is limited to considering only the direction around a field where the maximum concentration occurs will significantly overestimate the true probability of there being an exceedance of the target concentration.***

When DPR calculates a worker exposure for an applicator, DRP knows that this activity will actually happen for a given application. For bystanders, it is actually unlikely that any person will be at the edge of the buffer zone in the location with the maximum concentration for the entire 24 hours following an application. Yet, this is what the "maximum concentration" approach employed by DPR assumes. The "whole field" approach merely acknowledges that the probability of someone being at the point of maximum concentration for an entire exposure period is small. Therefore, the "whole field" approach allows a buffer zone to be estimated by more closely approximating a true probability of someone actually being exposed.

EPA has found this approach to be reasonable and conservative. Arysta agrees with EPA's position and requests that DPR reconsider use of the "whole field" approach.

EM: A discussion of buffer zones or other mitigation measures is inappropriate for an exposure assessment. This section has been deleted.

Attachments

Department of Pesticide Regulation

Mary-Ann Warmerdam
Director

Arnold Schwarzenegger
Governor

M E M O R A N D U M

TO: Randy Segawa, Environmental Program Manager I
Environmental Monitoring Branch

FROM: Terrell Barry, Ph.D., Research Scientist III
Environmental Monitoring Branch
(916) 324-4140

Original signed by

DATE: September 22, 2008

SUBJECT: DEVELOPMENT OF SUB-CHRONIC AIR CONCENTRATION ESTIMATES ASSOCIATED WITH A SINGLE FUMIGANT APPLICATION

Background

The Worker Health and Safety (WHS) branch previously requested air concentration estimates associated with a single fumigant for various sample averaging times less than or equal to 24 hours (hrs) (Barry, 2008). Estimates for iodomethane and chloropicrin were produced for use in the WHS exposure appraisals. The exposure appraisals also include sub-chronic exposure scenarios. Thus, two-week air concentration estimates were requested. For both chloropicrin and iodomethane. In addition, 30-day iodomethane air concentration estimates were requested for comparison with the Air Resources Board (ARB) ambient air concentration data for methyl bromide because the use pattern of iodomethane is expected to be similar to methyl bromide. Thus, the ARB methyl bromide ambient monitoring results can be used as a surrogate for the eventual iodomethane ambient air concentrations.

Methods

The sub-chronic exposure air concentration estimates were produced by extension of the 24 hr air concentration estimates (see Barry, 2008). The same single study flux profiles were used to produce flux profiles of 2-week (chloropicrin and iodomethane) and 30-day duration (iodomethane only). The chloropicrin study flux profiles were based on two-week field studies and were adequate without fitting or extrapolation. Flux profiles for five application methods are available: broadcast/untarp, bed/untarp, bed/tarp, broadcast/tarp, and bed/drip/tarp. (Beard et al., 1996; Rotandardo, 2004). The broadcast/tarp application method has three flux profiles from three separate field studies in Arizona, Washington, and Florida (Table 1).

For iodomethane WHS requested both 2-week and 30-day estimates (Table 2). As part of the registration process the registrant conducted eight studies to characterize the flux profile of iodomethane following application to soil by three different methods: broadcast/tarp, bed/tarp, and drip/tarp (Baker et al., 2001; Baker et al., 2002a; Baker et al., 2002b; Baker et al., 2003; Baker et al., 2004a; Baker et al., 2004b; Baker et al, 2004c). In contrast to the chloropicrin studies, the iodomethane studies were conducted to 10 or 11 days. Consequently, in order to estimate 2-weeks or 30-days, a three parameter lognormal function was fit to the 10 or 11 days

iodomethane flux profiles. This function was integrated from the end of measured values out to 14 days or 30 days and the resulting integration added to the measured flux in order to extend the flux estimates out to 2-weeks or 30-days (Table 3).

The procedure to estimate the 2-week and 30-day average air concentration was a follows:

1. Simulate the generic 24-hr centerline downwind air concentrations based on the 100ug/m^2sec generic flux.
2. Adjust the generic 24-hr air concentration to 2-week or 30-day average air concentration. This is the averaging time adjustment factor (development of this adjustment factor will be presented below).
3. Develop each application method flux profile so that it extends for the 2-week or 30-day interval. This is the flux profile development.
4. Calculate the average 24-hr flux over that period and divide by 100. This number represents the average flux on any given day over the 2-week or 30-day interval scaled to the 100ug/m^2sec generic flux.
5. Multiply the 2-week or 30-day average air concentration by the scaled average 24-hr flux to obtain the estimated 2-week or 30-day air concentration for a particular study. This estimates represents the 2-week or 30-day air concentration for an application made at the application rate used in the study.
6. Adjust the 2-week or 30-day air concentration estimate for a particular study to obtain estimates for application rates other than that used in the study.

These steps are illustrated in the EXCEL spreadsheets for iodomethane and chloropicrin in Appendix A.

1. Simulate the generic 24-hour centerline downwind air concentrations

These generic 24-hour centerline downwind air concentration estimates are produced using the 100ug/m^2sec generic flux and the Department of Pesticide Regulation (DPR) standard weather conditions of 1.4 m/s and C stability. See Barry (2008) for method details.

2. Averaging time adjustment factor

The adjustment factors to obtain the 2-week and 30-day average air concentrations from the generic 24-hr air concentrations were derived based upon the U.S. Environmental Protection Agency (EPA) Modeling Guidelines. The 2-week and 30-day average air concentration is the air concentration that would be measured by an air sampler at a particular spot if that air sampler continually drew air over the 2-week or 30-day sampling period.

The basic equation relating air concentrations averaged over different sampling times can be found in Turner (1994) and was reviewed in Barry (2000):

$$\chi_s = \chi_k \left(t_k / t_s \right)^p$$

where:

χ_κ = base concentration
χ_s = desired concentration
t_k = base averaging interval (shorter interval)
t_s = desired averaging interval (longer interval)
p = power law exponent

The adjustment factor, or multiplier is the portion of the equation shown below:

$$\left(t_k / t_s \right)^p$$

The value of p, the power law exponent varies, depending upon the range of averaging times of interest. For example, in U.S. EPA air toxics modeling guidelines (U.S. EPA, 1992a; U.S. EPA, 1992b) the value of p is between 0.096 and 0.29 to obtain the recommended multiplier for adjusting a 1 hr air concentration to between a 3 hr and an annual air concentration. The progression of the values of p and resulting multipliers for adjusting a 1 hour air concentration are shown below:

Averaging Time	Exponent	Multiplier
3 hr	p = 0.096	0.9
8 hr	p = 0.17	0.7
24 hr	p = 0.28	0.4
annual	p = 0.28	0.08

For the sub-chronic exposure assessment an average 24 hr air concentration will be adjusted to a 2 week or a 30 day air concentration. Based upon the above relationships, p = 0.28 is the appropriate exponent value for these adjustments. The multipliers are 0.48 for 2 weeks and 0.39 for 30 days. The justification for this exponent value and the multipliers is shown below.

First, to conform to the U.S. EPA exponent values, adjustment of the 1 hr to 24 hr is as follows:

$$multiplier_{1hr \rightarrow 24hr} = \left(1/24 \right)^{0.28} = 0.41$$

The 1 hr to 2 weeks (336 hrs) multiplier:

$$multiplier_{1hr \rightarrow 336hr} = \left(1/336 \right)^{0.28} = 0.196$$

The 1 hr to 30 days (720 hrs) multiplier:

$$multiplier_{1hr \rightarrow 720hr} = \left(1/720 \right)^{0.28} = 0.158$$

By extension of the equation -

The 24 hr to 2 weeks (336 hrs) multiplier:

$$multiplier_{24hr \rightarrow 336hr} = \left(24/336 \right)^{0.28} = 0.48$$

The 24 hr to 30 day (720 hr) multiplier:

$$multiplier_{24hr \rightarrow 720hr} = \left(24/720 \right)^{0.28} = 0.39$$

The ratio of the 24 hr multiplier to the 2 week multiplier and the 24 hr multiplier to the 30 day multiplier illustrates that p = 0.28 is the appropriate multiplier for adjusting a 24 hr air concentration to averaging times between 24 hrs and annual:

$$1hr \rightarrow 336hr : 1hr \rightarrow 24hr = 0.196 / 0.41 = 0.48$$

$$1hr \rightarrow 720hr : 1hr \rightarrow 24hr = 0.158 / 0.41 = 0.39$$

3. Flux profile development

Table 3 shows a summary of the subchronic flux estimates for iodomethane. Two of the studies (Guadalupe, drip/tarp and Oxnard, bed/tarp) measured flux that projected 100 percent loss of the applied mass within the 10 days of the application. These measured flux profiles were used "as is" and zeros were used to fill in the remaining days out to 30 days.

For the remaining iodomethane studies a 3 parameter log-normal function was fit to the measured daily flux and used to extend the flux profiles to 30 days. The function was integrated from the end of measured values to 14 days. The resulting flux was added to the measured flux to estimate the 2-week cumulative flux. Similarly, the function was integrated from the end of measured values to 30 days and the result was added to the measured flux to estimate the 30 day cumulative flux.

4. Calculate the average 24-hr flux over the desired period

This number represents the average flux on any given day during the 2-week or 30-day interval. Where necessary the 2-week and 30-day average 24-hr flux estimates were adjusted to prevent projected mass loss from exceeding applied mass. Final flux estimates are shown in Table 3.

5. Multiply the 2-week or 30-day average air concentration by the scaled average 24-hr flux to obtain the estimates 2-week or 30-day air concentration for a particular study

This adjustment scales the generic 2-week or 30-day average air concentration from the 100 ug/m^{2}sec generic flux to the flux observed for the actual study application rate. It is accomplished by dividing the average 2-week or 30-day flux by the 100ug/m^{2}sec generic flux to get a scaled flux value. The generic concentrations are multiplied by the scaled flux value to estimate the 2-week or 30-day air concentration for an application made at the application rate used in the study.

6. Adjust the 2-week or 30-day air concentration estimate for a particular study to obtain estimates for application rates other that that use in the study

Since air concentrations are assumed to be proportional to flux and flux is assumed to be proportional to application rate, 2-week or 30-day air concentration estimates for other application rates can be obtained by applying an adjustment factor that expresses the desired application rate as a proportion of the study application rate.

Results

Appendix A shows results of the procedure for both Chloropicrin and Iodomethane. Appendix B shows the 3 parameter log-normal fits to develop the Iodomethane flux profiles. Appendix C contains the Chloropicrin and Iodomethane flux profiles used to calculate the average 24-hr flux values.

References

Baker, F., L. Estigoy, M. Gillis, and T. Belcher, 2001. Environmental (off-site) monitoring and direct flux/indirect flux determination of iodomethane (TM-425) under field conditions. PTRL Report No. 975W-1. DPR Vol. 52875-026 #185705.

Baker, F.C., L. Estigoy, and T.I. Belcher, 2002a. Environmental (off-site) monitoring and indirect flux determination of iodomethane (TM-425) under field conditions. TRL Report #11420-W; MRID # 45879101. DPR Vol. 52875-046 #204110.

Baker, F.C., L. Estigoy, R. Reiss, M.D. Nelson, and M. Bolda, 2002b. Volatility of iodomethane (TM-425) under field conditions in California and Florida. PTRL Report #893-W1; DPR Vol. 52875-007 #185658.

Baker, F.C., L. Estigoy, and T.I. Belcher, 2003. Environmental (off-site) monitoring and indirect flux determination of iodomethane (TM-425) under field conditions following tarped/raised bed/drip irrigation application. PTRL Report #1198W-1; DPR Vol. 52875-056 #209311.

Baker, F., R.L. Hiler, and T. Belcher, 2004a. Worker and applicator exposure under field conditions during tarped/raised bed/ shallow shank injection application. PTRL West Inc. Study Project No. 1253W. DPR Vol. 52875-0064 #204111

Baker, F.C., R. Hiler, L. Estigoy, and T.I. Belcher, 2004b. Environmental (off-site) monitoring and indirect flux determination of iodomethane (TM-425) under field conditions following tarped/raised bed/drip irrigation application. PTRL Report #1256W-1; DPR Vol. 52875-063 #214831.

Baker, F.C., L. Estigoy, T.I. Belcher, and B. Lange, 2004c. Environmental (off-site) monitoring and indirect flux determination of iodomethane (TM-425) under field conditions following tarped/raised bed/drip irrigation application. PTRL Report #1315W-1; DPR Vol. 52875-089 #214831.

Barry, T. 2008. Screening level air concentration estimates for WHS Exposure Appraisals. Memorandum to Randy Segawa, dated August 21, 2008. Environmental Monitoring Branch, Department of Pesticide Regulation, Sacramento, California 85812.

Barry, T. 2000. Peak to mean air concentration estimation for fumigants. Memorandum dated November 6, 2000 to Kean S. Goh, PhD. Environmental Monitoring and Pest Management Branch, DPR, Sacramento, CA. EM00-12.

Beard, K.K., P.G. Murphy, D.D. Fontaine, and J.T. Weinberg. 1996. Monitoring of potential worker exposure, field flux and off-site air concentration during chloropicrin field application. Chloropicrin Manufacturers Task Force c/o/ Niklor Chemical Company, Inc. 2060 East 220the Street, Long Beach, California 90810. Laboratory Project Study ID HEH 160. DPR, Registration Library Volume Number 199-072,

Rotondaro, A. 2004. Monitoring of chloropicrin emissions from field and greenhouse drip irrigation applications, and implied worker inhalation exposures from application of chloropicin by shank injection, drip irrigation systems and at tree replant sites. Chloropicrin Manufacturer's Task Force. DPR Data Volume 199-0112.

Turner, D.B. 1994. Workbook of atmospheric dispersion estimates. Lewis Publishers, Boca Raton, FL.

U.S. EPA. 1992a. U.S. EPA, Screening Procedures for Estimating the Air Quality Impact of Stationary Sources-Revised. Office of Air Quality Planning and Standards. Office of Air and Radiation. U.S. EPA. Research Triangle Park, NC 27711. EPA-450/R-92-019

U.S. EPA. 1992b. Workbook of screening techniques for assessing impacts of toxic air pollutants (Revised). Office of Air Quality Planning and Standards. Office of Air and Radiation. U.S. EPA. Research Triangle Park, NC 27711. EPA-454/R-92-024.

Table 1. Summary of application rates and flux estimates from chloropicrin studies used to estimate off-site air concentrations.

Study Location	Application Method	Study Application Rate[a] (lb/acre)	Study Effective Broadcast Application Rate (lb/acre)	2-week 24 hr average flux (ug/m^2sec)
Arizona	Broadcast/Untarp	171	171	10.39
Arizona	Bed/Untarp	149	86	5.39
Arizona	Broadcast/Tarp	332	332	12.37
Arizona	Bed/Tarp	377	189	21.45
Washington	Broadcast/Tarp	343	343	9.54
Florida	Broadcast/Tarp	346	346	12.33
California	Bed/Drip/Tarp	300	156	2.24

[a] This application rate is the "treated acre" rate. For broadcast application methods the Study Application Rate and the Study Effective Broadcast Application Rate will be the same. For bed type applications an adjustment must be made to the Study Application Rate to account for the portions of the field that are untreated

Table 2. Iodomethane studies used to estimate off-site air concentrations.

Study	Application Method	Study Treated Acre Application Rate[a]	Study Effective Broadcast Application Rate	175 lb/acre Adjustment Factor	87.5 lb/acre Adjustment Factor
Watsonville, California	Broadcast/Tarp	252	252	0.69	0.35
Manteca, California	Broadcast/Tarp	242	242	0.72	0.36
LaSelva Beach, California	Drip/Tarp	235	162	1.08	0.54
Camarillo, California	Drip/Tarp	175	119	1.47	0.74
Guadalupe, California	Drip/Tarp	174	139	1.26	0.63
Oxnard, California	Bed/Tarp	244	171	1.02	0.51
Guadalupe, California	Bed/Tarp	179	143	1.22	0.61

a. This application rate is the “treated acre” rate which is only the treated soil area excluding nontreated areas such as furrows. For broadcast application methods the Study Application Rate and the Study Effective Broadcast Application Rate will be the same. For bed type applications an adjustment must be made to the Study Application Rate to account for the portions of the field that are untreated.

Appendix A

Iodomethane - 2 week concentrations

				vol 52875-026 Manteca Field Study		vol 52875-007 Watsonville Field Study		vol 52875-056 LaSelva Beach Field Study			vol 52875-063 Camarillo Field Study			vol 52875-089 Guadalupe Field Study			vol 52875-046 Oxnard Field Study			vol 52875-064 Guadalupe Field Study		
		24hr	2 week																			
feet	meters	generic con	generic conc	242 lbs/ac	175 lbs/ac	252 lbs/ac	175 lbs/ac	162 lbs/ac	175 lbs/ac	87.5 lbs/ac	119 lbs/ac	175 lbs/ac	87.5 lbs/ac	139 lbs/ac	175 lbs/ac	87.5 lbs/ac	171 lbs/ac	175 lbs/ac	87.5 lbs/ac	143 lbs/ac	175 lbs/ac	87.5 lbs/ac
10	3.04	2589.13	1242.78	274.65	197.75	168.77	116.45	90.35	97.58	48.79	114.09	167.71	84.42	160.07	201.69	100.84	196.98	200.92	100.46	157.58	192.25	96.13
50	15.2	2350.75	1128..6	249.37	179.54	153.23	105.73	82.03	88.59	44.30	103.58	152.27	76.65	145.33	183.12	91.56	178.85	182.42	91.21	143.08	174.55	87.28
100	30.4	2018.72	968.98	214.15	154.18	131.59	90.80	70.45	76.08	38.04	88.95	130.76	65.83	124.81	157.25	78.63	153.58	156.66	78.33	122.87	149.90	74.95
300	91.2	1373.99	659.52	145.75	104.94	89.56	61.80	47.95	51.78	25.89	60.54	89.00	44.80	84.95	107.03	53.52	104.53	106.62	53.31	83.63	102.02	51.01
500	152	1083.24	519.96	114.91	82.74	70.61	48.72	37.80	40.82	20.41	47.73	70.17	35.32	66.97	84.38	42.19	82.41	84.06	42.03	65.93	80.43	40.22
###	760	379.24	182.04	40.23	28.97	24.72	17.06	13.23	14.29	7.15	16.71	24.56	12.37	23.45	29.54	14.77	28.85	29.43	14.71	23.08	28.16	14.08
		2 week adj*	0.48																			
			flux adjustment	0.221		0.1358		0.0727			0.0918			0.1288			0.1585			0.1268		
			app rate multiplier#		0.72		0.69		1.08	0.54		1.47	0.74		1.26	0.63		1.02	0.51		1.22	0.61

* this adjustment converts the generic 24hr conc to a generic 2week conc

** this adjustment converts the 2 week generic air concentration (based on 100ug/m2sec) to an air concentration based on average 24hr flux over the 2 week flux profile from the study. e.g. from Table 3: 0.221=(22.1ug/m2sec)/(100ug/m2sec) and (0.221)*(1242.78) = 274.65ug/m3

this multiplier scales the concentrations from the study to the desired application rate e.g.: (0.72)*(274.655) = 197.75

the multiplier is calculated as: 175/242 = 0.72 and scales the application rate from 242lb/ac to 175lb/ac

Any additional broadcast application rates can be obtained by calculating the app rate multiplier.

Concentrations shown are model results and 2 decimal places are retained to minimized rounding differences in calculations

Concentrations should be rounded to 2 significant figures for use in the Exposure Appraisal

Appendix A
Iodomethane - 30 day concentrations

				vol 52875-026 Manteca Field Study		vol 52875-007 Watsonville Field Study		vol 52875-056 LaSelva Beach Field Study			vol 52875-063 Camarillo Field Study			vol 52875-089 Guadalupe Field Study			vol 52875-046 Oxnard Field Study			vol 52875-064 Guadalupe Field Study		
		24hr	30 day																			
feet	**meters**	**generic con**	**generic conc**	**242 lbs/ac**	**175 lbs/ac**	**252 lb/ac**	**175 lb/ac**	**162 lbs/ac**	**175 lbs/ac**	**87.5 lb/ac**	**119 lb/ac**	**175 lbs/ac**	**87.5 lbs/ac**	**139 lbs/ac**	**175 lbs/ac**	**87.5 lbs/ac**	**171 lbs/ac**	**175 lbs/ac**	**87.5 lbs/ac**	**143 lbs/ac**	**175 lbs/ac**	**87.5 lbs/ac**
10	3.04	2589.13	1009.76	105.72	76.12	65.43	45.15	34.33	37.08	18.54	43.32	63.68	32.06	60.99	76.85	38.42	74.72	76.22	38.11	59.88	73.05	36.53
50	15.2	2350.75	916.79	95.99	69.11	59.41	40.99	31.17	33.66	16.83	39.33	57.82	29.10	55.37	69.77	34.89	67.84	69.20	34.60	54.37	66.33	33.16
100	30.4	2018.72	787.30	82.43	59.35	51.02	35.20	26.77	28.91	14.45	33.78	49.65	24.99	47.55	59.92	29.96	58.26	59.43	29.71	46.69	56.96	28.48
300	91.2	1373.99	535.86	56.10	40.39	34.72	23.96	18.22	19.68	9.84	22.99	33.79	17.01	32.37	40.78	20.39	39.65	40.45	20.22	31.78	38.77	19.38
500	152	1083.24	422.46	44.23	31.85	27.38	18.89	14.36	15.51	7.76	18.12	26.64	13.41	25.52	32.15	16.08	31.26	31.89	15.94	25.05	30.56	15.28
###	760	379.24	147.90	15.49	11.15	9.58	6.61	5.03	5.43	2.72	6.35	9.33	4.70	8.93	11.26	5.63	10.94	11.16	5.58	8.77	10.70	5.35
		30 Day adj*	0.39																			
			flux adjustment**	0.1047		0.0648		0.0340			0.0429			0.0604			0.0740			0.0593		
			app rate multiplier#		0.72		0.69		1.08	0.54		1.47	0.74		1.26	0.63		1.02	0.51		1.22	0.61

* this adjustment converts the generic 24hr conc to a generic 30 Day conc
** this adjustment converts the 30 day generic air concentration (based on 100ug/m2sec) to an air concentration based on average 24hr flux over the 30 day flux profile from the study. e.g. from Table 3: 0.1047=(10.47ug/m2sec)/(100ug/m2sec) and (0.1047)*(1009.7607) = 105.72ug/m3
# this multiplier scales the concentrations from the study to the desired application rate e.g.: (0.720)*(105.72) = 75.12
the multiplier is calculated as: 175/242 = 0.72 and scales the application rate up from 242lb/ac to 175lb/ac
Any additional broadcast application rates can be obtained by calculating the app rate multiplier.

Concentrations shown are model results and 2 decimal places are retained to minimized rounding differenced in calculations
Concentrations should be rounded to 2 significant figures for use in the Exposure Appraisal

Appendix A
Chloropicrin 2 week averages

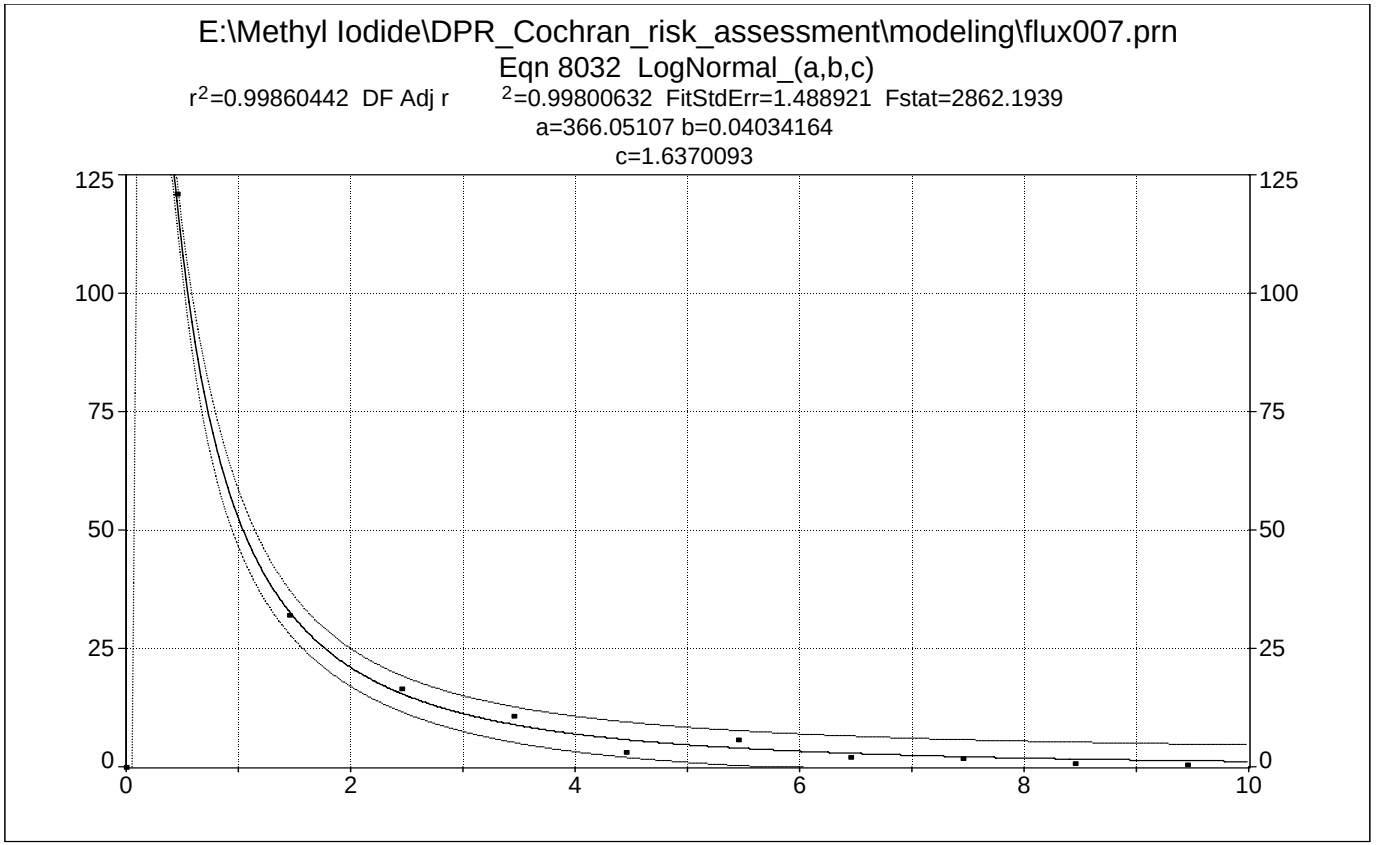
		24hr	2 week	AZ broad/untarp			AZ bed/untarp			AZ bed/tarp			AZ broad/tarp			WA broad/tarp			FL broad/tarp			CA bed/drip/tarp	
feet	**meter**	**generic con**	**generic conc**	**171 lb/ac**	**175 lb/ac**	**500 lb/ac**	**86 lb/ac**	**175 lb/ac**	**250 lb/ac**	**189 lb/ac**	**350 lb/ac**	**500 lb/ac**	**332 lb/ac**	**350 lb/ac**	**500 lb/ac**	**343 lb/ac**	**350 lb/ac**	**500 lb/ac**	**346 lb/ac**	**350 lb/ac**	**500 lb/ac**	**156 lb/ac**	**300 lb/ac**
10	3.04	2589.13	1242.78	129.13	132.09	377.56	66.99	136.32	194.73	266.58	493.17	706.43	153.73	162.03	232.14	118.56	120.93	173.10	153.24	155.07	221.42	27.84	53.53
50	15.2	2350.75	1128.6	117.24	119.93	342.80	60.82	123.77	176.80	242.03	447.76	641.39	139.58	147.12	210.76	107.65	109.80	157.16	139.13	140.80	201.04	25.28	48.60
100	30.4	2018.72	968.98	100.68	102.99	294.38	52.23	106.28	151.83	207.85	384.52	550.80	119.86	126.34	180.99	92.44	94.29	134.96	119.48	120.91	172.64	21.71	41.74
300	91.2	1373.99	659.52	68.52	70.10	200.36	35.55	72.34	103.34	141.47	261.71	374.88	81.58	85.99	123.19	62.92	64.18	91.86	81.32	82.29	117.50	14.77	28.41
500	152	1083.24	519.96	54.02	55.27	157.96	28.03	57.03	81.47	111.53	206.33	295.56	64.32	67.79	97.12	49.60	50.60	72.42	64.11	64.88	92.64	11.65	22.40
###	760	379.24	182.04	18.91	19.35	55.30	9.81	19.97	28.52	39.05	72.24	103.47	22.52	23.73	34.00	17.37	17.71	25.35	22.44	22.71	32.43	4.08	7.84
		2 week adj*	0.48																				
			flux adjustment	0.1039			0.0539			0.2145			0.1237			0.0954			0.1233			0.0224	
			app rate multiplier#		1.023	2.924		2.035	2.907		1.85	2.65		1.054	1.51		1.02	1.46		1.012	1.445		1.923

* this adjustment converts the generic 24hr conc to a generic 2week conc
** this adjustment converts the 2 week generic air concentration (based on 100ug/m2sec) to an air concentration based on average 24hr flux over the 2 week flux profile from the study. e.g. from Table 1: 0.1039=(10.39ug/m2sec)/(100ug/m2sec) and (0.1039)*(1242.78) = 129.3ug/m3
# this multiplier scales the concentrations from the study to the desired application rate e.g.: (1.023)*(129.13) = 132.09
the multiplier is calculated as: 175/171 = 1.023 and scales the application rate up from 171lb/ac to 175lb/ac
Any additional broadcast application rates can be obtained by calculating the app rate multiplier.
Example: bed/tarp 250 app rate multiplier = 250/189 = 1.323
the concentrations in the "bed/tarp 189" column multipled by 1.323 gives estimated concentration for 250lb effective broadcast
this scenario would be 500lbs in the beds and beds 50% of the field area.

Concentrations shown are model results and 4 decimal placed are retained to minimized rounding differenced in calculations
Concentrations should be rounded to 2 significant figures for use in the Exposure Appraisal

Appendix B. Iodomethane 30-Day Flux Profile Development

007 Watsonville, California
Broadcast/tarp



Rank 1 Eqn 8032 LogNormal_(a,b,c)

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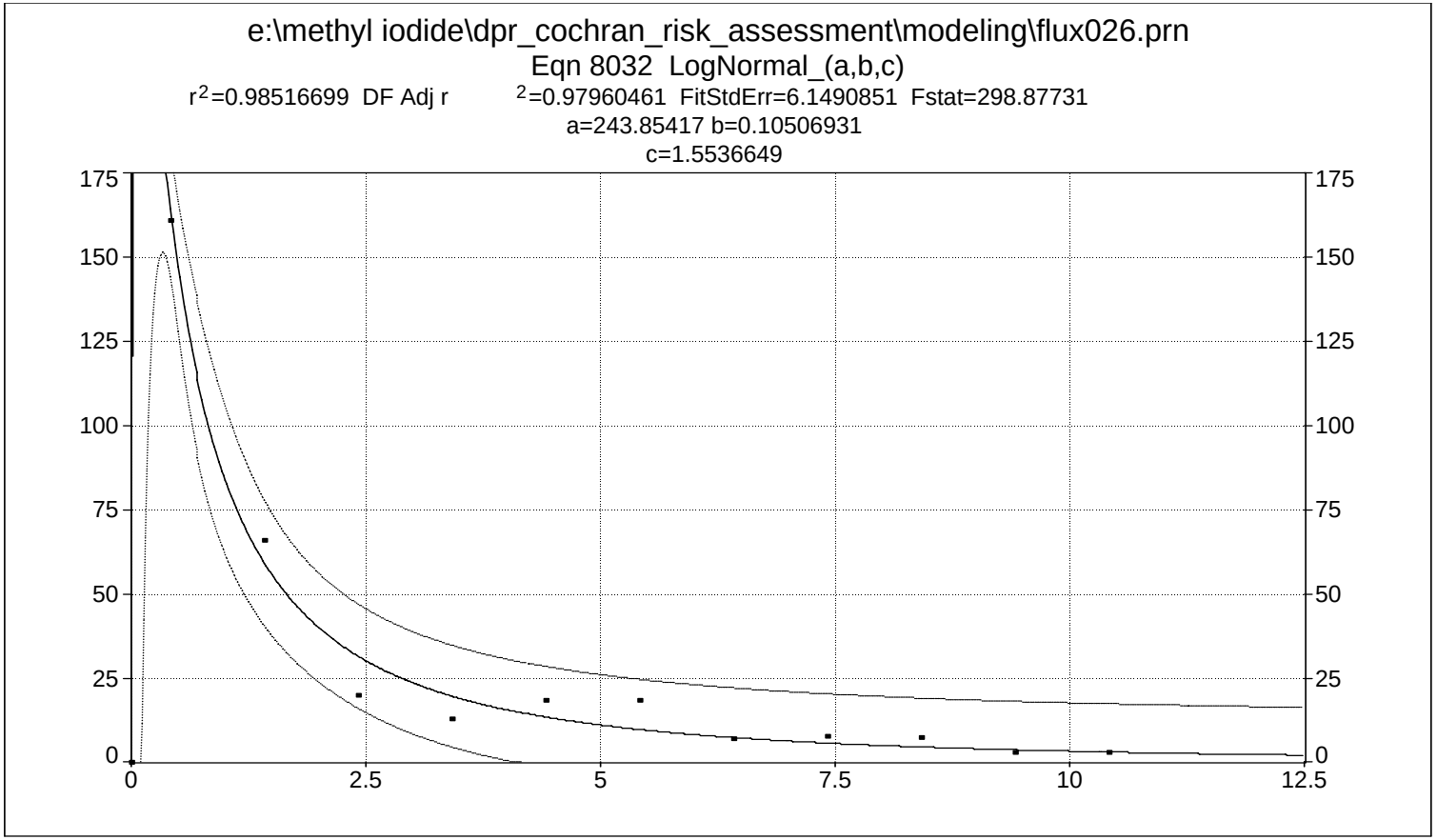
1		0.0000000	0.0000000								1
2		0.4600000	121.30000	121.21224	0.0877648	0.0723535	117.77941	124.64506	116.35704	126.06743	1
3		1.4600000	32.200000	33.105312	-0.905312	-2.811529	29.919536	36.291089	28.421531	37.789093	1
4		2.4600000	16.800000	15.645902	1.1540984	6.8696332	13.941254	17.350550	11.812567	19.479237	1
5		3.4600000	11.000000	9.0727609	1.9272391	17.520355	7.5096807	10.635841	5.3002481	12.845274	1
6		4.4600000	3.3000000	5.8797181	-2.579718	-78.17328	4.4127679	7.3466683	2.1460100	9.6134262	1
7		5.4600000	5.9000000	4.0904287	1.8095713	30.670700	2.7560509	5.4248065	0.4067895	7.7740678	1
8		6.4600000	2.3000000	2.9902720	-0.690272	-30.01183	1.7961628	4.1843812	-0.644908	6.6254515	1
9		7.4600000	1.9000000	2.2679552	-0.367955	-19.36606	1.2058527	3.3300576	-1.326025	5.8619355	1
10		8.4600000	1.0000000	1.7698504	-0.769850	-76.98504	0.8259742	2.7137267	-1.790983	5.3306840	1
11		9.4600000	0.5600000	1.4129763	-0.852976	-152.3172	0.5727308	2.2532217	-2.121800	4.9477528	1

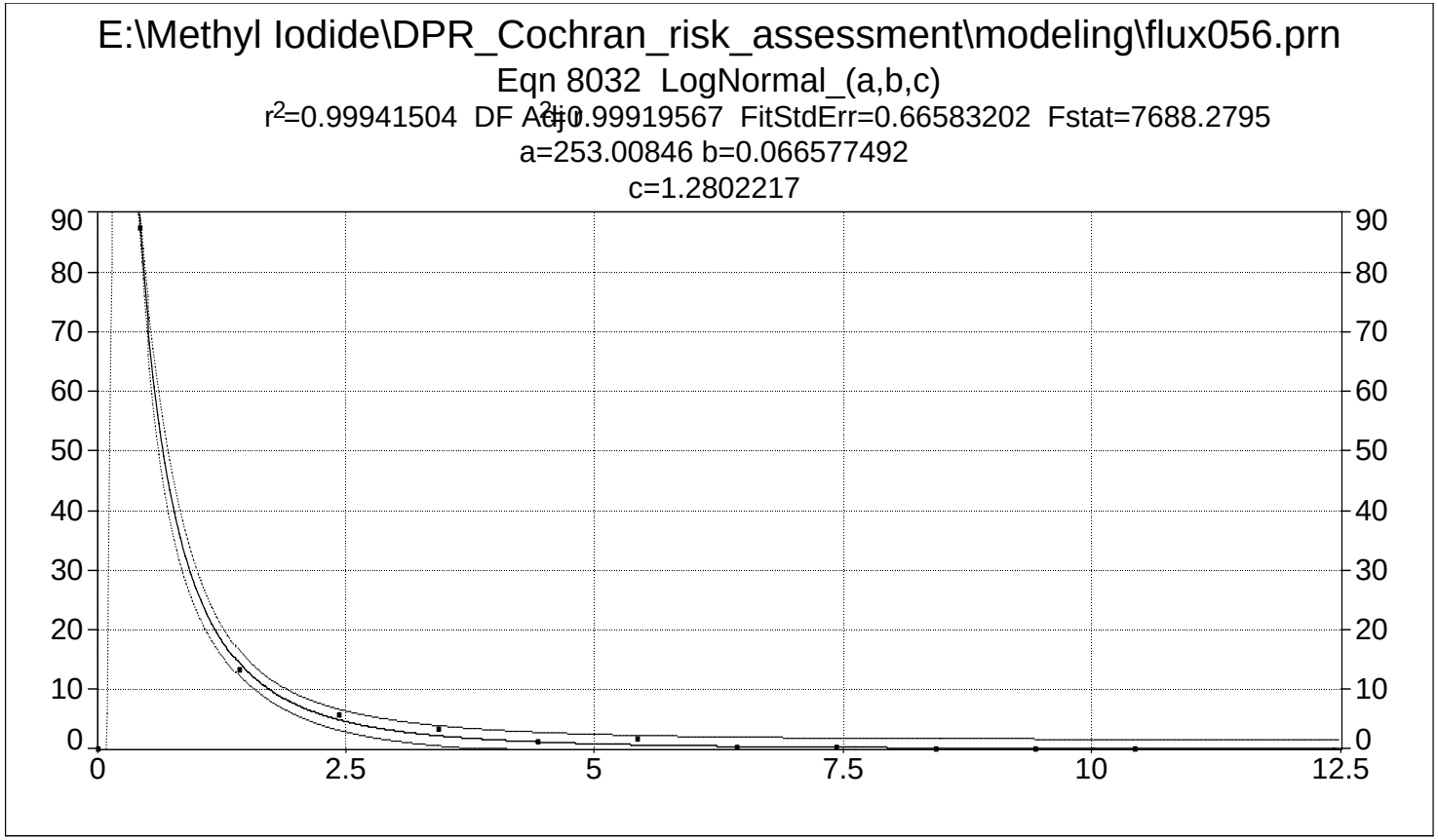
026 Manteca
Broadcast/tarp



Rank 1 Eqn 8032 LogNormal_(a,b,c)

XY	*	X Value	Y Value	Y Predict	Residual	Residual%	95% Confidence Limits		95% Prediction Limits		Weights
1		0.0000000	0.0000000								1
2		0.4300000	161.20000	161.62053	-0.420527	-0.260873	147.71704	175.52401	141.95328	181.28777	1
3		1.4300000	66.000000	59.422012	6.5779885	9.9666492	46.921775	71.922248	40.720421	78.123602	1
4		2.4300000	20.000000	31.593718	-11.59372	-57.96859	24.755255	38.432182	16.093455	47.093982	1
5		3.4300000	13.000000	19.684956	-6.684956	-51.42274	13.734926	25.634986	4.5556325	34.814280	1
6		4.4300000	18.500000	13.421508	5.0784921	27.451308	7.7227323	19.120284	-1.610778	28.453794	1
7		5.4300000	18.500000	9.7064289	8.7935711	47.532817	4.3461762	15.066682	-5.200814	24.613672	1
8		6.4300000	7.0000000	7.3199966	-0.319997	-4.571380	2.3698197	12.270173	-7.444753	22.084746	1
9		7.4300000	8.0000000	5.6968555	2.3031445	28.789307	1.1713012	10.222410	-8.931002	20.324713	1
10		8.4300000	7.5000000	4.5441430	2.9558570	39.411427	0.4255713	8.6627146	-9.962966	19.051252	1
11		9.4300000	3.0000000	3.6972963	-0.697296	-23.24321	-0.045840	7.4404328	-10.70773	18.102318	1
12		10.430000	3.0000000	3.0578933	-0.057893	-1.929778	-0.345569	6.4613560	-11.26262	17.378408	1

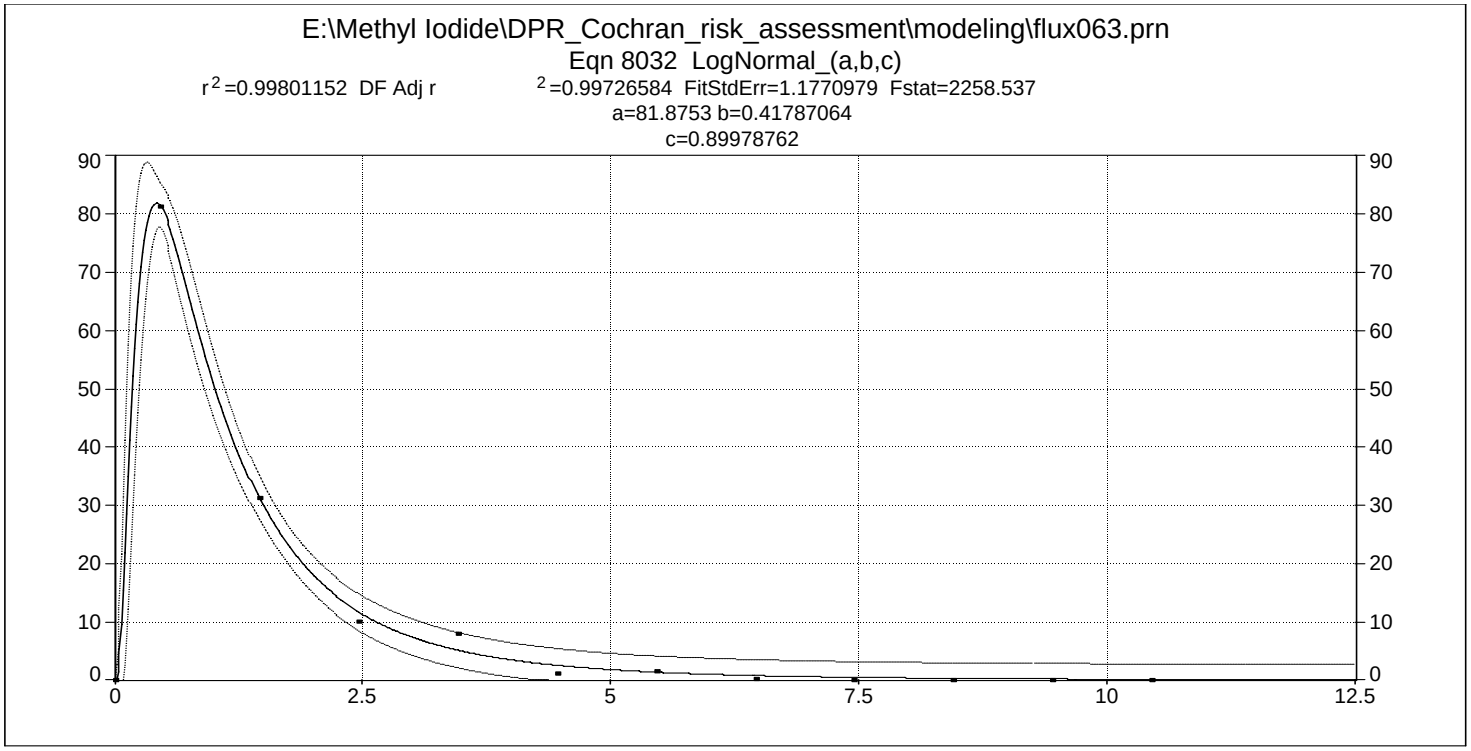
056 LaSelva Beach, California
Drip/Tarp



Rank 1 Eqn 8032 LogNormal_(a,b,c)

XY	*	X Value	Y Value	Y Predict	Residual	Residual%	95% Confidence Limits		95% Prediction Limits		Weights
1		0.0000000	0.0000000								1
2		0.4300000	87.600000	87.517959	0.0820408	0.0936539	86.011767	89.024151	85.387864	89.648054	1
3		1.4300000	13.400000	14.348797	-0.948797	-7.080578	12.876518	15.821077	12.242546	16.455049	1
4		2.4300000	5.7000000	4.8826428	0.8173572	14.339599	3.9656399	5.7996458	3.1192419	6.6460438	1
5		3.4300000	3.3500000	2.2099065	1.1400935	34.032641	1.4168010	3.0030120	0.5076418	3.9121712	1
6		4.4300000	1.3700000	1.1707592	0.1992408	14.543124	0.5537230	1.7877954	-0.456945	2.7984638	1
7		5.4300000	1.7000000	0.6863966	1.0136034	59.623728	0.2172734	1.1555199	-0.891185	2.2639787	1
8		6.4300000	0.2500000	0.4321646	-0.182165	-72.86585	0.0742734	0.7900559	-1.115987	1.9803167	1
9		7.4300000	0.2700000	0.2869597	-0.016960	-6.281369	0.0108052	0.5631142	-1.244363	1.8182827	1
10		8.4300000	0.0950000	0.1985869	-0.103587	-109.0388	-0.017364	0.4145373	-1.323032	1.7202055	1
11		9.4300000	0.1120000	0.1420635	-0.030063	-26.84237	-0.029065	0.3131923	-1.373843	1.6579704	1
12		10.430000	0.0500000	0.1044352	-0.054435	-108.8704	-0.032879	0.2417489	-1.408028	1.6168980	1

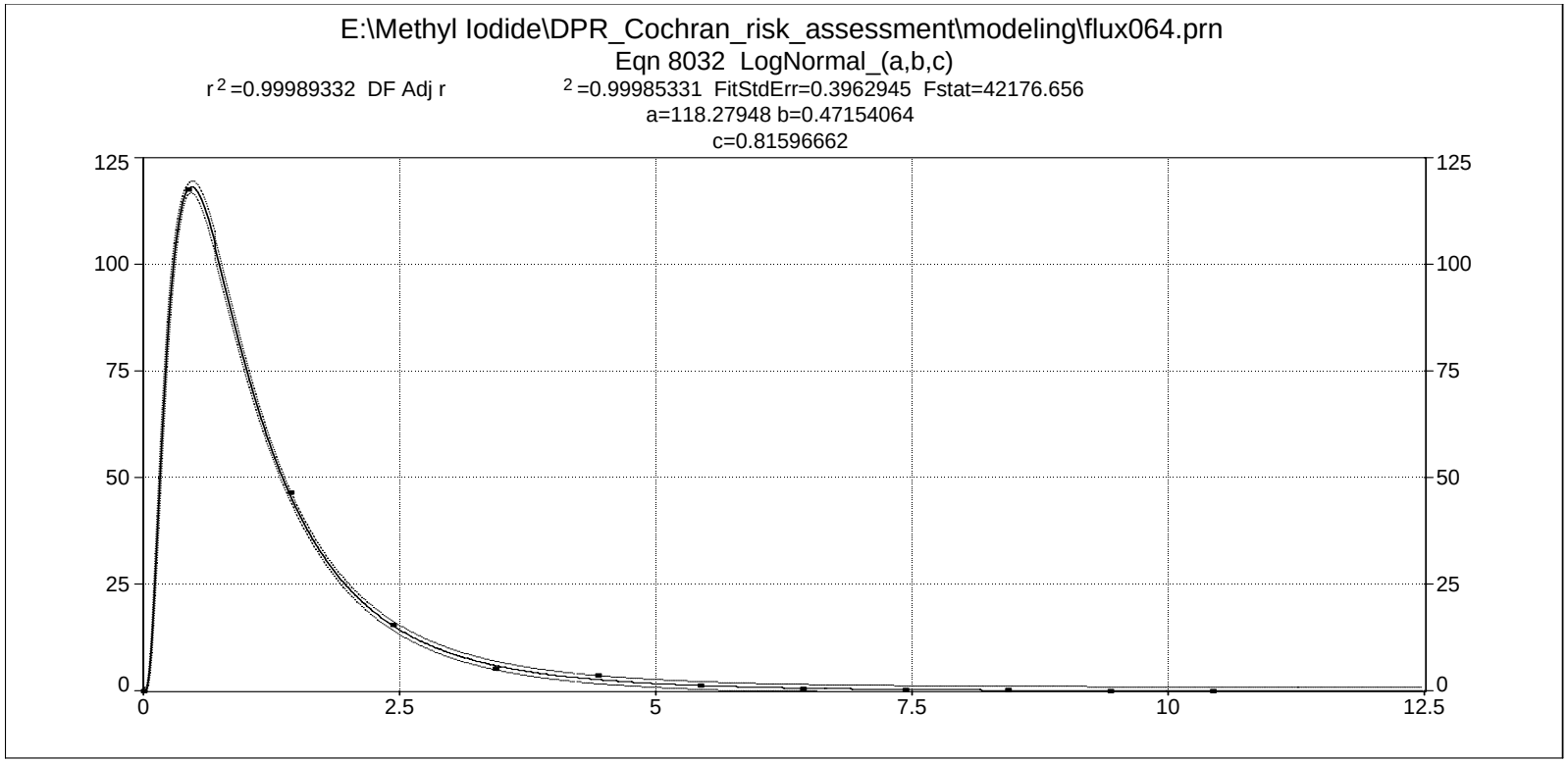
063 Camarillo, California
Drip/Tarp



Rank 1 Eqn 8032 LogNormal_(a,b,c)

XY	*	X Value	Y Value	Y Predict	Residual	Residual%	95% Confidence Limits		95% Prediction Limits		Weights
1		0.0000000	0.0000000								1
2		0.4600000	81.400000	81.410097	-0.010097	-0.012404	78.747555	84.072639	77.644525	85.175668	1
3		1.4600000	31.400000	31.145217	0.2547834	0.8114122	28.544839	33.745594	27.423340	34.867093	1
4		2.4600000	10.200000	11.756312	-1.556312	-15.25796	10.034303	13.478320	8.5852371	14.927386	1
5		3.4600000	8.0000000	5.1843372	2.8156628	35.195785	3.7144208	6.6542536	2.1427828	8.2258916	1
6		4.4600000	1.3000000	2.5676056	-1.267606	-97.50812	1.4893233	3.6458879	-0.305214	5.4404251	1
7		5.4600000	1.7000000	1.3855146	0.3144854	18.499139	0.6268568	2.1441725	-1.383233	4.1542618	1
8		6.4600000	0.3700000	0.7983049	-0.428305	-115.7581	0.2666348	1.3299750	-1.917035	3.5136450	1
9		7.4600000	0.1600000	0.4844065	-0.324407	-202.7541	0.1084439	0.8603691	-2.204784	3.1735973	1
10		8.4600000	0.1100000	0.3065380	-0.196538	-178.6709	0.0371015	0.5759745	-2.369839	2.9829152	1
11		9.4600000	0.0800000	0.2008490	-0.120849	-151.0613	0.0049367	0.3967613	-2.469129	2.8708267	1
12		10.460000	0.0500000	0.1355201	-0.085520	-171.0402	-0.008982	0.2800221	-2.531178	2.8022184	1

064 Guadalupe. California
Bed/Tarp



Rank 1 Eqn 8032 LogNormal_(a,b,c)

XY	*	X Value	Y Value	Y Predict	Residual	Residual%	95% Confidence Limits		95% Prediction Limits		Weights
1		0.0000000	0.0000000								1
2		0.4350000	117.70000	117.70300	-0.003004	-0.002553	116.80657	118.59944	116.43522	118.97079	1
3		1.4350000	46.700000	46.660998	0.0390019	0.0835158	45.776674	47.545322	45.401750	47.920246	1
4		2.4350000	15.600000	15.627740	-0.027740	-0.177821	14.988843	16.266637	14.526892	16.728588	1
5		3.4350000	5.5000000	6.1211787	-0.621179	-11.29416	5.6289493	6.6134080	5.0984535	7.1439039	1
6		4.4350000	3.7000000	2.7200787	0.9799213	26.484361	2.3978679	3.0422894	1.7674523	3.6727050	1
7		5.4350000	1.5000000	1.3299475	0.1700525	11.336832	1.1256154	1.5342796	0.4104755	2.2494195	1
8		6.4350000	0.5500000	0.7001924	-0.150192	-27.30770	0.5698866	0.8304981	-0.205709	1.6060934	1
9		7.4350000	0.3000000	0.3909902	-0.090990	-30.33008	0.3064695	0.4755110	-0.509466	1.2914462	1
10		8.4350000	0.3000000	0.2290643	0.0709357	23.645248	0.1731325	0.2849960	-0.669159	1.1272878	1
11		9.4350000	0.1500000	0.1396659	0.0103341	6.8893972	0.1019019	0.1774299	-0.757610	1.0369414	1
12		10.435000	0.1000000	0.0880843	0.0119157	11.915697	0.0620959	0.1140727	-0.808773	0.9849413	1

Appendix C – Chloropicrin (2-week) and Iodomethane (30-Day) Flux Profiles

Chloropicrin daily integrated flux profiles (ug/m^{2}sec - day)

Day	AZ broad/untarp 171 lb/ac	AZ bed/untarp 86 lb/ac	AZ bed/tarp 189 lb/ac	AZ broad/tarp 332 lb/ac	WA broad/tarp 343 lb/ac	FL broad/tarp 346 lb/ac	CA bed/drip/tarp 156 lb/ac
1	85.700	66.320	79.90	79.450	4.83	16.110	22.250
2	38.470	6.820	91.47	71.960	10.15	24.910	4.770
3	11.300	1.720	59.66	11.600	13.31	25.490	0.980
4	5.970	0.350	29.96	3.500	4.93	17.870	0.350
5	2.380	0.100	14.22	1.125	4.54	17.150	0.550
6	1.050	0.015	6.20	1.580	4.48	17.640	0.130
7	0.195	0.035	3.96	0.910	33.93	20.230	0.064
8	0.165	0.015	3.97	0.920	31.48	18.230	0.036
9	0.035	0.015	6.56	0.560	11.44	10.160	0.050
10	0.095	0.015	2.58	0.520	5.73	2.290	0.970
11	0.015	0.015	0.51	0.595	3.66	0.552	0.520
12	0.000	0.015	0.60	0.160	1.90	0.993	0.240
13	0.020	0.015	0.47	0.175	1.78	0.619	0.240
14	0.030	0.015	0.22	0.170	1.33	0.394	0.240
Proportion Applied Mass Lost	0.6246	0.6138	0.6864	0.6264	0.3379	0.3650	0.1520

007 Watsonville, California
Broadcast/Tarp

Day Midpoint	Proportion of 24hr (day)	Daily integrated flux (ug/m^{2}sec - day)	Daily mass loss (lb/acre)
0.46	0.92	111.596	85.9289
1.46	1.00	32.200	24.7940
2.46	1.00	16.800	12.9360
3.46	1.00	11.000	8.4700
4.46	1.00	3.300	2.5410
5.46	1.00	5.900	4.5430
6.46	1.00	2.300	1.7710
7.46	1.00	1.900	1.4630
8.46	1.00	1.000	0.7700
9.46	1.00	0.560	0.4312
10.46	1.00	1.150	0.8855
11.46	1.00	0.950	0.7315
12.46	1.00	0.790	0.6083
13.46	1.00	0.670	0.5159
14.46	1.00	0.580	0.4466
15.46	1.00	0.500	0.3850
16.46	1.00	0.430	0.3311
17.46	1.00	0.380	0.2926
18.46	1.00	0.330	0.2541
19.46	1.00	0.300	0.2310
20.46	1.00	0.260	0.2002
21.46	1.00	0.240	0.1848
22.46	1.00	0.210	0.1617
23.46	1.00	0.190	0.1463
24.46	1.00	0.170	0.1309
25.46	1.00	0.160	0.1232
26.46	1.00	0.140	0.1078
27.46	1.00	0.130	0.1001
28.46	1.00	0.120	0.0924
29.46	1.00	0.110	0.0847

026 Manteca
Broadcast/tarp

Day Midpoint	Proportion of 24hr (day)	Daily integrated flux (ug/m^{2}sec - day)	Daily mass loss (lb/acre)
0.43	0.86	161.20	106.747
1.43	1.00	66.00	50.820
2.43	1.00	20.00	15.400
3.43	1.00	13.00	10.010
4.43	1.00	18.50	14.245
5.43	1.00	18.50	14.245
6.43	1.00	7.00	5.390
7.43	1.00	8.00	6.160
8.43	1.00	7.50	5.775
9.43	1.00	3.00	2.310
10.43	1.00	3.00	2.310
11.43	1.00	2.56	1.971
12.43	1.00	2.17	1.671
13.43	1.00	1.86	1.432
14.43	1.00	1.61	1.240
15.43	1.00	1.40	1.078
16.43	1.00	1.23	0.947
17.43	1.00	0.00	0.000
18.43	1.00	0.00	0.000
19.43	1.00	0.00	0.000
20.43	1.00	0.00	0.000
21.43	1.00	0.00	0.000
22.43	1.00	0.00	0.000
23.43	1.00	0.00	0.000
24.43	1.00	0.00	0.000
25.43	1.00	0.00	0.000
26.43	1.00	0.00	0.000
27.43	1.00	0.00	0.000
28.43	1.00	0.00	0.000
29.43	1.00	0.00	0.000

056 LaSelva Beach, California
Drip/Tarp

Day Midpoint	Proportion of 24hr (day)	Daily integrated flux (ug/m^{2}sec - day)	Daily mass loss (lb/acre)
0.43	0.86	75.336	58.0087
1.43	1.00	13.400	10.3180
2.43	1.00	5.700	4.3890
3.43	1.00	3.350	2.5795
4.43	1.00	1.370	1.0549
5.43	1.00	1.700	1.3090
6.43	1.00	0.250	0.1925
7.43	1.00	0.270	0.2079
8.43	1.00	0.095	0.0732
9.43	1.00	0.112	0.0862
10.43	1.00	0.050	0.0385
11.43	1.00	0.078	0.0601
12.43	1.00	0.060	0.0462
13.43	1.00	0.047	0.0362
14.43	1.00	0.037	0.0285
15.43	1.00	0.030	0.0231
16.43	1.00	0.024	0.0185
17.43	1.00	0.020	0.0154
18.43	1.00	0.016	0.0123
19.43	1.00	0.014	0.0108
20.43	1.00	0.011	0.0085
21.43	1.00	0.010	0.0077
22.43	1.00	0.008	0.0062
23.43	1.00	0.007	0.0054
24.43	1.00	0.006	0.0046
25.43	1.00	0.005	0.0039
26.43	1.00	0.005	0.0031
27.43	1.00	0.004	0.0031
28.43	1.00	0.003	0.0023
29.43	1.00	0.003	0.0023

063 Camarillo, California
Drip/Tarp

Day Midpoint	Proportion of 24hr (day)	Daily integrated flux (ug/m^{2}sec - day)	Daily mass loss (lb/acre)
0.46	0.92	74.888	57.6638
1.46	1.00	31.400	24.1780
2.46	1.00	10.200	7.8540
3.46	1.00	8.000	6.1600
4.46	1.00	1.300	1.0010
5.46	1.00	1.700	1.3090
6.46	1.00	0.370	0.2849
7.46	1.00	0.160	0.1232
8.46	1.00	0.110	0.0847
9.46	1.00	0.080	0.0616
10.46	1.00	0.050	0.0385
11.46	1.00	0.094	0.0724
12.46	1.00	0.066	0.0508
13.46	1.00	0.048	0.0370
14.46	1.00	0.035	0.0270
15.46	1.00	0.026	0.0200
16.46	1.00	0.020	0.0154
17.46	1.00	0.015	0.0116
18.46	1.00	0.012	0.0092
19.46	1.00	0.009	0.0069
20.46	1.00	0.007	0.0054
21.46	1.00	0.006	0.0046
22.46	1.00	0.005	0.0039
23.46	1.00	0.004	0.0031
24.46	1.00	0.003	0.0023
25.46	1.00	0.002	0.0015
26.46	1.00	0.002	0.0015
27.46	1.00	0.002	0.0015
28.46	1.00	0.001	0.0008
29.46	1.00	0.001	0.0008

90 Guadalupe, California
Drip/Tarp

Day Midpoint	Proportion of 24hr (day)	Daily integrated flux (ug/m^{2}sec - day)	Daily mass loss (lb/acre)
0.48	0.96	125.856	96.80
1.48	1.00	26.000	20.10
2.48	1.00	9.520	7.34
3.48	1.00	5.700	4.36
4.48	1.00	5.400	4.16
5.48	1.00	4.500	3.46
6.48	1.00	2.100	1.64
7.48	1.00	1.200	0.90
8.48	1.00	0.630	0.49
9.48	1.00	0.210	0.16
10.48	1.00	0.150	0.11
11.48	1.00	0.000	0.00
12.48	1.00	0.000	0.00
13.48	1.00	0.000	0.00
14.48	1.00	0.000	0.00
15.48	1.00	0.000	0.00
16.48	1.00	0.000	0.00
17.48	1.00	0.000	0.00
18.48	1.00	0.000	0.00
19.48	1.00	0.000	0.00
20.48	1.00	0.000	0.00
21.48	1.00	0.000	0.00
22.48	1.00	0.000	0.00
23.48	1.00	0.000	0.00
24.48	1.00	0.000	0.00
25.48	1.00	0.000	0.00
26.48	1.00	0.000	0.00
27.48	1.00	0.000	0.00
28.48	1.00	0.000	0.00
29.48	1.00	0.000	0.00

046 Oxnard, California
Bed/Tarp

Day Midpoint	Proportion of 24hr (day)	Daily integrated flux (ug/m^{2}sec - day)	Daily mass loss (lb/acre)
0.43	0.86	186.4	74.4
1.43	1.00	71.0	53.8
2.43	1.00	29.0	22.4
3.43	1.00	11.0	8.9
4.43	1.00	7.0	5.4
5.43	1.00	8.0	6.3
6.43	1.00	0.0	0.0
7.43	1.00	0.0	0.0
8.43	1.00	0.0	0.0
9.43	1.00	0.0	0.0
10.43	1.00	0.0	0.0
11.43	1.00	0.0	0.0
12.43	1.00	0.0	0.0
13.43	1.00	0.0	0.0
14.43	1.00	0.0	0.0
15.43	1.00	0.0	0.0
16.43	1.00	0.0	0.0
17.43	1.00	0.0	0.0
18.43	1.00	0.0	0.0
19.43	1.00	0.0	0.0
20.43	1.00	0.0	0.0
21.43	1.00	0.0	0.0
22.43	1.00	0.0	0.0
23.43	1.00	0.0	0.0
24.43	1.00	0.0	0.0
25.43	1.00	0.0	0.0
26.43	1.00	0.0	0.0
27.43	1.00	0.0	0.0
28.43	1.00	0.0	0.0
29.43	1.00	0.0	0.0

064 Guadalupe, California
Bed/Tarp

Day Midpoint	Proportion of 24 hr (day)	Daily integrated flux (ug/m^{2}sec - day)	Daily mass loss (lb/acre)
0.435	0.87	78.8472	74.4
1.435	1.00	35.9590	53.8
2.435	1.00	12.0120	22.4
3.435	1.00	4.2350	8.9
4.435	1.00	2.8490	5.4
5.435	1.00	1.1550	6.3
6.435	1.00	0.4235	0.0
7.435	1.00	0.2310	0.0
8.435	1.00	0.2310	0.0
9.435	1.00	0.1155	0.0
10.435	1.00	0.0770	0.0
11.435	1.00	0.0439	0.0
12.435	1.00	0.0293	0.0
13.435	1.00	0.0200	0.0
14.435	1.00	0.0139	0.0
15.435	1.00	0.0100	0.0
16.435	1.00	0.0069	0.0
17.435	1.00	0.0054	0.0
18.435	1.00	0.0039	0.0
19.435	1.00	0.0031	0.0
20.435	1.00	0.0023	0.0
21.435	1.00	0.0015	0.0
22.435	1.00	0.0015	0.0
23.435	1.00	0.0010	0.0
24.435	1.00	0.0008	0.0
25.435	1.00	0.0008	0.0
26.435	1.00	0.0006	0.0
27.435	1.00	0.0005	0.0
28.435	1.00	0.0004	0.0
29.435	1.00	0.0003	0.0

Table 3. Summary of the iodomethane 2-week and 30-day factors to estimate the sub-chronic air concentrations.

Study (Application Method)	Study Effective Broadcast Application Rate (lb/ac)	3 Parameter Log-Normal Function R^2	First Sampling Interval Duration (hrs)	First Sampling Interval Proportion of 24 hrs	Study Reported Measured Proportion Mass Lost	2-week 24 hr average flux (ug/m^{2}sec)	2-week Mass lost (lb/ac)	2-week Proportion of Mass Applied	30-Day 24hr average flux (ug/m^{2}sec)	30-Day Mass Lost (lb/ac)	30-Day Proportion of Mass Applied
Watsonville, California (broadcast/tarp)	252	99.7 percent	22	0.92	0.58	13.58	146.0	0.58	6.48	150.0	0.59
Manteca, California (broadcast/tarp)	242	98.5 percent	19	0.86	0.94	22.1	238.0	0.98	10.47	242.0	1.00
LaSelva Beach, California (drip/tarp)	162	99.9 percent	19	0.86	0.45	7.27	78.4	0.48	3.40	78.5	0.48
Camarillo, California (drip/tarp)	119	99.8 percent	22	0.92	0.83	9.18	98.9	0.83	4.29	99.0	0.83
Guadalupe, California (drip/tarp)	139	-[1]	23	0.96	1.00	12.88	139.0	1.00	6.04	139.0	1.00
Oxnard, California (bed/tarp)	171	-[1]	19	0.86	1.00	15.85	171.0	1.00	7.40	171.0	1.00
Guadalupe, California (bed/tarp)	143	99.9%	21	0.87	0.97	12.68	136.8	0.96[2]	5.93	136.9	0.96[2]

[1] These two studies measured flux that results in 100 percent mass loss within the first 10 days.
[2] This mass loss differs slightly from 0.97 due to rounding difference between the study report and calculations in this memorandum.

Appendix A. Estimated Chloropicrin 2-week and Iodomethane 2-week and 30-Day Sub-chronic Off-site Air Concentrations.

Department of Pesticide Regulation

Mary-Ann Warmerdam
Director

Arnold Schwarzenegger
Governor

MEMORANDUM

TO: Randy Segawa, Environmental Program Manager I
Environmental Monitoring Branch

FROM: Terrell Barry, Ph.D., Research Scientist III
Environmental Monitoring Branch
(916) 324-4140

Original signed by

DATE: August 21, 2008

SUBJECT: SCREENING LEVEL AIR CONCENTRATION ESTIMATES FOR WORKER HEALTH AND SAFETY EXPOSURE APPRAISALS

Background

The Department of Pesticide Regulation (DPR) exposure appraisals have relied exclusively on air concentrations measured in monitoring studies. However, measured air concentrations are limited in the context of estimating exposure because a measured air concentration results from a unique combination of application and meteorological conditions. The maximum air concentration associated with an application is unknown because it is unlikely that the highest air concentration present was captured by the finite set of air samplers. In addition, due to the dependence of measured air concentrations on specific application conditions, it is not possible to apply results obtained from a single study directly to other conditions. Methods have been develop using air dispersion models to generalize results from single monitoring studies so that results can be applied to other conditions.

Air dispersion models are mathematical models that describe and quantify the dispersal of pollutants in the atmosphere following release from point, line, volume, or area sources. Thus, the atmospheric processes known to disperse pollutants emitted from sources are characterized in an air dispersion model, allowing the estimation (prediction) of air concentrations at receptors located off-site around a source. In the case of soil fumigants it is only necessary to consider areas sources. More complex considerations are required to model commodity and structural fumigants.

The U.S. Environmental Protection Agency (U.S. EPA) Office of Air and Radiation and Office of Air Quality Planning and Standards administers the program which reviews and accepts candidate models as “preferred,” “alternative,” or “screening,” and maintains air dispersion model codes. This process insures uniformity in the models and modeling procedures among users. The “preferred” model status is required for State Implementation Plan revisions for existing sources and for New Source Review and Prevention of Significant Deterioration programs (40 CFR 51, Federal Register, 2005). The “preferred” models related to DPR applications are the AMS/EPA Regulatory Model (AERMOD) (U.S. EPA, 2004) and CALPUFF (Scire et al., 2000). The “alternative” model status allows for reviewed models to be used in

regulatory applications with case-by-case justification (Section 3.2, Appendix W, 40 CFR 51, Federal Register 2005). The reviewing authority in this case is DPR and the "alternative" model related to DPR applications is Industrial Source Complex Short Term Version 3 (ISCST3) air dispersion model (U.S. EPA, 1995). The ISCST3 model was a "preferred" model prior to the promulgation of the AERMOD model in December 2006 (40 CFR 51, Federal Register, 2005).

Since the 1990's, DPR has used the ISCST3 air dispersion model extensively (Johnson et al, 1999; Barry, 2000a, Johnson and Barry, 2005) to estimate off-site fumigant air concentrations. For the purposes of this project, DPR is not required to shift to either AERMOD or CALPUFF because these applications are not related to the State Implementation Plan or the Prevention of Significant Deterioration programs. In addition, the improvements gained by use of AERMOD are not implemented in the area source portion of that model. Use of CALPUFF has been considered. However, CALPUFF is a complex model that requires extensive meteorological inputs that are not readily available. While it is likely CALPUF will be integrated into the DPR modeling program in the future, at this time it is not in use.

The ISCST3 model uses a steady-state Gaussian plume dispersion equation to estimate downwind air concentrations from point, volume, and area pollutant sources. For fixed meteorological conditions, the Gaussian plume algorithm produces downwind air concentrations that are directly proportional to the emission rate (flux) of a pollutant. In addition, DPR has assumed that flux is directly proportional to the application rate (Segawa et al., 2000). The resulting proportional linkage between application rate and concentration simplifies calculations under fixed meteorological conditions.

The ISCST3 model can be used in three distinct ways: (1) the screening mode, (2) the PERFUM model, and (3) the FEMS model. For a chosen emission scenario, the screening mode produces a single air concentration estimate at a receptor (a point location at a specified distance from the source) using a single set of worst-case meteorological conditions. This means that a single downwind centerline set of air concentration estimates at various distances is the result of the analysis. Although there are differences in their approaches, the PERFUM and FEMS models are "probabilistic" in the sense that for a chosen emission scenario, historical weather data is used to produce multiple air concentration estimates at each receptor. This produces a distribution of air concentrations at a given receptor over the span of the meteorological data. Use of these distributions requires defining one or more key percentiles (e.g. 95th percentile) concentrations corresponding to key percentiles identified by risk managers.

The Worker Health and Safety (WHS) branch has chosen the screening mode for this project. This memorandum describes the method employed by DPR using air dispersion modeling to estimate screening level worst case air concentrations under the range of application methods

and rates expected for a given chemical. The fumigants, iodomethane, and chloropicrin will provide examples of this method.

Throughout this memorandum the air concentrations and flux represent time weighted averages (TWA) that are either measured over a single sampling interval or are composites of shorter time intervals. Air concentration results are dependent upon sample interval duration. If fumigant air concentrations at a fixed location were measured at 1 minute intervals for 24 hours (hrs) the resulting 24 point plot would show a sharply fluctuating function with many peaks and valleys due to the intermittency with which the fumigant plume contacted the air sampler. Fumigant application site monitoring seldom uses 1 minute sampling intervals. Instead, sampling intervals of 2 to 12 hrs are employed. An air sampler at a fixed location accumulates intermittent deposits of fumigant mass during a sampling interval. The total mass collected is divided by the total volume of air pulled through the sampler during the sampling interval and this quotient become the air concentration for that sampling interval. Flux measurements are based upon air concentration measurements so the same properties apply. Thus, a single sampling interval concentration measurement represents a TWA of the peaks and valley in the hidden, high frequency concentration function during the sampling interval. The same TWA properties apply to composites of several shorter intervals of varying duration into a longer average. The longer average is constructed as an average weighted according to the individual sampling interval durations.

Methods

There are two components to the process of obtaining air concentration estimates for use in a screening level exposure appraisal: (1) generic ISCST3 simulation results which can be adapted to the specifics of an exposure scenario and (2) specific elements in the exposure scenario which are utilized to adapt the generic simulation results. The generic ISCST3 simulation results consist of downwind air concentration estimates generated using fixed meteorological conditions and using a nominal flux of 100 ug/m^2s. Sets of generic concentration estimates are produced for different acreages and meteorological condition combinations. Exposure scenario elements are used to choose appropriate acreage and meteorological conditions and to adjust the downwind air concentrations. Exposure scenario elements consist of four, interrelated kinds of parameters: (1) expected application parameters (chemical, application size, application method and rate), (2) flux estimates from field studies, (3) health threshold averaging time and possibly concentration, and (4) meteorological conditions. Each input class will be discussed below.

(1) Expected Application Parameters

These parameters are either available from use patterns for registered pesticides, or must be specified for a new pesticide that is in the registration process. Typically, the largest single day application acreage labeled or expected is simulated as a square field. The largest single day application acreage may reflect label conditions or physical limitations on the size of an application that can be made in a single day. Although other field geometries may be more common in practice, for simulation and comparison purposes the square field presents a uniform case across chemicals, application methods and rates. In addition to the largest single day application acreage, the largest allowed application rate is also used. The largest allowed application rate may be smaller than the maximum labeled rate.

The application method must be adequately described and studied in at least one reviewed field study so that a flux profile can be developed. The flux profile characterizes the progression of flux values over time following the application. The application rate used for air dispersion modeling is the "effective broadcast application rate" (Barry et al., 2004) defined as the total mass of chemical applied to a field divided by the size of the field. This method of designating the application rate removes the consideration of "treated" versus "broadcast" acres. It makes no difference whether the total mass is applied to rows or broadcast because the application is modeled as a uniform area source.

(2) Flux Estimates from Field Studies

The flux profile is typically presented as a plot or table showing the flux value observed for each averaging period of the field study. The flux profile for an application method must be developed before air dispersion modeling to estimate air concentrations under various use scenarios can be conducted. The flux profile can be developed using either the back-calculation method (Johnson et al., 1999), or a direct flux estimation method (e.g., Majewski, et al., 1995). The fully characterized flux profile will have averaging intervals that match the sampling intervals used in the field study. These averaging intervals may not match the Health Threshold averaging time. In that case additional analysis is required to obtain the flux estimates used to adjust the generic centerline concentrations. The analysis method used to obtain the centerline adjustment flux values must be fully described. The relationship between the flux profile averaging times and the time of day should be preserved in the process of adjusting the generic centerline concentrations. Thus, a day flux is used only with the day conditions centerline and a night flux is used only with the night conditions centerline. In cases of averaging intervals that span sunrise or sunset, both day and night air concentration estimates should be calculated.

(3) Health Threshold Averaging Time and Concentration

The Health Threshold averaging time must be specified in order to designate the proper averaging time for the air concentration estimates. The health threshold concentration is not always used directly in the air dispersion modeling but it is required if the exposure appraisal includes distances to specific air concentrations. If the Health Threshold averaging time is significantly shorter than the sampling intervals in the field study and the fumigant of interest has very short-term irritant properties then it may be necessary to apply a peak-to-mean adjustment (Barry, 2000b) to the estimated air concentrations. Application of the peak-to-mean adjustment can be viewed as a component of risk management and should be discussed with the exposure assessment team. Thus, the peak-to-mean adjustment is not necessarily applied simply because the flux sampling interval is longer than the desired Health Threshold Averaging Time.

(4) Meteorological Conditions

The meteorological data is considered screening level and represents reasonable worst case. The choice of screening level meteorological conditions depend upon the Health Threshold averaging time and, for averaging times shorter than 24 hrs, night versus day. For a Health Threshold averaging time of 24 hrs (e.g. methyl bromide) the screening conditions are wind speed of 1.4 m/s and atmospheric stability of slightly unstable (Class C in the Pasquill-Gifford classification scheme) (Johnson and Barry, 2005). For Health Threshold averaging times shorter than 24 hrs, day screening conditions are wind speed of 1.0 m/s and atmospheric stability class of neutral (Class D in the Pasquill-Gifford classification scheme) (Barry et al., 2004) and night screening conditions are wind speed of 1.0 m/s and atmospheric stability moderately stable (Class F in the Pasquill-Gifford classification scheme) (Barry, 2000c, Barry et al. 2004).

Example 1: Estimated Iodomethane Air Concentrations

The U.S. EPA recently granted iodomethane a conditional registration (U.S. EPA, 2007). As part of the registration process the registrant conducted eight studies to characterize the flux profile of iodomethane following application to soil by three different methods: broadcast/tarp, bed/tarp, and drip/tarp (Baker et al., 2001; Baker et al., 2002 a; Baker et al., 2002b; Baker et al., 2003; Baker et al., 2004a; Baker et al., 2004b; Baker et al, 2004c).

Iodomethane is under review for registration in California. The DPR iodomethane exposure appraisal will use off-site air concentrations that were estimated using screening air dispersion modeling. The process to produce those air concentration estimates is described and illustrated in this section. The full set of air concentration estimates developed for the WHS chloropicrin exposure appraisal are shown in Appendix A. Table 1 shows the iodomethane field studies conducted, the treated area application rate, the effective broadcast application rate, and the proportional factor needed to adjust from the effective broadcast rate in the study to the expected

label application rates. Some of the field studies were conducted at application rates higher than those now labeled under the federal conditional registration. The proportion of the study effective broadcast rate can be used to adjust air concentrations to the desired effective broadcast application rate for various use scenarios. The 175 lb/acre adjustment factor is calculated by dividing 175 lb/ac by the study effective broadcast application rate.

Table 2 shows the flux estimates for three averaging times obtained from each study flux profile. The three averaging times shown (24, 8, and 1 hr) are those requested by WHS and included in the DPR iodomethane exposure appraisal. The flux estimates in Table 2 are the highest flux values obtained using the study flux profiles and a rolling average method where necessary to obtain the highest flux for each of the desired Health Threshold averaging periods (24, 8, and 1 hr). The total interval of time associated with each TWA flux is shown in parentheses in Table 2. The TWA intervals vary because studies do not always have sampling interval durations that match the Health Threshold averaging time. Ideally, the TWA flux should be over a period equal to or shorter than the desired Health Threshold averaging time. For a constant flux, an air concentration measured at a particular receptor is a function of averaging time. Under those conditions, air concentrations taken over shorter intervals will be higher relative to those taken over longer intervals. This phenomenon is well described in air dispersion theory literature (Csanady, 1973; Pasquill, 1974)

To calculate the 24 hr screening air concentration estimates the appropriate flux estimates were obtained by taking rolling weighted averages until the largest 24 hr flux was obtained. The interval durations for the 24 hr flux were between 19 and 24 hrs. In all cases the first 24 hrs yielded the highest 24 hr TWA flux. For the 8 hr air concentration estimates the flux estimates were obtained by taking rolling weighted averages of sampling periods between 2 and 4 hrs duration. Thus, the 8 hr flux estimates are based on 6 hr to and 8 hr weighted averages.

To calculate 1 hr screening air concentrations it is necessary to estimate maximum 1 hr flux. Obtaining 1 hr flux estimates can be problematic. In most studies the sampling intervals will be longer than 1 hr, and commonly no smaller than 4 hrs. However, several of the Iodomethane studies had early sampling intervals of 2 or 3 hrs. Thus, the 1 hr air concentration estimates flux estimates measured in sampling intervals ranging from 2 to 4 hrs were used directly. An alternative is to use a “peak-to-mean” adjustment to account for estimating a shorter duration concentration from longer duration concentrations (Barry, 2000b). WHS has opted not to use the peak to mean adjustments for the 1 hr modeled air concentrations because iodomethane is not an acute irritant (unlike chloropicrin or other irritants) and the averaging times of the sampling intervals were judged close enough to 1 hr to use directly from the study results.

The process of producing the 24 hr screening air concentration estimates for the Manteca broadcast/tarp application method and a 40 acre square field is illustrated in Table 3. The

remaining estimates for other application methods and locations can be found in Appendix A. The third column of Table 3 shows the generic downwind centerline air concentrations at 6 distances between 3.04 m (10 ft) and 760 m (2500 ft) from the application edge. These air concentrations were produced at a receptor height of 1.2 m representing the human breathing zone using the ISCST3 model with inputs of a 40 acre square source, generic flux (100 ug/m^2sec), the standard weather data for 24 hrs (1.4 m/s wind speed and C stability; see Johnson and Barry, 2005). These generic downwind centerline air concentrations can be used for any fumigant that uses a 24 hr Health Threshold averaging time. Only the fumigant/application method combination specific adjustment for the flux and application rate is needed to produce scenario specific air concentration estimates.

For this Manteca Broadcast/Tarp application method iodomethane study, the adjustment factors are as follows (see Table 2, row 2):

The field study has a 24 hr TWA flux estimate = 160.2 ug/m^2s

The flux adjustment factor (multiplier) for the generic air concentrations is calculated as:

$$(160.2 \text{ ug/m}^2\text{s}) / (100 \text{ ug/m}^2\text{s}) = 1.602$$

This multiplier is applied to the downwind centerline concentrations as follows:

3.04 m generic downwind centerline air concentration = 2589.13 ug/m^3

3.04 m 242 lb/ac broadcast/tarp downwind centerline air concentration =

$$(1.602)(2589.13 \text{ ug/m}^3) = 4147.8 \text{ ug/m}^3$$

The 4147.8 ug/m^3 result is shown in column 4 of Table 3.

The next application rate factor is calculated.

The 175 lb/ac application rate adjustment =

$$(175/242) = 0.72$$

The 3.04 m 175 lb/ac broadcast/tarp downwind centerline concentration =

$$(0.72)(4147.8) = 2986.4$$

It is recommended that the air concentration estimates be rounded to 2 significant figures for use in the exposure appraisals.

The generic downwind centerline air concentrations for averaging times shorter than 24 hrs use the standard weather conditions for day (1.0 m/s and D stability) and night (1.0 m/s and F stability). The relationship between the flux profile as it was developed in the field study and the diurnal cycle is preserved. Thus, to produce the estimates, the highest day averaging time flux is matched with the day standard weather conditions, while the highest night averaging time flux is matched with the night standard weather conditions. The scenario producing the highest off-site air concentration is emphasized in the air concentration estimation. As an example of the shorter averaging time, Tables 4 and 5 show the day 1 hr TWA and the day 8 hr TWA (respectively) iodomethane air concentration estimates for the Manteca study.

The Generic day 1 hr air concentrations (Table 4) are produced with the standard day meteorological conditions (D-stability and 1 m/s wind speed) and generic flux of 100 ug/m^{2}sec.

The calculations are as follows:

The Manteca broadcast/tarp field study has a 1 hr TWA flux estimate = 481.0 ug/m^{2}sec (Table 2).

The flux adjustment factor (multiplier) is calculated as:

$$(481.0 \text{ ug/m}^2\text{s}) / (100 \text{ ug/m}^2\text{s}) = 4.810$$

This multiplier is applied to the downwind centerline concentrations as follows:

3.04 m generic downwind centerline air concentration = 5181.70 ug/m^3

3.04 m 242 lb/ac broadcast/tarp downwind centerline air concentration =

$$(4.810)(5181.70 \text{ ug/m}^3) = 24924.0 \text{ ug/m}^3$$

The 24924.000 ug/m^3 result is shown in column 4 of Table 4.

The results for the 175 lb/ac application rate are shown in column 5 of Table 4.

The 175 lb/ac application rate adjustment =

$$(175/242) = 0.72$$

The 3.04 m 175 lb/ac broadcast/tarp downwind centerline concentration =

$$(0.72)(24924.0) = 17945.3$$

The Generic day 8 hr air concentrations are produced with the standard day meteorological conditions (D-stability and 1 m/s wind speed) and generic flux of 100 ug/m^{2}sec. The Generic Day 8 hr air concentrations are the same as the Generic Day 1 hr TWA concentrations because the meteorological conditions and the generic flux are the same. The difference in final screening air concentrations is accounted for in the flux estimates, which are measured over different averaging times. The calculations are as follows:

The field study has an 8 hr flux estimate = 313.7 ug/m^{2}sec (Table 2).

The flux adjustment factor (multiplier) for the generic air concentrations is calculated as:

$$(313.7 \text{ ug/m}^2\text{s}) / (100 \text{ ug/m}^2\text{s}) = 3.14$$

This multiplier is applied to the downwind centerline concentrations as follows:

3.04 m generic downwind centerline air concentration = 5181.700 ug/m^3

3.04 m 242 lb/ac broadcast/tarp downwind centerline air concentration =

$$(3.14)(5181.70\text{ug/m}^3) = 16270.5 \text{ ug/m}^3$$

The 16270.500 ug/m^3 result is shown in column 4 of Table 5.

The next application rate factor is calculated.

The 175lb/ac application rate adjustment =

$$(175/242) = 0.72$$

The 3.04m 175lb/ac broadcast/tarp downwind centerline concentration =

$$(0.72)(16270.5) = 11714.8$$

Estimated air concentrations for all 8 iodomethane field studies under all meteorological and averaging time scenarios can be found in Appendix A.

Example 2: Chloropicrin

The full set of air concentration estimates developed for the WHS chloropicrin exposure appraisal are shown in Appendix B. Flux profiles for 5 application methods are available: broadcast/untarp, bed/untarp, bed/tarp, broadcast/tarp, and bed/drip/tarp. (Beard, 1996; Rotandardo, 2004). The broadcast/tarp application method has three flux profiles from three separate field studies in Arizona, Washington, and Florida. The Health Threshold averaging times for the chloropicrin exposure appraisal are 24, 6, and 1 hr. A summary of the field study application methods and rates and the flux estimates used for the chloropicrin exposure appraisal are shown in Table 6.

The process of producing the night 1 hr chloropicrin air concentration estimates for the Arizona broadcast/tarp application method and a 40 acre square field is illustrated in Table 7. The estimates for other application methods and locations can be found in Appendix B. The shortest sampling interval in the Arizona broadcast/tarp field study was 6 hrs. Consequently the 1 hr air concentration estimation will begin with results for the 6 hr averaging time. Then the peak-to-mean adjustment is made to the 6 hr air concentrations to obtain the 1 hr air concentration estimates. The WHS branch has requested the use of the peak-to-mean adjustment because chloropicrin is an irritant at low concentrations.

The third column of Table 7 shows the generic night 6 hr downwind centerline air concentrations at 6 distances between 3.04 m (10 ft) and 760 m (2500 ft) from the application edge. These air concentrations were produced at a receptor height of 1.2 m (representing the human breathing zone) using the ISCST3 model with inputs of a 40 acre square source, generic flux (100 ug/m^{2}sec), the standard weather data for 6 hr night conditions (1 m/s wind speed and F stability). These generic downwind centerline air concentrations can be used for any fumigant that uses a 6 hr threshold averaging time, and, in fact were used to produce the chloropicrin night 6 hr air concentration estimates (see Appendix B). These concentrations are considered 6 hr concentrations because the averaging time on the flux estimate is 6 hours. The 6 hr sampling interval is the shortest interval in the Beard et al. (1996) study. Hence, in this case it is used as the basis to generate 1 hr air concentrations using peak-to-mean adjustment methods (Barry, 2000b).

For this Arizona Broadcast/Tarp application method chloropicrin study, the adjustment factors are as follows (see Table 7):

The field study has a night 6 hr flux estimate = 30.15 ug/m^{2}sec

The 332 lb/acre application rate flux adjustment factor (multiplier) for the generic air concentrations is calculated as:

$$(30.15\ ug/m^2s) / (100\ ug/m^2s) = 0.3015\ (Table\ 6).$$

This flux adjustment multiplier is applied to the 6 hr generic downwind centerline concentrations as follows:

3.04 m generic downwind centerline 6 hr air concentration = 8329.80 ug/m^3

3.04 m 332 lb/ac broadcast/tarp downwind centerline air concentration =

$$(0.3015)(8329.80\ ug/m^3) = 2511.4\ ug/m^3$$

The night 6 hr air concentration estimate of 2511.4 ug/m^3 is shown for the downwind distance of 3.04 m in column 4 of Table 7. The next step is to develop the 1 hr air concentration estimate for this application rate by applying the peak-to-mean adjustment to the 6 hr estimates as follows:

The peak-to-mean adjustment for 6 hrs to 1 hr = 2.45

This multiplier is applied to the 6 hr air concentration estimates in column 4 of Table 7 as follows:

$$(2.45)*(2511.4) = 6153.0$$

Results of this adjustment are shown in column 5 of Table 7.

The next application rate is calculated.

The estimates for 350 lb/ac application rates are made as follows:

$$\text{application rate adjustment} = (350/332) = 1.0542$$

This adjustment is applied to the 332 lb/ac 6 hr TWA concentrations in column 4 of Table 7:

$$(1.0542)*(2511.4) = 2647.6$$

Results are shown in Column 6 of Table 7. The peak-to-mean adjustment of 2.45 is then applied to the 350 lb/acre 6 hr air concentration estimates shown in Column 6 to produced the 1 hr air concentration estimates:

$$(2.45)*(2647.6) = 6486.5$$

The 1 hr air concentration estimates for 350 lb/ac are shown in Column 7 or Table 7.

It is recommended that the air concentration estimates be rounded to 2 significant figures for use in the exposure appraisals.

Summary

These air dispersion modeling methods can be used to produce worst case exposure appraisal air concentration estimates for any fumigant that has a developed flux profile. The Health Threshold averaging time, application rates, and maximum field size are fumigant specific. However, the basic procedures would be similar.

References

Baker, F., L. Estigoy, M. Gillis, and T. Belcher, 2001. Environmental (off-site) monitoring anddirect flux/indirect flux determination of iodomethane (TM-425) under field conditions. PTRL Report No. 975W-1. DPR Vol. 52875-026 #185705.

Baker, F.C., L. Estigoy, and T.I. Belcher, 2002a. Environmental (off-site) monitoring and indirect flux determination of iodomethane (TM-425) under field conditions. PTRL Report #11420-W; MRID # 45879101. DPR Vol. 52875-046 #204110.

Baker, F.C., L. Estigoy, R. Reiss, M.D. Nelson, and M. Bolda, 2002b. Volatility of iodomethane (TM-425) under field conditions in California and Florida. PTRL Report #893-W1; DPR Vol. 52875-007 #185658.

Baker, F.C., L. Estigoy, and T.I. Belcher, 2003. Environmental (off-site) monitoring and indirect flux determination of iodomethane (TM-425) under field conditions following tarped/raised bed/drip irrigation application. PTRL Report #1198W-1; DPR Vol. 52875-056 #209311.

Baker, F., R.L. Hiler, and T. Belcher, 2004a. Worker and applicator exposure under field conditions during tarped/raised bed/ shallow shank injection application. PTRL West Inc. Study Project No. 1253W. DPR Vol. 52875-0064 #204111

Baker, F.C., R. Hiler, L. Estigoy, and T.I. Belcher, 2004b. Environmental (off-site) monitoring and indirect flux determination of iodomethane (TM-425) under field conditions following tarped/raised bed/drip irrigation application. PTRL Report #1256W-1; DPR Vol. 52875-063 #214831.

Baker, F.C., L. Estigoy, T.I. Belcher, and B. Lange, 2004c. Environmental (off-site) monitoring and indirect flux determination of iodomethane (TM-425) under field conditions following tarped/raised bed/drip irrigation application. PTRL Report #1315W-1; DPR Vol. 52875-089 #214831.

Barry, T. 2000a. Estimation of methyl isothiocyanate during the Earlimart incident. Memorandum dated November 14, 2000 to Kean Goh, Environmental Monitoring Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, California, 95812-4015. EM00-17.Available at: <http://em/localdocs/pubs/reviews/emreview.htm>.

Barry, T. 2000b. Peak –to-mean air concentration estimation for fumigants. Memorandum dated November 6, 2000 to Kean Goh, Environmental Monitoring Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, California, 95812-4015. EM00-12. Available at: <http://em/localdocs/pubs/reviews/em0012.pdf>.

Barry, T. 2000c. Metam-sodium shank application buffer zone development. Memorandum dated November 13, 2000 to Kean Goh, Environmental Monitoring Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, California, 95812-4015. EM01-01.Available at: <http://em/localdocs/pubs/reviews/em0101.pdf>.

Barry, T., R. Segawa, and P. Wofford. 2004. Development of Methyl Isothiocyanate buffer zones. Memorandum dated February 24, 2004 to John S. Sanders, Chief, Environmental Monitoring Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, California, 95812-4015. EM04-09. Available at: <http://em/localdocs/pubs/reviews/em0409.pdf>.

Beard, K.K., P.G. Murphy, D.D. Fontaine, and J.T. Weinberg. 1996. Monitoring of potential woker exposure, field flux and off-site air concentration during chloropicrin field application. Chloropicrin Manufacturers Task Force c/o/ Niklor Chemical Company, Inc. 2060 East 220the Street, Long Beach, California 90810. Laboratory Project Study ID HEH 160. Department of Pesticide Regulation, Registration Library Volume Number 199-072,

Csanady, G.T. 1973. Turbulent diffusion in the environment. Reidel Publishing Company. pp428.

Federal Register. 2005. Revision to the guideline on air quality models: Adoption of a preferred general purpose (flat and complex terrain) dispersion model and other revisions; final rule. Wednesday, November 9, 2005. Part III. Environmental Protection Agency. 40 CFR Part 51 (including Appendix W).

Johnson, B. and T. Barry. 2005. Estimation of methyl bromide flux for Siemer studies TC199.1 and F1.1 and use of standard weather conditions. Memorandum dated October 3, 2005 to Randy Segawa, Environmental Monitoring Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, California, 95812-4015. EM05-19. Available at: <http://em/localdocs/pubs/reviews/em0519.pdf>.

Johnson, B., T. Barry, and P Wofford. 1999. Workbook for Gaussian modeling analysis of air concentration measurements. Environmental Monitoring Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, California, 95812-0415. EH99-03. Available at: <http://www.cdpr.ca.gov/docs/emon/pubs/ehapreps/eh9903.pdf>.

Environmental Protection Agency. Office of Air Quality Planning and Standards. Emissions Monitoring and Analysis Division. Research Triangle Park, North Carolina. EPA-454/B-03-001.

Majewski, M.S., M.M. McChesney, J.E. Woodrow, H.H. Prueger, and J.N. Seiber. 1995. Aerodynamic measurements of methyl bromide volatilization from tarped and nontarped fields. J. Environ. Qual. Vol 24:742-752.

Pasquill, F. 1974 Atmospheric Diffusion. Second Edition. Wiley & Sons, Inc. pp429.

Rotondaro, A. 2004. Montioring of chloropicrin emissions from field and greenhouse drip irrigation applications, and implied worker inhalation exposures from applicaitn of chloropicring by shank injection, drip irrigation systems and at tree replant sites. Chloropicrin Manufacturer's Task Force. Department of Pesticide Regulation Data Volume 199-0112.

Scire, J.S., D.G. Strimaits and R.J. Yamartino. 2000. A user's guide to the CALPUFF dispersion model (version 5). Earth Tech, Inc. Concord, MA.

Segawa, R., T. Barry, and B. Johnson. 2000. Recommendations for methyl bromide buffer zones for field fumigations. Memorandum dated January 21, 2000 to John S. Sanders, Chief, Environmental Monitoring Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, California, 95812-4015. Available at: <http://www.cdpr.ca.gov/docs/specproj/tribal/recsformebrbuffzones.pdf>.

U.S. EPA. 1995. User's guide for the Industrial Source Complex (ISC3) dispersion models. Volume I–User's Instructions. U.S. Environmental Protection Agency. Office of Air Quality Planning and Standards. Emissions, Monitoring, and Analysis Division. Research Triangle Park, North Carolina 27711. EPA-454/B-95-003a.

U.S. EPA. 2007. Pesticide Fact Sheet. Iodomethane. Available at: <http://www.epa.gov/opprd001/factsheets/iodomethane.pdf>.

Table 1. Iodomethane studies used to estimate off-site air concentrations.

Study	Application Method	Study Treated Acre Application Rate[a]	Study Effective Broadcast Application Rate	175 lb/acre Adjustment Factor	87.5 lb/acre Adjustment Factor
Watsonville, California	Broadcast/Tarp	252	252	0.69	0.35
Manteca, California	Broadcast/Tarp	242	242	0.72	0.36
Oxnard, California	Bed/Tarp	244	171	1.02	0.51
Guadalupe, California	Bed/Tarp	179	143	1.22	0.61
LaSelva Beach, California	Drip/Tarp	235	162	1.08	0.54
Camarillo, California	Drip/Tarp	175	119	1.47	0.74
Guadalupe, California	Drip/Tarp	174	139	1.26	0.63

a. This application rate is the "treated acre" rate which is only the treated soil area excluding nontreated areas such as furrows. For broadcast application methods the Study Application Rate and the Study Effective Broadcast Application Rate will be the same. For bed type applications an adjustment must be made to the Study Application Rate to account for the portions of the field that are untreated. See the text for details of the calculation.

Table 2. Flux estimates for iodomethane studies used to estimate off-site air concentrations. With the exception of LaSelva Beach, the 8 hr and 1 hr scenarios both exhibited the highest flux and highest air concentrations during the day. Both day and night air concentrations were provided for the LaSelva Beach study (See Appendix A). The remainder of the studies focused on the day scenario.

Study Location	Application Method	Study Application Rate[a]	Study Effective Broadcast Application Rate	24 hr flux (ug/m^{2}sec) (hrs)[b]	8 hr flux (day) (ug/m^{2}sec) (hrs)	1 hr flux (day) (ug/m^{2}sec) (hrs)
Watsonville, California	Broadcast/ Tarp	252	252	120.9 (22.0)[b]	234.2 (8.1)	N/A[c]
Manteca, California	Broadcast/ Tarp	242	242	160.2 (19.0)	313.7 (8.0)	481.0 (3.3)
Oxnard, California	Bed/Tarp	244	171	186.4 (18.9)	265.6 (8.2)	535.0 (2.6)
Guadalupe, California	Bed/Tarp	179	143	117.7 (21.0)	153.1 (7.0)	171.4 (3.0)
LaSelva Beach, California	Drip/Tarp	235	162	87.6 (19.0)	187.5 (7.0)	198.0 (3.0)
Camarillo, California	Drip/Tarp	175	119	81.4 (22.0)	153.4 (8.0)	242.1 (4.0)
Guadalupe, California	Drip/Tarp	174	139	131.1 (23.0)	296.1 (7.0)	429.8 (3.0)

a. This application rate is the "treated acre" rate. For broadcast application methods the Study Application Rate and the Study Effective Broadcast Application Rate will be the same. For bed type applications an adjustment must be made to the Study Application Rate to account for the portions of the field that are untreated. See the text for details of the calculation.

b. The number in parentheses is the sampling interval duration in hrs.

c. It was not possible to estimate a 1 hr flux for this study.

Table 3. Screening 24 hr air concentration estimates for a square 40 acre iodomethane Manteca broadcast/tarp application. The generic 24 hr air concentrations are produced with the standard 24 hr meteorological conditions (C-stability and 1.4 m/s wind speed) and generic flux of 100 ug/m^{2}sec. The direct proportionality of air concentrations to flux and flux to application rate allows a simple adjustment of the generic 24 hr air concentrations to obtain air concentrations for other application rates and flux values. In this case, the field study had an effective broadcast application rate of 242 lb/ac with a flux of 160.2 ug/m^{2}sec. The first step adjusts for the flux by using the multiplier (160.2/100) = 1.602. Thus, for example, (1.602)(2589.13) = 4147.8. The second step adjusts for application rate. The 175 lb/ac application rate adjustment is (175/242) = 0.72 and the final screening air concentration estimate is obtained by (0.72)(4147.8) = 2986.4. Air concentration estimates should be rounded to two significant figures. Small rounding differences may occur.

Distance (ft)	Distance (m)	Generic 24 hr Air concentration (ug/m^3)	242 lb/ac application rate Air concentration (ug/m^3)	175 lb/ac application rate Air concentration (ug/m^3)
10	3.04	2589.13	4147.8	2986.4
50	15.2	2350.75	3765.9	2711.5
100	30.4	2018.72	3234.0	2328.5
300	91.2	1373.99	2201.1	1584.8
500	152	1083.24	1735.4	1249.5
2500	760	379.24	607.6	437.4

Table 4. Screening day 1 hr air concentration estimates for a square 40 acre iodomethane Manteca broadcast/tarp application. The generic day 1hr air concentrations are produced with the standard day meteorological conditions (D-stability and 1 m/s wind speed) and generic flux of 100 ug/m^{2}sec. The direct proportionality of air concentrations to flux and flux to application rate allows a simple adjustment of the generic day 1hr air concentrations to obtain air concentrations for other application rates and flux values. In this case, the field study had an effective broadcast application rate of 242 lb/ac with a 1 hr flux of 481.0 ug/m^{2}sec. The first step adjusts for the flux by using the multiplier (481.0/100) = 4.81. Thus, for example, (4.81)(5181.70) = 24924.00. The second step adjusts for application rate. The 175 lb/ac application rate adjustment is (175/242) = 0.72 and the final screening air concentration estimate is obtained by (0.72)(24924.0) = 17945.3. Air concentration estimates should be rounded to two significant figures. Small rounding differences may occur.

Distance (ft)	Distance (m)	Generic Day 1 hr Air Concentration (ug/m^3)	242 lb/ac application rate Air concentration (ug/m^3)	175 lb/ac application rate Air concentration (ug/m^3)
10	3.04	5181.700	24924.00	17945.30
50	15.2	4838.100	23271.30	16755.30
100	30.4	4444.500	21378.00	15392.20
300	91.2	3178.900	15290.50	11009.20
500	152	2560.200	12314.60	8866.50
2500	760	1044.900	5026.00	3618.70

Table 5. Screening day 8 hr air concentration estimation for a square 40 acre iodomethane Manteca broadcast/tarp application. The generic day 8 hr air concentrations are produced with the standard day meteorological conditions (D-stability and 1 m/s wind speed) and generic flux of 100 ug/m^{2}sec. The generic day 8 hr air concentrations are the same as the generic day 1 hr air concentrations because the meteorological conditions and the generic flux are the same. The difference in air concentrations is accounted for in the flux estimates, which are measured over different averaging times. The direct proportionality of air concentrations to flux and flux to application rate allows a simple adjustment of the generic day 8 hr air concentrations to obtain air concentrations for other application rates and flux values. In this case, the field study had an effective broadcast application rate of 242 lb/ac with a day 8 hr flux of 313.7 ug/m^{2}sec. The first step adjusts for the flux by using the multiplier (313.7/100) = 3.14. Thus, for example, (3.14)(5181.70) = 16270.5. The second step adjusts for application rate. The 175 lb/ac application rate adjustment is (175/242) = 0.72 and the final screening air concentration estimate is obtained by (0.72)(16270.5) = 11714.8. Air concentration estimates should be rounded to two significant figures. Small rounding differences may occur.

Distance (ft)	Distance (m)	Generic Day 8 hr Air Concentration (ug/m^3)	242 lb/ac application rate Air concentration (ug/m^3)	175 lb/ac application rate Air concentration (ug/m^3)
10	3.04	5181.70	16270.5	11714.8
50	15.2	4838.10	15191.6	10938.0
100	30.4	4444.50	13955.7	10048.1
300	91.2	3178.90	9981.7	7186.9
500	152	2560.20	8039.0	5788.1
2500	760	1044.90	3281.0	2362.3

Table 6. Flux estimates for chloropicrin studies used to estimate off-site air concentrations. With the exception of the California Bed/Drip/Tarp study, all sampling intervals were either 6 or 12 hrs.

Study Location	Application Method	Study Application Rate[a] (lb/acre)	Study Effective Broadcast Application Rate (lb/acre)	24 hr flux (ug/m^2sec)	6 hr flux (day) (ug/m^2sec)[b]	6 hr flux (night) (ug/m^2sec)[b]
Arizona	Broadcast/Untarp	171	171	86	50	180
Arizona	Bed/Untarp	149	86	66	114	113
Arizona	Bed/Tarp	377	189	108	132	142
Arizona	Broadcast/Tarp	332	332	111	211	30
Washington	Broadcast/Tarp	343	343	34	70	20
Florida	Broadcast/Tarp	346	346	28	58	22
California	Bed/Drip/Tarp	300	156	22	47[c]	5[c]

a. This application rate is the "treated acre" rate. For broadcast application methods the Study Application Rate and the Study Effective Broadcast Application Rate will be the same. For bed type applications an adjustment must be made to the Study Application Rate to account for the portions of the field that are untreated
b. For 1 hr concentrations, the 6 hr flux was used to estimate 6 hr air concentrations. Then a peak-to-mean adjustment was made to the 6 hr air concentrations to derive the 1 hr air concentrations.
c. These two flux estimates are 8 hr due to the sampling intervals in the study

Table 7. Screening night 6 hr and night 1 hr air concentration estimates for a square 40 acre chloropicrin Arizona broadcast/tarp application. In this field study (Beard, 1996) the shortest sampling interval averaging time was 6 hrs. So, the generic night 1 hr air concentrations were produced starting with the standard 6 hr meteorological conditions (F-stability and 1 m/s wind speed) and generic flux of 100 ug/m^{2}sec. A peak-to-mean adjustment (Barry, 2000b) is made to obtain 1 hr generic air concentration estimates. Direct proportionality of air concentrations to flux and flux to application rate allows a simple adjustment of the generic night 6 hr air concentrations to obtain air concentrations for other application rates and flux values. In this case, the field study had an effective broadcast application rate of 332 lb/ac with a flux of 30.15 ug/m^{2}sec. The first step adjusts for application rate by using the multiplier (30.15/100) = 0.3015. Thus, for example, (0.3015)(8329.80) = 2511.4. The 350lb/ac application rate adjustment is (350/332) = 1.0542 and the air concentration estimate is obtained by (1.0542)(2511.4) = 2647.6. The peak-to-mean adjustment was made to the 6-hr estimates: for the 332 lb/acre application rate (2.45)(2511.4) = 6153.0 and for the 350 lb/acre application rate (2.45)(2647.6) = 6486.5. Air concentration estimates should be rounded to 2 significant figures. Small rounding differences may occur.

Distance (ft)	Distance (m)	Generic Night 6 hr Air Concentration (ug/m^3)	332 lb/ac Application Rate Night 6 hr Air Concentration (ug/m^3)	332 lb/ac Application Rate Peak-to-Mean Adjusted Night 1 hr Air Concentration (ug/m^3)	350 lb/ac Application Rate Night 6 hr Air Concentration (ug/m^3)	350 lb/ac Application Rate Peak-to-Mean Adjusted Night 1 hr Air Concentration (ug/m^3)
10	3.04	8329.8	2511.4	6153.0	2647.6	6486.5
50	15.2	8285.1	2498.0	6120.0	2633.3	6451.7
100	30.4	8058.3	2429.6	5952.5	2561.3	6275.1
300	91.2	6419.2	1935.4	4741.7	2040.3	4998.7
500	152	5341.6	1610.5	3945.7	1697.8	4159.6
2500	760	2377.9	716.9	1756.5	755.8	1851.7

Iodomethane
40ac 1hr day

All Concentrations are ug/m3**
Concentrations should be rounded to 2 significant figures for use in the Exposure Appraisal

			vol 52875-007 Watsonville broad/tarp		**vol 52875-026 Manteca broad/tarp**		**vol 52875-046 Oxnard bed/tarp**			**vol 52875-056 LaSelva Beach drip/tarp**			**vol 52875-063 Camarillo drip/tarp**			**vol 52875-064 Guadalupe bed/tarp**			**vol 52875-089 Guadalupe drip/tarp**		
distance (	**distance (r**	**Nominal flux concentration 100ug/m**2/sec**	**252 lb/ac**	**175 lb/ac**	**242 lb/ac**	**175 lb/ac**	**171 lb/ac**	**175 lb/ac**	**87.5 lb/ac**	**162 lb/ac**	**175 lb/ac**	**87.5 lb/ac**	**119 lb/ac**	**175 lb/ac**	**87.5 lb/ac**	**143 lb/ac**	**175 lb/ac**	**87.5 lb/ac**	**139 lb/ac**	**175 lb/ac**	**87.5 lb/ac**
10	3.04	5181.70	N/A	N/A	24924.0	17945.3	27722.1	28276.5	14138.3	10259.8	11080.5	5540.3	12539.7	18433.4	9279.4	8860.7	10810.1	5405.0	22281.3	28074.5	14037.2
50	15.2	4838.10			23271.3	16755.3	25883.8	26401.5	13200.8	9579.4	10345.8	5172.9	11708.2	17211.1	8664.1	8273.2	10093.2	5046.6	20803.8	26212.8	13106.4
100	30.4	4444.50			21378.0	15392.2	23778.1	24253.6	12126.8	8800.1	9504.1	4752.1	10755.7	15810.9	7959.2	7600.1	9272.1	4636.1	19111.3	24080.3	12040.2
300	91.2	3178.90			15290.5	11009.2	17007.1	17347.3	8673.6	6294.2	6797.8	3398.9	7692.9	11308.6	5692.8	5435.9	6631.8	3315.9	13669.3	17223.3	8611.6
500	152	2560.20			12314.6	8866.5	13697.1	13971.0	6985.5	5069.2	5474.7	2737.4	6195.7	9107.7	4584.8	4377.9	5341.1	2670.5	11008.9	13871.2	6935.6
2500	760	1044.90			5026.0	3618.7	5590.2	5702.0	2851.0	2068.9	2234.4	1117.2	2528.7	3717.1	1871.2	1786.8	2179.9	1089.9	4493.1	5661.3	2830.6
		flux adjustment*			4.81		5.35			1.98			2.42			1.71			4.3		
		app rate multiplier#				0.72		1.02	0.51		1.08	0.54		1.47	0.74		1.22	0.61		1.26	0.63

* this adjustment converts the 100ug.m**2/sec to the flux from the study e.g.: (4.81)*(5181.7) = 24924
\# this multiplier scales the concentrations from the study to the desired application rate e.g.: (0.72)*(24924) = 17945
the application rate multiplier is calculated as: 175/242 = 0.72 and scales the application rate down from 242lb/ac to 175lb/ac
Any additional effective broadcast application rates can be obtained by calculating the app rate multiplier.
Example: drip/tarp 87.5 app rate multiplier = 87.5/171 = 0.51
the concentrations in the "drip/tarp 171" column multipled by 0.51 gives estimated concentration for 87.5lb effective broadcast
this scenario would be 175lbs in the beds and beds 50% of the field area.

Chloropicrin
40ac 1hr night

All Concentrations are ug/m3**

			vol 199-073			vol 199-073			vol 199-073			vol 199-073			vol 199-073			vol 199-073			Vol 199-112	
		24hr	**AZ broad/untarp**			**AZ bed/untarp**			**AZ bed/tarp**			**AZ broad/tarp**			**WA broad/tarp**			**FL broad/tarp**			**CA bed/drip/tarp**	
feet	**meters**	**generic conc**	**171 lb/ac**	**175 lb/ac**	**500 lb/ac**	**86 lb/ac**	**175 lb/ac**	**250 lb/ac**	**189 lb/ac**	**350 lb/ac**	**500 lb/ac**	**332 lb/ac**	**350 lb/ac**	**500 lb/ac**	**343 lb/ac**	**350 lb/ac**	**500 lb/ac**	**346 lb/ac**	**350 lb/ac**	**500 lb/ac**	**156 lb/ac**	**300 lb/ac**
10	3.04	8329.800	36793.6	37654.6	107584.5	23020.2	46846.2	66919.8	29005.9	53716.0	76735.1	6153.0	6486.5	9266.4	4063.2	4146.1	5923.0	4428.5	4479.9	6399.7	1071.4	2060.4
50	15.2	8285.100	36596.2	37452.5	107007.2	22896.7	46594.8	66560.7	28850.3	53427.8	76323.3	6120.0	6451.7	9216.7	4041.4	4123.9	5891.2	4404.8	4455.9	6365.3	1065.7	2049.4
100	30.4	8058.300	35594.4	36427.3	104077.9	22269.9	45319.3	64738.7	28060.5	51965.2	74234.0	5952.5	6275.1	8964.4	3930.8	4011.0	5729.9	4284.2	4333.9	6191.1	1036.5	1993.3
300	91.2	6419.200	28354.3	29017.8	82907.9	17740.1	36101.1	51570.5	22352.8	41395.2	59134.4	4741.7	4998.7	7141.0	3131.3	3195.1	4564.4	3412.8	3452.4	4931.8	825.7	1587.8
500	152	5341.600	23594.4	24146.5	68990.0	14762.0	30040.8	42913.3	18600.4	34446.2	49207.5	3945.7	4159.6	5942.2	2605.6	2658.8	3798.2	2839.9	2872.8	4103.9	687.1	1321.3
2500	760	2377.900	10503.4	10749.2	30712.0	6571.6	13373.1	19103.5	8280.3	15334.3	21905.5	1756.5	1851.7	2645.3	1159.9	1183.6	1690.8	1264.2	1278.9	1826.9	305.9	588.2
		flux adjustment**	1.8029			1.128			1.4213			0.3015			0.1991			0.217			0.0525	
		peak-to-mean adjustment***	2.450			2.450			2.450			2.450			2.450			2.450			2.450	
		app rate multiplier#		1.0234	2.924		2.035	2.907		1.8519	2.6455		1.0542	1.506		1.0204	1.4577		1.0116	1.4451		1.9231

* These estimated air concentrations involve 2 adjustments to the 6hr TWA air concentrations: 1) flux and 2) peak-to-mean for 6 hr to 1 hr.
** this adjustment converts the 100ug.m**2/sec to the flux from the study e.g.: (1.8029)**(8330) = 15018.16
*** note that the Peak-to-Mean 100ug/m**2/sec concentrations were obtained by adjusting the 6hr air concentrations with the peak-to-mean adjustment of 2.45:
(15018.16)*(2.45) = 36794.49

this multiplier scales the concentrations from the study to the desired application rate e.g.: (1.0234)*(36794) = 37655
the multiplier is calculated as: 175/171 = 1.0234 and scales the application rate up from 171lb/ac to 175lb/ac
Any additional broadcast application rates can be obtained by calculating the app rate multiplier.
Example: bed/tarp 250 app rate multiplier = 250/189 = 1.323
the concentrations in the "bed/tarp 189" column multipled by 1.323 gives estimated concentration for 250lb effective broadcast
this scenario would be 500lbs in the beds and beds 50% of the field area.

Concentrations should be rounded to 2 significant figures for use in the Exposure Appraisal

Chloropcirin
40ac 6hr day

All Concentrations are ug/m3**

			vol 199-073			vol 199-073			vol 199-073			vol 199-073			vol 199-073			vol 199-073			Vol 199-112	
		24hr	AZ broad/untarp			AZ bed/untarp			AZ bed/tarp			AZ broad/tarp			WA broad/tarp			FL broad/tarp			CA bed/drip/tarp	
feet	**meters**	**generic conc**	**171 lb/ac**	**175 lb/ac**	**500 lb/ac**	**86 lb/ac**	**175 lb/ac**	**250 lb/ac**	**189 lb/ac**	**350 lb/ac**	**500 lb/ac**	**332 lb/ac**	**350 lb/ac**	**500 lb/ac**	**343 lb/ac**	**350 lb/ac**	**500 lb/ac**	**346 lb/ac**	**350 lb/ac**	**500 lb/ac**	**156 lb/ac**	**300 lb/ac**
10	3.04	5181.7	2567.5	2627.6	7507.5	5912.8	12032.6	17188.6	6823.3	12636.0	18050.9	10933.9	11526.5	16466.5	3649.0	3723.4	5319.1	2995.0	3029.8	4328.1	2419.9	4653.6
50	15.2	4838.1	2397.3	2453.4	7009.6	5520.8	11234.7	16048.8	6370.8	11798.1	16854.0	10208.9	10762.2	15374.6	3407.0	3476.5	4966.4	2796.4	2828.9	4041.1	2259.4	4345.0
100	30.4	4444.5	2202.2	2253.8	6439.4	5071.6	10320.7	14743.2	5852.5	10838.3	15482.8	9378.3	9886.6	14123.8	3129.8	3193.7	4562.3	2568.9	2598.7	3712.3	2075.6	3991.6
300	91.2	3178.9	1575.1	1612.0	4605.7	3627.4	7381.8	10545.0	4186.0	7752.0	11074.0	6707.8	7071.4	10101.9	2238.6	2284.2	3263.2	1837.4	1858.7	2655.2	1484.5	2854.9
500	152	2560.2	1268.6	1298.3	3709.3	2921.4	5945.1	8492.6	3371.3	6243.3	8918.7	5402.3	5695.1	8135.8	1802.9	1839.7	2628.1	1479.8	1497.0	2138.5	1195.6	2299.3
2500	760	1044.9	517.7	529.9	1513.9	1192.3	2426.4	3466.1	1375.9	2548.1	3640.0	2204.8	2324.3	3320.5	735.8	750.8	1072.6	604.0	611.0	872.8	488.0	938.4
		flux adjustment*	0.4955			1.1411			1.3168			2.1101			0.7042			0.578			0.467	
		app rate multiplier#		1.0234	2.924		2.035	2.907		1.8519	2.6455		1.0542	1.506		1.0204	1.4577		1.0116	1.4451		1.9231

* this adjustment converts the 100ug.m**2/sec to the flux from the study e.g.: (0.4955)*(5182) = 2568
# this multiplier scales the concentrations from the study to the desired application rate e.g.: (1.0234)*(2568) = 2628
the multiplier is calculated as: 175/171 = 1.0234 and scales the application rate up from 171lb/ac to 175lb/ac
Any additional broadcast application rates can be obtained by calculating the app rate multiplier.
Example: bed/tarp 250 app rate multiplier = 250/189 = 1.323
the concentrations in the "bed/tarp 189" column multipled by 1.323 gives estimated concentration for 250lb effective broadcast
this scenario would be 500lbs in the beds and beds 50% of the field area.

Concentrations should be rounded to 2 significant figures for use in the Exposure Appraisal

Iodomethane
40ac 24hr

All Concentrations are ug/m3**
Concentrations should be rounded to 2 significant figures for use in the Exposure Appraisal

			vol 52875-007		vol 52875-026		vol 52875-046			vol 52875-056			vol 52875-063			vol 52875-064			vol 52875-089		
		Nominal flux	Watsonville		Manteca		Oxnard			LaSelva Beach			Camarillo			Guadalupe			Guadalupe		
		concentration	broad/tarp		broad/tarp		bed/tarp			drip/tarp			drip/tarp			bed/tarp			drip/tarp		
distance (	distance (r	100ug/m**2/sec	252 lb/ac	175 lb/ac	242 lb/ac	175 lb/ac	171 lb/ac	175 lb/ac	87.5 lb/ac	162 lb/ac	175 lb/ac	87.5 lb/ac	119 lb/ac	175 lb/ac	87.5 lb/ac	143 lb/ac	175 lb/ac	87.5 lb/ac	139 lb/ac	175 lb/ac	87.5 lb/ac
10	3.04	2589.13	3130.3	2159.9	4147.8	2986.4	4826.1	4922.7	2461.3	2268.1	2449.5	1224.8	2107.6	3098.1	1559.6	3047.4	3717.8	1858.9	3394.4	4276.9	2138.4
50	15.2	2350.75	2842.1	1961.0	3765.9	2711.5	4381.8	4469.4	2234.7	2059.3	2224.0	1112.0	1913.5	2812.9	1416.0	2766.8	3375.5	1687.8	3081.8	3883.1	1941.6
100	30.4	2018.72	2440.6	1684.0	3234.0	2328.5	3762.9	3838.2	1919.1	1768.4	1909.9	954.9	1643.2	2415.6	1216.0	2376.0	2898.8	1449.4	2646.5	3334.6	1667.3
300	91.2	1373.99	1661.2	1146.2	2201.1	1584.8	2561.1	2612.3	1306.2	1203.6	1299.9	650.0	1118.4	1644.1	827.6	1617.2	1973.0	986.5	1801.3	2269.6	1134.8
500	152	1083.24	1309.6	903.7	1735.4	1249.5	2019.2	2059.6	1029.8	948.9	1024.8	512.4	881.8	1296.2	652.5	1275.0	1555.5	777.7	1420.1	1789.4	894.7
2500	760	379.24	458.5	316.4	607.6	437.4	706.9	721.1	360.5	332.2	358.8	179.4	308.7	453.8	228.4	446.4	544.6	272.3	497.2	626.5	313.2
		flux adjustment*	1.209		1.602		1.864			0.876			0.814			1.177			1.311		
		app rate multiplier#		0.69		0.72		1.02	0.51		1.08	0.54		1.47	0.74		1.22	0.61		1.26	0.63

* this adjustment converts the 100ug.m**2/sec to the flux from the study e.g.: (1.209)*(2517.4) = 3043.5
\# this multiplier scales the concentrations from the study to the desired application rate e.g.: (0.69)*(3043.5) = 2100.0
the application rate multiplier is calculated as: 175/252 = 0.69 and scales the application rate down from 252lb/ac to 175lb/ac
Any additional effective broadcast application rates can be obtained by calculating the app rate multiplier.
Example: drip/tarp 87.5 app rate multiplier = 87.5/171 = 0.51
the concentrations in the "drip/tarp 171" column multipled by 0.51 gives estimated concentration for 87.5lb effective broadcast
this scenario would be 175lbs in the beds and beds 50% of the field area.

Chloropicrin
40ac 1hr day

All Concentrations are ug/m3**

			vol 199-073			vol 199-073			vol 199-073			vol 199-073			vol 199-073			vol 199-073			Vol 199-112	
		24hr	AZ broad/untarp			AZ bed/untarp			AZ bed/tarp			AZ broad/tarp			WA broad/tarp			FL broad/tarp			CA bed/drip/tarp	
feet	**meters**	**generic conc**	**171 lb/ac**	**175 lb/ac**	**500 lb/ac**	**86 lb/ac**	**175 lb/ac**	**250 lb/ac**	**189 lb/ac**	**350 lb/ac**	**500 lb/ac**	**332 lb/ac**	**350 lb/ac**	**500 lb/ac**	**343 lb/ac**	**350 lb/ac**	**500 lb/ac**	**346 lb/ac**	**350 lb/ac**	**500 lb/ac**	**156 lb/ac**	**300 lb/ac**
10	3.04	5181.7	6290.5	6437.7	18393.3	14486.5	29479.9	42112.1	16717.0	30958.2	44224.8	26788.1	28240.0	40342.8	8939.9	9122.3	13031.7	7337.8	7422.9	10603.9	5928.6	11401.4
50	15.2	4838.1	5873.3	6010.8	17173.6	13525.9	27525.1	39319.7	15608.5	28905.4	41292.2	25011.7	26367.4	37667.7	8347.1	8517.4	12167.6	6851.2	6930.7	9900.7	5535.5	10645.3
100	30.4	4444.5	5395.5	5521.8	15776.5	12425.5	25285.8	36120.8	14338.7	26553.8	37932.9	22976.9	24222.3	34603.3	7668.1	7824.5	11177.7	6293.9	6366.9	9095.3	5085.2	9779.3
300	91.2	3178.9	3859.1	3949.4	11284.0	8887.2	18085.5	25835.2	10255.6	18992.4	27131.3	16434.1	17324.8	24749.8	5484.5	5596.4	7994.8	4501.6	4553.9	6505.3	3637.1	6994.6
500	152	2560.2	3108.0	3180.7	9087.8	7157.5	14565.6	20807.0	8259.6	15296.0	21850.8	13235.6	13952.9	19932.8	4417.1	4507.2	6438.8	3625.5	3667.6	5239.2	2929.3	5633.2
2500	760	1044.9	1268.5	1298.2	3709.0	2921.2	5944.7	8492.0	3371.0	6242.8	8918.0	5401.9	5694.6	8135.2	1802.8	1839.5	2627.9	1479.7	1496.8	2138.3	1195.5	2299.1
		flux adjustment*	0.4955			1.1411			1.3168			2.1101			0.7042			0.578			0.467	
		peak-to-mean adjustment***	2.450			2.450			2.450			2.450			2.450			2.450			2.450	
		app rate multiplier#		1.0234	2.924		2.035	2.907		1.8519	2.6455		1.0542	1.506		1.0204	1.4577		1.0116	1.4451		1.9231

* These estimated air concentrations involve 2 adjustments to the 6hr TWA air concentrations: 1) flux and 2) peak-to-mean for 6 hr to 1 hr.
** this adjustment converts the 100ug.m**2/sec to the flux from the study e.g.: (0.4955)*(5181.7) = 2567.532
*** note that the Peak-to-Mean 100ug/m**2/sec concentrations were obtained by adjusting the 6hr air concentrations with the peak-to-mean adjustment of 2.45:
(2567.532)*(2.45) = 6290.45

this multiplier scales the concentrations from the study to the desired application rate e.g.: (1.0234)*(6290) = 6438
the multiplier is calculated as: 175/171 = 1.0234 and scales the application rate up from 171lb/ac to 175lb/ac
Any additional broadcast application rates can be obtained by calculating the app rate multiplier.
Example: bed/tarp 250 app rate multiplier = 250/189 = 1.323
the concentrations in the "bed/tarp 189" column multipled by 1.323 gives estimated concentration for 250lb effective broadcast
this scenario would be 500lbs in the beds and beds 50% of the field area.

Concentrations should be rounded to 2 significant figures for use in the Exposure Appraisal

Chloropicrin
40ac 1hr night

All Concentrations are ug/m3**

			vol 199-073			vol 199-073			vol 199-073			vol 199-073			vol 199-073			vol 199-073			Vol 199-112	
		24hr	**AZ broad/untarp**			**AZ bed/untarp**			**AZ bed/tarp**			**AZ broad/tarp**			**WA broad/tarp**			**FL broad/tarp**			**CA bed/drip/tarp**	
feet	**meters**	**generic conc**	**171 lb/ac**	**175 lb/ac**	**500 lb/ac**	**86 lb/ac**	**175 lb/ac**	**250 lb/ac**	**189 lb/ac**	**350 lb/ac**	**500 lb/ac**	**332 lb/ac**	**350 lb/ac**	**500 lb/ac**	**343 lb/ac**	**350 lb/ac**	**500 lb/ac**	**346 lb/ac**	**350 lb/ac**	**500 lb/ac**	**156 lb/ac**	**300 lb/ac**
10	3.04	8329.800	36793.6	37654.6	107584.5	23020.2	46846.2	66919.8	29005.9	53716.0	76735.1	6153.0	6486.5	9266.4	4063.2	4146.1	5923.0	4428.5	4479.9	6399.7	1071.4	2060.4
50	15.2	8285.100	36596.2	37452.5	107007.2	22896.7	46594.8	66560.7	28850.3	53427.8	76323.3	6120.0	6451.7	9216.7	4041.4	4123.9	5891.2	4404.8	4455.9	6365.3	1065.7	2049.4
100	30.4	8058.300	35594.4	36427.3	104077.9	22269.9	45319.3	64738.7	28060.5	51965.2	74234.0	5952.5	6275.1	8964.4	3930.8	4011.0	5729.9	4284.2	4333.9	6191.1	1036.5	1993.3
300	91.2	6419.200	28354.3	29017.8	82907.9	17740.1	36101.1	51570.5	22352.8	41395.2	59134.4	4741.7	4998.7	7141.0	3131.3	3195.1	4564.4	3412.8	3452.4	4931.8	825.7	1587.8
500	152	5341.600	23594.4	24146.5	68990.0	14762.0	30040.8	42913.3	18600.4	34446.2	49207.5	3945.7	4159.6	5942.2	2605.6	2658.8	3798.2	2839.9	2872.8	4103.9	687.1	1321.3
2500	760	2377.900	10503.4	10749.2	30712.0	6571.6	13373.1	19103.5	8280.3	15334.3	21905.5	1756.5	1851.7	2645.3	1159.9	1183.6	1690.8	1264.2	1278.9	1826.9	305.9	588.2
		flux adjustment**	1.8029			1.128			1.4213			0.3015			0.1991			0.217			0.0525	
		peak-to-mean adjustment***	2.450			2.450			2.450			2.450			2.450			2.450			2.450	
		app rate multiplier#		1.0234	2.924		2.035	2.907		1.8519	2.6455		1.0542	1.506		1.0204	1.4577		1.0116	1.4451		1.9231

* These estimated air concentrations involve 2 adjustments to the 6hr TWA air concentrations: 1) flux and 2) peak-to-mean for 6 hr to 1 hr.
** this adjustment converts the 100ug.m**2/sec to the flux from the study e.g.: (1.8029)**(8330) = 15018.16
*** note that the Peak-to-Mean 100ug/m**2/sec concentrations were obtained by adjusting the 6hr air concentrations with the peak-to-mean adjustment of 2.45:
(15018.16)*(2.45) = 36794.49

this multiplier scales the concentrations from the study to the desired application rate e.g.: (1.0234)*(36794) = 37655
the multiplier is calculated as: 175/171 = 1.0234 and scales the application rate up from 171lb/ac to 175lb/ac
Any additional broadcast application rates can be obtained by calculating the app rate multiplier.
Example: bed/tarp 250 app rate multiplier = 250/189 = 1.323
the concentrations in the "bed/tarp 189" column multipled by 1.323 gives estimated concentration for 250lb effective broadcast
this scenario would be 500lbs in the beds and beds 50% of the field area.

Concentrations should be rounded to 2 significant figures for use in the Exposure Appraisal

Iodomethane
40ac 8hr day

All Concentrations are ug/m3**
Concentrations should be rounded to 2 significant figures for use in the Exposure Appraisal

			vol 52875-007		**vol 52875-026**		**vol 52875-046**			**vol 52875-056**			**vol 52875-063**			**vol 52875-064**			**vol 52875-089**		
		Nominal flux concentration	**Watsonville broad/tarp**		**Manteca broad/tarp**		**Oxnard bed/tarp**			**LaSelva Beach drip/tarp**			**Camarillo drip/tarp**			**Guadalupe bed/tarp**			**Guadalupe drip/tarp**		
distance (	**distance (r**	**100ug/m**2/sec**	**252 lb/ac**	**175 lb/ac**	**242 lb/ac**	**175 lb/ac**	**171 lb/ac**	**175 lb/ac**	**87.5 lb/ac**	**162 lb/ac**	**175 lb/ac**	**87.5 lb/ac**	**119 lb/ac**	**175 lb/ac**	**87.5 lb/ac**	**143 lb/ac**	**175 lb/ac**	**87.5 lb/ac**	**139 lb/ac**	**175 lb/ac**	**87.5 lb/ac**
10	3.04	5181.70	12125.2	8366.4	16270.5	11714.8	13783.3	14059.0	7029.5	9689.8	10465.0	5232.5	7928.0	11654.2	5866.7	7928.0	9672.2	4836.1	15337.8	19325.7	9662.8
50	15.2	4838.10	11321.2	7811.6	15191.6	10938.0	12869.3	13126.7	6563.4	9047.3	9771.0	4885.5	7402.3	10881.4	5477.7	7402.3	9030.8	4515.4	14320.8	18044.2	9022.1
100	30.4	4444.50	10400.1	7176.1	13955.7	10048.1	11822.4	12058.8	6029.4	8311.2	8976.1	4488.1	6800.1	9996.1	5032.1	6800.1	8296.1	4148.1	13155.7	16576.2	8288.1
300	91.2	3178.90	7438.6	5132.7	9981.7	7186.9	8455.9	8625.0	4312.5	5944.5	6420.1	3210.1	4863.7	7149.7	3599.2	4863.7	5933.7	2966.9	9409.5	11856.0	5928.0
500	152	2560.20	5990.9	4133.7	8039.0	5788.1	6810.1	6946.3	3473.2	4787.6	5170.6	2585.3	3917.1	5758.1	2898.7	3917.1	4778.9	2389.4	7578.2	9548.5	4774.3
2500	760	1044.90	2445.1	1687.1	3281.0	2362.3	2779.4	2835.0	1417.5	1954.0	2110.3	1055.1	1598.7	2350.1	1183.0	1598.7	1950.4	975.2	3092.9	3897.1	1948.5
		flux adjustment*	2.34		3.14		2.66			1.87			1.53			1.53			2.96		
		app rate multiplier#		0.69		0.72		1.02	0.51		1.08	0.54		1.47	0.74		1.22	0.61		1.26	0.63

* this adjustment converts the 100ug.m**2/sec to the flux from the study e.g.: (2.34)*(5181.7) = 12125
\# this multiplier scales the concentrations from the study to the desired application rate e.g.: (0.69)*(12125) = 8366
the application rate multiplier is calculated as: 175/252 = 0.69 and scales the application rate down from 252lb/ac to 175lb/ac
Any additional effective broadcast application rates can be obtained by calculating the app rate multiplier.
Example: drip/tarp 87.5 app rate multiplier = 87.5/171 = 0.51
the concentrations in the "drip/tarp 171" column multipled by 0.51 gives estimated concentration for 87.5lb effective broadcast
this scenario would be 175lbs in the beds and beds 50% of the field area.

Chloropcirin
40ac 6hr day

All Concentrations are ug/m3**

			vol 199-073			vol 199-073			vol 199-073			vol 199-073			vol 199-073			vol 199-073			Vol 199-112	
		24hr	AZ broad/untarp			AZ bed/untarp			AZ bed/tarp			AZ broad/tarp			WA broad/tarp			FL broad/tarp			CA bed/drip/tarp	
feet	**meters**	**generic conc**	**171 lb/ac**	**175 lb/ac**	**500 lb/ac**	**86 lb/ac**	**175 lb/ac**	**250 lb/ac**	**189 lb/ac**	**350 lb/ac**	**500 lb/ac**	**332 lb/ac**	**350 lb/ac**	**500 lb/ac**	**343 lb/ac**	**350 lb/ac**	**500 lb/ac**	**346 lb/ac**	**350 lb/ac**	**500 lb/ac**	**156 lb/ac**	**300 lb/ac**
10	3.04	5181.7	2567.5	2627.6	7507.5	5912.8	12032.6	17188.6	6823.3	12636.0	18050.9	10933.9	11526.5	16466.5	3649.0	3723.4	5319.1	2995.0	3029.8	4328.1	2419.9	4653.6
50	15.2	4838.1	2397.3	2453.4	7009.6	5520.8	11234.7	16048.8	6370.8	11798.1	16854.0	10208.9	10762.2	15374.6	3407.0	3476.5	4966.4	2796.4	2828.9	4041.1	2259.4	4345.0
100	30.4	4444.5	2202.2	2253.8	6439.4	5071.6	10320.7	14743.2	5852.5	10838.3	15482.8	9378.3	9886.6	14123.8	3129.8	3193.7	4562.3	2568.9	2598.7	3712.3	2075.6	3991.6
300	91.2	3178.9	1575.1	1612.0	4605.7	3627.4	7381.8	10545.0	4186.0	7752.0	11074.0	6707.8	7071.4	10101.9	2238.6	2284.2	3263.2	1837.4	1858.7	2655.2	1484.5	2854.9
500	152	2560.2	1268.6	1298.3	3709.3	2921.4	5945.1	8492.6	3371.3	6243.3	8918.7	5402.3	5695.1	8135.8	1802.9	1839.7	2628.1	1479.8	1497.0	2138.5	1195.6	2299.3
2500	760	1044.9	517.7	529.9	1513.9	1192.3	2426.4	3466.1	1375.9	2548.1	3640.0	2204.8	2324.3	3320.5	735.8	750.8	1072.6	604.0	611.0	872.8	488.0	938.4
		flux adjustment*	0.4955			1.1411			1.3168			2.1101			0.7042			0.578			0.467	
		app rate multiplier#		1.0234	2.924		2.035	2.907		1.8519	2.6455		1.0542	1.506		1.0204	1.4577		1.0116	1.4451		1.9231

* this adjustment converts the 100ug.m**2/sec to the flux from the study e.g.: (0.4955)*(5182) = 2568
# this multiplier scales the concentrations from the study to the desired application rate e.g.: (1.0234)*(2568) = 2628
the multiplier is calculated as: 175/171 = 1.0234 and scales the application rate up from 171lb/ac to 175lb/ac
Any additional broadcast application rates can be obtained by calculating the app rate multiplier.
Example: bed/tarp 250 app rate multiplier = 250/189 = 1.323
the concentrations in the "bed/tarp 189" column multipled by 1.323 gives estimated concentration for 250lb effective broadcast
this scenario would be 500lbs in the beds and beds 50% of the field area.

Concentrations should be rounded to 2 significant figures for use in the Exposure Appraisal

Chloropicirn
40ac 6hr night

All Concentrations are ug/m3**

			vol 199-073			vol 199-073			vol 199-073			vol 199-073			vol 199-073			vol 199-073			Vol 199-112	
		24hr	AZ broad/untarp			AZ bed/untarp			AZ bed/tarp			AZ broad/tarp			WA broad/tarp			FL broad/tarp			CA bed/drip/tarp	
feet	**meters**	**generic conc**	**171 lb/ac**	**175 lb/ac**	**500 lb/ac**	**86 lb/ac**	**175 lb/ac**	**250 lb/ac**	**189 lb/ac**	**350 lb/ac**	**500 lb/ac**	**332 lb/ac**	**350 lb/ac**	**500 lb/ac**	**343 lb/ac**	**350 lb/ac**	**500 lb/ac**	**346 lb/ac**	**350 lb/ac**	**500 lb/ac**	**156 lb/ac**	**300 lb/ac**
10	3.04	8329.8	15017.8	15369.2	43912.0	9396.0	19120.9	27314.2	11839.1	21924.9	31320.5	2511.4	2647.6	3782.2	1658.5	1692.3	2417.5	1807.6	1828.5	2612.1	437.3	841.0
50	15.2	8285.1	14937.2	15286.7	43676.4	9345.6	19018.3	27167.6	11775.6	21807.3	31152.4	2498.0	2633.3	3761.9	1649.6	1683.2	2404.6	1797.9	1818.7	2598.1	435.0	836.5
100	30.4	8058.3	14528.3	14868.3	42480.8	9089.8	18497.7	26423.9	11453.3	21210.3	30299.6	2429.6	2561.3	3658.9	1604.4	1637.1	2338.7	1748.7	1768.9	2527.0	423.1	813.6
300	91.2	6419.2	11573.2	11844.0	33840.0	7240.9	14735.1	21049.2	9123.6	16896.0	24136.5	1935.4	2040.3	2914.7	1278.1	1304.1	1863.0	1393.0	1409.1	2013.0	337.0	648.1
500	152	5341.6	9630.4	9855.7	28159.2	6025.3	12261.5	17515.6	7592.0	14059.7	20084.7	1610.5	1697.8	2425.4	1063.5	1085.2	1550.3	1159.1	1172.6	1675.1	280.4	539.3
2500	760	2377.9	4287.1	4387.4	12535.5	2682.3	5458.4	7797.4	3379.7	6258.9	8941.0	716.9	755.8	1079.7	473.4	483.1	690.1	516.0	522.0	745.7	124.8	240.1
		flux adjustment*	1.8029			1.128			1.4213			0.3015			0.1991			0.217			0.0525	
		app rate multiplier#		1.0234	2.924		2.035	2.907		1.8519	2.6455		1.0542	1.506		1.0204	1.4577		1.0116	1.4451		1.9231

* this adjustment converts the 100ug.m**2/sec to the flux from the study e.g.: (1.8029)*(8330) = 15018
\# this multiplier scales the concentrations from the study to the desired application rate e.g.: (1.0234)*(15018) = 15369
the multiplier is calculated as: 175/171 = 1.0234 and scales the application rate up from 171lb/ac to 175lb/ac
Any additional broadcast application rates can be obtained by calculating the app rate multiplier.
Example: bed/tarp 250 app rate multiplier = 250/189 = 1.323
the concentrations in the "bed/tarp 189" column multipled by 1.323 gives estimated concentration for 250lb effective broadcast
this scenario would be 500lbs in the beds and beds 50% of the field area.

Concentrations should be rounded to 2 significant figures for use in the Exposure Appraisal

Chloropicrin
40ac 24hr

All Concentrations are ug/m3**

			vol 199-073			vol 199-073			vol 199-073			vol 199-073			vol 199-073			vol 199-073			Vol 199-112	
			AZ			AZ			AZ			AZ			WA			FL			CA	
		24hr	AZ broad/untarp			AZ bed/untarp			AZ bed/tarp			AZ broad/tarp			WA broad/tarp			FL broad/tarp			CA bed/drip/tarp	
feet	**meters**	**generic conc**	**171 lb/ac**	**175 lb/ac**	**500 lb/ac**	**86 lb/ac**	**175 lb/ac**	**250 lb/ac**	**189 lb/ac**	**350 lb/ac**	**500 lb/ac**	**332 lb/ac**	**350 lb/ac**	**500 lb/ac**	**343 lb/ac**	**350 lb/ac**	**500 lb/ac**	**346 lb/ac**	**350 lb/ac**	**500 lb/ac**	**156 lb/ac**	**300 lb/ac**
10	3.04	2589.1	2218.9	2270.8	6488.0	1717.1	3494.3	4991.7	2787.2	5161.6	7373.5	2869.5	3025.1	4321.5	878.5	896.4	1280.6	712.0	720.3	1028.9	576.1	1107.9
50	15.2	2350.7	2014.6	2061.7	5890.7	1559.0	3172.6	4532.1	2530.6	4686.4	6694.6	2605.3	2746.5	3923.6	797.6	813.9	1162.7	646.5	654.0	934.2	523.0	1005.9
100	30.4	2018.7	1730.0	1770.5	5058.7	1338.8	2724.5	3891.9	2173.2	4024.5	5749.1	2237.3	2358.6	3369.4	685.0	698.9	998.5	555.1	561.6	802.2	449.2	863.8
300	91.2	1374.0	1177.5	1205.1	3443.0	911.2	1854.4	2649.0	1479.1	2739.1	3913.0	1522.8	1605.3	2293.3	466.2	475.7	679.6	377.8	382.2	546.0	305.7	587.9
500	152	1083.2	928.3	950.1	2714.5	718.4	1462.0	2088.4	1166.1	2159.5	3084.9	1200.6	1265.6	1808.0	367.5	375.0	535.8	297.9	301.3	430.5	241.0	463.5
2500	760	379.2	325.0	332.6	950.3	251.5	511.8	731.2	408.3	756.0	1080.0	420.3	443.1	633.0	128.7	131.3	187.6	104.3	105.5	150.7	84.4	162.3
		flux adjustment*	0.857			0.6632			1.0765			1.1083			0.3393			0.275			0.2225	
		app rate multiplier#		1.0234	2.924		2.035	2.907		1.8519	2.6455		1.0542	1.506		1.0204	1.4577		1.0116	1.4451		1.9231

* this adjustment converts the 100ug.m**2/sec to the flux from the study e.g.: (0.857)*(2589.132) = 2218.886
# this multiplier scales the concentrations from the study to the desired application rate e.g.: (1.0234)*(2218.886) = 2270.808
the multiplier is calculated as: 175/171 = 1.0234 and scales the application rate up from 171lb/ac to 175lb/ac
Any additional broadcast application rates can be obtained by calculating the app rate multiplier.
Example: bed/tarp 250 app rate multiplier = 250/189 = 1.323
the concentrations in the "bed/tarp 189" column multipled by 1.323 gives estimated concentration for 250lb effective broadcast
this scenario would be 500lbs in the beds and beds 50% of the field area.

Concentrations should be rounded to 2 significant figures for use in the Exposure Appraisal

Mary-Ann Warmerdam
Director

Department of Pesticide Regulation

Arnold Schwarzenegger
Governor

M E M O R A N D U M

TO: Randy Segawa, Agriculture Program Supervisor IV
Environmental Monitoring Branch

FROM: Terrell Barry, Ph.D., Research Scientist III
Environmental Monitoring Branch
(916) 324-4140

Original signed by

DATE: November 21, 2006

SUBJECT: REVIEW OF THE DOCUMENTS IN THE AUGUST 9, 2006 AND SEPTEMBER 29, 2006 ENVIRONMENTAL PROTECTION AGENCY POSTINGS ON THE METHYL BROMIDE E-DOCKET OPP-2005–123

Documents Reviewed:

The August 9, 2006, Environmental Protection Agency (EPA) posting on the Methyl Bromide E-Docket #OPP-2005–123 the includes:

0229 – Federal Register Notice Vol 71 No. 153 P45400 Inorganic Bromide: Tolerance Actions

0230 – The Readers Guide to the Methyl Bromide E-Docket #OPP-2005-0123

0231 – EPA 738-R-06-026 Report of Food Quality Protection Act (FQPA) Tolerance Reassessment and Risk Management Decision (TRED) for Methyl Bromide, and Reregistration Eligibility Decision (RED) for Methyl Bromide's Commodity Uses

0232 – Appendices to 0231

0233 – Qualitative Assessment of the Impact of Changes in the Use of Methyl Bromide for Plant Protection an Quarantine (PPQ) Purpose in Support of the Reregistration Eligibility Decision (RED)

0234 – Qualitative Assessment of the Impact of Changes in the Use of Methyl Bromide on Non-Quarantine Commodities in Support of the Reregistration Eligibility Decision (RED)

0235 – Qualitative Assessment of the Impact of Changes in the Use of Methyl Bromide on Dry Cured Pork Product Facilities in Support of the Reregistration Eligibility Decision (RED)

0236 – Qualitative Assessment of the Impact of Changes in the Use of Methyl Bromide in Structural and Food Processing Facilities in Support of the Reregistration Eligibility Decision (RED)

0237 – Agency Responses to Phase 5 Public Comments Related to Methyl Bromide's Commodity Risk Assessments and Risk Mitigation Options Proposal

0238 – Federal Register Notice Vol 71 No. 153 P45546 Methyl Bromide Tolerance Reassessment and Risk Management Decision (TRED) for Methyl Bromide, and Reregistration Eligability Decision (RED) for Methyl Bromide's Commodity Uses: Notice of Availability

The September 29, 2006 Environmental Protection Agency (EPA) posting on the Methyl Bromide E-Docket #OPP-2005–123 includes the documents:

0240 – Impact Assessments for Postharvest Use of Methyl Bromide

0241 – Federal Register Notice Vol 71 No. 189 P57505 Methyl Bromide: Tolerance Reassessment and Risk Management Decision for Methyl Bromide and Reregistration Eligibility Decision for Methyl Bromide's Commodity Uses: Extension of Comment Period

0242 – Buffer Zone Look-up Tables for Methyl Bromide's Commodity Uses

0243 – Updated Rates and Exposure Times for Methyl Bromide's TRED/RED Label Table.

Review:

My review will only pertain to the sections of these documents that are related to producing the air concentrations and buffer zones used in the RED. I previously reviewed the Methyl Bromide: Phase 5 Health Effects Division (HED) Human Health Risk Assessment of Commodity Uses. PC Code: 053201, DP Bar Code: D304623 March 10, 2006 (See comments submitted to the Docket by R. Segawa on 5/30/2006 EPA-HQ-OPP-2005-0123-0222).

This risk assessment was not revised and re-issued. Instead, an Addendum to Phase 5 Health Effects Division (HED) Human Health Risk Assessment for Commodity Uses. PC Code: 053201, DP Barcode: D304619 was issued. This addendum addresses comments that required specific clarifications or model re-runs. These documents are part of 0232 – Appendices to 0231.

Review of each of the documents are listed below.

0229 – Federal Register Notice Vol 71 No. 153 P45400 Inorganic Bromide: Tolerance Actions

This document states that EPA is revoking 12 specific inorganic bromide tolerances resulting from MeBr soil fumigations because EPA has classified MeBr as a non-food use pesticide with regard to soil fumigant uses. This document does not need to be reviewed in the context of MeBr inhalation exposures.

0230 – The Readers Guide to the Methyl Bromide E-Docket #OPP-2005-0123

No review is necessary. This document simply lists the contents of the August 8, 2006 posting.

0231 – EPA 738-R-06-026 Report of Food Quality Protection Act (FQPA) Tolerance Reassessment and Risk Management Decision (TRED) for Methyl Bromide, and Reregistration Eligibility Decision (RED) for Methyl Bromide's Commodity Uses

Only Sections directly related to modeled air concentrations were reviewed.

The main conclusion of this document is: "The Agency has determined that MeBr's commodity uses are eligible for reregistration provided that the risk mitigation measures outlined in this document are adopted and label amendments are made to reflect these measures" (page 9). The risk mitigation measures include the same types of measures CDPR has implemented for MeBr commodity and space fumigations. The main exception is the allowance of the horizontal aeration of PPQ facilities. Although CDPR regulations do not allow this method of aeration, much of my review will discuss this particular aeration technique because it poses a high potential for acute exposure. Thus, the modeling employed to characterize this aeration method must be carefully reviewed.

Pages 24–26. IV. Risk Management, Reregistration, and Tolerance Reassessment Decision. D. Regulatory Rationale. 2. Residential Risks. It is stated that the acute inhalation exposure level of concern (LOC) is 1ppm as an 8-hr Time Weighted Average (TWA). This is in contrast to CDPR 0.630ppm 8hr TWA LOC. Examination of the model input files shows that the LOC used to develop the buffer zones is 1ppm 4hr TWA. EPA is proposing buffer zoned based upon the 1ppm 4hr TWA. This LOC will results in longer required buffer zones.

Examples of mitigation techniques to reduce potential exposure, and thus buffer zone size, are given in this section. The list of mitigation techniques is reasonable and consistent with discussions with EPA staff.

Pages 27–33. IV. Risk Management, Reregistration, and Tolerance Reassessment Decision. E. Residential Bystander and Occupational Risk Mitigation. This section describes the rationale for risk management decisions. CDPR EM staff participated in discussions and submitted comments that were part of the development of this section. The Site-specific Fumigation Management Plan (FMP) is similar in concept to the Site Plan in California Regulations. The buffer zones are included in the FMP, the required size will be specified in Agency look-up tables or by other alternative methods. EPA has decided to use the 99th percentile "whole field" distance outputs from the PERFUM model to specify the required buffer zones. EPA states on Page 30: "…an analysis by the Agency has determined that the distances for scenarios modeled using the 99th percentile whole field distance outputs are in many cases is similar to the distances currently required by California's permit conditions for MeBr commodity fumigations." I have not reviewed this analysis and thus I cannot judge the extent to which this analysis compared the buffer zone results. However, any similarity of buffer zone size between the proposed EPA tables and the California tables is likely due to chance rather than equivalent risk mitigation conditions. The LOC's used by EPA and CDPR are different: EPA using 1ppm 4hr TWA (EPA states they are using a 1ppm 8hr TWA but the modeling uses a 1ppm 4 hr TWA to establish the buffer zones) versus California using 0.630ppm 8hr TWA (effective 1.26ppm 4hr TWA) so it is impossible to perform a direct comparison of maximum direction and whole field results.

Page 30 – availability of Buffer Zone Tables. The TRED states: " The Agency will provide information in the form of look-up tables for commodity fumigators to follow to ensure that workers and bystanders are protected. These table will be available on the Agency's internet website…" However, the buffer zone tables are not available now so there is no opportunity for review. We can use the partial results in the Phase 5 risk assessment and the Phase 5 Addendum but this assumes that nothing changes in the interim.

Page 30 – It should be clarified that the "ground level local exhaust ventilation" is a horizontal release. This type of aeration simply lays a conduit on the ground and directs the flow parallel to and along the ground rather than vertically. Although not impossible, this aeration scenario is a significant challenge to model as will be discussed later in this review.

0232 – Appendices to 0231

There are 9 Appendices to 0231. Only Appendix I contains air concentration estimation methods and results. The appendices are listed below:

Appendix A: Methyl Bromide Commodity Use Patterns Eligible for Registration

Appendix B: Table of Generic Data Requirements and Studies Used to Make the Reregistration Decision for Methyl Bromide

Appendix C: Bibliography

Appendix D: Technical Support Documents

Appendix E: Generic Data Call-In (to be inserted after approval) – this appendix is currently empty

Appendix F: Product-Specific Data Call-In (to be inserted after approval) – this appendix is currently empty

Appendix G: EPA's Batching of Methyl Bromide Products for Meeting Acute Toxicity Data Requirements for Reregistration – Product batching was not developed for methyl bromide products

Appendix H: List of Registrants Sent Data Call-Ins – this appendix is empty

Appendix I: List of Available Related Documents and Electronically Available Forms –

The "Methyl Bromide: Phase 5 Health Effect Division (HED) Human Health Risk Assessment for Commodity Uses: PC Code: 053201, DP Barcode: D304623" and the "Methyl Bromide: Addendum to Phase 5 Health Effect Division (HED) Human Health Risk Assessment for Commodity Uses: PC Code: 053201, DP Barcode: D304619" are contained in this appendix.

The Phase 5 risk assessment was previously reviewed. However, no PERFUM input files were available at the time of the review. This review of the TRED/RED included examination of the PERFUM input files.

PERFUM simulation Scenarios:

General comment: the risk assessment specifies the LOC as 1ppm 8hr TWA however, for all the scenarios the averaging time is 4 hours. Therefore the effective LOC is 1ppm 4hr TWA. This is a more stringent LOC that the EPA specified LOC, therefore, the buffer zone results are larger than needed. This is also more stringent than the CDPR LOC of 0.210ppm 24hr TWA.

Scenario 1 – Chamber During Treatment

The model setup for the enclosure is consistent with how CDPR modeled the treatment period. However, the assumed leakage rate during the holding period is very different. EPA uses the PERFUM input files from Scenario 2 – Aeration with No Stack to produce this scenario. This method of specifying the flux releases all the mass lost during treatment in 1 hour followed by

3 hours of 0 flux. While this is an appropriate method to simulate the Aeration with No Stack scenario, it is not the best method to simulate the treatment period. This is not how leakage occurs during the treatment period. This flux profile structure will cause buffer zones for the treatment period to be significantly larger that if a more realistic, lower steady loss is assumed.

The CDPR modeling has used either 30% or 75% loss in 24 hours. The flux is assumed to be steady over the 24hr period (e.g., 3% per hour). With a steady loss, if the holding period is less than 24 hours, less than 30% or 75% will be lost.

A comparison of flux profile and percent loss maximum direction buffer zone (meters) results are shown below. This comparison shows for 50000 cubic feet volume the EPA results for the 10% loss from Table 8 page 40 and the 75% loss from Table 7, no stack aeration page 39. Only 10% and 75% loss can be easily compared because those are the results available in the Phase 5 risk assessment.

Max Direction Percentile	10% loss in 24 hours		75% loss in 24 hours	
	EPA[1]	Steady[2]	EPA	Steady
95	205	0	755	120
99	230	0	855	145
99.9	240	0	890	190

[1] 4hr TWA air concentration produced assuming a large 1hour flux followed by zero flux for the remaining 3 hrs of the averaging period.
[2] 4hr TWA air concentration produced assuming a steady flux for 24 hours. Therefore, each of the 4 hours in the averaging period has the same, nonzero flux.

EPA 99th percentile proposed Whole Field Buffers (m) from Table 7, page 39 and Table 8, page 40, of Phase 5 risk assessment*

$1000ft^3$			$10000ft^3$			$50000ft^3$			$100000ft^3$		
75%	10%	1%	75%	10%	1%	75%	10%	1%	75%	10%	1%
15	0	0	95	15	0	260	75	0	385	120	0

*these buffers are calculated using the 1 hour flux followed by 3 hours zero flux

The effect of releasing all the mass lost in one hour on buffer zone length is readily apparent. Even the Whole Field buffers are larger than those required under the maximum direction when a steady flux is used.

Scenario 2 – Aeration with No Stack

This model setup of the enclosure is consistent with how CDPR modeled this scenario. I was able to reproduce the EPA results shown in Table 7 of the Phase 5 risk assessment for this scenario. However, as discussed above, the averaging time and LOC are different and appropriate comparison to California regulations is difficult.

EPA 99th percentile proposed Whole Field Buffers (m) from Table 7. Application rate is 4lb/1000ft3. Page 39-40 of Phase 5 risk assessment

$1000ft^3$		$10000ft^3$		$50000ft^3$		$100000ft^3$	
95% loss	75% loss	95% loss	75% loss	95% loss	75% loss	95% loss	75% loss
20	15	115	95	295	260	440	385

These buffers were produced by modeling 4-hour periods where the flux all occurs in the first hour followed by 3 hours of zero flux. So, for the 95% loss scenario, the loss will be 3.8lb/1000ft3 in 1 hour.

Scenario 3 – Aeration with Stack (building downwash included)

This scenario assumes that the stack will be influenced by building downwash. Therefore, it is similar to CDPR short stack scenario. I was able to reproduce the EPA results shown in Table 7 of the Phase 5 risk assessment for this scenario. However, as discussed above, the averaging time and LOC are different and appropriate comparison to California regulations is difficult.

EPA 99th percentile proposed Whole Field Buffers (m) from Table 7. Application rate is 4lb/1000ft3. Page 39-40 of Phase 5 risk assessment

$1000ft^3$ sd[1] =0.24m		$10000ft^3$ sd=0.77m		$50000ft^3$ sd=1.71m		$100000ft^3$ sd=2.43m	
Exit Velocity = 0.51m/s							
95% loss	75% loss	95% loss	75% loss	95% loss	75% loss	95% loss	75% loss
0	0	50	40	200	160	280	230
Exit Velocity = 10.16 m/s							
95% loss	75% loss	95% loss	75% loss	95% loss	75% loss	95% loss	75% loss
0	0	20	0	45	40	105	90

[1]SD = Stack Diameter

These buffers were produced by modeling 4-hour periods where the flux all occurs in the first hour followed by 3 hours of zero flux. So, for the 95% loss scenario, the loss will be 3.8lb/$1000ft^3$ in 1 hour.

Scenario 4 – Aeration with Portable Stack not near building

This method uses a portable stack with the exit flow directed straight up, perpendicular to the ground. California does not specifically allow this method. The permit for such a method would be as a no stack release since the stack would not meet the criteria of either of the stack release categories. The method that EPA has used to model this scenario appears acceptable. However, it must be assumed that the ground level, vertically directed stack is not influenced by any nearby structures since that is the way this scenario was modeled. Guidelines to calculate the required separation between obstructions and stack releases should be included on the EPA Web site for assembling the Site Plan.

Addendum

Scenario 5 – Aeration with Mobile Ground Level Source Not Near Building (horizontal stack) (Note: this scenario was significantly changed in the addendum. The comments below pertain to the addendum results)

California does not allow this method of aeration. This method has the potential for significant acute exposure. It presents a difficult and complex modeling problem because the exit velocity is horizontal rather than vertical. There are several suggested methods to model this type of scenario. EPA has employed one of those methods. However, there may be more appropriate alternatives. The method that EPA has used, along with some alternative, are discussed below.

The EPA modeling used the EPA Guidelines suggested by CDPR in our previous review that specified setting the vertical exit velocity to 0.001m/s. This effectively removes the vertical mechanical plume rise. However, the question as to what to do with the stack diameter and height remains. The EPA Guidelines do not suggest for horizontal stacks a method to adjust the stack diameter or height. The main question is how, or whether, to constrain the volumetric exchange to remain at the actual rate. In this scenario EPA chose to maintain the volumetric exchange by calculating an effective diameter. An effective stack height must also be chosen. This is a method used by Canada and certainly is a valid option for some situations. However, because some of the volumetric exchange rates that EPA is interested in modeling are quite large the effective diameter becomes very large (effective stack diameters between 5.48m and 775.2m). The effective stack height used was one half the effective diameter so effective stack heights vary between 2.74m and 388m, depending upon the exit velocity scenario. This effective stack height alone will lead to non-representative results because for all but the smallest effective stack diameters the release height is much higher than the actual release height (ground level) and the plume may not even touch down at receptor level before the downwind distance is beyond the 1440m limit of PERFUM. If EPA elects to retain the effective diameter approach to model this scenario, one option would be to set the effective stack height at either one half the actual diameter or at the actual diameter of the conduit used to release the plume.

Below is a comparison for PPQ (EV) Horizontal Stack/50000 cubic feet/95%mass released shown in Table 7 page 5 of the Addendum to Phase 5. I used two different stack heights, but kept the same exit velocity = 0.001m/s and effective diameter = 173.34m. For my test I ran the PERFUM model using a stack height of one half the diameter of the minimum stack for 50000 cubic feet (1.7195/2 = 0.86m). This is closer to reality but may still be a higher release height than the actual release height. Results are shown below.

Stack Ht = 86.7m	Stack Ht = 0.86m
Full Exit Velocity	
195	230
240	305
315	540

As expected, the buffer zones are larger for the shorter stack height. However, these estimates are only presented to illustrate the significant effect of stack height. Without further analysis and more detailed information on the scenario the best approach cannot be specified.

Another modeling option specified in the Guidance for Air Dispersion Modeling issued by the Texas Commission on Environmental Quality (TCEQ) <www.tceq.state.tx.us/assets/public/permitting/air/Guidance/NewSourceReview/rg25.pdf>. Their specifications are: Stack exit velocity = 0.001m/s: stack exit diameter = 0.001m; actual release height.

If EPA elects to continue support for the horizontal ground level aeration method and wants to be sure that the exposure is accurately characterized by the modeling then considerable effort should be devoted to characterizing the actual risk associated with this method. Although it can be argued that the ISC model is not ideal for this scenario, there really is not a better modeling alternative. This may be one scenario where at least one monitoring study should be required in order assist in quantifying the risk. The monitoring data would be used to help define the appropriate modeling approach, not to characterize risk directly. This simply is not a typical exposure scenario, potential for exposure to hazardous concentrations seems high and the appropriate modeling treatment is debatable. It may be beneficial, before the modeling is finalized, to consult with modelers who regularly work in the industrial permitting area and who have experience modeling horizontal stacks.

Remainder of Addendum – with the exception of the PPQ horizontal stacks, the addendum generally addresses the CDPR comments. In addition, EPA has done a nice job of responding to the MBIP comments and modeling. The only additional comment I have is on Page 9 EPA should make it clear that the ISC model alone, not PERFUM, should be used for the site specific analysis where on-site measured air concentrations collected under a specific set of conditions

are compared to modeled concentrations. The on-site measured air concentrations must be collected in such a way that the results are an accurate reflection of the process. For example, the Addendum notes that at the flour mill there was a 2 hour gap between aeration and the sampling interval. Those sampling results would not be an accurate reflection of the aeration process. Also, as noted in the Addendum, on-site meteorological data must also be collected and used in the analysis.

0233 – Qualitative Assessment of the Impact of Changes in the Use of Methyl Bromide for Plant Protection an Quarantine (PPQ) Purpose in Support of the Reregistration Eligibility Decision (RED)

This assessment could be significantly affected by how the scenarios are modeled. All comments concerning modeling in the Risk Assessment and Addendum apply to this assessment of impacts to PPQ facilities.

Additional comments:

Page 10. Table 4. This table characterizes throughput at PPQ fumigation facilities. Of particular importance to the TRED/RED is the number of fumigations per day. The buffer zones were developed in such a way that each “application” in the simulation is an independent event. It has not been established whether the buffer zones are protective if multiple fumigations are conducted either sequentially or simultaneously (or both). Theoretically, so long as not more than six sequential fumigations per day are conducted the buffer zones should still be protective at the desired level (e.g., whole field 99% or other choice). This is because in the PERFUM simulations a new, independent fumigation is initiated sequentially, every 4 hrs. So long as the buffer zone is not exceeded in any one of the 4hr periods, multiple sequential fumigations will not cause an exceedence of the 1ppm 4hr average at the buffer zone distance, even if the wind was in exactly the same direction for 24 hr. However, there are two additional scenarios that should be considered. First if more than 6 sequential fumigations are conducted in 24 hours the threshold concentration (1ppm 4hr time weighted average) may be exceeded at the buffer zone distance because this implies that a new fumigation is initiated after an interval of less than 4 hours. The second scenario is that of multiple fumigations conducted simultaneously. The magnitude of this risk is dependent upon a number of factors, including the spatial separation between the simultaneous fumigations. Table 4 lists some facilities as conducted an average of 8 to 13 fumigations a day with the maximum number of fumigations conducted at between 14 and 141 per day. Those facilities may need site-specific modeling to establish that the proposed buffer zones are protective. CDPR has used the concept of independent sources to characterize the effect on receptors of multiple applications in proximity to each other.

Page 12. Footnote. For space fumigations and non-certified chambers, loss rate during treatment should be measured rather than assumed if is desired to use less than 2–3% per hour.

Pages 13 – 15. Treatment Buffers. As discussed in the review of the modeling, the assumption that all gas lost during the treatment holding period is lost in the first hour is not supported by data collected by CDPR. In addition, this method of simulating the treatment holding period loss leads to buffers larger than actually required. The loss during treatment holding is constant and gradual. On page 15 it is stated that a 4hour emission estimate was used to construct Table 6 buffer zones. The emission estimate used is for 1 hour, not 4 hours. The air concentration estimate is for 4hrs.

0234 – Qualitative Assessment of the Impact of Changes in the Use of Methyl Bromide on NonQuarantine Commodities in Support of the Reregistration Eligibility Decision (RED)

This assessment could be significantly affected by how the scenarios are modeled. All comments concerning modeling in the Risk Assessment apply to this assessment of impacts on NonQuarantine Commodities.

Additional Comments:

Page12. Table 4. The text states that "Table 4 examines a range of loss rates: 1, 5, 10 and 25% of the gas lost over 24 hours." This is not correct. As discussed in the review of the modeling in the Risk Assessment and in document 0234 above, and stated on Page 11 of this document, the loss is modeled as if it is lost over 1 hour. The air concentration estimate is a 4 hour average. These results do not reflect a 24hour process.

0235 – Qualitative Assessment of the Impact of Changes in the Use of Methyl Bromide on Dry Cured Pork Product Facilities in Support of the Reregistration Eligibility Decision (RED)

This assessment could be significantly affected by how the scenarios are modeled. All comments concerning modeling in the Risk Assessment apply to this assessment of impacts on Dry Cured Pork Product Facilities.

Additional Comments:

Page12. Table 4. The text states that "Table 4 examines a range of loss rates: 1, 5, 10 and 25% of the gas lost over 24 hours." This is not correct. As discussed in the review of the modeling in the Risk Assessment and in document 0234 above, and stated on Page 11 of this document, the loss is modeled as if it is lost over 1 hour. The air concentration estimate is a 4 hour average. These results do not reflect a 24hour process.

Page 14. Improving Gas Retention. It may be very difficult to obtain a significant reduction in buffer zone size with this option. Before any improvement in gas retention is approved as a

mitigation measure two exercises should be conducted. First, the initial loss rate should be measured with using a well-documented protocol. Then, modeling should be used to characterize the size of the loss reduction necessary to significantly reduce buffer zone size.

0236 – Qualitative Assessment of the Impact of Changes in the Use of Methyl Bromide in Structural and Food Processing Facilities in Support of the Reregistration Eligibility Decision (RED)

This assessment could be significantly affected by how the scenarios are modeled. All comments concerning modeling in the Risk Assessment apply to this assessment of impacts on Structural and Food Processing Facilities Commodities.

Additional Comments:

Page 14. The discussion in the last paragraph refers to low loss rates of 5 to 10% per 24-hour period for new, well-sealed steel or concrete facilities. CDPR monitoring indicates that the loss rate may be 1% to 3% per hour (24% to 72% for 24 hours) even for newer, well-sealed concrete facilities.

Page14 and Table 5. The text states that "Table 4 examines a range of loss rates: 5, 10 and 25% of the gas lost over 24 hours." This is not correct. As discussed in the review of the modeling in the Risk Assessment and in document 0234 above, and stated on Page 11 of this document, the loss is modeled as if it is lost over 1 hour. The air concentration estimate is a 4 hour average. These results do not reflect a 24hour process.

Page 16. Improving Gas Retention. It may be very difficult to obtain a significant reduction in buffer zone size with this option. Before any improvement in gas retention is approved as a mitigation measure two exercises should be conducted. First, the initial loss rate should be measured with using a well-documented protocol. Then, modeling should be used to characterize the size of the loss reduction necessary to significantly reduce buffer zone size.

0237 – Agency Responses to Phase 5 Public Comments Related to Methyl Bromide's Commodity Risk Assessments and Risk Mitigation Options Proposal

No Review required.

0238 – Federal Register/vol. 71, No. 153/Wednesday, August 9, 2006/ Notices/Page 45546. Methyl Bromide Tolerance Reassessment and Risk Management Decision (TRED) for Methyl Bromide, and Reregistration Eligibility Decision (RED) for Methyl Bromide's Commodity Uses; Notice of Availability.

No review is required. This document only provides the notice of posting, background discussion, and how to comment.

0240 – Impact Assessments for Postharvest Use of Methyl Bromide

No review required. This documents simply states that, if new information becomes available BEAD will reevaluate the impacts.

0241 – Federal Register Notice Vol 71 No. 189 P57505 Methyl Bromide: Tolerance Reassessment and Risk Management Decision for Methyl Bromide and Reregistration Eligibility Decision for Methyl Bromide's Commodity Uses: Extension of Comment Period

No review is required. This document only provides the notice of posting, background discussion, and how to comment.

0242 - Buffer Zone Look-up Tables for Methyl Bromide's Commodity Uses

For each table I attempted to verify the 500,000ft^3 scenario.

1.0 Treatment

1a. Treatment 24 hrs or greater

I could not find the PEFRUM input files for the 1lb/1000ft^3 through 4lb/1000ft^3 in this table so I could not verify those results.

I did verify 9lb/1000ft^3 and 500,000ft^3 volume. The simulation method is reasonable and similar to CDPR methods. However, the assumption of 25% or less of applied mass lost in 24 hours is not consistent with measured loss in the CDPR data set. We have observed 30% to 70% loss in 24 hours for noncertified spaces.

1b. Treatment up to 8hr & 4lbs/1000ft^3

I verified 4lbs/1000ft^3. The method of simulation described at the bottom of this table is discussed above. Assuming all mass lost in 24 hours is lost in the first hours is not a realistic scenario and, as shown above, leads to larger buffer zones than if a uniform loss over 24 hours is assumed.

1c. Treatment up to 8hrs & greater than 4lbs/1000ft^3

I was unable to verify the buffer zones for 9lbs/1000ft^3 and 500,000ft^3. According to the description below the table the input and output files should be located under the subdirectory labeled"4hrs 4 emissions" and use a flux of 38145g/s lost uniformly over 24hrs. Instead, the entries in the buffer zone table were found in the subdirectory "4hrs 1emission." This means that the same scenario used for Table 1b was used for Table 1c. However, the flux used appears to be incorrect since 38145g/s was used as the base flux. According to the calculations for the scenarios in Table 1b the base flux should be 915322g/sec lost over 1 hr followed by 3 hours of zero flux. The buffer zones using this flux would be much larger.

If the 500,000ft^3 output from the subdirectory labeled"4hrs 4 emissions" is used then the buffer zones for Table 1c should be:

25%	300
10%	150
5%	70
1%	0

All other columns in this table would need to be correct also. However, this correction would not address the assumed low 24hour loss rate discussed above.

2.0 Aeration, No Stack

2a. Aeration greater than 8 hrs & greater than 4lbs/1000ft^3

I verified both 9lbs and 15lbs/1000ft^3 for 500,000ft^3. The simulation method is consistent with CDPR methods.

2b. Aeration up to 8hrs & up to 4lbs/1000ft^3

I verified the 4lbs/1000ft^3 and 500,000ft^3 scenario. All mass released is assumed to occur over the first hour of aeration. The simulation method is consistent with CDPR methods.

2c. Aeration up to 8hrs & greater than 4lbs/1000ft^3

The notation at the bottom of the table indicates that emissions are assumed to occur over a 24-hour period. However, the heading of the table indicates aeration of up to 8 hrs so use of a 24-hour uniform emission would not be correct to match this stated scenario.

In fact, the intended scenario is not clear since the values in the buffer zone table for the uniform flux profile over 24 hours do not match those found in the "4hr 4 emissions" directory. I could not find the buffer zone values shown Table 2c in any of the PERFUM output files. So, I am not clear what scenario was used.

Buffer zone values from the "4hr 4emission" subdirectory for 9lb/1000 ft^3 and volume 500,000ft^3 are shown below:

99% 730
95% 710
90% 690
75% 620
50% 475

These buffer zones are in contrast to those shown in Table 2c for 9lb/1000ft^3 and volume 500,000ft^3:

99% 305
95% 300
90% 290
75% 265
50% 210

If the scenario is intended to reflect aeration of up to 8hrs then the 1 hour of emissions followed by 3 hours of zero flux is most representative. Aeration occurs relatively quickly even for no stack facilities if any type of forced air is used to aerate (e.g. portable fans).

Stack Aeration Tables (Table 3 through Table 22)

For all the buffer zone tables for stack aeration with building effects, the building dimensions and stack height used have a significant effect on the air concentrations and thus, the buffer zones. The building dimensions and stack characteristics used to generate these buffer zone tables are shown below:

Volume (ft^3)	Building Dimensions L x W x H			Stack Ht. above top of building (m)	Stack Ht. above ground (m)	Stack Diameter (m)	Exit Velocity (m/s)
	(m)	(m)	(m)				
25,000	9.6	9.6	7.6	3.1 &,15.2	10.7 & 22.8	1.22	10.16
50,000	13.6	13.6	7.6	3.1 & 15.2	10.7 & 22.8	1.72	10.16
100,000	11.1	11.1	22.9	3.0 & 15.2	25.9 & 38.1	2.43	10.16
250,000	17.6	17.6	22.9	3.0 & 15.2	25.9 & 38.1	2.43	25.4
500,000	24.9	24.9	22.9	3.0 & 15.2	25.9 & 38.1	3.44	25.4
750,000	30.5	30.5	22.9	3.0 & 15.2	25.9 & 38.1	4.21	25.4
1,000,000	35.2	35.2	22.9	3.0 & 15.2	25.9 & 38.1	4.86	25.4

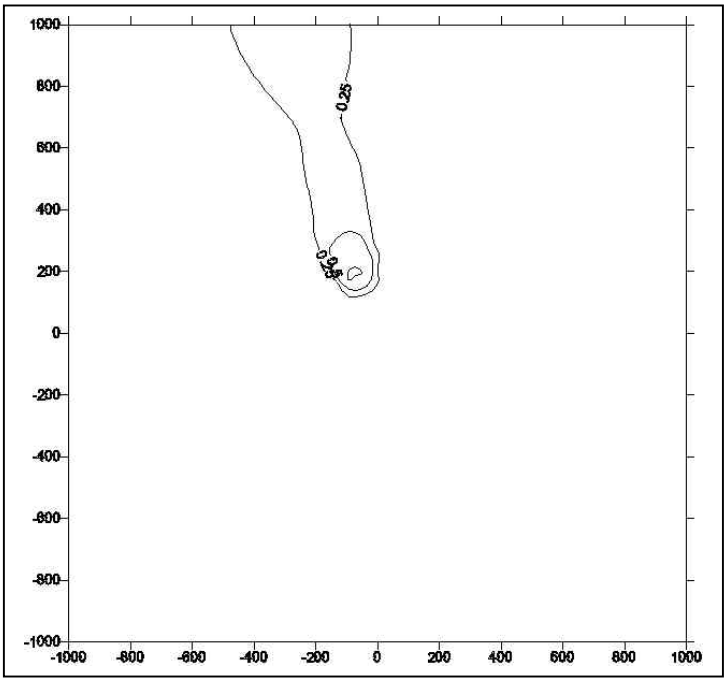
The buffer zone results are highly dependent upon these building inputs. The larger volume building dimensions are very tall buildings (about 9 stories), and thus may be representative of mills but not necessarily of other types of facilities. This should be clearly stated. The buildings allowed to operate using these tables should closely match the dimensions used to generate the tables.

I was unable to verify that the PERFUM2 inputs properly use the stack height and building effects information. The PERFUM2 input instructions state to specify the stack height as the height above the building height. The actual stack height above ground is the building height plus the stack height above the top of the building. However, the PERFUM2 input does not simply add those two heights and enter it as the total stack height with a base elevation of 0.0 meters. Instead, the ISC3 input files indicate that the stack base elevation (Zs, the source base elevation) is specified as the building height and the stack height is entered as 3.0m (10ft) or 15.2m (50ft). The assumption then is that the proper total stack height is used in the model runs. However, it is my understanding that the stack base elevation feature is used in the context of complex terrain applications, not in the way that the PERFUM2 model is using it. I suggest that whether the building effects are properly implemented should be verified.

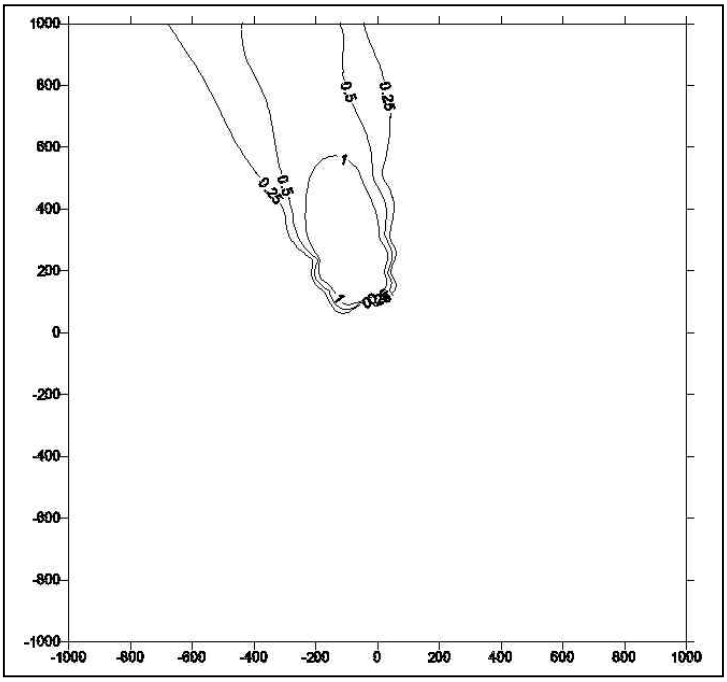
I did do two simple stack source runs to explore the possible difference between the inputs:

1) the stack base elevation = 0.0m and stack height = 35.0m with a building 34m tall
2) the stack base elevation = 34.0m and stack height = 1.0m with the same building 34m tall

The results, shown below with the same concentration contour levels, are quite different:



Base elevation = 0.0m
Stack Height = 35.0m
Concentration Contours (ug/m^3) : 0.25, 0.5, 1.0



Base elevation = 34.0m
Stack Height = 1.0m
Concentration Contours (ug/m^3): 0.25, 0.5, 1.0

The remainder of my review will assume for the time being that the building effects are properly modeled.

3.0 Aeration, 10ft Stack Height, 1 Air exchange every minute

3a. Aeration greater than 8 hours, greater than 4lb/1000ft^3

I was able to verify the 15lb/1000ft^3 and volume 500,000ft^3 scenario. However, at the air exchange rate of this scenario the flux profile would not be uniform for 24 hours. Even for the larger volumes the majority of the mass would be released quickly. The emissions pattern will be similar to the 4hours 1 emission flux profile. Therefore, in some cases the buffer zones may not be large enough.

3b. Aeration period up to 8 hours, up to 4lb/1000ft^3

I was able to verify the 15lb/1000ft^3 and volume 500,000ft^3 scenario. This modeling method is consistent with CDPR methods.

3c. Aeration up to 8 hours, greater than 4lb/1000ft^3

I was unable to verify the 15lb/1000ft^3 and volume 500,000ft^3 scenario. From the description at the bottom of the table (and from the other tables I have already checked) I believe the output files in the “4hr 4 emissions” subdirectory results should be used. Instead of zero for all entries, I found for 15lb/1000ft^3 and volume 500,000ft^3 the results shown below:

99% 65m
95% 60m
90% 60m
75% 0m
50% 0m

Other cells may also be in error but I did not check any others. Even with these corrections, at the air exchange rate of this scenario the flux profile would not be uniform for 24 hours. It is difficult to justify the use of this flux profile for this scenario. Even for the larger volumes the majority of the mass would be released quickly. The emissions pattern will be similar to the 4hours 1 emission flux profile. Therefore, in some cases the buffer zones may not be large enough.

4.0 Aeration, 10ft Stack Height, 1 Air exchange every 2 minutes

This air exchange rate is equivalent to 0.5EV so these outputs are easily checked with the outputs provided.

4a. Aeration greater than 8 hours, greater than 4lb/1000ft^3

I was able to verify the 15lb/1000ft^3 and volume 500,000ft^3 scenario. However, at the air exchange rate of this scenario the flux profile would not be uniform for 24 hours. Even for the larger volumes the majority of the mass would be released quickly. The emissions pattern will be similar to the 4hours 1 emission flux profile. Therefore, in some cases the buffer zones may not be large enough.

4b. Aeration period up to 8 hours, up to 4lb/1000ft^3

I was able to verify the 15lb/1000ft^3 and volume 500,000ft^3 scenario. This modeling method is consistent with CDPR methods.

4c. Aeration up to 8 hours, greater than 4lb/1000ft^3

I was unable to verify the 15lb/1000ft^3 and volume 500,000ft^3 scenario. From the description at the bottom of the table (and from the other tables I have already checked) I believe the output files in the “4hr 4 emissions” subdirectory results should be used. Instead of zero for all entries, I found for 15lb/1000ft^3 and volume 500,000ft^3 the results shown below:

99% 155m
95% 150m
90% 145m
75% 125m
50% 85m

Other cells may also be in error but I did not check any others. The other possibility, since the companion table in 3.0 had different entries is that I was unable to locate the correct result file to check the buffer zones. If this is the case then the description at the bottom of the table is not adequate for the reader to locate the correct output.

Even with these corrections, at the air exchange rate of this scenario the flux profile would not be uniform for 24 hours. It is difficult to justify the use of this flux profile for this scenario. Even for the larger volumes the majority of the mass would be released quickly. The emissions pattern will be similar to the 4hours 1 emission flux profile. Therefore, in some cases the buffer zones may not be large enough.

5.0 through 17.0

I did not check the remaining stack aeration tables. All comments previously made will apply to these tables.

18.0 Aeration, Portable 50ft stack, 1 Air exchange every minute

18a. Aeration up to 8 hours, greater than 4lb/1000ft^3

I was able to verify the 15lb/1000ft^3 and volume 500,000ft^3 scenario. However, at the air exchange rate of this scenario the flux profile would not be uniform for 24 hours. Even for the larger volumes the majority of the mass would be released quickly. The emissions pattern will be similar to the 4hours 1 emission flux profile. Therefore, in some cases the buffer zones may not be large enough.

18b. Aeration period up to 8 hours, up to 4lb/1000ft^3

I was able to verify the 15lb/1000ft^3 and volume 500,000ft^3 scenario. This modeling method is consistent with CDPR methods.

18c. Aeration up to 8 hours, greater than 4lb/1000ft^3

I was able to verify the 15lb/1000ft^3 and volume 500,000ft^3 scenario. At the air exchange rate of this scenario the flux profile would not be uniform for 24 hours. It is difficult to justify the use of this flux profile for this scenario. Even for the larger volumes the majority of the mass would be released quickly. The emissions pattern will be similar to the 4hours 1 emission flux profile. Therefore, in some cases the buffer zones may not be large enough.

19.0 through 22.0

Similar comment as for 18.0 and 19.0 will apply to these tables. I did not check these tables.

23.0 through 27.0

I did not check these tables because I made comments on the modeling of the PPQ scenario earlier in my review of "Addendum Scenario 5 – Aeration with Mobile Ground Level Source Not Near Building (horizontal stack)" that, if implemented, would significantly change the values in these tables.

0243 – Updated Rates and Exposure Times for Methyl Bromide's TRED/RED Label Table

No comment required. This is simply a list of application rates and exposure times.

Department of Pesticide Regulation

Mary-Ann Warmerdam
Director

Arnold Schwarzenegger
Governor

M E M O R A N D U M

TO: Randy Segawa, Senior Environmental Research Scientist
Environmental Monitoring Branch

FROM: Terrell Barry, Ph.D., Senior Environmental Research Scientist *Original signed by*
Bruce Johnson, Ph.D., Senior Environmental Research Scientist *Original signed by*
Environmental Monitoring Branch
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DATE: September 19, 2005

SUBJECT: VERIFICATION OF PROBABILISTIC EXPOSURE AND RISK MODEL FOR FUMIGANTS 24-HOUR PERIOD MAXIMUM CONCENTRATION CALCULATIONS

Summary

The probabilistic exposure and risk model for fumigants (PERFUM) (version compiled on 11/31/2004) was evaluated by comparing PERFUM results to those obtained in Johnson (2001). Comparative analysis was based upon results from a 40 acre field, Ventura meteorology and 24-hour time-weighted average concentration, maximum buffer percentiles only. At the highest flux of 292.2ug/m^{2}s, when calms processing was removed from PERFUM, there was good correspondence between PERFUM and Johnson (2001) for percentiles less than or equal to 90%. For the flux of 292.2 ug/m^{2}s the higher percentile buffers were not comparable due to the PERFUM restriction of a maximum buffer of 1440m. This restriction was not present in Johnson (2001). At lower flux there was good agreement over all percentiles with the exception of the 99.9 percentile. In that case, our buffer estimates were lower (shorter) than the PERFUM estimates. Flagpole height of 1.5 m, used in PERFUM, versus 1.2 m, used in Johnson (2001), had only a minor effect on output. Cubic spline interpolation cases were checked and found to be in good agreement. We checked percentile calculations and found some minor differences. In summary, for 24-hour time-weighted average concentrations, we believe PERFUM (version compiled on 11/31/2004) is acceptable.

Background

The "Probabilistic Exposure and Risk Model" (PERFUM, Sciences International 2004) (version compiled on 11/31/2004) is a modeling system which uses the U.S. Environmental Protection Agency (EPA) model known as the Industrial Source Complex Short Term (ISCST3) together with custom programming that estimates buffer zone distributions based on flux profiles, acreage, acute reference concentrations, and hourly meteorological data. The conceptual framework stemmed from Johnson (2001) who analyzed the effectiveness of methyl bromide buffer zones in California. The PERFUM modeling system, however, provides many convenient features for performing percentile analysis.

The PERFUM approach employs transects of receptors in a grid radiating away from a field. The software creates control files for ISCST3 that incorporate modeling constraints input by the user. The software also runs ISCST3 (which has been encoded as a subroutine to the main PERFUM module), which provides air concentration estimates at each node of the receptor transect system. PERFUM analyzes each concentration transect output by ISCST3 to determine buffer zone distance. For each exposure period, these calculations are performed anew and the final result is a distribution of buffer zones.

There are two kinds of buffer zone distributions: whole field and maximum direction. Whole field distributions sample from the required distribution length all the way around a field. A single exposure interval will yield many buffer zones, one from each transect radiating away from the field. The longest buffer zone distances will stem from downwind directions and the shortest distances will stem from the upwind directions. The maximum direction distributions are comprised of only one buffer zone estimate for each period. That buffer zone estimate is the absolute maximum over all transects during each interval.

To evaluate methyl bromide buffer zones in California Johnson (2001) developed programming modules to run ISCST3 and provide buffer zone distance percentile distributions. Minor modifications were made to these modules to obtain buffer zone estimates for Ventura meteorological data and thus, provide an independent basis for comparison to the output from PERFUM.

Objective

The objective of this work is to derive Ventura-only buffer zone estimates from analysis software developed to evaluate methyl bromide buffer zones (Johnson 2001) and compare these distributions to the Ventura-only output from PERFUM. This work was confined to testing the maximum distance buffer zone and 24-hour averages.

Methods

The Ventura meteorological data used by Johnson (2001) had been provided to Dr. Richard Reiss (the developer of PERFUM). The first step in this project was to verify that the Ventura meteorological data distributed with PERFUM was the same meteorological data employed in Johnson (2001). The meteorological data sets were identical.

The next step was to develop buffer zone percentiles exclusively for Ventura from the Johnson (2001) analysis. Files containing buffer zone distances, date of meteorology, and county code for each buffer zone distance had previously been stored. The simple approach required creating a computer program to read in the buffer zone file, and estimate percentiles

only for Ventura. There were 25 such files, reflecting the five acreages x five flux values used in Johnson (2001). The FORTRAN program PRCNTILE.FOR was created to run this analysis. It was tested by calculating percentiles for all of the data from four counties and comparing to the output in Table 5.2.1 (Johnson 2001). The results matched, therefore PRCNTILE.FOR was working properly. Then PRCNTILE.FOR was constrained to include only the Ventura based data. This provided the Ventura-only percentiles. In subsequent paragraphs, the citation "Johnson (2001–Ventura only)" will refer to analysis based only on the Ventura portion of the output used to develop Johnson (2001).

For PERFUM the highest flux used was 292.2 ug/m^{2}s in order to match the highest flux in Johnson (2001). PERFUM allows for using reduced fluxes via an application rate scheme. The highest application rate corresponds to the stated flux. Lower application rates can be input. PERFUM takes the ratio of the lower application rate to the higher application rate to adjust the flux. The actual program mechanics, however, don't require resimulation of the lower flux once the concentration estimates from the highest flux are obtained. Since concentration and flux are proportional, it is only necessary to use the ratio of the lower flux to the highest flux as a factor to adjust the concentration vector.

PERFUM was modified by inserting code that printed out all of the buffer zone transects. The PERFUM "test day" statements were duplicated and set up to print out all of the cases. PERFUM handles abbreviated data sets. For purposes of testing code modifications or checking individual transect calculations, it was not necessary to simulate five years of meteorological data.

In addition to comparing percentile distributions, specific examples of buffer zone estimation for specific transects were checked. PERFUM uses a cubic spline interpolation to estimate required buffer zones along a transect. Also, percentile calculations were checked. The methodology employed in PERFUM to estimate percentiles is probably not technically the most accurate. However, the sample sizes are large enough that technically accurate percentiles are practically the same. The methodology used in PERFUM for estimating the percentiles is similar to that employed in Johnson (2001).

Results

Estimation of buffer zones

PERFUM was run with conditions as follows: Start flux hour 1; 40 acres; flux 292.2 ug/m^{2}s constant each hour; test day 990201; flagpole 1.2 (all discrete receptors were set to 1.2m flagpole height); 24 hour interval; target concentration 815ug/m^3; square field; fine mesh. Except for the mesh (receptor locations) these conditions matched a subset of conditions in Johnson (2001). Taking the test output from this particular run (which gives in part the node by node concentrations within each transect at each application level for the test day), we imported

individual transects into TableCurve (v5.0) and used the TableCurve cubic spline feature to interpolate buffer zones at 815ug/m^3. Table 1 shows that PERFUM estimates and the TableCurve estimates are virtually identical.

Table 1. Comparison of cubic spline interpolation from Table Curve to PERFUM cubic spline interpolation to obtain buffer zone at 815 ug/m3.

Transect Number	PERFUM Buffer Estimate (m)	Table Curve Cubic Spline Estimate of Distance (m) at 815 ug/m3
177	424.4	424.45
178	424.2	424.2
158	187.8	187.75
164	306.5	306.5
134	68.5	68.48

Estimation of Percentiles

PERFUM was run with the same conditions as in the estimation of buffer zones section, except the flagpole height was set to 1.5m (all discrete receptors were set to 1.5m flagpole height). PERFUM was modified to print out all of the buffer zones for each day. A program, CHKDIST.FOR, was written to read in these buffer zones, extract the maximum buffer zone for each day, sort the maximum buffer zones, and assign a probability based on rank. There were 1796 buffer zones, one maximum for each day. The lowest buffer zone was assigned a probability of 1/1796, the next lowest was assigned 2/1796, and so on. The highest buffer zone was assigned 1=1796/1796. This output file, consisting of buffer zone lengths and assigned cumulative probabilities, was imported into Excel and buffer zone values at key percentiles were interpolated.

This was a test of PERFUM estimation of percentiles. There are some minor discrepancies between the two percentile derivations (Table 2). The buffer zone estimations at the highest percentiles reflect the PERFUM limitation to 1440m as the maximum buffer zone size. The largest difference in this comparison was 5 meters at the 99th percentile. This difference would be approximately 1 part in 285 or about 0.4%. The cause of the difference between the two estimations is unknown.

Table 2. Comparison of percentiles based on PERFUM output calculated by PERFUM and calculated by CHKDIST.FOR.

Percentile	PERFUM	CHKDIST
99.99	1440	1440
99.9	1440	1440
99	1435	1440
97	1305	1306
95	1190	1192
90	1010	1014
85	905	907
80	830	833
70	715	716
60	620	621
50	540	540

Comparison to Johnson (2001)

Johnson (2001) presents results for the combination of weather from four counties. As described above, results restricted to Ventura only were compared to PERFUM. Since the meteorological data used was identical, any differences between PERFUM and

Johnson (2001-Ventura only) would have to be due to differences in processing the ISCST3 output or running the ISCST3 model. One difference, as shown in Table 3, is the height of the receptors. The height set in the PERFUM distribution files is 1.5m. However, Johnson (2001) ran with a receptor height of 1.2m. When this is changed, only minor differences occur in the PERFUM output (Table 3). We determined that calms processing was the primary cause of differences between PERFUM and Johnson (2001-Ventura only). PERFUM uses calms processing as described in U.S. EPA (2003), reflecting a U.S. EPA policy on performing calculations for days with calm hours. Johnson (2001) did not use calms processing, so calm hours were assigned a concentration of 0 and the 24-hour concentration was calculated as the average of the noncalm hours. The number of noncalm hours was used in the denominator to find the average concentration. Under the calms processing policy for 24-hour periods, a denominator of 18 hours is required when the number of noncalm hours is less than 18. When the number of noncalms hours is 18 or greater, noncalms and calms processing will yield identical 24-hour averages.

Table 3. Comparison of PERFUM buffer zone estimates t
from Johnson (2001) restricted to

Percentile	PERFUM 40 acres, flagpole 1.5m, fine grid	PERFUM 40 acres, flagpole 1.2m, fine grid	PERFUM, 40 acres, flagpole 1.2m, all calms processing undone*	Estimate Johnson based Ventura (2001) only
99.99	1440	1440	1440	2946
99.9	1440	1440	1440	2605
99	1435	1435	1440	1687
97	1305	1305	1405	1407
95	1190	1195	1245	1254
90	1010	1015	1055	1059
85	905	905	945	946
80	830	835	870	870
70	715	715	745	746
60	620	620	660	663
50	540	540	580	583

*See text.

In PERFUM, calms processing has been taken out of the ISCST3 portion of the code, and inserted into the PERFUM portion of the code. For the purpose of comparison, we modified PERFUM code in order to "undo" the calms processing. With that change, the percentile estimate from about 90% and below matched very well with the percentiles from Johnson (2001-Ventura only) (Table 3). The upper percentiles, however, cannot match because PERFUM transects are bounded at 1440m. In order to assess the upper percentiles, a further comparison was made between PERFUM and Johnson (2001–Ventura only) using the two lowest flux rates specified in Johnson, 104ug/m^{2}s and 39 ug/m^{2}s (Table 4). For these lower fluxes, the upper percentiles were not obscured by the PERFUM 1440m limitation. The

agreement is good, with the exception of the 99.9 percentile. In both cases, the PERFUM buffer zone estimate was substantially larger than Johnson (2001–Ventura only). For the 104ug/m^{2}s case, PERFUM estimated 1005m, while Johnson (2001-Ventura only) estimated 885m. For the 39 ug/m^{2}s case, PERFUM estimated 280m compared to 243m. The other differences were unimportant.

Table 4. Comparison of PERFUM buffer zone estimates to estimates from Johnson (2001) restricted to Ventura for lower flux rates.

	Flux = 104 ug/m2s		Flux = 39 ug/m2s	
Percentile	PERFUM, 40 acres, flagpole 1.2m, all calms processing is undone*	Estimates based on Johnson (2001) for Ventura only	PERFUM, 40 acres, flagpole 1.2m, all calms processing is undone*	Estimates based on Johnson (2001) for Ventura only
99.99	1050	1045	305	301
99.9	1005	885	280	243
99	550	554	115	112
97	440	441	70	72
95	385	391	50	51
90	305	310	20	20
85	270	276	5	0
80	240	246	5	0
70	195	195	5	0
60	160	158	5	0
50	135	132	5	0

*See text.

Because of the matches between the percentiles from 90% and below, we are in substantial agreement with the performance of PERFUM for 24-hour maximum value calculations. In addition, in the cases we checked, PERFUM correctly interpolated the downwind distance corresponding to the health threshold. In checking the percentile calculations, we arrived at approximately the same numbers, but found small unexplained differences. Examination at lower fluxes indicated that the 99.9 percentile differences were large, with PERFUM estimating larger buffer zones than Johnson (2001–Ventura only). Other percentiles for the lower fluxes compared very well.

References

Johnson, Bruce. 2001. Evaluating the effectiveness of methyl bromide soil buffer zones in maintaining acute exposures below a reference air concentration. Environmental Protection Agency, Department of Pesticide Regulation, Environmental Monitoring Branch, and Environmental Hazards Assessment Program, 1001 I Street, Sacramento, California 95812. EH00-10.

Sciences International. 2004. Detailed Description of Probabilistic Exposure and Risk model for Fumigants (PERFUM).

Table Curve v5.0. Systat Software, Richmond, California.

U.S. EPA. 2003. Appendix W. Guidelines for Air Quality Modeling.