



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PREVENTION, PESTICIDES, AND TOXIC SUBSTANCES
WASHINGTON, D.C. 20460

August 23, 2007

SUBJECT: Iodomethane: Revised HED Human Health Risk Assessment Which Incorporates Results of Human Iodine Monitoring; DP Barcode: D339055, PC Code: 000011

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Attached is HED's risk assessment of the fumigant, iodomethane. HED has evaluated the hazard and exposure data and conducted exposure assessments, as needed, to estimate the risk to human health that will result from the proposed uses of iodomethane. This risk assessment used the Reference Concentration (RfC) methodology developed by the Agency's Office of Research and Development (ORD) as well as a chemical-specific physiologically-based pharmacokinetic (PBPK) model for use in margin of exposure (MOE) calculations. It differs from the previous assessment (i.e., D325080, 1/5/2006) in that it incorporates the results of the observational human study (MRID 470286-01), and updated HECs based on this information, as well as some changes in the PBPK models used to develop them. The occupational and residential exposure analyses essentially are similar to the previous assessment with only minor changes being made in the occupational assessment which were identified in the revised Arysta iodomethane assessment (MRID 470866-01, 3/23/07).

This risk assessment addresses both exposures in general population and for those occupationally exposed. Exposures will occur primarily via inhalation. Drinking water exposure is also anticipated at some level. Although iodomethane is proposed to be used as an agricultural pesticide, it is considered a non-food use chemical since it is quickly degraded or metabolized and subsequently incorporated into natural plant constituents. The levels of iodide released from iodomethane degradation/metabolism are lower than those expected to cause toxic effects. Furthermore, enforcement of tolerances would not be possible since no iodide-free samples are available and residue field trials show evidence of control samples with higher iodide residues than iodomethane treated samples. Moreover, iodide is ubiquitous in the environment and a required nutrient. Finally, iodomethane residues must dissipate in the soil prior to planting. Accordingly, HED concluded tolerances are not required for iodomethane. As a result, a dietary risk assessment has not been conducted.

Information pertaining to the selection and use of air models for predicting off-target risks to bystanders has also been updated to reflect the methods that have been used to develop the risk estimates herein (i.e., based on the PERFUM model), to provide more extensive characterization of the modeling methods, and to provide further clarification pertaining to the selection of PERFUM for this assessment and the potential utility of other modeling systems (e.g., FEMS or CALPUFF).

This risk assessment relies on human monitoring data in which human subjects were intentionally exposed to iodomethane in order to quantify their exposures during the application process and observational human data intended to quantify iodine levels. These data can be identified by the following information:

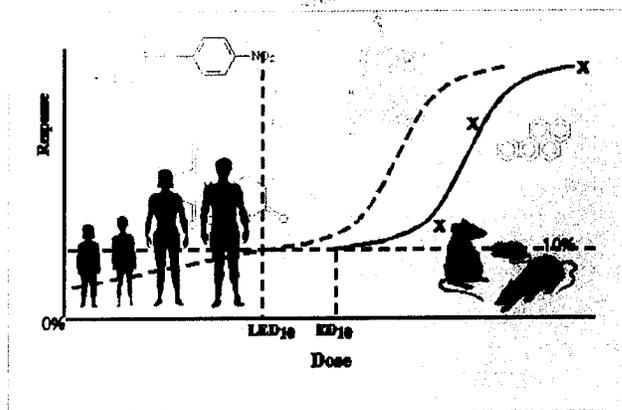
- MRID 455938-20: flat fume application in Manteca CA;
- MRID 463852-04: shank raised bed application in Guadalupe CA;
- MRID 458791-02: shank raised bed application in Marina CA (near Oxnard);
- MRID 462037-02: drip irrigation application in LaSelva CA;
- MRID 463852-03: drip irrigation application in Camarillo CA; and
- MRID 464636-02: drip irrigation application in Guadalupe CA
- MRID 470286-01: observational human iodine monitoring study.

Results of these reviews indicate that there are no concerns related to the ethical conduct of these studies that would preclude their use for risk assessment purposes.

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," <http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf>).

HUMAN HEALTH RISK ASSESSMENT

Iodomethane



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Office of Pesticide Programs
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1.0 Executive Summary

The Health Effects Division (HED) of EPA's Office of Pesticide Programs has conducted a human health risk assessment for the active ingredient, iodomethane, also referred to as methyl iodide. The proposed use of iodomethane is as a pre-plant soil fumigant in strawberries, tomatoes, peppers, perennial crop ornamentals, nurseries, cut flowers, turf, and tree and vines. Iodomethane has been identified as a possible replacement for methyl bromide, a fumigant with numerous registered uses that is subject to phase out under the accords of the Montreal Protocol because it is an ozone depleter.

With the exception of the experimental use permit currently in effect, there are no registered pesticidal uses of iodomethane at present. There are, however, some industrial and commercial uses. Currently, it is used as an intermediate in the manufacture of some pharmaceuticals, in methylation processes, and in the field of microscopy.

Although iodomethane will be used as an agricultural pesticide, it is considered a non-food use chemical since it is quickly degraded or metabolized and subsequently incorporated into natural plant constituents. The levels of iodide released from iodomethane degradation/metabolism are lower than those expected to cause toxic effects. Furthermore, iodomethane residues must dissipate in the soil prior to planting to prevent phytotoxicity. Accordingly, HED concludes that tolerances are not required for iodomethane at this time. As a result, a risk assessment has not been conducted for the dietary exposure scenario. The U.S. population, however, may be exposed to iodomethane through drinking water; therefore, a qualitative drinking water risk assessment has been conducted and no risks have been identified from this potential source of exposure.

In the general population, exposure to iodomethane is anticipated to occur via inhalation or oral (drinking water) routes but not through the dermal route. Dermal exposure to iodomethane of any significance is not expected based on the delivery systems used (e.g., soil injection or drip irrigation), packaging (i.e., pressurized cylinders), and emission reduction technologies (e.g., tarping). The high vapor pressure of iodomethane also makes significant dermal exposure unlikely. The general public, however, may be exposed to fumigants in air because of their volatility following application. Specifically, fumigants can off-gas into air and be transported off-site by winds to those in proximity to treated fields (i.e., bystanders). Consequently, the Agency conducted a quantitative human health risk assessment for nondietary exposure only via the inhalation route. For the purpose of conducting inhalation risk assessments, the current iodomethane database provides sufficient information to assess risks to the human population following iodomethane exposure via the inhalation route. Exposures may be acute (≤ 24 hours), short-term (1-30 days), intermediate-term (1 month-6 months), or long-term in duration. Proposed use patterns are believed, however, to lead predominantly to acute and short-term exposures. Acute exposures have been quantitatively assessed because this duration is the key concern due to the anticipated use pattern of iodomethane, its emission profile, and the nature of its toxicity. Additionally, for these same reasons, it is believed that acute assessments are health protective for other durations of exposure.

Iodomethane has a severe to moderate acute toxicity profile; it is severely toxic *via* the oral route (Toxicity Category II), corrosive to the eye (Toxicity Category I) and a severe dermal irritant (Toxicity Category II). Via the inhalation route, it has been classified as a Category IV chemical (slightly toxic) with an LC_{50} of 4 mg/L.

The pattern of toxicity attributed to iodomethane exposure *via* the inhalation route includes developmental toxicity (manifested as fetal losses and decreased live births), histopathology findings (respiratory tract lesions and salivary gland squamous cell metaplasia), thyroid toxicity, neurotoxicity and generalized systemic toxic effects (body weight and body weight gain decreases). The critical effects of iodomethane exposure via the inhalation route are the fetal losses observed in two developmental toxicity studies in rabbits, the histopathological lesions reported in three studies, and the neurotoxic effects (clonic convulsions, decreased body temperature and motor activity) seen in the acute neurotoxicity study in rats. The guideline inhalation chronic toxicity/carcinogenicity study in rats and the carcinogenicity study in mice revealed that chronic exposure to iodomethane resulted in an increased incidence of thyroid follicular cell tumors. The sustained perturbation of thyroid hormone homeostasis characteristic of iodomethane exposure (observed in rats, mice, and rabbits) has been established as the operative mode of action (MOA) for this tumorigenic response. As a result, HED's Cancer Assessment Review Committee (CARC) has identified iodomethane as "not likely to be carcinogenic to humans at doses that do not alter rat thyroid hormone homeostasis."

An extensive mechanistic data set, as well as a physiologically-based pharmacokinetic (PBPK) model, are available for iodomethane. These data and model constitute a sophisticated effort to better characterize the toxicity profile for this compound in terms of developmental toxicity, respiratory tract lesions, and thyroid hormone perturbations identified as the critical effects of iodomethane exposure. In addition, the use of a PBPK model that takes into consideration the toxicokinetic aspect of iodomethane exposure enables the Agency to use chemical-specific parameters to determine the most appropriate dose metric and internal dose in calculating human equivalent concentrations (HECs) instead of the default inputs used in the Agency's Reference Concentration (RfC) methodology. The Agency has reviewed these data and their usefulness to calculate human equivalent concentrations (HECs) based on chemical-specific data. In general, the model and the mechanistic studies used to provide its inputs are considered adequate and their results have been incorporated into this risk assessment.

Based on the toxicity profile and the major exposure routes of iodomethane, endpoints have been selected for the residential/bystanders and occupational human health risk assessments. HED is currently using the reference concentration (RfC) methodology along with a PBPK model to derive the human equivalent concentration (HEC) for inhalation exposures in this risk assessment. Under the RfC methodology and the PBPK model approach, endpoint selection is based on the HECs which are derived from the NOAELs of the selected studies. The specific concentrations and endpoints for the exposure scenarios are summarized below:

- **Acute inhalation:** Three critical endpoints have been identified for this risk assessment: nasal histopathology in the subchronic inhalation toxicity study in rats, the fetal losses in the developmental toxicity study in rabbits, and neurotoxicity in rats. An HEC of 4.5 or 5.8 ppm was selected (bystander and occupational risk assessments, respectively) from the NOAEL of 21 ppm based on degeneration of the olfactory epithelium. For the developmental endpoint, HED selected an HEC of 7.4 or 23 ppm (bystander and occupational risk assessments, respectively) from the NOAEL of 10 ppm based on fetal losses and decreased fetal weights in a developmental toxicity study in rabbits at the LOAEL of 20 ppm. The HEC for the neurotoxicity endpoint is 10 ppm (for both bystander and occupational exposures) based on

clonic convulsions, decreased body temperature, and decreased motor activity. An uncertainty factor (UF) of 30X defines the HED level of concern.

- **Short-term and Intermediate inhalation (bystander):** HED selected an **HEC of 1.25 ppm** from the **NOAEL of 5 ppm** based on decreased pup weight and weight gain, decreased thymus weights, and delays in vaginal patency acquisition seen in the multigeneration reproduction toxicity study at the LOAEL of 20 ppm. An uncertainty factor (UF) of 30X defines the HED level of concern.
- **Short-, Intermediate- term inhalation (occupational):** HED selected an **HEC = 3.7 ppm** from the **NOAEL of 21 ppm** based on minimal-mild degeneration of the olfactory epithelium seen at the LOAEL of 70 ppm in the subchronic inhalation toxicity study in rats. An uncertainty factor (UF) of 30X defines the HED level of concern.
- **Long- term inhalation:** HED selected an **HEC = 0.89 ppm or 3.75 ppm (bystander and occupational risk assessments, respectively)** from the **NOAEL of 5 ppm** based increased incidence of salivary gland squamous cell metaplasia seen at the LOAEL of 20 ppm from the chronic toxicity/carcinogenicity study in rats. An uncertainty factor (UF) of 30X defines the HED level of concern.

Releases of fumigants such as iodomethane can be categorized in two distinct manners that include addressing exposures from known area sources (e.g., a treated agricultural field) and also by evaluating available ambient air levels from multiple area sources that could occur from many applications in a region (e.g., several farms in a specific valley).

The evaluation of bystander exposures that can result from known area sources considered field volatility data directly from several studies, results from an Agency developed Gaussian air plume model (Industrial Source Complex Short-Term Model, ISCST3), and results from PERFUM (i.e., Probabilistic Exposure and Risk model for Fumigants) which is a modeling system based on ISCST3 that allows for incorporation of actual meteorological data into probabilistic assessments. In fact, the FIFRA Science Advisory Panel (SAP) evaluated three such modeling systems for fumigants (i.e., PERFUM, FEMS & SOFEA©) in August and September of 2004. For known area sources (i.e., treated agricultural fields), HED first used monitoring data to assess bystander exposures to iodomethane. Risks exceeded HED's level of concern based on these data for certain situations but these data are limited because they are specific to the conditions of each study. In addition, the Industrial Source Complex - Short Term model (ISCST3) was used to further characterize exposures by extrapolating to conditions under which empirical data are not be available in previous assessments. ISCST3 results have not been reported herein because the PERFUM model has been used instead and it uses ISCST3 as its core processor but allows for more flexibility since it uses actual weather conditions over 5 years instead of constrained weather conditions as in ISCST3.

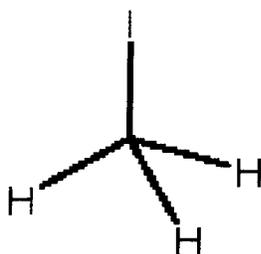
Example PERFUM results (i.e., predicted buffer distances) based on Ventura California weather data and the Watsonville California flat fume flux emission profile were evaluated. For a 10 acre field, the maximum and whole field buffer distances were as follows for each endpoint of concern at the 99th percentile of exposure at the maximum application rate and an uncertainty factor of 30: maximum and whole field buffers are 65 and 5 meters, respectively for nasal lesions; maximum and whole field buffers are both 5 meters for fetal loss; and maximum and whole field buffers are 40 and 5 meters for neurotoxicity. If any factors are reduced then predicted buffer distances change, but in a non-linear Gaussian fashion. For example, if all other factors are held constant and the application rate was reduced to 75 percent of the maximum application rate (131 lb ai/acre) then distances for the nasal lesion maximum buffer would be reduced to 25 meters. Similar trends can be observed in the results for a 40 acre field. In a 40 acre field, the maximum and whole field buffer distances were as follows for each endpoint of concern at the 99th percentile of exposure at the maximum application rate and an uncertainty factor of 30: maximum and whole field buffers are 185 and 55 meters, respectively for nasal lesions; maximum and whole field buffers are 70 and 5 meters, respectively for fetal loss; and maximum and whole field buffers are 130 and 5 meters, respectively for neurotoxicity. For comparative purposes, results for Ventura California weather data and flux profiles for different application methods were also considered. In some cases (e.g., Guadalupe California tarped raised bed application and LaSelva California drip irrigation flux) , predicted buffer distances are generally farther than those presented above for the Watsonville flat fume flux profile. For example, predicted buffers were as follows for Guadalupe (40A & 99th %tile of exposure): maximum and whole field buffers are 460 and 310 meters, respectively for nasal lesions; maximum and whole field buffers are 225 and 130 meters, respectively for fetal loss; and maximum and whole field buffers are 365 and 220 meters, respectively for neurotoxicity. In addition to the comparisons described above solely among flux types, a comparison was also completed that evaluated differences concurrently among meteorological data and flux profile. For results based on the selection of meteorological data, it appears that results for Bradenton Florida have higher associated buffer distances than (in order) Ventura California, Tallahassee Florida, Flint Michigan, and Bakersfield California. These results are consistent with the sensitivity analysis completed by the model developer and presented during the 2004 FIFRA Scientific Advisory Panel review of PERFUM.

Exposures from ambient sources were qualitatively evaluated based on physical-chemical properties and environmental fate characteristics. Ambient air monitoring data were not available since iodomethane is not currently widely used. Ambient-air exposures could potentially occur in proximity to agricultural areas where there is significant use during a particular growing season on a regional basis (e.g., in coastal areas of California during field fumigation prior to strawberry growing season). However, HED does not believe that ambient air exposures to bystanders are likely to be a significant concern based on a comparison of the characteristics of iodomethane with those of methyl bromide and the ambient air monitoring data available for methyl bromide.

Iodomethane is very soluble in water, so there is the possibility of leaching to ground water and/or transporting to surface water through runoff, if slicing or removal of the tarpaulin coincides with, or is followed soon by, a rain event. Based on environmental fate data, the residual contents in soils, and Tier I and II model estimated concentrations, HED does not expect iodomethane to adversely impact ground water or surface water.

Exposures exceed the level of concern for some workers involved in the application of iodomethane when no respiratory protection is used (e.g., tractor drivers, co-pilots, shovelers for raised beds). Conversely, risks were not of concern for all workers involved in post-application activities even without respiratory protection. For those involved in applications, air-purifying organic vapor-removing respirators (APRs) which reduce exposure levels by a factor of 10, were considered and exposures were reduced below the level of concern for all workers involved in application. For workers who enter fields days after application to prepare for planting (e.g., tarp cutters or hole punchers), exposures were not of concern 5 days after application (which reflects the available data) without any sort of respiratory protection. This is also the case for planters where exposures were not of concern 7 days after application without any sort of respiratory protection (which also reflects the available data). SCBA, as a mitigation option, is not required for any scenario since PF10 air purifying respirators reduce exposures to levels that are not of concern. Current requirements for entry of post-application workers into previously treated fields are dictated by the Worker Protection Standard as described in PR 93-7 for various other fumigants. Similar requirements are recommended for iodomethane as for methyl bromide where there is a 48 hour entry prohibition.

2.0 Ingredient Profile



Iodomethane

| | |
|--------------------|-------------------|
| Empirical Formula: | CH ₃ I |
| Molecular Weight: | 141.95 |
| CAS Registry No.: | 74-88-4 |
| PC Code: | 000011 |
| Chemical Class: | Alkyl Iodide |

Iodomethane is a colorless, liquid at normal temperatures and pressures and has a sweet ethereal odor. Iodomethane has a specific gravity of 2.28 at 20 °C, vapor pressure of 375 torr at 20 °C, boiling point of 42.5 °C, and octanol/water partition coefficient (log P_{ow}) of 1.51. It is soluble in water at 1.75 g/100 mL at 20 °C, and is miscible in alcohols and ether.

Iodomethane is a pre-plant soil biocide used to control insects, plant parasitic nematodes, soil borne pathogens, and weed seeds. The proposed uses are for growing strawberries, fresh market tomatoes, peppers, perennial crop ornamentals, nurseries, cut flowers, turf, and tree and vines.

Iodomethane is stored as a liquid under pressure but volatilizes rapidly following soil injection. It is applied by shallow shank broadcast flat fume (flat fume); raised bed shallow shank injection (raised bed); or raised bed drip irrigation (drip irrigation). A maximum effective broadcast application rate of 175 lb ai/acre has been proposed for use in various crops. This proposed application rate is the basis for the modeling completed in this assessment. The impacts of different cropping systems have also been considered in that the effective broadcast rate would be adjusted to account for the area treated beds cover per gross acre (i.e., raised bed culture in this assessment for most crops such as strawberries has been evaluated based on 50% of the area/gross acre being treated at an effective rate of 175 lb ai/acre which equates to a total amount used in raised bed culture of 88 lb ai/gross acre farmed). [Note: The field volatility and worker exposure monitoring data were generated at application rates which ranged between approximately 175 and 260 lb ai/acre.]

3.0 Metabolism

3.1 Description of Primary Crop Metabolism

Plant metabolism studies conducted on strawberries and tomatoes found iodomethane to be extensively metabolized and incorporated into the plant constituents, primarily carbohydrates. Iodide levels in the raw commodities were comparable to background levels found in control samples.

3.2 Description of Livestock Metabolism

There are no significant livestock feed items concerned with this assessment so livestock metabolism studies are not required.

3.3 Description of Rat Metabolism

A rat metabolism study comparing absorption after oral and inhalation administration is available. The data in this study indicate that iodomethane is quickly absorbed through both routes of exposure (maximum blood concentration at 2-4 hours). In contrast, the elimination profile indicates that excretion of ¹⁴C-labeled iodomethane is biphasic with the initial half-life of 5-7 hours and a terminal half-life of approximately 116-136 hours. These half-lives, however, are measured on the basis of the ¹⁴C radiolabel and may not accurately reflect the amount of iodomethane or iodide remaining in the body since the methyl and iodide moieties of iodomethane are expected to quickly dissociate after administration. Radioactivity accumulates in a variety of tissues including the thyroid (radioactivity concentration of 106-198 µg/g tissue). A second rat metabolism study was conducted to quantify the levels of inorganic iodide in rat serum after a two-day exposure (6 hrs/day) *via* the inhalation route. The results of this study indicate that inorganic iodide serum levels increase dramatically (↑300-1000 fold) during the exposure period and remained elevated during the 18 hours following exposure (↑63-400 fold).

4.0 Hazard Characterization/Assessment

4.1 Hazard Characterization

4.1.1 Database Summary

Studies available and acceptable (animal, human, general literature)

The registrant has submitted a complete database *via* the inhalation route including an acute neurotoxicity study, developmental studies in rats and rabbits, subchronic inhalation toxicity study in rats, as well as a multigeneration reproductive toxicity study and a combined chronic/carcinogenicity study in rats. All of the inhalation studies received to date have been classified as acceptable. The registrant has also conducted and submitted an Observational Human Study to better characterize the typical physiological distribution of inorganic iodide between the fetus and its mother (a critical parameter in the iodomethane PBPK model). At this time, subchronic oral toxicity studies have been submitted to the Agency. Since iodomethane has been classified as a non-food use chemical, only a screening level assessment of the oral toxicity studies has been completed.

In the peer-reviewed literature there are several reports indicating that iodomethane is toxic to the central nervous system, as well as the respiratory tract.¹ Moreover, numerous published articles indicate that methyl iodide is genotoxic due to its methylating capabilities.² Interestingly, the only evidence of genotoxicity observed in the guideline studies submitted to the Agency is an induction of structural chromosome aberrations (clastogenesis).

Metabolism, toxicokinetic, mode of action data

As stated above, a rat metabolism study comparing absorption after oral and inhalation administration is available. The data indicate that iodomethane or its metabolites accumulate in a variety of tissues including the thyroid (radioactivity concentration of 106-198 µg/g tissue) and is quickly absorbed through both oral and inhalation routes of exposure (maximum blood concentration at 2-4 hours). Also available is a rat metabolism study intended to quantify the levels of inorganic iodide in the rat serum and describe the kinetics for serum iodide accumulation/elimination after iodomethane exposure. As was noted in the guideline metabolism study, this special study indicated that while accumulation of iodide is rapid the elimination profile is slow and biphasic in nature.

¹ Robinson, DA *et al.* (2003). "Three-dimensional mapping of the lesions induced by beta-beta'-iminodipropionitrile, methyl iodide and methyl methacrylate in the rat nasal cavity." *Toxicol. Pathol.* **31**(3):340-347.

Chamberlain, MP *et al.* (1999). Methyl iodide toxicity in rat cerebellar granule cells in vitro: the role of glutathione." *Toxicology* **139**(2-3):27-37.

Chamberlain, MP *et al.* (1998). "Investigations of the pathways of toxicity of methyl iodide in the rat nasal cavity." *Toxicology* **129**(2-3):169-181

Reed, CJ *et al.* (1995). "Olfactory toxicity of methyl iodide in the rat." *Arch. Toxicol.* **70**(1):51-56

Bonnefoi, MS (1992). "Mitochondrial glutathione and methyl iodide-induced neurotoxicity in primary neural cell cultures." *Neurotoxicology* **13**(2):401-412

² Bolt, HM and Gansewendt, B. (1993) "Mechanisms of carcinogenicity of methyl halides." *Crit. Rev. Toxicol.* **23**(3):237-253.

Xu, DG *et al.* (1993). "DNA methylation of monohalogenated methanes of F344 rats." *J. Tongji Med. Univ.* **13**(2):100-104

Toxicokinetic and mode of action data have been submitted by the registrant in support of a physiologically based pharmacokinetic (PBPK) model including: i) Mode of Action Study for Iodomethane-related Fetotoxicity Study in Rabbits; ii) Combined Baseline Inhalation Exposure Study of Iodomethane-Related Fetotoxicity in Rabbits; iii) *In vivo* Two Day Inhalation Mechanistic Toxicity Study in the Rat; iv) Iodomethane: Analysis of Select Biomarkers in Rabbit Tissue; v) Iodomethane: Pulmonary Function Study in Rabbits; vi) Iodomethane: *In vitro* Partition Coefficients in Rat and Rabbit Tissues and Human Blood; vii) Iodomethane: Select Biomarkers in Rabbit Tissues after Inhalation Exposure; viii) Effects of Methyl Iodide on Deiodinase Activity; ix) Derivation of Human Reference Toxicity Values for Methyl Iodide using Physiologically Based Pharmacokinetic (PBPK) Modeling; x) Magnetic Resonance Imaging and Computational Fluid Dynamics Simulations of Rabbit Nasal Airflows; xi) Uptake of MeI by the Rabbit Nasal Cavity; xii) Uptake of MeI by the Rat Nasal Cavity; xiii) *In vivo* Gas Uptake in Rabbits; xiv) The Pharmacokinetics of Sodium Iodide (NaI) in Pregnant Rabbits; xv) *In vitro* GSH Conjugation Study in Rat, Rabbit, and Human Blood and Tissues with MeI, and xvi) Observational Human Study.

The Observational Human Study was not intended to provide NOAELs/LOAELs for risk assessment purposes but rather to better characterize the typical physiological distribution of inorganic iodide between the fetus and its mother (a critical parameter in the iodomethane PBPK model). In the study, maternal and cord blood samples were collected from 92 mothers delivering at full-term (37-41 weeks gestation) and 31 mothers delivering pre-term (29 to < 37 weeks gestation).³ It is important to note that **study participants were not exposed to any test article** and that the samples used in this study were aliquots of samples routinely collected during labor and delivery.

The Agency has reviewed these data and its usefulness to calculate human equivalent concentrations (HECs) based on chemical-specific data. The mechanistic and observational human studies were intended to either define the dose metric or provide compound-specific inputs for the PBPK model. To derive HECs using the PBPK model, internal dose metrics are predicted for the test species in which the adverse effect occurred and then the version of the PBPK model for humans is used to predict the inhalation exposure concentration (HEC) that would result in the same dose metric as in the animal. The model is a sophisticated effort to describe the kinetics of methyl iodide following inhalation exposure and the kinetics of iodide as a metabolite. It describes nasal tract dosimetry and glutathione (GSH) depletion in the rat to evaluate nasal toxicity, iodide kinetics in the pregnant rabbit to address developmental toxicity, and distribution of methyl iodide to the brain to describe the dose metric for neurotoxic effects. The model has also been parameterized for the human and Monte Carlo analyses were performed to describe human variability. The review was carried out using the framework described in Clark et al., 2004. The results of the evaluation are described focusing on the rat and human nasal modeling, the rabbit and human pregnancy modeling, the rat and human neurotoxicity model, modeling human variability, and model documentation. The strengths and limitations of the modeling were identified. The nasal modeling for rat and human was concluded to be adequate to estimate a human equivalent concentration. Selection of the appropriate degree of GSH depletion to predict nasal olfactory toxicity is dependent on additional factors beyond the PBPK/PD modeling, including judgments about the relationship of this measure with toxicity and the linkage of the time-course of exposure concentrations with the prediction of GSH depletion. The pregnancy modeling was found to be adequate to estimate a range of human equivalent concentrations. The human variability analysis was considered to provide perspective on the default value of 3 to address

³ Cord blood was used as a surrogate for fetal blood.

human pharmacokinetic variability. Similarly, the neurotoxicity model was found to be adequate to estimate a human equivalent concentration based on iodomethane brain concentrations. In general, the model and mechanistic studies used to provide its inputs are considered adequate and their results have been incorporated into this risk assessment. For a more detailed description of the model evaluation, the reader is referred to Appendix A of this document

Sufficiency of studies/data

At this time, the Agency is conducting a quantitative human health risk assessment for exposure *via* the inhalation route only. For the purpose of conducting inhalation risk assessments, the current iodomethane database provides sufficient information to assess risks to the human population following iodomethane exposure *via* the inhalation route.

4.1.2 Endpoints

The general public may be exposed to fumigants in air because of their volatility following application. Specifically, fumigants can off-gas into air and be transported by diffusion and wind off-site. In addition, the U.S. population may be exposed to iodomethane through the drinking water.

The pattern of toxicity attributed to iodomethane exposure *via* the inhalation route includes developmental toxicity (manifested as fetal losses and decreased live births), histopathology findings (respiratory tract lesions and salivary gland squamous cell metaplasia), thyroid toxicity, neurotoxicity and generalized systemic toxic effects (body weight and body weight gain decreases).

Developmental and/or offspring toxicity is observed in both rats and rabbits. Two developmental toxicity studies in rabbits conducted *via* the inhalation route have been reviewed by the Agency. In the guideline study, an increase in fetal losses was noted at the highest exposure concentration. Subsequently, the registrant conducted a phased exposure rabbit developmental toxicity study in which animals were exposed for different time periods. This second study reproduced the fetal losses seen in the guideline study and defined a narrow dosing window which may elicit this effect. Only exposure on gestation days (GD) 23-24 or GD 25-26 resulted in fetal losses. It is noteworthy, that the time of fetal loss coincides with the time of ontogeny of fetal thyroid function in the rabbit (GD22). Given the essential role of iodine in the proper function of the thyroid gland (both iodine deficiency and excess can have profound effects on thyroid function and thyroid hormone biosynthesis) and the fact that iodomethane exposure may lead to an excess accumulation of iodine in the thyroid, a mode of action (MOA) for the fetal losses involving perturbations of fetal thyroid function as a result of excess iodide has been proposed. In the case of rats, no fetal losses were reported in the developmental toxicity study yet a decrease in the number of live births was reported in the multigeneration reproduction toxicity study. It is interesting to note, however, that while iodomethane exposure in the developmental study ceased on GD17 (before ontogeny of rat fetal thyroid function), *in utero* exposure during the multigeneration toxicity continued until GD20 (*i.e.* during ontogeny of fetal thyroid function). Thus, the data suggest that fetal losses may have occurred in the rat developmental study had exposure continued beyond GD17. Similar effects have been reported for another iodine-rich compound, amiodarone (an antiarrhythmic drug), after treatment of pregnant rabbits and rats.⁴

⁴ Amiodarone printed label. Food and Drug Administration

The histopathological changes caused by iodomethane exposure occurred in the respiratory tract, and the salivary and thyroid glands. The respiratory tract histopathology was characterized by lesions of the nasal cavity described as degeneration of the olfactory epithelium (portal of entry effects). These lesions were identified in the 13-week inhalation toxicity study, the multigeneration reproductive toxicity study, and the combined chronic toxicity/carcinogenicity study in rats and were limited to the extrathoracic region with no involvement of the tracheobronchial or pulmonary regions. Furthermore, they did not appear to progress with time (*i.e.* nasal lesions of comparable severity were seen after 4, 13, and 52 weeks of exposure at the same concentration) thus suggesting the nasal lesions were the result of reaching a critical concentration (C_{max}) rather than time-dependent (*i.e.* $C \times t$; Haber's law). In contrast, a $C \times t$ relationship is assumed for all systemic effects.

Frank evidence of thyroid toxicity was reported in the combined chronic toxicity/carcinogenicity study in rats, the MOA study in rabbits, and the carcinogenicity study in mice. Indications of thyroid toxicity included enlarged thyroids, increased thyroid weights, increased incidence of ultimobranchial thyroid cysts, follicular cell hyperplasia, follicular cell adenomas, and thyroid cytoplasmic vacuolation, as well as perturbations of the thyroid-pituitary axis (decreases in T3 and T4 in conjunction with increases in TSH and rT3). These results are consistent with reports in the open literature linking excess iodine to thyroid hormone perturbations and eventually thyroid tumor formation.⁵

In regards to the potential role of iodomethane as a neurotoxicant, the inhalation acute neurotoxicity study in rats revealed that iodomethane exposure elicited clonic convulsions (repetitive mouth and jaw movement), a 2-3°C decrease in body temperature, and an 80% decrease in motor activity in the absence of neuropathology.

4.1.3 Dose-response

The primary exposure pathway for iodomethane is *via* inhalation. Exposures may be acute (less than 24 hours), short-term (1-30 days), intermediate-term (1 month-6 months), or long-term in duration.

4.1.3.1 Inhalation Exposure

The critical effects of iodomethane exposure via the inhalation route are the fetal losses observed in two developmental toxicity studies in rabbits, the histopathological lesions reported in three studies, and the neurotoxic effects seen in the acute neurotoxicity study in rats. In evaluating the risks that a compound may pose to human health after exposure via the inhalation route, different methodologies have been historically used by the USEPA and the California Department of Pesticide Regulation (CDPR). An example of CDPR's methodology, and the species-specific parameters used in this approach can be found in the CDPR website and their MeBr risk assessment, Appendix G at the following web address (www.cdpr.ca.gov/docs/dprdocs/methbrom/append_g.pdf). As OPP

⁵Zhu, Y. *et al.* "Excess iodine induces the expression of thyroid solid cell nests in lymphocytic thyroiditis-prone BB/W rats." *Autoimmunity* (1995) **20**:201-106

Kanno, J. *et al.* "Tumor-promoting effects of both iodine deficiency and iodine excess in the rat thyroid" *Toxicol. Path.* (1992) **20**(2):226-235

understands the importance to harmonize with other regulatory agencies, fumigant risk assessments will present HECs derived using EPA's RfC methodology as well as CDPR's methodology, when available.⁶

In this risk assessment, endpoint selection will be based on the endpoints occurring at the lowest HECs (which may or may not be the lowest animal NOAEL) derived using the RfC methodology or PBPK model. In both approaches, different HECs may be calculated for the same experimental NOAEL due to: 1) the different algorithms used to derive HECs for systemic *versus* portal of entry effects; 2) different dose metrics used in the PBPK model or 3) the time adjustments conducted for non-occupational *versus* occupational exposure scenarios. The differences between systemic *versus* portal of entry effects, arise from the use of different calculations to estimate the inhalation risk to humans which are dependent on the regional gas dose ratio (RGDR). In the case of systemic *versus* portal of entry effects, different RGDRs are derived for each type of toxicity. For non-occupational *versus* occupational exposure, the differences arise because while it is presumed that non-occupational exposure may occur 24 hours/day, 7 days/week; occupational exposure occurs only during the course of an average workweek (8 hours/day and 5 days/week). The iodomethane PBPK model, on the other hand, uses MOA data to derive internal dose metrics in the test species which are then used to extrapolate to humans and calculate HECs. A more detailed description and evaluation of the PBPK model are available in Appendix A of this document. For further details on the critical studies used for endpoint selection and the iodomethane toxicity profile the reader is referred to Appendix B. For additional information on the methodologies used in this risk assessment and the HEC arrays, please refer to Appendix C. The toxicity endpoints selected for risk assessment are presented below.

Acute Inhalation Exposure

Endpoint selection for acute inhalation exposures was based on four co-critical studies: a subchronic inhalation toxicity study in rats, two developmental toxicity studies in rabbits, and an acute neurotoxicity study in rats briefly described below:

Subchronic Inhalation Toxicity Study in rats

In a subchronic inhalation toxicity study (MRID 45593810), iodomethane (99.7% a.i.; Lot/batch # 007403/02) was administered via whole-body inhalation to CrI:CD~(SD)IGS BR rats (20/sex/concentration) for 6 hours/day, 5 days/week for 13 weeks at analytical concentrations of 0, 5, 21, or 70 ppm (0, 0.029, 0.12, or 0.41 mg/L/day). Ten rats/sex/concentration were sacrificed after 4 weeks, and the remaining 10 rats/sex/concentration were sacrificed after 13 weeks. There were no effects of treatment on mortality, ophthalmology, urinalysis, hematology, organ weights, or gross pathology .

The systemic LOAEL for this study is 70 ppm based on initial decreases in body weights, body weight gains, and food consumption (males). The NOAEL is 21 ppm (HEC = 3.8 or 15.8 ppm for non-occupational and occupational risk assessments, respectively).

The port-of-entry LOAEL is 70 ppm based on degeneration of the olfactory epithelium. The NOAEL is 21 ppm (HEC = 4.5 or 5.8 ppm for non-occupational and occupational risk assessments, respectively).

⁶ At this time, CDPR has not conducted a risk assessment for iodomethane; thus, CDPR HECs are not available for iodomethane.

Developmental Toxicity Study in rabbits

In a developmental toxicity study (MRID 45593811), groups of 24 female New Zealand White rabbits were dynamically exposed to iodomethane vapor (Lot/batch # 007403/02; 99.6% a.i.) in whole-body inhalation chambers at analytical concentrations of 0, 2, 10, or 20 ppm (0, 0.012, 0.058, or 0.12 mg/L/day) six hours per day on gestation days (GDs) 6 through 28.

The maternal NOAEL is 20 ppm; no maternal LOAEL was identified. The developmental toxicity LOAEL is 20 ppm based on increased fetal losses and decreased fetal weights (↓20%). The developmental toxicity NOAEL is 10 ppm (HEC = 7.4 or 23 ppm for non-occupational and occupational risk assessments, respectively).

In a developmental toxicity study (MRID 46077001) iodomethane (99.7% a.i., Batch# 02/Lot# 007403) was administered via the inhalation route (whole body) to 24 New Zealand White rabbits/group at concentrations of 0 or 20 ppm during GD 6-28 (Control and Group 2), GD 6-14 (Group 3), GD 15-22 (Group 4), GD 23-24 (Group 5), GD 25-26 (Group 6), or GD 27-28 (Group 7) for 6 hours/exposure day. This study was not intended to fulfill the guideline requirement or establish NOAELs and LOAELs but rather was conducted to determine the critical period of exposure during gestation that resulted in fetal loss as observed in a previously evaluated guideline developmental toxicity study in rabbits.

Acute Neurotoxicity Study in rats

In an acute neurotoxicity study in rats (MRID45593817) iodomethane (100% a.i., Batch/Lot# 007403) was administered *via* the inhalation route (whole body) to 12 CrI:CD®(SD)IGS BR rats/sex/group at concentrations of 0, 27, 93, or 401 ppm for 6 hours.

The NOAEL is 27 ppm (HEC = 10 ppm for both bystander and occupational risk assessments). The LOAEL is 93ppm based on clonic convulsions, decreased body temperatures, and decreased motor activity.

Dose and Endpoint for Risk Assessment: Three critical endpoints have been identified for this risk assessment: nasal histopathology in the Subchronic Inhalation Toxicity Study in rats, fetal losses in two developmental toxicity studies in rabbits, and neurotoxic effects (clonic convulsions, decreased body temperatures, and decreased motor activity). **Using the iodomethane PBPK model developed by Arysta (iodomethane registrant) and reviewed by the Agency, the HEC for nasal histopathology is 4.5 or 5.8 ppm for non-occupational and occupational risk assessments, respectively. For the fetal losses, the Agency has derived an HEC of 7.4 or 23 ppm for the non-occupational and occupational risk assessments, respectively while the HEC for neurotoxicity is 10 ppm for both bystander and occupational risk assessments.**⁷

⁷ For the dose metric used in the neurotoxicity assessment (inorganic iodide brain concentration), steady state is reached within the first 8 hrs of exposure. Therefore, a time adjustment for longer periods of exposure is not required since blood concentration will not vary after steady state is reached.

The nasal histopathology was reported after a 13-week exposure to iodomethane, however, data from the published literature indicate that nasal lesions can occur after acute exposures (≈ 2 hrs. at 100 ppm) if the time profile of the exposure concentration leads to an overall iodomethane exposure of ≥ 200 ppm/hr.⁸ Based on this information in conjunction with the iodomethane PBPK and PERFUM models, HED and ORD scientists have concluded that an HEC of 4.5 or 5.8 ppm for non-occupational and occupational risk assessments, respectively, is appropriate for this risk assessment.

The proposed MOA for nasal histopathology involves glutathione (GSH) depletion as a key event in the toxicity pathway leading to damage of the nasal olfactory epithelium. Consequently, GSH depletion is the dose metric used in the PBPK model for interspecies extrapolation to determine the NOAEL for the nasal lesions. Using the HEC of **4.5 or 5.8 ppm for non-occupational and occupational risk assessments**, respectively, results in a 24-hr time-weighted average GSH depletion of $\approx 50\%$ (*i.e.*, the level of GSH depletion commonly cited in the literature as critical for development of nasal histopathology). It should be noted that the emission profile of iodomethane suggests that during peak emissions GSH depletion is likely lower than 50% (*e.g.* 38%). The PBPK model of iodomethane implements a complex description of the nasal tissues to address different airflow pathways and tissue types. For the olfactory epithelium there are five compartments, divided into two major groupings. The top four layers represent the olfactory epithelial cells which are linked by diffusion of the chemical from one layer to the next (and back in the opposite direction). The fifth layer is the blood exchange layer representing the lamina propria. Chemical exchanges in and out of this layer with the top four layers, as well as the bloodstream, lead to distribution throughout the body. In the model, GSH concentration is calculated as a volume weighted average across the layers in the olfactory epithelium. While in humans the top four layers (*i.e.*, the olfactory epithelial cells) are of equal thickness and volumes in the model, the fifth layer is substantially thicker. Under these circumstances, the volume weighted average is overwhelmed by the 5th layer leading to a potential underestimation of overall GSH depletion (5 compartment average) in spite of substantial depletion in the top 4 layers. In order to protect the olfactory sensory cells and the epithelial cell layer above the lamina propria, the Agency has used the four compartment average rather than the 5 compartment average used by the registrant. Also noteworthy is that in the previous assessment a GSH depletion of $\approx 25\%$ was used as the dose metric to define the point of departure for the nasal toxicity risk assessment. In this current assessment, however, the Agency has selected 50% GSH depletion. This change is due to the additional refinements in the PBPK model that allow Agency scientists to calculate GSH depletion in distinct layers of the olfactory epithelium thus ensuring that no single layer has more than the 50% GSH depletion commonly cited in the literature as critical for development of nasal histopathology. Moreover, the model describes GSH depletion resulting from conjugation with methyl iodide, metabolic consumption, synthesis, and degradation in each of the four top layers. It does not, however, fully account for the impact of GSH diffusion across layers thus potentially overestimating the extent of GSH depletion in each of the top layers (Figure 1).

⁸ Reed, CJ *et al.* (1995). "Olfactory Toxicity of Methyl Iodide in the Rat" *Arch Toxicol.* **70**:51-56

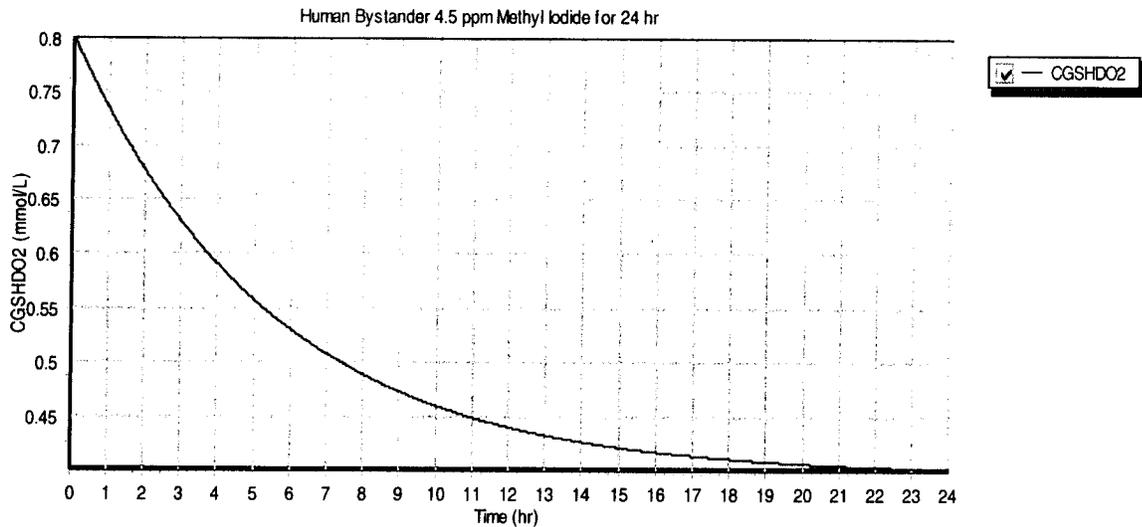


Figure 1: Predicted glutathione concentration in the olfactory epithelium of an adult human exposed to 4.5 ppm methyl iodide for 24 hr. The majority of the depletion occurs in the first 8 hours while near steady state is achieved by 24 hrs.

The endpoint of fetal losses identified in the developmental toxicity studies in rabbits is also considered appropriate for this risk assessment since it is presumed that developmental effects may be the outcome of an acute exposure. In the case of iodomethane, this presumption has been substantiated by the results of the phased developmental toxicity study in rabbits in which fetal losses were observed after two 6 hr exposures. Excess serum iodide has been implicated as a critical element in the MOA proposed for this endpoint. In a MOA study submitted by the registrant, excess iodide has been shown to lead to fetal thyroid hormone disruptions (Wolff-Chaikoff effect) resulting in fetal loss. Consequently, the dose metric used for this assessment is the area under the concentration curve (AUC) for fetal serum inorganic iodide during a single day of exposure. Based on this dose metric, an **HEC of 7.4 ppm is calculated for the non-occupational risk assessment and 23 ppm for the occupational risk assessment.** This HEC is based, in part, on the findings in the Observational Human Study that human fetal serum iodide levels are approximately equivalent to the maternal levels. Although data in support of this presumption were previously available from the peer reviewed literature, the Agency had concluded that the evidence was not sufficiently robust (*i.e.* limited and often indirect) to derive an HEC based on a 1:1 ratio of fetal:maternal serum iodide levels. Consequently, an HEC of 4 ppm was used in the previous risk assessment which assumes an equivalent distribution of fetal serum iodide in rabbits and humans (*i.e.*, assume that - like rabbit fetuses - the human fetus concentrates iodide relative to its mother). This assumption, however, has not been supported by the results of the observational human study. Instead the observational human study indicates that human fetuses do not concentrate iodide relative to their mother thereby leading to a fetal:maternal serum inorganic iodide ratio of ≈ 1 . The highest ratio identified in the study is 1.2 (*i.e.*, fetal serum iodide concentration is 20% higher than the maternal concentration). It is this ratio that was used to parameterize the iodomethane PBPK model.

For the neurotoxicity endpoints (clonic convulsions, decreased body temperature, and decreased motor activity), the steady state brain iodomethane concentration is used as the dose metric. An HEC = 10 ppm is used for both bystander and occupational risk assessments since steady state is achieved in 8 hrs of exposure.

For all endpoints described in this section, an UF of 30X defines HED's level of concern.

Note: For a more detailed description of the PBPK evaluation, refer to Appendix A of this risk assessment.

Short-, and Intermediate-term Inhalation Exposure

Non-occupational Exposure

In a two-generation reproduction toxicity study, iodomethane (99.7% a.i.; Lot/batch # 007403/02) was administered via whole-body inhalation to Crl:CD[®](SD)IGS BR rats (30/sex/concentration) for 6 hours/day at nominal concentration levels of 0, 5, 20, or 50 ppm (equivalent to analytical concentrations of 0, 5, 21, and 50 ppm). The P animals were exposed to the test article for at least 70 days prior to mating to produce the F₁ litters. Exposure of the P males continued throughout mating and until the day prior to euthanasia. The P females continued to be exposed throughout mating and through gestation day (GD) 20, at which point exposure was discontinued. Daily exposure of the P females was reinitiated on lactation day (LD) 5 and continued until the day prior to euthanasia. After weaning, F₁ animals (30/sex/concentration) were selected, equalized by sex, to become the parents of the F₂ generation and, beginning on post-natal day (PND) 28, were exposed to the same concentration test atmosphere as their dam.

The systemic parental NOAEL is 20 ppm (HEC = 5 ppm) and the LOAEL is established at 50 ppm based on decreases in body weight, body weight gain, changes in organ weights (adrenal glands, testis, cauda epidymis, epidymis, and thymus) as well as gross pathology and histopathology findings.

The port of entry NOAEL is 20 ppm (HEC = 3.2 ppm) and the LOAEL is 50 ppm based on minimal-mild degeneration of the olfactory epithelium.

The offspring NOAEL is 5 ppm (HEC = 1.25 ppm) and the LOAEL is 20 ppm based on decreases in body weight, body weight gain, as well as lower absolute and relative thymus weights.

The reproductive NOAEL is 5 ppm (HEC = 1.25 ppm) and the LOAEL is 20 ppm based on delays in attainment of vaginal patency.

Dose and Endpoint for Risk Assessment: HEC of 1.25 ppm based on decreased pup weight and weight gain, decreased thymus weights, and delays in vaginal patency acquisition. The duration of exposure in the multigeneration reproduction toxicity is appropriate for short- and intermediate-term risk assessments and it yields the lowest HEC (*ie.* most health protective exposure concentration) for these exposure scenarios. An UF of 30X defines HED's level of concern in accordance with guidance provided in the RfC methodology (see section 4.2 below).

Occupational Exposure

See non-occupational exposure above for brief executive summary. Different HECs have been calculated for occupational exposures due to the time adjustments made for the exposure scenarios.

Systemic parental NOAEL is 20 ppm (HEC = 15 ppm).

Port of entry NOAEL is 20 ppm (HEC = 3.7 ppm).

Offspring NOAEL is 5 ppm (HEC = 3.75 ppm).

Reproductive NOAEL is 5 ppm (HEC = 3.75 ppm).

Dose and Endpoint for Risk Assessment: HEC of 3.75 ppm based on minimal-mild degeneration of the olfactory epithelium. The duration of exposure in the multigeneration reproduction toxicity is appropriate for short- and intermediate-term risk assessments and it yields the lowest HEC (*ie.* most health protective exposure concentration) for these exposure scenarios. An UF of 30X defines HED's level of concern in accordance with guidance provided in the RfC methodology (see section 4.2 below).

Long-term Inhalation Exposure

Non-occupational and Occupational Exposure

In a combined chronic toxicity/carcinogenicity study in rats (MRID 45612401), iodomethane (99.7% a.i., Batch No. 02/Lot # 007403) was administered to CrI:CD®(SD)IGS BR rats *via* whole body inhalation at concentrations of 0, 5, 20, or 60 ppm for 6 hours/day 5 days/week. Sixty animals/sex/concentration were exposed to 0, 5, or 20 ppm iodomethane while 70/sex were exposed at the 60 ppm level. Animals were observed for morbidity and mortality twice daily and clinical observations once daily. Once a week a detailed physical examination was conducted including but not limited to evaluations of changes in appearance, autonomic activity (*e.g.* lacrimation, piloerection, pupil size, breathing patterns), gait, posture, response to handling, stereotypic and/or bizarre behavior. In addition, evaluations of clinical chemistry, hematology, urinalysis, gross pathology and histopathology parameters were conducted.

The systemic NOAEL is 5 ppm (HEC = 0.89 or 3.75 ppm for non-occupational and occupational risk assessments, respectively); the LOAEL is established at 20 ppm based on increased incidence of salivary gland squamous cell metaplasia.

The NOAEL for port of entry effects (respiratory tract) is 20 ppm (HEC = 3.2 or 4.2 ppm for non-occupational and occupational risk assessments, respectively) and the LOAEL is 60 ppm based on degeneration of the olfactory epithelium.

Dose and Endpoint for Risk Assessment: HEC of 0.89 ppm or 3.75 ppm for non-occupational and occupational risk assessments, respectively based on increased incidence of salivary gland squamous cell metaplasia. This is the study of the longest duration available in the iodomethane database and it yields the lowest HEC (*ie.* most health-protective) for this exposure scenario. An UF of 30X defines HED's level of concern in accordance with guidance provided in the RfC methodology (see section 4.2 below).

4.1.3.2 Dietary Exposure

Although iodomethane is used as an agricultural pesticide, it is considered a non-food use chemical since it is quickly degraded or metabolized and subsequently incorporated into natural plant constituents. The levels of iodide released from iodomethane degradation/metabolism are lower than those expected to cause toxic effects. Furthermore, enforcement of tolerances would not be possible since no iodide-free samples are available and residue field trials show evidence of control samples with higher iodide residues than iodomethane treated samples. Moreover, iodide is ubiquitous in the environment and a required nutrient. Finally, iodomethane residues must dissipate in the soil prior to planting. Accordingly, HED concluded tolerances are not required for iodomethane. As a result, a risk assessment has not been conducted for this exposure scenario. The U.S. population, however, may be exposed to iodomethane through drinking water; therefore, a qualitative drinking water risk assessment was conducted and no risks were identified from this potential exposure.

4.1.3.3 Dermal Exposure

Exposure to iodomethane is anticipated via inhalation or oral (drinking water) routes but not through the dermal route. Dermal exposure to iodomethane of any significance is not expected based on the delivery systems used (e.g., soil injection or drip irrigation), packaging (i.e., pressurized cylinders), and emission reduction technologies (e.g., tarping). The high vapor pressure of iodomethane also makes significant dermal exposure unlikely and quantifying any potential low level exposures very difficult. Therefore, a quantitative dermal exposure assessment has not been completed. Since HED does not have adequate data to quantify dermal risk, PPE for dermal protection should be based on the acute toxicity of the end-use product as described in the Worker Protection Standard and mitigation measures for dermal exposure described in PR Notice 93-7.

4.1.3.4 Classification of Carcinogenic Potential

The Cancer Assessment Review Committee (CARC) evaluated the rodent bioassays and mechanistic data available for iodomethane. Evidence of carcinogenicity in the iodomethane database manifested as an increased incidence of thyroid follicular cell tumors observed in both the Inhalation Chronic Toxicity/Carcinogenicity Study in Rats and the Carcinogenicity Study in Mice. The committee concluded that the key event influencing the thyroid tumor response is the sustained stimulation of cell proliferation by TSH, consistent with the increase in thyroid follicular cell tumors only. Based on the evidence that rats are substantially more sensitive than humans to the development of thyroid follicular cell tumors in response to thyroid hormone imbalance, the CARC classified iodomethane as "not likely to be carcinogenic to humans at doses that do not alter rat thyroid hormone homeostasis."

4.1.4 Endocrine Disruption

Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, iodomethane may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

4.2 Uncertainty Factors

Iodomethane has been classified as a non-food use pesticide. Consequently, this chemical is not subject to the FQPA (1996) and the 10X FQPA factor does not apply.

When conducting inhalation risk assessments, the magnitude of the UFs applied is dependent on the methodology used to calculate risk. This risk assessment is based on the RfC methodology developed by the Office of Research and Development (ORD) and the PBPK model developed by the registrant for the derivation of inhalation reference concentrations (RfCs) and human equivalent concentrations (HECs) for use in margin of exposure (MOE) calculations. Since both of these approaches take into consideration the pharmacokinetic (PK) but not pharmacodynamic (PD) differences between test species and humans, the UF for interspecies extrapolation may be reduced to 3X while the UF for intraspecies variation is retained at 10X.⁹ Thus, when using the RfC methodology the overall UF is customarily 30X.

⁹ A 3X UF for interspecies extrapolation is retained to account for the PD differences between animals and humans which are not accounted for in the RfC methodology or the PBPK model.

4.3 Summary of Toxicological Endpoint Selection

| Table 1: Summary of Toxicological Dose and Endpoints for Use in Iodomethane Human Health Inhalation Risk Assessment | | | | | | |
|---|------------------|---|----------------------------------|--|---------------------|------------------------|
| Risk Assessment | | Study | NOAEL/LOAEL | Endpoint | HED HECs | CPDR HECs ¹ |
| Acute [†] | Non-occupational | Subchronic Inhalation Toxicity Study in Rat | NOAEL = 21 ppm LOAEL = 70 ppm | Degeneration of the olfactory epithelium | 4.5 ppm UF=30 | N.A. |
| | | Developmental Study in Rabbits | NOAEL = 10 ppm LOAEL = 20 ppm | Developmental effects: fetal loss | 7.4 ppm UF = 30 | |
| | | Acute Neurotoxicity Study in Rats | NOAEL = 27 ppm LOAEL = 93 ppm | Clonic convulsions, decreased body temperature, and decreased motor activity | 10 ppm UF = 30 | |
| | Occupational | Subchronic Inhalation Toxicity Study in Rat | NOAEL = 21 ppm LOAEL = 70 ppm | Degeneration of the olfactory epithelium | 5.8 ppm UF=30 | |
| | | Developmental Study in Rabbits | NOAEL = 10 ppm LOAEL = 20 ppm | Developmental effects: fetal loss | 23 ppm UF = 30 | |
| | | Acute Neurotoxicity Study in Rats | NOAEL = 27 ppm LOAEL = 93 ppm | Clonic convulsions, decreased body temperature, and decreased motor activity | 10 ppm UF = 30 | |
| Short-, Intermediate-Term, Inhalation (1-6 months exposure) | Non-occupational | Multigeneration Reproductive Toxicity Study in Rats | NOAEL = 5 ppm LOAEL = 20 ppm | Offspring effects: decreased body weight, weight gain, and thymus weights Reproductive effects: Delays in vaginal patency | 1.25 ppm UF = 30 | N.A. |

Table 1: Summary of Toxicological Dose and Endpoints for Use in Iodomethane Human Health Inhalation Risk Assessment

| Risk Assessment | | Study | NOAEL/LOAEL | Endpoint | HED HECs | CPDR HECs [†] |
|------------------------|------------------|---|--|---|---------------------|------------------------|
| | Occupational | Multigeneration Reproductive Toxicity Study in Rats | NOAEL = 5 ppm LOAEL = 20 ppm | Offspring effects: decreased body weight, weight gain, and thymus weights Reproductive effects: Delays in vaginal patency | 3.75 ppm UF = 30 | |
| Long-term (> 6 months) | Non-occupational | Chronic/ Carcinogenicity Study in Rats | NOAEL = 5 ppm LOAEL = 20 ppm | Squamous cell metaplasia | 0.89 ppm UF = 30 | N.A. |
| | Occupational | Chronic/ Carcinogenicity Study in Rats | NOAEL = 5 ppm LOAEL = 20 ppm | Squamous cell metaplasia | 3.75 ppm UF = 30 | |
| Cancer | | | Not likely to be carcinogenic to humans at doses that do not alter rat thyroid hormone homeostasis | | | |

[†] At this time, CDPR has not conducted a risk assessment for iodomethane (pending submission of additional data).

[†] HECs calculated using PBPK model

5.0 Public Health Data

Over the past century, only 11 incidents of iodomethane poisoning have been reported in the published literature¹⁰. In general, symptoms of iodomethane intoxication in humans were related to effects on the nervous system ranging from somnolence to ataxia, seizures, delirium and coma in severe cases. In some patients, cerebellar lesions and damage of the third, fourth, or sixth cranial nerve pathways as well as spinal cord lesions producing motor and sensory disturbances have been reported. Latent symptoms of iodomethane intoxication include psychological disorders such as depression. In addition to neurological effects, iodomethane exposure has also been linked to congestive changes in the lungs and oliguric renal failure. It is noteworthy, however, that in most of these incidents the precise iodomethane exposure concentration is unknown though it appears that exposure was to high levels (due in part to use of inadequate protective devices) resulting from industrial uses and far exceeding those proposed for regulatory purposes in this risk assessment or anticipated agricultural uses.

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

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

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

¹⁰Hermouet, C. et al. "Methyl iodide poisoning: Report of two cases" *Am. J. Ind. Medicine* (1996) 30: 759-764 & Appel, G.B. et al. "Methyl iodide intoxication" *Annals of Int. Med* (1975) 82:534-536

6.0 Non-Occupational Exposure Assessment and Characterization

The exposures and resulting risks that are anticipated associated with the proposed uses of iodomethane in the general population are addressed in this section. An integrated approach has been used that considers monitoring data, the possibility of incidents, and the use of computer modeling to evaluate the possibility of off-target transport that occurs from volatilization under varied meteorological conditions. Monitoring data indicate that iodomethane volatilizes after application to agricultural fields and that inhalation exposure is possible when individuals are in proximity to specific application events. After application, iodomethane typically volatilizes from soil rapidly with a large portion of the total mass being emitted in the first 24 hours. This is illustrated in Figure 2 by the emissions profile from two tarped flat fume applications, which a common cultural practice for tomato and strawberry production. Once emitted into the atmosphere, iodomethane may be sufficiently persistent so that exposures could occur within general regions where iodomethane may be used (i.e., ambient exposures). However, since iodomethane is not a registered product no data are available for purposes of quantifying ambient exposures.

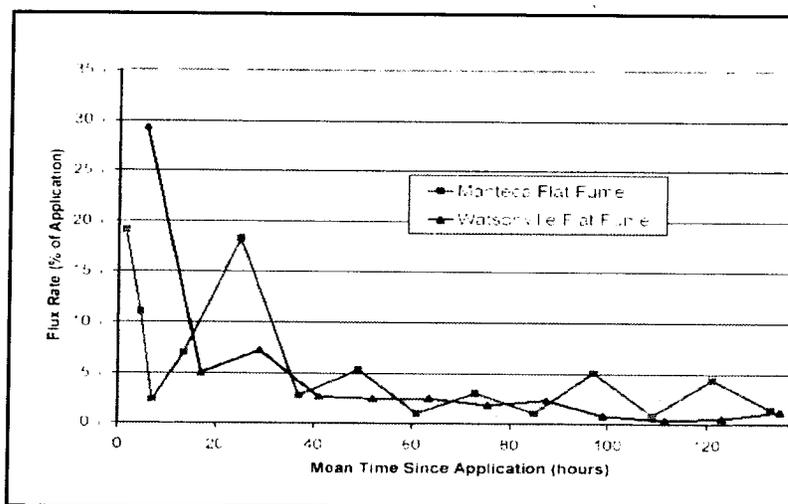


Figure 2: Iodomethane Emission Profiles For Tarped Flat Fume Applications In California

Iodomethane is not registered at this time, thus it is not in widespread use, so a comprehensive evaluation of incidents is also not possible. However, iodomethane would be commercially formulated with chloropicrin so the incident rates associated with chloropicrin could also be expected with any iodomethane combination product because application practices will be similar in most circumstances to other existing chloropicrin uses. Dermal exposures in the general population are not anticipated because of the volatility of iodomethane and the fact that all iodomethane products would be restricted use pesticides which precludes direct dermal contact since the product is only a liquid that could get on the skin prior to application. Dermal incidents would be expected to be generally attributable to accidents or equipment failure as with other similar types of chemicals during application. Dermal exposures have not been addressed herein due to the lack of opportunity for exposure and the volatility of iodomethane. Exposures from drinking water and food residues are also considered negligible and have been addressed below as well (i.e., iodomethane labels are considered to be non-food uses).

Because most mass of iodomethane is rapidly emitted into the atmosphere after field applications, acute exposure scenarios are of key concern to residential bystanders (i.e., those who are in the proximity of the emissions resulting from a iodomethane application). Bystander exposure to iodomethane, or any fumigant for that matter, depends on two main factors: (1) the rate of emissions from a treated field into the atmosphere (described as flux) and (2) how those resulting emissions are dispersed in the air over and around the treated field. Emission rates from treated fields (i.e., flux) are affected primarily by the amount of fumigant applied (which is proportional to the rate and area treated), the application method and equipment used, sealing technologies use to reduce emission levels, and the field conditions where factors such as soil type, moisture, and amount of organic material may impact emission rates. Once iodomethane, or any other fumigant, has been emitted into the atmosphere, meteorological conditions and the topography at the site determine how the fumigant is dispersed. For example, if winds are high and the atmosphere is unstable, then emitted fumigant concentrations are more likely to be reduced because greater mixing and dispersion will occur. Under such conditions, the likelihood of a bystander being exposed to a fumigant at a concentration of concern is relatively lower. On the other hand if winds are light and the atmosphere is stable, then the emitted fumigant is more likely to build in concentration and be at higher levels in proximity to the treatment area. Topography, as well as other factors, can also cause winds from certain directions to be predominant which can predispose certain populations to higher exposure levels (e.g., a school located in a valley where prevailing winds from a treated field approach it or a similar situation with prevailing onshore coastal winds in California or Florida).

This section describes the potential exposure scenarios associated with the use of iodomethane. These include residential bystander exposure from two key sources including: known sources from a single application site (i.e., area sources such as at the edge of a treated field) and ambient air levels that result from many applications within a region. There are no homeowner uses of iodomethane so this aspect of the risk assessment focuses on those types of exposures that may occur from professional uses of iodomethane that can lead to exposures in residential environments. *Section 6.1: Residential Bystander Exposure And Risk Estimates* describes how exposure and risk estimates were calculated for the general population who may be exposed living in proximity to individual application sites or within regions where iodomethane use may routinely occur. *Section 6.2: Bystander Risk Characterization* describes the factors that should be considered when interpreting the results of this risk assessment.

6.1 Residential Bystander Exposure and Risk Estimates

Residential bystander exposure may occur because of emissions from treated fields as indicated above. An integrated approach has been used to calculate risks from known sources from a single application site that is based on air modeling, incident information, and monitoring data. Ambient exposures have been addressed qualitatively since monitoring data for this purpose are not available at this time.

When considering the potential risks of bystanders for single application known sources (e.g., a farm field), it is important to note that they were developed based on an integrated, iterative process that reflects a variety of methods used to calculate them. It is also important that results based on incidents, monitoring data, and modeling be considered in conjunction with one another to ensure consistency in the overall characterization of the risks associated with iodomethane use. This integrated approach allows for more predictive capability to other use situations (i.e., it is less constrained by the circumstances of the incident or particular field study) yet it still considers empirical monitoring data reflective of actual iodomethane applications. There are a number of

volatility studies which quantified iodomethane emissions from treated fields. These data are limited in their utility because they provide results only for the specific conditions under which the experiments were conducted. Risks have been calculated using the empirical results of these studies.

Since there are no currently registered pesticide uses of iodomethane, no incidents associated with its use as a soil fumigant according to labeled practices have occurred which only makes a comparison of monitoring results and modeling results possible. [Note: In one case there was an incident due to equipment failure during manufacturing that is not related to proper use under label guidance.]

Models have also been used to estimate potential risks from iodomethane to bystanders under varying conditions. The first modeling approach was based on the deterministic use of the Agency's *Industrial Source Complex* model (ISCST3) which provides off-site air concentration estimates and the second approach which is based on a distributional model called the *Probabilistic Exposure and Risk Model For Fumigants* (PERFUM) which calculates distances at which target concentrations are achieved at varied percentiles of exposure. PERFUM also can provide distributions of air concentrations at varied distances from the perimeter of treated fields. It develops distributions based on 5 years of meteorological data. It also probabilistically addressed variability in the emissions for iodomethane.

As indicated above, no monitoring data are available to evaluate iodomethane exposures from ambient air. Iodomethane does appear, however, to be less stable in the environment than methyl bromide, of similar or lesser volatility, and it will be used at lower application rates so it is likely that ambient levels will be lower than those generally seen with methyl bromide (see Agency risk assessment for methyl bromide D337288 – April 10, 2007 for further information).

The potential risks related to exposures from a single application area source such as a treated farmfield for bystanders are described below in *Section 6.1.1: Bystander Exposures And Risks From Known Sources* while the potential risks associated with exposures to ambient air are described below in *Section 6.1.2: Ambient Bystander Exposure From Multiple Regional Sources*. Each section provides a description of the methods used and the results.

6.1.1 Bystander Exposures and Risks From Known Sources

As noted, residential bystander exposure may occur because of emissions due to single applications from known sources such as treated fields or structures. The methods used to assess the exposures and risks related to these uses are described below in *Section 6.1.1.1: Methods Used To Calculate Bystander Exposures And Risks From Known Sources*. The results calculated for all scenarios of interest based on the most appropriate method for that scenario are presented in *Section 6.1.1.2: Bystander Exposures And Risks From Known Sources*.

6.1.1.1 Methods Used To Calculate Bystander Exposures And Risks From Known Sources

As indicated above, the Agency's calculation of bystander exposures and risks from known sources has been an iterative process based on the ability to provide additional predictive capabilities yet consider all possible sources of information that could be used to characterize the overall risk picture associated with a chemical. The interrelationship of these factors is illustrated in Figure 3. This approach is also consistent with general Agency guidance on the use of air models.

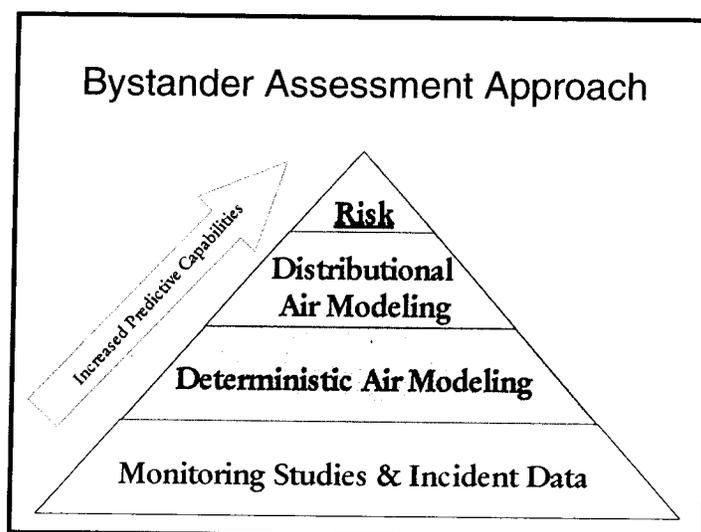


Figure 3: Iterative Approach To Bystander Risk Assessment

As indicated in Figure 3 above, three sources of information have been used for assessing bystander risks. Each source has a unique level of predictive capability but each result has been carefully considered in context with each other in order to develop an overall characterization of the risks associated with iodomethane use. Each method is described below along with a description of how they were used and how they should be interpreted in context. Regardless of which approach is utilized, it is clear that there can be possible human health effects associated with the use of soil fumigant chemicals based on calculated risk estimates.

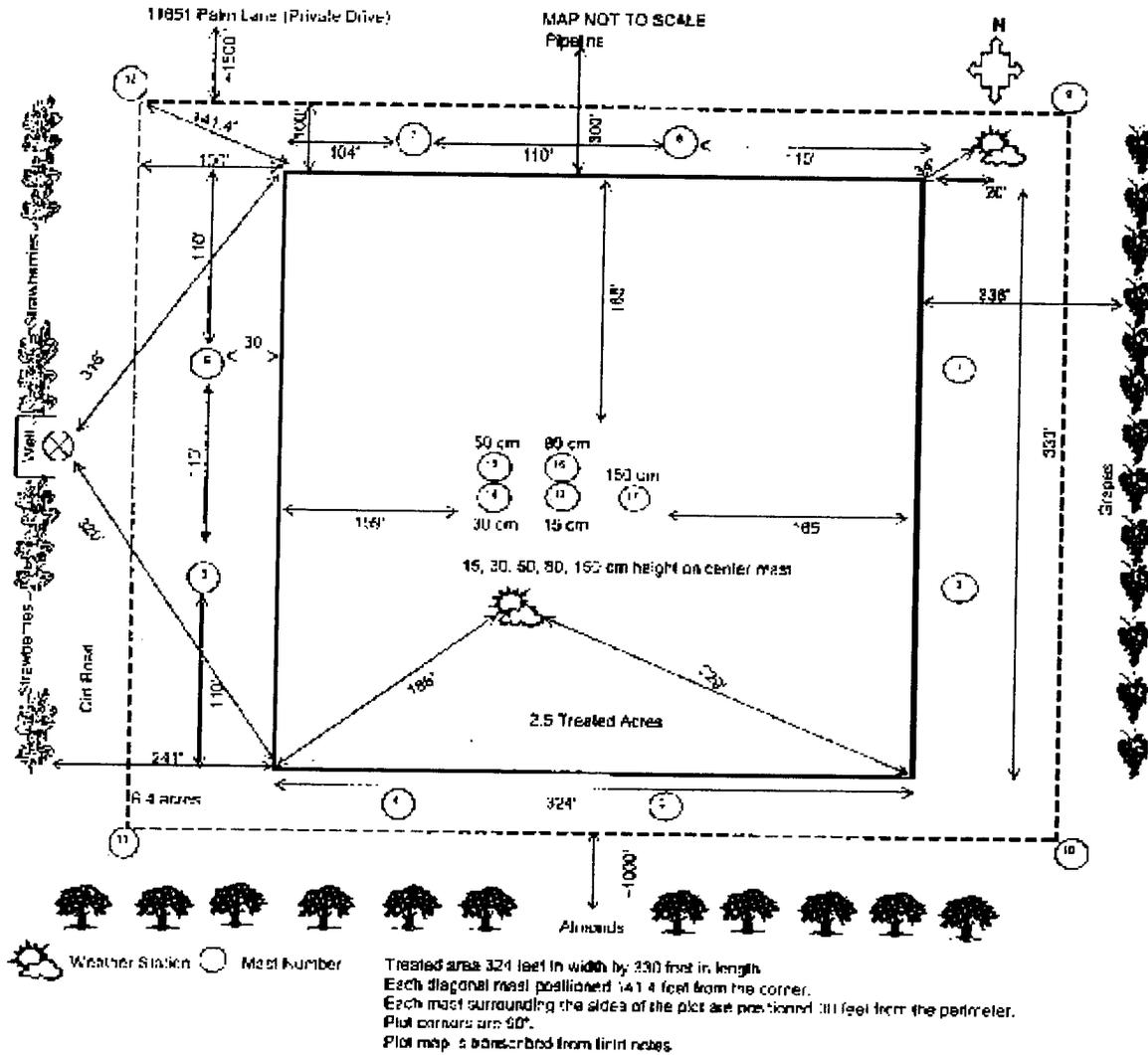
Source Type 1: Field Level Monitoring Studies & Incident Data

Incident Data - As indicated above, the incident analysis that has been completed for iodomethane is presented above in *Section 5: Public Health Data* and has limited applicability for interpreting the proposed agricultural uses. This inherent limitation is because iodomethane has not yet been registered for pesticide use under FIFRA and has only seen limited experimental pesticide use where no significant incidents have occurred as described above.

Monitoring Studies - Field volatility studies typically measure fumigant air concentrations produced by a single fumigant application under specific conditions (e.g., application rate and method, area treated, soil conditions, meteorological conditions). In these studies, air samplers positioned in and around a treated field continuously sample air after the fumigant has been applied in order to quantify the emissions from that specific field. Sampling times can vary but generally range from about 2 to 12 hours, so that the samples represent the average air concentrations for the intervals used. Usually, shorter times are used at the beginning because fumigants generally off-gas the most within the first 24 hours after application and shorter sampling times provide a better means for characterizing peak emission periods that are expected to be associated with higher exposures. For iodomethane, a number of monitoring studies were considered in the development of the risk assessment. These have been described in detail in the previous assessments (D325080, 1/5/06). An example of the information that can be generated by a field monitoring study, based on the Manteca California flat fume flux study for iodomethane, is illustrated by Figure 4 and Table 2. In this study,

iodomethane was applied using a tarped shallow shank broadcast flat fume method to a 324 feet (98.8 meters) by 330 feet (100.6 meters) field at a rate of 241 pounds ai per treated acre in September 2001. A standard 1 mil tarp was placed over the application plot. Application began at 9:05 AM and was complete at 11:45 AM.

Figure 4: Sampler Location And Site Layout For Manteca Flat Fume Flux Study



| Sampler ID | 9/18 12:00 – 15:00 | 9/18 15:00-18:00 | 9/18 18:00-20:00 | 9/18, 20:00 9/19, 07:00 | 9/19/01 07:00-19:00 | 9/19, 19:00 9/20, 07:00 | 9/20 07:00-12:00 |
|-------------------|-------------------------------|-----------------------------|-----------------------------|------------------------------------|--------------------------------|------------------------------------|-----------------------------|
| 1 | 198 | 661 | 255 | 778 | 168 | 345 | 50 |
| 2 | 1,728 | 1,216 | 990 | 766 | 268 | 335 | 96 |
| 3 | 1,821 | 1,524 | 1,714 | 824 | 416 | 231 | 119 |
| 4 | 1,288 | 1,234 | 652 | 526 | 261 | 185 | 75 |
| 5 | 37 | 32 | 7 | 108 | 15 | 175 | 4 |
| 6 | 32 | 21 | 2 | 39 | 8 | 167 | 3 |
| 7 | 56 | 17 | 2 | 182 | 3 | 129 | 3 |
| 8 | ND | 42 | 0 | 252 | 28 | 146 | 2 |
| 9 | 40 | 13 | 0 | 985 | 3 | 272 | 3 |
| 10 | 571 | 569 | 1,998 | 869 | 199 | 281 | 89 |
| 11 | 30 | 25 | 15 | 179 | 7 | 165 | 3 |
| 12 | 25 | 18 | 0 | 13 | 4 | 54 | 3 |
| 13 | 8,785 | 6,227 | 7,961 | 14,379 | 2,610 | 7,124 | 811 |
| 14 | 5,689 | 3,758 | 5,251 | 7,105 | 1,391 | 2,373 | 425 |
| 15 | 3,279 | 2,339 | 3,141 | 3,128 | 724 | 1,329 | 236 |
| 16 | 2,820 | 1,331 | 2,208 | 1,610 | 559 | 938 | 186 |
| 17 | 1,653 | 986 | 676 | 244 | 249 | 238 | 77 |

Results based on using monitoring data directly from field volatility studies for risk assessment purposes are summarized below. There are several limitations to this approach that should be considered in the overall context of related methods available for calculating risks associated with fumigant use. Essentially, the monitoring data are both spatially and temporally limited. For example, data do not reflect the values that would occur under different conditions. Varying weather conditions, for example, can significantly change the air concentrations at specific sites around a treated area. Since there is such a large range of potential weather conditions which could exist, it is not possible for monitoring studies to inherently capture the entire range of potential exposures. Another example would be that air concentrations are measured by fixed samplers positioned at various distances and directions around the treated area, both downwind and upwind, as well as at points in between. This makes it difficult to interpolate between sampler locations, if so desired, to develop risk estimates in-between the locations. Based on these factors, the use of monitoring data for trends analysis is difficult without a modeling approach. This premise is consistent with the general Agency approach for the use of air monitoring data related to the air permitting process. More information regarding the utility of monitoring data and its limitations described above can be found in

Appendix W to 40CFR51 which presents Agency policy related to the selection and use of air models (http://www.epa.gov/scram001/guidance/guide/appw_05.pdf). Essentially, monitoring data in this assessment were used in a manner consistent with this guidance.

Source Type 2: Deterministic Air Modeling

Air dispersion modeling uses mathematical formulas to characterize how atmospheric processes will disperse a pollutant emitted by a source. For the fumigants, the Agency has used dispersion models to estimate the downwind concentration of fumigants emitted from sources such as treated fields or structures for this purpose as is consistent with the guidance provided in 40CFR51. This treatment is consistent with standard model development and implementation methods. Dispersion models require the categorization and/or input of data which includes:

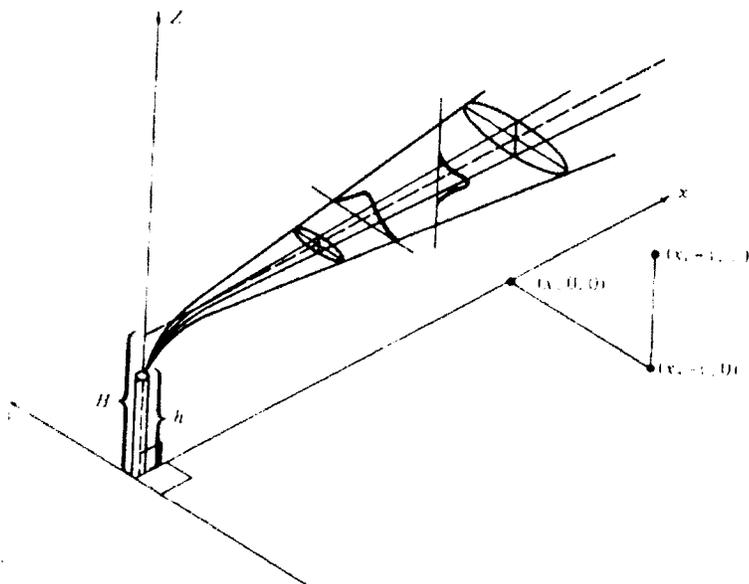
- Meteorological conditions such as wind speed and direction as well as the amount of atmospheric turbulence (also known as the “stability class”);
- Flux rate (the mass of fumigant emitted per area per time);
- Surface roughness (accounts for topography effects); and
- Application Specifics (application method, sealing techniques, application rate, field size, etc.).

The Agency maintains a *Guideline on Air Quality Models* (hereafter, Guideline) as described above. The Guideline provides the Agency's guidance on the regulatory applicability of air quality dispersion models in general. In order to be included in Appendix W, as a recommended model, models must go through an extensive peer review and testing process. This peer review process defines how specific models can be used in an acceptable manner to calculate dispersion estimates for a variety of sources like point (e.g., a stack on a building) and area sources (e.g., a fumigated field). This assessment was developed based on the guidance provided in Appendix W.

In producing the fumigant risk assessments, the Agency considered various air dispersion models that are currently listed or have previously been listed in Appendix W. The first of these models is the Industrial Source Complex Short Term Model (V3) (ISCST3) model which was utilized for a number of years by the Agency to quantify the movement of airborne pollutants for a variety of regulatory situations. ISCST3 was the Agency's recommended air dispersion model up until the end of 2005. It was also used as the sole basis for the earliest iodomethane assessments. ISCST3 was replaced by the American Meteorological Society/Environmental Protection Agency Regulatory Model (AERMOD) in December of 2005 as the preferred air dispersion model for near-field, steady state sources. Both ISCST3 and AERMOD are “Gaussian Plume” models, in which airborne concentrations are assumed to have a normal probability distribution. Figure 5 illustrates the basic premise of ISCST3 and the Gaussian plume concept. It should also be noted that neither ISCST3 or AERMOD retain a memory of the movement of the fumigant plume from hour to hour (e.g., they would not track changes in an emitted plume should the wind direction change) and they do not quantitatively address calm conditions. For this assessment, a process has been used where calm conditions (e.g., hours with calm wind conditions) are dropped from calculations and a time-weighted average result is calculated without those values. This approach is consistent with how ISCST3 has been historically used. For chemicals such as iodomethane, the impact on the calculated exposures due to handling calms in this manner is attenuated because 8 or 24 hour time-weighted averages are the basis for the results. However, for chemicals where risk estimates are based on shorter duration toxicity endpoints (e.g., 1

hour), this phenomenon can significantly impact the results if the weather data used in the assessment include a high percentage of calm periods. AERMOD has enhancements from ISCST3 related to how structural releases are modeled such as improved downdraft algorithms for building effects. The third model that the Agency considered was CALPUFF v.5 which was recently adopted by the Agency as the preferred model for assessing near-field air concentrations under complex meteorological conditions. CALPUFF is a "Gaussian Puff" model and is similar to ISCST3 and AERMOD in that it assumes that air concentrations follow a normal probability distribution. Unlike the plume model, however, CALPUFF retains a memory of the movement of the fumigant plume from hour to hour which allows it to track emitted plumes that change direction with shifting wind patterns. It also has an enhanced treatment of calm conditions relative to ISCST3 or AERMOD because it can account for the plume being stable in calm conditions then moving again once winds pick up instead of skipping over such conditions. ISCST3, AERMOD, and CALPUFF are described in more detail in Appendix D. [Note: There is a yet unapproved version of CALPUFF (v6) which has not been officially accepted by the Agency. The major upgrade is that it can complete sub-hourly calculations where v5 can only do calculations based on hourly increments. This is described as well in Appendix D.] It should be noted that the Agency used ISCST3 as the basis for its deterministic assessments. At the time the results based upon ISCST3 were developed neither AERMOD nor CALPUFF v5 were approved models. At this time, the Agency has not opted to use them directly since neither can readily be used in the distributional manner that is currently being employed by the Agency as described below. The Agency would accept and review submissions using these modeling platforms as they are accepted models in the Agency Guideline as outlined in Appendix W.

Figure 5: Illustration of ISCST3 Gaussian Plume Approach



Before a modeling analysis can be done, one of the most important parameters for ISCST3, the flux must be determined. As an example, for field applications it is usually expressed in units of micrograms per square meter per second ($\mu\text{g}/\text{m}^2/\text{sec}$). In essence, flux represents how quickly the pesticide moves or volatilizes into the surrounding atmosphere from a treated surface. Three general methods are used to estimate flux from treated fields. These are discussed briefly below. The first two methods measure flux from sampling directly in treated fields, and the third is an indirect, back-calculating method that estimates flux using samples from downwind locations and solves for them

using ISCST3. For iodomethane, most flux estimates for pre-plant field applications were completed using the indirect back-calculating method. In some cases, however, flux values were determined using the aerodynamic method.

ISCST3 Flux Method 1: Chamber The first method is a direct sampling method for determining flux that uses emission data measured in a flux chamber placed in a treated field. A flux chamber is basically a box which encloses a small defined area of a treated field, from which air samples are obtained representing defined durations (e.g., air is pulled through a charcoal trap collecting emitted pesticide over a continuous length of time such as 2 to 12 hours). Since the surface area is defined by the area of the chamber, and the quantity of pesticide emitted per unit time is defined by the air concentration, this method directly measures flux. A possible issue with flux chambers is that the conditions within the chamber (e.g., temperature, wind, air stability) are not generally identical to those outside the chamber in the treated field; since flux rates can be significantly affected by these factors, flux rates measured in these chambers may not always represent actual flux rates in the field. Flux chambers are not often used for estimating flux and, in fact, no such field study data were available for use in this assessment.

ISCST3 Flux Method 2: Aerodynamic Flux A second direct method used is known as the aerodynamic flux method.¹¹ In this method, air samplers are set up in treated fields at various heights on a mast (e.g., 15, 30, 90, and 150 cm from the ground). Using measured air concentrations at these various heights, a vertical gradient of concentrations can be estimated for different time points which can be integrated across all heights to estimate the flux rate at each time point after application. Some studies are available using this method to determine flux rates.

ISCST3 Flux Method 3: Indirect Back-Calculation The method most often used to determine flux rates is the indirect or back-calculation method. [Note: EPA used CDPR's technique (<http://www.cdpr.ca.gov/docs/empm/pubs/ehapreps/eh9903.pdf>).] This method uses measured air concentrations taken in a typical field fumigation study in which air samplers are located at various positions around the field. The measured air concentrations, together with information about weather conditions which occurred when the samples were obtained, are used as inputs into the ISCST3. The model assumes that these air concentrations result from a Gaussian plume, the plume being distributed around the treated field as a result of the wind and weather conditions. The model then estimates the flux rate that would be required to emit the plume and to obtain the air concentrations measured.

11

Majewski, MS, Glotfelty, DE, Seiber, JN. 1989. A comparison of the aerodynamic and the theoretical-profile-shape methods for measuring pesticide evaporation from soil. *Atmospheric Environment*, 23:929-938

Majewski, MS, Glotfelty, DE, Kyaw Tha Paw U, Seiber, JN. 1990. A field comparison of several methods for measuring pesticide evaporation rates from soil. *Environmental Science and Technology*, 24:1490-1497.

Parnele, LH, Lemon, ER, Taylor, AW. 1972. Micrometeorological measurement of pesticide vapor flux from bare soil and corn under field conditions. *Water Air Soil Pollut.* 1:433-451

Aside from the estimation of the flux for all application methods, there are a number of other key inputs that must also be defined such as the size and shape of a treated field, wind speed, and atmospheric stability in order to run ISCST3. Atmospheric stability is a measure of how turbulent the atmosphere is at any given time. Stability is affected by solar radiation, wind speed, cloud cover, and temperature, among other factors. If the atmosphere is unstable, then more off-field/source movement of airborne residues is possible without a large increase in air concentrations because the residues are carried up into the atmosphere and moved away from the field or other source, thereby lowering the air concentration in proximity to the field/source. To simplify the ISCST3 modeling process, the transport of fumigant vapors from a source, a single wind direction, wind speed, and stability category are used for a given period.

A range of atmospheric conditions representing the continuum from relatively stable (low windspeed & calm) to unstable conditions (high windspeeds & unsettled) were evaluated using ISCST3. Under relatively stable atmospheric conditions, the modeling produces results that represent highly exposed individuals (i.e., ISCST3, as used for these situations, results in exposure estimates at the upper percentiles of an anticipated exposure distribution). Two key inputs are the basis for this conclusion. First, only a constant downwind direction is considered which would be highly unlikely in any outdoor environment. Secondly, the quantitative inputs used to define atmospheric conditions are based on constant wind speed and atmospheric stability over a particular period, which are also unlikely to occur in an outdoor environment over an 8 or 24 hour period such as considered for iodomethane field uses. Conversely, unsettled conditions may reduce risk estimates but it is believed that even these conditions can result in conservative estimates because wind direction is constrained to a single direction over a particular period.

Source Type 3: Distributional Air Modeling

The monitoring data and ISCST3 methods described above are deterministic methods that provide results that are limited in utility. For example, it is difficult to extrapolate to varying distances using monitoring data and analyses using ISCST3 which provide high-end point estimates of exposure and risk because of the manner in which meteorological data are input, especially for a stable atmosphere. In response to these methods, the pesticide industry developed three models that are essentially pre- and post-processors for the air models described above that incorporate the ability to complete distributional and/or probabilistic analyses. Each of the three has ISCST3 as their core processor while FEMS has an option for selecting between processors based on ISCST3 or CALPUFF (V 5 or 6). The three models which were developed include: **Probabilistic Exposure and Risk model for Fumigants (PERFUM)**, the **Fumigant Emissions Modeling System (FEMS)**, and the **Soil Fumigant Exposure Assessment System (SOFEA)**. Each model was reviewed by the FIFRA Scientific Advisory Panel (SAP) in 2004 (<http://www.epa.gov/oscpmont/sap/meetings/2004/index.htm>). The SAP concluded that each of the three models could provide scientifically defensible estimates of the bystander exposures and risks associated with soil fumigation practices and also suggested modifications and additional data that could further refine risk estimates. See Appendix D for more details regarding each model including contact information pertaining to how one could obtain the system. [Note: Arysta Life Sciences, the petitioner for iodomethane registration, developed the PERFUM model.]

PERFUM and FEMS were designed specifically to take the concentration outputs from the air dispersion models and use them to produce buffer zone outputs in a distributional format. [Note: In the context of presenting modeling results the term "buffer zone" does not refer to any manner of

regulatory decision pertaining to risk mitigation for iodomethane. It refers to the distances determined based on a target concentration defined by the HEC or Human Equivalent Concentration adjusted by an uncertainty factor. Different uncertainty factor values were evaluated in this assessment to ascertain their impact upon the predicted results.]

Recently, PERFUM was modified to also provide air concentration information for selected distances from the perimeter of the treated field. PERFUM also has been modified since the SAP version in order to evaluate structural sources which have been used by the Agency to evaluate structural releases of fumigants. SOFEA was designed to calculate fumigant concentrations in air arising from treated fields for multiple sources across entire agricultural regions. A generalized flowchart for these models is shown in Figure 6.

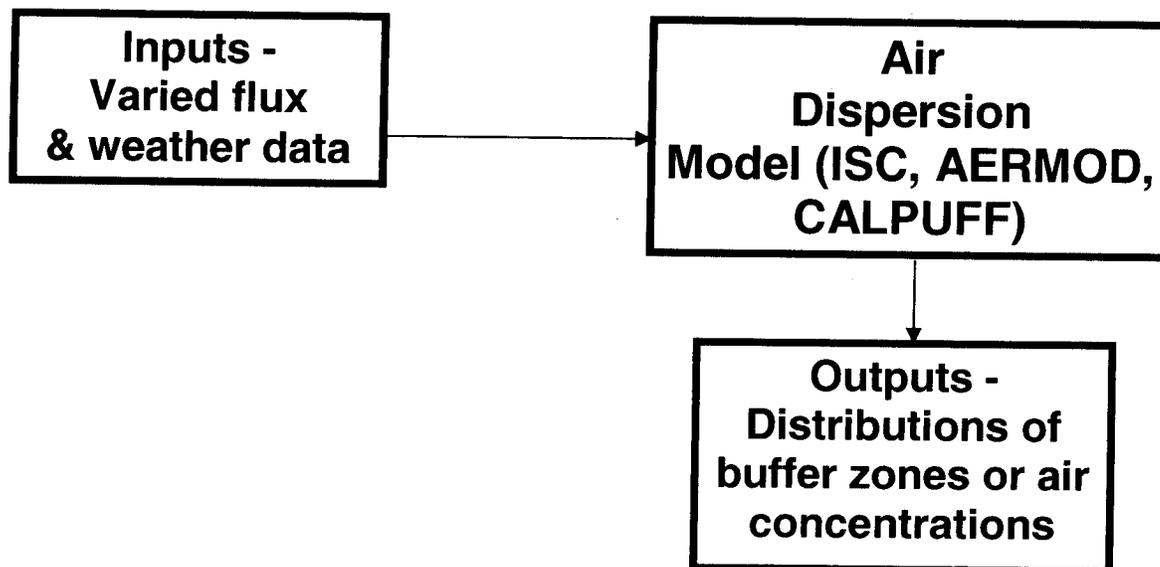


Figure 6: Operational Flowchart For Distributional Models Such As PERFUM

Selection of a Distributional Model - The conclusions of the 2004 SAP meetings were that all three of the distributional and/or probabilistic modeling options were scientifically viable and represented a level of refinement above the deterministic analyses that had been completed using ISCST3. For a number of reasons detailed below, PERFUM was selected at that time to evaluate bystander risks from pre-plant soil applications including:

- PERFUM's developers revised the model to incorporate some of the SAP's recommended changes in time for the Agency to use PERFUM in the revised Phase 1 risk assessments for the soil fumigants;
- PERFUM was significantly faster and more efficient to run than others at that point in time; and
- PERFUM provided greater resolution than the other options on the period of peak emission and highest potential exposure which is of key interest to the Agency because of the acute toxicity associated with soil fumigants. At that time, FEMS used emissions from a single field over a whole year so that the few days of fumigant exposure occurring after an application were attenuated over that entire year.

It is believed that results from a distributional and/or probabilistic model, instead of the deterministic results based on ISCST3, provide more comprehensive information for risk managers when evaluating the potential risks associated with pre-plant soil fumigation. PERFUM remains the model which has been used to develop the Agency's fumigant assessments but it should be noted that the Agency believes that submissions based on the other aforementioned distributional/probabilistic models such as FEMS or SOFEA can be of equal scientific validity and would also be evaluated and considered in its risk management process provided all appropriate supporting documentation were available for review (e.g., documentation of flux rate calculations and weather data analysis).

Use of the Probabilistic Exposure and Risk model for Fumigants (PERFUM) - PERFUM allows users to develop an understanding of the distributions of potential bystander exposures and thus more fully characterize the range of risks resulting to bystanders around treated fields. In this assessment, the PERFUM model has been used in order to calculate differing percentiles of exposure associated with pre-plant soil fumigation. ISCST3 is an integral part of the PERFUM model and in fact the basic physics and code of ISCST3 remain unchanged. Many of the inputs used for PERFUM are similar to those used for modeling done using the ISCST3 model (e.g., field sizes and back-calculated flux rates). There is additional information required for completing a PERFUM analysis as opposed to an ISCST3 assessment. The differences are that each PERFUM analysis is based on 5 years of meteorological data and enhanced flux profiles which account for changes in weather and flux over the periods of concern instead of the static inputs used for the ISCST3 analyses.

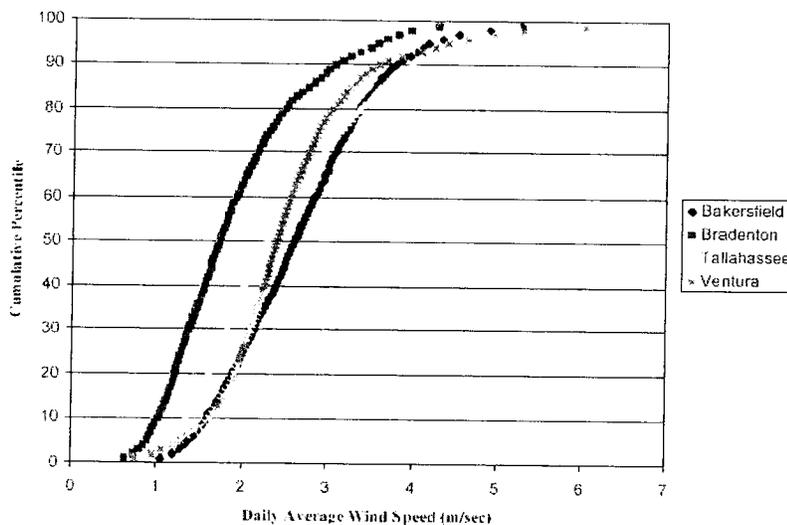
Since actual meteorological data are integrated into PERFUM for each analysis, data representative of the locations where iodomethane use occurs were identified and used in the analysis. For example, major pre-plant uses occur on strawberries and tomatoes in Florida and California. Some use in Michigan (or elsewhere in that region) also occurs on various crops. As a result, the following locations and sources of meteorological data were used in this assessment:

- Bakersfield California (Source: ASOS or Automated Surface Observing System operated by the FAA) to represent inland California locations;
- Ventura California (Source: CIMIS or California Irrigation Management Information System) to represent coastal California locations;
- Flint Michigan (Source: NWS or National Weather Service) to represent central Michigan and other upper midwest locations;
- Tallahassee Florida (Source: NWS or National Weather Service) to represent inland Florida locations; and
- Bradenton Florida (Source: FAWN or Florida Automated Weather Network) to represent coastal Florida.

In this assessment, 5 years or 1825 days of meteorological data were considered in each calculation. Bradenton, Bakersfield, and Ventura data were in the range of 1997 through 2003 but Tallahassee and Flint were in the late 1980s through early 1990s. [Note: Please refer to the SAP background documents for PERFUM for further information concerning these data including how they were processed for incorporation into PERFUM, pertinent quality control issues associated with the data, and other information related to their selection (<http://www.epa.gov/scipoly/sap/2004/index.htm>).]

Figure 7 provides a comparison of the distributions of daily average windspeeds for selected stations in California and Florida that can help characterize the deterministic assessments and different PERFUM results for the different stations. [Note: For context, CDPR regulated methyl bromide at 1.4 m/s windspeed.]

Figure 7: Distribution of Daily Average Windspeeds At Selected Meteorological Stations



Flux (i.e., field volatility or emissions) data were treated in a manner similar to that used for the ISCST3 analysis described above. Data from each of the 8 flux studies were used in conjunction with appropriate meteorological information. In some cases, studies that quantified emissions from the same application method were available in both Florida and California. In those cases, only meteorological data from the same state were used in the PERFUM analysis. PERFUM also considers the uncertainties associated with daily flux profiles by probabilistically sampling flux based on the range defined by the coefficient of variation associated with those data. This function was used in this assessment since the monitoring data were collected in a manner where it could be used. [Note: In other recent assessments, monitoring data were insufficient for this purpose.] Table 3 below provides a summary of the analyses that were completed using PERFUM. There is a significant difference with PERFUM compared to ISCST3 with regard to flux values. ISCST3 used a single emission ratio which does not account for changes over time in flux. Alternatively, PERFUM samples flux distributions over time periods of interest. The Agency verified the hourly flux values based on the monitoring data developed by Arysta and these values were used in the PERFUM assessment as the basis for the calculations. [Note: All emission/flux values represented in Table 3 are based on the use of LDPE or HDPE films. High barrier film use is not reflected herein although current iodomethane research under the 2007 Experimental Use Permit will produce flux data based on the use of high barrier and metalized films.]

| Table 3: Summary Of PERFUM Analyses Completed For Iodomethane | | | | | | | | |
|---|-----------------------------|-------------------------|-----------------------------|-------------------------|----------------------------|--------------------------------|---------------------------------|---------------------------------|
| Weather Station Location | Flux Study Summary | | | | | | | |
| | Watsonville CA Flat Fume | Manteca CA Flat Fume | Plant City FL Raised Bed | Oxnard CA Raised Bed | Guadalupe CA Raised Bed | La Selva CA Drip Irrigation | Camarillo CA Drip Irrigation | Guadalupe CA Drip Irrigation |
| Ventura CA | X | X | NA | X | X | X | X | X |
| Bakersfield CA | X | X | NA | X | X | X | X | X |
| Flint MI | X | X | X | X | X | X | X | X |
| Tallahassee FL | X | X | X | NA | NA | X | X | X |
| Bradenton FL | X | X | X | NA | NA | X | X | X |

X = analysis completed, NA = analysis not appropriate; Tarps were used in all cases. Note: All analyses completed using all HECs of concern.

The following describes the process and data upon which the analyses to develop these emission profiles were based. Data from the Manteca California flat fume emissions study were used to calculate flux estimates using the aerodynamic method based on the following equations. The resulting flux estimates are presented in Table 4. Flux estimates were calculated using the indirect method for all other sites which utilizes a regression analysis that relates measured concentration estimates to field conditions and application rates. An example of the results that were calculated based on Oxnard California emissions data from a raised bed study are presented in Table 5.

Flux, estimated based on the aerodynamic method, was determined using the following equations:

$$Flux = \frac{-(0.42^2)(c_{80} - c_{30})(WS_{80} - WS_{30})}{\theta_m \theta_c \ln(80/30)^2}$$

$$Ri = \frac{(9.8)(0.8 - 0.3)(T_{80} - T_{30})}{\left(\frac{T_{80} + T_{30}}{2} + 273.16\right)(WS_{80} - WS_{30})^2}$$

where

if $Ri > 0$, $\theta_m = (1 + 16Ri)^{0.333}$ and $\theta_c = 0.885(1 + 34Ri)^{0.4}$

if $Ri < 0$, $\theta_m = (1 - 16Ri)^{-0.333}$ and $\theta_c = 0.885(1 - 22Ri)^{-0.4}$

| Period | Day/Hour | Flux Rate (ug/m ² -s) |
|--------|--------------------------------|----------------------------------|
| 1 | Day 0, Hours 0 - 3 | 481 |
| 2 | Day 0, Hours 3 - 6 | 276 |
| 3 | Day 0, Hours 6 - 8 | 87 |
| 4 | Day 0, Hours 8 - 19 | 48 |
| 5 | Day 0, Hour 19 - Day 1, Hour 6 | 115 |
| 6 | Day 1, Hours 6 - 19 | 17 |
| 7 | Day 1, Hour 19 - 24 | 34 |

| Sampling Period | Reported Flux (ug/m ² -s) | Regression Type | EPA Estimated Flux (ug/m ² -s) | r ² |
|-----------------------------|--------------------------------------|-----------------|---|----------------|
| 10/17, 13:00 - 15:00 | 535 | Major axis | 587 | 0.26 |
| 10/17, 15:00 - 17:30 | 179 | Major axis | 140 | 0.66 |
| 10/17, 17:30 - 21:00 | 111 | Major axis | 120 | 0.92 |
| 10/17, 21:00 - 10/18, 7:30 | 134 | Major axis | 102 | 0.69 |
| 10/18, 07:30 - 19:00 | 90 | Major axis | 68 | 0.36 |
| 10/18, 19:00 - 10/19, 08:00 | 45 | Major axis | 52 | 0.57 |
| 10/19, 08:00 - 13:00 | 34 | Major axis | 43 | 0.57 |

PERFUM works by establishing a grid with receptor points around a field built with spokes and rings then it calculates air concentrations at each point for each day over 5 years of weather data. The numbers of receptors for varying sized fields is summarized in Table 6 and Figure 8 below. The information calculated at each grid location is then used to calculate distances in each array (or spoke protruding outwards from the treated field in the center of Figure 8) where a target concentration of concern is achieved. Target concentrations are defined by dividing the HEC by the uncertainty factor of interest for that particular analysis. PERFUM compiles these results for each array (or spoke) then ultimately compiles them across all spokes and weather days using two techniques (i.e., referred to as a “whole field” or “maximum” buffer results which are described below). Each receptor corresponds to an x- and y-coordinate. Figures 9, 10 and 11 below, provide an example of daily PERFUM output where a contour plot has been developed that describes the distances where a target concentration has been achieved around the perimeter of a treated field for three distinct weather days. Each plot pertains to one application using the same emission rate and field size but the difference between the plots is that each presents the results (i.e., distance where a target concentration of concern is achieved) for a single, separate day of varied weather conditions.

Table 6: Receptor Points for Various Field Sizes in PERFUM

| Grid Type | Field Size (Acres) | Number of Spokes | Number of Rings | Numbers of Receptors (Spokes * Distances) |
|------------------|---------------------------|-------------------------|------------------------|--|
| Fine | 1 | 96 | 28 | 2,688 |
| | 5 | 132 | 28 | 3,696 |
| | 10 | 152 | 28 | 4,256 |
| | 20 | 188 | 28 | 5,264 |
| | 40 | 232 | 28 | 6,496 |
| Coarse | 1 | 24 | 28 | 672 |
| | 5 | 33 | 28 | 924 |
| | 10 | 38 | 28 | 1,064 |
| | 20 | 47 | 28 | 1,316 |
| | 40 | 58 | 28 | 1,624 |

Note: Fine grid option was used for methyl bromide analysis.
The maximum distance used for PERFUM calculations on each spoke is ≥ 1440 meters.

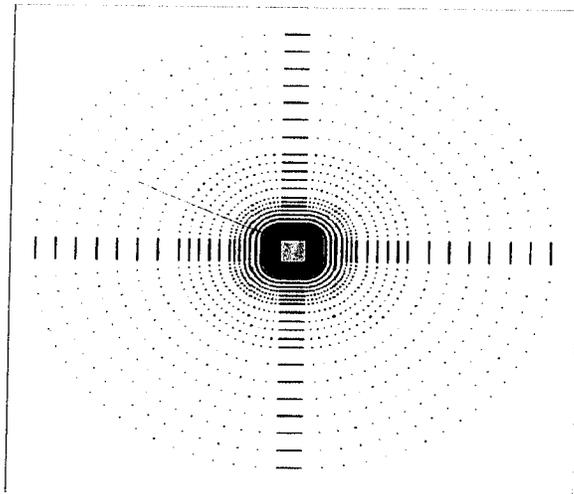


Figure 8: PERFUM Receptor Grid

Whole field buffer results are calculated using PERFUM by compiling the results for all arrays (i.e., using the entire perimeter) of each day's contour line outputs. PERFUM compiles all of the locations (i.e., x and y coordinates) along the contours in each of the plots into one distribution and essentially produces an overall contour plot for the 5 years of weather data (see Figure 12 below). The user can then select a percentile of the distribution of interest (e.g., 95th percentile or 99th percentile). In essence, the "whole field" buffer results represent the entire range of possible exposures regardless of location relative to the treated field.

Maximum buffer results from PERFUM are calculated by compiling only the farthest distances from the contours produced for each weather day. The black dot in each plot (Figures 9 through 11) represents the maximum distance buffer for that day which would be the only point selected for that day used in this calculation. PERFUM also generates these maximum distance buffers across 5 years of weather data which is presented in Figure 12 below. The user can then select a percentile of the distribution of interest (e.g., 95th percentile or 99th percentile). In summary, the maximum buffer results can be thought of as a way of providing more resolution around the upper percentiles of possible exposure. In a physical sense, it can also possibly be applicable to individuals who live in an area with strong prevailing winds due to topography or other factors (e.g., in a valley or coastal situation where on-shore winds are predominant).

Note that in Figure 12 the whole field buffer contour is within the boundary of the maximum buffer contour. This trend would always be expected if the percentiles considered in each case were of the same numerical value (e.g., 95th %tile whole and 95th %tile maximum) because the maximum buffer distribution represents only the farthest distance for each weather day and not all of the values as in the whole field buffer distribution.

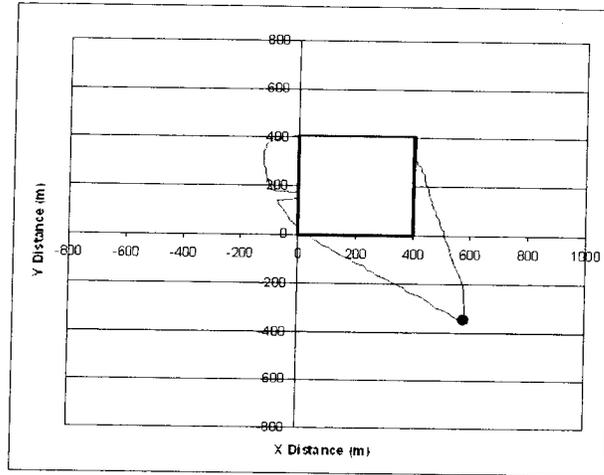


Figure 9: Example PERFUM Output - Day 1

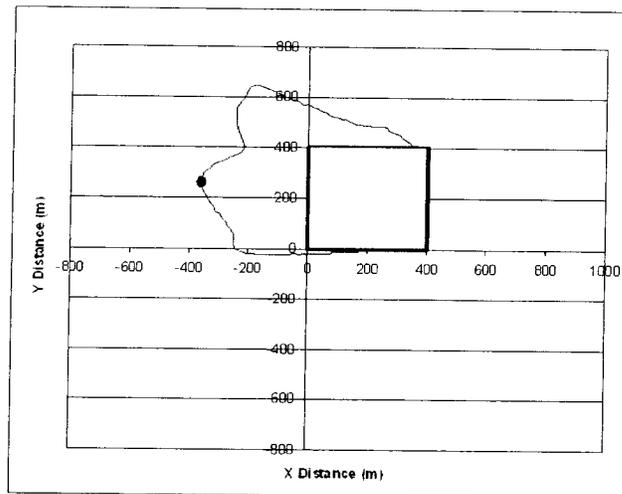


Figure 10: Example PERFUM Output - Day 2

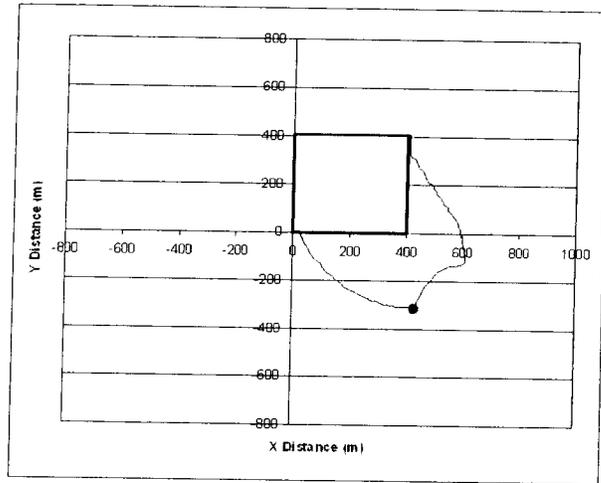
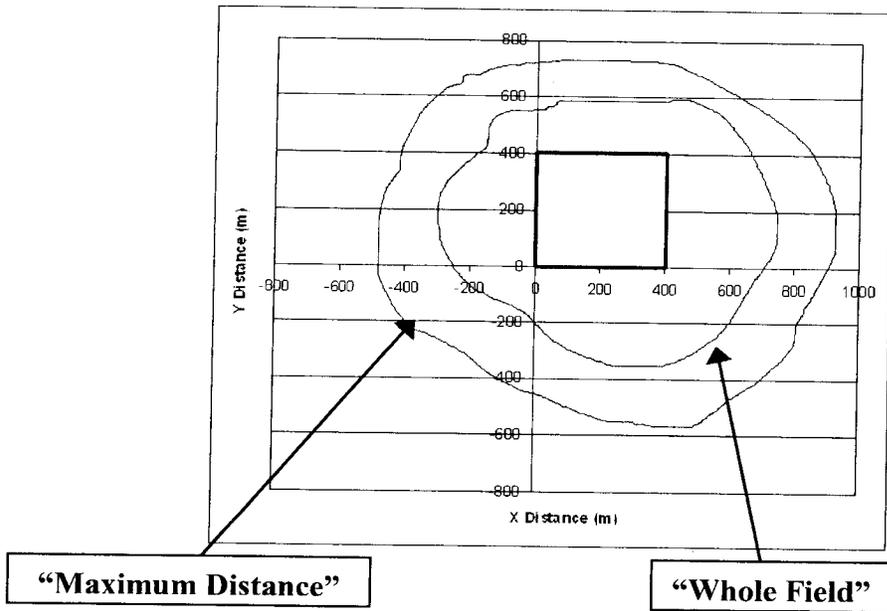


Figure 11: Example PERFUM Output - Day 3

Figure 12: Whole Field vs. Maximum Buffer Distance Example



PERFUM can generate the types of outputs discussed above assuming the toxicity results from different exposure periods from 1 to 24 hours depending on the exposure duration and toxicity concern for the fumigant. When the distributional results from PERFUM are considered, they can be described by the following statements:

- **Maximum Distance Buffer:** The maximum concentration (e.g., at 95th percentile) provides a buffer zone whereby there will not be an exceedence for 95 percent of application days. It follows that if a person was at the location of the maximum concentration on any given day they would have a 95 percent chance of being at a location with a concentration less than the target.
- **Whole Field Buffer:** The whole field distribution (e.g., at 95th percentile) provides, on average, 95 percent of the perimeter of the buffer zone will have a concentration below the target. It follows if a person was placed randomly onto the perimeter of a buffer zone on a random day they would have a 95 percent chance that the concentration at their location is less than the target.

6.1.1.2 Bystander Exposures And Risks From Known Sources

The risks for bystanders from known sources (i.e., farmfields) are presented in this section. For modeling analysis purposes, known sources such as farmfields are treated as area sources from a single application.

Monitoring Studies And Incident Data: A series of monitoring studies conducted using varied application methods and locations were reviewed. The information extracted from these studies was summarized in the previous assessments and should be referenced as appropriate (D325080 – January 5, 2006). Potential risks have been calculated based on these summarized results for each HEC of concern and are presented below for comparison to the modeling results. [Note: Minor errors were noted by Arysta in their revised risk assessment document for iodomethane (MRID 470866-01, 3/23/07) related to the interpretation of the monitoring data. These were verified and corrected herein as appropriate. Additionally, some studies were conducted at effective broadcast application rates up to approximately 250 lb ai/acre which is higher than the current proposed application rate of 175 lb ai/acre. Air concentrations were not adjusted for the purposes of this analysis since many factors (e.g., field conditions such as percent soil moisture or percent organic matter) can impact emissions and resulting air concentrations.]

Deterministic Air Modeling: Deterministic air modeling based on ISCST3 was completed for all uses. However, since the distributional air modeling described below is based on PERFUM that contains ISCST3 as its core processor ISCST3 results have not been presented herein since any changes would be superseded through the use of PERFUM since it represents a refinement of the ISCST3 approach (see D325080 – January 5, 2006 if so desired to review the ISCST3 analyses).

Distributional Air Modeling: This approach is based on the PERFUM model and is believed to provide the most refined, scientifically defensible approach for calculating and characterizing risks because it incorporates actual weather data and it links flux profiles to the appropriate time of day when calculating results. It is also based on the proven technology of ISCST3. PERFUM has been used to assess the potential risks calculated based on each emissions study that has been generated for iodomethane. Results have been calculated using PERFUM for each HEC of concern with the appropriate associated durations of exposure (i.e., 8 or 24 hours).

Monitoring Studies And Incident Data: Section 5 above describes the limited incident information related to iodomethane. Essentially, no pesticide related incidents have been reported under proper use conditions as would be expected since iodomethane has only been used for research purposes to date and it is not a registered pesticide at this time.

Potential risks to bystanders from pre-plant agricultural field fumigations calculated using iodomethane monitoring data are presented below. Air concentrations based on volatility data were generally reported on a per sample basis (e.g., 3 hour duration air samples) and as time-weighted averages (8 or 24 hour TWAs depending upon the HEC of concern). These were calculated using field volatility data that were usually collected around the perimeter of treated sites including downwind locations. Samples were collected at sites located within 150 feet or so from the perimeter of the treated field, depending upon the study design, and within treated fields for use in the aerodynamic flux calculations. It is clear, as described above, that downwind locations will have higher concentrations associated with them because emitted plumes will be pushed in that direction if there is a prevailing wind. For the data considered in this assessment, wind directions varied which makes defining “downwind locations” for the available data complex. There are other micrometeorological and site specific factors (e.g., topography and roughness) which also add to the complexity of the analysis.

Given these difficulties, and to ensure that this assessment is health protective, the Agency has calculated acute MOEs using the maximum time-weighted average (TWA) from the monitoring data for each site where data are available. These maximum TWAs were compared to the three acute HECs to calculate MOEs based on each toxicological endpoint of concern. The highest TWAs were always observed in the first 24 hours after application since most iodomethane is emitted from treated fields within that period. For the majority of the pre-plant field volatility data collected (6 of 8 monitoring sites for all HEC estimates), risks do not exceed HED’s acute level of concern independent of the toxic effect of concern (i.e., MOEs >30). Results based on the Manteca and the Oxnard California monitoring data are of concern regardless of which HEC the results were based. The Manteca results are based on a sampling device in proximity to the field which Arysta Corporation commented on as not being representative of a likely exposure situation. The Agency agrees that it is a likely high-end estimate but it should also be noted that the next highest 24 hour TWAs for Manteca were 1.0 and 0.5 ppm which do not alter the conclusions that there is a concern based on air concentrations monitored at this site. Similar results are noted for the penultimate 8 hour TWA from Manteca which is 1.3 ppm. Risk estimates for the maximum monitored values from each treated field are presented below in Table 7.

Table 7: Iodomethane Maximum Time-weighted Average Air Concentrations Based On Pre-Plant Agricultural Field Volatility Data And Resulting Risk Estimates Reported As Margins Of Exposure

| Application Method | TWA Air Concntrations (ppm) | | Acute MOEs For Each HEC | | |
|---|-----------------------------|-----------------|---------------------------|------------------------|--------------------------|
| | Max 8 hour TWA | Max 24 hour TWA | HEC = 4.5 (nasal lesions) | HEC = 7.4 (fetal loss) | HEC = 10 (neurotoxicity) |
| Manteca CA Broadcast, flat fume | 2.479 | 1.988 | 2.3 | 3.7 | 4.0 |
| Watsonville CA Broadcast, flat fume | 0.074 | 0.061 | 74.3 | 122.1 | 135.4 |
| Plant City FL* Tarped Raised Bed, Shallow Shank injection | 0.098 | 0.066 | 67.7 | 111.4 | 102.3 |
| La Selva CA Drip irrigation, tarped | 0.071 | 0.071 | 63.1 | 103.8 | 141.0 |
| Oxnard CA Tarped Raised Bed, Shallow Shank injection | 0.440 | 0.347 | 13.0 | 21.3 | 22.7 |
| Guadalupe CA Tarped Raised Bed, Shallow Shank injection | 0.197 | 0.103 | 43.6 | 71.6 | 50.7 |
| Camarillo CA Tarped Raised Bed, Drip Irrigation | 0.121 | 0.060 | 74.4 | 122.4 | 82.7 |
| Guadalupe CA Tarped Raised Bed, Drip Irrigation | 0.239 | 0.120 | 37.6 | 61.9 | 41.9 |

Note: MOEs calculated for nasal lesions and fetal loss are based on the 24 hour TWA while the neurotoxicity-based MOEs use the 8 hour TWAs. MOEs are calculated based on the following (HEC/TWA air concentration). MOEs < 30 are of concern. [Note: For informative purposes, 8 hour TWAs were also used to estimate risks from nasal lesions and fetal loss using the 8 hour HECs for those endpoints. Results were similar for these analysis to the 24 hour analysis associated with these effects.]

* There was a rain event during this study 24 hours after application so only ones determined prior to that event were considered.

Distributional Air Modeling: Exposures to bystanders from pre-plant agricultural field fumigations and their associated risks, calculated using a modeling approach based on PERFUM, are presented in this section. Risk estimates based on actual field volatility monitoring data are presented above and a deterministic modeling approach using ISCST3 has been described in previous assessments. However, monitoring data are limited because they represent only the conditions in which the studies were actually conducted or meteorological conditions are constrained in ISCST3 which results in conservative estimates of exposure. Therefore, in order to better characterize the risks associated with the use of iodomethane for various conditions (e.g., distance from emission source, actual meteorological conditions, application method, etc.), exposures have also been calculated using PERFUM.

The analyses which were completed using PERFUM are based on the 34 combinations of flux and meteorological data which are available (refer to Table 3 above). In addition, the impact of field size and shape, application rates, “whole vs. maximum buffer” statistics, and target concentrations (i.e., HECs coupled with uncertainty factor) were evaluated. The field sizes and shapes (N=9) that were considered include:

- 1 acre (square, rectangle oriented on its side, rectangle oriented on its end);
- 5 acres (square, rectangle oriented on its side, rectangle oriented on its end);
- 10 acres (square);

- 20 acres (square); and
- 40 acres (square).

The maximum effective broadcast application rate that was considered for pre-plant soil applications in this assessment is 175 lb ai/acre. In raised bed culture, the percent of the total area cropped varies depending upon the width of the beds being created. In the emissions studies which were conducted using raised beds approximately 50 percent of the total field surface area was covered with the raised beds which translates to an 88 lb ai/gross acre treated application rate which could conversely be reported as the 175 lb ai/acre effective broadcast rate with 50 percent bed surface area per cropped acre. In limited nursery use situations a desired gross acreage application rate of 125 lb ai/acre is desired but the emissions data for this purpose are limited since the highest cropped area for raised beds is approximately 50 percent and achieving a 125 lb ai/acre would require much wider beds that account for 70 percent or so of the gross acreage in production. As such, for these uses it is recommended that the raised bed results at the maximum effective broadcast rate be considered for regulatory purposes. In addition to these maximum application rates, a range of other application rates were evaluated in order to assess the impact of lowering rates including 75, 50, and 25 percent of the maximums for each use pattern.

The risk estimates presented below represent results for the acute duration of exposure because they compare either 8 hour or 24 hour time-weighted average concentrations calculated with PERFUM to three acute HECs of concern (i.e., 24 hour TWAs compared to 4.5 ppm for nasal lesions or 7.4 ppm for fetal loss and 8 hour TWAs compared to 10 ppm for neurotoxicity – all have a total applicable uncertainty factor of 30). The impact of altering target concentrations (i.e., the combination of HEC coupled with uncertainty factor) was also considered to allow for a broader characterization of the risks associated with iodomethane. The target concentrations that were considered in for each flux profile and meteorological input combination (N=34) are summarized in Table 8.

| Endpoint | HEC | Target Conc .At Varied UF Values (ppm) | | | |
|---------------|-------|--|------|------|-------|
| | (ppm) | 30 | 10 | 3 | 1 |
| Nasal Lesions | 4.5 | 0.15 | 0.45 | 1.50 | 4.50 |
| Fetal Loss | 7.4 | 0.25 | 0.74 | 2.47 | 7.40 |
| Neurotoxicity | 10 | 0.33 | 1.00 | 3.33 | 10.00 |

Note: PERFUM analyses are based on an 24 hour exposure TWA for nasal lesions and fetal loss. Conversely, an 8 hour averaging time is used for neurotoxicity because of available information pertaining to the time-to-toxic effect. This can significantly impact results because of the shape of flux profiles.

All totaled, when varied emissions and meteorological data (N=34), field sizes/shapes (N=9), and target concentrations (N=12) are considered, approximately 3,700 PERFUM outputs were generated in order to evaluate the potential risks associated with pre-plant uses in agricultural fields. [Note: Within each output file are results for varied application rates (e.g., 100, 75, 50 and 25 percent of maximum application rate). If these are considered as well, then this assessment is based on approximately 14,600 PERFUM outputs.]

It should be acknowledged that a myriad of micro-environmental conditions and factors can impact how iodomethane will volatilize and disperse from any given treated field on a particular day. With this premise, it would be logical to evaluate basic factors which could influence flux (e.g., soil type, soil temperature, percent water, etc.) and also micro-climates (e.g., topography) and thus ultimately impact results. However, PERFUM cannot easily address specific changes in these factors because it is not a *First Principles Model* where the approach would be to build a predictive tool from basic fate characteristics. Instead, PERFUM is an empirical model which utilizes field study and actual meteorological data to predict results and since field study data are the basis for the PERFUM predictions it follows that results based on empirical monitoring and those calculated with PERFUM would be similar (see http://www.epa.gov/scram001/guidance/guide/appw_03.pdf for additional guidance pertaining to air model validation).

It should also be acknowledged that the nomenclature incorporated into PERFUM uses the term “buffer zone” which equates to the distance downwind at which a specific target concentration (i.e., combination of HEC and UF) is met based on the desired statistical parameters. The use of this term does not imply any regulatory decision with regard to the implementation of buffer zones associated with updating proposed iodomethane labels. Any required labeling for iodomethane will be developed in the Agency’s regulatory process.

It is clear that given the number of possible permutations of PERFUM inputs and ways of presenting the outputs that there are many possible approaches for interpreting the results. The central goal, however, was to quantify how potential risks change with factors such as application method, distance from the treated field, percentile of exposure, selected statistical basis (i.e., whole vs. maximum buffer approach), application rate, and field size/shape. Each of these factors has been considered and very detailed results pertaining to each are available in the PERFUM outputs available through the docket. In order to summarize the analyses which have been completed and to illustrate the general approach, a selected number of tabular and graphical interpretations of the results are presented below. Most of the information presented below is based on the Ventura California meteorological data inputs as an example. [Note: Additional analyses are provided below that allow for comparison between all combinations of weather and flux inputs so that the longest predicted buffers can be determined.]

Tables 9 and 10 present PERFUM results (i.e., predicted buffer distances) based on Ventura California weather data and the Watsonville California flat fume flux emission profile for iodomethane for 10 and 40 acre fields, respectively. In these tables results for each HEC of concern (i.e., nasal lesions, fetal loss, and neurotoxicity) are presented for different percentiles of exposure, different application rates, the nature of the PERFUM output (i.e., maximum distance or whole field buffers), and different uncertainty factors. It should be noted that PERFUM analyses were completed for an uncertainty factor = 1 but they are not included in these tables because essentially most/all predicted buffer results were 0 meters. For a 10 acre field, the maximum and whole field buffer distances were as follows for each endpoint of concern at the 99th percentile of exposure at the maximum application rate and an uncertainty factor of 30: maximum and whole field buffers are 65 and 5 meters, respectively for nasal lesions; maximum and whole field buffers are both 5 meters for fetal loss; and maximum and whole field buffers are 40 and 5 meters, respectively for neurotoxicity. If any factors are reduced then predicted buffer distances change, but in a non-linear Gaussian fashion. For example, if all other factors are held constant and the application rate was reduced to 75 percent of the maximum

application rate (131 lb ai/acre) then distances for the nasal lesion maximum buffer would be reduced to 25 meters. Similar trends can be observed in the results for a 40 acre field. In a 40 acre field, the maximum and whole field buffer distances were as follows for each endpoint of concern at the 99th percentile of exposure at the maximum application rate and an uncertainty factor of 30: maximum and whole field buffers are 185 and 55 meters, respectively for nasal lesions; maximum and whole field buffers are 70 and 5 meters, respectively for fetal loss; and maximum and whole field buffers are 130 and 5 meters, respectively for neurotoxicity. Tables 9 and 10 are summaries of a variety of analyses that were completed using PERFUM based on the hierarchy presented in Table 3 above. These outputs are examples based on analyses using the combination of Ventura California weather data and the results of the Watsonville California flat fume flux study which only represent a small portion of the approximate 14,600 PERFUM analyses completed. As indicated above, similar analyses using other weather/flux combinations could be completed using PERFUM outputs files which are available through the iodomethane docket.

The information that is included in Tables 9 and 10 can also be graphically presented (as can the results of any of the completed PERFUM analysis). Figures 13 and 14 present the maximum and whole field buffer distances for 10 acre fields based on an uncertainty factor of 30 that were calculated using the Ventura California weather data and the Watsonville California flat fume flux profile. In these graphs, buffer distance results are plotted versus the percentile of exposure at varying application rates (i.e., maximum of 175 lb ai/A and 75 percent rate of 131 lb ai/A) for each endpoint of concern (i.e., nasal lesions, fetal loss, and neurotoxicity). Figures 15 and 16 are similar in nature except they present the results for 40 acre fields. When reviewing the results in Figures 13 through 16 note that the scale of the “y” axis are similar for direct comparison. Generally, results based on nasal lesions provide the farthest predicted buffer distances followed closely by results based on neurotoxicity. Predicted buffer distances are generally lower based on the developmental effect (i.e., fetal loss).

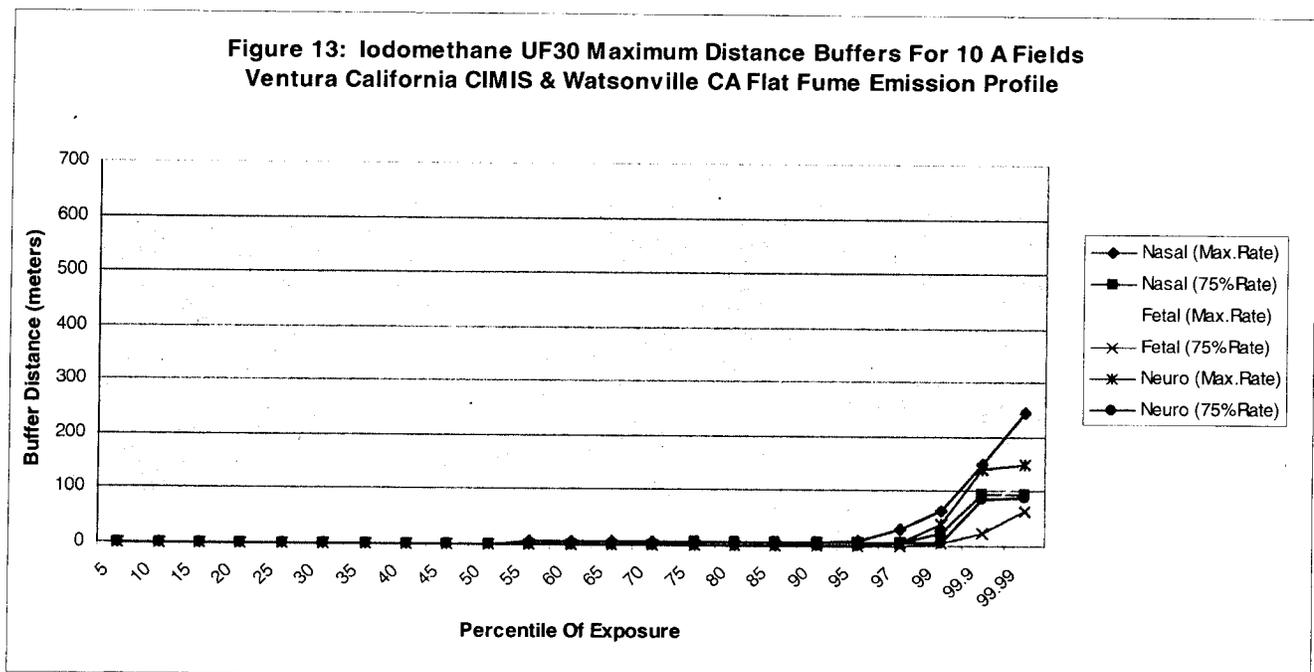
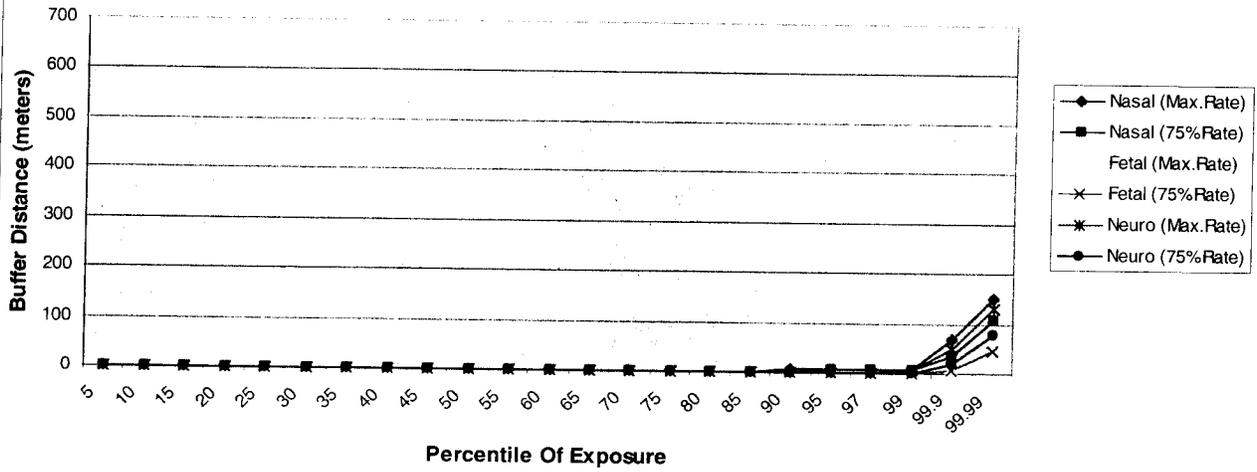


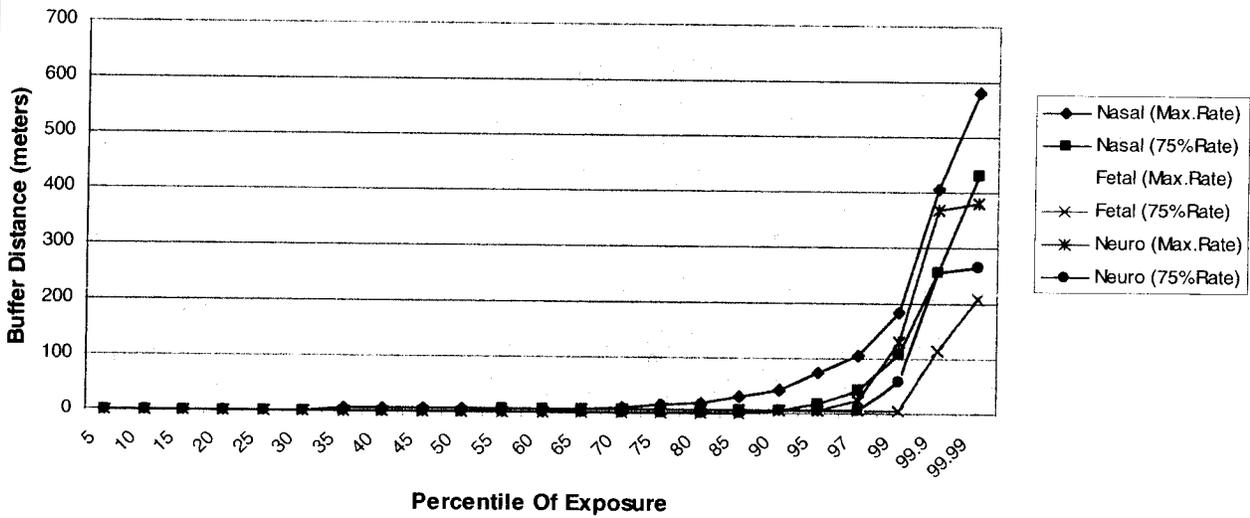
Table 10: Iodomethane PERFUM Buffer Distributions For A 40 Acre Square Field Based On Ventura CA Weather And Watsonville Flat Fume Flux Profile

| Percentile Of Exposure | Results For Nasal Lesion HEC (4.5 ppm) | | | | Results For Fetal Loss HEC (7.4 ppm) | | | | Results For Neurotoxicity HEC (10.0 ppm) | | | |
|------------------------|--|--------------------|------------------------|--------------------|--------------------------------------|--------------------|------------------------|--------------------|--|--------------------|------------------------|--------------------|
| | Max. Rate (175 lb ai/A) | | 75% Rate (131 lb ai/A) | | Max. Rate (175 lb ai/A) | | 75% Rate (131 lb ai/A) | | Max. Rate (175 lb ai/A) | | 75% Rate (131 lb ai/A) | |
| | Max. Buffer | Whole Field Buffer | Max. Buffer | Whole Field Buffer | Max. Buffer | Whole Field Buffer | Max. Buffer | Whole Field Buffer | Max. Buffer | Whole Field Buffer | Max. Buffer | Whole Field Buffer |
| 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 15 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 20 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 30 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 35 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 40 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 45 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 50 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 55 | 5 | 0 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 60 | 5 | 0 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 65 | 5 | 0 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 70 | 10 | 0 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 75 | 15 | 0 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 80 | 20 | 5 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 85 | 30 | 5 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 90 | 45 | 5 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 95 | 75 | 10 | 20 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 97 | 105 | 20 | 45 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 99 | 185 | 55 | 110 | 15 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 99.9 | 405 | 195 | 255 | 120 | 85 | 115 | 115 | 40 | 155 | 155 | 255 | 95 |
| 99.99 | 580 | 390 | 430 | 280 | 230 | 210 | 210 | 160 | 345 | 380 | 265 | 230 |
| UF = 30 | | | | | | | | | | | | |
| 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 15 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 20 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 30 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 35 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 40 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 45 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 50 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 55 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 60 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 65 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 70 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 75 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 80 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| UF = 10 | | | | | | | | | | | | |

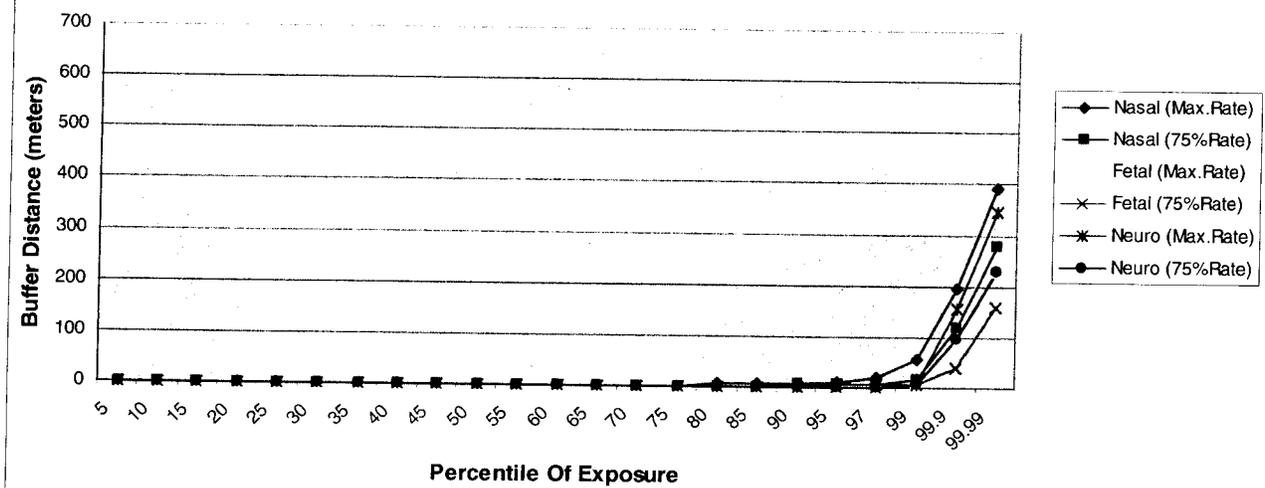
**Figure 14: Iodomethane UF30 Whole Field Buffers For 10 A Fields
Ventura California CIMIS & Watsonville CA Flat Fume Emission Profile**



**Figure 15: Iodomethane UF30 Maximum Distance Buffers For 40 A Fields
Ventura California CIMIS & Watsonville CA Flat Fume Emission Profile**



**Figure 16: Iodomethane UF30 Whole Field Buffers For 40 A Fields
Ventura California CIMIS & Watsonville CA Flat Fume Emission Profile**



For comparative purposes, similar graphs are presented below in Figures 17 and 18 that are based on results for Ventura California weather data but flux profiles for different application methods. In Figure 17, the flux profile is for the Guadalupe California tarped raised bed application while Figure 18 presents the LaSelva California drip irrigation application results. In both of these examples, predicted buffer distances are generally farther than those presented above for the Watsonville flat fume flux profile. For example, predicted buffers were as follows for Guadalupe (40A & 99th %tile of exposure): maximum and whole field buffers are 460 and 310 meters, respectively for nasal lesions; maximum and whole field buffers are 225 and 130 meters, respectively for fetal loss; and maximum and whole field buffers are 365 and 220 meters, respectively for neurotoxicity.

**Figure 17: Iodomethane UF30 Maximum Distance Buffers For 40 A Fields
Ventura California CIMIS & Guadalupe CA Tarped Raised Bed Emission Profile**

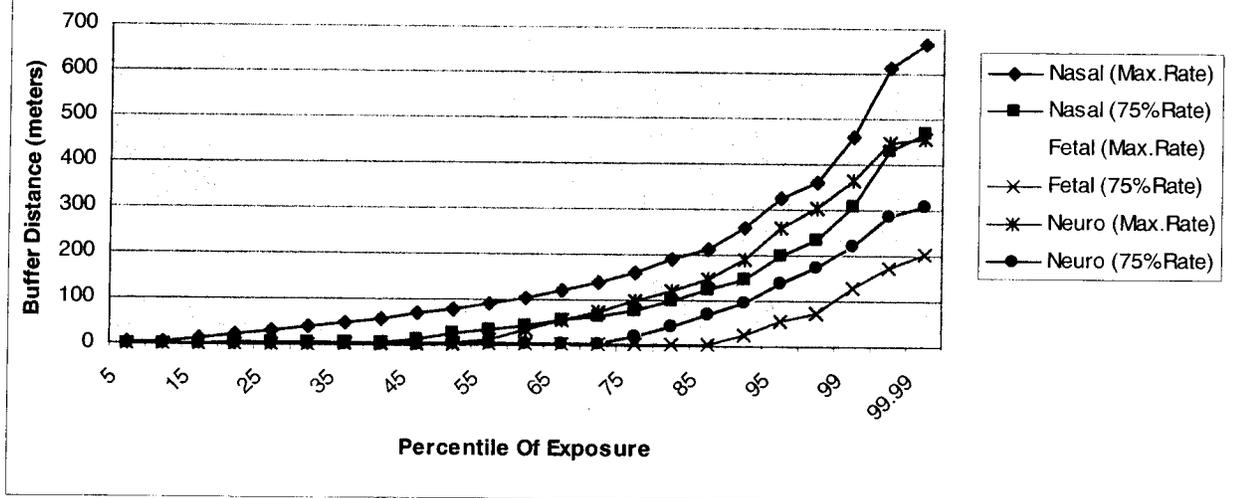


Figure 18: Iodomethane UF30 Maximum Distance Buffers For 40 A Fields
Ventura California CIMIS & LaSelva CA Drip Irrigation Emission Profile

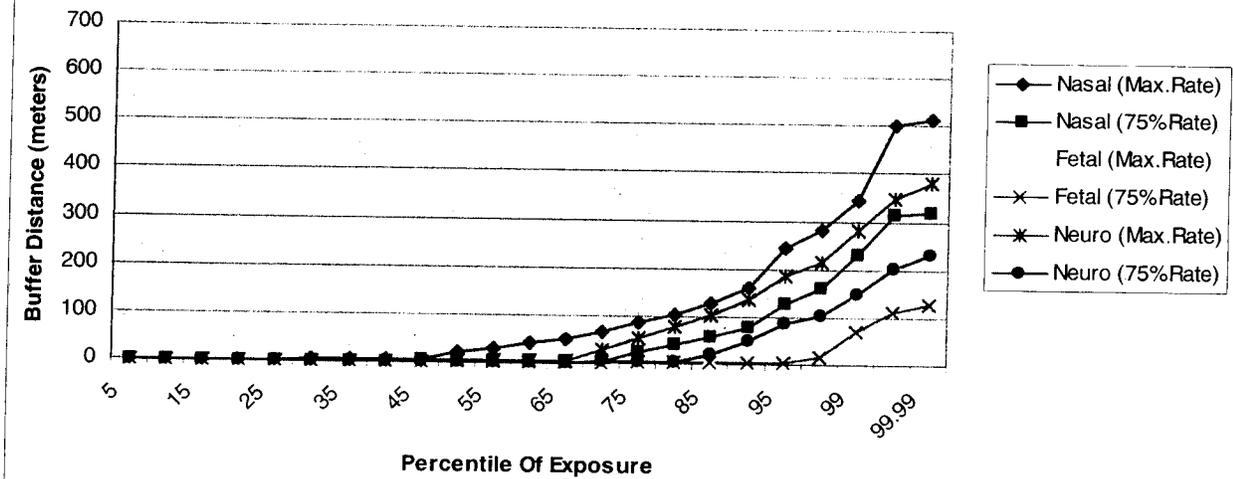


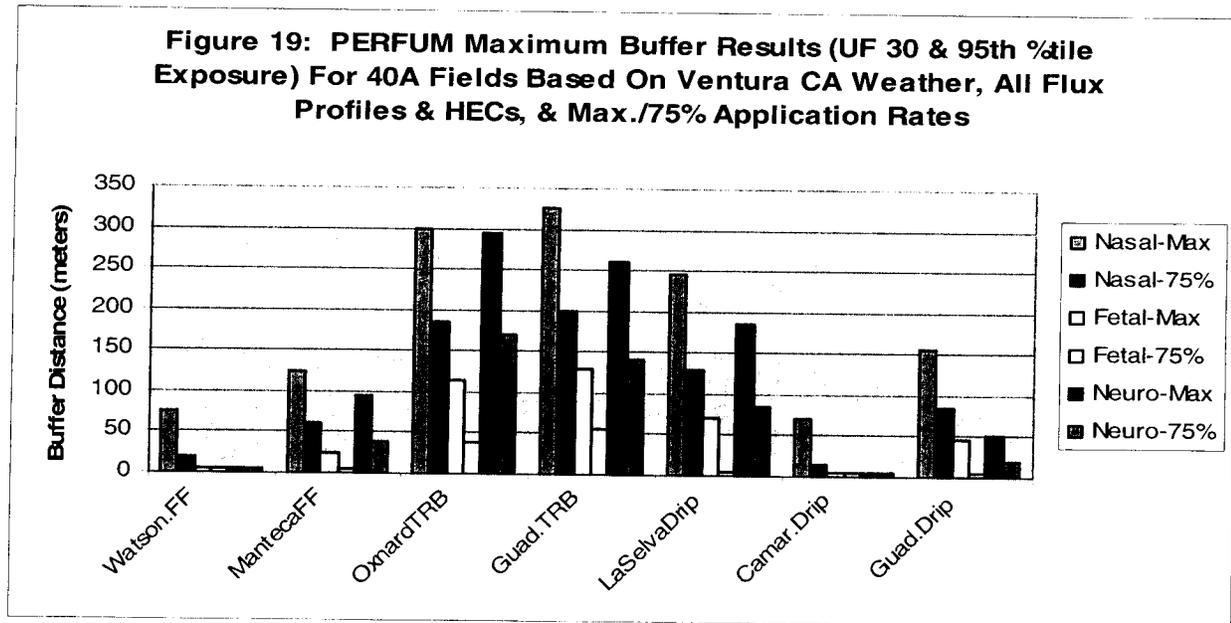
Table 11 provides a comparison of results for selected percentiles of exposure among flux profiles for a 40 acre field at varied application rates (i.e., maximum and 75%) for each HEC of concern based on an uncertainty factor of 30. The largest range, however, was observed in the drip irrigation results (i.e., approximately a factor of 2). In 6 cases, predicted buffer distances were greatest based on the nasal lesion HEC which were followed by distances predicted using the neurotoxicity and developmental (i.e., fetal loss) HECs, respectively. In two cases only at the highest percentiles of exposure (e.g., 99.9 and 99.99th percentiles), results based on the neurotoxicity HEC were actually greater than those predicted for nasal lesions based on the Guadalupe California drip irrigation flux study and the Manteca California flat fume flux study. This is critical for consideration in risk management because more severe neurotoxicity effects have been identified at exposure levels similar to those predicted for nasal lesions. It is believed that the shape of the flux profile for these two sites impacts this outcome (i.e., more is proportionally emitted during an 8 hour period than for the other HECs where a 24 hour averaging time is used). Figures 19 and 20 below graphically present the results for the 95th percentile of exposure presented in Table 11 for comparative purposes. Note the “y” axis scales are identical for ease of comparison between maximum and whole buffer PERFUM results.

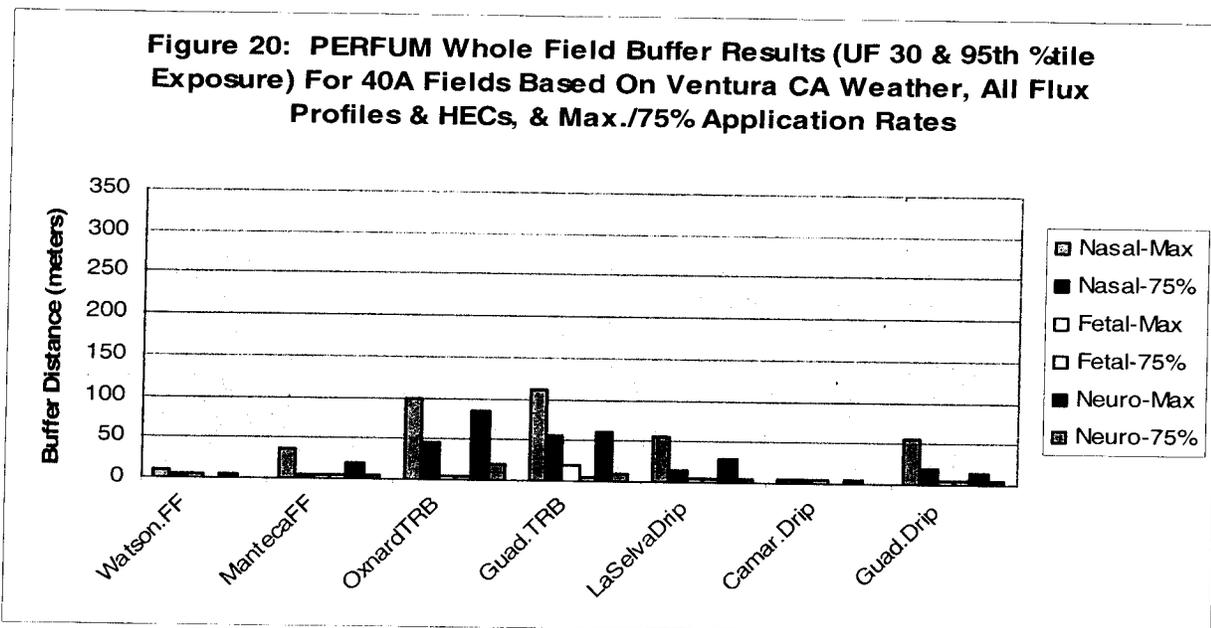
Table 11 - Comparison Of Results For Iodomethane PERFUM Buffer Distributions Based On A 40 Acre Square Field, Ventura California Weather Data, And All Flux Profiles At A UF=30

| Perc. Of Expo. | Nasal Lesion Results | | | | Developmental (Fetal Loss) Results | | | | Neurotoxicity Results | | | |
|---------------------------------------|----------------------|--------------------|-------------------|--------------------|------------------------------------|--------------------|-------------------|--------------------|-----------------------|--------------------|-------------------|--------------------|
| | 175 lb ai/A | | 75% (131 lb ai/A) | | 175 lb ai/A | | 75% (131 lb ai/A) | | 175 lb ai/A | | 75% (131 lb ai/A) | |
| | Max Buffer | Whole Field Buffer | Max Buffer | Whole Field Buffer | Max Buffer | Whole Field Buffer | Max Buffer | Whole Field Buffer | Max Buffer | Whole Field Buffer | Max Buffer | Whole Field Buffer |
| Flux - Watsonville CA Flat Fume | | | | | | | | | | | | |
| 50 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 75 | 15 | 0 | 5 | 0 | 5 | 0 | 0 | 0 | 5 | 0 | 0 | 0 |
| 90 | 45 | 5 | 5 | 5 | 5 | 0 | 5 | 0 | 5 | 0 | 5 | 0 |
| 95 | 75 | 10 | 20 | 5 | 5 | 5 | 5 | 0 | 5 | 5 | 5 | 0 |
| 99 | 185 | 55 | 110 | 15 | 70 | 5 | 5 | 5 | 130 | 5 | 60 | 5 |
| 99.9 | 405 | 195 | 255 | 120 | 185 | 85 | 115 | 40 | 370 | 155 | 255 | 95 |
| 99.99 | 580 | 390 | 430 | 280 | 185 | 230 | 210 | 160 | 380 | 345 | 265 | 230 |
| Flux - Manteca CA Flat Fume | | | | | | | | | | | | |
| 50 | 25 | 0 | 5 | 0 | 5 | 0 | 0 | 0 | 5 | 0 | 5 | 0 |
| 75 | 50 | 5 | 10 | 0 | 5 | 0 | 5 | 0 | 25 | 0 | 5 | 0 |
| 90 | 90 | 20 | 35 | 5 | 5 | 5 | 5 | 0 | 50 | 5 | 15 | 5 |
| 95 | 125 | 35 | 60 | 5 | 25 | 5 | 5 | 5 | 95 | 20 | 40 | 5 |
| 99 | 255 | 95 | 155 | 45 | 100 | 20 | 45 | 5 | 295 | 70 | 175 | 30 |
| 99.9 | 425 | 250 | 295 | 165 | 230 | 120 | 160 | 65 | 520 | 265 | 320 | 180 |
| 99.99 | 480 | 405 | 380 | 300 | 305 | 240 | 195 | 165 | 565 | 435 | 425 | 310 |
| Flux - Oxnard CA Tarped Raised Bed | | | | | | | | | | | | |
| 50 | 60 | 0 | 5 | 0 | 5 | 0 | 0 | 0 | 25 | 0 | 5 | 0 |
| 75 | 150 | 5 | 70 | 0 | 25 | 0 | 5 | 0 | 130 | 0 | 50 | 0 |
| 90 | 250 | 40 | 140 | 5 | 85 | 5 | 5 | 0 | 235 | 20 | 125 | 5 |
| 95 | 300 | 100 | 185 | 45 | 115 | 5 | 40 | 5 | 295 | 85 | 170 | 20 |
| 99 | 425 | 240 | 280 | 140 | 195 | 85 | 100 | 15 | 390 | 225 | 235 | 130 |
| 99.9 | 530 | 390 | 350 | 260 | 250 | 180 | 145 | 95 | 470 | 365 | 305 | 220 |
| 99.99 | 565 | 520 | 355 | 345 | 265 | 240 | 165 | 140 | 500 | 460 | 320 | 300 |
| Flux - Guadalupe CA Tarped Raised Bed | | | | | | | | | | | | |
| 50 | 80 | 0 | 25 | 0 | 5 | 0 | 0 | 0 | 5 | 0 | 5 | 0 |
| 75 | 160 | 5 | 80 | 5 | 40 | 0 | 5 | 0 | 100 | 0 | 20 | 0 |
| 90 | 260 | 55 | 150 | 15 | 90 | 5 | 25 | 5 | 190 | 10 | 95 | 5 |
| 95 | 325 | 110 | 200 | 55 | 130 | 20 | 55 | 5 | 260 | 60 | 140 | 10 |
| 99 | 460 | 250 | 310 | 155 | 225 | 95 | 130 | 35 | 365 | 185 | 220 | 100 |
| 99.9 | 615 | 410 | 430 | 285 | 305 | 210 | 175 | 120 | 450 | 335 | 285 | 205 |
| 99.99 | 665 | 550 | 470 | 385 | 350 | 295 | 205 | 185 | 455 | 425 | 310 | 275 |
| Flux - LaSelva CA Drip Irrigation | | | | | | | | | | | | |
| 50 | 20 | 0 | 5 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 0 |
| 75 | 85 | 0 | 25 | 0 | 5 | 0 | 5 | 0 | 55 | 0 | 5 | 0 |
| 90 | 160 | 20 | 80 | 5 | 35 | 5 | 5 | 0 | 135 | 5 | 50 | 0 |
| 95 | 245 | 55 | 130 | 15 | 70 | 5 | 5 | 5 | 185 | 30 | 85 | 5 |
| 99 | 345 | 165 | 230 | 90 | 150 | 45 | 70 | 5 | 280 | 135 | 150 | 60 |
| 99.9 | 500 | 325 | 315 | 205 | 215 | 140 | 110 | 70 | 350 | 265 | 205 | 145 |
| 99.99 | 515 | 435 | 320 | 295 | 225 | 205 | 130 | 110 | 380 | 340 | 230 | 205 |
| Flux - Camarillo CA Drip Irrigation | | | | | | | | | | | | |
| 50 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 75 | 5 | 0 | 5 | 0 | 5 | 0 | 0 | 0 | 5 | 0 | 0 | 0 |
| 90 | 45 | 5 | 5 | 5 | 5 | 0 | 0 | 0 | 5 | 0 | 0 | 0 |

Table 11 - Comparison Of Results For Iodomethane PERFUM Buffer Distributions Based On A 40 Acre Square Field, Ventura California Weather Data, And All Flux Profiles At A UF=30

| Perc. Of Expo. | Nasal Lesion Results | | | | Developmental (Fetal Loss) Results | | | | Neurotoxicity Results | | | |
|-------------------------------------|----------------------|--------------------|-------------------|--------------------|------------------------------------|--------------------|-------------------|--------------------|-----------------------|--------------------|-------------------|--------------------|
| | 175 lb ai/A | | 75% (131 lb ai/A) | | 175 lb ai/A | | 75% (131 lb ai/A) | | 175 lb ai/A | | 75% (131 lb ai/A) | |
| | Max Buffer | Whole Field Buffer | Max Buffer | Whole Field Buffer | Max Buffer | Whole Field Buffer | Max Buffer | Whole Field Buffer | Max Buffer | Whole Field Buffer | Max Buffer | Whole Field Buffer |
| 95 | 70 | 5 | 15 | 5 | 5 | 5 | 5 | 0 | 5 | 5 | 5 | 0 |
| 99 | 165 | 55 | 90 | 10 | 50 | 5 | 5 | 5 | 145 | 5 | 70 | 5 |
| 99.9 | 325 | 170 | 225 | 105 | 175 | 70 | 110 | 25 | 320 | 145 | 225 | 85 |
| 99.99 | 425 | 320 | 325 | 245 | 245 | 185 | 135 | 115 | 360 | 295 | 255 | 195 |
| Flux - Guadalupe CA Drip Irrigation | | | | | | | | | | | | |
| 50 | 45 | 0 | 10 | 0 | 5 | 0 | 0 | 0 | 5 | 0 | 5 | 0 |
| 75 | 70 | 5 | 25 | 5 | 5 | 0 | 5 | 0 | 15 | 0 | 5 | 0 |
| 90 | 120 | 35 | 60 | 5 | 25 | 5 | 5 | 5 | 25 | 5 | 5 | 5 |
| 95 | 155 | 55 | 85 | 20 | 45 | 5 | 5 | 5 | 50 | 15 | 20 | 5 |
| 99 | 355 | 125 | 245 | 70 | 175 | 40 | 90 | 5 | 360 | 50 | 235 | 20 |
| 99.9 | 630 | 330 | 425 | 235 | 330 | 175 | 240 | 110 | 655 | 325 | 480 | 230 |
| 99.99 | 795 | 535 | 590 | 410 | 480 | 340 | 365 | 255 | 890 | 555 | 550 | 410 |





In addition to the comparisons described above among flux types, a comparison was also completed that evaluated differences concurrently among meteorological data and flux profile (Table 12 & Figure 21). These results are based on a 40 acre field and an uncertainty factor of 30 at the maximum application rate for each method. Results are also presented for each HEC of concern. For results based on the selection of meteorological data, it appears that results for Bradenton Florida have higher associated buffer distances than (in order) Ventura California, Tallahassee Florida, Flint Michigan, and Bakersfield California. These results are consistent with the sensitivity analysis completed by the model developer and presented at the 2004 FIFRA Scientific Advisory Panel meeting (<http://www.epa.gov/oscpmont/sap/meetings/2004/index.htm>). It is also important to note that similar trends are observed as described in the analysis presented above (Table 11 & Figures 19, 20) where results based on neurotoxicity are similar to those observed for nasal lesions that indicates similar results for a more severe toxicological effect. It is anticipated that these general trends would be observed regardless of the field size, uncertainty factor basis, or application rate if a similar analysis was completed using different factors.

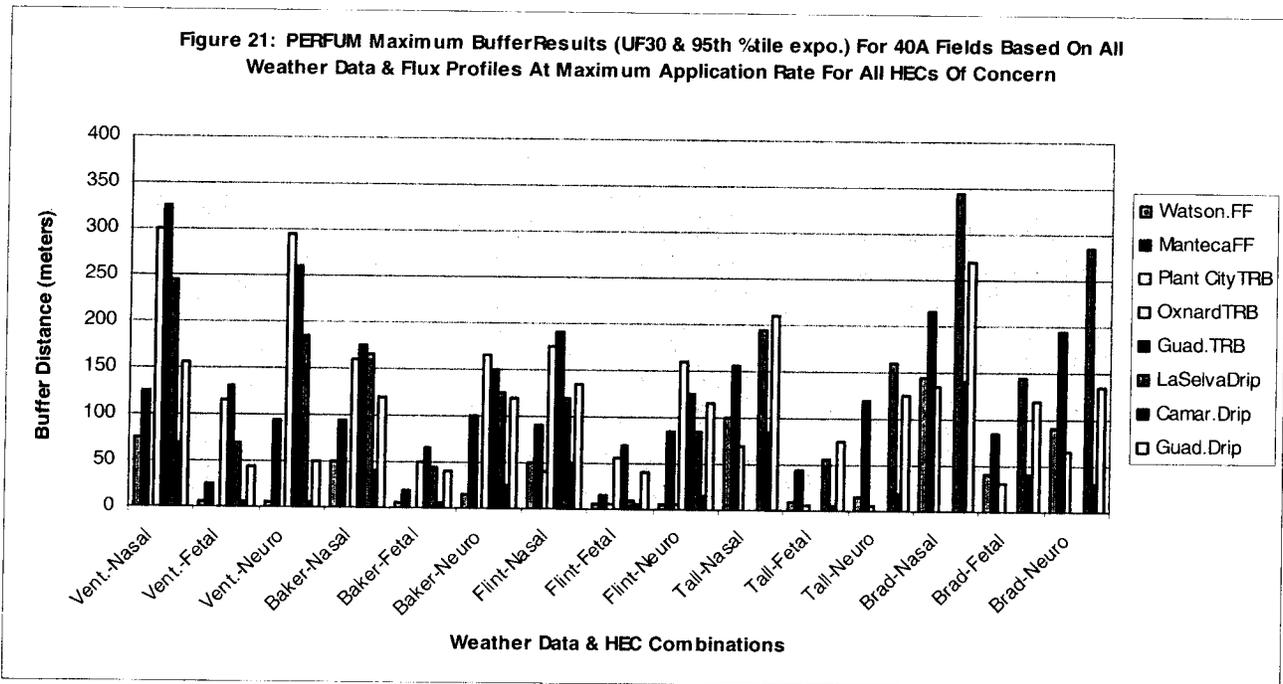
| Table 12 - Comparison Of Results For Iodomethane PERFUM Buffer Distributions Based On A 40 Acre Square Field, All Weather Data, And All Flux Profiles At A UF=30 And Maximum Application Rate (175 lb ai/A) For All HECs Of Concern | | | | | | | | | | | | | | | | |
|---|------------|------------|-------|----------------|------------|-------|----------|------------|-------|----------------|------------|-------|--------------|------------|-------|--|
| %tile Of Expo. | Ventura CA | | | Bakersfield CA | | | Flint MI | | | Tallahassee FL | | | Bradenton FL | | | |
| | Nasal | Fetal Loss | Neuro | Nasal | Fetal Loss | Neuro | Nasal | Fetal Loss | Neuro | Nasal | Fetal Loss | Neuro | Nasal | Fetal Loss | Neuro | |
| Flux - Watsonville CA Flat Fume | | | | | | | | | | | | | | | | |
| 50 | 5 | 0 | 0 | 5 | 0 | 0 | 5 | 0 | 0 | 10 | 0 | 0 | 30 | 5 | 5 | |
| 75 | 15 | 5 | 5 | 15 | 5 | 5 | 10 | 5 | 0 | 35 | 5 | 5 | 60 | 5 | 10 | |
| 90 | 45 | 5 | 5 | 35 | 5 | 5 | 35 | 5 | 5 | 70 | 5 | 5 | 105 | 20 | 55 | |
| 95 | 75 | 5 | 5 | 50 | 5 | 15 | 50 | 5 | 5 | 100 | 10 | 15 | 145 | 40 | 90 | |
| 99 | 185 | 70 | 130 | 80 | 10 | 65 | 90 | 15 | 5 | 155 | 40 | 80 | 230 | 85 | 175 | |
| 99.9 | 405 | 185 | 370 | 115 | 30 | 130 | 145 | 45 | 85 | 235 | 70 | 125 | 310 | 125 | 260 | |
| 99.99 | 580 | 185 | 380 | 120 | 35 | 140 | 150 | 45 | 120 | 240 | 75 | 140 | 330 | 145 | 265 | |

Table 12 - Comparison Of Results For Iodomethane PERFUM Buffer Distributions Based On A 40 Acre Square Field, All Weather Data, And All Flux Profiles At A UF=30 And Maximum Application Rate (175 lb ai/A) For All HECs Of Concern

| %tile Of Expo. | Ventura CA | | | Bakersfield CA | | | Flint MI | | | Tallahassee FL | | | Bradenton FL | | |
|--|------------|------------|-------|----------------|------------|-------|----------|------------|-------|----------------|------------|-------|--------------|------------|-------|
| | Nasal | Fetal Loss | Neuro | Nasal | Fetal Loss | Neuro | Nasal | Fetal Loss | Neuro | Nasal | Fetal Loss | Neuro | Nasal | Fetal Loss | Neuro |
| Flux - Manteca CA Flat Fume | | | | | | | | | | | | | | | |
| 50 | 25 | 5 | 5 | 25 | 5 | 15 | 15 | 0 | 5 | 40 | 5 | 15 | 70 | 5 | 50 |
| 75 | 50 | 5 | 25 | 45 | 5 | 40 | 40 | 5 | 30 | 70 | 5 | 45 | 110 | 30 | 95 |
| 90 | 90 | 5 | 50 | 70 | 5 | 75 | 70 | 5 | 60 | 115 | 30 | 95 | 170 | 60 | 150 |
| 95 | 125 | 25 | 95 | 95 | 20 | 100 | 90 | 15 | 85 | 155 | 45 | 120 | 215 | 85 | 195 |
| 99 | 255 | 100 | 295 | 130 | 45 | 150 | 145 | 50 | 155 | 215 | 75 | 170 | 325 | 140 | 295 |
| 99.9 | 425 | 230 | 520 | 175 | 70 | 225 | 240 | 90 | 260 | 355 | 130 | 280 | 415 | 195 | 410 |
| 99.99 | 480 | 305 | 565 | 190 | 70 | 235 | 245 | 90 | 290 | 360 | 130 | 415 | 425 | 210 | 445 |
| Flux - Plant City FL Tarped Raised Bed | | | | | | | | | | | | | | | |
| 50 | NA | NA | NA | NA | NA | NA | 5 | 0 | 0 | 5 | 0 | 0 | 20 | 0 | 0 |
| 75 | NA | NA | NA | NA | NA | NA | 5 | 0 | 0 | 15 | 5 | 0 | 60 | 5 | 5 |
| 90 | NA | NA | NA | NA | NA | NA | 20 | 5 | 5 | 45 | 5 | 5 | 105 | 10 | 35 |
| 95 | NA | NA | NA | NA | NA | NA | 40 | 5 | 5 | 70 | 5 | 5 | 135 | 30 | 65 |
| 99 | NA | NA | NA | NA | NA | NA | 75 | 5 | 5 | 110 | 10 | 40 | 215 | 65 | 135 |
| 99.9 | NA | NA | NA | NA | NA | NA | 125 | 25 | 100 | 210 | 55 | 85 | 260 | 105 | 185 |
| 99.99 | NA | NA | NA | NA | NA | NA | 130 | 25 | 105 | 215 | 55 | 95 | 285 | 130 | 190 |
| Flux - Oxnard CA Tarped Raised Bed | | | | | | | | | | | | | | | |
| 50 | 60 | 5 | 25 | 55 | 5 | 35 | 30 | 0 | 5 | NA | NA | NA | NA | NA | NA |
| 75 | 150 | 25 | 130 | 90 | 5 | 85 | 75 | 5 | 40 | NA | NA | NA | NA | NA | NA |
| 90 | 250 | 85 | 235 | 135 | 30 | 135 | 130 | 30 | 110 | NA | NA | NA | NA | NA | NA |
| 95 | 300 | 115 | 295 | 160 | 50 | 165 | 175 | 55 | 160 | NA | NA | NA | NA | NA | NA |
| 99 | 425 | 195 | 390 | 225 | 85 | 225 | 270 | 105 | 225 | NA | NA | NA | NA | NA | NA |
| 99.9 | 530 | 250 | 470 | 280 | 120 | 280 | 400 | 175 | 390 | NA | NA | NA | NA | NA | NA |
| 99.99 | 565 | 265 | 500 | 285 | 125 | 295 | 410 | 185 | 400 | NA | NA | NA | NA | NA | NA |
| Flux - Guadalupe CA Tarped Raised Bed | | | | | | | | | | | | | | | |
| 50 | 80 | 5 | 5 | 70 | 5 | 35 | 50 | 5 | 5 | NA | NA | NA | NA | NA | NA |
| 75 | 160 | 40 | 100 | 110 | 20 | 75 | 95 | 15 | 30 | NA | NA | NA | NA | NA | NA |
| 90 | 260 | 90 | 190 | 150 | 45 | 120 | 150 | 45 | 90 | NA | NA | NA | NA | NA | NA |
| 95 | 325 | 130 | 260 | 175 | 65 | 150 | 190 | 70 | 125 | NA | NA | NA | NA | NA | NA |
| 99 | 460 | 225 | 365 | 250 | 100 | 215 | 300 | 120 | 220 | NA | NA | NA | NA | NA | NA |
| 99.9 | 615 | 305 | 450 | 305 | 125 | 325 | 390 | 180 | 365 | NA | NA | NA | NA | NA | NA |
| 99.99 | 665 | 350 | 455 | 305 | 130 | 345 | 410 | 190 | 375 | NA | NA | NA | NA | NA | NA |
| Flux - LaSelva CA Drip Irrigation | | | | | | | | | | | | | | | |
| 50 | 20 | 0 | 5 | 35 | 5 | 5 | 5 | 0 | 0 | 15 | 0 | 0 | 60 | 5 | 5 |
| 75 | 85 | 5 | 55 | 75 | 5 | 40 | 30 | 5 | 5 | 75 | 5 | 10 | 140 | 35 | 110 |
| 90 | 160 | 35 | 135 | 125 | 20 | 90 | 80 | 5 | 45 | 150 | 30 | 100 | 260 | 95 | 205 |
| 95 | 245 | 70 | 185 | 165 | 45 | 125 | 120 | 10 | 85 | 195 | 55 | 160 | 345 | 145 | 285 |
| 99 | 345 | 150 | 280 | 235 | 85 | 195 | 185 | 65 | 165 | 300 | 110 | 240 | 475 | 220 | 430 |
| 99.9 | 500 | 215 | 350 | 340 | 125 | 260 | 385 | 145 | 270 | 475 | 205 | 310 | 660 | 330 | 555 |
| 99.99 | 515 | 225 | 380 | 375 | 125 | 275 | 460 | 175 | 275 | 490 | 210 | 315 | 685 | 350 | 560 |
| Flux - Camarillo CA Drip Irrigation | | | | | | | | | | | | | | | |
| 50 | 5 | 0 | 0 | 5 | 0 | 0 | 5 | 0 | 0 | 5 | 0 | 0 | 30 | 5 | 5 |

Table 12 - Comparison Of Results For Iodomethane PERFUM Buffer Distributions Based On A 40 Acre Square Field, All Weather Data, And All Flux Profiles At A UF=30 And Maximum Application Rate (175 lb ai/A) For All HECs Of Concern

| %tile Of Expo. | Ventura CA | | | Bakersfield CA | | | Flint MI | | | Tallahassee FL | | | Bradenton FL | | |
|-------------------------------------|------------|------------|-------|----------------|------------|-------|----------|------------|-------|----------------|------------|-------|--------------|------------|-------|
| | Nasal | Fetal Loss | Neuro | Nasal | Fetal Loss | Neuro | Nasal | Fetal Loss | Neuro | Nasal | Fetal Loss | Neuro | Nasal | Fetal Loss | Neuro |
| 75 | 5 | 5 | 5 | 10 | 5 | 5 | 10 | 5 | 5 | 25 | 5 | 5 | 65 | 5 | 5 |
| 90 | 45 | 5 | 5 | 25 | 5 | 10 | 30 | 5 | 5 | 60 | 5 | 5 | 110 | 20 | 15 |
| 95 | 70 | 5 | 5 | 40 | 5 | 25 | 50 | 5 | 15 | 85 | 5 | 20 | 140 | 40 | 30 |
| 99 | 165 | 50 | 145 | 65 | 5 | 55 | 90 | 10 | 60 | 135 | 30 | 55 | 220 | 75 | 85 |
| 99.9 | 325 | 175 | 320 | 110 | 20 | 105 | 135 | 40 | 95 | 225 | 65 | 110 | 290 | 130 | 155 |
| 99.99 | 425 | 245 | 360 | 115 | 25 | 110 | 165 | 50 | 125 | 230 | 70 | 135 | 315 | 130 | 170 |
| Flux - Guadalupe CA Drip Irrigation | | | | | | | | | | | | | | | |
| 50 | 45 | 5 | 5 | 45 | 5 | 15 | 40 | 5 | 15 | 60 | 5 | 15 | 95 | 25 | 35 |
| 75 | 70 | 5 | 15 | 65 | 5 | 45 | 70 | 5 | 45 | 105 | 25 | 40 | 145 | 50 | 60 |
| 90 | 120 | 25 | 25 | 95 | 25 | 90 | 105 | 25 | 80 | 165 | 55 | 85 | 215 | 85 | 100 |
| 95 | 155 | 45 | 50 | 120 | 40 | 120 | 135 | 40 | 115 | 210 | 75 | 125 | 270 | 120 | 135 |
| 99 | 355 | 175 | 360 | 170 | 65 | 185 | 230 | 90 | 220 | 295 | 120 | 195 | 400 | 190 | 250 |
| 99.9 | 630 | 330 | 655 | 245 | 105 | 290 | 400 | 145 | 730 | 460 | 195 | 345 | 525 | 270 | 390 |
| 99.99 | 795 | 480 | 890 | 250 | 105 | 290 | 450 | 145 | 1440 | 505 | 210 | 370 | 530 | 285 | 410 |



In addition to the comparative analyses presented above, other factors were evaluated relative to their possible impacts on PERFUM-based buffer zone predictions. These included evaluating the effect of field size and shape on results as well as discerning if there are significant seasonal differences in results since many fumigant use patterns are seasonal in nature. Figure 22 illustrates differences associated with increasing field sizes and the results indicate that, as expected, buffer distances increase relative to field size. Similar trends are observed regardless of the application rate or whether or not the results are based on maximum or whole field buffer results.

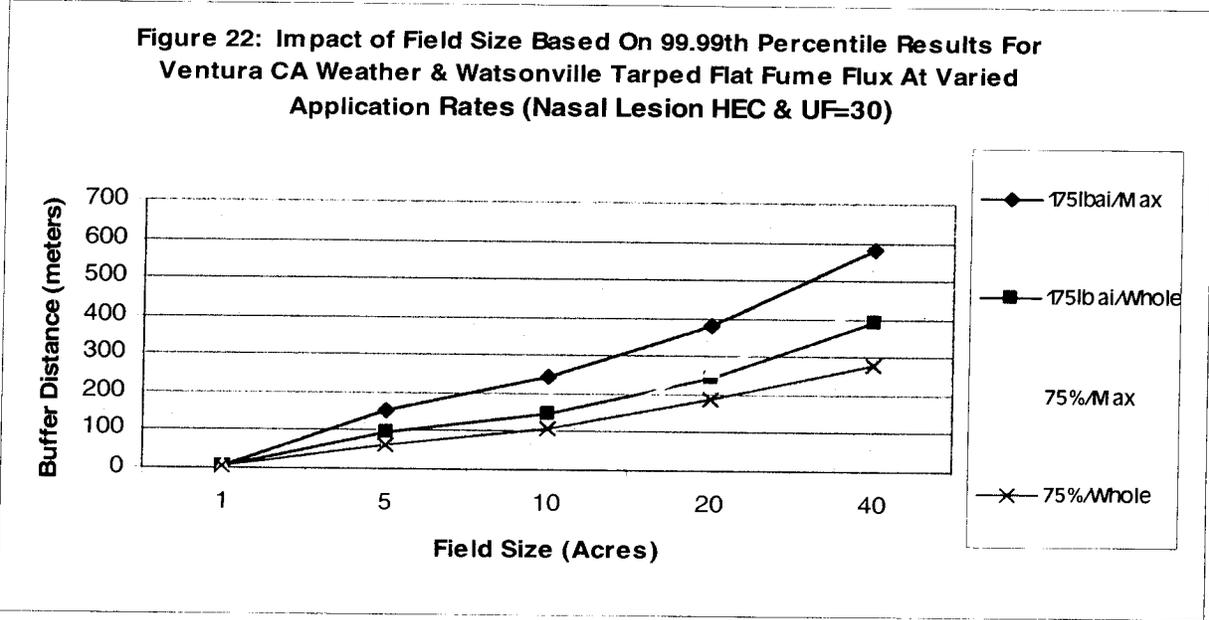
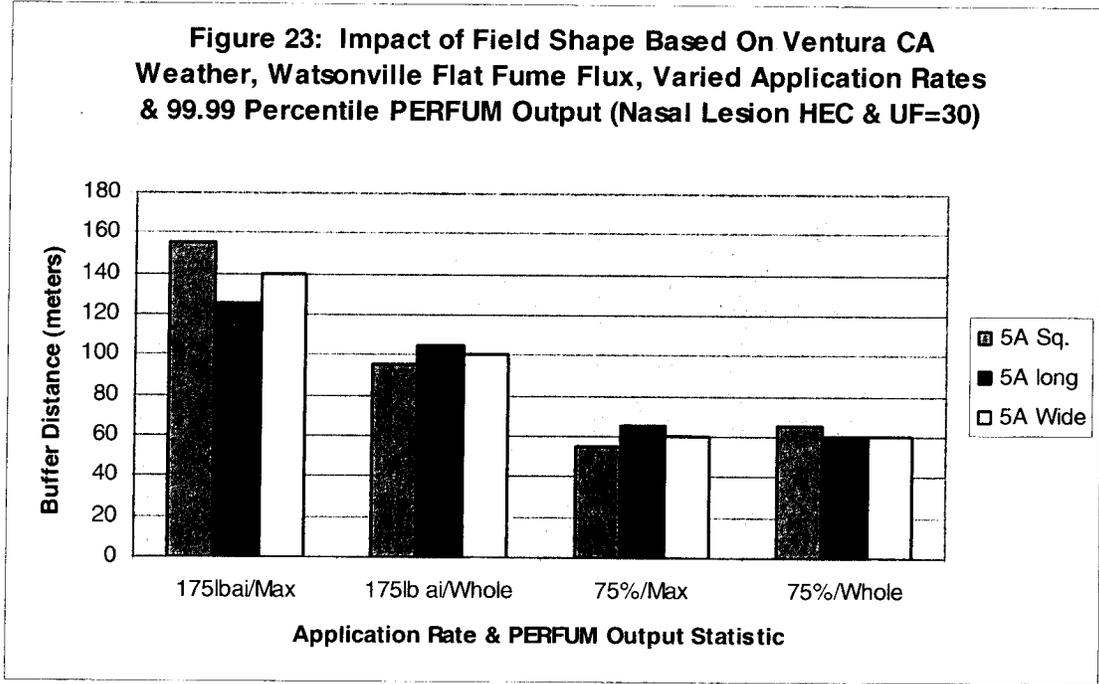


Figure 23 illustrates differences based on field shape. In this analysis, results for a square 5 acre field and rectangular fields (i.e., based on a 2:1 aspect ratio) oriented alternatively on perpendicular sides were calculated. Results were essentially similar for all field orientations. The results of this analysis may also be sensitive to different weather conditions, site topography, and field aspect ratio but these factors were not evaluated in more detail because their relevance is likely more significant to specific use sites than to the development of generally applicable buffer estimates using PERFUM.



The seasonal impacts of changing weather patterns have been evaluated in every PERFUM analysis. Table 13 below provides an example of the outputs that are available. In this type of analysis PERFUM compiles distributions based on only the specific month's worth of meteorological data from the 5 years used for the analysis so each of the distributions is based on 5 months instead of 5 years of data. [Note: For comparative purposes, the corresponding 5 year distribution for Table 13 is included in Table 10 above for whole fields, maximum application rate with an uncertainty factor of 30 based on nasal lesions.] It appears in this case that longer buffer distances are predicted in the cooler winter months which may be due to an overall trend toward a more stable atmosphere in those months due to less convective heating and atmospheric turbulence than in the spring and summer months which are more conducive to rapid dispersion conditions.

| Table 13: Iodomethane PERFUM Monthly Whole Field Buffer Distributions For A 40 Acre Square Field For The Nasal Lesion HEC Based On Ventura CA Weather And Watsonville CA Flat Fume Flux At The Maximum Application Rate And With An Uncertainty Factor = 30 | | | | | | | | | | | | |
|---|-------------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Percentile Of Exposure | PERFUM Monthly Buffer Distributions | | | | | | | | | | | |
| | JAN | FEB | MAR | APR | MAY | JUN | JUL | AUG | SEP | OCT | NOV | DEC |
| 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 15 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 20 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 30 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 35 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 40 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 45 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 50 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 55 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 60 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 65 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 70 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 75 | 5 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 80 | 5 | 5 | 5 | 0 | 5 | 5 | 0 | 5 | 5 | 5 | 5 | 5 |
| 85 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 90 | 10 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 95 | 40 | 25 | 10 | 5 | 10 | 5 | 5 | 10 | 10 | 5 | 15 | 20 |
| 97 | 70 | 45 | 20 | 10 | 15 | 10 | 10 | 15 | 15 | 15 | 30 | 40 |
| 99 | 145 | 85 | 55 | 30 | 30 | 25 | 20 | 30 | 40 | 35 | 75 | 90 |
| 99.9 | 400 | 275 | 155 | 105 | 50 | 180 | 35 | 50 | 120 | 165 | 180 | 190 |
| 99.99 | 575 | 395 | 225 | 160 | 80 | 320 | 40 | 65 | 160 | 200 | 310 | 265 |

In the previous risk assessment completed for iodomethane (D325080, 1/5/06) an older version of the PERFUM model was used. Modifications were made to this system since that time. One key piece of output information that was not available in previous analyses was the capability to provide actual air concentration data from the established receptor grid in PERFUM. In order to address this a new version of PERFUM (2.1.3) was compiled on December 12, 2006 which provides concentration outputs in concentric rings around treated fields. These outputs are provided for distances out to 1440 meters in 30 different rings. [Note: Only 15 of 30 rings have been presented below for illustrative purposes.] A distribution of air concentrations is provided for each ring for each exposure averaging period after application begins (e.g., 24 hours in this case). As with the outputs presented in Tables 9 and 10 above, there are thousands of PERFUM analyses which were completed for the purposes of this assessment. Each set of air concentration outputs can be evaluated through review of the PERFUM output files available through the docket. An example output is provided below in Table 14 for informational purposes which represents the results in the first 24 hour period after application using the Ventura California weather and Watsonville California flat fume flux profile at the maximum application rate of 175 lb ai/acre.

Table 14: PERFUM Air Concentration Outputs For Watsonville CA Flat Fume and Ventura CA Weather Data Based On Maximum Application Rate For The First 24 Hour Period After Application

| %tile | Air Concentrations (ug/m3) At Varied Distances From Edge Of Treated Field (meters) | | | | | | | | | | | | | | |
|-------|--|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|-------|-------|
| | 5m | 7m | 10m | 15m | 20m | 30m | 50m | 70m | 80m | 90m | 100m | 120m | 150m | 180m | 210m |
| 5 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 10 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 15 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 20 | 26.1 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 0.0 | 0.0 |
| 25 | 61.0 | 43.5 | 43.5 | 26.1 | 26.1 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 |
| 30 | 95.8 | 78.4 | 78.4 | 61.0 | 43.5 | 43.5 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 |
| 35 | 130.6 | 130.6 | 113.2 | 95.8 | 78.4 | 61.0 | 43.5 | 26.1 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 | 8.7 |
| 40 | 182.9 | 182.9 | 165.5 | 148.0 | 130.6 | 95.8 | 61.0 | 43.5 | 26.1 | 26.1 | 26.1 | 8.7 | 8.7 | 8.7 | 8.7 |
| 45 | 235.1 | 235.1 | 217.7 | 182.9 | 165.5 | 130.6 | 78.4 | 61.0 | 43.5 | 43.5 | 43.5 | 26.1 | 8.7 | 8.7 | 8.7 |
| 50 | 304.8 | 287.4 | 269.9 | 235.1 | 217.7 | 165.5 | 113.2 | 78.4 | 78.4 | 61.0 | 61.0 | 43.5 | 26.1 | 8.7 | 8.7 |
| 55 | 357.0 | 339.6 | 322.2 | 287.4 | 252.5 | 217.7 | 148.0 | 113.2 | 95.8 | 78.4 | 78.4 | 61.0 | 43.5 | 26.1 | 26.1 |
| 60 | 409.3 | 391.9 | 374.4 | 339.6 | 304.8 | 252.5 | 182.9 | 148.0 | 130.6 | 113.2 | 95.8 | 78.4 | 61.0 | 43.5 | 26.1 |
| 65 | 478.9 | 461.5 | 426.7 | 391.9 | 357.0 | 304.8 | 235.1 | 182.9 | 165.5 | 148.0 | 130.6 | 113.2 | 78.4 | 61.0 | 43.5 |
| 70 | 531.2 | 513.8 | 496.4 | 444.1 | 409.3 | 357.0 | 269.9 | 217.7 | 200.3 | 182.9 | 165.5 | 130.6 | 113.2 | 95.8 | 78.4 |
| 75 | 600.9 | 583.4 | 548.6 | 513.8 | 478.9 | 409.3 | 322.2 | 269.9 | 235.1 | 217.7 | 200.3 | 182.9 | 148.0 | 113.2 | 95.8 |
| 80 | 670.5 | 653.1 | 618.3 | 566.0 | 531.2 | 461.5 | 374.4 | 322.2 | 287.4 | 269.9 | 252.5 | 217.7 | 182.9 | 148.0 | 130.6 |
| 85 | 722.8 | 705.3 | 687.9 | 635.7 | 600.9 | 531.2 | 444.1 | 374.4 | 339.6 | 322.2 | 304.8 | 269.9 | 217.7 | 200.3 | 165.5 |
| 90 | 809.8 | 792.4 | 757.6 | 722.8 | 670.5 | 618.3 | 513.8 | 444.1 | 409.3 | 391.9 | 357.0 | 322.2 | 269.9 | 235.1 | 217.7 |
| 95 | 931.8 | 914.3 | 879.5 | 844.7 | 792.4 | 722.8 | 618.3 | 531.2 | 496.4 | 461.5 | 444.1 | 409.3 | 357.0 | 304.8 | 269.9 |
| 97 | 1018.8 | 1001.4 | 966.6 | 931.8 | 896.9 | 809.8 | 687.9 | 600.9 | 566.0 | 531.2 | 513.8 | 461.5 | 391.9 | 357.0 | 322.2 |
| 99 | 1280.1 | 1262.7 | 1227.8 | 1193.0 | 1140.7 | 1053.7 | 914.3 | 809.8 | 757.6 | 722.8 | 687.9 | 618.3 | 548.6 | 478.9 | 426.7 |
| 99.9 | 2298.9 | 2264.1 | 2229.2 | 2168.3 | 2116.0 | 2011.5 | 1750.3 | 1523.9 | 1419.4 | 1349.7 | 1280.1 | 1140.7 | 1001.4 | 879.5 | 792.4 |

Nasal Lesion HEC = 26124 ug/m3 with threshold of 871 ug/m3 at UF=30
Fetal Loss HEC = 42959 ug/m3 with threshold of 1432 ug/m3 at UF=30
Neurotoxicity HEC = 58053 ug/m3 with threshold of 1935 ug/m3 at UF=30

6.1.2 Ambient Bystander Exposure From Multiple Area Sources

Exposures from ambient sources were qualitatively evaluated based on physical-chemical properties and environmental fate characteristics. No applicable data were available since iodomethane is not routinely screened for by CARB (California Air Resources Board) or similar organizations which would be expected because it is not a widely used chemical. Ambient-air exposures could potentially occur in proximity to agricultural areas where there is significant use during a particular growing season on a regional basis (e.g., in coastal areas of California during field fumigation prior to strawberry growing season). However, HED does not believe that ambient air exposures to bystanders are likely to be a significant concern based on a comparison of the characteristics of iodomethane with those of methyl bromide and the ambient air monitoring data available for methyl bromide (i.e., iodomethane dissipates/degrades faster in the environment and it is less volatile).

6.2 Bystander Risk Characterization

It is believed that the data and methodologies used in the development of this assessment represent the state-of-the-science relating to pesticides that can be characterized as fumigants. However, it is clear that there is an ongoing evolution relating to the types of data that could be used to complete such assessments in the future. Essentially, all data that were currently available were used herein but those data clearly have limitations related to overall quality, as well as temporal and spatial limitations. It is also clear that the PERFUM modeling framework provides significant amounts of information appropriate for risk managers to consider but that there are other systems that could be considered as robust for the same types of analyses. As indicated above, submissions based on other viable modeling frameworks would be considered for risk management purposes.

Some of the limitations and considerations that have been identified that should be considered in the interpretation of these results include:

- All of the data used for this analysis have been generated in California with the exception of one tarped raised bed flux study conducted in Plant City Florida which is a major strawberry production area. Tarped, raised beds also represent the major cultural practice associated with methyl bromide in that region of the county which would be the likely niche that proposed iodomethane uses will challenge. Iodomethane use would also be anticipated in other areas of the eastern seaboard up through Michigan where methyl bromide is also used but no data are available for those regions. An experimental use permit was issued by the Agency for iodomethane in 2007 under which 3 additional field emissions studies (i.e., flux) are to be completed that will evaluate emissions at the proposed label rate of 175 lb ai/acre using tarps other than HDPE or LDPE (i.e., high or low density polyethylene) such as high barrier or metalized films. Since these studies were not complete at the time this document was prepared the associated results have not been included herein. It is possible that high barrier films or possible reduced rates, due to higher gas retention levels in soil or other benefits such as mating disruption that occurs with metalized films which enhance pest control and allow for lower rates, may lower emissions and would thus reduce the PERFUM predicted buffer estimates in this document. These data will be reviewed and considered upon submission to the Agency.
- Factors such as soil type, solar radiation levels, or farming practices themselves may impact the overall amounts of iodomethane emitted and the rate at which it is emitted over time, thus buffer outputs predicted using PERFUM could be impacted but it is not possible to quantify this sensitivity at this point. PERFUM is not a first-principles model (i.e., it cannot predict results for

incremental changes in soil conditions parameters such as soil temperature or percent moisture). Instead, PERFUM is an empirical model that is calibrated to specific emissions profiles that then serve as the basis for predicted results. This is a very common modeling approach when first-principles models are not available. Additionally, the flux profiles that were used as the basis for the PERFUM results in this assessment were defined based on two techniques including the aerodynamic flux method and the back calculation method (which was used for most inputs). At this point, the Agency treats results based on all of these methods similarly as there is no information in the applicable literature to suggest that any are inherently biased to over- or under-prediction of flux.

- The premise of the PERFUM-predicted buffer zones is based on the following conditional probabilities which by definition, implies that individuals are at a location where the time-weighted average concentration of iodomethane can be of concern. There are several probabilities related to an exposure event which must be met for deleterious effects to occur from iodomethane exposure. These include:
 - For the developmental effect (i.e., fetal loss), an exposed individual must be female and at a critical phase of the pregnancy for the effect to occur;
 - An exposed individual has to be in proximity to a iodomethane application/aeration event for a sufficient duration for the effect to occur - there are 3 key factors to consider for this element including:
 - that the types of applications considered in this assessment are either seasonal or infrequent which limits the number of possible adverse exposure events,
 - time-activity data indicate that many parts of the population move from site to site on a daily basis (e.g., to go to work and back) which limits the overall number of possible adverse exposures events, and
 - time-activity data indicate that most individuals spend a majority of their daily time indoors and for intermittent exposure sources such as this it is known that being indoors typically reduces exposures to contaminants relative to outdoor air but the PERFUM results do not account for this exposure reduction factor.
- A multi-faceted approach was used to evaluate risks using monitoring and the distributional model, PERFUM. Monitoring data have temporal and spatial limitations as has been discussed above. Incident data could also be informative but are lacking in this case since iodomethane is not registered as a pesticide. However, for many fumigants, most incidents in the general population are believed to be associated with a significant equipment failure, atmospheric inversion, or misuse of some sort, intentional or not. This trend would also be anticipated for iodomethane. However, because the endpoints of concern associated with iodomethane may not be readily attributable to an exposure event, it is highly likely that individuals in the general population would not associate such health issues with a previous exposure to iodomethane. For this reason, it is possible that iodomethane incidents in the general population could be under-reported. Effects that would be likely to be experienced in the general population after a iodomethane incident would be irritant effects from its companion chemical, chloropicrin, for many applications. It should also be noted that the proposed formulations of iodomethane expected to be in use, if registered, could contain from 25 to 75 percent chloropicrin so irritant effects in incidents would be expected from exposure to that material.

- PERFUM modeling results (or any distributional model for that matter) can provide risk managers with much needed information about the range of risks expected in the general population. At this time, policy development is ongoing with regard to defining how appropriate selections of PERFUM outputs can be defined for risk management purposes
- It is believed that PERFUM provides the most refined estimates of risk because it can consider actual weather data and also integrate flux distributions in order to develop distributional estimates of buffer distances and concentrations at various distances from a source. PERFUM uses ISCST3 as its core processor which is an existing Gaussian plume technology that has been utilized for air permitting by the Agency for many years (see *Technology Transfer Network Support Center for Regulatory Air Models* at <http://www.epa.gov/scram001/tt22.htm#isc>). Several issues need to be considered related to the modeling analysis which was completed herein. These include:
 - It has been assumed that there is a linear relationship between application rate and flux, but this assumption has not been validated with emissions data conducted in similar conditions but at different application rates. The California Department of Pesticide Regulation has used this assumption in previous fumigant assessments.
 - The treatment of calm periods (wind speeds below 1 m/s) in PERFUM/ISCST3 is also an uncertainty. PERFUM runs the ISCST3 model in the “regulatory default option” (the default setting for ISCST3), which includes the use of the calms processing routine as is described in Agency guidance. The calms processing routine for wind speeds below 1 m/s essentially ignores any hourly sequence in the calculations that meets this criteria. This approach can possibly skew results for shorter averaging times because an analysis period that contained several calm hours would be dominated by any period where there was a windspeed above 1m/s. This is a common approach in Gaussian plume modeling. PUFF-based models such as CALPUFF have meander algorithms that can account for calm conditions by accounting for static or near static plume conditions and representing such events in the results. Whether or not buffer estimates are enhanced or under-reported as a result of this phenomenon depends upon the nature of the weather data used for the calculations. Preliminary analysis related to this issue do not indicate significant differences when hourly calculation steps are used especially when 24 hour time weighted average exposures are calculated. If less than hourly steps (e.g., minute by minute calculations such as in CALPUFF v6) are used, the effect is attenuated because the relative percentage of calm periods in the available weather data seems to be diminished.
 - The PERFUM analyses completed for this assessment are based on the assumption that an application has an equal probability of occurring each day out of the 5 years of weather data. This method does not take into account the seasonal use patterns of fumigants in different regions of the country. Table 13 above provides an example of monthly distributional results which could be examined if so desired for every PERFUM output. The result for each month is based on 5 months worth of weather data instead of 5 years when all months are considered. It should also be noted that the selection of the sources of weather data for this assessment, as mentioned above, represent a range of mean windspeed values as described in the SAP document for PERFUM. The locations of the Florida and California stations were intentionally selected based on this range and their coastal and inland locations.

- Different field sizes and aspect ratios were considered in this assessment (most fields were square in shape for this analysis). As field size increases so do predicted buffer zones which is similar to what is noted based on increases in application rates. Field aspects were also examined and the orientation did impact results although it is difficult to ascertain any general prediction based on this analysis since field orientations relative to prevailing wind directions will vary from site to site or region to region.
- The use of a maximum 40 acre field in the risk assessment may possibly understate potential exposure received by bystanders near treated fields that are larger.
- PERFUM was recently modified to also produce distributions of concentrations at various receptor ring distances from the edge of a treated field or source. This capability was added near the completion timeframe of this assessment. As appropriate, this capability will be utilized in the development of risk management decisions.
- Several factors also need to be considered in the interpretation of the results associated with the assessment of exposures from ambient air. It would not be unexpected if iodomethane could be measured in areas of high regional use during the height of the use season. In comparison with methyl bromide, it is expected that given the relative environmental fate characteristics, that iodomethane levels in ambient air would be lower because it is more short-lived in the environment and less volatile. Iodomethane is also not an ozone depleter like methyl bromide.
- Three different toxic effects of concern were evaluated in this assessment including the formation of nasal lesions, developmental impacts (i.e., fetal loss), and neurotoxicity. The HECs associated with each effect were developed through a sophisticated pharmacokinetic modeling approach that also helped to establish the appropriate averaging times for developing the time-weighted average exposure concentrations used in the assessment. As indicated above, 24 hours was used to evaluate results based on the nasal lesions and developmental effects while an 8 hour averaging time was used for assessing the neurotoxicity. In the previous assessment, it appeared that there was a spread between where less adverse nasal lesion effects and the more adverse developmental effects could occur. Results based on the neurotoxicity effect, however, provide similar results to those for the nasal lesions which indicate that effects more severe than nasal lesions could occur at similar or just slightly higher exposures. [Note: In most cases predicted buffers are lower on the order of 10 to 20 percent but in some cases predicted buffers for neurotoxicity actually exceed those for nasal lesions.] This is probably due to the shorter averaging time for the neurotoxicity and the shape of the emissions profile quantified in some of the flux studies.

6.3 Residue Profile

There is no reasonable expectation of finite residues to be incurred in/on food and feed crops when iodomethane is used as a preplant soil fumigant in/on strawberries and tomatoes, so this use is considered to be a non-food use, and tolerances are not needed. (Refer to Section 3.1.)

6.4 Water Exposure/Risk Pathway

Iodomethane is very soluble in water, so there is the possibility of leaching to ground water and/or transporting to surface water through runoff, if slicing or removal of the tarpaulin coincides with, or is followed soon by, a rain event. Therefore, a qualitative drinking water assessment was performed for this risk assessment.

Tier II PRZM/EXAMS for surface water and Tier I SCIGROW for ground water were used to estimate iodomethane concentrations in drinking water. Since iodomethane is a volatile compound, additional input parameters like DAIR (vapor phase diffusion coefficient) and ENPY (enthalpy of vaporization) were activated during the PRZM-EXAMS simulation. In the absence of monitoring data, the concentration of iodomethane in ground water was estimated using SCIGROW, which has limited capability to perform vapor phase transport of iodomethane to groundwater. The assessments were based on maximum application rate of iodomethane for pepper in Florida and generally represent upper-bound estimates of iodomethane concentrations that might be found in surface water and groundwater. Based on environmental fate data, the residual contents in soils, and Tier I and II models estimated concentrations, Agency does not expect iodomethane to adversely impact ground water or surface water.

7.0 Aggregate Risk Assessment

The physical/chemical characteristics, the environmental fate data, and results of metabolism studies in plants assure that there is no reasonable expectation of finite residues to be incurred in/on food and drinking water when iodomethane is applied according to label directions. Therefore, this fumigant does not require food tolerances, is considered to be a 'non-food use' chemical, and is not subject to the amendments to the Federal Food, Drug, and Cosmetic Act (FFDCA) promulgated under the Food Quality Protection Act (FQPA) of 1996, and an aggregate risk assessment is not required.

8.0 Cumulative Risk Assessment and Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to iodomethane and any other substances and iodomethane does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that iodomethane has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at www.epa.gov/pesticides/cumulative

9.0 Occupational Exposure Assessment And Characterization

In this assessment, a number of iodomethane-specific monitoring studies were available to evaluate the exposures of applicators as well as those otherwise involved in that process (e.g., co-pilots, shovelmen). Likewise monitoring data were also available to assess the possible exposures that could occur after application events such as for planters, tarp cutters and tarp removers. [Note: Tarp cutter and tarp remover data were generated in a period 5 days in fields covered with typical polyethylene films and not high barrier or metalized films. Planting activities were monitored 7 days after application.]

The occupational tasks associated with the anticipated use of iodomethane along with the corresponding risks are described below. Risks from chronic exposures have not been calculated because iodomethane use is expected to be highly seasonal. Iodomethane is not expected to be used every working day for more than 6 months, for commercial applicators or large scale growers based on available information. Additionally, in smaller scale production, applications are thought to be infrequent because growers would often times just treat their own fields once (or maybe twice) each year. Risks from short- and intermediate-term exposures, based on average values, were calculated but not presented below because acute risks, calculated based on maximum monitored values are protective of possible exposures of this duration.

Section 9.1: Occupational Risk Assessment provides the risk estimates for each work task considered in this assessment while *Section 9.2: Occupational Risk Characterization* describes the issues that should be considered when interpreting these results.

9.1 Occupational Risk Assessment

Occupational exposures were quantified in six worker monitoring studies which used iodomethane under field conditions. [Note: As a reminder, all studies involved the use of a typical polyethylene tarp during application which should be considered in the interpretation of this assessment. High barrier films are not represented in these data.]

The application techniques that were monitored include:

- MRID 455938-20: flat fume application in Manteca CA;
- MRID 463852-04: shank raised bed application in Guadalupe CA;
- MRID 458791-02: shank raised bed application in Marina CA (near Oxnard);
- MRID 462037-02: drip irrigation application in LaSelva CA;
- MRID 463852-03: drip irrigation application in Camarillo CA; and
- MRID 464636-02: drip irrigation application in Guadalupe CA.

The tasks that were monitored in these studies are listed below. Planting in all cases occurred 7 days after application and post-application, pre-plant activities (e.g., hole punching or tarp removal) occurred 5 days after application.

- a) Tractor Driver
- b) Co-pilot (reported as 1st Tarp Monitor in MRID 458791-02)
- c) Drip Applicator
- d) Drip Line Tender (sometimes reported as 2nd Applicator)

- e) Planter
- f) Shoveler
- g) Tarp Monitor
- h) Hole Puncher
- i) Tarp Cutter
- j) Tarp Remover
- k) Tarp Remover Driver

It is important to consider that in this assessment all available worker exposure monitoring data have been used directly for risk assessment purposes. The data were used as conducted with no adjustment for application rate although it is likely that typical use rates for iodomethane will be less than those considered in the occupational exposure monitoring studies especially since the current proposed label maximum application rate is lower than monitored in some of the studies (i.e., 175 lb ai/acre instead of approximately 235 lb ai/acre). The data included in these studies also reflect the use of tarps and various types of emission controls. As such, the results of the monitoring data are specific to those conditions but likely represent what would be encountered in agricultural use situations. It is clear, however, that the elements of any application can impact exposure levels based on several factors (e.g., care of operator, equipment condition, field preparation). Finally, it should be noted that the duration of most exposure monitoring periods ranged from 3 to approximately 7 hours which could be expected to represent what could happen in typical agriculture.

In a typical pesticide handler assessment, the Agency uses normalized estimates of surrogate exposure data based on similar equipment and with similar levels of protective equipment or clothing. Additionally, in typical post-application worker assessments, exposures are scaled based on how residues decay over time. These approaches have not been used in the occupational assessments presented below due to methodological issues and that much of the exposures associated with iodomethane would be directly related to its specific physical-chemical properties such as vapor pressure or stability in treated soil. For example, it is not clear how changes in various parameters or conditions from application event to application event (e.g., temperature, emission reduction methods such as tarps or application methods) may directly impact exposures. As noted above, the currently proposed maximum application rate for iodomethane is 175 lb ai/acre and some of the occupational monitoring data were collected at an exaggerated application rate of approximately 235 lb ai/acre based on the proposed labels at the time the data were collected. No scaling of the exaggerated application rate occupational exposure data was completed for the purposes of this assessment based on the lack of direct knowledge of how exposures could be quantitatively impacted.

The corresponding exposure and risk estimates associated with these activities are presented in Table 15 for each HEC of concern.

Table 15: Occupational Risks Associated With Proposed Iodomethane Uses

| Task | Application Method (Number of monitoring events) | 8 Hour Time Weighted Air Concentration (ppm) | | | Acute MOEs Nasal Lesions | | | Acute MOEs Fetal Loss | | | Acute MOEs Neurotoxicity | | |
|---------------------|---|--|-----------------------|-----------|--------------------------|------------|-----------|-----------------------|------------|-----------|--------------------------|------------|-----------|
| | | TWA | With PF 10 | With SCBA | TWA | With PF 10 | With SCBA | TWA | With PF 10 | With SCBA | TWA | With PF 10 | With SCBA |
| | | Tractor Driver | Tarped Raised Bed (4) | 1.029 | 0.10290 | 0.00103 | 5.6 | 56.4 | 5636.5 | 22.4 | 223.5 | 22351.8 | 9.7 |
| Co-pilot | Tarped Broadcast Flat Fume (2) | 0.024 | 0.00240 | 0.00002 | 241.7 | 2416.7 | 241666.7 | 958.3 | 9583.3 | 958333.3 | 416.7 | 4166.7 | 416666.7 |
| | Tarped Raised Bed & Broadcast Flat Fume (4) | 0.648 | 0.06480 | 0.00065 | 9.0 | 89.5 | 8950.6 | 35.5 | 354.9 | 35493.8 | 15.4 | 154.3 | 15432.1 |
| Drip Applicator | Drip Application (6) | 0.240 | 0.02397 | 0.00024 | 24.2 | 242.0 | 24196.9 | 96.0 | 959.5 | 95953.3 | 41.7 | 417.2 | 41718.8 |
| Drip Line Tender | Drip Application (sometimes 2nd applicator) (6) | 0.147 | 0.01469 | 0.00015 | 39.5 | 394.8 | 39482.6 | 156.6 | 1565.7 | 156569.1 | 68.1 | 680.7 | 68073.5 |
| Planter | All Application Methods (22) | 0.007 | 0.00070 | NA | 828.6 | 8285.7 | NA | 3285.7 | 32857.1 | NA | 1428.6 | 14285.7 | NA |
| Shovel | Tarped Raised Bed (8) | 0.760 | 0.07600 | NA | 7.6 | 76.3 | NA | 30.3 | 302.6 | NA | 13.2 | 131.6 | NA |
| | Tarped Broadcast Flat Fume (4) | 0.117 | 0.01170 | NA | 49.6 | 495.7 | NA | 196.6 | 1965.8 | NA | 85.5 | 854.7 | NA |
| Tarp Monitor | Tarped Raised Bed (6) | 1.114 | 0.11140 | NA | 5.2 | 52.1 | NA | 20.6 | 206.5 | NA | 9.0 | 89.8 | NA |
| Hole Puncher | Tarped Raised Bed (4) | 0.070 | 0.00700 | NA | 82.9 | 828.6 | NA | 328.6 | 3285.7 | NA | 142.9 | 1428.6 | NA |
| Tarp Cutter | Drip Application (6) | 0.017 | 0.00165 | NA | 351.5 | 3515.2 | NA | 1393.9 | 13939.4 | NA | 606.1 | 6060.6 | NA |
| | Tarped Broadcast Flat Fume (2) | 0.006 | 0.00060 | NA | 966.7 | 9666.7 | NA | 3833.3 | 38333.3 | NA | 1666.7 | 16666.7 | NA |
| Tarp Remover | Tarped Broadcast Flat Fume (2) | 0.013 | 0.00130 | NA | 446.2 | 4461.5 | NA | 1769.2 | 17692.3 | NA | 769.2 | 7692.3 | NA |
| Tarp Remover Driver | Tarped Broadcast Flat Fume (2) | 0.024 | 0.00240 | NA | 241.7 | 2416.7 | NA | 958.3 | 9583.3 | NA | 416.7 | 4166.7 | NA |

No samples were reported as <ND - containing no detectable residues or <LOQ - containing no quantifiable residues.

PF10 = Protection factor 10, air purifying respirator used to reduce exposure concentrations.

SCBA = Self-contained breathing apparatus used to reduce exposure. These are only applicable/viable in limited scenarios. These reduce exposures 10, 000 times.

Nominal flow rate for all samples was 0.05 liters/minute. No samples reported as <LOD or <LOQ.

For some scenarios, results are presented based on application equipment due to differences in exposure rates for each technique.

Sample durations ranged from approximately 1 to 7 hours. Most samples were 3 hours in duration or longer.

MOEs (Margins of exposure) are of concern if <30. MOEs calculated by (HEC/TWA).

Overall, the data indicate that exposures exceed the level of concern for some workers involved in the application of iodomethane when no respiratory protection is used (e.g., tractor drivers, co-pilots, shovelers for raised beds). Conversely, risks were not of concern for all workers involved in post-application activities even without respiratory protection. For those involved in applications, air-purifying organic vapor-removing respirators (APRs), which reduce exposure levels by a factor of 10, were considered and exposures were reduced below the level of concern for all workers involved in application. For workers who enter fields days after application to prepare for planting (e.g., tarp cutters or hole punchers), exposures were not of concern 5 days after application (which reflects the available data) without any sort of respiratory protection. This is also the case for planters where exposures were not of concern 7 days after application without any sort of respiratory protection (which also reflects the available data). SCBA, as a mitigation option, is not required for any scenario since PF10 air purifying respirators reduce exposures to levels that are not of concern.

Current requirements for entry of post-application workers into previously treated fields are dictated by the Worker Protection Standard as described in PR 93-7 for various other fumigants. Similar requirements are recommended for iodomethane as for methyl bromide where there is a 48 hour entry prohibition based on modeling that has been done and available monitoring data.

9.2 Occupational Risk Characterization

There are several issues that should be considered when interpreting the results of this risk assessment. Compared to most occupational assessments, the data used to complete this assessment are plentiful in that 78 chemical-specific monitoring events were considered in this analysis and the data are of high quality suitable for risk assessment purposes.

The monitored events represent standard agricultural practices which are similar in most part to current methyl bromide cultural practices. All data were developed using standard low or high-density polyethylene tarps and do not reflect the use of high barrier films which could alter exposure levels. For example, they could lower exposures during application because they retain more residues than normal tarps but they could increase tarp cutter exposures because residues are retained over a longer period. Also, the use of engineering controls such as modern programmable controllers (e.g., the Arysta Symmetry® system) are not reflected in the monitoring data. It is possible that these systems could reduce exposures by better controlling field application circumstances such as shutting off nozzles in a more systematic manner at the end of each treatment swath to facilitate turning without losing material into the atmosphere thereby reducing the possibility of exposure.

The results of the occupational risk assessment should also be considered in the context of incident data. Major fumigant incidents typically also occur from mechanical problems, accidents, or operator error. This trend would also still be expected with iodomethane use.

10.0 Data Needs and Label Requirements

10.1 Toxicology

There are no additional data required at this time.

10.2 Residue Chemistry

There are no additional data required at this time.

10.3 Occupational and Residential Exposure

The assessment of occupational and residential risks associated with the use of iodomethane is complex. There was a significant amount of data available, but additional data are still required. These include both occupational monitoring of various workers and data to better assess exposures in the general population. The types of data, guideline citations, and example scenarios which need to be addressed are presented below with final determinations of scenarios made in consultation with the Agency. Data requirements are also pending the completion of the 3 emissions studies to be completed using high barrier films under the 2007 Experimental Use Permit. These studies will be evaluated upon submission to the Agency and further determinations of additional data needs will be completed at that time.

OPPTS Guideline 835.8100 - Field volatility from soil

Volatility studies to determine flux for ISCST3 modeling purposes in major use regions of country for significant application methods (e.g., mid-Atlantic for raised beds or drip irrigation). Exact studies to be determined after direct consultation with the Agency.

OPPTS Guideline 875.1300 - Inhalation exposure for applicators (outdoors)

Pre-Plant Field - (e.g., rig drivers & tenders, tarpers, tarp removers). An example includes monitoring with the use of high barrier films.

OPPTS Guideline 875.2500 - Inhalation exposure for postapplication workers

Pre-Plant Field - (e.g., planters, irrigators). An example includes monitoring with the use of high barrier films.

Requirements For Special Studies

- Meteorological data for probabilistic modeling purposes.
- Projections for product use by major use region, frequency, application parameters (e.g., rate, acres treated, data, application equipment and emission control technologies used).
- Measurements of indoor air concentrations for residences in proximity of treated areas.
- Ambient air monitoring in key growing regions.

Appendix A: Review Of PBPK/PD Model



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NATIONAL CENTER for COMPUTATIONAL TOXICOLOGY
Research Triangle Park, NC 27711

June 18, 2007

Office of
Research and Development

TXR #: 0054604
MEMORANDUM

SUBJECT: IODOMETHANE: Review of Methyl Iodide PBPK/PD Model. DP Barcode: D312630; PC Code: 000011.

FROM: Hugh Barton, Ph.D.
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TO: Elizabeth Méndez, Ph.D.
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Health Effects Division (7509C)

SUMMARY

This memo updates specific aspects of previous reviews of the PBPK/PD model for methyl iodide. In particular, it discusses 1) updated modeling for estimating human equivalent concentration (HECs) based upon the rabbit reproductive toxicity endpoint using new data to describe the human placental distribution of iodide, 2) new modeling for estimating HECs based upon the rat nasal toxicity, and 3) modeling to estimate HECs based upon the rat neurotoxicity. To derive HECs based upon each of these endpoints, an internal dose metric is predicted for the animal species in which the toxicity occurred and then the version of the PBPK model for humans is used to determine the inhalation exposure concentration (HEC) predicted to give the same internal dose metric as in the animal.

1. HECs based upon rabbit reproductive toxicity

Toxicity (LOAEL) was observed in rabbits exposed to 20 ppm for 14 days and in a second study for 2 days. The 14-day study also exposed rabbits at 10 and 2 ppm. To evaluate health effects in the developing organism, the dose metric used was the area under the concentration curve for iodide in fetal serum (AUCCAF_I). The model version used was meidpr.csl, though very similar results for the rabbit were confirmed using the previous version meinoepa.csl. Previous analyses (e.g., Fig 4 in Sweeney et al., 2005) had demonstrated that a simplified model in which alveolar gas exchange was modeled directly rather than including the complex description for the nasal compartments gave very similar results with the full model. Therefore, the simplified model was used to estimate the dose metric in both rabbits and humans.

Using rabbit meidpr.csl with the parameters defined in the file pregrabbit.m (and additional m files called by the procedure) with the additional changes noted here simulations were carried out at 20 ppm for 6 hr per day for 1, 2, and 14 days (CONC=20, TCHNG=6, QAC=12, NFET=4.6, VFETC=0.049), at 10 ppm for 1, 2, and 14 days (CONC=10, TCHNG=6, QAC=12, NFET=4.6, VFETC=0.049), and at 2 ppm for 1 and 14 days (CONC=2, TCHNG=6, QAC=12, NFET=5.5, VFETC=0.062). It should be noted that for 20 ppm the number of fetuses and their volume was assumed to be the same as at 10 ppm; dose-specific values would change these values since substantial toxicity was observed resulting in fewer live fetuses and a smaller fetal volume.

The pattern of the predicted fetal serum iodide concentrations are illustrated for 10 ppm exposure, 6 hr per day, for 14 days (Figure 1). Increasing blood concentrations are predicted during the exposure, followed by a decline during the post-exposure period. However, concentrations do not return to baseline starting values, so the concentrations build up over several days to an oscillating pseudo-steady state. These results are similar to those shown at 2 ppm in Figure 1 of Sweeney (2007).

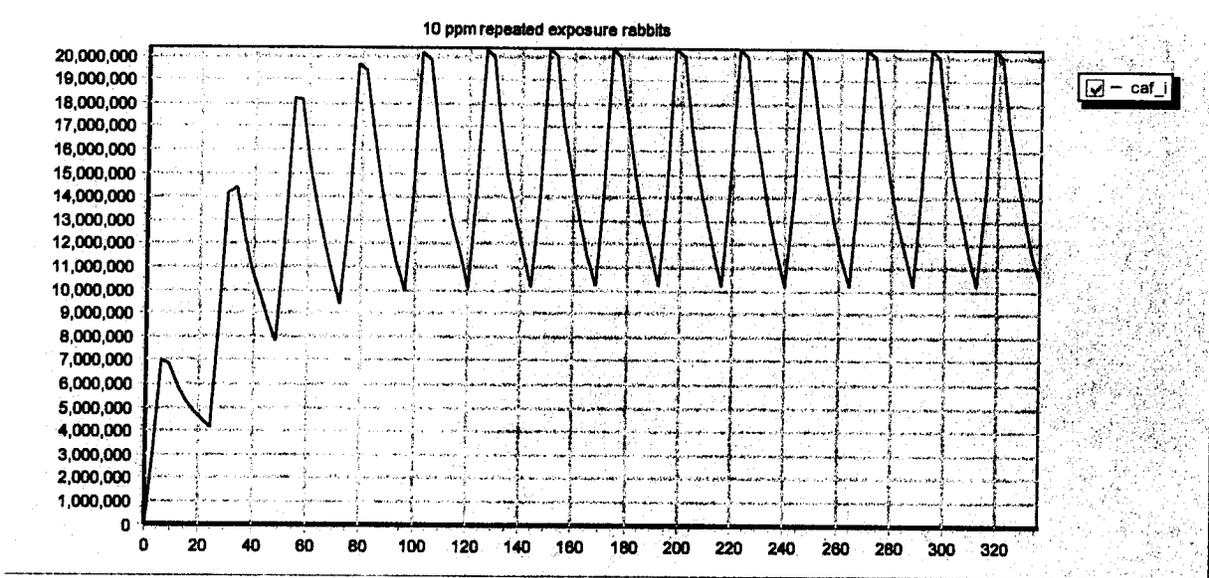


Figure 1: Simulation of fetal serum iodide (CAF_I) during 14 daily (336 hrs) exposures. Units of CAF_I are ng/L. Results show simulated build up of iodide with repeated exposures.

The area under the fetal serum concentration curve can be predicted over the course of the simulated exposure (Table 1). In addition, for each exposure period, the average daily AUC can be calculated by dividing the total AUC by the number of days of exposure. Alternatively, one could calculate the AUC for the last day, but that was not considered here.

Table 1: Predicted AUC for iodide in fetal serum of exposed rabbits.

| <i>Concentration</i> | <i>Time (hr)</i> | <i>Total Iodide AUC in Fetal Serum (ng/L*hr)</i> | <i>Average Daily Iodide AUC in Fetal Serum (ng/L*hr)</i> |
|----------------------|----------------------|--|--|
| 20 ppm | 24 (1 day) | 3.14421e+008 | 3.1 e+008 |
| | 48 (2 days) | 8.87976e+008 | 4.4 e+008 |
| | 336 (14 days) | 9.20217e+009 | 6.6 e+008 |
| 10 ppm | 24 | 1.18817e+008 | 1.2 e+008 |
| | 48 | 3.71964e+008 | 1.9 e+008 |
| | 336 | 4.6949e+009 | 3.4 e+008 |
| 2 ppm | 24 | 1.41103e+007 | 1.4 e+007 |
| | 336 | 7.30980e+008 | 5.2 e+007 |

Since the iodide is not entirely cleared within 24 hrs, the average daily AUC for fetal serum iodide during the first 2 days exposure at 20 ppm is 40% higher than the value following a single day exposure (see Table 1). The fetal serum iodide daily average AUC associated with adverse effects is predicted to be 4.4e+8 ng/L*hr for the 2-day exposure. Predictions of the daily average AUC following 14 days exposure are 50% higher than the 2-day average; a higher value would be expected given the greater magnitude of effect in the 14-day toxicity study as compared to 2-day study.

At 10 ppm, the AUC predicted for 1 day exposure is 1.18817e+008 ng/L*hr. The accumulation predicted with repeated daily exposures is somewhat greater at 10 ppm than at 20 ppm, so the daily average AUC following 2 days is 57% greater than following a single day. The daily average AUC following 14 days at 10 ppm is nearly triple the value following 1 day. It also represents 75% of the average daily AUC at 20 ppm from 2-days exposure, which is associated with effects. Finally, the daily average AUC for 14 days at 10 ppm falls within the range of the AUCs predicted from 1 and 2 days exposures at 20 ppm; there are no data demonstrating effects following 1-day exposure. Therefore, use of the predicted AUC following 1 day exposure at 10 ppm would provide a health protective margin between the LOAEL and NOAEL, while the average daily AUC after 14 days would approximate the AUC value associated with effects.

At 2 ppm there is again a buildup of iodide during the course of the 14 day exposure so that there is a nearly 4-fold increase in the daily average AUC as compared to 1 day. In addition, the AUC value is 2-3-fold below the values predicted for 1 and 2 days exposures at 10 ppm and 6-fold below the average daily value predicted following 14 days exposure at 10 ppm. The lower AUCs predicted for 2 ppm are consistent with the lack of observed effects.

The HEC was predicted to match the one day AUC value for the rabbit following 10 ppm exposure for six hours ($AUCCAF_I=1.19e+8$) using human parameter values in prehum.m. A revised value for the alveolar ventilation rate (QAC) of 16.4 L/hr was used consistent with the breathing rate (630 breaths per minute), volume (15 mL/breath), and assumed dead space volume of 1/3, so alveolar ventilation is 2/3 of total ventilation, used in the full model (for a 70 kg adult versus the 61.1 kg pregnant female). In addition, values of $CLTRANS1C=0.15$ and $CLTRANS2C=0.12$ were used, consistent with the fetal to maternal plasma ratios (Nguyen, 2007). For $CONC=7$, $AUCCAF_I = 1.12775e+008$, while for $CONC=8$, $AUCCAF_I = 1.27031e+008$. Linear interpolation gives $HEC = 7.4$ ppm to match the 1 day $AUCCAF_I$ at 10 ppm in the rabbit and this value was confirmed. These results differ from the results reported by Sweeney (2007) for one day without prior exposure due to its use of a lower alveolar ventilation rate.

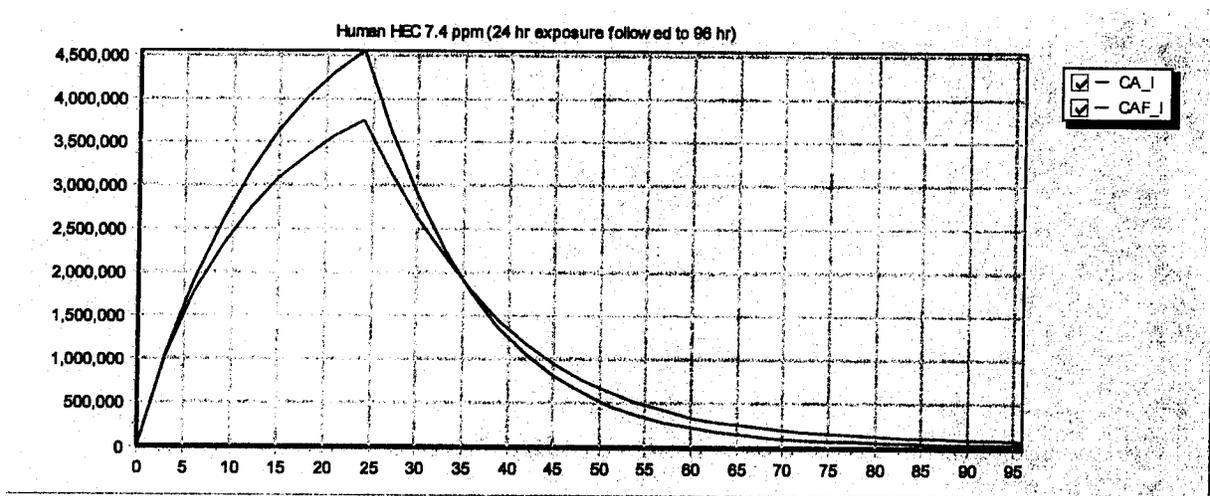


Figure 2: Predicted human maternal (CA_I) and fetal (CAF_I) serum iodide during a 24 hr constant concentration exposure to 7.4 ppm followed until 96 hr.

Clearance of iodide from the mother to the fetus ($CLTRANS1C=0.15$) and fetus to the mother ($CLTRANS2C=0.12$) were set to give a ratio of 1.2 observed for the full term fetal to maternal serum iodide concentrations (Rayburn et al., 2007). As shown in Figure 2, at 7.4 ppm the fetal concentrations are generally lower than maternal until becoming slightly higher after 36 hr during the clearance of the iodide following cessation of exposure. At much lower exposure concentrations, the fetal level would modestly exceed the maternal levels. It appears that at these concentrations limitations of modeled transporter capacity results in the lower fetal levels, though this was not directly confirmed. However, the simulations of maternal and fetal levels ($CA_I 4.55948e+006$, $CAF_I 3.73814e+006$, ratio 0.82) are consistent with the ratio of 0.85 (95% confidence interval: 0.72 to 0.99) reported for the preterm measurements.

The HEC for the worker scenario (also assumed to be a pregnant female exposed for 8 hr) is 23 ppm, matching the rabbit dose metric, $AUCCAF_I 1.18775e+008$. At the end of exposure, $T=8.0$, maternal and fetal serum iodide levels ($CA_I 7.69453e+006$, $CAF_I 5.55314e+006$, respectively) are highest and the ratio is 0.72 just falling within the confidence interval for the fetal to maternal serum iodide reported for the preterm measurements.

Finally, the iodide component of this model was based upon an early version of the perchlorate and iodide model developed by R.A. Clewell, E.A. Merrill and coworkers. A new publication presents their latest model for iodide during pregnancy (Clewell et al., 2007). Any further development or application of the methyl iodide model should evaluate whether the parameter values in the new version of the perchlorate and iodide model would impact the estimates for the methyl iodide model.

2. HECs based upon rat nasal toxicity

The following sections on nasal anatomy, pathology, and the appropriate dose metric were developed in consultations with Dr. Douglas C Wolf, DVM, PhD.

Nasal Olfactory Epithelium Anatomy and Pathology

There is no substantial difference in the mucosa across species (cell types, mucosa thickness, function). The fundamental difference across species is the number of cells at risk or area of tissue at risk which is much greater in the rodent than in primates including humans (Harkema, 1991; Talamo et al., 1995). While there are not major differences in the thickness of the epithelial layer across species, there may be differences in the submucosal or lamina propria or blood exchange layer below. There appears to be limited characterization of these thicknesses in humans in the olfactory region.

In general, epithelial surfaces exposed to irritant chemicals undergo a necrotic process which includes epithelial cellular degeneration, cell death, mucosal erosion, and finally ulceration. Erosion is classically defined as necrotic loss of the epithelium down to, but not including, the basement membrane. An ulcer is a more severe lesion which includes complete loss of the epithelium, damage and loss of the basement membrane and degeneration and necrosis of the underlying subepithelial tissue. The subepithelial tissue may be lamina propria, submucosa, or dermis depending on the organ affected. The earliest lesion in the pathogenesis would be erosion, or necrotic loss of the epithelium. With continued exposure to the irritant chemical it will become an ulcer.

Examples of erosions caused by methyl iodide are presented in the paper by Reed et al (1995) in Figures 3 and 4 which shows a loss of most of the olfactory epithelium but the basement membrane is intact. Figure 8 of this paper shows degenerated olfactory cells on the way to necrosis that will become an erosion in time, in this case even without additional exposure. An erosion is considered a lesion and is thus adverse. With continued exposure, the lesion would progress to an ulceration with associated damage of the lamina propria (submucosa).

PBPK Model Structure and Dose Metrics

The PBPK model for methyl iodide implements a complex description of the nasal tissues to address different air flow pathways and tissue types. For the olfactory epithelium there are 5 compartments, which may be considered in two groupings. Chemical in the air phase is transferred to the mucus layer, which sits on top of the 5 tissue compartments. The top 4 layers

(the thickness of which is described by the model parameter WOE) represent the olfactory epithelial cells above the basement membrane. The compartments are linked by diffusion of the chemical from one compartment to the next (and back in the reverse direction). The bottom layer (the thickness of which is described by the model parameter WOX) is the blood exchange layer representing the lamina propria beneath the olfactory epithelium. Chemical diffuses in and back out of this layer from the compartment above and also exchanges into the blood, which circulates to the remainder of the body.

The four top compartments are a modeling approach to create a gradient of chemical moving through the epithelial tissue. However, specific cells such as the olfactory sensory cells extend from the top of the epithelial tissue to the basement membrane, while others, such as the sustentacular cells, may be more localized within the epithelial tissue. Therefore, the four diffusion linked compartments are a modeling simplification, rather than a detailed representation of the tissue architecture.

The model describes glutathione (GSH) conjugation of methyl iodide in each of these compartments along with changes in GSH concentrations resulting from its metabolic consumption, synthesis, and degradation. Based upon the description of the olfactory epithelial damage and the progression from damage above the basement membrane to greater damage including the lamina propria or blood exchange layer, there are several options for how dose metrics could be calculated. Protecting the olfactory sensory epithelial cells from damage would be consistent with preventing excessive GSH depletion in the top four compartments. The dose metric (CGSHDO2) calculates the average GSH concentration in the olfactory epithelial tissue. Because these compartments are of equal thickness (WOE/4) and equal volume in the model, this is also the volume weighted average. The GSH depletion in the blood exchange layer in the model is calculated as GSDOEX1.

The model also calculates the volume weighted average GSH concentration in all 5 olfactory tissue layers, CGSHDO. This dose metric was originally proposed and used in analyses for methyl iodide. This concentration (CGSHDO) is the appropriate value for comparing to measured GSH concentration data in rats exposed to methyl iodide because those studies have taken the entire olfactory tissue. In the rat, where the values of WOE and WOX are similar, 0.008 cm and 0.005 cm respectively, CGSHDO is modestly more dependent upon the GSH concentration in the top 4 compartments than in the 5th blood exchange layer. However, it has been proposed based upon reviews of literature that the 5th layer in humans is substantially thicker than the epithelial layer above the basement membrane (with values proposed of 0.05 cm for young children and thicker for adults). With these thicknesses, the volume weighted average GSH concentration in the entire tissue stack is dominated by the 5th layer. As methyl iodide exposure concentrations increase, this can result in predicted GSH concentrations that show limited GSH depletion in the 5 compartment average (CGSHDO), while there is very substantial depletion predicted in the epithelial layer (the 4 compartment average - CGSHDO2). Therefore, while it is appropriate to calibrate the model using CGSHDO with the rat tissue GSH concentration data, it is appropriate to use the 4 compartment average (CGSHDO2) to protect the olfactory sensory cells and the epithelial cell layer above the basement membrane.

Nasal HEC Calculations and Comparisons for Children

The following calculations simulate glutathione depletion in the nasal olfactory epithelial layer (represented in the model as 4 compartments to address diffusion of chemical through this cell layer) using the average depletion in the four compartments. The thickness of the epithelial layer (WOE) is set to 0.006 cm based upon values in Sangari et al (2000). The thickness of the blood exchange layer (lamina propria) was based upon Inagi (1992). For the adults, the thickness of the blood exchange layer (WOX) was 0.08 cm (based upon female and older adults; males can be somewhat thicker). For infants and children, WOX was 0.05 cm for young children and 0.08 cm for older children. The simulations for children use age appropriate body weight, nasal, and ventilation parameters as reported by Kimbell et al (2005). However, the other parameters are those for the male adult (e.g. fractional liver volume). Therefore, the children's simulations were used to evaluate whether children would potentially be similar, more, or less sensitive than adults. The results are essentially the same across ages, with slightly more depletion predicted for adults. Figure 3 illustrates the time course for glutathione depletion for exposure to a constant concentration for 24 hours.

Adult Bystander

PREGHUM,

WOE=0.006, WOX=0.08

CONC = 4.5

| | | |
|------------------|------------------|-------------------|
| T 24.0000 | GSHL 5.38930 | GSHK 1.34583 |
| CGSHDR 0.517287 | CGSHEO 0.767024 | CGSHDO 0.742106 |
| CGSHWR1 0.519963 | CGSHWR2 0.532058 | CA_I 4.78470e+006 |
| CA 0.0937393 | | |

GSDOE11 = 0.2747 GSDOE21 = 0.3789 GSDOE31 = 0.4524 GSDOE41 = 0.4993

GSDOEX1 = 0.7677 CGSHDO2 = 0.4013

%GSH Depletion

GSDOE11 = 66 GSDOE21 = 53 GSDOE31 = 43 GSDOE41 = 38

CGSHDO2 = 50%

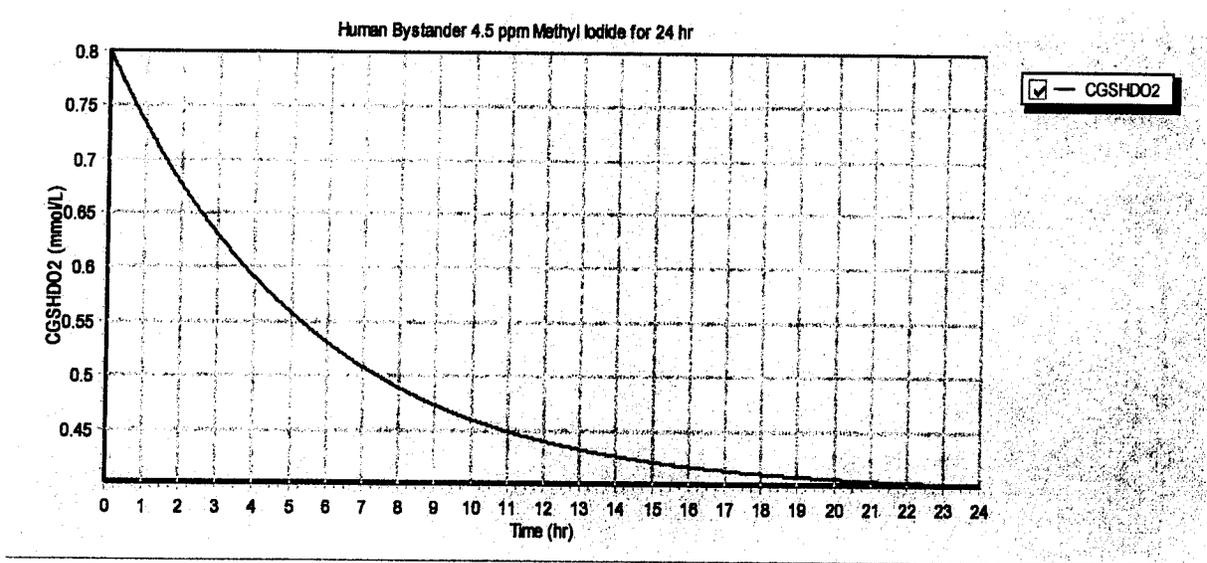


Figure 3: Predicted glutathione concentration in the olfactory epithelium of an adult human exposed to 4.5 ppm methyl iodide for 25 hr. The majority of the depletion occurs in the first 8 hours while near steady state is achieved by 24 hrs.

Adult Worker

PREGHUM,

WOE=0.006, WOX=0.08

CONC = 5.8

T 8.00000

GSHL 5.42681

GSHK 1.33688

CGSHDR 0.551752

CGSHEO 0.768624

CGSHDO 0.743154

CGSHWR1 0.553692

CGSHWR2 0.562702

CA_I 3.30147e+006

CA 0.117731

GSDOE11 = 0.2723 GSDOE21 = 0.3771 GSDOE31 = 0.4510 GSDOE41 = 0.4980

GSDOEX1 = 0.7689 CGSHDO2 = 0.3996

%GSH Depletion

GSDOE11 = 66 GSDOE21 = 53 GSDOE31 = 44 GSDOE41 = 38

CGSHDO2 = 50%

Child Bystander Comparisons (4.5 ppm 24 hr exposure simulations)

MALEHUM

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

CONC=4.5

3 mth child

T 24.0000

GSHL 5.10641

GSHK 1.30321

CGSHDR 0.515045

CGSHEO 0.707207

CGSHDO 0.688253

CGSHWR1 0.517356

CGSHWR2 0.526987

CA_I 8.26293e+006

CA 0.0954332

GSDOE11 = 0.2823 GSDOE21 = 0.3892 GSDOE31 = 0.4661 GSDOE41 = 0.5173

GSDOEX1 = 0.7212 CGSHDO2 = 0.4137

%GSH Depletion

GSDOE11 = 65 GSDOE21 = 51 GSDOE31 = 42 GSDOE41 = 35
CGSHDO2 = 48%

1 yr child

T 24.0000 GSHL 5.03787 GSHK 1.31169
CGSHDR 0.507248 CGSHEO 0.710143 CGSHDO 0.674122
CGSHWR1 0.509062 CGSHWR2 0.518926 CA_I 1.02666e+007
CA 0.0979689

GSDOE11 = 0.2791 GSDOE21 = 0.3856 GSDOE31 = 0.4618 GSDOE41 = 0.5120
GSDOEX1 = 0.7059 CGSHDO2 = 0.4096

%GSH Depletion

GSDOE11 = 65 GSDOE21 = 52 GSDOE31 = 42 GSDOE41 = 36
CGSHDO2 = 49%

5 yr child

T 24.0000 GSHL 5.20771 GSHK 1.32844
CGSHDR 0.517452 CGSHEO 0.753799 CGSHDO 0.732253
CGSHWR1 0.519696 CGSHWR2 0.530108 CA_I 8.54572e+006
CA 0.0947935

GSDOE11 = 0.2776 GSDOE21 = 0.3815 GSDOE31 = 0.4548 GSDOE41 = 0.5015
GSDOEX1 = 0.7569 CGSHDO2 = 0.4038

%GSH Depletion

GSDOE11 = 65 GSDOE21 = 52 GSDOE31 = 43 GSDOE41 = 37
CGSHDO2 = 50%

10 yr child

T 24.0000 GSHL 5.25865 GSHK 1.33700
CGSHDR 0.518774 CGSHEO 0.755114 CGSHDO 0.734226
CGSHWR1 0.521008 CGSHWR2 0.531480 CA_I 8.28109e+006
CA 0.0965349

GSDOE11 = 0.2779 GSDOE21 = 0.3818 GSDOE31 = 0.4552 GSDOE41 = 0.5019
GSDOEX1 = 0.7590 CGSHDO2 = 0.4042

%GSH Depletion

GSDOE11 = 65 GSDOE21 = 52 GSDOE31 = 43 GSDOE41 = 37
CGSHDO2 = 49%

15 yr child

T 24.0000 GSHL 5.39196 GSHK 1.34753
CGSHDR 0.528735 CGSHEO 0.766466 CGSHDO 0.741662
CGSHWR1 0.530721 CGSHWR2 0.540318 CA_I 6.00127e+006
CA 0.0943843

GSDOE11 = 0.2812 GSDOE21 = 0.3848 GSDOE31 = 0.4580 GSDOE41 = 0.5050
GSDOEX1 = 0.7667 CGSHDO2 = 0.4073

%GSH Depletion

GSDOE11 = 65 GSDOE21 = 52 GSDOE31 = 43 GSDOE41 = 37

CGSHDO2 = 49%

3. HECs based upon rat neurotoxicity

The rat neurotoxicity study results have been proposed to be evaluated using the steady state brain concentration predicted at the NOAEL of 27 ppm (6 hr exposure). Model simulations are shown here for the NOAEL (see Figure 4) and the LOAEL of 93 ppm (6 hr exposure) (see Figure 5).

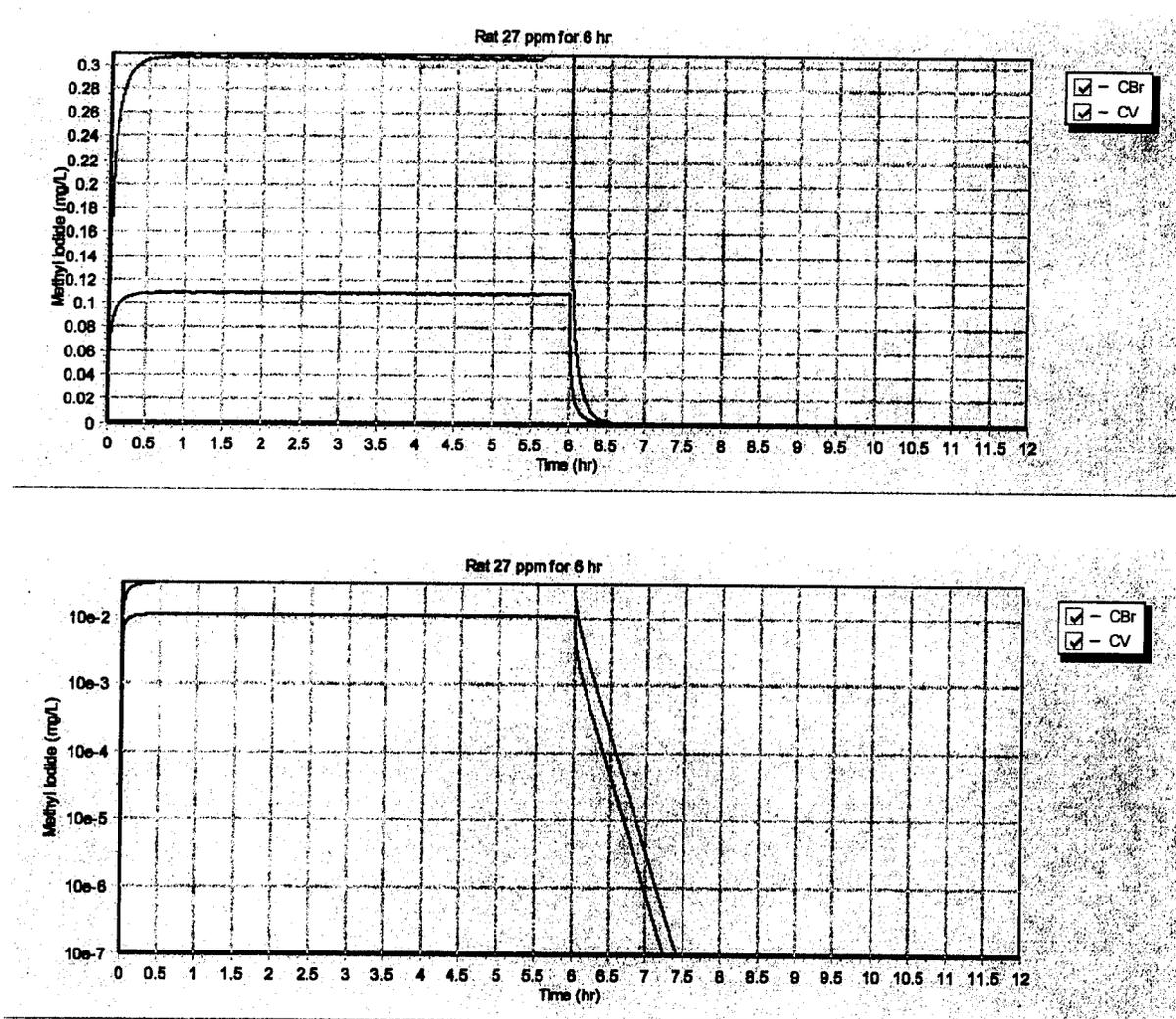


Figure 4: Predicted rat brain (CBr) and venous blood (CV) concentrations of methyl iodide during and following a 6 hr exposure at the NOAEL of 27 ppm. Top graph is normal scale, while bottom graph is semi log showing the predicted linear rapid decline post-exposure.

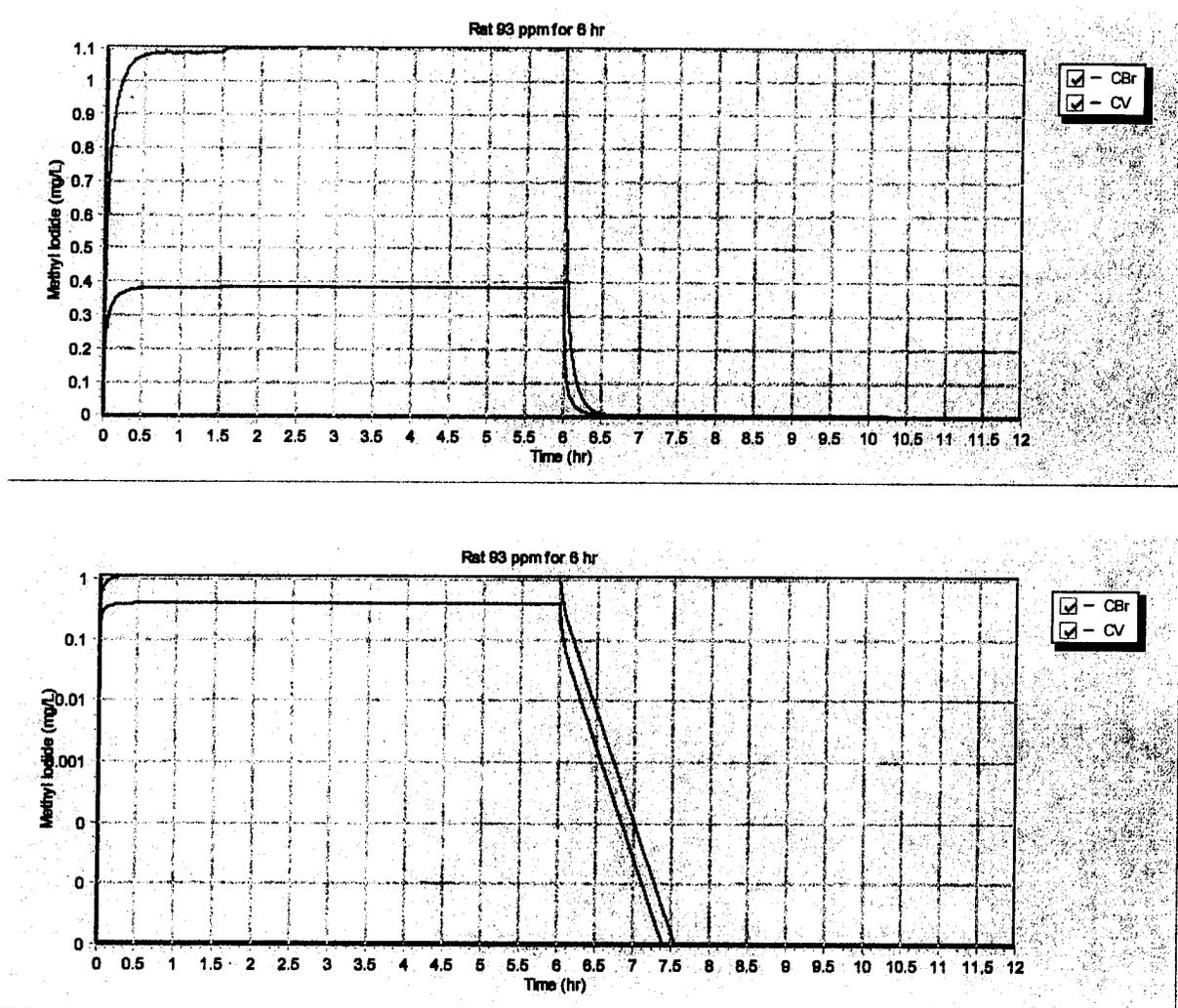


Figure 5: Predicted rat brain (CBr) and venous blood (CV) concentrations of methyl iodide during and following a 6 hr exposure at the LOAEL of 93 ppm. Top graph is normal scale, while bottom graph is semi log showing the predicted linear rapid decline post-exposure.

The steady state brain concentration at the NOAEL is 0.1 mg/L, while at the LOAEL it is 0.4 mg/L demonstrating a nearly linear relationship with exposure concentration in this range for this dose metric.

The HEC for the bystander adult pregnant female to match the steady state rat brain concentration of 0.1 mg/L is 10 ppm for 24 hr exposure (see Figure 6). The worker HEC is also predicted to be 10 ppm for 8 hr. These values are the same because steady state is predicted to be achieved in 8 hrs (see Figure 6). Using the body weights and respiration rates described above for children of different ages, a limited analysis indicates accounting for these factors would result in similar predicted brain concentrations as adults at steady state. This analysis does not take into account changes in age-specific organ volumes or metabolic capability in infants, which might be expected to have an impact on the predictions.

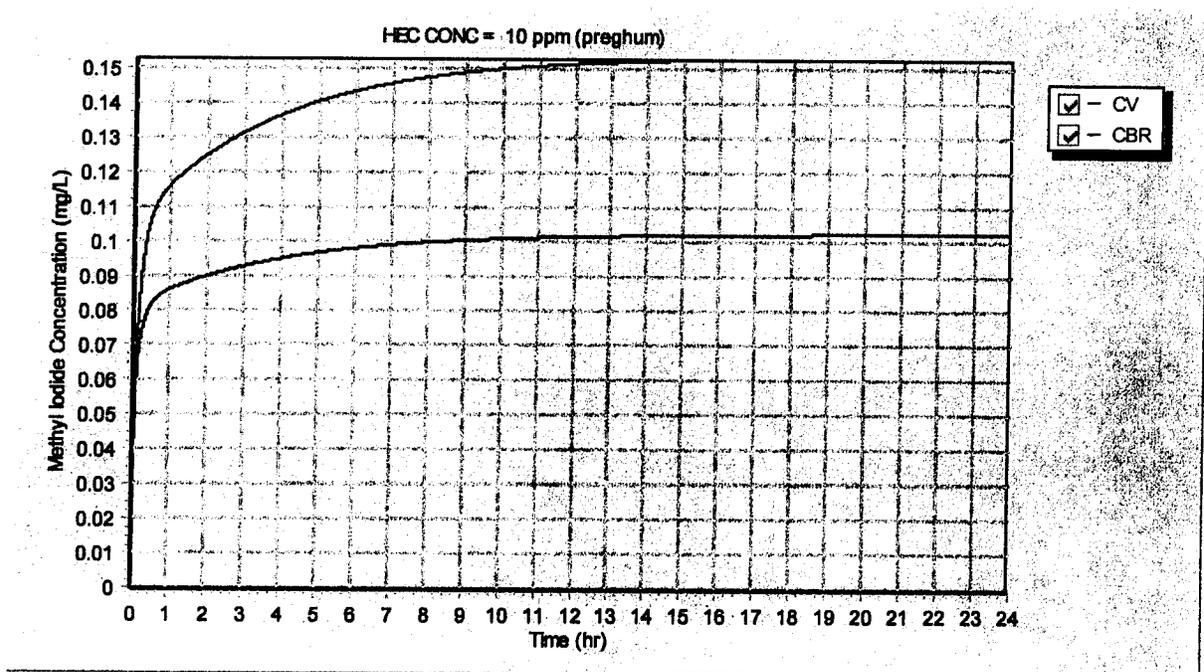


Figure 6: Predicted Brain (CBr) and Venous Blood (CV) concentrations in a pregnant human exposed to 10 ppm methyl iodide.

Because the neurobehavioral measurements in the rats were made several hours after the exposure ended, these effects appear to be different than the classic volatile anesthetic effects that are dependent upon the current blood concentration (presumed a surrogate for current brain concentration). Thus, there is some uncertainty around use of the steady state brain methyl iodide concentration for extrapolation across species. This dose metric does correlate with the effect in that it is higher at the LOAEL than the NOAEL.

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Appendix B: Toxicity Profile

Iodomethane Toxicity Profile

| Guideline No./Study Type | MRID No. (year)/Classification/Exposure Conditions | Results |
|---|--|--|
| <p>870.1100 Acute Oral - Rat</p> | <p>45593803 (2001) Acceptable/Guideline.</p> | <p>LD₅₀ = 79.8 mg/kg (males); 131.9 mg/kg (females) Clinical signs: decreased activity, breathing abnormalities, salivation, nasal/ocular discharge, dark material around facial area and eyes, partially closed eyelids, pale skin, soft feces, prostration, tremors, and wobbly gait. Gross pathology: red lungs (congestion) and abnormal GI contents in decedents. The Up/Down procedure was used in SD rats. Toxicity Category II</p> |
| <p>870.1100 Acute Oral - Mouse</p> | <p>45593804 (2001) Acceptable/Guideline</p> | <p>LD₅₀ = 155 mg/kg (males); 214 mg/kg (females) Clinical signs: urine and fecal stain, decreased food consumption, salivation, decreased or no defecation, dilated pupils, piloerection, rough hair coat, prostration, hypothermia, decreased activity, breathing abnormalities, skin blue in color over the entire body (anoxemia), hunched posture and wobbly gait. Gross pathology: red fluid in thoracic cavity, abnormal GI contents, red glandular mucosa (congestion) of the stomach, and dilated kidney pelvis in decedents. The Up/Down procedure was used in CD-1 mice. Toxicity Category II</p> |
| <p>870.1200 Acute Dermal - Rat</p> | <p>45593805 (2001) Acceptable/Guideline</p> | <p>LD₅₀ >2000 mg/kg (limit test) There were no deaths. Clinical signs: severe dermal irritation (at 500 and 2000 mg/kg) and hemorrhage (2000 mg/kg) at the dosing site. Decreased defecation, soft stools, decreased food consumption, breathing abnormalities, and dark material around the facial area. Gross pathology: Unremarkable Toxicity Category III</p> |

| | | |
|--|--|---|
| 870.1300 Acute Inhalation - Rat | 45593806 (2001) Acceptable/Guideline 581, 710, 797 or 1198 ppm | LC₅₀ = 691 ppm = 4 mg/L (combined sexes) The test article was administered as a vapor in a dynamic whole-body chamber for 4 hours. Clinical signs: gasping, ataxia, hypoactivity, nasal discharge, labored respiration, rales, and red material around nose. Gross pathology: dark pituitary, dark red lungs, distended gas-filled and congested stomach, hemorrhagic thymus, dark red adrenal glands, and distended intestines in decedents. Toxicity Category IV |
| 870.2400 Primary Eye Irritation - Rabbit | 45593807 (2001) Acceptable/Guideline | Corrosive: Corneal opacity, conjunctivitis, iritis, corneal neo-vascularization, sloughing of corneal epithelium, blanching of nictitating membrane, and corneal bulging. Toxicity Category I |
| 870.2500 Primary Skin Irritation - Rabbit | 45593808 (2001 Acceptable/Guideline | Well defined erythema and blanching, slight-severe edema, lightening, extended erythema beyond the test sites and desquamation. Toxicity Category II |
| 870.2600 Dermal Sensitization (Magnassun-Kligman Maximization Test) - Guinea Pig | 45593809 (2001) Acceptable/Guideline | Not a dermal sensitizer |
| 870.3100 Subchronic Feeding - Rat | | Not required by the Agency |
| 870.3100 Subchronic Feeding - Mice | | Not required by the Agency |
| 870.3100 Subchronic Feeding - Mice | | Not required by the Agency |
| 870.3150 Subchronic Feeding - Dog | | Not required by the Agency |
| 870.3200 21-Day Dermal - Rat | | Not required by the Agency |
| 870.3465 13-Week Inhalation - Rat | 45593810 (2002) Acceptable/Guideline 0, 5, 21, or 70 ppm in a whole-body chamber, 6 h/day, 5 days/week for 4 weeks (interim sacrifice) or 13 weeks | NOAEL = 21 ppm (0.12 mg/L/day) LOAEL = 70 ppm (0.41 mg/L/day) based on initial decreases in body weights, body weight gains, and food consumption (males); and nasal degeneration. |

| | | |
|--|--|---|
| 870.3100 Subchronic Feeding - Rat | | Not required by the Agency |
| 870.3700 Inhalation Developmental Toxicity - Rat | 45593812 (2002) Acceptable/Guideline 0, 5, 20, 60 ppm in a whole-body inhalation chamber, 6 h/day on GDs 6-19. | Maternal NOAEL = 20 ppm (0.12 mg/L/day) Maternal LOAEL = 60 ppm (0.35 mg/L/day) based on decreased body weight gain (↓19%; ↓5-6% absolute body weight). Developmental NOAEL = 60 ppm (0.35 mg/L/day) Developmental LOAEL was not observed |
| 870.3700 Inhalation Developmental Toxicity - Rabbit | 45593811 (2002) Acceptable/Guideline 0, 2, 10, or 20 ppm in a whole-body inhalation chamber, 6 h/day, on GDs 6-28. | Maternal NOAEL = 20 ppm Maternal LOAEL: Not identified Developmental NOAEL = 10 ppm Developmental LOAEL = 20 ppm based on increased fetal losses and decreased fetal weights (↓20%). |
| Guideline No./Study Type | MRID No. (year)/Classification/Exposure Conditions | Results |
| Non-guideline Inhalation Phased-Exposure Developmental Toxicity - Rabbit | 46077001 (2003) Acceptable/non-guideline 0 or 20 ppm from GD6-28; 20 ppm from GDs 6-14, 15-22, 23-24, 25-26, or 27-28 in a whole-body inhalation chamber 6hrs/day | This study was not intended to fulfill the guideline requirement or establish NOAELs and LOAELs but rather was conducted to determine the critical period of exposure during gestation that resulted in fetal loss as observed in a previously evaluated guideline developmental toxicity study in rabbits. Increased fetal losses at 20 ppm on GD 6-28 (↑21%), 23-24 (↑9%), and 25-26 (↑11%) |
| 870.3800 Inhalation 2-Generation Reproductive Toxicity - Rat | 45710301 (2001) Acceptable/guideline 0, 5, 20, or 50 ppm in whole body inhalation chamber Note: Offspring not directly exposed until PND 28 | Parental systemic NOAEL = 20 ppm Parental systemic LOAEL = 50 ppm based on decreased body weight gain, body weight, organ weight changes, gross pathology, and histopathology findings. Portal of entry NOAEL = 20 ppm Portal of entry LOAEL = 50 ppm based on degeneration of the olfactory epithelium Offspring NOAEL = 5 ppm Offspring LOAEL = 20 ppm based on decreases in body weight gain, body weight, and thymus weights Reproductive NOAEL = 5 ppm Reproductive LOAEL = 20 ppm based on delays in vaginal patency |
| 870.4100 Chronic Feeding Toxicity - Dog | - | Not required by the Agency |
| 870.4200 Carcinogenicity Feeding - Mouse (18 months) | - | Not required by the Agency. |

| | | |
|--|--|---|
| 870.3100 Subchronic Feeding - Rat | | Not required by the Agency |
| 870.4300 Chronic Feeding Toxicity/Carcinogenicity- Rat. | 46512401 (2005) Acceptable/non-guideline 0, 5, 10, 60 ppm in a whole body inhalation chamber for 6 hrs/day, 5days/week | Systemic NOAEL = 5 ppm Systemic LOAEL = 20 ppm based on increased incidence of salivary gland squamous cell metaplasia. Portal of entry NOAEL = 20 ppm Portal of entry LOAEL = 60 ppm based on degeneration of the olfactory epithelium. At 60 ppm, perturbations of the thyroid- pituitary axis as well thyroid histopathology findings were reported. |
| 870.5100 Bacterial Reverse Mutation Test (Ames Assay) | 45593813 (2001) | Nonmutagenic in <i>Salmonella typhimurium</i> strains TA98, TA100, TA1535, and TA1537; and in <i>Escherichia coli</i> . |
| 870.5300 <i>In Vitro</i> Mammalian Cell Mutation Test in Chinese Hamster Ovary Cells | 45593815 (2001) | Negative |
| 870.5375 <i>In Vitro</i> Chromosomal Aberration in Chinese Hamster Ovary | 45593814 (2001) | Positive for the induction of structural chromosome aberrations (clastogenesis), but negative for induction of numerical aberrations in CHO cells in this assay. |
| 870.5395 <i>In Vivo</i> Micronucleus Assay in Mice | 45593816 (2001) | Negative |
| 870.6200 Inhalation Acute Neurotoxicity - Rats | 45593817 (2002) Acceptable/Guideline 0, 27, 93, 401 ppm whole-body, 6-hour exposure. | Systemic NOAEL = 27 ppm. Systemic LOAEL = 93 ppm based on FOB findings (clonic convulsions in 1/12 females, decreased body temperature), and decreased motor activity (↓75-78% in males, 81-84% in females). Portal of entry effects not assessed |
| 870.6200 Feeding Subchronic Neurotoxicity - Rats | - | Not required by the Agency |

| | | |
|---|-----------------|---|
| 870.3100 Subchronic Feeding - Rat | | Not required by the Agency |
| 870.7485 Metabolism - Rat | 45641401 (2002) | <p>Sprague-Dawley rats were orally dosed or exposed via inhalation with [¹⁴C] CH₃I. Maximum blood concentrations were achieved within 4 hours (oral) and 0-2 hours (inhalation), and were proportional to dose/concentration. Initial t_{1/2} was 5.1-7.2 hours, and terminal t_{1/2} was 116-136 hours.</p> <p>Radioactivity recovery was low in the main test due to inefficient CO₂ trapping. Overall recovery in the supplementary test was increased due to increased recovery of carbon dioxide. Recovered radioactivity was primarily as CO₂ (39.40-60.81% dose) and in the urine (26.50-33.40% dose) in all treated groups, while feces accounted for <2% dose. Radioactivity remained in the carcasses (11.92-14.39% dose) of all treated animals 168 hours following treatment in the main test. Elimination t_{1/2} were 17.8-22.3 hours for urine and 29.7-38.0 hours for feces in all treatment groups of the main test. The elimination t_{1/2} was 5.8-6.8 hours for CO₂ in all treatment groups of the supplementary test.</p> <p>At 0-1 hour post-treatment in orally treated rats and 233 ppm inhalation exposed rats, relatively high levels of radioactivity were observed in the liver and GI tract. Radioactivity was relatively high in the kidney, lung, and nasal turbinates of the 25 ppm inhalation exposed rats and in the kidney, thyroid, and lung of the 233 ppm inhalation exposed rats. At 6 hours post-oral dosing, tissue concentrations increased in the spleen (at 1.5 mg/kg only), kidney, brain, thyroid, lung, nasal turbinates, and fat (at 1.5 mg/kg only). Tissue concentrations decreased in all tissues of the inhalation exposed rats at 6 hours after exposure. At 168 hours post-dose, radioactivity had declined in all tissues and was highest in the kidney, liver, and thyroid. Tissue concentrations increased (not proportionally) with dose.</p> <p>The major metabolites were expired CO₂, and N-(methylthioacetyl) glycine and S-methyl glutathione which were excreted in the urine. Minor metabolites were methylthioacetic acid, methyl mercapturic acid, and S-methyl cysteine.</p> |
| 870.7600 Dermal Penetration - Rat | — | Not required by the Agency |

| | | |
|--|---|---|
| 870.3100 Subchronic Feeding - Rat | | Not required by the Agency |
| Non-guideline Observational Human Study | 47028601 (2007) Acceptable/non-guideline | This study is not a toxicity study (subjects were not exposed to any test substance) and was not intended to provide NOAELs/LOAELs for risk assessment purposes but rather was designed to characterize the typical physiological distribution of inorganic iodide between the fetus and its mother during various stages of pregnancy in unexposed individual . The distribution ratio obtained from this study <u>was</u> used to parameterize the iodomethane PBPK model and further reduce uncertainty in the interspecies extrapolation. |

Appendix C: Methodologies for Inhalation Risk Calculations and Human Equivalent Concentration Arrays

METHODOLOGIES FOR INHALATION RISK CALCULATIONS

In evaluating the risks that a compound may pose to human health after exposure *via* the inhalation route, different methodologies have been historically used by the USEPA and the California Department of Pesticide Regulation (CDPR). The Agency's approach to calculating risks due to inhalation exposure is based on the guidance methodology developed by the Office of Research and Development (ORD) for the derivation of inhalation reference concentrations (RfCs) and human equivalent concentrations (HECs) for use in margin of exposure (MOE) calculations (RfC methodology). An example of CDPR's methodology, and the species-specific parameters used in this approach can be found in the CDPR methyl bromide risk assessment, Appendix G (www.cdpr.ca.gov/docs/dprdocs/methbrom/append_g.pdf). As OPP understands the importance to harmonize, to the extent possible, with other regulatory agencies, this risk assessment will present HECs derived using both methodologies. Furthermore, in the case of iodomethane, a chemical-specific PBPK model has been developed by the registrant and reviewed by Agency experts. Hence, the PBPK model has been used to calculate HECs for those endpoints where appropriate mechanistic data are available to identify a suitable chemical-specific dose metric. A more detailed explanation of the review of this PBPK model is available in Appendix A of this document.

The RfC methodology applies a dosimetric adjustment that takes into consideration not only the differences in ventilation rate (MV) but also the physicochemical properties of the inhaled compound, the type of toxicity observed (*e.g.* systemic vs. port of entry) and the pharmacokinetic (PK) **but not pharmacodynamic** (PD) differences between animals and humans. Based on the RfC guidance (1994), the methodology for RfCs derivation is an estimate of the quantitative dose-response assessment of chronic non-cancer toxicity for individual inhaled chemicals and includes dosimetric adjustment to account for the species-specific relationships of exposure concentration to deposited/delivered dose. This adjustment is influenced by the physicochemical properties of the inhaled compound as well as the type of toxicity observed (*e.g.* systemic vs. port of entry), and takes into consideration the PK differences between animals and humans. Though the RfC methodology was developed to estimate toxicity of inhaled chemicals over a lifetime, it can be used for other inhalation exposures (*e.g.* acute and short-term exposures) since the dosimetric adjustment incorporates mechanistic determinants of disposition that can be applied to shorter duration of exposures provided the assumptions underlying the methodology are still valid. These assumptions, in turn, vary depending on the type of toxicity observed and will be discussed later on in this document. Thus the derivation of a HEC for inhaled gases is described by the following equation:

$$\text{HEC} = \text{POD}_{\text{study}} * \frac{D_{\text{animal exposure (hrs / day)}}}{D_{\text{human exposure (hrs / day)}}} * \frac{W_{\text{animal exposure (days / wk)}}}{W_{\text{human exposure (days / wk)}}} * \text{RGDR}$$

Where:

POD_{study}: Point of departure identified in the critical toxicology study

D_{animal exposure}: Duration of animal exposure (hrs/day; days/wk)

D_{anticipated exposure}: Anticipated human duration of exposure (hrs/day; days/wk)

RGDR: Regional Gas Dose Ratio

For gases eliciting both port of entry and systemic effects, calculations to estimate the inhalation risk to humans are dependent on the regional gas dose ratio (RGDR). In the case of systemic effects, the RGDR is defined as the ratio of the blood:gas partition coefficient of the chemical for the test species to humans ($H_{b/g \text{ animal}}/H_{b/g \text{ human}}$). When this ratio is unknown or when the $H_{b/g \text{ animal}} > H_{b/g \text{ human}}$ a default value of 1.0 is used as the RGDR. This default is based on the observation that for chemicals where partition coefficient data are available in both rats and humans the RGDR value has usually been comparable or slightly higher than 1. Thus, the use of an RGDR of 1 results in a protective calculation of the inhalation risk. Some of the key assumptions fundamental to the use of the RfC methodology to derive a HEC based on systemic effects include:

- 1) all the concentrations of inhaled gas within the animal's body are periodic with respect to time (*i.e.* periodic steady state - the concentration vs time profile is the same for every week). Periodicity must be attained for at least 90% of the exposure.
- 2) in the respiratory tract, the air, tissue, capillary blood concentration are in equilibrium with respect to each other.
- 3)systemically, the blood and tissue concentrations are in equilibrium with respect to each other.

In the case of iodomethane, the physicochemical properties and metabolism data for the compound indicate that these conditions (*i.e.* periodicity and equilibrium between different compartments) will be achieved in a very short period of time. Under these conditions, therefore, the use of the RfC methodology to estimate acute inhalation risk is appropriate.

When the critical toxic effect in a study occurs in the respiratory tract (*i.e.* port of entry effects), the RGDR is not related to the blood:gas partition coefficient of the compound but rather the ratio of the minute volume (MV) to the surface area (SA) of the affected region. In these instances, attaining periodicity or equilibrium between the compartments is not critical (since the effect is a function of the direct interaction between the inhaled compound and the affected region in the respiratory tract) and the RGDR may be calculated using the following equation:

$$RGDR = \frac{MV_{\text{animal}}/SA_{\text{animal}}}{MV_{\text{human}}/SA_{\text{human}}}$$

Where:

MV_{animal}: Minute volume for the test species (varies depending on body weight)

SA_{animal}: Surface area of the affected region in animals

MV_{human}: Minute volume for humans (default value is 13.8 l/min)

SA_{human}: Surface area of the affected region in humans

The MV_{animal} is calculated using the allometric scaling provided in USEPA (1988a). The equation for calculation of the MV_{animal} is:

$$\ln MV_{\text{animal}} = b_0 + b_1 \ln(BW)$$

Where:

$\ln MV_{\text{animal}}$: natural logarithm of the minute volume

b_0 : species specific intercept used in the algorithm to calculate minute volumes based on body weight

b_1 : species specific coefficient used in the algorithm to calculate minute volumes based on body weight

$\ln BW$: natural logarithm of the body weight (expressed in kg)

The values for the species-specific parameters used to calculate the MV_{animal} based on body weight and the values for the surface areas of various regions of the respiratory tract (extrathoracic, thoracic, and pulmonary) are provided in the EPA document “Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry” (1994).

The magnitude of the UFs applied is dependent on the methodology used to calculate risk. When using the methodology developed by CDPR, a 100X UF is applied (10X for interspecies extrapolation and 10X for intraspecies variation). In contrast, the RfC methodology and the PBPK model take into consideration the PK differences but not the PD differences. Consequently, the UF for interspecies extrapolation may be reduced to 3X (to account for the PD differences) while the UF for intraspecies variation is retained at 10X. Thus, the UF when using the RfC methodology or the PBPK model is 30X.

Hazard Assessment Array

| HEC Array for Non-Occupational Risk Assessment [§] | | | | | | | | | | | | |
|---|-----------------------------|----------------|----|---|----|----|-------|-----------|-------|-------|----|---|
| Relevant Study | LOAEL (ppm) | NOAEL (ppm) | Da | Dh | Wa | Wh | RGDR* | HEC (ppm) | inter | Intra | UF | |
| ACUTE EXPOSURE | | | | | | | | | | | | |
| <i>ACN- Rat</i> | <i>Systemic</i> | 93 | 27 | <i>PBPK model used for dosimetric adjustment</i> | | | | 10 | 3 | 10 | 1 | |
| Dev Rat | Maternal Systemic | 60 | 20 | Not Applicable; the LOAEL for the dams is based on decreases in body weight and body weight gain which are not expected to occur as the result of a single exposure | | | | | | | | |
| | Developmental | Not identified | 60 | 6 | 24 | 1 | 1 | 1 | 15 | 3 | 10 | 1 |
| <i>Dev Rabbit[‡]</i> | Maternal | Not identified | 20 | 6 | 24 | 1 | 1 | 1 | 5 | 3 | 10 | 1 |
| | <i>Developmental</i> | 20 | 10 | <i>PBPK model used for dosimetric adjustment</i> | | | | 7.4 | 3 | 10 | 1 | |
| <i>Subchronic Inhalation Study - Rat</i> | <i>Local</i> | 70 | 21 | <i>PBPK model used for dosimetric adjustment</i> | | | | 4.5 | 3 | 10 | 1 | |
| SHORT TERM EXPOSURE | | | | | | | | | | | | |
| <i>ACN-Rat</i> | <i>Systemic</i> | 93 | 27 | <i>PBPK model used for dosimetric adjustment</i> | | | | 10 | 3 | 10 | 1 | |
| Devel Rat | Maternal Systemic | 60 | 20 | 6 | 24 | 7 | 7 | 1 | 5.0 | 3 | 10 | 1 |
| | Developmental | Not identified | 60 | 6 | 24 | 7 | 7 | 1 | 15 | 3 | 10 | 1 |
| <i>Dev Rabbit</i> | Maternal Systemic | Not identified | 20 | 6 | 24 | 7 | 7 | 1 | 5.0 | 3 | 10 | 1 |
| | <i>Developmental</i> | 20 | 10 | <i>PBPK model used for dosimetric adjustment</i> | | | | 7.4 | 3 | 10 | 1 | |
| <i>Subchronic Inhalation Study - Rat</i> | Systemic | 70 | 21 | 6 | 24 | 5 | 7 | 1 | 3.75 | 3 | 10 | 1 |
| | <i>Local[¶]</i> | 70 | 21 | <i>PBPK model used for dosimetric adjustment</i> | | | | 4.5 | 3 | 10 | 1 | |
| MultiGen Repro: Rat | Parental Systemic | 50 | 20 | 6 | 24 | 7 | 7 | 1 | 5 | 3 | 10 | 1 |
| | Parental Local [¶] | 50 | 20 | Not applicable | | | | 3.20 | 3 | 10 | 1 | |
| | Offspring | 20 | 5 | 6 | 24 | 7 | 7 | 1 | 1.25 | 3 | 10 | 1 |
| | Reproductive Effects | 20 | 5 | 6 | 24 | 7 | 7 | 1 | 1.25 | 3 | 10 | 1 |

| HEC Array for Non-Occupational Risk Assessment [§] | | | | | | | | | | | | |
|---|-----------------------------|----------------|-------------|--|-----------|----------|----------|----------|-------------|----------|-----------|----------|
| INTERMEDIATE TERM EXPOSURE | | | | | | | | | | | | |
| Relevant Study | | LOAEL (ppm) | NOAEL (ppm) | D a | Dh | Wa | Wh | RGDR | HEC (ppm) | Inter | Intra | UF |
| <i>ACN-Rat</i> | <i>Systemic</i> | 93 | 27 | <i>PBPK model used for dosimetric adjustment</i> | | | | | 10 | 3 | 10 | 1 |
| Devel Rat | Maternal Systemic | 60 | 20 | 6 | 24 | 7 | 7 | 1 | 5.0 | 3 | 10 | 1 |
| | Developmental | Not identified | 60 | 6 | 24 | 7 | 7 | 1 | 15 | 3 | 10 | 1 |
| Dev Rabbit | Maternal Systemic | Not identified | 20 | 6 | 24 | 7 | 7 | 1 | 5.0 | 3 | 10 | 1 |
| | <i>Developmental</i> | 10 | 20 | <i>PBPK model used for dosimetric adjustment</i> | | | | | 7.4 | 3 | 10 | 1 |
| <i>Subchronic Inhalation Study - Rat</i> | Systemic | 70 | 21 | 6 | 24 | 5 | 7 | 1 | 3.75 | 3 | 10 | 1 |
| | <i>Local[¶]</i> | 70 | 21 | <i>PBPK model used for dosimetric adjustment</i> | | | | | 4.5 | 3 | 10 | 1 |
| MultiGen Repro: Rat | Parental Systemic | 50 | 20 | 6 | 24 | 7 | 7 | 1 | 5.00 | 3 | 10 | 1 |
| | Parental Local [¶] | 50 | 20 | Not applicable | | | | | 3.20 | 3 | 10 | 1 |
| | Offspring | 20 | 5 | 6 | 24 | 7 | 7 | 1 | 1.25 | 3 | 10 | 1 |
| | Reproductive | 20 | 5 | 6 | 24 | 7 | 7 | 1 | 1.25 | 3 | 10 | 1 |
| LONG TERM EXPOSURE | | | | | | | | | | | | |
| MultiGen Repro: Rat | Parental Systemic | 50 | 20 | 6 | 24 | 7 | 7 | 1 | 5.00 | 3 | 10 | 1 |
| | Parental Local [¶] | 50 | 20 | Not applicable | | | | | 3.20 | 3 | 10 | 1 |
| | Offspring | 20 | 5 | 6 | 24 | 7 | 7 | 1 | 1.25 | 3 | 10 | 1 |
| | Reproductive | 20 | 5 | 6 | 24 | 7 | 7 | 1 | 1.25 | 3 | 10 | 1 |
| Chronic/Carcinogenicity: Rat | Systemic | 20 | 5 | 6 | 24 | 5 | 7 | 1 | 0.89 | 3 | 10 | 1 |
| | <i>Local[¶]</i> | 60 | 20 | Not applicable | | | | | 3.20 | 3 | 10 | 1 |

[§] Bolded studies used for endpoint selection.

[†] Italicized HECs derived from PBPK model

N.A. = not applicable

[¶] Local effects (nasal lesions) did not progress with time (i.e. nasal lesions of comparable severity were seen after 4, 13, and 52 weeks of exposure at the same concentration). Therefore, it appears that this effects is not a function of C x t thus a time adjustment is not appropriate.

* Input parameters for the derivation of RGDRs were obtained from "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry" (USEPA, 1994) Tables 4-4, 4-5, and 4-6.

Key for Array Table

LOAEL: Lowest observed adverse effect level

NOAEL: No observed adverse effect level

Da: Daily animal exposure (hrs/day)

Dh: Anticipated daily human exposure (hrs/day)

Wa: Weekly animal exposure (days/week)

Wh: Anticipated weekly human exposure (days/week)

RGDR: Regional Gas Dose Ratio

HEC: Human Equivalent Concentration

inter: interspecies extrapolation uncertainty factor

intra: intraspecies variation uncertainty factor

UF: Other uncertainty factor(s)

| HEC Array for Occupational risk assessments [§] | | | | | | | | | | | | |
|--|------------------------------------|----------------|-------------|---|----|----|----|-------|-----------|-------|-------|----|
| Relevant Study | | LOAEL (ppm) | NOAEL (ppm) | Da | Dh | Wa | Wh | RGDR* | HEC (ppm) | inter | Intra | UF |
| ACUTE EXPOSURE | | | | | | | | | | | | |
| <i>ACN-Rat</i> | <i>Systemic</i> | 93 | 27 | <i>PBPK model used for dosimetric adjustment</i> | | | | | 10 | 3 | 10 | 1 |
| Dev Rat | Maternal Systemic | 60 | 20 | Not Applicable; the LOAEL for the dams is based on decreases in body weight and body weight gain which are not expected to occur as the result of a single exposure | | | | | | | | |
| | Developmental | Not identified | 60 | 6 | 8 | 1 | 1 | 1 | 45 | 3 | 10 | 1 |
| <i>Dev Rabbit</i> [‡] | Maternal Systemic | Not identified | 20 | 6 | 8 | 1 | 1 | 1 | 15 | 3 | 10 | 1 |
| | <i>Developmental</i> | 20 | 10 | <i>PBPK model used for dosimetric adjustment</i> | | | | | 23 | 3 | 10 | 1 |
| <i>Subchronic Inhalation Study - Rat</i> | <i>Local</i> | 70 | 21 | <i>PBPK model used for dosimetric adjustment</i> | | | | | 5.8 | 3 | 10 | 1 |
| SHORT TERM EXPOSURE | | | | | | | | | | | | |
| <i>ACN-Rat</i> | <i>Systemic</i> | 93 | 27 | <i>PBPK model used for dosimetric adjustment</i> | | | | | 10 | 3 | 10 | 1 |
| Dev Rat | Maternal Systemic | 60 | 20 | 6 | 8 | 7 | 7 | 1 | 15 | 3 | 10 | 1 |
| | Developmental | Not identified | 60 | 6 | 8 | 7 | 7 | 1 | 45 | 3 | 10 | 1 |
| <i>Dev Rabbit</i> | Maternal Systemic | Not identified | 20 | 6 | 8 | 1 | 1 | 1 | 15 | 3 | 10 | 1 |
| | <i>Developmental</i> | 20 | 10 | <i>PBPK model used for dosimetric adjustment</i> | | | | | 23 | 3 | 10 | 1 |
| <i>Subchronic Inhalation Study - Rat</i> | Systemic | 70 | 21 | 6 | 8 | 5 | 5 | 1 | 15.75 | 3 | 10 | 1 |
| | <i>Local</i> [¶] | 70 | 21 | <i>PBPK model used for dosimetric adjustment</i> | | | | | 5.8 | 3 | 10 | 1 |
| MultiGen Repro: Rat | Parental Systemic | 50 | 20 | 6 | 8 | 5 | 5 | 1 | 15 | 3 | 10 | 1 |
| | <i>Parental Local</i> [¶] | 50 | 20 | <i>Not applicable</i> | | | | | 4.20 | 3 | 10 | 1 |
| | Offspring | 20 | 5 | 6 | 8 | 5 | 5 | 1 | 3.75 | 3 | 10 | 1 |
| | Reproductive | 20 | 5 | 6 | 8 | 5 | 5 | 1 | 3.75 | 3 | 10 | 1 |

| INTERMEDIATE TERM EXPOSURE | | | | | | | | | | | | |
|--|-----------------------------|----------------|----------|--|----------|----------|----------|----------|-------------|----------|-----------|----------|
| <i>ACN-Rat</i> | <i>Systemic</i> | 93 | 27 | <i>PBPK model used for dosimetric adjustment</i> | | | | | 10 | 3 | 10 | 1 |
| Devel Rat | Maternal Systemic | 60 | 20 | 6 | 8 | 7 | 7 | 1 | 15 | 3 | 10 | 1 |
| | Developmental | Not identified | 60 | 6 | 8 | 7 | 7 | 1 | 45 | 3 | 10 | 1 |
| <i>Dev Rabbit</i> | Maternal Systemic | Not identified | 20 | 6 | 8 | 1 | 1 | 1 | 15 | 3 | 10 | 1 |
| | <i>Developmental</i> | 20 | 10 | <i>PBPK model used for dosimetric adjustment</i> | | | | | 23 | 3 | 10 | 1 |
| <i>Subchronic Inhalation Study - Rat</i> | Systemic | 70 | 21 | 6 | 8 | 5 | 5 | 1 | 15.75 | 3 | 10 | 1 |
| | <i>Local</i> [¶] | 70 | 21 | <i>PBPK model used for dosimetric adjustment</i> | | | | | 5.8 | 3 | 10 | 1 |
| MultiGen Repro: Rat | Parental Systemic | 50 | 20 | 6 | 8 | 5 | 5 | 1 | 15.00 | 3 | 10 | 1 |
| | Parental Local [¶] | 50 | 20 | Not applicable | | | | | 4.20 | 3 | 10 | 1 |
| | Offspring | 20 | 5 | 6 | 8 | 5 | 5 | 1 | 3.75 | 3 | 10 | 1 |
| | Reproductive | 20 | 5 | 6 | 8 | 5 | 5 | 1 | 3.75 | 3 | 10 | 1 |
| Chronic/Carcinogenicity: Rat | Systemic | 20 | 5 | 6 | 8 | 5 | 5 | 1 | 3.75 | 3 | 10 | 1 |
| | Local [¶] | 60 | 20 | Not applicable | | | | | 4.20 | 3 | 10 | 1 |

| LONG TERM EXPOSURE | | | | | | | | | | | | |
|-------------------------------|------------------------------|-----------|----------|----------------|----------|----------|----------|----------|-------------|----------|-----------|----------|
| MultiGen Repro: Rat | Parental Systemic | 50 | 20 | 6 | 8 | 5 | 5 | 1 | 15.00 | 3 | 10 | 1 |
| | Parental Local ^{†‡} | 50 | 20 | Not applicable | | | | | 4.20 | 3 | 10 | 1 |
| | Offspring | 20 | 5 | 6 | 8 | 5 | 5 | 1 | 3.75 | 3 | 10 | 1 |
| | Reproductive | 20 | 5 | 6 | 8 | 5 | 5 | 1 | 3.75 | 3 | 10 | 1 |
| Chronic/Carcinogenicity : Rat | Systemic | 20 | 5 | 6 | 8 | 5 | 5 | 1 | 3.75 | 3 | 10 | 1 |
| | Local [¶] | 60 | 20 | Not applicable | | | | | 4.20 | 3 | 10 | 1 |

[§] Bolded studies used for endpoint selection.

[‡] Italicized HECs derived from PBPK model

N.A. = not applicable

[¶] Local effects (nasal lesions) did not progress with time (*i.e.* nasal lesions of comparable severity were seen after 4, 13, and 52 weeks of exposure at the same concentration). Therefore, it appears that this effects is not a function of C x t thus a time adjustment is not appropriate.

[‡] An uncertainty factor for extrapolation from subchronic to chronic exposure is not recommended since the endpoint, nasal lesions, did not progress with time.

* Input parameters for the derivation of RGDRs were obtained from "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry" (USEPA, 1994) Tables 4-4, 4-5, and 4-6.

| Key for Array Table | |
|---------------------|---|
| LOAEL: | Lowest observed adverse effect level |
| NOAEL: | No observed adverse effect level |
| Da: | Daily animal exposure (hrs/day) |
| Dh: | Anticipated daily human exposure (hrs/day) |
| Wa: | Weekly animal exposure (days/week) |
| Wh: | Anticipated weekly human exposure (days/week) |
| RGDR: | Regional Gas Dose Ratio |
| HEC: | Human Equivalent Concentration |
| inter: | interspecies extrapolation uncertainty factor |
| intra: | intraspecies variation uncertainty factor |

Appendix D: Model Information and History

Industrial Source Complex 3 (ISC3)

ISC3 (http://www.epa.gov/scram001/dispersion_alt.htm) was developed by the U.S. Environmental Protection Agency (EPA) as a replacement for ISC2. ISC3 is a steady-state Gaussian plume model which can be used to assess pollutant concentrations from a wide variety of sources including point and area sources. ISC3 operates in both long-term and short-term modes. OPP has operated the model in short-term mode in its fumigant assessments and used the designation ISCST3. ISCST3 allows for three different types of outputs: (1) summaries of high values (highest, second highest, etc.) by receptor for each averaging period and source group combination, (2) summaries of overall maximum values (e.g., the maximum 50) for each averaging period and source group combination, and (3) tables of concurrent values summarized by receptor for each averaging period and source group combination for each day of data processed. The third output option was used when OPP ran the ISCST3 model. These outputs can be produced all the way down to an hourly basis.

Up until the end of 2005, ISC3 was the Agency's recommended air dispersion model for steady state sources. It should be noted that ISC3 can still be used as an alternative to the recommended models in Appendix W in regulatory applications with case-by-case justification (see Appendix W to 40 CFR Part 51, Section 3.2).

The ISCST3 model allows for the conservative assessment of concentrations of fumigants coming off of treated fields under specific meteorological and application conditions. However, one of the main weaknesses of ISCST3 is in its treatment of calm periods. A calm period in ISCST3 is when the wind speed is less than 1.0 m/s. When this occurs, ISCST3 assumes that there is no wind blowing and assigns a wind speed of 0.0 m/s and this can result in a misrepresentation of the fumigant plume. For the Agency's fumigant assessments, ISCST3 was run using the "regulatory option" for addressing calm periods.

American Meteorological Society/Environmental Protection Agency Regulatory Model (AERMOD)

AERMOD (http://www.epa.gov/scram001/dispersion_prefrec.htm#aermod) was developed by American Meteorological Society (AMS) and the U.S. Environmental Protection Agency (EPA). ISC was replaced by AERMOD as the preferred air dispersion model for near-field, steady state sources in the Agency's *Guidelines on Air Quality Models* as of December 9, 2005. AERMOD is a Gaussian plume model which can be used to assess pollutant concentrations from a wide variety of sources including point and area sources. AERMOD incorporates air dispersion based on planetary boundary layer turbulence structure and scaling concepts, including treatment of both surface and elevated sources, and both simple and complex terrain. The AERMOD modeling system consists of two pre-processors and the dispersion model. The meteorological preprocessor AERMET, uses meteorological data and surface characteristics to calculate boundary layer parameters (e.g. mixing height, friction velocity, etc.) needed to run AERMOD. The terrain pre-processor AERMAP both characterizes the terrain and generates receptor grids for AERMOD. AERMOD allows for three different types of outputs: (1) summaries of high values (highest, second highest, etc.) by receptor for each averaging period and source group combination, (2) summaries of overall maximum values (e.g., the maximum 50) for each averaging period and source group combination, and (3) tables of concurrent values summarized by receptor for each averaging period

and source group combination for each day of data processed. These outputs can be produced all the way down to an hourly basis.

As the replacement to ISC3, AERMOD currently contains new or improved algorithms for: 1) dispersion in both the convective and stable boundary layers; 2) plume rise and buoyancy; 3) plume penetration into elevated inversions; 4) computation of vertical profiles of wind, turbulence, and temperature; 5) the urban nighttime boundary layer; 6) the treatment of receptors on all types of terrain from the surface up to and above the plume height; 7) the treatment of building wake effects; 8) an improved approach for characterizing the fundamental boundary layer parameters; and 9) the treatment of plume meander. Many of these improvements have little to no effect on OPP's approach to modeling fumigant applications as area sources.

AERMOD allows for the conservative assessment of concentrations of fumigants coming off of treated fields under specific meteorological and application conditions. However, AERMOD has a similar weakness to ISC3 in its treatment of calm periods. A calm period in AERMOD is when the wind speed is less than 1.0 m/s. When this occurs, AERMOD assumes that there is no wind blowing and assigns a wind speed of 0.0 m/s and this can result in a misrepresentation of the fumigant plume. Also, AERMOD does not allow for the probabilistic treatment of variables such as the meteorological conditions.

CALPUFF

CALPUFF (http://www.epa.gov/scram001/dispersion_prefrec.htm#calpuff) is a non-steady-state meteorological and air quality modeling system developed by the Atmospheric Studies Group at TRC Solutions. It is maintained by the model developers and distributed by TRC (<http://www.src.com/html/calpuff/calpuff1.htm>). CALPUFF v.5 has been adopted by the Agency in its *Guideline on Air Quality Models* as the preferred model for assessing long range transport of pollutants and on a case-by-case basis for certain near-field applications involving complex meteorological conditions (i.e., non-steady state). The modeling system consists of three main components and a set of preprocessing and postprocessing programs. The main components of the modeling system are CALMET (a diagnostic 3-dimensional meteorological model), CALPUFF (an air quality dispersion model), and CALPOST (a postprocessing package).

The output files that CALPUFF creates for each run include unformatted data files containing grids of time-averaged concentrations, time-averaged dry deposition fluxes, and time-averaged wet deposition fluxes. These outputs in CALPUFF v.5 can be produced all the way down to an hourly basis. The post-processing program CALPOST is designed to produce ranked tabulations of averages of selected concentration data from these data files. CALPOST writes a text file containing the input data summary and output tables.

Although CALPUFF v.5 is on the Agency's guideline for air models, there is also currently a CALPUFF v.6 that has not yet been reviewed by the Agency. CALPUFF v.6 includes a number of technical enhancements over v.5 but the major one that could have effects on OPP's modeling of fumigant emissions is the option to use subhourly (i.e., 1 minute, 5 minute, etc.) meteorological data.

Probabilistic Exposure and Risk model for FUMigants (PERFUM)

PERFUM (<http://www.exponent.com/practices/health/PERFUM.html>) was developed to address the issue of bystander exposures following agricultural applications of fumigants. The core of the PERFUM modeling system is the US EPA dispersion model ISCST3 which at the time PERFUM was developed was the Agency's recommended air dispersion model for steady state sources. ISCST3 as described above calculates concentrations but is not designed to determine a buffer zone. PERFUM was designed to specifically take the ISCST3 outputs and use them to produce buffer zone outputs in a distributional format.

PERFUM allows users to develop an understanding of the distributions of potential bystander exposures and thus more fully characterize the range of risks resulting to bystanders around treated fields. ISCST3 is an integral part of the PERFUM model and the basic physics and code of ISCST3 remain unchanged. PERFUM essentially provides ISCST3 with daily meteorological data over 5 years as well as flux estimates within the uncertainty of those data. PERFUM then uses this information to create distributional outputs for pre-defined receptor locations.

Fumigant Emissions Modeling System (FEMS)

FEMS (<http://www.sullivan-environmental.com>) was developed to address the issue of bystander exposures following agricultural applications of fumigants. FEMS allows the user to define a number of options prior to running the model including: the fumigant to be applied, the frequency of fumigation, the sealing method employed, field size and shape, consecutive day/contiguous field applications, application season, the averaging time for the concentrations, and the dispersion model used (ISCST3, CALPUFF v.5, or CALPUFF v.6). FEMS also allows the user to include Monte Carlo treatments of all the key model inputs like meteorological conditions, emissions data, day the application starts, etc.

Once the core dispersion model is selected, FEMS simulates the application of a fumigant and it's off-gassing over a 4 day simulation using 4 hour time steps. The model estimates fumigant concentrations at various receptors beyond the perimeter of the applied field that are matched to the averaging time of interest for the user. Aside from estimating the fumigant concentrations, FEMS keeps track of the number of times that concentrations exceed the concentration of concern at each receptor.

Once FEMS completes the modeling simulation, the distribution of concentrations is computed for each receptor. FEMS produces two main outputs. The first is a frequency distribution that looks at the number of times that concentrations exceed the concentration of concern at each receptor. The second involves establishing the distributions of concentrations for each receptor and then taking the maximum number of periods per averaging time of interest above the concentration of concern and computing them as a function of distance from the field. Buffer zones are then established based on the most conservative concentrations that were modeled as a function of distance.

Soil Fumigant Exposure Assessment System (SOFEA)

SOFEA (<http://www.epa.gov/oscpmont/sap/meetings/2004/index.htm>) was developed to evaluate and manage human inhalation exposure potential associated with agricultural applications of fumigants. SOFEA calculates fumigant concentrations in air arising from volatility losses from treated fields for entire agricultural regions using multiple sources (treated fields), GIS information, agronomic specific variables, user specified buffer zones and field re-entry intervals. SOFEA uses a modified version of ISCST3 as its dispersion model. SOFEA also uses Monte Carlo techniques to vary the following parameters: weather information, field size, application date, application rate, application method, pesticide degradation rates in air, sealing method, field re-treatment, and buffer setbacks.

Multi-year, multiple field simulations can be conducted with SOFEA using random field placement in all agricultural areas or by selectively placing fields in historical or prospective use areas. Regional land use information can be used to refine the placement of treated fields, dispersion calculations, and exposure assessments. SOFEA has been previously used for regulatory decision making in California.