# Methyl Iodide (Iodomethane)

# RISK CHARACTERIZATION DOCUMENT FOR INHALATION EXPOSURE

## Volume IV – Part 2

## Responses to Public Comments

## $CH_3I$

**Department of Pesticide Regulation**

**California Environmental Protection Agency**

**February 2010**

## List of Comments

Public Comments (in alphabetical order) on the August 2009 Draft RCD

A. Arysta LifeScience NA, LLC

B. California Rural Legal Assistance

C. Dr. Kathleen Collins

D. Natural Resources Defense Council

E. Pesticide Action Network

F. Dr. Amber Wise

G. Worksafe

Arysta LifeScience

July 9, 2009

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

Dear Ms. Downs,

**SUBJECT:** IODOMETHANE: Arysta LifeScience NA, LLC Additional Comments to the Risk Characterization Document (RCD)

Arysta LifeScience NA is providing these additional, enclosed comments to the California Department of Pesticide Regulation (DPR) on the draft RCD for Iodomethane.

Arysta previously provided comments to DPR specifically related to Volume I (Health Risk Assessment) and Volume II (Bystander and Occupational Exposure Assessment) of the Iodomethane Risk Characterization Document on April 30, 2009. This enclosed document sets out key points regarding the toxicological and exposure data; and the *PBPK* and *PERFUM* models. Arysta believes these points and this information will be helpful to DPR in conducting its review. Please forward these comments to the appropriate scientists in the Medical Toxicology and Worker Health and Safety Branches. Arysta wishes to reserve its right to provide further comment during the public comment period.

Should the Department have any questions concerning the comments submitted, please contact Becky Rhodes at becky.rhodes@arystalifescience.com or at 865-850-3824; or Arysta Regulatory Consultant, Jim Wells at jwells@esalle.net or at 916-443-2793; or Arysta Regulatory Consultant, Robert Ehn at robertehn@sbcglobal.net or 559-297-9322. We look forward to feedback from the Medical Toxicology and Worker Health and Safety scientists.

Sincerely,

Jim Wells

Jim Wells
Regulatory Agent/Consultant for Arysta LifeScience North America

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

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1

Iodomethane: Arysta LifeScience NA, LLC
Comments to DPR

2

Appendix A

Midas 50:50 Label
(Florida Only)

3

Appendix A

Midas 50:50 Label
(states other than Florida)

4

Appendix B

PBPK Modeling

5

Appendix C

Selected References

6

Appendix C
Selected References:

Using Mode of Action and Life Stage Information to Evaluate the Human Relevance of Animal Toxicity Data

7

Appendix C
Selected References:

IPCS Framework for Analyzing the Relevance of a Noncancer Mode of Action for Humans

8

Appendix C
Selected References:

IPCS Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis

FINAL

# IODOMETHANE: Arysta LifeScience NA, LLC Comments to DPR

By

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July 9, 2009

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## EXECUTIVE SUMMARY

The toxicology of iodomethane has been thoroughly studied. A robust data base describes effects of overexposure and offers mechanistic insight for these effects. The data base allows for a clear delineation of effect and no-effect levels, which, in turn, permit confident estimates of safe exposure levels for each exposure scenario of concern with soil fumigant use.

Building on this database, Arysta developed physiologically-based pharmacokinetic (PBPK) models for iodomethane. The data and the models constitute a sophisticated effort to better characterize the toxicity profile for iodomethane in terms of developmental toxicity, respiratory tract lesions, and transient neurotoxicity, identified as the critical effects of acute iodomethane exposure. In addition, the use of PBPK models that take into consideration the toxicokinetic aspect of iodomethane exposure enables the use of chemical-specific parameters to determine the most appropriate dose metric and internal dose in calculating HECs instead of default inputs otherwise used. The EPA has reviewed these data and models and evaluated their utility to calculate HECs based on chemical-specific data. The PBPK models and the mechanistic studies used to provide its inputs were considered acceptable by the EPA and the study results were incorporated into the EPA risk assessment.

In reviewing the draft DPR assessment of iodomethane, Arysta notes seven major points of difference between Arysta's assessment of iodomethane and DPR"s assessment of iodomethane. These major points are:

1) DPR selected the No-Observed Effect Level (NOEL) of 2 ppm in rabbits as the basis for the developmental toxicology evaluation compared to Arysta's and EPA's selection of the 10 ppm No Observed Adverse Effect Level (NOAEL);
2) DPR selected dose metrics for human equivalent concentration (HEC) determination without consideration of the modes of action (MOA) of iodomethane, while Arysta and EPA identified dose metrics appropriate to the MOA for derivation of the HECs;
3) DPR took the position that MOAs for effects from acute exposure to iodomethane are unknown, while Arysta and EPA have evaluated the evidence for iodomethane MOAs and determined that the weight of the evidence supports postulated MOAs;
4) DPR recommended application of an uncertainty factor (UF) of 300, while Arysta and EPA agree that a UF of 30 is appropriate;
5) DPR recommends that a developmental neurotoxicity study (DNT) needs to be conducted, while Arysta and EPA believe available data are adequate to protect from any potential developmental neurotoxicity;
6) DPR used acceptable chronic oral iodide intake to assess potential risk from acute iodomethane exposure, while Arysta maintains that this is inappropriate; and
7) DPR used outdated methods for exposure assessment in the RCD, while Arysta supports use of the best available scientific data and exposure assessment methods.

These differences derive from DPR's failure to incorporate a mode-of-action analysis into their assessments. The postulated MOA for fetal loss in iodomethane-exposed rabbits is accumulation of excess fetal plasma iodide and resulting perturbation of fetal thyroid function.

There are measurable key events critical to induction of the adverse effect on the rabbit fetuses which support the postulated MOA and comport with internationally recognized tools for using animal-derived data to assess the potential for human toxicity, tools such as the International Programme for Chemical Safety framework for carcinogenic and noncarcinogenic effects.

The key events for iodomethane acute toxicity are quantifiable and consistent, and show a concordance of dose-response. There is a remarkable temporal association between the window of susceptibility of the fetal rabbits and the ontogeny of the rabbit fetal thyroid. The MOA is biologically plausible given the specific sensitivity of developing rabbits to iodide. Data supporting alternative MOAs is less robust, less specific and less biologically plausible than the postulated MOA. The weight of the evidence supports the MOA for fetal loss in iodomethane-exposed rabbits to be an accumulation of excess fetal plasma iodide and resulting perturbation of fetal thyroid function

In developing acute HEC values, DPR used overly conservative toxicological and/or modeling assumptions to derive an HEC. The table below illustrates how these very conservative assumptions translate into very different HECs for DPR as compared to EPA for the same effect in the same target population.

IODOMETHANE ACUTE HEC COMPARISON

| Acute Toxicity Endpoint | US EPA HEC[1] | | DPR HEC | |
|---|---|---|---|---|
| | Occupational | Bystander | Occupational | Bystander |
| Nasal Olfactory Epithelial Degeneration | 5.8 ppm | 4.5 ppm | 2.8 ppm | 2.2 ppm |
| Transient Neurotoxicity | 10 ppm | 10 ppm | 3.4 ppm | 3.4 ppm |
| Rabbit Fetus | 23 ppm | 7.4 ppm | 0.22 ppm | 0.24 ppm |

[1] Values from the EPA Iodomethane Risk Assessment, 2007, are supported by Arysta

With regard to estimating exposure, there are a number of advanced probabilistic modeling tools available to estimate concentrations downwind of fumigant applications. Most notably, the Probabilistic Exposure and Risk model for FUMigants (PERFUM) model, sponsored by Arysta, has the capability of estimating buffer zone distances and air concentrations following fumigant applications and allows the user to employ historical meteorological datasets. One of the principal reasons that Arysta sponsored the development of PERFUM was that, in the early stages of EPA's current analysis of the fumigants in 2004, there were no available tools to employ historical meteorological data and provide probabilistic exposure estimates for fumigants. EPA used PERFUM as the principal basis for establishing national buffer zones for the soil fumigants as documented in the revised Reregistration Eligibility Decisions (REDs) for the five soil fumigants registered prior to the beginning of the analysis and registration decision for iodomethane. By not availing themselves of this resource, DPR's assessment provides far less perspective on expected bystander exposures than is possible using state-of-the-art methods.

Overall, the assumptions DPR chose to use in the risk characterization for iodomethane overstate risk by approximately 30-fold or greater. It is Arysta's position that the extra-conservatism DPR has applied to its risk characterization of iodomethane in not necessary to protect public health.

## TABLE OF CONTENTS

Executive Summary ..... 2

Introduction ..... 5

Major Points of Difference Between the DPR and Arysta's Assessment of Iodomethane . 8

- Mode-Of-Action ..... 9
- Acute HEC Values ..... 12
- Human Exposure Assessment ..... 17
- Conservatism in DPR's Assessment ..... 24

Iodomethane Toxicology Narrative ..... 25

Iodomethane PBPK Model Explanation ..... 42

References ..... 47

Appendices ..... 53

- A. MIDAS 50:50 Label ..... 53
- B. Iodomethane PBPK Description ..... 54
- C. Selected Papers ..... 130

## INTRODUCTION

Arysta LifeScience NA, LLC (Arysta) welcomes the opportunity to present comments to the Expert Panel convened to review the Department of Pesticide Regulation's (DPR) Medical Toxicology Branch's Methyl Iodide (Iodomethane) Risk Characterization Document for Inhalation Exposure. Arysta's comments are presented in the following sections:

I. Illustrations of major points of difference between the DPR assessment of iodomethane and Arysta's assessment of iodomethane. This section will address:
   A. Mode-of-Action for developmental toxicity endpoint in rabbits
   B. Derivation of acute HEC values
   C. Human exposure assessment
   D. DPR's overly conservative approach to assessment of iodomethane toxicity and exposure;

II. Brief narrative of iodomethane toxicology;

III. An explanation of the PBPK model developed by Arysta and used by DPR.

IV. Appendices

Arysta holds a worldwide license for the registration, development, and commercialization of iodomethane (CAS Registry No. 74-88-4; also known as methyl iodide) as an agricultural soil fumigant. Iodomethane is the key ingredient in MIDAS®, a next generation soil fumigant that is a drop-in alternative for 85% of the current soil fumigation use of methyl bromide, an ozone depleting substance. Iodomethane was registered by the Environmental Protection Agency (EPA) Office of Pesticide Programs (OPP) in October, 2007 for use in growing high-value crops such as strawberries, tomatoes, and peppers for the control of soil-borne pathogens, weed seeds, nematodes and insects. It can be applied with existing equipment with minor modifications. MIDAS can be applied at 20-50% lower rates per acre than methyl bromide and other registered fumigants with no reduction in performance. Based on results from the testing conducted under the 2006 and 2007 EPA OPP approved Experimental Use Permit program, MIDAS provided up to 19% greater yields of fresh market tomatoes when compared to methyl bromide.

It is important to note that soil fumigants such as iodomethane are applied to bare soil (no crops present) using application techniques such as:

Shank application to raised beds or flat fields -
A series of steel shanks suspended from a tool bar and pulled behind a tractor which deposits the fumigant at the base of the shank as much as 6-15 inches beneath the soil surface. The same tractor is equipped to cover the treated area with a tarp in the same single pass through the field, thus minimizing the ability for the fumigant to escape from the soil area to which it is applied. Shank application can be made to a raised bed or a flat field, the latter often referred to as broadcast or flat fume.

Drip application to raised beds -
Irrigation equipment that deposits water through emitters from black plastic tubing can be also used to apply fumigants. After the drip irrigation equipment is installed in the field;

the area to be treated (including the drip irrigation line itself) is covered over with the tarp. Fumigants are injected into the lines delivering the water to the field through the emitters underneath the tarps. With drip application, tarps are not removed until the end of the growing season, minimizing exposure to workers.

Tarps and Films

Many individuals in the fumigant industry use the terms "tarps" and "films" interchangeably for the materials that cover fumigated areas. All iodomethane applications in California will use a tarp or film to cover the treated area.

Films or tarps differ in composition. There are standard tarps, and there are highly retentive (also known as high barrier) films. Highly retentive films allow less of the fumigation application to escape into the air above the treated area than do the standard tarps. Note that all of the DPR exposure assessments in the risk characterization document for iodomethane assume the use of standard tarps.

Numerous safeguards are in place on the MIDAS labeling to help reduce exposure to workers and bystanders. Following below is a brief description of some of those safeguards. A complete label is attached in Appendix A for your review.

Restricted Use

The MIDAS label identifies it as a restricted use pesticide due to acute toxicity. As a restricted use pesticide, only Certified Applicators (certified by the state and trained by Arysta) in the proper handling, worker protection, and application of MIDAS and handlers under their direct supervision may be present in the treatment area during application. Certified Applicators are individuals who have successfully completed a state-sanctioned training program and passed a certification examination. In addition, Arysta requires the Certified Applicator to be formally trained and qualified by Arysta. Moreover, the EPA requires that a Certified Applicator be present on site during all applications.

Personal Protection

MIDAS labels require the following personal protection:

Applicators and other handlers must wear (to include tractor drivers, co-pilots, shovelers, cross ditchers, and tarp monitors):

- Loose fitting or well ventilated long-sleeved shirt and long pants;
- Shoes plus socks;
- An air-purifying respirator with a 3M Brand No. 60928 cartridge filter, or equivalent (MSHA/NIOSH approved number prefix TC-23C);
- Full face shield or safety glasses with brow, temple and side protection if the air concentration of chloropicrin is less than 0.1 ppm. If the air concentration of chloropicrin is greater than 0.1 ppm, but less than 4 ppm, wear a full face respirator or face-sealing goggles with a half-face respirator. If the chloropicrin concentration is greater than 4 ppm;
- A full face respirator of one of the following types if the air concentration of chloropicrin exceeds 4 ppm: (a) a supplied-air respirator (MSHA/NIOSH approval number prefix TC-19C) OR (b) a self-contained breathing apparatus (SCBA) (MSHA/NIOSH approval number prefix TC-13F).

Other handlers (to include planters, hole punchers, tarp cutters, tarp removers, and tarp remover drivers) present on the application site from the start of the application until 14 days following the end of the application; and within the buffer zone from the start of the application until 48 hours following the end of the application must wear:

- Loose fitting or well ventilated long-sleeved shirt and long pants.
- Shoes plus socks.
- Full face shield or safety glasses with brow, temple and side protection. DO NOT wear goggles.

Post-Application Safety Procedures

Early re-entry (within 5 days after the application for non-highly retentive films, within 10 days after application with highly retentive films) is limited to tarp inspection, tarp repair, and flood prevention (including cross ditching). Tarp removal within 14 days of the start of the application requires a minimum of two trained employees to be present during the operation. Non-handler personnel are prohibited from being present during the tarp removal.

Buffer Zone Requirements

Areas adjacent to the iodomethane-treated area are referred to as the buffer zone. The buffer zone extends from the edge of the treated area in all directions. The minimum buffer zone distance for MIDAS is 25 feet and must be maintained from the start of the application until 48 hours following the end of the application.

The Certified Applicator must use an appropriate means to manage and maintain the buffer zone such as posting fumigant warning signs around the perimeter of the buffer zone at potential points of entry, using trained workers to patrol the buffer zone, or other equivalent means. Unprotected workers and bystanders, in general, are not permitted in the buffer zone from the start of the application until 48 hours following the end of the application. There can be no occupied nursing homes, hospitals, or prisons; and no occupied licensed schools, licensed day care facilities and licensed assisted living facilities (licensed by state or local governments) within ¼ mile of the fumigated area during the buffer zone period.

MIDAS is currently registered in 47 states; and is under review in 6 countries. As a true fumigant, iodomethane offers many value-added benefits including:

- Breaks down rapidly in the sunlight and UV light.
- Following proper use directions, this product does not impact groundwater quality.
- Accepted as a non-ozone depleting compound by EPA.
- Does not leave a detectable residue in the soil and is not transmitted to plants or food products.
- In April, 2009, EPA conferred the Ozone Layer Protection Award on Arysta Lifescience in recognition of bringing MIDAS® to the soil fumigant market.

Arysta is committed to working with DPR and the expert panel to ensure a fair evaluation of the active ingredient iodomethane; and to providing any additional information that would assist the panel in their review.

## I. ILLUSTRATIONS OF MAJOR POINTS OF DIFFERENCE BETWEEN THE DPR ASSESSMENT OF IODOMETHANE AND THE ARYSTA ASSESSMENT OF IODOMETHANE

There are seven major points of difference between Arysta's assessment of iodomethane (submitted to DPR in July 2007) and the DPR draft RCD. These major points are:

1) DPR selected the No-Observed Effect Level (NOEL) of 2 ppm in rabbits as the basis for the developmental toxicology evaluation compared to the Arysta and EPA selection of the 10 ppm No Observed Adverse Effect Level (NOAEL);

2) DPR selected dose metrics for human equivalent concentration (HEC) determination without consideration of the modes of action (MOA) of iodomethane, while Arysta and EPA identified dose metrics appropriate to the MOA for derivation of the HECs;

3) DPR took the position that MOAs for effects from acute exposure to iodomethane are unknown, while Arysta and EPA have evaluated the evidence for iodomethane MOAs and determined that the weight of the evidence supports postulated MOAs;

4) DPR recommended application of an uncertainty factor (UF) of 300, while Arysta and EPA agree that a UF of 30 is appropriate;

5) DPR recommends that a developmental neurotoxicity study (DNT) be conducted, while Arysta and EPA believe available data protect from any potential developmental neurotoxicity;

6) DPR used acceptable chronic oral iodide intake to assess potential risk from acute odomethane exposure, while Arysta maintains that this is inappropriate; and

7) DPR used outdated methods for exposure assessment in the RCD, while Arysta supports use of the best available scientific data and exposure assessment methods.

These and other issues are detailed in this comment document.

As pointed out by Boobis, et al., (2008) "structured frameworks are extremely useful in promoting transparent, harmonized approaches to the risk assessment of chemicals". Human relevance frameworks for determining whether data support a postulated Mode-Of-Action for several toxicity endpoints have been described by international groups of experts. Most prominent among these is the work on global harmonization of approaches to risk assessment performed by the experts of the International Programme on Chemical Safety (IPCS) of the World Health Organization. Their work, and the work of other independent expert panels, has been published (Boobis, et al., 2006; Seed, et al, 2005; Meek, et al, 2003). The consensuses on elements of a Mode-Of-Action Evaluation according to the IPSC are listed in the paragraph below. In those paragraphs an overview of a MOA and Human Relevance Analysis is described which incorporate mechanistic data for iodomethane developmental toxicity in rabbits into human health risk assessment.

I A. Mode-of-Action for developmental toxicity endpoint in rabbits.

A MOA for the developmental toxicity endpoint in rabbits is evaluated in this section using the approach developed by the International Programme on Chemical Safety (IPCS; Sonich-Mullin et al., 2001; Boobis et al., 2006). The IPCS framework is used as a tool to organize the evaluation and presentation of data into approximately nine sections. These sections are:

- Postulated Mode of Action
- Key events – critical to induction of effect
- Concordance of dose-response
- Temporal association
- Strength, consistency and specificity of association of response with key events
- Biological plausibility and coherence
- Alternative MOAs
- Uncertainties, inconsistencies, data gaps
- Assessment of postulated MOA

The Postulated MOA for Iodomethane

The postulated MOA for fetal loss in iodomethane-exposed rabbits is accumulation of excess fetal plasma iodide and resulting perturbation of fetal thyroid function.

Key Events Critical to the Induction of the Effect

There are measurable key events critical to induction of the adverse effect on the rabbit fetuses that support the postulated MOA. A body of experimental data defines and measures the key events consistently. These key events described by data include:

1. Excess iodide is concentrated in the rabbit fetal plasma compared to the maternal plasma of iodomethane-treated rabbits. This concentration of iodide in the rabbit fetus has been determined in two studies that measured unlabeled iodide (Sloter et al., 2005a, 2005b) and in one study that measured radiolabeled iodide (Morris et al., 2005).
2. Colloid was significantly depleted from the thyroid lumen in fetal rabbits exposed to 20 or 25 ppm iodomethane during GDs 23-26 compared to controls (Sloter et al., 2005a, 2005b)
3. Follicular cell hypertrophy was identified in fetal thyroids of rabbits exposed to 20 or 25 ppm iodomethane on GDs 23-26.
4. Increased fetal TSH was reported after 3 or 4 days of 20 ppm iodomethane exposure, 6 hours per day, and there was no effect on maternal TSH (Sloter, et al, 2005b).

Concordance of Dose-Response

There is a clear dose dependency of the key events with the adverse effect, such that increased iodomethane exposure to rabbits during the window of susceptibility increases the incidence and severity of the key events and increases the incidence of late resorptions.

1. Fetal plasma iodide concentrations increase with increasing iodomethane dose. Fetal plasma iodide levels were higher following exposure to 25 ppm iodomethane than 20 ppm iodomethane (Sloter et al., 2005a, 2005b). Fetal plasma iodide concentration increased after each consecutive 6-hour daily exposure to 20 ppm iodomethane during GD 23-26 (Sloter et al., 2005b).

2. Colloid depletion in the thyroids of fetal rabbits exposed to iodomethane during GDs 23-26 increased with increasing exposure. Colloid depletion occurred in the thyroids of only one in twenty fetuses in rabbits exposed to 20 ppm iodomethane for two days, on GD 23 and 24, and the incidence and severity of colloid depletion increased with increasing exposure during GDs 23-26 (Sloter 2005b). Colloid depletion occurred in thyroids of approximately half of the fetuses (~56%) exposed to 25 ppm iodomethane for two days on GD 23-24, and in approximately 99% of fetuses exposed to 25 ppm iodomethane for four days on GDs 23-26 (Sloter et al., 2005a, 2005b).
3. A dose-related increase in rabbit fetal serum TSH was reported with increasing iodomethane exposure. During GD23-26, circulating fetal TSH concentration increased with an increase in the number of 6-hour 20 ppm iodomethane exposures (Sloter et al., 2005b).

Temporal Association

The temporal relationships for the key events, the ontogeny of the fetal thyroid and for the adverse effect are clear. The fetal rabbit is sensitive to the effects of iodomethane exposure only during the first days of fetal thyroid function.

1. There is a window of susceptibility of the developing rabbit to iodomethane exposure between GD 23 and GD 26 (Nemec 2003). Fetal loss is not increased in rabbits when iodomethane exposure occurs on any other days of gestation.
2. The rabbit fetal thyroid begins to function on GD 22 (Sloter, et al., 2005a).

Strength, Consistency and Specificity of Association of Response with Key Events

The evidence to support the key events in the postulated MOA is strong and consistent.

1. Excess iodide is concentrated in the fetal plasma compared to maternal plasma of iodomethane-treated rabbits, and this has been measured in studies using two different experimental designs (Sloter et al, 2005 a, 2005b; Morris et al, 2005).
2. Effects of excess iodide on thyroid function are well known, and include inhibition of thyroid hormone release from the thyroid (called the Wolff-Chaikoff effect) and inhibition of thyroid hormone production. The decrease in circulating thyroid hormones triggers an increase in thyroid stimulating hormone (TSH) which acts on the follicular cells of the thyroid.
3. The effects on rabbit fetal thyroid structure and function following iodomethane exposure at 20 and 25 ppm are well documented in studies performed by Arysta.
4. The importance of thyroid function in fetal viability is also well known.

Biological Plausibility and Coherence

The MOA is consistent with what is known about rabbit sensitivity to iodide and consistent with the lack of sensitivity of rats to iodide and to developmental toxicity from iodomethane exposure.

1. Fetal rabbits are known to be sensitive to excess iodide. Rabbits fed diets containing excess iodide exhibited fetal loss that has been described in the literature since the 1960's (e.g., Arrington et al., 1965).
2. Iodide is concentrated in fetal rabbits compared to the doe in control rabbits and in rabbits exposed to iodomethane or sodium iodide (NaI). The fetal:maternal plasma iodide ratio is ~9 in control rabbits, ~6 in iodomethane-treated rabbits

3. The effects of excess iodide on the thyroid are known, and include inhibition of thyroid hormone synthesis, and thyroid follicular cell hypertrophy, and all these effects are observed in fetal rabbits following iodomethane exposure.
4. The histopathology of the thyroids of rabbit fetuses exposed to iv NaI exhibit similar histopathology to the rabbit fetuses exposed to iodomethane, though the degree of severity was lower, as was the systemic dose of iodide.

Alternative MOAs to explain fetal loss in rabbits

Three possible alternative MOAs for developmental effects of iodomethane in rabbits were identified by DPR. These include methylation of DNA, systemic depletion of glutathione, and altered cholesterol metabolism resulting in decreased estrogen. These MOAs are considered below.

1. DNA Methylation
   - Iodomethane is negative for mutagenicity and a detailed evaluation o of the available data in the literature indicates that iodomethane does not form DNA adducts, but that the methyl group from iodomethane is incorporated de novo in DNA synthesis (Mileson and McDonald, 2005, summarized in this document beginning on page 34).
   - There is no information to explain why rabbits would be more sensitive than rats to this MOA
   - Methyl bromide (MeBr) is similar in methylation capacity to iodomethane, yet no increase in late resorptions was reported in the rabbit developmental toxicity study submitted to support MeBr.
2. Glutathione (GSH) Depletion
   - Slight decreases in maternal plasma GSH were observed in iodomethane-exposed rabbits.
   - Decreases in fetal plasma GSH were observed but no decreases in liver GSH occurred, which suggests significant GSH capacity remains available for metabolism of iodomethane in the fetal rabbit.
   - MeBr and methyl chloride (MeCl) can decrease GSH, but neither cause late resorptions in rabbits.
3. Altered Cholesterol Metabolism resulting in 15-16% decreases in estradiol in rabbits exposed to 25 ppm iodomethane (not statistically significant decreases)
   - This effect is expected to occur in rats as well as rabbits, and it is possible that the rabbit is more sensitive than the rat to decreased estradiol though the evidence to support this is equivocal.
   - Estrogen generally increases towards the end of gestation, so there is a general temporal association with the effect, but not a specific temporal association.
   - The measured decrease in estradiol was small compared to the 25 ppm iodomethane exposure concentration, suggesting this is not a likely MOA for fetal loss in rabbits exposed to iodomethane.

Uncertainties, inconsistencies, data gaps

1. There are no uncertainties or inconsistencies in the data that support the postulated MOA that fetal loss in iodomethane-exposed rabbits is due to excess fetal plasma iodide and resulting perturbation of fetal thyroid function.

2. The only possible missing data that could aid in proving the postulated MOA would be data from an inhalation study of NaI or KI exposure that delivered the identical dose of iodide to rabbits that is delivered by a 20 ppm inhalation exposure to iodomethane. In this study, an increase in fetal loss would be expected following inhalation exposure to NaI during GD 23-26. This one piece of missing data is not critical as support for the postulated MOA because the weight of the evidence is sufficient to support the MOA; the MOA does not have to be proven.

Assessment of postulated MOA

The weight of the evidence supports the postulated MOA with a high degree of certainty. The key events are quantifiable and consistent, and show a concordance of dose-response. There is a remarkable temporal association between the window of susceptibility of the fetal rabbits and the ontogeny of the rabbit fetal thyroid. The MOA is biologically plausible given the specific sensitivity of developing rabbits to iodide. The data supporting the alternative MOAs was less robust, less specific and less biologically plausible than the postulated MOA. The weight of the evidence supports the MOA for fetal loss in iodomethane-exposed rabbits to be an accumulation of excess fetal plasma iodide and resulting perturbation of fetal thyroid function.

I. B. Derivation of acute HEC values

Nasal Olfactory Epithelial Degeneration HEC

EPA determined HECs of 4.5 ppm for bystander and 5.8 ppm for occupational risk assessment from the NOAEL of 21 ppm based on degeneration of the olfactory epithelium observed at 70 ppm. Arysta supports these HECs. The EPA used the iodomethane PBPK model to derive these HECs based on a dose metric of glutathione (GSH) depletion in the nasal olfactory epithelium. A GSH depletion of approximately 50% in the nasal olfactory epithelial cell layer (not including the blood exchange layer) was the basis for the current HECs. In contrast, DPR identified a bystander HEC for this endpoint of 2.2 ppm for a 24 hour exposure, and an occupational HEC of 2.8 ppm, based on a dose metric of 25% GSH depletion in the nasal olfactory epithelial cell layer.

Mode of Action Evaluation to Determine HEC Basis

Histopathologic changes caused by iodomethane exposure occurred in the respiratory tract of rats. 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 multigenerational 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 x t; Haber=s law). In contrast, a C x t relationship is assumed for all systemic effects.

The weight of evidence suggests that the mode of action responsible for iodomethane effects in the olfactory epithelium of rats is glutathione (GSH) depletion. A variety of potential modes of action of iodomethane on the nasal olfactory epithelium were investigated in a study by Chamberlain (1998a). This in vitro study ruled out two potential modes of action: (1) cellular

protein methylation and (2) cytochrome P450 metabolism of iodomethane to formaldehyde. The only parameter studied that correlated with the site-selective lesion of the olfactory epithelium is GSH depletion catalyzed by conjugation of GSH and iodomethane by glutathione S-transferase (GST) theta.

GSH depletion as a key factor in the mode of action of iodomethane on the nasal epithelium of rats was confirmed in a second study by Chamberlain (1998b). In the second study, rats pretreated with an isopropyl ester of GSH to increase tissue GSH levels were protected against the nasal effects of iodomethane. Alternatively, rats pretreated with phorone and buthionine sulphoximine to deplete GSH tissue levels exhibited a potentiated response to the nasal effects of iodomethane exposure (Chamberlain et al., 1998b). This study concluded that GSH depletion by conjugation with iodomethane is the mode of action for the nasal effects and a detoxification pathway for iodomethane.

Nasal Epithelial Degeneration – Dose Metric Identification

The histopathology in the nasal olfactory epithelium was reported in rats after 13-weeks of daily exposure to iodomethane; however, data from the published literature indicate that nasal lesions can occur in rats after acute exposures if the time profile of the exposure concentration leads to an overall iodomethane exposure of greater than or equal to 200 ppm/hr (for example, approximately 2 hours at 100 ppm) (Reed et al, 1995). The proposed mode of action for nasal histopathology involves glutathione (GSH) depletion as a key event in the toxicity pathway leading to damage of the nasal olfactory epithelium (Chamberlain et al., 1998). Consequently, GSH depletion is the dose metric used in the PBPK model for interspecies extrapolation to determine the NOAEL for the nasal lesions and identify the HEC. A number of researchers have presented data that indicate that in order for GSH-related toxicity to be produced in tissues other than the liver (including nasal tissue) GSH concentrations in extrahepatic tissues must (1) drop below 50% of control and (2) remain depleted (Frederick et al., 1992; Plopper et al., 2001; Lee et al., 2005).

Two examples of research programs that have characterized GSH depletion in the respiratory tract are summarized for the compounds naphthalene and propylene oxide. These examples illustrate the function of the GSH detoxification pathway in the respiratory tract tissue. Cellular structure and function may be disrupted when GSH levels are reduced to approximately 40% of normal control levels, while normal cell structure and function are maintained during sustained GSH depletion to approximately 50% of control levels.

Naphthalene Example.

Studies performed on naphthalene provide data to clarify the relationship between GSH depletion and the susceptibility of the respiratory tract tissue to damage from chemical exposure. These studies show that a substantial depletion in GSH in respiratory tissue is necessary for toxicity to occur.

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

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

Propylene Oxide Example.

A combination of studies was performed using propylene oxide exposure to evaluate the degree of GSH depletion required for minimal damage to occur in nasal tissue of rats (Rios-Blanco, et al., 2003; Lee et al., 2005). Cell proliferation and GSH levels were measured in the same nasal epithelial tissue. An exposure to 50 ppm propylene oxide for either 3 days or 4 weeks (20 days) resulted in GSH levels that were 43% of control levels. No alteration in cell proliferation compared to control occurred in the nasal epithelium of the rats exposed to 50 ppm propylene oxide for 3 days or 4 weeks (Figure 6 of Lee et al., 2005). There was no difference in the amounts of GSH depletion or cell proliferation observed after 3 days or 4 weeks of exposure to 50 ppm propylene oxide. The next highest exposure level (300 ppm) resulted in a significant increase in cell proliferation and GSH levels in the nasal epithelia that were 16% of control. The dose response curves for cell proliferation and GSH levels of exposed rats were used by the authors to determine that a daily GSH depletion in the nasal epithelium of approximately 60% is required for an increase in cellular proliferation over controls to occur.

Iodomethane Data

Himmelstein, (2005) examined the GSH levels in the nasal epithelium at various times during and after iodomethane exposure in rats. Exposure of rats to 25 ppm for 6 hours per day for 2 days resulted in GSH levels that gradually dropped during exposure and then rebounded when exposure ended, such that GSH levels returned to normal levels or greater 15 hours after exposure ended. The same pattern occurs in the nasal epithelium of rats exposed to 100 ppm iodomethane.

The data from the naphthalene studies demonstrate that a substantial depletion of GSH is required before the cells are susceptible to toxicity, and that the cells can withstand a transient 90% GSH depletion with no adverse effect, but a longer severe depletion results in toxicity to sensitive cells. The data from the propylene oxide studies demonstrate that the nasal epithelial cells remain normal even with a sustained 57% GSH depletion due to daily exposure to propylene oxide.

Nasal Olfactory Epithelial Degeneration – Appropriate Dose Metric

The available evidence demonstrates that a substantial depletion of GSH is necessary for nasal epithelial cells to become susceptible to toxicity, and this depletion must be sustained for toxicity to occur. A transient 50% depletion of GSH achieved only at the end of a 24-hour iodomethane exposure is an appropriate dose metric (or NOAEL) for the acute exposure endpoint of nasal toxicity because the benchmark GSH depletion would barely be achieved, and not sustained.

Transient Neurotoxicity HEC

EPA determined an HEC of 10 ppm for both the bystander and occupational risk assessments from the NOAEL of 27 ppm based on brief, reversible signs of neurotoxicity including decreased motor activity and decreased body temperature observed at the LOAEL of 93 ppm. Arysta supports this HEC. The dose metric used to derive the HEC for the endpoint of transient neurotoxicity is steady state concentration of iodomethane in the brain. Steady state concentration of iodomethane in the brain was determined using the PBPK models for the rat and human. In contrast, DPR identified a bystander HEC for this endpoint of 3.4 ppm based on the cumulative iodomethane concentration (area under the concentration curve; AUC) in the brain.

Mode of Action Evaluation to Determine HEC Basis

The inhalation acute neurotoxicity study in rats revealed that 6 hour exposure to 93 ppm iodomethane elicited transient behavioral signs of neurotoxicity. These signs of neurotoxicity included: an 80% decrease in motor activity, a 2-3°C decrease in body temperature, and in 1 of 12 females, clonic convulsions (repetitive mouth and jaw movement), in the absence of neuropathology. All effects were transient, and recovery was complete. Clinical signs of neurotoxicity were not observed in any of the subjects in the subchronic or chronic studies performed on iodomethane.

A wide variety of inhaled solvents are known to produce anesthetic or sedative effects in animals and humans, similar to those reported for iodomethane, by altering nerve cell membrane properties (Snyder and Andrews, 1996). Iodomethane may depress spontaneous and evoked activity of neurons in the brain, possibly through non-specific actions with the lipid matrix of the nerve membrane or, as with anesthetic agents, by a more specific action on the $GABA_A$ receptor chloride channel, or by inhibition of neurotransmission at excitatory NMDA receptors (Balster, 1998; Trevor and White, 2004). These modes of action have not been linked specifically to iodomethane, but the temporal association, the type of the effects and the transient nature of the effects are similar, and suggest that the effects of iodomethane on the nervous system are due to the concentration of the parent compound in the brain. Accordingly, an HEC based on steady state concentration of iodomethane in the brain, as EPA has determined, is the appropriate basis for establishing bystander and occupational risk from transient acute neurotoxicity that may result from iodomethane.

Transient Neurotoxicity – Dose Metric Identification

Based upon a consideration of the likely modes of action, the neurological effects of iodomethane in rats are best explained by the impact of the parent chemical on the central nervous system. The steady state concentration of iodomethane in the brain identified by PBPK modeling reflects the concentration of parent compound in the brain.

Transient Neurotoxicity – Appropriate Dose Metric

Iodomethane exerts general sedative effects on the brain, possibly through non-specific actions with the lipid matrix of the nerve membrane or, as with anesthetic agents, by a more specific action on the $GABA_A$ receptor chloride channel, or by inhibition of neurotransmission at excitatory NMDA receptors (Balster, 1998; Trevor and White, 2004). Though the specific MOA for transient neurotoxicity has not been characterized, any of the proposed modes of action described support the use of the steady state concentration of iodomethane in the brain as the appropriate internal dose measure for PBPK modeling.

Developmental Toxicity in Rabbits – HEC

EPA determined HECs of 7.4 ppm for bystander, and 23 ppm for occupational risk assessment from the NOAEL of 10 ppm based on fetal losses and decreased fetal weights in a developmental toxicity study in rabbits exposed to the Lowest Observed Adverse Effect Level (LOAEL) of 20 ppm. Arysta supports these HECs. EPA used the iodomethane PBPK model to derive the HECs. The dose metric used to derive the HECs for the developmental toxicity endpoint is the level of fetal serum iodide after a single day of maternal exposure. In contrast, DPR identified a bystander HEC for this endpoint of 0.24 ppm, and an occupational HEC of 0.22 ppm based on the rabbit study NOEL of 2 ppm using a dose metric in the PBPK model of maternal serum iodide.

Mode of Action Evaluation to Determine HEC Basis

The MOA for developmental toxicity in rabbits has been described in detail. The weight of the evidence supports the MOA for fetal loss in iodomethane-exposed rabbits to be accumulation of excess fetal plasma iodide and resulting perturbation of fetal thyroid function.

Developmental Toxicity– Dose Metric Identification

The biochemical measure associated with the developmental effects observed in rabbits following iodomethane exposure is fetal iodide accumulation. Data from studies published prior to 1985 suggested there are important species differences in fetal iodide accumulation, such that guinea pigs, sheep and rabbits possess an active mechanism for transporting iodide from mother to fetus, while other animals such as rats do not concentrate iodide in the fetus (Logothetopoulos and Scott, 1956; Roti et al. 1983).

Studies performed by Arysta with rabbits confirmed that control fetal rabbits have blood iodide levels that are approximately 9 times the iodide levels in maternal blood (Sloter, 2005a). The rabbit has been shown to be more sensitive with regard to fetal viability than the rat, hamster and swine when dosed with potassium iodide or sodium iodide in feed at certain times during gestation (Arrington et al., 1965). Iodide accumulation in the rabbit fetus is the critical step in the mode of action that ultimately leads to fetal loss in rabbits exposed to iodomethane.

In contrast to rabbits, the human fetus was not believed to concentrate iodide from the maternal circulation in such high ratios. Available data from the literature indicate that normal human fetal iodide concentrations are generally lower than or equal to human maternal concentrations, resulting in a fetal/maternal plasma iodide concentration ratio of approximately 1. Arysta performed a study designed to characterize the fetal and maternal plasma iodide concentrations in unexposed human subjects (Rayburn et al., 2007). The fetal and maternal iodide concentrations and fetal/maternal plasma iodide ratios characterized in the Rayburn study (2007) confirm that the human conceptus does not highly concentrate iodide relative to the maternal circulation as the rabbit does. These data have been used to inform the PBPK modeling and increase the certainty in the human health risk assessment. The human fetal/maternal plasma iodide ratio for premature deliveries is less than one, supporting the conclusion that iodide could not be concentrated in premature infants as it is in the rabbit.

Developmental Toxicity – Appropriate Dose Metric

The identified mode of action for fetal loss in iodomethane-exposed rabbits is accumulation of excess fetal plasma iodide and resulting perturbation of fetal thyroid function.

This mode of action supports the use of the cumulative iodide concentration (area-under-the-curve or AUC) in fetal blood as an appropriate internal dose measure for PBPK modeling.

I. C. Human exposure assessment

Deterministic vs. probabilistic air dispersion modeling

The basis for the estimation of air concentrations and bystander buffer zones is dispersion modeling. Dispersion models estimate downwind concentrations based on estimates of flux rates and a characterization of the meteorology near the source. These models have been used for regulatory decisions since the 1970s. The flux rate is defined as the mass of material off-gassing from the field per unit area of the application per unit time. A common unit to express flux rates is microgram per square meter per sec ($\mu g/m^2/sec$). The flux rate data collected by iodomethane are discussed in the next section. This section discusses the air dispersion methods applied by DPR.

The main difference between the methods used by DPR and the methods recommended by Arysta is the choice between using simplistic assumptions about meteorology (DPR) and using historical meteorological data from California (Arysta). The use of historical meteorological data allows the estimation of concentrations in all types of meteorological conditions and allows the characterization of typical and worst-case concentrations. It also allows a probabilistic assessment of air concentrations given the variability in meteorology that could occur for a given application.

Instead of using actual meteorological data and applying probabilistic methods, DPR used a deterministic air dispersion modeling approach to estimate bystander exposures. DPR's approach assumes a 1 m/sec wind speed, stable atmospheric conditions, and a constant wind direction to estimate 1-hr and 8-hr average concentrations. To estimate 24-hour average concentrations, DPR assumes a 1.4 m/sec wind speed, slightly unstable atmospheric conditions, and a constant wind direction. The reasoning for DPR's assumptions is unexplained, but clearly do not represent real-world conditions. Over the course of even a few hours, wind direction, wind speed, and atmospheric stability nearly always vary. Therefore, the use of constant values for these parameters is unrealistic and makes the DPR results difficult to interpret.
The illogical nature of DPR's calculations can be observed by comparing the concentration estimates averaged over 8-hours and 24-hours in Table 13 of Volume II. These concentrations are intended to be "maximum" concentrations at different distances from the edge of the field and refer to the concentrations at 152 meters from the edge of a 40-acre field where iodomethane was applied at the maximum usage rate. For a given "maximum" 8-hour average concentration, the corresponding "maximum" 24-hour average concentration should not be less than one-third of the "maximum" 8-hour average concentration. Even if the concentration over the other 16 hours of the day was zero, the "maximum" 24-hour average concentration would be one-third of the "maximum" 8-hour average concentration. However, in a number of cases, the "maximum" 24-hour concentration is less than one-third of the "maximum" 8-hour concentration. For example, for the drip irrigation estimate at 152 meters in Table 13, the "maximum" 8-hour concentration is 9.5 $\mu g/L$, while the "maximum" 24-hour concentration is 1.7 $\mu g/L$. Even if the concentration were zero for the other 16 hours of the day, given a concentration of 9.5 $\mu g/L$ for the first 8 hours, the "maximum" 24-hour concentration would be 3.2 $\mu g/L$.

There is a long history of using historical meteorological data for air dispersion analysis. The EPA recommends the use of historical data in its Guideline for Air Quality Monitoring,

where it specifically states: "Five years of representative meteorological data should be used when estimating concentrations with an air quality model.[1]" The use of 5-years of historical meteorological data in air dispersion modeling allows the modeler to provide robust estimates of the worst-case concentrations. It also allows the modeler to provide a perspective on the relative frequency of different concentrations occurring, which is critical for risk management. Historical meteorological data are plentiful, particularly in California where there are existing National Weather Service (NWS) stations as well as stations in agricultural areas from the California Irrigation Management Information System (CIMIS).

There are a number of advanced probabilistic modeling tools available to estimate concentrations downwind of fumigant applications. Most notably, the Probabilistic Exposure and Risk model for FUMigants (PERFUM) model, sponsored by Arysta, has the capability of estimating buffer zone distances and air concentrations following fumigant applications and allows the user to employ historical meteorological datasets[2]. One of the principal reasons that Arysta sponsored the development of PERFUM was that, in the early stages of EPA's current analysis of the fumigants in 2004, there were no available tools to employ historical meteorological data and provide probabilistic exposure estimates for fumigants. EPA used PERFUM as the principal basis for establishing national buffer zones for the soil fumigants as documented in the revised Reregistration Eligibility Decisions (REDs) for the five soil fumigants registered prior to the beginning of the analysis and registration decision for iodomethane[3]. By not availing themselves of this resource, DPR's assessment provides far less perspective on expected bystander exposures than is possible using state-of-the-art methods.

Available Flux Data for Bystander Assessments

Flux rates are a chemical-specific parameter. Therefore, Arysta has conducted eleven field studies for iodomethane applications since 2000 to estimate the flux rate of iodomethane under various field conditions and application scenarios. Three different application methods were used, each representing a potential application method for iodomethane. The application methods evaluated include:

- Shallow shank broadcast flat fume (flat fume)
- Raised bed shallow shank injection (raised bed)
- Raised bed drip irrigation (drip irrigation).

With the flat fume method, a tractor is driven across a flat field (i.e., an application site where a crop will be planted) and the fumigant is applied by injection by driving shanks into the ground (8-12 inches) and a plastic tarp is covered over the field after the shank is pulled up (see Figure 1). With raised bed, the field is prepared in beds (see Figure 2) and the tractor is driven across the beds, the fumigant is applied by shanks, and a plastic tarp covered over the field. With drip irrigation, the field is also prepared in beds. The beds are covered with a plastic tarp

[1] http://www.epa.gov/scram001/guidance/guide/appw_05.pdf

[2] Available for download at: http://www.exponent.com/perfum/

[3] See EPA's websites for the relevant documents: http://www.epa.gov/oppsrrd1/reregistration/soil_fumigants/index.htm.

prior to application and the fumigant is applied through subsurface drip lines (see Figure 3). To date, Arysta has conducted two studies for flat fume (Manteca and Watsonville, CA), six studies for raised bed (Oxnard and Guadalupe, CA; Plant City and Dover, FL; Bainbridge, GA; Hart, MI), and three studies for drip irrigation (La Selva Beach, Camarillo, Guadalupe, CA). The three most recent studies (Bainbridge, Dover, and Hart) included the application of Midas®50:50 which is a mixture of chloropicrin and iodomethane in equal quantities by weight. The first eight studies were iodomethane applications.

All of the application methods used plastic tarps to cover the field before or immediately after field application. The tarps limit the migration of fumigant gas from the field, thus reducing the flux rates and downwind air exposures while increasing the efficacy of the product by keeping it in the ground longer.

The first eight studies all employed High Density Polyethylene (HDPE) tarps (i.e., a standard plastic). The last three studies used highly retentive tarps that allow less penetration of iodomethane through the tarps and into the atmosphere. These studies also used the Symmetry® application method, which leads to reduced emissions due to automatic shank shut-off, zero shank tip leakage, and a better covering of the shank trace. The field areas in the studies ranged from 0.4-2.5 acres. The target application rate ranged from 150-235 lbs iodomethane/treated acre for the eight studies with only iodomethane. The target application rate for the Midas 50:50 studies was 150 lbs/acre, including 75 lbs of iodomethane/acre and 75 lbs of chloropicrin/acre.

Figure 1. Example of a flat fume application

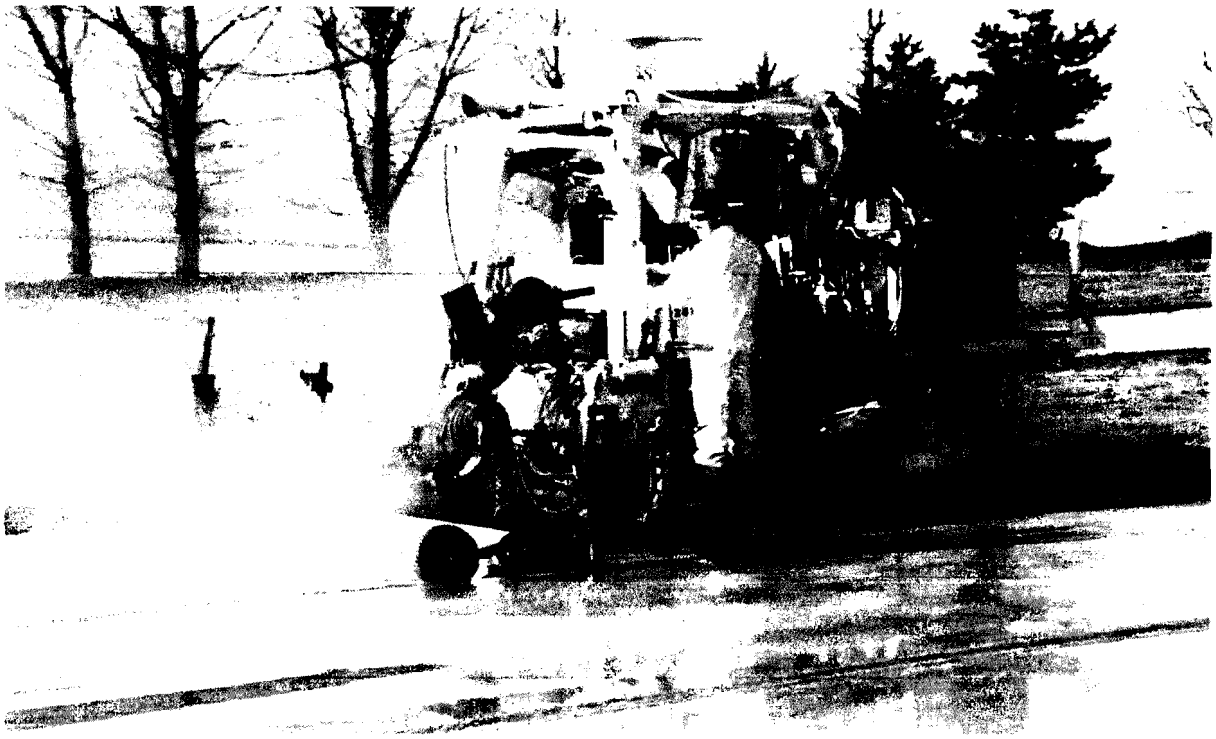


Figure 2. Example of a raised bed application

Figure 3. Example of a drip irrigation application

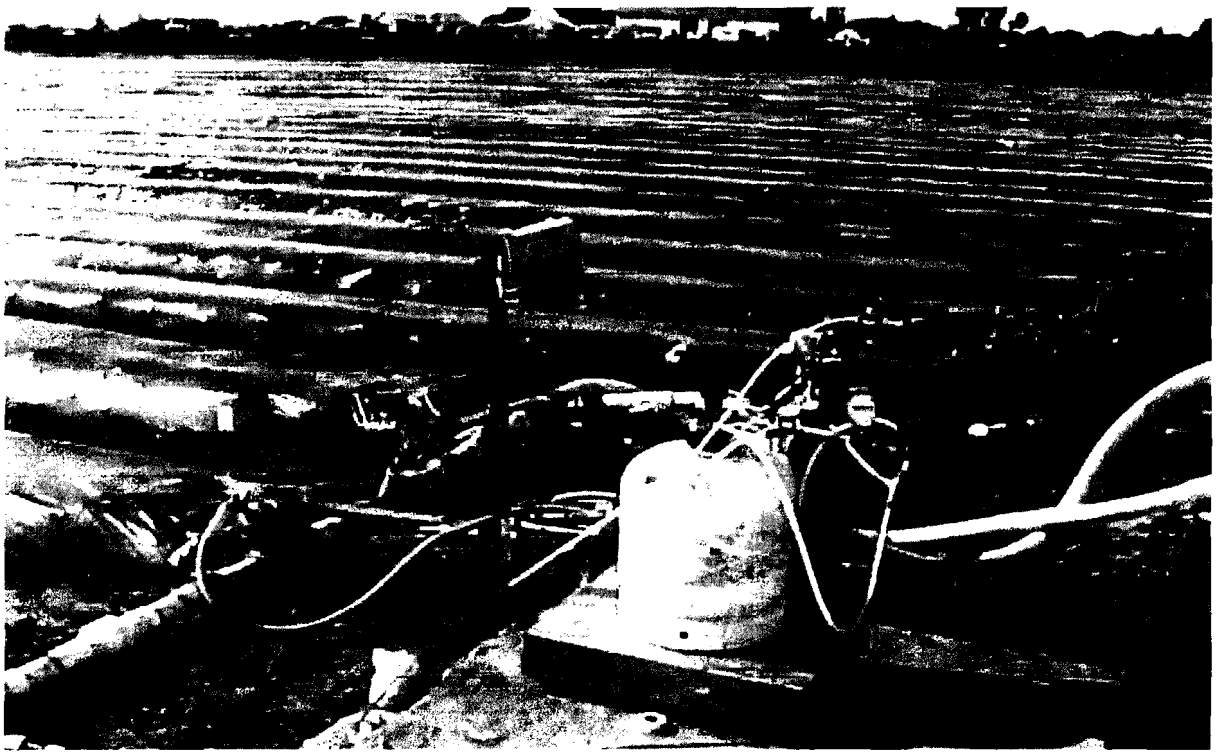


Table 1 below summarizes the estimated mass loss over the first 24-hours and the entire monitoring period (1-2 weeks) for each study. For the iodomethane studies with standard HDPE tarps, the mass loss over the first 24-hours ranged from 35-71%. For the Midas®50:50 studies with highly retentive tarps, the mass loss over the first 24-hours ranged from 3.8-12% depending on the study and estimation technique.

DPR did not use the Plant City, Florida raised bed study in the draft RCD, perhaps because it was conducted outside of California. However, it clearly provides similar results to the Oxnard and Guadalupe-I, California-based raised bed studies. Therefore, there was no reason for DPR to exclude studies conducted outside of California.

Table 1. Mass loss of iodomethane in the flux studies

| Location | Type of Application | Mass Loss (Direct/Indirect) | |
|---|---|---|---|
| | | 24-Hours | Monitoring Period |
| Manteca, CA | Flat fume | 48% / 51% | 93% |
| Watsonville, CA | | 35% | 57% |
| Guadalupe-I, CA | Raised bed | 60% | 96% |
| Oxnard, CA | | 54% | 102% |
| Plant City, FL | | 56% | 71% |
| Dover, FL | Raised bed/ low permeability tarp and Symmetry® application rig | 5.7% / 12% | 14% / 29% |
| Bainbridge, GA | | 7.2% / 8.4% | 17% / 23% |
| Hart, MI | | 3.8% / 5.0% | 24% / 33% |
| Camarillo, CA | Drip irrigation | 50% | 83% |
| La Selva Beach, CA | | 42% | 62% |
| Guadalupe II, CA | | 71% | 100% |

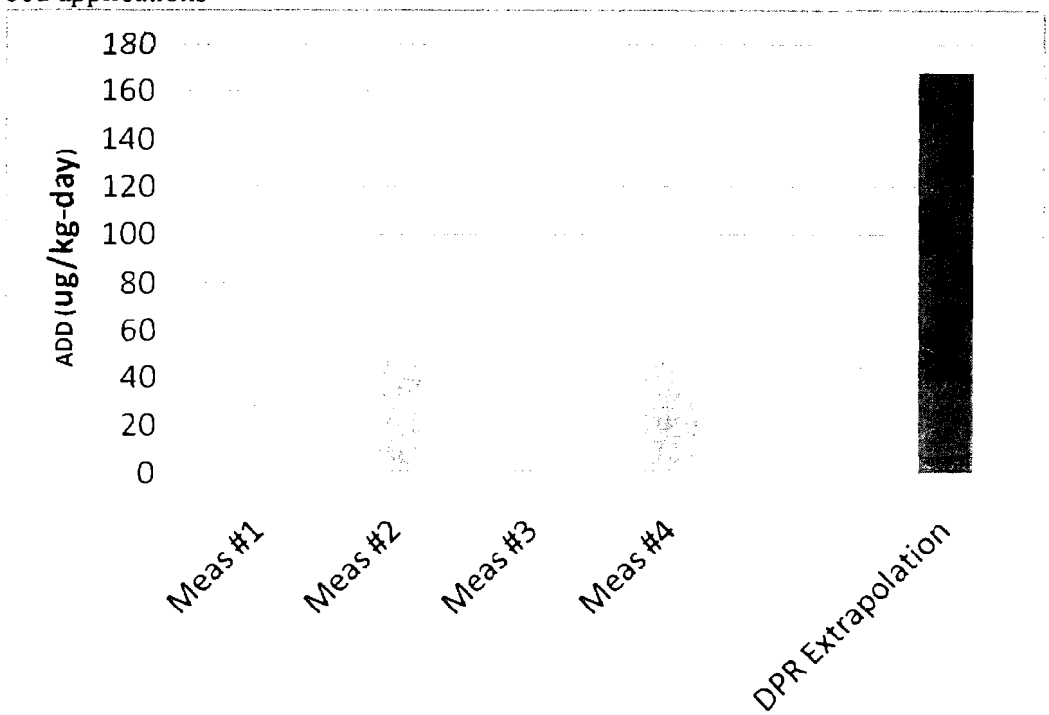
DPR's methodology for extrapolating upper-bound air concentrations for applicator exposure

A subset of the flux studies included measurements of the exposures to workers, including the Oxnard (raised bed), Guadalupe-I (raised bed), La Selva Beach (drip irrigation), Camarillo (drip irrigation), Guadalupe-II (drip irrigation), and Manteca (flat fume). These studies included personal exposure measurements for applicators, drivers, hole punchers, planters, shovelers, tarp cutters, tarp removers, and tarp monitors, depending on the study. These measurements included the full complement of individuals that may be involved in applying iodomethane and provide a large dataset for risk assessment. The DPR RCD provides a complete summary of the worker data.

DPR applied an overly conservative methodology to estimate exposures for workers applying iodomethane. Arysta has provided six occupational exposure field studies with multiple measurements of worker tasks in each study. The U.S. EPA estimated occupational risks with the average and maximum value for each of the worker tasks. Instead of applying this reasonable methodology, DPR developed an extrapolation method based on a lognormal distribution in an attempt to estimate a 95$^{th}$ percentile value. Given that there are less than 20 measurements for the occupational exposure scenarios, DPR's exposure estimates are higher than the maximum measured value in every case, sometimes by more than a factor of three. DPR provides no justification for its assumption of a log-normal distribution.

For example, for drivers and applicators in the shallow-shank, tarped-bed injection studies, the four measured values from the occupational exposure studies were 8.7, 46.9, 2.1, and 47.3 μg/kg-day. DPR applied its extrapolation procedure to these four data points to estimate a 95$^{th}$ percentile value, which resulted in 168 μg/kg-day. These values are summarized in Figure 4. Thus, in this case, the value DPR used for risk assessment is 3.6 times higher than any measured value.

Figure 4. Measured and extrapolated absorbed daily dose values for drivers and applicators for tarped bed applications




DPR's bystander exposure estimates using peak-to-mean extrapolations

DPR estimated "seasonal" exposure by calculating a 2-week average concentration for someone continually living at 152 meters from the edge of the treated field following an application. This assumption seems particularly unlikely. Over the course of a 2-week period, even someone that by chance lives right at 152 meters from the edge of the field will go other places, such as work or school or to other places for recreation or to run errands. Furthermore, DPR's methodology for estimating the 2-week average concentration is based on something DPR calls "peak-to-mean" theory. The peak-to-mean theory is based on measurements made in the 1950-1960s of the variability in air pollution concentrations at sampling points downwind of continuously-emitting smoke stacks. For fumigants, the emissions are not continuous and the source is more widely dispersed (an area source versus a point source for a smoke stack). In fact, CDPR acknowledges that this theory may overestimate concentrations for an area source[4]. The basis for the peak-to-mean formula is that plumes tend to meander due to small changes in the wind direction. Therefore, a given sampling point may be exposed to the centerline of the plume (peak concentration) one moment and to the tail of the plume at another point in time. Thus, it is essentially the greater variability in wind direction over longer time periods that is the basis for the peak-to-mean theory.

In contrast, the emission rates for iodomethane dramatically decline after the first 24-hours after the application, as evidenced in all of the flux studies. Therefore, the primary reason

[4] Barry, T. (2002) Peak-to-mean air concentration estimation for fumigants. DPR internal memorandum

for lower concentrations over a 2-week period is the reduction in the emission rate. Peak-to-mean theory is used to estimate the impact of variability due to changes in the wind direction and the looping of the plume. Therefore, it was misapplied to estimate seasonal exposures by DPR.

The most appropriate way to estimate a long-term average concentration is to use a dispersion model, such as PERFUM, with historical meteorological data. This would allow one to account for changing wind directions and wind speed instead of just assuming low wind speed and a constant wind direction.

I. D. DPR's overly conservative approach to assessment of iodomethane toxicity and exposure

One key advantage to approaching risk characterization through the use of mechanistic information is the refinement in risk assessors ability to predict exposure levels that are meaningful for toxicity and the threshold below which effects will not occur. Regulating exposures to extra-ordinary levels below the effect threshold for the exposed population does not increase safety. In the draft risk characterization for iodomethane, DPR has used overly conservative assumptions which are not necessary to protect public health. Examples of these overly conservative approaches have been identified in the introduction to Section I but also include:

1. Using a respiration rate in iodomethane-exposed rabbits which produced an approximately 70% increase in iodide dose estimation over that predicted by the iodomethane PBPK Model;
2. DPR assumed all rat respiratory cells are impaired at 25% reduction of GSH levels when others (Frederick et al., 1992; Plopper et al., 2001; Lee et al., 2005) showed that respiratory cells can withstand 50-90% reduction in GSH. This leads to an overestimation of the target tissue dose of iodomethane. As a result, critical NOAELS, and HEC values, for acute toxicity were underestimated by DPR:

   Nasal Epithelial cell degeneration in rats:
   Arysta HEC = 4.5 ppm
   DPR HEC = 2.2 ppm

   Transient neurotoxicity in rats
   Arysta HEC = 10 ppm
   DPR HEC = 3.4 ppm

   Developmental toxicity in rabbits
   Arysta HEC = 7.4 ppm
   DPR HEC = 0.24 ppm.

3. Arysta measured air values for applicators at a treated field which ranged from 2.1 to 47.3 μg/kg/day. DPR used these data to extrapolate to an upper-bound estimate (95th percentile level) of the four measured air concentrations to derive an upper bound estimate of 168 μg/kg/day – a value 3.5-fold greater than the highest measured value in the data set.
4. DPR assumed that application workers are in the field 8 hrs/day, 7 days/week for 3 months when they are not. DPR used flux data generated from an incomplete application, i.e., an application that was still underway when the air samples DPR evaluated were collected.

DPR calculated inflated field flux rates:

| | Flux Rate calculated using all field data | DPR calculation |
|---|---|---|
| 1-hr | 151 $\mu g/m^2$ | 535 $\mu g/m^2$ |
| 8-hr | 134 $\mu g/m^2$ | 266$\mu g/m^2$ |
| 24-hr | 131 $\mu g/m^2$ | 187 $\mu g/m^2$ |

5. As pointed out in section I.C., validated probabilistic models for estimating air concentrations are available for these estimates. However, DPR relied on deterministic models and assumed constant worst case constant meteorological conditions to estimate fumigant concentrations downwind from a treated field, e.g.,
   - 1 and 8 hr peak: constant wind speed on 1m/sec at a constant direction
   - 24 hr peak: constant wind speed on 1.4m/sec at a constant direction;
6. One meter per second is the lowest value the DPR dispersion model will accept. DPR assumed that bystanders living near a treated field remain at the same location 152 meters from the field for 14 days instead of considering intermittent bystander exposure.
7. DPR assumed that methyl bromide could be a suitable surrogate for airborne iodomethane. This is an invalid assumption. Airborne methyl bromide is long-lived; iodomethane remains in the atmosphere less than 0.1% of the time methyl bromide remains in the atmosphere.

Overall, the assumptions DPR chose to use in the risk characterization for iodomethane overstate risk by approximately 30-fold or greater.

## II. BRIEF NARRATIVE OF IODOMETHANE TOXICOLOGY

Iodomethane has been thoroughly studied and has a robust data base to describe effects of overexposure as well as offer mechanistic insight for these effects. The data base allows for a clear delineation of effect and no-effect levels, which, in turn, permit confident estimates of safe exposure levels for each exposure scenario of concern with soil fumigant use.

Acute Toxicity Overview.

Undiluted iodomethane has a moderate to severe acute toxicity profile. It is moderately toxic via the oral route (Toxicity Category II, acute oral LD50 = 79.8 mg/kg in males and 131.9 mg/kg in females), severely corrosive to the eye (Toxicity Category I) and a moderate dermal irritant (Toxicity Category II). Via the inhalation route, it has been classified as a Category IV (slightly toxic) with an $LC_{50}$ of 4 mg/L. The critical effects of acute duration iodomethane exposure are: 1) fetal losses observed in a developmental toxicity study in rabbits, 2) histopathologic lesions in the nasal epithelium reported in rats, and 3) transient neurotoxicity observed in rats.

An acute inhalation neurotoxicity was performed in rats. Whole body exposures were 0, 27, 93, and 401 ppm for 6 hours. The systemic NOAEL was 27 ppm, and the systemic LOAEL was 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 were not assessed.

Iodomethane metabolism was studied in Sprague-Dawley rats. The test animals were

orally dosed at 1.5 or 24 mg/kg or exposed by inhalation to 25 or 233 ppm [$^{14}C$] $CH_3I$. 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. Recovered radioactivity was primarily as $CO_2$ (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 $time_2$ was 5.8-6.8 hours for $CO_2$ in all treatment groups of the supplementary test. A first-pass hepatic effect appeared to occur following bolus oral dosing.

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. The major metabolites were expired $CO_2$, 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.

Repeated-dose Toxicity Overview.

The most likely route of human exposure to iodomethane is inhalation and the pattern of toxicity attributed to iodomethane exposure via the inhalation route includes developmental toxicity (manifested in rabbits as late stage fetal losses and decreased live births) and 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).

Rats were exposed to 5, 21, or 70 ppm in a whole-body chamber, 6 h/day, 5 days/week for 4 weeks (interim sacrifice) or 13 weeks. The NOAEL was 21 ppm (0.12 mg/L/day) and the LOAEL was 70 ppm (0.41 mg/L/day) based on initial decreases in body weights, body weight gains, and food consumption (males); and nasal degeneration.

Mice received oral exposure to 0, 133, 400 or 1200 ppm iodomethane microencapsulated in the diet. Increased thyroid weights, accumulation of follicular colloid, hyperkeratosis of esophagus was observed at the lowest dose tested, 133 ppm group. The NOAEL was 133 ppm based on adaptive response of thyroid and decreased body weight less than 10% with corresponding decreased food consumption.

Developmental toxicity and reproductive function testing has been conducted with iodomethane by the inhalation route. A rat inhalation developmental toxicity was completed at 0, 5, 20, 60 ppm in a whole-body inhalation chamber. Exposures were 6 h/day on GDs 6-19. The maternal NOAEL was 20 ppm (0.12 mg/L/day) and the maternal LOAEL was 60 ppm (0.35 mg/L/day) based on decreased body weight gain (919%; 95-6% absolute body weight). The developmental NOAEL was 60 ppm (0.35 mg/L/day) and a developmental LOAEL was not observed.

An inhalation developmental toxicity study was also conducted in rabbits. Exposures were 0, 2, 10, or 20 ppm in a whole-body inhalation chamber, 6 h/day, on GDs 6-28. The maternal NOAEL was 20 ppm and a maternal LOAELwas not identified. The developmental NOAEL was 10 ppm and the developmental LOAEL was20 ppm based on increased fetal losses and decreased fetal weights (20%).

An inhalation phased-exposure developmental toxicity study was also conducted in rabbits at 0 or 20 ppm from GD6-28. Exposure were 20 ppm from GDs 6-14, 15-22, 23-24, 25-26, or 27-28 in a whole-body inhalation chamber 6hrs/day. The study was not intended to fulfill a 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. No maternal or developmental toxicity was observed for females exposed during gestation days 6-14, 15-22, or 27-28. An increase in late resorptions with or without a corresp0onding decrease in the number of viable fetuses was noted for females exposed during gestation days 6-28, 23-24 and 25-26. At exposure to 20 ppm airborne iodomethane, the critical window for developmental toxicity in rabbits was GD 23-26.

Reproductive function was studies in rats exposure to 0, 5, 20, or 50 ppm iodomethane in whole body inhalation chambers. The study tested two generations of rats. Offspring were not directly exposed to iodomethane vapor until PND 28. The parental systemic NOAEL was 20 ppm and the parental systemic LOAEL was 50 ppm based on decreased body weight gain, body weight, organ weight changes, gross pathology, and histopathology findings.
The portal of entry NOAEL was 20 ppm and the portal of entry LOAEL was 50 ppm based on degeneration of the olfactory epithelium. Offspring NOAEL was 5 ppm and offspring LOAEL was 20 ppm. Overall, based on decreases in body weight gain, body weight, and thymus weights the reproductive NOAEL was 5 ppm and the reproductive LOAEL = 20 ppm based on delays in vaginal patency.

Carcinogenicity and Genetic Toxicity Overview.

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 was established by the EPA Office of Pesticide Program's (OPP) Health Effects Division (HED) as the operative mode of action (MOA) for this tumorigenic response. As a result, EPA 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. Arysta suggests that a standard hazard descriptor from the Revised Guidelines for Carcinogen Risk Assessment should be adopted by EPA OPP to describe the findings by the CARC group (EPA, 2005). Arysta recommends the classification: Not Likely to Be Carcinogenic to Humans.

Arysta has used several lines of research and analysis to investigate and characterize the potential carcinogenicity and risks posed by chronic exposure to iodomethane. Arysta sponsored long-term iodomethane exposure studies in rats and mice as part of the data package submitted to support registration. The two chronic studies were: 1) a 2-year inhalation study in male and female rats (Kirkpatrick, 2005, DPR Doc. No. 52875-094), and 2) an 18-month dietary study (encapsulated iodomethane) in male and female mice (Harriman, 2005, DPR Doc. No. 52875-099). An increase in thyroid tumors compared to controls was observed in only the high-dose

groups of male rats (inhalation) and male mice (oral), which were statistically significant in male rats only. A slight increase in proliferative lesions of the uterus and cervix of female mice was observed in the 18-month study of mice exposed to microencapsulated iodomethane in the diet. In the dietary study, the number of female mice with fibromas present in the uterus or cervix was low, though the incidence was slightly increased in the high-dose group compared to controls.

The follicular cell thyroid tumors have been evaluated in detail and determined to result from chronic alterations in thyroid-pituitary function due to excessive iodide exposure. Rodents are particularly sensitive to this non genotoxic mode of thyroid tumor development. Arysta generated mechanistic data to examine the effects of iodomethane on thyroid and pituitary hormones in rats, and performed a critical review of all available genotoxicity studies of iodomethane.

The proliferative lesions in the uterus and cervix in female mice was evaluated by a Pathology Working Group (PWG) that provided a final diagnosis for the lesions as fibromas that they determined were not associated with iodomethane treatment (Hardisty, 2005). Early carcinogenicity studies on iodomethane provide inadequate information and are inappropriate for assessing the carcinogenicity of iodomethane as determined by authoritative bodies (e.g., NTP). Based on a thorough evaluation of the data that is summarized below, Arysta recommends the classification for iodomethane of Not Likely to Be Carcinogenic to Humans.

Thyroid Tumor Evaluation

The EPA Risk Assessment Forum (RAF) developed guidance for interpretation of thyroid follicular cell tumors in rodents (U.S. EPA, 1998). The EPA RAF guidance for interpretation of thyroid follicular cell tumors in rodents identified three types of follicular cell tumors: those that result from alterations in thyroid-pituitary function, those that result from mutagenic changes in the DNA of the thyroid, and those that result from a combination of altered thyroid pituitary function and genotoxicity (U.S. EPA, 1998). Alterations in thyroid-pituitary function that result in follicular cell tumors in rodents are characterized by a chronic reduction in circulating thyroid hormones and an increase in thyroid stimulating hormone (TSH). The RAF recommends that a margin of exposure (MOE) or similar procedure based on nonlinearity of effects be used to conduct a risk assessment of thyroid tumors when the sole mode of action is alterations in pituitary and thyroid hormones.

An evaluation of the thyroid follicular cell tumors based on the RAF criteria identified in rodents following chronic iodomethane exposure indicated that the sole mode of action causing these tumors is alteration of pituitary and thyroid hormone levels. The mode of action was characterized based on data from the chronic rat study and additional short-term studies performed on iodomethane. A summary of the evaluation is presented in this document.

Follicular Tumor Data

In the chronic rat exposure study, groups of 60-70 rats/sex/group were exposed via inhalation to 0, 5, 20, or 60 ppm iodomethane for 6 hours/day, 5 days/week for 104 weeks. Exposure of rats to iodomethane for two years resulted in a significant increase in benign thyroid follicular cell adenoma in the high dose group of males only. No significant increases in thyroid gland carcinoma were observed in male rats, and no increases in tumor rates were observed among female rats. Neoplastic changes in the thyroids of high dose male rats were accompanied by non-neoplastic changes including alterations in thyroid and pituitary hormone levels, follicular cell hyperplasia and cytoplasmic vacuolation, and increased thyroid weight at the 52-

week sacrifice. Females appeared less sensitive to the thyroid effects from iodomethane exposure than males, based on smaller changes in thyroid hormone levels in exposed rats compared to controls and a lower incidence of histomorphologic findings. Incidences of thyroid tumors observed among male rats exposed for life are shown in Table 2.

Table 2. Thyroid follicular cell tumors among male Fisher F344 rats treated with iodomethane via inhalation for two years (Kirkpatrick, 2005).

| Ppm | 0 | 5 | 20 | 60 | trend[1] |
|---|---|---|---|---|---|
| Adenoma | 2/60 | 2/60 | 4/60 | 13/70* | p<0.001 |
| Carcinoma | 2/60 | 0/60 | 0/60 | 4/70 | NS |
| Adenoma or carcinoma | 4/60 | 2/60 | 4/60 | 15/70* | p<0.001 |

NS, not significant
* Significantly different from controls in pair-wise comparisons with controls (Fischer Exact Test), p<0.01.
[1] one-sided trend test

Male and female CD-1 mice received encapsulated iodomethane in the diet for 18-months, resulting in a slight increase in a combined incidence of thyroid follicular cell tumors (benign and malignant combined) among male mice, significant by trend test only (Table 3).

Table 3. Thyroid follicular cell tumors among male CD-1 mice treated with microencapsulated iodomethane in the diet for 18 months (Harriman 2005).

| Ppm | 0 | 5 | 20 | 60 | trend[1] |
|---|---|---|---|---|---|
| mg/kg-d | 0 | 8 | 28 | 84 | |
| Adenoma or carcinoma | 0/50 | 0/50 | 1/50 | 3/49 | p=0.0184 |

[1] one-sided trend test

Thyroid mechanistic data

A full evaluation of the mechanistic data examining the iodomethane-induced perturbation of thyroid hormones is described in a risk assessment of the rat thyroid tumors submitted to DPR and EPA (Mileson et al., 2005, MRID # 46512402). Mechanistic data were compared to criteria described in EPA guidance for interpretation of thyroid follicular cell tumors in rodents (Risk Assessment Forum, (RAF) 1998, EPA/630/R-97/002).

The EPA RAF guidance for interpretation of thyroid follicular cell tumors in rodents identified three types of follicular cell tumors: those that result from alterations in thyroid-pituitary function, those that result from mutagenic changes in the DNA of the thyroid, and those that result from a combination of altered thyroid pituitary function and genotoxicity (U.S. EPA, 1998). Alterations in thyroid-pituitary function that result in follicular cell tumors in rodents are characterized by a chronic reduction in circulating thyroid hormones and an increase in TSH. The RAF recommends that a margin of exposure (MOE) or similar procedure based on nonlinearity of effects be used to conduct a risk assessment of thyroid tumors when the sole mode of action is alterations in pituitary and thyroid hormones.

Collectively, the mechanistic data indicate that iodomethane exerts actions via elevated iodide centrally on the thyroid to decrease circulating thyroid hormone levels, resulting in an increase in circulating TSH, which stimulates follicular cell hyperplasia and other proliferative lesions in rodents. In the male rat and male mouse carcinogenicity studies, the dose levels that

caused significant thyroid hormone perturbation (i.e., the high dose groups) were the same doses that stimulated increased tumor formation. The available data indicate that a mechanism of thyroid-hormone perturbation is operative for iodomethane.

In order to determine whether thyroid follicular cell tumors that occur in a rodent study are the result of alterations in the thyroid pituitary function or genotoxicity, mechanistic data identified by the RAF were evaluated. Included in the mechanistic data evaluated are: 1) knowledge of how and where the chemical affects thyroid function (including changes in thyroid and pituitary hormone levels), 2) reversibility of effects when test article exposure ceases, 3) progression of follicular changes following prolonged exposure, 4) characterization of potential genotoxicity, 5) effects of exposure to compounds of similar structure, and 6) correlations between doses that produce thyroid effects and tumors.

Briefly, statistically significant effects on pituitary and thyroid hormone levels of male and female rats in the chronic inhalation exposure study were observed only in the high dose groups (Tables 4 and 5) (Kirkpatrick, 2005). Serum thyroid stimulating hormone (TSH) levels were elevated above controls in male rats exposed to 60 ppm at the 26-, 52-, and 104-week time points, though the differences were statistically significant only at week 26 and 104. After 26 weeks of exposure, circulating TSH levels increased from 2.46 μg/ml in controls to 30.53 μg/ml in the 60 ppm-exposed males, an increase greater than 12-fold. This increase in TSH level was dose-dependant; an increase in TSH level was observed in the 20 ppm-exposed males at the same time point but this increase was not statistically significant. The data on rat thyroid weights and morphology following chronic exposure to iodomethane demonstrate that iodomethane has a specific effect on the rat thyroid, increasing thyroid size through stimulation of cellular hyperplasia.

Table 4. Summary of Thyroid hormone data from WIL-418019M, 24-Month Inhalation Study of Iodomethane In Rats (Males)

| Analysis Group: | 0 PPM | 5 PPM | 20 PPM | 60 PPM |
|---|---|---|---|---|
| TOTAL T3 (ng/dL) | | | | |
| WEEK 26 | 57.50±5.8 | 51.40±18.6 | 57.12±21.2 | 38.08±16.3 |
| WEEK 52 | 43.23±11.4 | 38.95±15.6 | 51.34±40.4 | 38.29±11.4 |
| WEEK 104 | 49.79±21.0 | 52.77±21.0 | 50.01± 20.8 | 44.28±15.9 |
| | | | | |
| TOTAL T4 (ug/dL) | | | | |
| WEEK 26 | 3.87±1.0 | 3.38±0.4 | 3.24±0.5 | 1.71±1.4** |
| WEEK 52 | 2.56±0.8 | 2.45±0.9 | 3.44±0.7 | 3.42±0.8* |
| WEEK 104 | 2.25±0.7 | 2.27±0.7 | 2.24±1.0 | 2.50±0.6 |
| | | | | |
| TSH (ug/mL) | | | | |
| WEEK 26 | 2.46±1.2 | 3.78±1.9 | 4.92±3.9 | 30.53±13.7** |
| WEEK 52 | 2.25±0.9 | 2.26±0.6 | 3.60±2.8 | 9.11±11.4 |
| WEEK 104 | 2.38±1.1 | 3.29±1.6 | 3.48±1.8 | 11.29±14.9** |
| | | | | |
| REVERSE T3 (ng/dL) | | | | |
| WEEK 26 | 0.13 ±0.05 | 0.12 ±0.05 | 0.11 ±0.05 | 0.15 ±0.03 |
| WEEK 52 | 0.09±0.03 | 0.09 ± 0.05 | 0.09 ± 0.04 | 0.19 ± 0.05** |
| WEEK 104 | 0.03 ±0.03 | 0.04 ±0.03 | 0.04 ± 0.03 | 0.07 ± 0.05** |

ug/dL = micrograms/deciliter, ng/dL = nangrams/deciliter, ug/mL = micrograms/milliliter

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Week 26 and 52 total T3 and reverse T3 compared using the Kruskal-Wallis test
All total T4 and TSH and week 104 total T3 and reverse T3 compared using Dunnett's test
* = Significantly different from the control group at 0.05
** = Significantly different from the control group at 0.01

Table 5. Summary of Thyroid hormone data from WIL-418019M, 24-Month Inhalation Study of Iodomethane in Rats (Females)

| Analysis Group: | 0 PPM | 5 PPM | 20 PPM | 60 PPM |
|---|---|---|---|---|
| TOTAL T3 (ng/dL) | | | | |
| WEEK 26 | 67.54±28.3 | 55.38±17.1 | 80.12±21.9 | 49.44±19.7 |
| WEEK 52 | 81.78±33.1 | 78.70±20.5 | 60.10 ±9.8 | 72.55±15.7 |
| WEEK 104 | 72.72±32.4 | 70.90±19.3 | 65.93±24.0 | 64.82±22.2 |
| TOTAL T4 (ug/dL) | | | | |
| WEEK 26 | 2.03±0.6 | 1.68±0.6 | 1.93±0.5 | 1.78±0.7 |
| WEEK 52 | 2.02±0.3 | 2.16±0.4 | 1.74±0.3 | 2.23±0.6 |
| WEEK 104 | 1.55±1.0 | 1.56±0.7 | 1.96±0.8 | 2.47±1.0** |
| TSH (ug/mL) | | | | |
| WEEK 26 | 1.76±0.6 | 1.76±0.5 | 2.09±0.7 | 12.92±13.4** |
| WEEK 52 | 2.61±0.7 | 3.33±1.9 | 2.87±1.3 | 5.49±6.4 |
| WEEK 104 | 2.52±1.0 | 2.93±1.8 | 3.78±2.9 | 3.98±6.3 |
| REVERSE T3 (ng/dL) | | | | |
| WEEK 26 | 0.10±0.05 | 0.11±0.03 | 0.15±0.05 | 0.19±0.09 |
| WEEK 52 | 0.12±0.04 | 0.14±0.06 | 0.09±0.02 | 0.33±0.16** |
| WEEK 104 | 0.05±0.03 | 0.09±0.04 | 0.20±0.12** | 0.24±0.12** |

ug/dL = micrograms/deciliter, ng/dL = nangrams/deciliter, ug/mL = micrograms/milliliter

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** = Significantly different from the control group at 0.01 using Dunnett's test

Additional thyroid-pituitary hormone data are available from a 2-day iodomethane exposure study in male rats (Table 6) (Himmelstein, 2005). In this study rats were exposed to 25 or 100 ppm iodomethane 6 hours/day for 2 days, and thyroid and pituitary hormone levels were measured 18 hours after the second day of exposure. Circulating TSH levels were increased significantly in a dose-dependant manner compared to controls in both exposure groups. Circulating triiodothironine (T3) and thyroxin (T4) levels were reduced in the 25 ppm exposed group, and the decreases reached statistical significance in the 100 ppm exposed group. The hormone changes observed in short-term and chronic rat exposure studies, and the alterations in thyroid weight and histology following chronic exposure, provide unequivocal evidence that iodomethane influences thyroid-pituitary function.

The action of iodomethane on the rat thyroid was identified as an effect due to iodide based (at least in part) on data from the 2-day exposure study in male rats and an understanding of the effects of iodide on thyroid function (Table 6) (Himmelstein, 2005). Exposure to iodomethane increases serum iodide level, and this increase in iodide is known to have a direct action on the thyroid function. A second potential site of iodomethane action on thyroid-pituitary function evaluated by Arysta (and discounted) is altered thyroid hormone metabolism in the peripheral tissues. In the short-term exposure study on male rats, two endpoints were measured to determine whether iodomethane exposure alters the metabolism and clearance of T4

(Himmelstein, 2005). The liver enzyme UDP-glucuronyltransferase (UDPGT), which inactivates T4 by conjugation, was measured, and reverse T3 (rT3), the inactive form of T3, which may result from deiodination of T4, were measured in rats exposed to 25 or 100 ppm iodomethane (Table 6). UDPGT and rT3 were unchanged compared to controls following 2 days of exposure to iodomethane. The lack of effects on UDPGT and rT3 in male rats exposed to iodomethane for 2 days indicates that T4 metabolism is not the primary site of iodomethane action on the thyroid-pituitary axis.

Table 6. Mean thyroid and pituitary hormone concentrations and UDP-glucuronyltransferase activity

| Analysis Group: | 0 PPM | 25 PPM | 100 PPM |
|---|---|---|---|
| TOTAL T3 (ng/dL)[a] | 74.1 ± 11.4 | 65.9 ± 9.2 | 50.8 ± 14.4[d,e] |
| | | | |
| TOTAL T4 (ug/dL)[a] | 3.4 ± 0.5 | 3.1 ± 0.8 | 2.1 ± 0.9[d,e] |
| | | | |
| TSH (ng/mL)[a] | 5.9 ± 1.4 | 10.9 ± 7.7[c,d] | 21.1 ± 11.2[c,d] |
| | | | |
| REVERSE T3 (ng/mL)[a] | 0.067 ± 0.049 | 0.119 ± 0.024 | 0.039 ± 0.037[f] |
| | | | |
| UDPGT (nmol/min/mg)[b] | 16.1 ± 3.1 | 17.5 ± 2.0 | 17.8 ± 4.8 |

a Mean ± standard deviation. The n = 10 for each group unless otherwise noted.
b The n = 5 per group.
c Statistically significant difference from control ($p < 0.05$) by Dunn's test.
d Statistically significant difference from control ($p < 0.05$) by Jonckheere-Terpstra trend test.
e Statistically significant difference from control ($p < 0.05$) by Dunnett's test.
f The n = 9 per group.

Table 7. Mean inorganic serum iodide concentration data for main inhalation exposures. Exposure paradigm was 6 hours/day for 2 days, beginning at hour 0 the first day and hour 24 on the second day (Himmelstein, DuPont, 14998, 2005).

| Inorganic Serum Iodide Concentration (ng/mL) by Exposure Concentration (ppm) | | | |
|---|---|---|---|
| Collection time (hour) | 0 ppm | 25 ppm | 100 ppm |
| 0 | 17 ± NA | NA ± NA | NA ± NA |
| 1 | 17 ± NA | 5,070 ± 721 | 22,900 ± 1,620 |
| 3 | 19 ± NA | 9,510 ± 3,800 | 60,300 ± 2,860 |
| 6 | 22 ± NA | 25,600 ± 1,940 | 53,800 ± 4,480 |
| 9 | 39 ± NA | 18,400 ± 1,550 | 52,500 ± 8,230 |
| 24 | 19 ± NA | 1,260 ± 83.9 | 8,170 ± 1,850 |
| 25 | 14 ± NA | 5,960 ± 576 | 27,200 ± 13,700 |
| 27 | 14 ± NA | 10,800 ± 1,100 | 55,200 ± 3,050 |
| 30 | 4.1 ± NA | 34,100 ± 8,170 | 83,200 ± 7,840 |
| 33 | 13 ± NA | 24,700 ± 1,310 | 58,300 ± 6,520 |
| 48 | 14 ± NA | 742 ± 141 | 4,500 ± 396 |
| 0-48 | 17 ± 9 | NA ± NA | NA ± NA |

The rapid increases in serum iodide and the lack of an effect on UDPGT and rT3 following iodomethane exposure support the position that iodide is the active metabolite of iodomethane that alters the thyroid-pituitary function in male rats. Iodide is essential for normal thyroid function, but iodide deficiency and excess both inhibit thyroid function (Ganong, 2003). The effects of excess iodide on the thyroid are well documented because pharmacologic doses of iodides were the original antithyroid agents used clinically to treat hyperthyroidism before development of thioamide drugs for that purpose (Greenspan et al., 2004). The primary action of high doses of iodide is inhibition of thyroid hormone production and release.

The dramatic increase in serum iodide following iodomethane exposure, followed by alterations on the thyroid and pituitary hormones characteristic of exposure to excess iodide, suggest that iodide released by metabolism of iodomethane acts directly on the thyroid to reduce hormone release and thereby alter the function of the thyroid-pituitary axis.

Reversibility of thyroid effects

The effects of iodomethane on the thyroid are reversible after short-term exposure. Reversibility of the effects of iodomethane on the thyroid that ultimately result in tumor formation can be evaluated based on data from short-term studies conducted in rats, and the known effects of excess iodide on thyroid function. The putative active metabolite of iodomethane responsible for alterations in thyroid-pituitary function in rats is iodide. Serum iodide levels increased in a dose-dependant manner in rats exposed to 25 ppm or 100 ppm iodomethane, followed by rapid decrease after cessation of exposure. Thus the elevated serum iodide is readily reversed following termination of iodomethane exposure. Effects of iodide are reversible upon discontinuance (Greenspan et al., 2004).

Thyroid lesion progression

The histomorphological data from the chronic rat study provide evidence of thyroid lesion progression from primarily hyperplasia observed after 52 weeks of exposure to an increase in adenomas after 104 weeks of exposure (MRID 46512401, DPR Doc. No. 52875-081).

Structural similarity and potential thyroid carcinogenicity

Potential chronic toxicity and carcinogenicity of two iodinated compounds have been evaluated in rats following oral exposure and the results reported in the literature. The inorganic iodide salt, potassium iodide was administered to rats in drinking water, while the organic compound, iodinated glycerol was administered to rats daily by gavage (Takegawa et al., 2000; NTP, 1990). Chronic exposure of rats to iodinated glycerol resulted in an increase in thyroid follicular cell adenomas and an increase in squamous cell metaplasia in the salivary glands.

Dose correlations with thyroid effects

A clear dose-response effect is observed in serum iodide level, alterations in thyroid hormone levels, thyroid histomorphology, and the thyroid follicular cell tumor incidence in male rats exposed to iodomethane. In male rats exposed to 25 ppm or 100 ppm iodomethane for 6 hours per day for 2 days serum iodide levels increased in a dose-dependant manner (Table 7). A dose response effect was observed in the circulating hormone levels in the chronic rat study, such that no significant changes in thyroid or pituitary hormone levels were identified in male rats exposed to 5 or 20 ppm iodomethane compared to controls, but alterations in thyroid hormone levels were significant in rats exposed to 60 ppm iodomethane. A similar dose response pattern was observed in the thyroid follicular cell tumor incidence. Tumor incidence was elevated in the male rats exposed to 60 ppm iodomethane but not in the low and mid-dose groups compared to controls. Thyroid tumor incidence was elevated only in male rats exposed 60 ppm iodomethane, the only dose that produced significant changes in thyroid hormone levels (DPR Doc. No. 52875-081).

Thyroid tumor evaluation conclusion

The thyroid tumor response following chronic iodomethane exposure is mediated by the sustained stimulation of cell proliferation by TSH, consistent with the increase in thyroid follicular cell tumors. The data on thyroid weights and morphology following exposure to iodomethane demonstrate that iodomethane has a specific effect on the rat thyroid, increasing thyroid size through stimulation of cellular hyperplasia. Alterations in circulating thyroid and pituitary hormones observed in short-term and chronic studies provide unequivocal evidence that iodomethane exposure at high concentrations influences thyroid-pituitary function in rodents. Collectively the mechanistic data suggest that iodomethane metabolized to iodide exerts actions centrally on the thyroid gland rather than peripherally to decrease thyroid hormone levels. In addition, the data collected in vitro and in vivo confirm that genotoxicity is unlikely to be a mode of action and explanation for the thyroid tumors observed in male rats and mice in the lifetime exposure studies. The sole mode of action identified for the development of thyroid tumors in rats exposed to iodomethane is alterations in pituitary and thyroid hormones.

The EPA OPP 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. Arysta suggests that a standard hazard descriptor from the Revised Guidelines for Carcinogen Risk Assessment be adopted to describe the findings; Arysta recommends the classification: Not Likely to Be Carcinogenic to Humans.

Evaluation of cervix / uterine fibromas

A pathology peer review and a Pathology Working Group (PWG) review were convened to evaluate a slight increase in proliferative lesions of the uterus and cervix of female mice observed in the 18-month study of mice exposed to microencapsulated iodomethane in the diet (Hardisty, 2005). The purpose of the PWG review was to provide a final diagnosis for proliferative mesenchymal lesions involving the uterus and/or cervix in female mice, and to discuss the relationship to treatment and relevance for risk assessment.

In the chronic dietary iodomethane exposure study, the number of female mice with fibromas present in the uterus or cervix was low, though the incidence was slightly increased in the high-dose group compared to controls. The PWG concluded that the fibromas were not associated with iodomethane treatment due to the: 1) low incidence, 2) appearance only at the terminal sacrifice, 3) microscopic size, 4) the absence of precursor lesions or other evidence of a treatment-related response involving the uterus or cervix, and 5) benign appearance with complete lack of any evidence of progression. The apparent increase in fibromas in the high-dose group as compared to the control group was considered to be due to the absence of fibromas in the control group in this study rather than a treatment-related increase.

Evidence for carcinogenicity from the literature

Early carcinogenicity studies on iodomethane included subcutaneous and intraperitoneal injection studies (described in IARC, 1986). Injection of iodomethane test article in the animal would result in high local concentrations in the tissues that overwhelm the detoxification ability of the cells and result in significant necrosis as observed in the cell survival data from in vitro mutagenicity studies performed at high doses. In one study, iodomethane was injected intraperitoneally in Strain A mice, a strain that develops lung tumors by an early age. Iodomethane produced no statistically significant increases in tumor formation at any dose group (by pair-wise comparisons or two-sided trend test), whereas positive controls (urethane) resulted in high incidences of lung tumors. These data provide inadequate information and are inappropriate for assessing the carcinogenicity of iodomethane. Authoritative bodies (IARC and NTP) did not classify iodomethane carcinogenicity based on these data, due to inadequacy. We now have two chronic exposure studies conducted by appropriate routes of administration (rats by inhalation, and mice by dietary administration). These data, along with significant mechanistic data and new genotoxicity studies, demonstrate that iodomethane does not pose a carcinogenic hazard to humans. Arysta concludes that the standard hazard descriptor from the Revised Guidelines for Carcinogen Risk Assessment, Not Likely to Be Carcinogenic to Humans, be adopted to characterize iodomethane.

Evaluation of the evidence for a mutagenic mechanism for carcinogenicity

A critical review of all available genotoxicity studies of iodomethane, including both the current EPA guideline genotoxicity studies and those published in the open literature was submitted to EPA (Mileson and McDonald, 2005). This review compared the findings of genotoxicity under GLP testing procedures to the studies of iodomethane genotoxicity published

in the open literature. The review of the genotoxicity data concludes that iodomethane is not genotoxic following in vivo exposures. The data collected in vitro and in vivo confirm that genotoxicity is unlikely to be a mode of action and explanation for the thyroid tumors observed in male rats and mice in the lifetime exposure studies.

The potential genotoxicity of iodomethane was evaluated in four sets of studies conducted and submitted by Arysta LifeScience North America to support registration. The four studies were conducted with iodomethane technical according to OPPTS guidelines. Specific precautions were taken in each assay to ensure the test article did not volatilize to ensure accurate dosimetry within the test system. The findings in the current GLP studies show that iodomethane was negative in the bacterial reverse mutation assay (Ames assay) with a full complement of strains of Salmonella typhimurium and Escherichia coli. Iodomethane did not cause mammalian cell gene mutations in vitro. It did not cause an increase in numerical chromosome aberrations in Chinese hamster ovary cells in vitro, but it did increase structural chromosome aberrations. Iodomethane was negative in the in vivo bone marrow micronucleus assay in mice, thus iodomethane did not cause chromosome damage in the whole animal (Table 7).

Additional genotoxicity studies of iodomethane have been published in the open literature. Some published studies have reported positive findings of mutagenic and clastogenic activity in vitro at high concentrations of iodomethane. Older studies in the literature (1985 and earlier) are difficult to compare with the recent studies conducted according to EPA guidelines because the raw data are rarely provided and different strains of cells or reagents may have been used than are optimal for the assay. There are often methodological deficiencies in the older studies, such as the use of cytotoxic doses or experimental procedures intended to evaluate or improve a then novel screening assay. Most of the early published mutagenicity studies (conducted in 1970's and 1980's) that used iodomethane as a test article considered it to be a "known carcinogen" based on an evaluation from the International Agency for Research on Cancer (described in IARC, 1986) that recognized tumors at injection sites following subcutaneous dosing of iodomethane as positive for carcinogenicity. Thus, iodomethane was used in many cases as one of a battery of chemicals to evaluate and optimize new tests for genotoxicity to determine whether those tests could identify carcinogens, assuming that iodomethane would be positive for mutagenicity.

Each study identified in the literature that investigated the potential mutagenicity or genotoxicity of iodomethane is reviewed briefly below, and in detail in Mileson & McDonald (2005). In general, given the limitations of the published studies, they are not inconsistent with the findings of the current GLP studies (Table 8). The studies in the open literature show the following: (1) iodomethane induces clastogenic effects in mammalian cells in vitro but does not appear to induce mutations in bacteria or mammalian cells at non-cytotoxic doses. (2) Treatment of rats with radiolabeled iodomethane resulted in measurable levels of radioactivity associated with methylated DNA bases; however, GC-MS analysis confirmed that the radiolabeled carbon atom was incorporated into the DNA base (from de novo synthesis) and not the result of direct methylation of DNA.

Bacteria and yeast

In addition to the battery of bacterial mutagenicity tests run under current guidance and GLP procedures (Wagner & Dakoulas, 2001), several older studies have been published related to iodomethane's mutagenic potential in standard and non-standard assays in bacteria

(Salmonella typhimurium and Escherichia coli) and yeast (Saccharomyces cervesia) (Rosenkranz and Poirier, 1979; Simmon, 1977, 1979a,b; Hemminki et al., 1980; Takahashi and Kawazoe, 1987a,b; Moura Duarte, 1972; McCann 1975) (Table 8). Substantial methodological and data reporting deficiencies occur throughout the reports in the public literature, such that that the findings on the potential iodomethane genotoxicity presented in these studies are not completely reliable. Reporting deficiencies in many of the older studies make it difficult to compare the findings in the published studies to those of the modern study (Mileson and McDonald, 2005). As observed in the GLP studies, doses that are sufficiently high to overwhelm cellular defenses result in significant cytotoxicity. In several studies (Rosenkranz and Poirer, 1979; Simmon, 1979a; Hemminki et al., 1980; Takahashi and Kawazoe, 1987a,b), it is likely that high cytotoxic test concentrations were employed (comparing doses used to the GLP study), although data on cell survival were not adequately reported. Methodological deficiencies in published studies include: (1) an insufficiently described assay in which high concentrations of iodomethane were applied to filter discs that were then dropped on plated bacterial cells (Rosenkranz and Poirier, 1979), (2) incubation of all yeast cells at the highest test concentration before serial dilution (Simmon, 1979b), and (3) evaluation of cell survival based on different incubation conditions than the evaluation of mutagenicity (Hemminki et al., 1980). Given the study limitations, the findings from the older published studies in bacteria do not necessarily conflict with the negative findings in the modern GLP studies.

Table 8. Summary comparison of genotoxicity findings in GLP and published studies of iodomethane

Summary comparison of genotoxicity findings in GLP and published studies of iodomethane

| | GLP Studies | | Published Literature Studies | | |
|---|---|---|---|---|---|
| Endpoint | Finding | Citation | Interpretation | Citation | Comment |
| Bacterial mutagenicity | - | Wagner 2001 | CBD<br>-/CBD<br>CBD<br>inadequate | Rosenkranz 1979<br>Simmon 1977, 1979a<br>Hemminki 1980<br>Takahashi 1987 | toxic doses likely, poor reporting<br>std assay neg.; closed study pos.--survival unknown<br>high toxic doses possible; survival questionable<br>very high doses used |
| Yeast recombinants | N/A | | CBD | Simmon 1979b | limited toxicity or survival data; technical problems; no dose response information |
| Fungi mutagenicity | N/A | | inadequate | IARC 1986 | reported neg. – no control for volatility |
| In vitro mammalian mutagenicity | - | San 2001 | CBD | Amacher 1984 | appears to be neg. based on current testing criteria |
| In Vitro mammalian clastogenicity | + | Gudi 2001a | -/+<br>+<br>+<br>Probably - | Clive 1979<br>Moore 1982<br>Moore 1985a,b<br>Amacher 1985 | mixed weak findings, no dose response<br>pos. dose response, low, moderate and high toxicity<br>pos. dose-response, low toxicity<br>appears neg. based on current testing criteria, data presentation make evaluation difficult |
| In vitro mammalian Cell transformation | N/A | | -<br>-/+ | Oshiro 1981<br>Pienta 1977 | iodomethane neg., other alkylating agents pos.<br>author called pos., but no dose-response |
| In vivo clastogenicity | - | Gudi 2001b | N/A | | |
| In vivo DNA adducts | N/A | | Probably - | Gensewendt 1991 | radioactivity incorporated into the DNA bases; no confirmation of direct methylation |

Abbreviations are: GLP = good laboratory practice; CBD =cannot be determined; N/A = not available; + or pos. = positive; - or neg. = negative

Mammalian cell in vitro

Iodomethane has been tested in a variety of mammalian cell test systems; some systems examined mutagenicity and others examined clastogenic potential. These include two modern GLP studies (Gudi and Brown, 2001; San and Clarke, 2001) and 9 earlier published studies (Pienta et al., 1977; Clive et al., 1979; Moore and Clive, 1982; Moore et al., 1985a,b; Oshiro et al., 1981; Amacher and Zelljadt, 1984; Amacher and Dunn, 1985; Coultier et al., 2001) (Table 8). The iodomethane studies conducted on mammalian cells in vitro indicate that iodomethane may cause clastogenic effects in cell culture but is not mutagenic. The findings of the GLP genotoxicity studies in vitro are reasonably consistent with the findings in the literature. The GLP study of San and Clark (2001, Table 8) was negative for induction of mutations in mammalian (CHO) cells. A similar study by Amacher and Zelljadt (1984), examined HGPRT revertants in CHO cells. Although reported as positive by the authors this study would probably be considered negative under current testing guidance due to the wide range of spontaneous mutant frequency, and as such, is consistent with the results of the guideline study of San and Clarke (2001).

The GLP study of Gudi and Brown (2001, Table 8) found a significant increase in structural chromosomal aberrations, but not numerical aberrations in CHO cells in vitro. This is generally consistent with published literature studies that suggest iodomethane may cause structural damage in mammalian cells in vitro. Mixed findings were observed by Clive et al. (1979) who suggested that the small colonies of L5178Y/TK+/- mouse lymphoma cells produced following iodomethane exposure reflected a clastogenic effect. The generally positive findings by Moore et al. (1985) and Moore and Clive (1982) of small colony formations in mouse lymphoma cells in vitro also were identified by the authors as indicative of a clastogenic effect and would be consistent with the guideline study of Gudi and Brown (2001). Amacher and Dunn (1985) report a weakly positive effect of iodomethane as a mutagen in mouse lymphoma cells, but limitations in the data (e.g., no significant increases over controls at lower doses and low cell survival at higher doses) suggest that this study should not carry significant weight in the evaluation of the potential mutagenicity of iodomethane, and would likely be considered as negative based on current guidelines.

Oshiro et al. (1981) reported that iodomethane did not cause cell transformation in mouse embryo cells, while the other alkylating agents evaluated in this study were positive. In contrast, Pienta et al. (1977) asserted that iodomethane caused cell transformation in hamster embryo cells, despite the lack of dose response or statistical significance. The weight of evidence suggests that iodomethane exposure to mammalian cells in vitro may result in clastogenicity but not mutagenicity or numerical chromosome aberrations.

Mammalian in vivo

Two studies have been conducted examining the potential of iodomethane to cause DNA adducts or genetic damage in vivo. These are (1) a GLP micronucleus assay in mice following intraperitoneal administration (Gudi and Krsmanovic, 2001, Table 8) and (2) a DNA adduct study in F344 rats (Gansewendt et al., 1991a).

In the guideline study, male and female mice treated with 0, 25, 50 or 100 mg/kg (the MTD) of iodomethane via intraperitoneal injection did not increase the incidence of micronucleated polychromatic erythrocytes in bone marrow (Gudi & Krsmanovic, 2001). Thus, iodomethane exposure did not cause chromosomal damage in mice in vivo.

The second in vivo study was published by Gansewendt et al. (1991a) to evaluate the potential DNA binding of iodomethane in rats. Groups of male and female F344 rats were exposed to radiolabeled iodomethane by oral gavage or via inhalation. Radioactivity associated with DNA was examined in the liver, lung, stomach and forestomach. [$^{14}$C]-radiolabel was measured in DNA purified from all four tissues, with levels of total radioactivity predominating in the stomach and forestomach. The stomach and forestomach were not target tissues of iodomethane carcinogenesis among rats treated for two years via inhalation. The levels of measured radioactivity in the DNA of various tissues do not make intuitive sense if the radioactivity is assumed to be associated with DNA adducts. For example, radioactivity associated with DNA was essentially the same in the lung following oral exposure as following inhalation exposure, although if adducts formed due to tissue contact with the reactive chemical, more radioactivity would be expected at the portal of entry for each route of exposure, the lungs for inhalation, and perhaps the stomach for oral exposure. Moreover, radioactivity associated with DNA was highest in the stomach and forestomach from both oral and inhalation exposures. The authors noted that in previously published inhalation studies with [$^{14}$C]methyl chloride, researchers had found that significant levels of the [$^{14}$C]-label was incorporated into the DNA during de novo synthesis of [$^{14}$C]methyl groups into the deoxynucleotides. The authors suspected that this might also have occurred with methyl bromide, since scientists had reported a remarkably long persistence (60 hr) of radioactivity in the stomach following inhalation exposures to [$^{14}$C]methyl bromide in rats. Based on these observations for structurally similar compounds, the authors attempted to determine whether the DNA binding of iodomethane was a result of direct methylation or de novo synthesis of radiolabeled carbon into the nucleotide base.

Gansewendt et al. (1991a) took two approaches to try to differentiate the location of the radiolabel. The first approach was to hydrolyze the DNA (either enzymatically or with acid hydrolysis), followed by high performance liquid chromatography (HPLC) separation of the bases. The collected fractions corresponding to the methylguanine adducts, were then analyzed by gas chromatography-mass spectrometry (GC-MS) in an attempt to confirm the radiolabeled adducts.

The authors observed increases in radioactivity in the HPLC fractions that corresponded to N7-methylguanine and O$^6$-methylguanine retention times, and estimated the DNA adduct levels based on the radioactivity in the fractions. However, the authors also noted that radioactivity in the fractions corresponding to guanine, cytosine, thymidine and adenosine clearly indicated that de novo synthesis of the radiolabel was occurring. In addition, Gansewendt et al. (1991a) observed that methylated DNA bases formed as a result of enzymatic hydrolysis and HPLC preparation of untreated calf thymus DNA. Importantly, the authors confirmed with GC-MS that the radiolabeled carbon from [$^{14}$C]iodomethane-treated rats was incorporated into the purine bases (i.e., de novo syntheses) in N3-methyladenine and N7-methylguanine[5] in liver. Levels of the O$^6$-methylguanine were too low to measure by GC-MS.

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[5] A full mass spectrum of the internal standard, N7-methyl-D$_3$-guanine, which was labeled with 3 deuterium atoms on the guanine moiety is shown in Figure 4 of the Gansewendt et al. (1991a). The derivatized molecular ion has as a mass of 312 amu, while the largest ion fragment is 297 amu, corresponding to the loss of the methyl group leaving the deuterated guanine ion. In the middle frame of Figure 4 of the paper, the authors measured the presence of N7-methylguanine adduct with a guanine moiety of 296 amu, which corresponds to a radiolabeled guanine ion containing a $^{14}$C in place of an unlabeled carbon with a molecular weight of 12. Thus, this spectrum confirms the location of the $^{14}$C is in the guanine not the methyl group.

In summary, Gansewendt et al. (1991a) measured increased radioactivity associated with methylated DNA bases, N7-methylguanine, N3-methyladenine and $O^6$-methylguanine. They confirmed by GC-MS that the carbon-14 radiolabel was present in the guanine portion of the molecule for N7-methylguanine and the adenine portion of the N3-methyladenine, whereas levels of $O^6$-methylguanine were too low to measure by GC-MS. The authors stated that a portion of the methylated DNA molecules likely resulted from direct methylation of DNA by iodomethane (i.e., true DNA adducts), but no evidence was presented in the paper to confirm that assertion. A more likely explanation of the results is that the radioactivity levels measured in the lung, liver, stomach and forestomach of rats are a result of de novo synthesis, and the levels of incorporation of the label reflect the background rates of cell synthesis in those tissues. This explanation is consistent with the observation that approximately the same levels of radioactivity per unit dose were observed in the four tissues following oral versus inhalation exposures -- because higher relative levels would be expected at the portal of entry if the label were the result of DNA methylation. It is also consistent with the fact that the highest levels were observed in the stomach and forestomach where cell turnover is much higher than in the liver or lung. This explanation is also consistent with the rapid breakdown of iodomethane in vivo. Very similar findings of radio-incorporation were observed with methyl bromide, which did not cause tumors in long-term inhalation studies (Gansewendt et al., 1991b). As such, genotoxicity is unlikely to be a mode of action that explains the thyroid tumors observed in male rats and mice in the lifetime exposure studies of iodomethane.

Thus, a weight of evidence evaluation of the available genotoxicity data in both the current EPA guideline genotoxicity studies and those in the open literature indicate that iodomethane does not cause mutations in bacteria or in mammalian cells in vitro. In mammalian cells in vitro, iodomethane may cause clastogenic effects in cell culture but it is not mutagenic. Clastogenicity was not observed following high dose exposures in vivo. A study conducted to examine the potential for formation of DNA adducts of iodomethane in vivo did not yield evidence that iodomethane causes DNA adducts, but did demonstrate that degraded iodomethane adds to the carbon pool which is incorporated into DNA during DNA synthesis. The data collected in vitro and in vivo confirm that genotoxicity is unlikely to be a mode of action and explanation for the thyroid tumors observed in male rats and mice in the lifetime exposure studies.

The review of the genotoxicity data concludes that iodomethane is not genotoxic following in vivo exposures; consequently genotoxicity is unlikely to be cause of the iodomethane-induced thyroid tumors in animals.

## IV. AN EXPLANATION OF THE PBPK MODEL DEVELOPED BY ARYSTA AND USED BY DPR.

Arysta developed an extensive mechanistic data set and physiologically-based pharmacokinetic (PBPK) models for iodomethane. These data and the models constitute a sophisticated effort to better characterize the toxicity profile for this compound in terms of developmental toxicity, respiratory tract lesions, and transient neurotoxicity, identified as the critical effects of acute iodomethane exposure. In addition, the use of PBPK models that take into consideration the toxicokinetic aspect of iodomethane exposure enables the use of chemical-specific parameters to determine the most appropriate dose metric and internal dose in calculating HECs instead of default inputs otherwise used. The EPA has reviewed these data and

models and evaluated their utility to calculate HECs based on chemical-specific data. The PBPK models and the mechanistic studies used to provide its inputs were considered acceptable by the EPA and the study results were incorporated into the U. S. EPA risk assessment. The iodomethane PBPK models are described in detail in Appendix A.

PBPK Modeling in the RCD

Arysta worked with DPR to perform the iodomethane PBPK modeling for the RCD. Input assumptions for each model run were as specified by DPR, and the model details were as described in Appendix A of this document. The resulting output was provided by Arysta to DPR in the model software files and Excel spreadsheets.

Clarification of model output and interpretation – Developmental Endpoint

The DPR documentation does not provide a clear explanation of how the occupational HEC of 0.22 ppm for the developmental endpoint was determined. The worker HEC of 0.22 ppm was determined assuming an elevated breathing rate and 40% mouth breathing. The workers were assumed to have previous iodomethane exposure (to reach steady state) and the AUC was calculated over the 96-hr interval from t = 144 hrs to t = 240 hrs (the last day of exposure plus 3 unexposed days), rather than from t = 0 to t = 96 (for a single exposure day without prior exposure, followed by 3 days unexposed). It is this accumulation of iodide over the preceding days and the higher worker breathing rate that produced an 8-hr occupational HEC that was lower than the 24-hr bystander HEC for this endpoint.

DPR Evaluation of Model Output – Developmental Endpoint

The DPR evaluation of the model fit to iodide data from the Sloter studies (2005a, 2005b) was incomplete and not consistent with standard practices of PBPK model evaluation (e.g., Chiu et al., 2007, U.S. EPA, 2000). The comparisons of model predictions to experimental data were limited to data from the 20 ppm "final" study, and should have included data from the 25 ppm "preliminary" study. DPR noted that the model "underestimated the maternal data, especially at hour 3" and that the "fit for both maternal and fetal data became poorer as time progressed." It is important to note that the deviation of the fit of the model from the experimental data is in the health-protective (conservative) direction and, overall, the fit is very good based on recognized methods for PBPK model evaluation (Chiu et al., 2007). A quantitative evaluation of the model fit to all the experimental data demonstrates that the average difference in plasma iodide prediction compared to measured levels through 4 days of iodomethane exposure is only 24 and 28 percent for fetal and maternal levels respectively. The U.S. EPA's has designated that a PBPK model would be acceptable for use in route-to-route extrapolation under an Enforceable Consent Agreement if the deviation of the model predictions from the experimental data did not exceed, on average, a factor of 2 (U.S. EPA, 2000).

Potential PBPK Modeling of Developmental Endpoint for DPR-identified NOEL

DPR has concluded that the LOEL for fetal loss in rabbits exposed to iodomethane should be 10 ppm, while Arysta believes that 10 ppm is the NOAEL for the developmental endpoint. If DPR maintains this conclusion regarding the developmental endpoint, then Arysta has determined HECs of 3.7 ppm for bystander and 7.7 ppm for occupational risk assessment from the DPR-selected NOEL of 2 ppm based on the dose metric of fetal plasma iodide AUC. These HECs were derived by correcting for the impact of successive days of dosing in the rabbit

developmental toxicity study using the PBPK model. This PBPK modeling is described in detail in Appendix A and summarized below.

The window of sensitivity for the effect of fetal loss from iodomethane exposure is gestation day 23 through 26, consequently, the relevant single day of exposure to produce the critical effect during the guideline study that is the basis of the NOAEL is a single day that was preceded by 17 or more days of iodomethane exposure (Nemec, 2002, 2003). In modeling repeated rabbit exposures to 10 ppm iodomethane, rabbit fetal plasma iodide increases with daily exposure, approaching steady state around day 5. In modeling repeated rabbit exposures to 2 ppm iodomethane, rabbit fetal plasma iodide increases with daily exposure, approaching steady state around day 7 and reaching steady state by day 14. A repeat exposure modeling scenario was used to derive an AUC corresponding to fetal plasma iodide level at steady state, assuming 13 previous days of exposure. This AUC provides an alternate NOAEL-equivalent internal dose for a single day 10 ppm iodomethane exposure in the rabbit. This one-day AUC is not the one-day AUC for the first day of exposure (GD 6), but rather an AUC that reflects the likely iodide profile that occurred during the window of susceptibility.

If 10 ppm is accepted as the rabbit NOAEL and prior exposure of the rabbit to iodomethane is taken into account in the model, the calculated bystander HEC is 26 ppm for this endpoint. This HEC can be compared to the HEC of 7.4 ppm, which results when the impacts of continued daily dosing prior to the window of susceptibility are not taken into account. Similarly, the worker (8 hr/day) HEC is calculated as 60 ppm if prior daily dosing is taken into account, compared to an HEC of 23 ppm when the impact of prior dosing is ignored. This repeat dose modeling of the rabbit exposure demonstrates the conservative nature of the EPA HECs of 7.4 ppm (non-occupational) and 23 ppm (occupational), which do not account for the prior-days dosing.

For California, the proposed HECs for the developmental endpoint, 3.7 ppm and 7.7 ppm for non-occupational and occupational exposures, do take into account the impacts of continued daily dosing during the days prior to the window of susceptibility in the rabbit study.

Data demonstrate that the rabbit fetus concentrates iodide relative to the doe, such that the rabbit fetal:maternal plasma iodide ratio is between 6 and 9. Arysta developed data to characterize the relationship between maternal and fetal iodide levels in humans, resulting in a fetal:maternal ratio of approximately 1 (Rayburn et al., 2007). This difference between rabbits and humans was used in the EPA risk assessment to derive a bystander HEC of 7.4 ppm corresponding to the rabbit NOAEL of 10 ppm, as the point of departure for risk assessment. Using the same assumption that EPA did regarding the differences between rabbit and human iodide pharmacokinetics, and correcting for the impact of successive days of dosing in the rabbit developmental toxicity study and the DPR-selected NOEL of 2 ppm, the corresponding bystander HEC for DPR is 3.7 ppm.

PBPK Modeling of the Nasal Olfactory Epithelial Degeneration Endpoint

The nasal histopathology was reported in rats after 13-weeks of daily exposure to iodomethane; however, data from the published literature indicate that nasal lesions can occur in rats after acute exposures if the time profile of the exposure concentration leads to an overall iodomethane exposure of greater than or equal to 200 ppm/hr (for example, approximately 2 hours at 100 ppm) (Reed et al, 1995). The design of the nasal olfactory epithelium (NOE) compartments of the PBPK model provides for iodomethane exposure to all cell layers in the compartment via diffusion through the cell stacks. Each compartment provides for diffusion of

iodomethane from the nasal lumen through a layer of mucus, through four layers of epithelial cells, and the blood exchange layer. This layered or "stacked" structure of the NOE compartment allows the model to approximate the iodomethane concentration gradient across nasal tissue from the mucus layer to the vascularized region under the basal lamina. This corresponds to the degeneration that occurred through the epithelium following exposure to high concentrations of iodomethane. The proposed mode of action for nasal histopathology involves glutathione (GSH) depletion as a key event in the toxicity pathway leading to damage of the nasal olfactory epithelium (Chamberlain et al., 1998). Consequently, GSH depletion is the dose metric used in the PBPK model for interspecies extrapolation to determine the NOAEL for the nasal lesions and identify the HEC.

As described in the MOA section, a transient 50% depletion of GSH achieved only at the end of a 24-hour iodomethane exposure is an appropriate NOAEL for the acute exposure endpoint of nasal toxicity because the benchmark GSH depletion would barely be achieved, and not sustained. The iodomethane PBPK model was ultimately run to determine GSH depletion in the epithelial layers separate from the blood exchange layer even though GSH is believed to diffuse through all layers. The EPA identified HECs for the nasal endpoint corresponding to a maximum decrease in GSH of 50% in the epithelial cell layer of the model. The HECs determined were 4.5 ppm for non-occupational risk assessments, and 5.8 ppm for occupational risk assessments. The HECs were derived based on incorporation of human-specific nasal mucosal thickness in the PBPK model in place of the default rat nasal mucosal thickness.

In discussions with EPA and DPR, both Agency and Department scientists indicated they wanted to ensure that HECs for bystanders would protect children from potential effects on the nasal olfactory epithelium following acute exposure. To identify HECs specifically for children, Arysta conducted simulations using age-specific nasal physiology and breathing parameters corresponding to a 3 month old child that were collected by Kimbell et al. (2005). Kimbell et al. (2005) provided age-specific nasal volumes and surface areas, but did not further subdivide these volumes and areas into the nasal vestibule, olfactory and respiratory regions, and nasopharynx as in Frederick et al. (1998, 2002). The relative fractional areas and volumes of the different regions were assumed to be the same in adults and children, and the ratio of tidal volume to body weight (TVOL/BW) is assumed to be constant across age groups. The key data from Kimbell et al. (2005) are presented in detail in Appendix A because the reference was a poster presented at the Society of Toxicology 2005 annual meeting. Data to describe the thickness of the nasal mucosa in children (age 0 to 1 year old) were obtained from Inagi et al. (1992). The HEC results were essentially the same for all ages, as reported by EPA (EPA, 2007).

PBPK modeling of Transient Neurotoxicity

Peak concentration of iodomethane in the brain is the appropriate dose metric for interspecies extrapolation, yielding an HEC of 10 ppm. Because brain concentration of iodomethane approaches steady state within a few hours, this HEC is applicable to both 24-hr and 8-hr (worker) exposures. Based upon a consideration of the mode of action, the neurological effects of iodomethane in rats are best explained by the impact of the parent chemical on the central nervous system. The component of the human PBPK model for the parent chemical is based upon measured values for partition coefficient (in human blood) and metabolism in quantitatively important human tissues (i.e., liver and kidney). The metabolic pathways for iodomethane are well understood and have been quantified in PBPK models in animals and humans for a number of halogenated solvents (methylene chloride, trichloroethylene,

tetrachloroethylene). In addition, a human PBPK model has been developed for a structurally similar chemical, methyl chloride (Jonsson et al., 2001). The results of the Jonsson et al. (2001) analysis indicated that the tissue partition coefficients determined in rats were consistent with the values estimated for humans via Markov chain Monte Carlo evaluation of human kinetic data. Confidence in the PBPK model predictions for the neurological effects of iodomethane in rats is considered medium-to-high.

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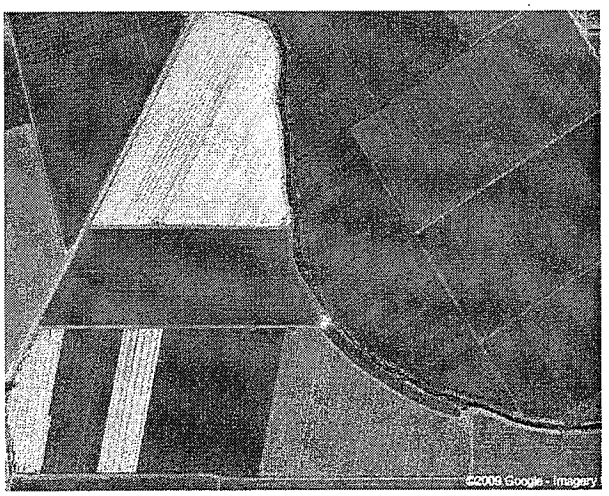
# DPR Methyl Iodide RCD
# Review of Exposure Assessment

Anne Katten, MPH
California Rural Legal Assistance Foundation
September 25, 2009

## The central coast is a patchwork of labor intensive crops



## Fields are often adjacent to schools and residential areas

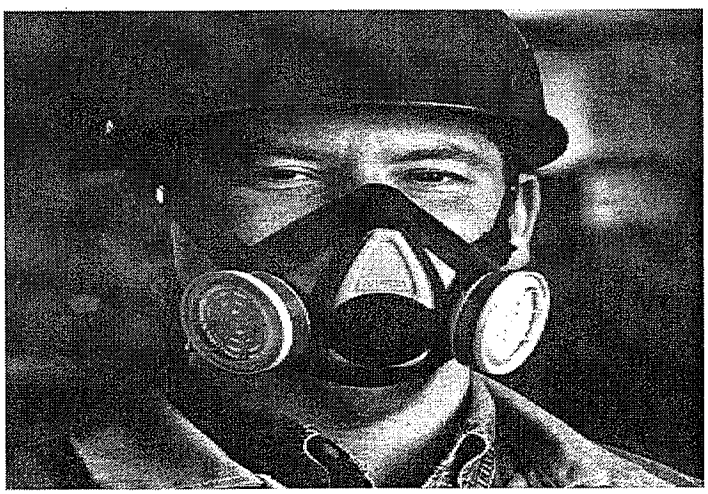
## DPR uses many reasonable assumptions in estimating exposure:

- Maximum label rate
- 95th percentile exposures to compensate for very small data sets
- Downwind exposures under fairly stable air conditions
- Indoor and outdoor exposures the same

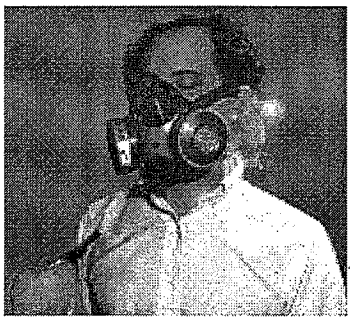
## Some assumptions in RCD underestimate worker exposure . .

- Unrealistic respiratory protection factor
- 3 months/year of application work
- 8 hour work day
- Negligible dermal exposure assumed
- Combined exposure with chloropicrin not evaluated

## RCD assumes respirator reduces air concentrations 10-fold



## Fit testing can be either quantitative or qualitative



## Most Common Agricultural Pesticide Violations 2006-2008

(Source DPR PUE Statistical Profile 2009)

| Type of Violation | Number of Violations |
|---|---|
| Personal Protective Equipment | 2284 |
| Handler Training | 2026 |

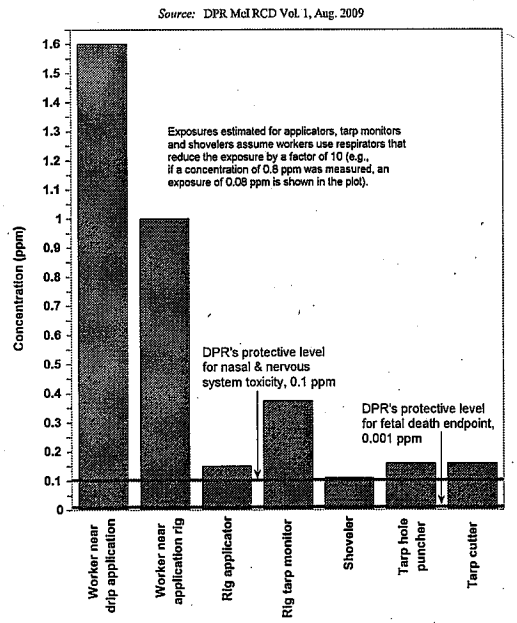
# Nicas and Neuhaus reviewed 7 respirator fit studies:

- 5 of 7 studies yielded a protection factor of <5.3
- Based on results recommend reducing half-mask respirator assigned protection factor from 10 to 5
- Found tendency to smaller protection factors in studies involving gases and small particles

Source: M. Nicas and J.Neuhaus JOEH Feb 2004

**DPR Predicted Worker Exposure Levels for Selected Tasks**

*Source:* DPR MeIRCD Vol. 1, Aug. 2009



## Applicators Who Travel Exposed 5 Months

| Counties | Month | 2007 Soil Fumigation |
|---|---|---|
| Ventura | June | 1,433 acres |
| Ventura | July | 1,152 acres |
| Ventura & Monterey | August | 4,926 acres |
| Ventura & Monterey | Septem ber | 6,494 acres |
| Monterey | October | 4,549 acres |

## 8 hour workday is not reasonable worst case in agriculture

- Seasonal workers are eager to work all hours offered
- Agricultural workers, including pesticide applicators, are only entitled to over-time pay after 10 hours of work (Wage Order 14)
- Irrigation workers are completely exempted from overtime pay requirements
- Exposure is extended during transit to and from work and often at home

## Dermal exposure potential significant during drip application

- Routine duties include repair of drip lines and of tears in tarp
- Label use directions prohibit wearing of gloves to keep vapors from being trapped
- MSDS both recommends use of gloves (Viton type) and states that users shouldn't wear gloves
- 100% dermal absorption should be assumed since no data is available

## Midas Label and MSDS Use Instructions

**User Safety Requirements**

- Do not wear jewelry, gloves, goggles, tight clothing or any rubber protective clothing/boots that can trap iodomethane or chloropicrin vapors against your skin. Iodomethane and chloropicrin vapors can be trapped inside clothing and cause skin injury.

**Skin Protection:** Avoid skin contact with this material. Wear protective clothing and gloves (NIOSH recommends Viton™ (gloves suits), Responder™ suits, Tychem 1000™ suits).

**User Safety Requirements:**

- Do not wear jewelry, gloves, goggles, tight clothing or any rubber protective clothing/boots that can trap iodomethane or chloropicrin vapors against your skin. Iodomethane and chloropicrin vapors can be trapped inside clothing and cause skin injury.

## Case study of acute methyl iodide dermal exposure

- 49 yr old male had regular job of carrying and loading tanks of MeI onto a truck
- Wore chemical protective suit and air-supply full-face respirator
- At end of shift saw breach in soles of suit
- Rash on genitalia, inner thighs, groin
- Fainted and in ER severe burns began to show on torso,, back, lower extremities
- Developed memory,concentration and task performance problems

Source:Schwartz AJIM 47:550-556 (2005)

## Limitations of exposure data

- Sampling times of 5 to 6 hours don't allow evaluation of shorter term peak exposures
- No measurements of concurrent chloropicrin exposure
- Exposure calculations assume body weight of 71.8 kg (160 lb). Two workers monitored weighed only 47 kg (100 lb)

## Risk of well water contamination

- Private rural wells are rarely monitored for contaminants
- According to Florida EPA groundwater.monitoring planned in Florida has not been initiated yet.

Date: 9/1/09
To: John Froines, Professor of Toxicology, UCLA
From: Kathleen Collins, Professor of Molecular and Cell Biology,
UC Berkeley, kcollins@berkeley.edu
Re: Summary of 8/21/09 testimony at legislative hearing

**The general biological responses to DNA damage by methylation are:**
1. DNA repair (if damage is at a low level),
2. Cell suicide (highly damaged human cells kill themselves or attract killers)
3. Genome mutation (cumulative increments of cancer risk)

DNA methylation reactions often yield modified bases that are unable to serve as template for a DNA polymerase. These DNA lesions will recruit repair activities both directly (by recognition of distorted DNA) and as the consequence of stalled DNA replication (when the DNA is being copied prior to cell division). However, there is growing awareness than some DNA modifications will be copied over by a DNA polymerase if they are not repaired in advance of DNA replication, thus increasing the probability of genome mutation. Genome mutation in somatic tissues (most of our body) accelerates the progression of cancer. Genome mutation in germline cells (cells that develop into sperm and egg) leads to infertility and disease inheritance.

**Mechanisms of carcinogenicity of methyl halides.**
**Bolt HM, Gansewendt B. Crit Rev Toxicol. 1993;23(3):237-53.**
"… methyl iodide, upon oral and inhalation administration to rats and mice, caused systemic DNA methylation. Specifically, 3-methyl-adenine, 7-methyl-guanine, and O6-methyl-guanine were formed"

O6-methyl-guanine is a particularly dangerous form of DNA methylation: it can be repaired, but it can also be replicated without repair (see below). Thus, the type of DNA methylation damage caused by methyl iodide has both short-term toxicity (from repair-induced delay of cell growth or damage-induced cell death) and cumulative long-term deleterious impact (by permanent genome mutation, leading for example to cancer).

**The structural basis for the mutagenicity of O(6)-methyl-guanine lesions.**
**Warren JJ, Forsberg LJ, Beese LS. Proc Natl Acad Sci USA. 2006;103(52):19701-6.**

"Methylating agents are widespread environmental carcinogens that generate a broad spectrum of DNA damage. Methylation at the guanine O(6) position confers the greatest mutagenic and carcinogenic potential. DNA polymerases insert cytosine and thymine with similar efficiency opposite O(6)-methyl-guanine (O6MeG). … Our structures reveal that both thymine and cytosine O6MeG base pairs evade proofreading by mimicking the essential molecular features of canonical substrates."

**Hazardous waste classification**
UC Berkeley Environmental Health & Safety (EH&S) regulations classify methyl iodide as the most toxic category of compound (zero-release, class C). This is a greater hazard level than most radioactivity (class B). See drain disposal pdf for complete guidelines.

*Class designation for hazardous waste disposal*

- Class A includes chemicals that pose little or no hazard in dilute aqueous solution.
- Class B includes chemicals of moderate hazard in dilute aqueous solution. These aqueous solutions are suitable for disposal down the drain with excess water.
- Class C includes chemicals that may not be drain disposed in any amount…requests for exceptions are made to EH&S who obtains any necessary additional information and coordinates review.

NATURAL RESOURCES DEFENSE COUNCIL

# NRDC Comments on the DPR Methyl Iodide Risk Characterization Document for Inhalation Exposure

September 25, 2009

Comments submitted by email to: mei_rcd_comment@cdpr.ca.gov

**ACTION:** Food and Agricultural Code (FAC) sections 13121-13130 require DPR to review the toxicology database of all pesticide active ingredients. In addition, before a substance is registered as a pesticide for the first time, FAC section 12824 requires DPR to conduct a thorough evaluation. FAC section 12824 also requires DPR to endeavor to eliminate from use in California any pesticide that endangers the agricultural or nonagricultural environment.

After a preliminary review of toxicology studies, DPR identified methyl iodide (iodomethane) as having potential adverse health effects which a more in-depth appraisal of risk could examine before a registration decision was made. During the risk characterization process, DPR evaluates the significance of the adverse effects. If DPR decides that use of, or certain uses of, the active ingredient iodomethane result in a significant adverse effect, action must be taken to mitigate the adverse effect. This may include use restrictions, or denial of registration.

## SUMMARY

1. NRDC strongly supports the rapid replacement of methyl bromide (MeBr) with safer alternatives that are non-ozone depleting.
2. Although methyl iodide (MeI) is a non-ozone depleting alternative to MeBr, there is evidence that it is significantly more toxic than MeBr, and it may also pose a significant threat to groundwater resources.
3. DPR's *Risk Characterization Document for Inhalation Exposure* commendably addresses some of the deficiencies in the *EPA Iodomethane Revised HED Human Health Risk Assessment* which NRDC had identified in comments submitted in January 2006.
4. There are some additional improvements needed to DPR's document as detailed in NRDC's comments; these changes may demonstrate even greater risks of MeI to human health.
5. The health risks associated with MeI indicate that it is not appropriate for use as an agricultural fumigant in California and should not be registered by DPR.

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**BACKGROUND**

In 2006, U.S. EPA issued a draft *Iodomethane Revised HED Human Health Risk Assessment* preliminary to registering this fumigant for agricultural use.[1] NRDC submitted technical and policy comments on the EPA draft.[2] In significant part, the NRDC comments stated:

> *NRDC believes…that there are other safer alternatives for MBr. If EPA concludes, however, that MI is needed to serve in an interim role as an alternative for MBr, it should not be a permanent one. EPA must assure that any such registration is time-limited and for limited applications only, and must include strong protections for workers and bystanders. Specifically, any such registration should include a phase-out schedule for this chemical.*

Unfortunately, on September 29, 2008, U.S. EPA granted conditional registration for all MeI products without any time limitations.[3] The EPA decision did not adequately address NRDC's specific concerns in the record. At that time, NRDC raised concerns about the inappropriate choice of 10 ppm as a NOAEL for fetal death in the rabbit developmental toxicity study, and the likely relevance of thyroid and other tumors to humans, as well as the genotoxicity of MeI, indicating the need for a cancer risk assessment.

DPR's current risk assessment is commendable in that it addresses these two major flaws of the EPA risk assessment and updates the summary of the science. The DPR risk assessment suggests that exposures to workers, bystanders, and residents from use of MeI in California would result in acute health risks up to 3000-fold larger than DPR's acceptable risk levels. Specifically, for bystanders and residents, acute margins of exposure (MOE) range from 0.1-11, compared to target MOEs of 117-342. In some cases (ie. fetal death among bystanders and residents) the MOE is less than unity, implying that those populations would be exposed at levels <u>above</u> the NOAEL (human equivalent). Cancer risk levels are also of significant concern, with risk levels in the range of $9 \times 10^{-5}$ for residents and workers; a cancer risk in this range is 90-fold above the level of concern EPA uses under the Food Quality Protection Act, and is 9-fold higher than the risk level (NSRL) under California's Proposition 65. In addition to the above issues, DPR identified a significant potential threat to shallow groundwater aquifers from iodide contamination. California relies on shallow groundwater aquifers in many parts of the State, and will rely even more on these aquifers in the future. Contamination imperils these limited water resources, and that threat must be fully resolved before this fumigant could be registered for use.

As a result of this additional information, and in light of the failure of U.S. EPA to adequately account for these concerns, NRDC opposes registration of MeI in California.

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[1] Federal Register Vol 71, No. 4, p. 901-903. January 6, 2006.
[2] NRDC Comments on the EPA Iodomethane Revised HED Human Health Risk Assessment. Docket: EPA-HQ-OPP-2005-0252, February 21, 2006.
[3] http://www.epa.gov/opp00001/factsheets/iodomethane_fs.htm.

## DETAILED COMMENTS

1. **MeBr should be phased out rapidly and replaced with safer alternatives that do not deplete the ozone layer.**

MeBr is the most powerful ozone-depleting chemical still in widespread use. After more than a decade's lead time, the deadline for phasing out MeBr fell on December 31, 2004, with exceptions allowed only for "critical uses." One condition for a critical use exemption is the absence of technologically and economically feasible alternatives. The MeBr exemptions allowed in 2005 and 2006 are estimated to cause more than 20 deaths from skin cancer, more than 4,000 other skin cancer cases, and more than 1,400 cataract cases, in the U.S. alone.[4] [5] The global health toll will be much larger. MeBr is also a direct threat to the health of people who work with it. Although both MeBr and MeI are toxic chemicals, MeI is not an ozone depleter, in part because it has an average lifetime in the atmosphere of about 1.5 days compared to 1.7 years for MeBr. There are a variety of chemical and non-chemical alternatives for MeBr. In general, it is important to move forward to use alternatives, but these alternatives should not present greater hazards to the environment or public health than MeBr itself.

2. **MeI is significantly more toxic than MeBr by most metrics.**

A comparison of the toxicity of MeBr and MeI suggests that MeI is approximately two orders of magnitude more acutely toxic, has about ten-fold greater subchronic toxicity, but may have slightly lower chronic toxicity (Figure 1). These findings are not surprising because MeI dissociates more rapidly than MeBr and is more reactive with tissues, thereby enhancing the toxicity of the chemical. Although there is evidence for carcinogenic effects from both MeBr and MeI, the latter is significantly more mutagenic, and the cancer data are considerably stronger. Based on consideration of the latest available data and the DPR assessment, NRDC has come to the conclusion that it is inappropriate to replace a toxic fumigant such as MeBr with one that has significantly greater overall toxicity.

*Figure 1: Methyl Bromide vs. Methyl Iodide Toxic Potency – Human Equivalent Concentrations (HECs)*

| | **Methyl Bromide** | **Methyl Iodide** |
|---|---|---|
| *Acute* | 21 ppm<br>Developmental tox, rabbit | 0.24 ppm<br>Fetal death, rabbit |

[4] Testimony of David Doniger, Climate Center Policy Director, Natural Resources Defense Council. Hearing on "Methyl Bromide: Are U.S. Interests Being Served by the Critical Use Exemption Process?" Subcommittee on Energy and Resources Committee on Government Reform U.S. House of Representatives. February 15, 2006

[5] Affidavit of Dr. Sasha Madronich. Natural Resources Defense Council v. U.S. Environmental Protection Agency and Michael O. Leavitt. US Court of Appeals for the District of Columbia Circuit. Docket No 04-1438

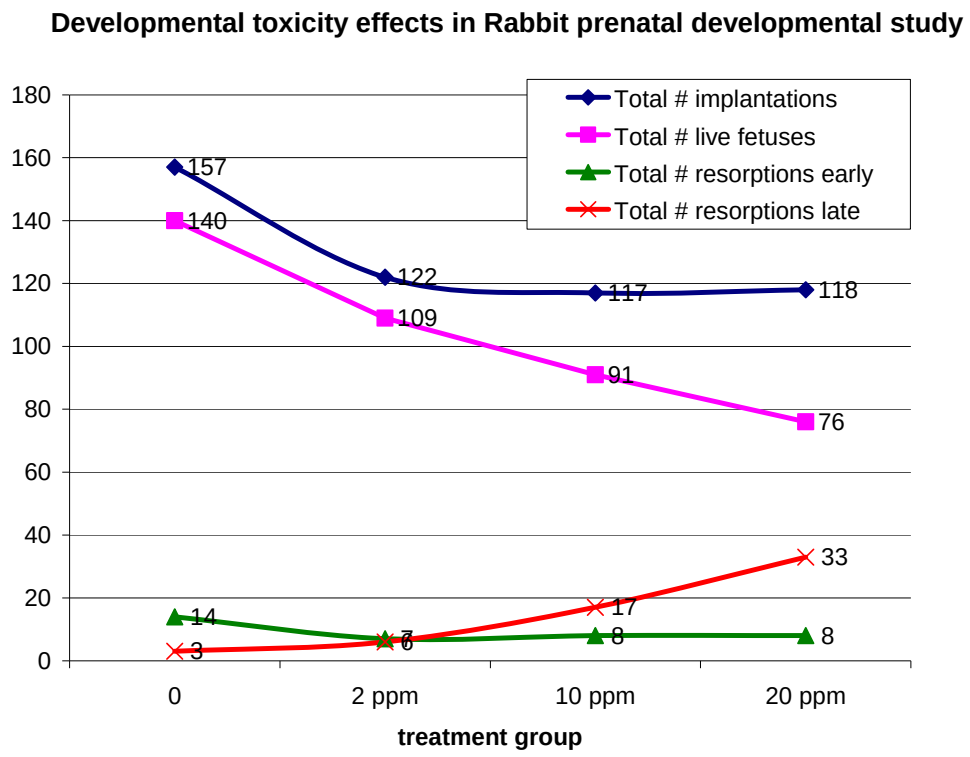
| | | |
|---|---|---|
| *Acute* | 25 ppm<br>Neurotox, dog | 3.4 ppm<br>Neurotox, rat<br>2.2 ppm<br>Olfactory epithelium degen, rat |
| *Subchronic* | 12 ppm, adult<br>Neurotox, rabbit | 1.4 ppm, adult<br>Developmental delay, rat |
| *Chronic* | 0.1 ppm, child<br>Nasal epithelial hyperplasia, rat | 0.6 ppm, child (0.5 ppm, infant)<br>Salivary gland metaplasia, rat |
| *Cancer Potency* | None calculated | $1.61 \times 10^{-2}$ mg/kg-day |

*Source: DPR MeI Health Risk Assessment, 2009; DPR MeBr Health Risk Assessment, 2005.*

3. **DPR's assessment should use a benchmark dose (BMD) approach to the developmental toxicity studies, and should choose a point of departure below 2 ppm.**

The rabbit developmental toxicity studies by Nemec (2002, 2009)[6] clearly showed a reduction in viable fetuses at 10 ppm (11% dead fetuses per litter). DPR was correct to reject U.S. EPA's obviously false choice of 10 ppm as a NOAEL. However, there is some evidence of developmental toxicity even at 2 ppm in rabbits (see figure below). It is currently preferable risk assessment practice to use a BMD approach to select a point of departure, rather than a NOAEL. Such an analysis would potentially demonstrate a point of departure (POD) below 2 ppm for this endpoint.

[6] Full references to the cited studies are in the DPR risk assessment unless otherwise specified.




4. **The absence of a developmental neurotoxicity study (DNT) is a critical data gap and appropriately requires an additional uncertainty factor of at least 10-fold.**

There is ample evidence that the brain is a sensitive target organ for MeI. This has been shown in humans, where neurological and psychiatric effects predominate in case reports of toxicity. ADME studies have shown that both the methyl and the iodide moities rapidly concentrate in brain tissue (preferentially in mitochondria) after inhalation exposure, and that the residues linger in brain for longer than in other tissues. There is also extensive evidence that excess iodide blocks thyroid gland function (it causes a reduction in circulating T4 and T3, and an increase in TSH), so excess iodide - like iodide deficiency - causes thyroid hormone alterations that are associated with developmental neurotoxicity. Excess iodide also has been associated with autoimmune thyroid disease. Thyroid hormone has many key roles during pregnancy, and controls critical events in human fetal development, such as neurogenesis, neuronal migration, synaptogenesis, and myelinogenesis (see Tables 1 and 2). For these reasons, a developmental neurotoxicity (DNT) study would likely find adverse effects at doses lower than those that cause effects in adult animals, and lower than those that cause fetal death in a standard developmental toxicity study. In the absence of a DNT study, it is necessary to incorporate an additional uncertainty factor to account for the critical data gap.

***Table 1: Thyroid Hormone During Pregnancy***

| Gestation Weeks | Fetal Thyroid Activity | Maternal Thyroid Activity | Critical Events |
|---|---|---|---|
| Conception to 12th week | None | Increase in TBG concentrations; Direct stimulation of maternal thyroid by hCG; increase in hormonal output by 30-50% | Cerebral neurogenesis and migration |
| 12th-20th week | Active trapping of iodide in fetal thyroid gland begins; some T4 production begins | Maternal T4 supplies most of circulating levels | Neurogenesis in basal ganglia, cerebrum; Organ of Corti formed in ear |
| 20th week to term | Functional fetal thyroid | Maternal T4 still supplies up to 30% of circulating levels | Cerebellar neurogenesis, Neuronal differentiation, process formation, synaptogenesis |
| Postnatal | Functional thyroid | None | Neuronal differentiation, process formation, synaptogenesis, gliogenesis, myelinogenesis |

TBG = thyroid binding globulin
HCG= human chorionic gonadotropin
Ref: Glinoer D. Potential consequences of maternal hypothyroidism on the offspring: Evidence and implications. Horm Res 55:109-114, 2001.

***Table 2: Biochemical Parameters in the Developing Brain Affected by Thyroid Hormone***

- Defects in migration of cortical neurons, resulting in ectopic neurons and disarray of cortical lamina
- Decreased rate of neuronal proliferation in the cerebellum
- Delayed changes in glucose transport rate and ketone body metabolizing enzymes
- Decreased Ornithine decarboxylase activity in the immature cerebellum
- Decreased tubulin content in microtubules, rate of turnover decreased, and tubulin-tyrosine ligase decreased
- Delayed capacity of microtubules to assemble, due to defect in microtubule-associated proteins
- Delayed myelin deposition
- Delayed development of myelin-associated enzymes
- Delayed development of GABAergic, muscarinic, and B-adrenergic receptors
- Altered activity of neurotransmitter enzymes such as tyrosine hydroxylase, monoamine oxidase, catachol-o-methyltransferase, choline acetyltransferase, acetylcholinesterase, and glutamic acid decarboxylase
- Alterations of the ion fluxes associated with NO, K-ATPase

5. **The MOE of 30 for endpoints other than fetal death is inappropriate and should be increased to protect children's health.**

It is inappropriate to choose an MOE of only 30 for health endpoints other than fetal death. As DPR itself points out, use of an MOE of 30 results in calculated RfCs that would not protect young children against excess iodide intake, thereby rendering the calculated RfCs meaningless. In addition, failure to use an additional UF for the neurotoxicity endpoint is rash for three reasons: (1) developmental neurotoxicity has not been evaluated (see above); (2) significant abnormalities were noted in female rats in Schaefer (2002) at 27 ppm, the level DPR selected as a NOAEL; and (3) neuropsychiatric effects (delirium, confusion, altered affect, personality and behavior changes, shortened attention span and difficulty concentrating) have been prominent in adult MeI exposure case reports, and these have not been assessed adequately (and probably cannot be adequately assessed) in laboratory animals. An MOE of 300 should therefore be used for all non-cancer endpoints. In addition, where the RfC exceeds the level (1 ppm) that would fail to protect children against excess iodide, the RfC should not be used.

6. **The evidence strongly supports a genotoxic mode of action for the carcinogenic effect of MeI; the cancer risk assessment should use a linear model, and should include astrocytomas and uterine fibromas as well as thyroid tumors.**

There are compelling data on the genotoxicity of MeI. This potent alkylating agent has been used for many years in the laboratory setting to intentionally generate mutations in research experiments. DPR's conclusion that "there was some indication of MeI as an alkylating agent based on alkylation of guanines from DNA of human lymphocytes" significantly understates the broad scientific use of MeI for exactly this purpose. MeI is a clastogen – it causes chromosomal aberrations in CHO cells and is positive in the mouse lymphoma assay. Almost all of the properly conducted genotoxicity and mutagenicity assays on MeI were positive, indicating significant likelihood that this chemical is a carcinogen through a mutagenic MOA. Notably, the positive findings were not just in *in vitro* test systems, but also in whole animal studies, where MeI has a clear systematic genotoxic effect (McCarroll, 2005).

The methyl group (as opposed to the iodide) is the alkylating moiety; the methyl group has been demonstrated in carbon radiolabeling studies (Sved, 2003) to rapidly accumulate in the thyroid immediately after inhalation of MeI, and to still be present in the gland 168 hours later. Elevated levels of the methyl ion also accumulate in the brain, where levels persist longer than in other organs (Hasegawa et al, 1971, Hasegawa, 1969); unfortunately concentrations in the uterus of the female rat were not measured in any of these studies. It is therefore clear that the reactive moiety that is known to interact with DNA and also to cause oxidative stress as shown by glutathione (GSH) depletion, physically reaches the target tissues (thyroid, brain) where cancers have been observed.

The cervical and uterine fibromas discussed on p. 63 of the DPR draft should not be dismissed. As stated in the document, the historical incidence of fibromas of the uterus

and cervix are very low, and 12.5 percent of the high-dose females developed this tumor, which is both statistically and biologically significant. DPR concludes that, "the possibility that the fibroma in the cervix in high dose females was treatment-related cannot be dismissed at this time." In such a situation, the appropriate response is to protect public health by assuring that the risk assessment protects against that endpoint. It is not appropriate to conclude that the study is acceptable and that the fibromas may be treatment-related, but then to fail to assess the potential risk. The rationale provided for failing to assess astrocytomas and uterine/cervical fibromas does not make sense: DPR states that these are not assessed because "the incidences for these tumors are much lower than those for thyroid tumors" (p. 149, lines 7-8). Yet these should be evaluated to be sure that they do not occur at lower doses or have a steeper dose-response than the thyroid tumors, irrespective of the incidence rates. In fact, a multiple-endpoint analysis is required by the he EPA Cancer Guidelines (EPA, 2005) that state, "Because an agent may induce multiple tumor types, the dose-response assessment includes an analysis of all tumor types, followed by an overall synthesis that includes a characterization of the risk estimates across tumor types, the strength of the mode of action information of each tumor type, and the anticipated relevance of each tumor type to humans, including susceptible populations and lifestages (e.g., childhood)."[7]

7. **Glutathione depletion should be considered a marker of an adverse effect, and should be used as a point of departure for risk assessment.**

Glutathione (GSH) depletion is a reliable marker of oxidative stress in the body. Although it is a physiological response to oxidative stress, depletion of GSH reduces the body's ability to respond to additional oxidative stressors (both endogenous and exogenous), thereby increasing the likelihood of tissue damage. In addition, there is evidence of significant heterogeneity across the population in the physiological response to oxidative stress, and data on MeI demonstrate that the fetus suffers significantly greater GSH depletion than the mother. It is therefore appropriate and health-protective to use GSH depletion itself as a regulatory endpoint, and to assure that human exposure will not result in significant depletion. DPR only uses GSH depletion as a dose metric to derive a human equivalent concentration (HEC) for epithelial damage, rather than as an endpoint in itself.

The percentage of GSH depletion that is physiologically significant is a matter of debate. U.S. EPA likely erred in choosing 50% GSH depletion as a dose metric, since such extreme depletion leaves no room to protect against cumulative or aggregate exposures to various oxidants. DPR chooses 25% GSH depletion (p.141, lines 27-28), which may not be sufficiently health-protective, especially for genetically susceptible individuals and the fetus. DPR should provide a clear rationale for choosing 25% GSH depletion rather than a lower number, in light of population variability, susceptible subgroups, and background exposures to other sources of oxidative stress.

8. **The risk assessment should use a respiratory rate for active people.**

[7] EPA Guidelines for Carcinogen Risk Assessment. 2005

In humans, the uptake of MeI is directly related to the respiratory rate, ranging up to 92% in a small group of mostly male volunteers (Morgan and Morgan, 1967). DPR was correct and appropriately precautionary to assume a default 100% retention/absorption of MeI. However, DPR also used average breathing rates for their analysis, assuming a low level of physical activity. In fact, workers, bystanders, and community residents will include inactive, moderately active, and very active people. For example, children commonly play and ride bicycles outdoors, adults jog or engage in other recreational activity, and workers are generally physically active. DPR notes that the MeI exposures would be higher by 15-20% if the breathing rates of active and very active persons are used (p. 166, lines 15-16). NRDC urges DPR to use the faster (reasonable upper bound) breathing rates in order to assure that active workers, bystanders, and community residents are adequately protected.

9. **MeI is likely to contaminate groundwater resources, which could pose a significant health hazard through contamination of drinking water.**

The DPR evaluation showed that MeI could contaminate shallow groundwater aquifers in areas such as Fresno County where such vulnerable drinking water aquifers exist. The DPR estimate includes an upper-bound estimate of up to 18 ppm of iodide in the ground water. Calculations of possible iodide intake from ground water contaminated at this level indicates exposure in the range of 0.337-1.929 mg/kg/day ($50^{th}$-$95^{th}$ percentile) for infants. The minimal risk level (MRL) for iodide is 0.01 mg/kg/day, which is exceeded by more than 3,000-fold at the $50^{th}$ percentile, and by more than 19,000-fold at the $95^{th}$ percentile. Although the drinking water risk assessment needs refinement and could be informed by more data, it would be inappropriate – and even reckless – to allow the use of MeI in California until this issue has been thoroughly studied and resolved. California faces a drinking water crisis, as the State's growing population and shrinking water resources are further challenged by drought, declining snow pack, and climate change. Protection of source water is an overriding priority in order to provide reliable drinking water supplies in the years to come. Widespread contamination of aquifers with excessive iodide is avoidable, and could cause health problems and cost millions of dollars for water treatment, for decades into the future.

In summary, if DPR proceeds with registering MeI as a replacement for MeBr, workers, their families, the public, and wildlife may be significantly harmed through exposure routes that include spray drift and water contamination. We therefore urge DPR to encourage non-toxic and less-toxic replacement options and not proceed with an ill-advised registration of MeI at this time.

Respectfully,

Gina Solomon, M.D., M.P.H.
Senior Scientist

October 12, 2009

Re: DPR's RCD for Methyl Iodide

To: DPR and Scientific Review Panel

We appreciate this opportunity to provide feedback on DPR's Risk Characterization Document for methyl iodide. These comments are made on behalf of Pesticide Action Network and the undersigned organizations.

Overall, we are impressed with DPR's work on the methyl iodide RCD. This work is a refreshing change from US EPA's and Arysta's approach that appeared to have little basis in science. As the Scientific Review Panel (SRP) members noted at their September 24–25 meeting, certain modifications to the DPR risk assessment will improve its accuracy, but the starting document was comprehensive and science-based and highlighted significant issues of concern with US EPA's approach.

We would like to begin by noting that the materials available for us to review were US EPA's and DPR's summaries of the original toxicology studies; we did not have access to the raw data. Some of our comments are a request for DPR and the SRP to take a closer look at the raw data, based on our concerns about past risk assessment practices that minimize apparent risks in questionable ways, and on comments in the toxicology summaries that suggest potential problems with specific studies or approaches.

We summarize our comments below. We are also attaching our February 21, 2006 comments on the US EPA risk assessment, to which we refer the reader for more detail on some of the points made in this letter.

# I. Toxicology

## *1. The potential for toxic effects based on the alkylation reactions of methyl iodide has not been fully explored by either CA DPR or US EPA*

Dosing of rats with labeled $^{14}CH_3I$ results in $^{14}C$ primarily in the kidneys, liver, thyroid, nasal turbinates, lung, and brain, indicating alkylation and potential damage in these tissues. This observation suggests that there are many possible routes of toxicity for methyl iodide that have not been evaluated in the risk assessment. Work by Gansewendt *et al.* indicates that dosing of rats with methyl iodide results in both N- and O-methylation of DNA.[1] Besides cancer, what are the potential physiological outcomes of these chemical reactions? Can insights into the potential outcomes be gleaned from studies on anti-cancer drugs that act by alkylating the DNA of tumor cells?

[1] Gansewendt, Xu, Foest, *et al.* DNA binding of methyl iodide in male and female F3445 rats. *Carcinogenesis* 1991 12(3):463–467.

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Methyl iodide is widely used in chemical synthesis because of its extraordinary ability to react with electron-rich molecules via methylation reactions. Methyl iodide is more reactive than methyl bromide because of the iodide ion's larger size, which alters the thermodynamics of the reaction through stabilization of the product molecules relative to the starting materials for a given substrate. For students of organic chemistry, this differential reactivity is more commonly phrased as "iodide is a better leaving group than bromide."

With some common knowledge of chemical reactions, one can see where methyl iodide fits into a continuum of methylating ability by evaluating the reactivity of a sequence of methylating agents. On one end of the spectrum is the weak alkylating agent, methanol ($CH_3OH$), which requires an acid catalyst, heat and some time for reactions to occur. At the other end of the spectrum are compounds like methyl triflate ($CH_3OSO_2CF_3$), one of the most powerful methylating agents known, which is so reactive that when this chemical is exposed to air, it reacts immediately with water vapor in the air, forming white fumes at the source of the methyl triflate vapors. In between these two extremes are the methyl halides, with methyl iodide a stronger alkylating agent than methyl bromide, which is a stronger alkylating agent than methyl chloride.

Because of this high reactivity and known alkylating ability, methyl iodide is treated with great respect by synthetic chemists, who handle it only in a hood under an inert atmosphere and use specially sealed bottles and syringes for transfer to ensure that none of this highly toxic chemical escapes. The proposed release of massive amounts of this chemical into the environment is contrary to safe chemical management practices, and scientists familiar with the chemical have expressed amazement that the EPA has actually registered it for use as a soil fumigant.

See sections 1.4.1–1.4.3 in PANNA's comment letter to US EPA for more detail on structure-activity relationships that provide insights into methyl iodide's alkylating abilities and its biological reactivity.

## 2. *Use of Benchmark Dose methodology is a more appropriate tool for evaluating many of the toxicological endpoints*

We agree with the SRP that the "NOAELs" selected by US EPA and CA DPR in several of the toxicity studies are not NOAELs, but LOAELs. Use of Benchmark Dose methodology is a more appropriate tool for evaluating such toxicological endpoints. Use of the BMD methodology would require DPR to select an appropriate point of departure (POD) for the acceptable level of toxic effects.

## 3. *Any level of fetal death induced by methyl iodide is unacceptable*

For developmental toxicity, we have serious reservations about any method used to select an "acceptable" percentage of fetal deaths as a valid POD, as DPR would have to make the assumption that fetal loss to some fraction of pregnant women would be an acceptable outcome. **We do not believe that any level of methyl-iodide-induced fetal death is an acceptable outcome, and we have serious ethical concerns about any analysis that requires DPR to select such an endpoint.** The data indicate that methyl iodide exposure causes fetal deaths in a relatively high percentage of the animals tested at doses to which people are likely to be exposed.

This fact alone is sufficient for DPR to refuse to register methyl iodide. DPR should not be in the position to decide for the people of California how many fetal deaths are "acceptable."

## 4. Carcinogenicity

We share DPR's, OEHHA's and the SRP's concerns about the cancer risk assessment that US EPA developed for methyl iodide. The data show that methyl iodide causes astrocytomas, lung tumors, and urinary and cervical tumors, in addition to thyroid tumors, which indicates that the mechanism of carcinogenesis selected by US EPA is incorrect. The non-threshold analysis conducted by DPR provides a cancer potency factor comparable to several other well-known and well-studied carcinogens, including formaldehyde, propylene oxide, perchloroethylene, and pentachlorophenol (see Table 1). DPR should re-do the cancer risk analysis including the correction factor to account for the additional sensitivity of infants and children.

**Table 1: Cancer Potency of Selected Chemicals**

| Chemical | Inhalation $Q_1$* (mg/kg-day) |
|---|---|
| Methyl iodide | 0.0161 (DPR RCD) |
| Chloropicrin | 2.2 (DPR RCD) |
| 1,3-Dichloropropene | 0.04 (DPR RCD) |
| Metam sodium | 0.185 (DPR RCD) |
| Formaldehyde | 0.021 (OEHHA 2005) |
| Propylene oxide | 0.013 (OEHHA 2005) |
| Pentachlorophenol | 0.018 (OEHHA 2005) |
| Perchloroethylene | 0.051 (OEHHA 2005) |
| Benzene | 0.1 (OEHHA 2005) |
| Ethylene oxide | 0.31 |
| Benzidine | 500 |
| Methylene chloride | 0.0035 |

DPR RCDs can be found at http://www.cdpr.ca.gov/docs/emon/pubs/tac/finlmenu.htm (finalized RCDs) and http://www.cdpr.ca.gov/docs/emon/pubs/tac/draftevals.htm (draft RCDs).
OEHHA 2005 = Cancer Potency Factors, OEHHA, May 2005, www.oehha.ca.gov/air/hot_spots/index.html

There are several indications that the chronic/carcinogenicity rat inhalation study may not be valid. We request that DPR staff and the SRP more carefully evaluate the raw data from this study to clarify several points:

- The survival rate of control groups (38–39%) was lower than that of the treated groups (43–51%). Is there any reasonable explanation for the high death rates in the control group? Was the control group being dosed inadvertently? What was the setup of the cages during treatment?
- DPR notes that: "Excess deaths in the 60 ppm rats occurred during months 5 and 6 of the study. Engineering corrections and changing cage placements stopped the mortality." If "excess deaths" were corrected by changing cage placements, how can DPR verify the accuracy of any of the dose levels?
- It is not clear if all tumors were reported in the study, or if all animals were examined—particularly those that died before termination. Pituitary adenomas and "undetermined" accounted for nearly all early deaths, yet no pituitary adenomas are reported in Table 21 (p. 58) in *Volume 1: Human Health Risk Assessment for Methyl Iodide*. Were these tumors excluded from the totals? Were all of the animals that died prior to termination examined?

## 5. Developmental toxicity and the validity of the PBPK model

We share DPR's, OEHHA's and the SRP's concerns about the developmental toxicity mode of action and the resulting PBPK model that US EPA used in their risk assessment. The PBPK model presented by EPA as part of the methyl iodide risk assessment is an interesting attempt at modeling, but leaves much to be desired in terms of certainty. In particular, the model relies on multiple assumptions for which little supporting data are provided or referenced. Some assumptions are flatly contradicted by data from the other studies, and the majority of these assumptions skew the results systematically in the direction of allowing greater exposures to methyl iodide. We elaborate on these assumptions in section 1.2 in PANNA's comment letter to US EPA. We cannot support the conclusions obtained using the PBPK model and urge DPR to use the default method that utilizes the NOAEL and both intra- and inter-species uncertainty factors of 10, plus an additional uncertainty factor of 10 to account for lack of data on the developmental neurotoxicity of methyl iodide.

## 6. The role of glutathione and the PBPK model

The alkylation of glutathione by methyl iodide is one of the primary biological mechanisms for detoxifying and excreting methyl iodide *in vivo*. We question several assumptions made by US EPA in its implementation of the PBPK model as it is used for determining the HECs for salivary gland metaplasia and request that DPR and the SRP review these assumptions. Specifically, the assumptions made do not account for the following: 1) exposures to glutathione-depleting substances beside methyl iodide, 2) damage to nasal epithelial tissues that would reduce glutathione production, 3) the difference in turnover rates of GSTT1 between rats and humans, and 4) the intrinsic variability in the human population of the ability to produce GSTT1, the enzyme that catalyzes the reaction of glutathione with electrophilic substances. We refer the reader to section 1.2 in PANNA's comment letter to US EPA for a more detailed discussion of this topic.

## 7. Inhalation dosing in animal studies does not match real-world exposures

A serious flaw in the HEC process is that test animal exposures to methyl iodide do not match anticipated human exposures. Most inhalation exposures for laboratory animals are set at a constant concentration for six hours per day, five days per week, providing time for the animals' repair systems to respond to the chemical insult during the "rest" periods (see Figure 1). For the methyl iodide developmental toxicity study, dosing occurred for six hours per day, seven days per week over the 28-day gestation period. The rest periods during these studies provide an opportunity for the laboratory animals to replenish depleted glutathione, excrete excess iodide and begin repairing methyl-iodide-damaged tissues.

**Figure 1:** Exposure pattern for laboratory animals exposed to methyl iodide via inhalation for a typical six hours per day, five days per week study.

Exposure patterns for people living near fumigant application sites are substantially different, with an exposure spike that may cause acute effects during the first day or two after the application, followed by a decreasing concentration over the next week or two (see Figure 2).

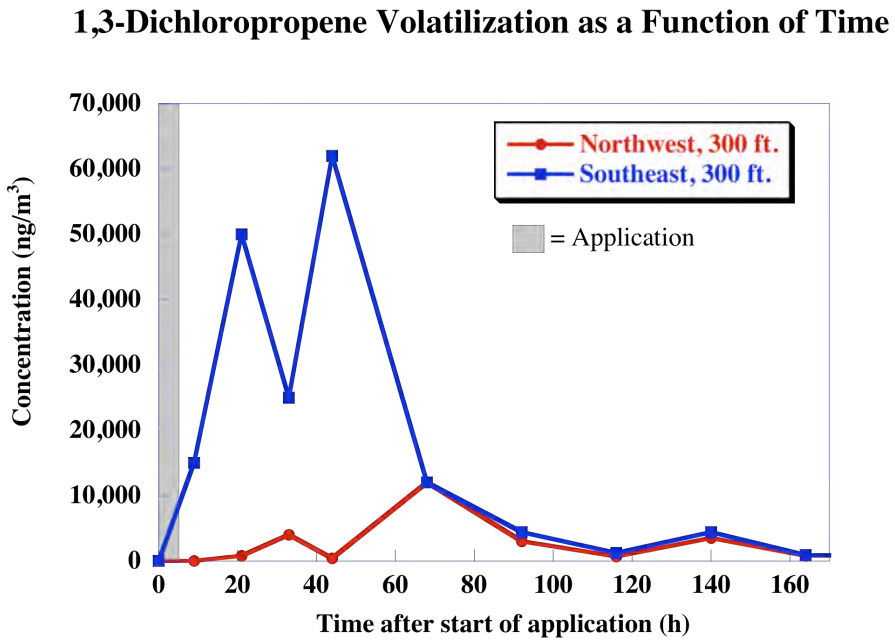


**Figure 2:** Exposure pattern for an actual application of 1,3-dichloropropene, a fumigant similar to methyl iodide in volatility.

Real-world exposure can be continuous (assuming one stays at home and the wind direction is constant), with no opportunity for recovery. The high spike in concentration is likely to have a significantly different toxic effect than the constant exposure experienced by laboratory animals.

Because of the possibility of mixed acute and sub-chronic effects, this failure in inhalation exposure dosing is likely to be one of the most significant flaws in current reference concentration (RfC) methodology that leads to an underestimation of the actual HEC, especially for GSH-dependent toxicity. Because the time course and duration of animal inhalation studies do not effectively mimic human exposures, the selected endpoints are not protective for real-world exposures.

## *8. Concurrent exposure to multiple fumigant chemicals has not been accounted for*

MIDAS® products are formulated with chloropicrin, a severe irritant, a glutathione depletor and a carcinogen.[2] Yet no analysis of the potential effects from concurrent exposures to methyl iodide and chloropicrin were conducted. This is a serious flaw in the risk assessment; however, it can reasonably be assumed that the combined presence of chloropicrin and methyl iodide will at least enhance cancer risk and glutathione depletion and may possibly exacerbate other effects.

[2] DPR 2009. Risk Characterization Document for Chloropicrin. http://www.cdpr.ca.gov/docs/emon/pubs/tac/draftevals.htm.

The net result of this enhancement is that toxic effects will be observed at lower doses than those determined in a risk assessment that accounts for exposure to only a single chemical.

# II. Exposure Assessment

## *1. Prior poisoning incident data indicate that if methyl iodide is approved for use, exposures above levels of concern are inevitable*

The use of other fumigants, particularly chloropicrin and metam sodium, has resulted in a number of mass poisoning incidents, where entire communities have been evacuated and tens of people have been taken to the emergency room. Table 2 summarizes some of the larger incidents.

**Table 2: Mass Poisoning Incidents Involving Fumigants**

Earlimart, CA (Tulare County)
November 1999, metam sodium
178 people

Arvin, CA (Kern County)
July 2002, metam sodium
270 people

Lamont, CA (Kern County)
October 2003, chloropicrin
235 people

Salinas, CA (Monterey County)
October 2005, chloropicrin
60 people

Yerington, NV
October 2007, chloropicrin
24 people

It is worth noting that chloropicrin and MITC (the active fumigant from metam sodium) are highly acrid and irritating gases and are easily detected by exposed populations. Because the response to other fumigants such as 1,3-dichloropropene, methyl bromide and methyl iodide will be more subtle (headaches, nausea, malaise, irritability, inability to concentrate) and easily confused with a viral or bacterial illness, fewer of these incidents will be noticed and reported, but will undoubtedly occur.

In some of these incidents, applicator error was the cause of fumigant drift. This is not unexpected; errors can reasonably be anticipated for any complex application method such as that used for fumigations. For other incidents (Yerington, NV is the most recent), no mistakes were made during the application, yet because the application was conducted under inversion conditions, a plume of chloropicrin drifted nearly a half-mile away in sufficient concentration to cause 28 workers to be taken to the hospital.

The onset of such poisoning incidents often coincides with inversion conditions. The role of inversion conditions in some of the poisoning incidents shown in Table 2 is discussed in greater detail in sections 2.1.2–2.1.5 of PANNA's comment letter to US EPA.

Since inversion conditions are quite common in California during fumigation season and since there is so little enforcement capacity, even a label restriction requiring fumigations to be conducted only during non-inversion conditions would not be sufficient to protect bystanders, as it would likely be widely ignored. Such behavior occurred at Moss Landing at a fumigation in August 2007, where a court order requiring that the fumigation was not to be conducted under inversion conditions was violated. The weather service predicted inversion conditions, yet the Monterey County Agricultural Commissioner himself approved the application and was there in person to watch. Such "enforcement" appears to be commonplace, and the growers' requests to have their fields fumigated in a timely way seem to override any concerns for poisoning adjacent communities and workers in nearby fields.

This incident illustrates the overriding problem with unenforceable mitigation measures printed on the pesticide label that are considered to be "law." Without local agencies with the field capacity to conduct significant numbers of inspections and the willingness of these agencies to enforce the label requirements, these restrictions are meaningless and will not prevent community poisonings. The only restriction that will prevent methyl iodide poisonings is for DPR to deny registration of this pesticide.

## *2. The SRP and DPR should carefully review the input parameters used in the ISCST3 exposure model*

California DPR's use of the ISCST3 model instead of PERFUM is laudable. Some questions and concerns remain. We do not have access to all of the details for how the analysis was conducted but suggest that the following issues be clarified by DPR staff and then reviewed by the SRP.

- **Because most of the observed poisonings occur during calm wind conditions, it is essential to ascertain that calms are being handled appropriately in the bystander exposure model.**
  Both PERFUM and ISCST3 are simple Gaussian plume models that do not adequately model concentrations at low wind speeds. In fact, results obtained using ISCST3 under these conditions are sufficiently misleading at low wind speeds that they are commonly thrown out of the overall results per US EPA Office of Air guidelines.[3] The following is the full text of paragraph 9.3.4.2 of these guidelines:

  9.3.4.2 Recommendations

  a. Hourly concentrations calculated with steady-state Gaussian plume models using calms should not be considered valid; the wind and concentration estimates for these hours should be disregarded and considered to be missing. Critical concentrations for 3- , 8-, and 24-hour averages should be calculated by dividing the sum of the hourly concentrations for the period by the number of valid or non-missing hours. If the total number of valid hours is less than 18 for 24- hour averages, less than 6 for 8-hour averages or less than 3 for 3-hour averages, the total concentration should be divided by 18 for the 24-hour average, 6 for the 8-hour average and 3 for the 3-hour average. For annual averages, the sum of all valid hourly concentrations is divided by the number of non-calm hours during the year. For models listed in Appendix

[3] *Guideline on Air Quality Models*, EPA 40 CFR Ch. I (7–1–03 Edition) Pt. 51, App. W, available from US EPA Air Quality Modeling Group, Support Center for Regulatory Atmospheric Modeling (SCRAM), http://www.epa.gov/ttn/scram/.

A, a post-processor computer program, CALMPRO has been prepared, is available on the SCRAM Internet Web site (subsection 2.3), and should be used.

b. Stagnant conditions that include extended periods of calms often produce high concentrations over wide areas for relatively long averaging periods. The standard steady-state Gaussian plume models are often not applicable to such situations. When stagnation conditions are of concern, other modeling techniques should be considered on a case-by-case basis (see also subsection 8.2.8).

c. When used in steady-state Gaussian plume models, measured site specific wind speeds of less than l m/s but higher than the response threshold of the instrument should be input as l m/s; the corresponding wind direction should also be input. Wind observations below the response threshold of the instrument should be set to zero, with the input file in ASCII format. *In all cases involving steady-state Gaussian plume models, calm hours should be treated as missing, and concentrations should be calculated as in paragraph (a) of this subsection. [Italics added]*

Note that section 9.3.4.2.a begins by underlining the inadequacy of Gaussian plume models under low wind conditions. Under these conditions, paragraph 9.3.4.2.c describes a procedure for discarding calm and near-calm results from PERFUM/ISCST3. However in the present case (methyl iodide gas originating at ground-level and being contained near the ground due to high atmospheric stability), discarding these results will result in substantially lower estimates of methyl iodide concentrations than actually exist in a real-world field fumigation. In this case, paragraph 9.3.4.2.b is applicable: "When stagnation conditions are of concern, other modeling techniques should be considered on a case-by-case basis."

Fortunately, in the last several years—in fact during the very range of years that the poisonings we have examined were occurring—the state-of-the-art in regulatory modeling has expanded to encompass these conditions. The American Meteorological Society has developed the AERMOD model that goes beyond ISCST3 and contains new and improved algorithms for dispersion in stable boundary layers.[4]

We are also aware that DPR has utilized the CalPUFF model to address calms. What is unclear is what, precisely, DPR did in the modeling of methyl iodide exposures and whether this modeling accurately predicts ground-level concentrations during calms. The risk assessment appears to be missing references to the documents that describe this methodology. We request that DPR include all relevant documentation and data (or provide references with links that enable access to this documentation) and that the SRP review this information to ensure that calms are being handled appropriately by the model. A check on the method would be to apply the model to the conditions that prevailed during a known poisoning incident that occurred during inversion conditions to determine if the model can accurately predict such events.

- **We request that DPR include the details of the field studies evaluated for use as the basis for the indirect back-calculation of the flux profile for methyl iodide for each application method and clarify how differences in soil temperature are accounted for by the model.**
  We are concerned about the possibility that the flux profile used in the exposure model

[4] *AERMOD: Latest Features and Evaluation Results*, Emissions Monitoring and Analysis Division, Office of Air Quality Planning and Standards, US Environmental Protection Agency, EPA-454/R-03-003, June, 2003, http://www.epa.gov/scram001/7thconf/aermod/eval.pdf.

may not adequately account for the high soil temperatures that are observed in summer fumigations in the Central Valley. Because the flux is highly dependent on soil temperature, the model may substantially underestimate concentrations if a flux profile derived from a field study conducted at moderate soil temperatures is used to estimate concentrations for a fumigation carried out at high soil temperatures.

DPR suggests that information on the relationship between flux and soil temperature is not available. On page 45 in *Volume II: Exposure Assessment for Methyl Iodide*, DPR notes that "Flux may also be a function of soil textures and temperatures. However, DPR does not have studies that adequately quantify the magnitude of the effect of those factors." We would like to suggest that DPR has access to multiple field monitoring studies of methyl bromide, chloropicrin, and 1,3-dichloropropene applications that could serve as a reasonable model for assessing changes in flux with temperature for methyl iodide. These data should be integrated into the methyl iodide exposure assessment.

We request that DPR provide clarification of which field studies were used to develop the flux profile and how soil temperatures may differ from those in the study from which the flux profile was determined. There should be an analysis of the various studies evaluated for creation of the flux profile (whether or not they were used or excluded). If different soil types, temperature conditions or other factors yielded different results, those variations should also be analyzed and presented. Limitations of each study should be discussed, and DPR's rationale for reducing the various study results to a final flux profile should be explained. We suggest presenting this information in a table to facilitate comparison of the various study conditions and results. Such a table should include columns for:

- Date and location
- Monitoring conducted by (e.g., CA DPR, registrant, etc.)
- Application rate (lbs active ingredient/acre)
- Acres treated
- Soil temperature
- Distance of monitoring stations to field border (feet); Alternatively, if a flux tower was used, specific parameters related to sampling heights on the tower
- Location of stations relative to prevailing wind direction (Upwind, Downwind, Variable)
- Maximum concentration at a single sampling station at a particular distance ($ng/m^3$)
- Calculated flux range
- Notes

## 3. *The documentation of the exposure model should explicitly describe how and when averaging is used in the data and in the implementation of the model*

We have observed some questionable practices related to averaging in the presentation of air monitoring results and in the inclusion of monitoring results in exposure models. Because we do not have access to the raw air monitoring data to verify the format of the results used for the MeI exposure assessment, we request that DPR clarify more explicitly how the studies were

conducted and how results were reported, including any averaging that might have been done on sampling results.

For example, consider a simple air monitoring study with four samplers placed at the cardinal directions around a field (see Figure 3). Data shown are imaginary but realistic, and are used to illustrate some of the issues associated with averaging data.

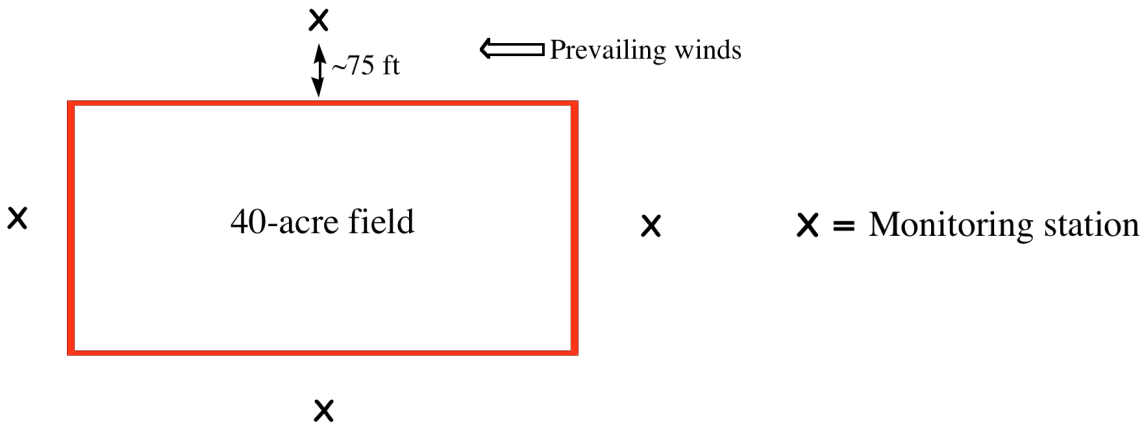


**Figure 3:** A simple sampling plan for a pesticide application site monitoring study.

A typical concentration profile from such a study might look like the upper left plot in Figure 4, where prevailing winds are from the southwest, with the plume from the application moving to the northeast. The peak concentration observed in this monitoring study was 25 ppm at the East sampler. The 24-hour average concentration at that site is 7.36 ppm, as shown in the upper right plot in Figure 4.

Both DPR and US EPA use a 24-hour average for bystander exposure estimates, in spite of the fact that concentration spikes lasting from a few hours to nearly a day are typical for these kinds of applications. The spikes are relevant, since glutathione depletion and increase in serum iodide levels are both relatively rapid responses to methyl iodide exposure: "At 25 ppm MeI, maximal GSH depletion (40 to 50% of control) was measured in the nasal epithelium, and about 30% in the other tissues, 3 to 6 hours after initiation of exposure" (Volume 1, p. 30). Serum iodide levels increased from 17 ppm in the control group to 5,070 ppm after one hour of exposure to 25 ppm of MeI and to 25,600 ppm after 6 hours of exposure (Volume 1, Table 8, p. 31).

The lower left and lower right plots in Figure 4 show another kind of concentration averaging that has been used in reporting the results of MITC monitoring in Washington state and possibly in other industry studies as well.[5] In this approach, concentrations observed at all samplers around the field (N, S, E, and W) are averaged for a particular sampling time, thus reducing the peak reported concentration from 25 ppm to 11.21 ppm for a "whole-field" average. A 24-hour average of exposures calculated in this way is only 3.26 ppm, a reduction by a factor of 7.7 from the actual peak exposure observed over a 2–3 hour time period.

[5] Hebert V, LePage J. 2007. Table 1 (p. 7) in *Analytical Summary Report: Near Field Emissions of MITC Following Shank Injection and Chemigation Metam Applications.* http://www.doh.wa.gov/EHP/Pest/wsumitcrpt.pdf.

Another place where averaging may be inappropriate is in the flux rate. It appears that both 8-hour and 24-hour TWA flux rates were used to estimate worker and bystander exposures. DPR and the SRP should carefully evaluate the appropriateness of 8- and 24-hour flux averaging times in light of the rapid onset of physiological effects due to MeI exposure.

Averages are also used for the assumed breathing rates to estimate worker exposures. Averaging is again used for worker exposure studies in which ADDs and SADDs are determined from several different studies. The SRP and DPR should evaluate whether this is an appropriate use of averaging as well.

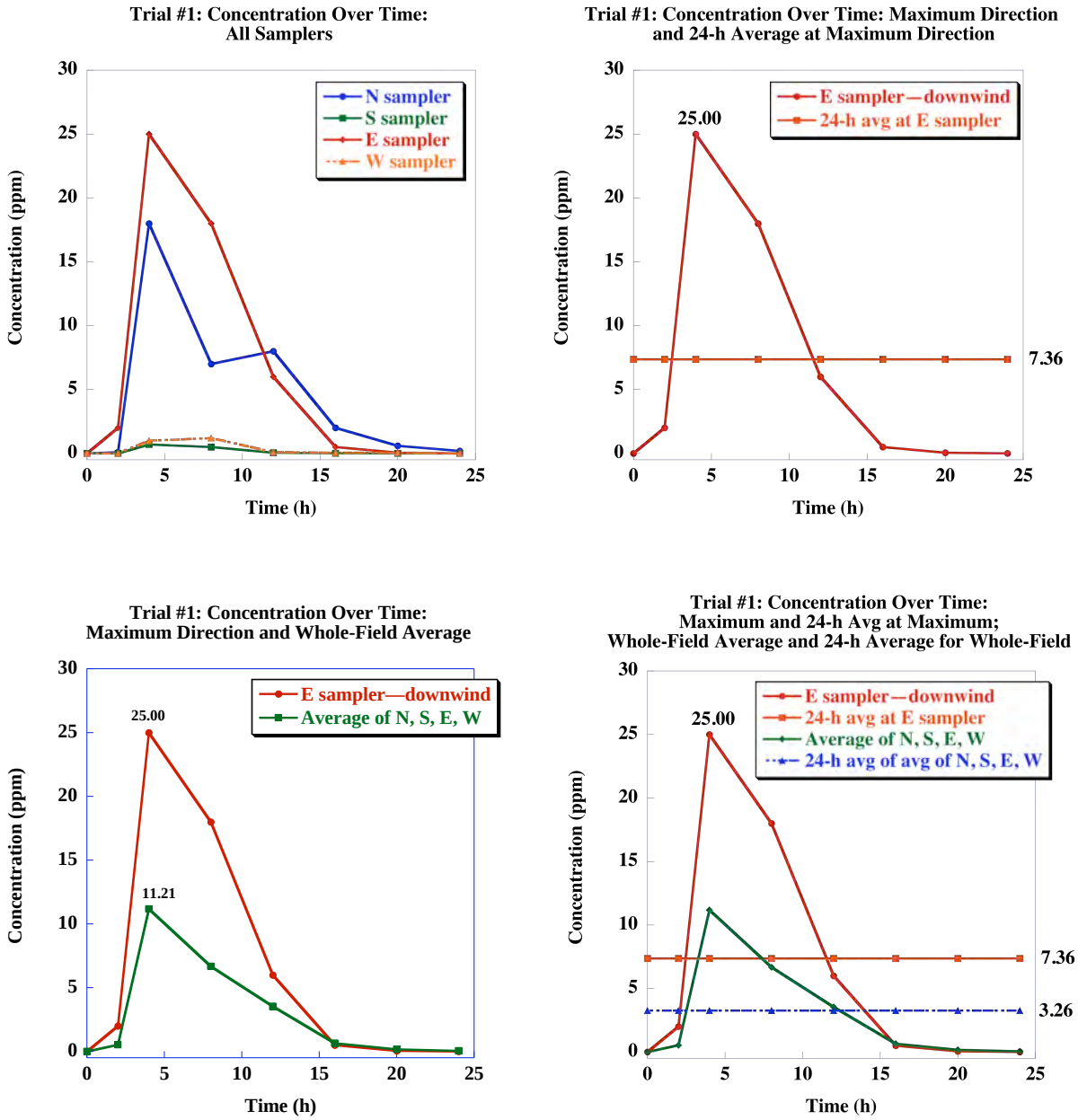


**Figure 4:** A typical sampling profile for a pesticide application, using imaginary but realistic data. The plot on the upper left shows results from all four sampling stations around the field and the plot in the upper

right focuses on only the highest concentration sample site and the 24-hour time-weighted-average concentration at that site.

## 4. Groundwater contamination remains a concern

At the Sept. 24–25 meeting, DPR clarified to the SRP that the department did not have sufficient information to guarantee that methyl iodide would not contaminate groundwater. In fact, the physical properties and reactivity of methyl iodide in groundwater are similar to those of DBCP, a fumigant that pollutes many wells in the Central Valley, making them unusable for drinking water. DPR's response to the SRP's questions indicated that once a groundwater problem was noticed, the department would know how to handle it because of their previous experience with DBCP.

Besides the fact that DPR's statement suggests that they have already decided to register the fumigant (making the SRP's review moot), we do not believe DPR should ever get to the point of having to remediate groundwater contamination, when such contamination is completely preventable by not permitting use of the chemical in the first place.

## 5. Subchronic exposure becomes problematic when fumigations are broken up into smaller application blocks

DPR conducted exposure modeling for a 40-acre field fumigation with a 500-foot buffer zone. In practice, our experience with methyl bromide fumigations indicates that growers will do whatever it takes to reduce the size of the required buffer zone, and few will accept a 500-foot buffer. The alternative is to break the application into smaller application blocks of 5–10 acres and/or use fumigants for which smaller buffer zones are acceptable for the blocks near sensitive sites. The result is that fumigation of the same 40-acre field would occur over a longer time period, such that subchronic exposure becomes a significant issue. Additionally, bystanders are exposed to multiple fumigants, often simultaneously.

For example, the Moss Landing fumigation mentioned above occurred on a 54-acre site. Because the grower did not want to use the buffer zone distances required for methyl bromide if all 54 acres were treated simultaneously, he chose to break the application into seven separate applications, using telone (1,3-dichloropropene) and chloropicrin for the fields closest to the neighborhood to the north and methyl bromide for the blocks furthest away from the neighborhood to the north (see Figure 5). The adjacent neighborhood was exposed to drift from these seven applications over the course of two months.

**Figure 5:** A typical grower response to requirements for large buffer zones for fumigation of many acres is to break the fumigation into smaller blocks that require smaller buffer zones.

The problem is exacerbated by the fact that fumigation is a seasonal activity and occurs at the same time of year for all farms that do fumigations for a particular crop. This results in some level of ambient exposure to the fumigants in use over the course of two to six months, depending on the location. Figure 6 below shows fumigant application patterns for 2005–2007 for Monterey and Ventura counties, illustrating the length of the fumigation season in the two areas.

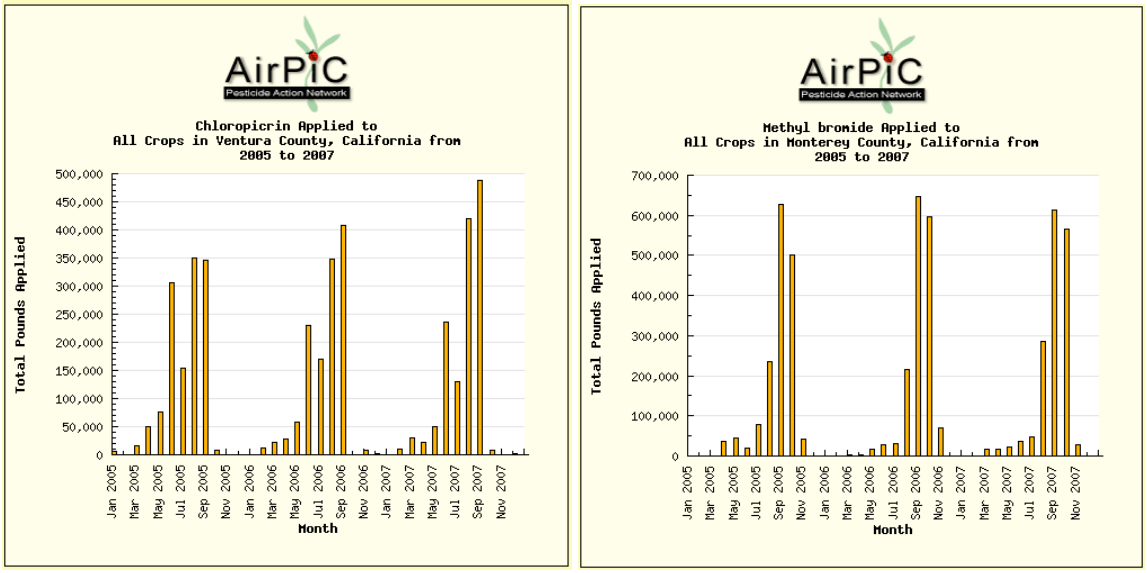


**Figure 6:** Seasonal applications of fumigants can occur over a several month period, resulting in both acute and subchronic exposures.

### *6. Occupational exposures are underestimated*

We refer the reader to the comment letter in this docket from Anne Katten with the California Rural Legal Assistance Foundation for a discussion of this issue, and include it here by reference.

## III. DPR should refuse to register methyl iodide for any uses in California.

The data indicate that methyl iodide poses many different risks to California workers, neighbors living near application sites, and people who drink groundwater that may become contaminated with methyl iodide. Fetal death appears to be the most sensitive endpoint, but cancer, neurotoxicity and thyroid toxicity are all significant concerns.

Our preliminary assessment is that once DPR accommodates the SRP's comments and concerns, the "acceptable" dose of methyl iodide is likely to be lower than the current "acceptable" dose, and the modeled exposures for four and eight hours will be higher than those for 24 hours currently described in DPR's risk assessment. It is difficult at this point to envision any new data that would indicate that methyl iodide could be used as a fumigant without significant adverse effects to workers and neighbors. The California Birth Defects Prevention Act (SB 950) requires the DPR Director to prohibit use of pesticides that have the potential for causing significant adverse health effects. MeI is such a pesticide and should not be registered by DPR.

We recognize that there will be extreme pressure on DPR from Arysta and from growers who would like to have methyl iodide for some special uses viewed as "critical." However, we are concerned that if methyl iodide is registered initially for just a few restricted uses, restrictions will likely be altered over time and methyl iodide use will quickly expand to fill the gap left by the methyl bromide phase-out.

An example already exists in which DPR initially placed severe restrictions on a pesticide that have since been eroded over time. In the early 1990s, DPR canceled all uses of the fumigant 1,3-dichloropropene after air concentrations of the pesticide were found to exceed levels of concern for cancer risk. The pesticide was reintroduced in 1994 with extensive restrictions—use of the chemical was permitted only under certain circumstances and in certain counties every third year. Within a few years, these restrictions were lifted, and in 2007 (the last year for which pesticide use reporting data are available), 1,3-dichloropropene was used in most agricultural counties across the state; a total of 9.59 million pounds of 1,3-dichloropropene was reported used statewide (see Figure 7 below).

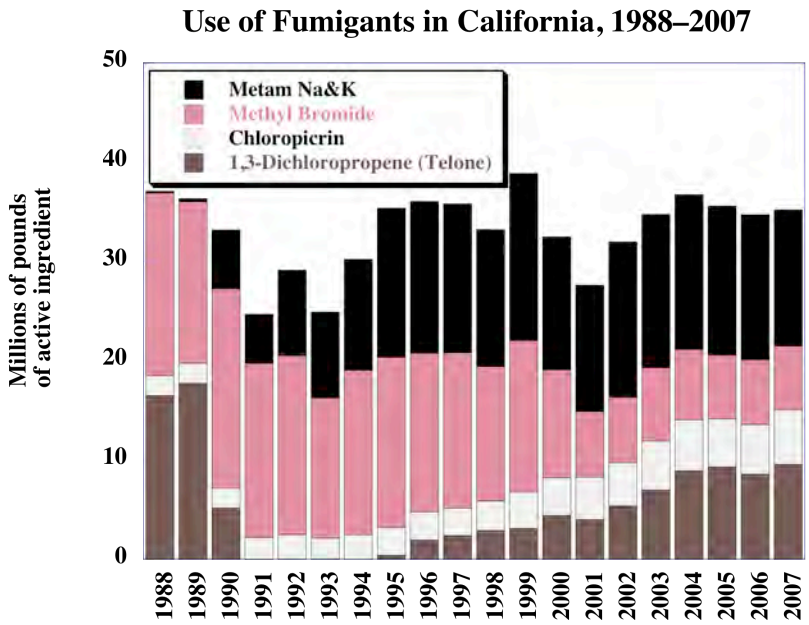


**Figure 7:** Trends in fumigant use in California between 1988 and 2007. *Data source:* CA DPR Pesticide Use Reporting data, http://www.cdpr.ca.gov/docs/pur/purmain.htm.

Instead of facilitating the use of highly toxic fumigants, DPR should focus on working with the state legislature and CDFA to incentivize use of non-fumigant methods for soil pest control. We refer DPR and the SRP to section 4.3 in PANNA's comment letter to US EPA for a discussion of promising alternatives.

Sincerely,

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Pesticide Action Network North America

Anne Katten, MPH
Pesticide and Work Safety Specialist
California Rural Legal Assistance Foundation

Robina Suwol, Executive Director
California Safe Schools

Traci Townsend, Program Manager
Pajaro Valley Health Action Team (PVHAT)
Planned Parenthood Mar Monte

Marilyn Lynds
Moss Landing Resident

Deborah Bechtel
Community & Children's Advocates Against Pesticide Poisoning

Paul S. Towers, Director
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Center for Environmental Health

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October 9, 2009

To California Department of Pesticide Regulation and the External Science Advisory panel,

I am a postdoctoral fellow at the Program for Reproductive Health and the Environment at UC-San Francisco. I understand the current step in this process is for the science advisory panel to comment on the CDPR's assessment of MeI, which I will discuss later in this letter. I am also writing today to highlight not only reproductive development and neurotoxicity concerns of methyl iodide, but to speak as a chemist. I am very concerned with the replacement of methyl bromide with methyl iodide. I agree with the 1986 decision to phase-out methyl bromide because of its reactivity with the ozone layer, but methyl iodide doesn't impact the ozone as much as methyl bromide not because it's *less* reactive, but because it's actually *more* reactive and will interact with humans, animals and the environment before reaching the upper atmosphere.

I received my PhD in Chemistry from UC-Berkeley a year and a half ago and when I speak to fellow chemists about the possibility of replacing something as toxic as methyl bromide with an even more reactive compound, they often laugh at me and think I'm not being serious. And since most chemists are unfamiliar with pesticide practices, when I tell them that we spray hundreds of pounds of methyl bromide on soil at a time, they are shocked. When I tell them methyl iodide is the proposed replacement for methyl bromide, they are stunned.

Methyl iodide is a registered carcinogen in California (prop 65) and is known to cause serious health effects such as thyroid hormone and central nervous system disruption, and neurotoxicity in addition to cancer.

Synthetic chemists use methyl iodide in their reactions because it is an extremely reactive alkylating agent, but we use it only under extremely protective conditions – in a fume hood, with appropriate personal safety equipment, and only then do we handle this liquid via a syringe in a sealed container to prevent exposure because we know it's an efficient DNA methylator that will increase our likelihood of cancer. And we use these precautions for when we are working with very small amounts—a few drops to a few milliliters. The USEPA has determined it safe to spray up to 175 pounds PER ACRE, 40 acres at a time of this compound onto fields with a buffer zone of 500 feet. The buffer zone is only 25 feet if you spray fewer acres.

At UCSF, a major focus of our group's research is how environmental factors may affect reproductive health and development. The thyroid hormone system regulates not only reproductive development, but also general metabolism, growth and neurodevelopment. The structure of the main thyroid hormone contains iodine, and is the reason iodine is an essential micronutrient. However, too much iodide exposure leads to suppression of thyroid hormone synthesis, and severe perturbations in the endocrine system. These can cause serious consequences on neurologic development and have long-term adverse reproductive health outcomes.

One of the toxicity endpoints of greatest concern to CDPR is perturbation of thyroid hormones of adults and fetus. (pg. 172, vol I) During fetal development, the mother is the only source of thyroid hormones for the baby and therefore, a perturbation in the mother can also lead to an imbalance in the fetus. Fetal development

is a period of rapid growth and development of essential organs and internal systems and very small perturbations can lead to severe adverse effects months and years down the road. Moreover, the populations that are most likely to be exposed to MeI are already exposed to other pesticides in their daily lives, and this leads to higher chemical body burdens and should be considered in the risk assessment.

In pregnant rats and rabbits, methyl iodide causes thyroid hormone disruptions, fewer viable fetuses, lower birth weight, and increased fetal death, especially during late pregnancy. According to its MSDS sheet, it's also a neurotoxicant that can be absorbed through the skin as well as inhaled. The USEPA's website states "short-term exposure may depress the central nervous system, irritate the lungs and skin, and affect the kidneys. While "long-term exposure may affect the central nervous system and cause skin burns."

While there is a high rate of volatilization (or evaporation into the air), and our low-organic matter soils in California have higher rates of volatilization compared to higher-organic matter soils, there are other degradation routes for MeI that are known to occur in the soil-water environment, and they all yield an iodide ion(pg. 6, vol 3). Iodomethane is also more persistent than methyl bromide in soil and water, which early investigators who studied the environmental fate & transport, suggested would lead to more groundwater contamination from methyl iodide. (Gan, Yates, et al, J. of Env. Qual., 26 , 4, 1107-1111, 1997). The CDPR estimates that inhalation exposure for bystanders and groundwater exposures together would surely exceed safety limits for iodide set by the National Academy of Science and ATSDR.

I agree that the CDPR's assessment is an improvement over the USEPA's assessment, and now I'll discuss some of the specific parts of the risk assessment I found important.

- CDPR more appropriately used a directional wind parameter in their calculations and found that estimated exposures for bystanders were 375 times higher than the determined safety limit and 3000 times higher than the limit for workers. Clearly, this is an additional reason to look carefully at allowing such a potent toxicant into our environment in such large amounts. The model used by EPA to calculate wind drift and bystander exposures did not take into account directional wind, which is most often the case in reality.

- CDPR recommends an extra 10-fold uncertainty factor because of the absence of sufficient pre-and post-natal developmental neurotoxicity data. This would result in an even higher benchmark dose as well as proportionally lower calculated reference concentrations. USEPA argues that MeI is a non-food use pesticide and consequently is not subject to the 10x safety factor required under the Food Quality Protection Act (appendices pg. 64 or C-4). Nevertheless, children will be exposed and they are more sensitive to carcinogens. CalEPA's OEHHA has published a detailed analysis of the greater sensitivity of children to carcinogens. Children are also more susceptible to thyroid hormone disruptions, as they are growing and developing faster. Additionally, children receive a higher dose because they breathe about twice as much air per pound of body weight than adults.

- The uncertainty factor CDPR recommends is 300 —10 times larger than USEPA. However, even if you only apply the 30x uncertainty factor to the USEPA 24-hour HEC for fetal death endpoint, the estimated excess iodide burden would be up to 10,400 ug/day. This is 30-90 times higher than tolerable upper limits set by the National Academies of Science and the ATSDR for iodide exposure.

- CDPR more correctly estimates exposures to iodide by including water sources as well--USEPA only considers exposure to MeI from air. CDPR found that **"**From both water and air, the calculated iodide

intakes under most cases are higher than established health standards for iodide. Thus, the recommended MeI RfCs for any duration should be much lower, at levels not to exceed 1ppb, for the protection of young children"(pg. C-4 and C-5 of appendices). The CDPR's assessment of groundwater fate discusses the lack of data on fate of iodide ions after application. The only studies in California show low levels of iodide in the soil but did not determine the ultimate fate of the iodide. Additionally, this study did not address long-term repeated application situations, which are typical for annual crops and how this might affect groundwater contamination.

- Determining a lower NOAEL for fetal death than USEPA is an improvement, but the more scientifically appropriate method is to use a benchmark dose model. These linear models are much better representations of the dose-response behavior. By using NOAEL methods, USEPA ignored the large percentage of fetal deaths during mid-range dose experiments.

- Rather than using overt health outcomes such as thyroid hormone tumors and fetal death to calculate reference concentrations, CDPR should use the doses that indicate earliest observed adverse endpoints such as the glutathione depletion seen in these experiments. The USEPA actually recommends this method of risk assessment, but the pesticide office does not use it.

- There is no safety factor considered or discussion of, background chemical exposures or co-exposure incidences—populations living in agricultural areas are also exposed to other pesticides year-round and these contribute to higher body burdens and increased overt health outcomes in these groups.

- The formulation of this pesticide is such that is mixed with another highly toxic fumigant, Chlorpicrin. I'm told this is because chlorpicrin is a strong lachrymator and this will aid workers in determining if they have been acutely exposed because methyl iodide has very little smell. There is nothing in the risk assessment that addresses the fact there will be simultaneous exposures to both of these chemicals.

In summary, California Department of Pesticide Regulation has done an improved risk assessment, but it's still incomplete. I encourage the science advisory panel to support their findings and even though I believe some improvements could be made in their findings that would probably lower reference concentrations, and there are a couple areas where there are some gaps in the data, I do not think more data or toxicity tests will somehow find this chemical safe to use as a soil fumigant. It is more toxic than the MeBr it's replacing and since CDPR concludes that people will most likely be exposed at levels much higher than the reference concentrations, allowing MeI to be used as a pesticide *will* have adverse effects on public health.

Sincerely,

Amber R. Wise, PhD

# WORKSAFE

A CALIFORNIA COALITION FOR WORKER OCCUPATIONAL SAFETY & HEALTH PROTECTION


**October 9, 2009**

## Public Health Protections for Older Children Working in Agriculture

Worksafe respectfully submits the following comments to the Methyl Iodide Scientific Advisory Board. These comments are a collaborative effort by Worksafe and Kathleen Burns, Ph.D. of Sciencecorps in Lexington Massachusetts.

Our comments focus on specific concerns of the risks to adolescent farm workers, particularly males, who may be exposed either by working in fields where MeI has been applied or by drift. Despite the special vulnerability of these older children, currently there are not adequate regulatory protections for these teen workers.

In addition to the rather specific comments provided below, we also support the more comprehensive comments that have been provided by the California Rural Legal Assistance Foundation, Pesticide Action Network, and the Natural Resources Defense Council.

**Key Points:**

I. The exposures of older children to Methyl Iodide (MeI) as a result of their work in agriculture require careful evaluation. Adolescents (ages 12 to 17) are routinely employed in agricultural work, which creates clear opportunities for exposure. Multiple hazardous situations where health damage can occur are prevalent in agricultural work. In addition, older children have elevated inhalation rates compared to adults, increasing their short term and cumulative exposure levels above those of many other members of the population.

II. Older children undergo intense and rapid brain development and substantial hormonal changes. They are highly susceptible to neurotoxic chemicals and MeI is a neurotoxin. Hormone disruptors also pose specific serious problems for older children, and MeI is a hormone disruptor. There is insufficient scientific information on which to base a claim that a "safe" level of exposure can be determined for older children.

III. Current California child labor laws do not adequately protect young workers from pesticide exposure. Yet teens do work in California's agricultural fields. Therefore, it is prudent public health policy to protect young workers from exposure to highly toxic pesticides such as methyl iodide. The best way to achieve this is by recommending against the approval of use of MeI use in the state.


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## I. Exposure

Those who work in the fields where MeI could be applied are likely to be exposed on a regular basis to MeI. All workers who performing tasks that disturb surface soil will bring MeI contamination to the surface and generate dust contaminated by MeI. Soil ingestion during outdoor work can be substantial (see US EPA Exposure Factors Handbook). Their near ground-level exposures at times, as well as dust generation during agricultural activities can yield intakes many times higher than a typical breathing zone (standing height) concentration.

Inhalation is much greater during manual labor and rates among adolescents doing this kind of work are among the highest, almost 60 m(3) for an 8 hour workshift (EPA Exposure Factors Handbook). Contamination of the 60 out of approximately 70 m(3) inhaled during a 24 hour period means that the proportion of uncontaminated air is small and the dose can be substantial.

As unskilled workers, teens are more likely to engage in labor-type jobs and often have minimal training in worker protection strategies. Thus, it is relevant to consider whether this poses a serious risk to this population subgroup.

## II. Susceptibility

Medical studies indicate the adolescent brain has a greater susceptibility to disruption than would be found in an adult. This is directly relevant to MeI, which is a neurotoxin. There are clearly developmental processes continuing into adolescence and the increased sensitivity that this generates has been illustrated in studies of many chemicals. Appendix A contains the abstracts of the studies discussed below.

White and Swartzwelder (2005) report on clear evidence that adolescence represents a unique stage of brain development. Changes in brain organization and function during adolescence are widespread, and include intense rewiring in the frontal lobes and other neocortical regions, as well as changes in a litany of subcortical structures.

Schweinsburg et al (2005) studied changes that occur in the frontal and parietal neural networks involved in spatial working memory over adolescence using functional MRI imaging. These substantial changes occurred as a part of normal brain development.

Walker et al (2004), evaluated adolescent stress sensitivity and vulnerability for the emergence of the mental disorders. They identified hormonal changes as a key element in expression of genetic vulnerabilities for psychopathology. They found both activational and organization effects of hormones on the adolescent brain that

contribute to developmental discontinuities in behavioral adjustment with implications for adult psychopathology.

Saddik et al (2005) studied the effects of solvent exposure on memory and motor dexterity in male working children ages 10 to 17. They found an association between exposure to solvents and neurobehavioral performance on a number of non-computerized tests for working children exposed to solvents in comparison with nonexposed working children and nonexposed children at school. Performance on memory tests and motor dexterity were reduced and mood tests indicated more anger and confusion than among the unexposed working or nonworking children

Abreu-Villaca et al (2004) studied the effects of the neurotoxin nicotine on the adolescent brain in a toxicological study using exposure levels typical of occasional to regular smokers. They found alterations in the levels of DNA in multiple regions of the brain, even at the lowest dose tested. The effects persisted at least 1 month posttreatment, with larger effects in females. The researchers concluded that during adolescence, the exposures elicited lasting cellular and neuritic damage at exposures approximately one-tenth of those in regular smokers. They described the adolescent brain as exquisite sensitivity to nicotine neurotoxicity, with potential lasting neurobehavioral damage.

Sisk and Foster (2004) report on a range of hormonal changes during adolescence and point to the remodeling and activation of neural circuits that occur as a result of hormonal influences. These researchers point to the hormonal-brain interactions as a critical element of development. This is directly relevant to MeI, which causes both hormonal disruption and neurotoxicity. They state:

> These influences of hormones on reproductive behavior depend in part on changes in the adolescent brain that occur independently of gonadal maturation. Reproductive maturity is therefore the product of developmentally timed, brain-driven and recurrent interactions between steroid hormones and the adolescent nervous system.
>
> (Sisk and Foster (2004).

The thyroid hormones are well known to have effects on the timing and levels of a wide range of hormones, including reproductive hormones described by Sisk and Foster. The finely tuned and highly susceptible hormonal balance that adolescents' physiology is working towards makes them especially susceptible to a hormonally disruptive chemical such as MeI.

Quantitative adjustments that incorporate greater safety factors are required in any assessment of risk that contemplates exposing children. In addition, the lack of adequate information regarding potential neurotoxic effects across the age span, and especially in high cognitive functioning, is a critical information gap can be partially addressed by a substantial additional margin of safety. To provide adequate protection,

it is necessary that research be carried out that can provide assurances of safety. At present there is no research of this type available on MeI so it is not possible to determine whether there is any safe level of exposure to MeI with respect to hormonal and neurological development. Greater wisdom would be demonstrated by not allowing the use of chemicals such as MeI in situations where children could plausibly be exposed.

We strongly recommended that potential harm to teen workers be evaluated by a team of objective specialists in adolescent pediatric neurology, neuro toxicity, endocrinology, and related fields. They are needed to evaluate the relevance of the toxic effects of MeI to older children, taking into account the unique susceptibilities of adolescents, their physiology, and likely exposure patterns.

It remains to be determined what the impacts of the neurotoxic and hormonally active chemical MeI is on adolescent hormone levels and neurological development may be. However, it is clear that this is an extremely critical sensitive period of development, and that abnormalities in physiology (e.g., levels of hormones) can cause serious disruption of normal growth and development.

## III. Lack of protection for older children working in agriculture

Despite the special vulnerability of these young workers, current California child labor laws do not adequately protect young workers from pesticide exposure.

First, it must be recognized that teen workers can be found working throughout California's agricultural fields, as documented by violations issued by the California Department of Industrial Relations to employers who have hired youth without valid work permits. State law requires that youth under the age of 18 must receive a work permit from their school, unless they have graduated. During coordinated EEEC sweeps over the last few summers to enforce the new Cal/OSHA heat regulation, there have been several instances where teen agricultural worked have been identified and questioned and their employers have been cited for hiring teen workers without a valid work permit. Worksafe's Executive Director participated in some sweeps and supervised summer interns who accompanied Cal/OSHA inspectors on other sweeps throughout the Central Valley. The point here is not whether they have a permit, but that this inspection process has confirmed the widespread presence of older children working in California's fields.

There is no regulation to prevent older children from working in or adjacent to fields that have been sprayed or fumigated. The primary restriction under California Labor code is that children ages 12-15 are prohibited from directly handling or applying pesticides (Labor Code 1294.1(a) and federal code 29 CFR 570.1). Teens ages 16 and 17 could be involved in the direct application of pesticides, assuming they met other certification and training requirements.

Youth workers may also be exposed to MeI through drift from an adjacent field during the work day. Between 1998 and 2003, about 12% of occupational pesticide illness reports were attributed to pesticide drift, as cited in MMWR 55(17); 486-488. There are no current regulations to require farmers applying pesticides in one field to notify workers employed by another farmer in an adjacent field. The only requirement is that farmers notify their own employees who are working within a quarter mile of the area being sprayed. It has been recommended to DPR that they issue more protective regulations to prevent exposure from drift. Until those regulations are in place, the prudent public health approach would be to prohibit the use of highly toxic pesticides such as methyl iodide.

## Appendix A. Abstracts of select cited studies.

### The effects of solvent exposure on memory and motor dexterity in working children.

Saddik B, Williamson A, Nuwayhid I, Black D. School of Health Information Management, Faculty of Health Sciences, the University of Sydney, Australia.
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Public Health Rep. 2005 Nov-Dec;120(6):657-63

OBJECTIVES: Children working in vehicle spray-painting, mechanical, and other trade workshops are at significant risk of exposure to organic solvents and, as a result, may be at significant risk of developing clinical and subclinical signs of neurotoxicity. This study reports on the association between exposure to solvents and neurobehavioral performance on a number of non-computerized tests for working children exposed to solvents in comparison with nonexposed working children and nonexposed children at school.
METHODS: A convenience cross-sectional sample of 300 male children aged 10-17 years was recruited for study. The exposed working group and the two nonexposed groups (working and nonworking school) were matched, as far as possible, on geographic location of residence and age. Neurotoxic effects were assessed through a questionnaire and the child's performance on a selection of neurobehavioral tests.
RESULTS: Exposed working children scored worse on the overall neurotoxicity symptoms score (mean=6.8; standard deviation [SD]=3.6) compared with the nonexposed working children (mean=1.3; SD=2.0) and school children (mean=1.2; SD=1.8). Analysis of the non-computerized neurobehavioral tests demonstrated that exposed working children performed significantly worse than the two nonexposed groups on the motor dexterity and memory tests. Results of the mood test showed that exposed working children were more angry and confused than the nonexposed groups.
CONCLUSION: There is an association between exposure to solvents and lower neurobehavioral performance, with significant neurobehavioral deficits among children exposed to solvents in comparison with working children not exposed to solvents and nonworking school children. Memory and motor dexterity appear to be particularly affected in solvent-exposed working children.

### Nicotine is a neurotoxin in the adolescent brain: critical periods, patterns of exposure, regional selectivity, and dose thresholds for macromolecular alterations.

Abreu-Villaca Y, Seidler FJ, Tate CA, Slotkin TA. Department of Pharmacology and Cancer Biology, Duke University Medical Center, 27710, Durham, NC, USA.
Brain Res. 2003 Jul 25;979(1-2):114-28

In the fetus, nicotine is a neuroteratogen that elicits cell damage and loss and subsequent abnormalities of synaptic function. We explored whether these effects extend into adolescence, the period when most people begin smoking. Beginning on

postnatal day 30, rats were given a 1 week regimen of nicotine infusions or twice-daily injections, at doses (0.6, 2 and 6 mg/kg/day) set to achieve plasma levels found in occasional to regular smokers. We assessed indices of cell packing density and cell number (DNA concentration and content), cell size (total protein/DNA ratio) and neuritic projections (membrane/total protein) in the midbrain, hippocampus and cerebral cortex, three regions known to be vulnerable to developmental effects of nicotine. With either route of administration, nicotine evoked shortfalls in DNA concentration and content, compensatory elevations of total protein/DNA, and reductions in the membrane/total protein ratio. Nearly all of the effects were apparent even at the lowest dose of nicotine and remained fully evident 1 month posttreatment. Although both males and females showed significant alterations, in general the effects were larger in females. Our results indicate that in adolescence, even a brief period of continuous or intermittent nicotine exposure, elicits lasting alterations in biomarkers associated with cellular and neuritic damage. As the effects are detected at exposures that produce plasma concentrations one-tenth of those in regular smokers, the exquisite sensitivity of the adolescent brain to nicotine neurotoxicity may contribute to lasting neurobehavioral damage even in occasional smokers.

**Age-related effects of alcohol on memory and memory-related brain function in adolescents and adults.**

White AM, Swartzwelder HS. Duke University Medical Center, Neurobiology Research Labs, Veterans Affairs Medical Center, Durham, North Carolina 27710, USA.
Recent Dev Alcohol. 2005;17:161-76

As detailed in this brief review, there is now clear evidence that adolescence represents a unique stage of brain development. Changes in brain organization and function during adolescence are widespread, and include intense rewiring in the frontal lobes and other neocortical regions, as well as changes in a litany of subcortical structures. Recent research suggests that, because of these changes in brain function, drugs like alcohol affect adolescents and adults differently. The available evidence, much of it from research with animal models, suggests that adolescents might be more sensitive than adults to the memory impairing effects of alcohol, as well as the impact of alcohol on the brain function that underlies memory formation. For instance, when treated with alcohol, adolescent rats perform worse than adults in spatial learning tasks that are known to require the functioning of the hippocampus. Alcohol disrupts hippocampal function, and does so more potently in adolescents than adults. In contrast, adolescents appear to be far less sensitive than adults to both the sedative and motor impairing effects of alcohol. While research on this topic is still in its infancy, the findings clearly suggest that adolescence represents a unique stage of sensitivity to the impact of alcohol on behavior and brain function.

**fMRI reveals alteration of spatial working memory networks across adolescence.**
Schweinsburg AD, Nagel BJ, Tapert SF. Department of Psychology, University of California, San Diego, La Jolla, California, USA.
J Int Neuropsychol Soc. 2005 Sep;11(5):631-44

Recent studies have described neuromaturation and cognitive development across the lifespan, yet few neuroimaging studies have investigated task-related alterations in brain activity during adolescence. We used functional magnetic resonance imaging (fMRI) to examine brain response to a spatial working memory (SWM) task in 49 typically developing adolescents (25 females and 24 males; ages 12-17). No gender or age differences were found for task performance during SWM. However, age was positively associated with SWM brain response in left prefrontal and bilateral inferior posterior parietal regions. Age was negatively associated with SWM activation in bilateral superior parietal cortex. Gender was significantly associated with SWM response; females demonstrated diminished anterior cingulate activation and males demonstrated greater response in frontopolar cortex than females. Our findings indicate that the frontal and parietal neural networks involved in spatial working memory change over the adolescent age range and are further influenced by gender. These changes may represent evolving mnemonic strategies subserved by ongoing adolescent brain development.

**Pubertal neuromaturation, stress sensitivity, and psychopathology.**
Walker EF, Sabuwalla Z, Huot R. Department of Psychology, Emory University, Atlanta, GA 30322, USA. psyefw@emory.edu
Dev Psychopathol. 2004 Fall;16(4):807-24.

Normal adolescent development is often accompanied by transient emotional and behavioral problems. For most individuals with postpubertal-onset adjustment problems, there is a resolution by early adulthood and relative stability through the adult life span. But for a minority, adjustment problems escalate during adolescence and portend the development of serious mental illness in adulthood. In this article, we explore adolescent behavioral changes and neurodevelopmental processes that might contribute to stress sensitivity and vulnerability for the emergence of the mental disorders. Of particular interest is the role that hormonal changes might play in the expression of genetic vulnerabilities for psychopathology. Drawing on recent findings from clinical research and behavioral neuroscience, we describe the ways in which postpubertal hormones might alter brain function and, thereby, behavior. It is concluded that there are both activational and organization effects of hormones on the adolescent brain, and these contribute to developmental discontinuities in behavioral adjustment. Implications for adult psychopathology and preventive intervention are discussed.

**The neural basis of puberty and adolescence.**

Sisk CL, Foster DL. Neuroscience Program and Department of Psychology, Michigan State University, East Lansing, Michigan 48824, USA. sisk@msu.edu <sisk@msu.edu>
Nat Neurosci. 2004 Oct;7(10):1040-7.

The pubertal transition to adulthood involves both gonadal and behavioral maturation. A developmental clock, along with permissive signals that provide information on somatic growth, energy balance and season, time the awakening of gonadotropin releasing hormone (GnRH) neurons at the onset of puberty. High-frequency GnRH release results from disinhibition and activation of GnRH neurons at puberty onset, leading to gametogenesis and an increase in gonadal steroid hormone secretion. Steroid hormones, in turn, both remodel and activate neural circuits during adolescent brain development, leading to the development of sexual salience of sensory stimuli, sexual motivation, and expression of copulatory behaviors in specific social contexts. These influences of hormones on reproductive behavior depend in part on changes in the adolescent brain that occur independently of gonadal maturation. Reproductive maturity is therefore the product of developmentally timed, brain-driven and recurrent interactions between steroid hormones and the adolescent nervous system.

Mary-Ann Warmerdam
*Director*

# Department of Pesticide Regulation

Arnold Schwarzenegger
*Governor*

## M E M O R A N D U M

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

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DATE: January 14, 2010

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

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The following are our responses to comments from Arysta LifeScience Corporation (Arysta) document "FINAL IODOMETHANE: Arysta LifeScience NA, LLC Comments to DPR, July 9, 2009" submitted to the Scientific Review Committee (SRC) at the September 2009 meeting. This memorandum addresses the listed major points of differences between the Arysta and DPR assessments relating to toxicology and risk assessment issues (Points 1 to 6). The cited differences have already been submitted to DPR for the April 2009 draft of the Volume I Risk Characterization Document (RCD), and the DPR responses are contained in Volume IV of the August 2009 draft of the RCD (http://www.cdpr.ca.gov/docs/risk/mei/mei_vol4_arysta.pdf). While the DPR positions on these points have not changed, this memorandum updates the responses due to incorporation of SRC recommendations.

**Point 1:** *DPR selected the No-observed Effect level (NOEL) of 2 ppm in rabbits as the basis for the developmental toxicology evaluation compared to Arysta's and EPA's selection of the 10 ppm No Observed Adverse Effect Level (NOAEL).*

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

In the current Volume I, the point of departure (POD) for the determination of HEC has been revised using the 1% benchmark response, instead of the NOEL, as recommended by the SRC. The $LED_{01}$ is 0.5 ppm using the nested logistic model. DPR noted in the Risk Appraisal section

that with the wide data variability for this endpoint, the application of 1% BMR to this dataset carries some uncertainty of being overly conservative than the data would allow for defining adverse effect level.

**Point 2:** *DPR selected dose metrics for human equivalent concentration (HEC) determination without consideration of the modes of action (MOA) of iodomethane, while Arysta and EPA identified dose metrics appropriate to the MOA for derivation of the HECs.*

**DPR Response:** DPR has provided detailed discussion on the dose metric selection since the first draft of the RCD. DPR includes HECs for all 8 possible scenarios to show the substantial impact on the HEC based on different dose metrics. It is important not to lose sight of the overall picture in the final analysis. Arysta's conclusion "...confidence in the PBPK model predictions for the reproductive/developmental effects of iodide in rabbits is considered moderate using fetal iodide and high using maternal iodide..." (Sweeney et al., 2009) should add further justification for DPR's choice of maternal instead of fetal serum iodide dose metric.

This issue on dose metrics is now moot because the SRC rejected the PBPK model and consequently, DPR derived the HECs using a non-chemical specific default methodology. However, DPR is in agreement with Arysta and USEPA that the current PBPK modeling is a valid tool that allows for deviation from the current default methodology.

**Point 3:** *DPR took the position that MOAs for effects from acute exposure to iodomethane are unknown, while Arysta and EPA have evaluated the evidence for iodomethane MOAs and determined that the weight of evidence supports postulated MOAs.*

**DPR Response:** DPR has provided detailed discussion on the MOA since the first draft of the RCD. In the current document, the MOA discussion is moved to Appendix A as it is an integral part of the physiologically based pharmacokinetic (PBPK) model review. The SRC also disagreed with Arysta and USEPA on the postulated MOAs. However, this issue on MOA no longer impacts the DPR's risk assessment because the SRC rejected the use of PBPK model in favor of a non-chemical specific default approach in the derivation of the HECs.

**Point 4:** *DPR recommended application of an uncertainty factor (UF) of 300, while Arysta and EPA agree that a UF of 30 is appropriate.*

**DPR Response**: DPR recommends the application of an additional uncertainty factor of 10-fold to the conventional UF of 30, for a total UF of 300. This additional UF is deemed necessary because the potential for MeI to cause developmental toxicity has not been adequately studied. It

is well recognized that conventional chronic and reproductive toxicity studies are not designed to sufficiently evaluate pre- or post-natal developmental toxicity. The SRC concurs with DPR for the need of an additional UF and recommends an at least 10-fold factor.

**Point 5:** *DPR recommends that a developmental neurotoxicity study (DNT) needs to be conducted, while Arysta and EPA believe available data are adequate to protect from any potential developmental neurotoxicity.*

**DPR Response:** It is well recognized that conventional chronic and reproductive toxicity studies are not designed to sufficiently evaluate pre- or post-natal developmental toxicity. The SRC concurs with DPR that developmental neurotoxicity has not been adequately studied. Instead of a specific DNT study to be conducted, the need for a more thoroughly investigation of developmental neurotoxicity from pre- and post-natal exposure to MeI was stated. This would include exploring the potential serious and irreversible nature of neurodevelopmental effects from maternal exposure that may be manifested beyond the observed fetal death at the end of gestation, and the potential toxicity from post-natal exposure to MeI or the resultant excess iodide added to the background iodide intake.

**Point 6:** *DPR used acceptable chronic oral iodide intake to assess potential risk from acute iodomethane exposure, while Arysta maintains that this is inappropriate.*

**DPR Response:** DPR have provided all the current health based standards available, including the Delange (2007) report of proposing updates of WHO standards. Our presentation also contains all the qualifiers for these standards, and clearly showed that the ATSDR standard includes a one-day period (ATSDR, 2004). We chose to compare the excess iodide exposure from MeI to the higher NAS's ULs (NAS, 2000) rather than the lower ATSDR's standard, which is applicable for acute (1-14 days) and chronic exposures in order to give as much allowance as possible for a single day exposure scenario. It is important to note that the RfC derived for subchronic and chronic exposure to MeI would exceed these iodide intake standards to a much greater extent than from the acute RfC. Thus, following Arysta's position that these iodide intake standards are applicable to chronic exposure scenarios, there should not be any further disagreement for an even greater public health concern for excess iodide from long term MeI exposures.

Mary-Ann Warmerdam
*Director*

# Department of Pesticide Regulation

Arnold Schwarzenegger
*Governor*

## M E M O R A N D U M

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

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DATE: January 12, 2010

SUBJECT: Response to Dr. Kathleen Collins Comments on the Draft Methyl Iodide Risk Characterization Document (August 2009) for Inhalation Exposure Volume I

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The following is our response to Dr. Kathleen Collins' comment on the Draft Methyl Iodide Risk Characterization Document (August 2009) for Inhalation Exposure Volume I.

**Comment:**
*The general biological responses to DNA damage by methylation are:*
*1. DNA repair (if damage is at a low level),*
*2. Cell suicide (highly damaged human cells kill themselves or attract killers)*
*3. Genome mutation (cumulative increments of cancer risk)*

*DNA methylation reactions often yield modified bases that are unable to serve as template for a DNA polymerase. These DNA lesions will recruit repair activities both directly (by recognition of distorted DNA) and as the consequence of stalled DNA replication (when the DNA is being copied prior to cell division). However, there is growing awareness than some DNA modifications will be copied over by a DNA polymerase if they are not repaired in advance of DNA replication, thus increasing the probability of genome mutation. Genome mutation in somatic tissues (most of our body) accelerates the progression of cancer. Genome mutation in germline cells (cells that develop into sperm and egg) leads to infertility and disease inheritance...*

*O6-methyl-guanine is a particularly dangerous form of DNA methylation: it can be repaired, but it can also be replicated without repair (see below). Thus, the type of DNA methylation damage caused by methyl iodide has both short-term toxicity (from repair-induced delay of cell growth or damage-induced cell death) and cumulative long-term deleterious impact (by permanent genome mutation, leading for example to cancer)...*

***Hazardous waste classification***
*UC Berkeley Environmental Health & Safety (EH&S) regulations classify methyl iodide as the most toxic category of compound (zero-release, class C). This is a greater hazard level than most radioactivity (class B). See drain disposal pdf for complete guidelines...*

**DPR Response:** DPR has discussed methyl iodide as an alkylation agent and calculated the oncogenic risk associated with human exposure in the risk characterization document.

Mary-Ann Warmerdam
*Director*

# Department of Pesticide Regulation

Arnold Schwarzenegger
*Governor*

## M E M O R A N D U M

TO: Joyce Gee, Ph.D.
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DATE: January 12, 2010

SUBJECT: Response to Natural Resources Defense Council Comments on the Draft Methyl Iodide Risk Characterization Document (August 2009) for Inhalation Exposure Volume I

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The following are our responses to Natural Resources Defense Council comments on the Draft Methyl Iodide Risk Characterization Document (August 2009) for Inhalation Exposure Volume I. These responses address only comments related to the concerns regarding the toxicology and risk assessment aspects.

**Detailed Comment #3**: ***DPR's assessment should use a benchmark dose (BMD) approach to the developmental toxicity studies, and should choose a point of departure below 2 ppm.***

**DPR Response**: As much as the benefit of benchmark dose approach is recognized, it is also well understood that some key determinants for its proper application can be subject to scientific debates of diverse opinion and are database- and endpoint-specific. The reason for DPR's hesitation in applying the BMD approach to fetal death endpoint was stated. However, at the recommendation of the SRC, benchmark dose analysis has been incorporated into the revised document. A discussion on the uncertainty associated with the benchmark dose at the level of benchmark response recommended by the SRC is also included in the revised document.

**Detailed Comment #4**: ***The absence of a developmental neurotoxicity study (DNT) is a critical data gap and appropriately requires an additional uncertainty factor of at least 10-fold.***

**DPR Response**: This comment concurs with DPR's use of 10-fold additional uncertainty factor.

**Detailed Comment #5**: ***The MOE of 30 for endpoints other than fetal death is inappropriate and should be increased to protect children's health.***

*It is inappropriate to choose an MOE of only 30 for health endpoints other than fetal death. As DPR itself points out, use of an MOE of 30 results in calculated RfCs that would not protect young children against excess iodide intake, thereby rendering the calculated RfCs meaningless. In addition, failure to use an additional UF for the neurotoxicity endpoint is rash for three reasons: (1) developmental neurotoxicity has not been evaluated (see above); (2) significant abnormalities were noted in female rats in Schaefer (2002) at 27 ppm, the level DPR selected as a NOAEL; and (3) neuropsychiatric effects (delirium, confusion, altered affect, personality and behavior changes, shortened attention span and difficulty concentrating) have been prominent in adult MeI exposure case reports, and these have not been assessed adequately (and probably cannot be adequately assessed) in laboratory animals. An MOE of 300 should therefore be used for all non-cancer endpoints. In addition, where the RfC exceeds the level (1 ppm) that would fail to protect children against excess iodide, the RfC should not be used.*

**DPR Response**: The recommended iodide limit is 1 ppb, not 1 ppm, as indicated in the comment. In the revised document, the acute and lifetime RfCs are now lower than the 1 ppb limit due to the lowering of the point of departure for the fetal death endpoint. It is recognized that the RfCs for exposure durations other than acute are higher than the 1 ppb limit. Contrary to the comment, an MOE of 300 for all non-cancer endpoints would still not be sufficient for addressing the excess iodide exposure for some duration scenarios. Instead of applying more additional UFs, the conclusion of the RCD is that the RfCs for MeI should not exceed 0.3 ppb for noncancer effect for any duration, and 0.04 ppb for cancer effect from lifetime exposure.

**Detailed Comment #6**: ***The evidence strongly supports a genotoxic mode of action for the carcinogenic effect of MeI; the cancer risk assessment should use a linear model, and should include astrocytomas and uterine fibromas as well as thyroid tumors.***

*There are compelling data on the genotoxicity of MeI. This potent alkylating agent has been used for many years in the laboratory setting to intentionally generate mutations in research experiments. DPR's conclusion that "there was some indication of MeI as an alkylating agent based on alkylation of guanines from DNA of human lymphocytes" significantly understates the broad scientific use of MeI for exactly this purpose...*

*It is not appropriate to conclude that the study is acceptable and that the fibromas may be treatment-related, but then to fail to assess the potential risk. The rationale provided for failing to assess astrocytomas and uterine/cervical fibromas does not make sense: DPR states that these are not assessed because "the incidences for these tumors are much lower than those for thyroid tumors" (p. 149, lines 7-8). Yet these should be evaluated to be sure that they do not occur at lower doses or have a steeper dose-response than the thyroid tumors, irrespective of the incidence rates... In fact, a multiple-endpoint analysis is required by the he EPA Cancer*

*Guidelines (EPA, 2005) that state, "Because an agent may induce multiple tumor types, the dose-response assessment includes an analysis of all tumor types, followed by an overall synthesis that includes a characterization of the risk estimates across tumor types, the strength of the mode of action information of each tumor type, and the anticipated relevance of each tumor type to humans, including susceptible populations and lifestages (e.g., childhood)."*

**DPR Response**: In the revised document, the discussions on MeI as an alkylating agent and genotoxicity have been expanded.

DPR's weight of evidence analysis includes all tumor data. In the August draft, the potency factors for astrocytomas and fibromas, which is the slope of the dose response relationship, did not need to be presented because lower incidences for these tumors resulted in lower potency factor and thus lower risk. In comparison, the higher incidences for thyroid tumors showed a steeper dose-response relationship. To avoid any confusion, potency slopes for all 3 tumor types are added to the revised document for comparison.

Cancer risks for MeI are calculated using both linear extrapolation and threshold approaches to accommodate the possible MOAs. For the linear extrapolation approach, risks calculation includes age-dependent adjustment factors. For the threshold approach, an additional 10-fold factor is added to the convention benchmark MOE of 30. Since the calculated risks are higher with the linear approach, the lower reference values derived from this approach are more pertinent for the protection against cancer risk.

**Detailed Comment #7**: ***Glutathione depletion should be considered a marker of an adverse effect, and should be used as a point of departure for risk assessment.***

*... It is therefore appropriate and health-protective to use GSH depletion itself as a regulatory endpoint, and to assure that human exposure will not result in significant depletion. DPR only uses GSH depletion as a dose metric to derive a human equivalent concentration (HEC) for epithelial damage, rather than as an endpoint in itself. The percentage of GSH depletion that is physiologically significant is a matter of debate. U.S. EPA likely erred in choosing 50% GSH depletion as a dose metric, since such extreme depletion leaves no room to protect against cumulative or aggregate exposures to various oxidants. DPR chooses 25% GSH depletion (p.141, lines 27-28), which may not be sufficiently health-protective, especially for genetically susceptible individuals and the fetus. DPR should provide a clear rationale for choosing 25% GSH depletion rather than a lower number, in light of population variability, susceptible subgroups, and background exposures to other sources of oxidative stress.*

**DPR Response**: In the revised document. GSH depletion is added as a toxicity endpoint. When its point of departure is compared to those for other acute systemic effects, GSH depletion is not the most sensitive endpoint. Since the Scientific Review Committee rejected the use of the

PBPK model, DPR calculates the HECs using a default methodology. The appropriateness of the 25 % GSH depletion as the dose metric is no longer an issue.

Mary-Ann Warmerdam
*Director*

# Department of Pesticide Regulation

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M E M O R A N D U M

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DATE: January 12, 2010

SUBJECT: Response to Pesticide Action Network comments on the Draft Methyl Iodide Risk Characterization Document (August 2009) for Inhalation Exposure Volume I

---

The following are our responses to Pesticide Action Network comments on the Draft Methyl Iodide Risk Characterization Document (August 2009) for Inhalation Exposure Volume I. These responses address only comments related to the concerns regarding the toxicology and risk assessment aspects.

**Comment #1**: ***The potential for toxic effects based on the alkylation reactions of methyl iodide has not been fully explored by either CA DPR or US EPA.***

*Dosing of rats with labeled 14CH3I results in 14C primarily in the kidneys, liver, thyroid, nasal turbinates, lung, and brain, indicating alkylation and potential damage in these tissues. This observation suggests that there are many possible routes of toxicity for methyl iodide that have not been evaluated in the risk assessment. Work by Gansewendt et al. indicates that dosing of rats with methyl iodide results in both N- and O-methylation of DNA.1 Besides cancer, what are the potential physiological outcomes of these chemical reactions? Can insights into the potential outcomes be gleaned from studies on anti-cancer drugs that act by alkylating the DNA of tumor cells?*

**DPR Response:** The risk assessments are based on outcomes from whole animal bioassays. The toxicity endpoints evaluated are the end result of MeI multiple effects, including alkylation, GSH depletion, and other reactions, in the body.

**Comment #2**: ***Use of Benchmark Dose methodology is a more appropriate tool for evaluating many of the toxicological endpoints.***

*We agree with the SRP that the "NOAELs" selected by US EPA and CA DPR in several of the*

*toxicity studies are not NOAELs, but LOAELs. Use of Benchmark Dose methodology is a more appropriate tool for evaluating such toxicological endpoints. Use of the BMD methodology would require DPR to select an appropriate point of departure (POD) for the acceptable level of toxic effects.*

**DPR Response**: As much as the benefit of benchmark dose approach is recognized, it is also well understood that some key determinants for its proper application can be subject to scientific debates of diverse opinion and are database- and endpoint-specific. The reason for DPR's hesitation in applying the BMD approach to fetal death endpoint was stated. However, at the recommendation of the SRC, benchmark dose analysis has been incorporated into the revised document. A discussion on the uncertainty associated with the benchmark dose at the level of benchmark response recommended by the SRC is also included in the revised document.

**Comment #3**: ***Any level of fetal death induced by methyl iodide is unacceptable.***

*For developmental toxicity, we have serious reservations about any method used to select an "acceptable" percentage of fetal deaths as a valid POD, as DPR would have to make the assumption that fetal loss to some fraction of pregnant women would be an acceptable outcome.* ***We do not believe that any level of methyl-iodide-induced fetal death is an acceptable outcome, and we have serious ethical concerns about any analysis that requires DPR to select such an endpoint.*** *The data indicate that methyl iodide exposure causes fetal deaths in a relatively high percentage of the animals tested at doses to which people are likely to be exposed. This fact alone is sufficient for DPR to refuse to register methyl iodide. DPR should not be in the position to decide for the people of California how many fetal deaths are "acceptable."*

**DPR Response**: We respect your view to categorically reject any chemical that demonstrated developmental toxicity. DPR has selected 1% excess risk as recommended by the Scientific Review Committee. However, with the wide data variability for this endpoint (*e.g.*, 1.8±6.4% death per litter at the controls), the application of 1% BMR to this dataset carries some uncertainty of being well within the at normal designation in the background distribution.

**Comment #4a**: ***Carcinogenicity***
*We share DPR's, OEHHA's and the SRP's concerns about the cancer risk assessment that USEPA developed for methyl iodide. The data show that methyl iodide causes astrocytomas, lung tumors, and urinary and cervical tumors, in addition to thyroid tumors, which indicates that the mechanism of carcinogenesis selected by US EPA is incorrect. The non-threshold analysis conducted by DPR provides a cancer potency factor comparable to several other well-known and well-studied carcinogens, including formaldehyde, propylene oxide, perchloroethylene, and*

*pentachlorophenol (see Table 1). DPR should re-do the cancer risk analysis including the correction factor to account for the additional sensitivity of infants and children.*

**DPR Response**: The revised document has included risk calculation with age-dependent adjustment factors.

**Comment #4b**: ***Carcinogenicity***
*There are several indications that the chronic/carcinogenicity rat inhalation study may not be valid. We request that DPR staff and the SRP more carefully evaluate the raw data from this study to clarify several points:*
*• The survival rate of control groups (38–39%) was lower than that of the treated groups (43–51%). Is there any reasonable explanation for the high death rates in the control group? Was the control group being dosed inadvertently? What was the setup of the cages during treatment?*
*• DPR notes that: "Excess deaths in the 60 ppm rats occurred during months 5 and 6 of the study. Engineering corrections and changing cage placements stopped the mortality." If "excess deaths" were corrected by changing cage placements, how can DPR verify the accuracy of any of the dose levels?*
*• It is not clear if all tumors were reported in the study, or if all animals were examined—particularly those that died before termination. Pituitary adenomas and "undetermined" accounted for nearly all early deaths, yet no pituitary adenomas are reported in Table 21 (p. 58) in Volume 1: Human Health Risk Assessment for Methyl Iodide. Were these tumors excluded from the totals? Were all of the animals that died prior to termination examined?*

**DPR Response**: In the revised document, the survival has been recalculated to exclude the loss of animal due to interim sacrifice and showed less difference between the control and treated groups. The difference between the control and treated group occurs mainly from weeks 92 to 103, and the report did not indicate the cause of the difference. Any inadvertent exposure would have been reported as part of the GLP requirement. In the calculation of cancer potency factor, survival time of each animal was taken into consideration.

The animals of each group are kept in cages when placed inside the exposure chamber. Page 31 of the report describes incidences of high dose deaths, associated with apparent excessive exposures due to apparent high exposure regions in the 60 ppm MeI chambers. After a series of corrective actions, there were no more clustered deaths in the high dose groups. Air concentrations in the chambers are measured and reported.

All the animals were examined and individual data were provided in the report. No pituitary adenomas were reported in Table 21 because they were not treatment related. The incidences for pituitary adenomas are now added as a footnote to the study summary.

**Comment #5:** ***Developmental toxicity and the validity of the PBPK model***
*We share DPR's, OEHHA's and the SRP's concerns about the developmental toxicity mode of action and the resulting PBPK model that US EPA used in their risk assessment... We cannot support the conclusions obtained using the PBPK model and urge DPR to use the default method that utilizes the NOAEL and both intra- and inter-species uncertainty factors of 10, plus an additional uncertainty factor of 10 to account for lack of data on the developmental neurotoxicity of methyl iodide.*

**DPR Response**: In **IV.A. Hazard Identification (page 129)** of the revised draft, DPR discusses that PBPK model has sufficient merit over the non-chemical-specific default approach. In the August draft, DPR used PBPK model to characterize marker for exposure and the model can be used to account for additional 16 hours of ambient MeI air exposures by workers. Since the SRC rejected the PBPK model, acute HECs are calculated using the DPR default methodology in the December 2009 final document. A 10-fold additional uncertainty factor is applied to the lack of information about developmental neurotoxicity.

**Comment #6**: ***The role of glutathione and the PBPK model***
*The alkylation of glutathione by methyl iodide is one of the primary biological mechanisms for detoxifying and excreting methyl iodide in vivo. We question several assumptions made by US EPA in its implementation of the PBPK model as it is used for determining the HECs for salivary gland metaplasia and request that DPR and the SRP review these assumptions. Specifically, the assumptions made do not account for the following: 1) exposures to glutathione depleting substances beside methyl iodide, 2) damage to nasal epithelial tissues that would reduce glutathione production, 3) the difference in turnover rates of GSTT1 between rats and humans, and 4) the intrinsic variability in the human population of the ability to produce GSTT1, the enzyme that catalyzes the reaction of glutathione with electrophilic substances...*

**DPR Response**: In the revised document, the PBPK model is not used to derive the HECs. While GSH depletion is no longer used as a dose metric, DPR evaluated GSH depletion as a toxicity endpoint. When its point of departure is compared to those for other acute systemic endpoints, GSH depletion is not the most sensitive endpoint.

**Comment #7**: ***Inhalation dosing in animal studies does not match real-world exposures***
*A serious flaw in the HEC process is that test animal exposures to methyl iodide do not match*

*anticipated human exposures. Most inhalation exposures for laboratory animals are set at a constant concentration for six hours per day, five days per week, providing time for the animals' repair systems to respond to the chemical insult during the "rest" periods (see Figure 1). For the methyl iodide developmental toxicity study, dosing occurred for six hours per day, seven days per week over the 28-day gestation period. The rest periods during these studies provide an opportunity for the laboratory animals to replenish depleted glutathione, excrete excess iodide and begin repairing methyl-iodide-damaged tissues.*

*Exposure patterns for people living near fumigant application sites are substantially different, with an exposure spike that may cause acute effects during the first day or two after the application, followed by a decreasing concentration over the next week or two (see Figure 2).*

*Real-world exposure can be continuous (assuming one stays at home and the wind direction is constant), with no opportunity for recovery. The high spike in concentration is likely to have a significantly different toxic effect than the constant exposure experienced by laboratory animals. Because of the possibility of mixed acute and sub-chronic effects, this failure in inhalation exposure dosing is likely to be one of the most significant flaws in current reference concentration (RfC) methodology that leads to an underestimation of the actual HEC, especially for GSH-dependent toxicity. Because the time course and duration of animal inhalation studies do not effectively mimic human exposures, the selected endpoints are not protective for real world exposures.*

**DPR Response**: The only toxicity studies available are those conducted with laboratory animals following guidelines established by the USEPA. To account for exposure durations longer than those used in the animal studies, an amortization factor is included in the HEC calculation, which lowers the no-effect dose from the animal study.

**Comment #8**: ***Concurrent exposure to multiple fumigant chemicals has not been accounted for.***
*MIDAS® products are formulated with chloropicrin, a severe irritant, a glutathione depletor and a carcinogen. Yet no analysis of the potential effects from concurrent exposures to methyl iodide and chloropicrin were conducted. This is a serious flaw in the risk assessment; however, it can reasonably be assumed that the combined presence of chloropicrin and methyl iodide will at least enhance cancer risk and glutathione depletion and may possibly exacerbate other effects. The net result of this enhancement is that toxic effects will be observed at lower doses than those determined in a risk assessment that accounts for exposure to only a single chemical.*

**DPR Response**: We recognize that MeI formulations contain various amounts of chloropicrin, ranging from 25% to 75%. There is a potential for cumulative risk issues as both chemicals have similar effects such as GSH depletion and developmental toxicity. While a discussion about

chloropicrin toxicity has been added to the revised document, there is no information on the exposure levels of chloropicrin when MeI formulations are used. Since the concentrations of MeI and chloropicrin are relative in the formulations, there should be greater concern about chloropicrin toxicity when the MeI formulation contains 75% chloropicrin, compared to the one containing 25% chloropicrin. The DPR chloropicrin risk assessment, with 100% chloropicrin as the active ingredient and 2% as a warning agent, is being reviewed by the California Scientific Review Panel. When finalized, information in that risk assessment could be used to determine the potential for cumulative toxicity when both chloropicrin and MeI are used.

# Department of Pesticide Regulation

Mary-Ann Warmerdam
*Director*

M E M O R A N D U M

Arnold Schwarzenegger
*Governor*

TO: Joyce Gee, Ph.D.
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DATE: January 12, 2010

SUBJECT: Response to Dr. Amber Wise Comments on the Draft Methyl Iodide Risk Characterization Document (August 2009) for Inhalation Exposure Volume I

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The following are our responses to Dr. Amber Wise's comments on the Draft Methyl Iodide Risk Characterization Document (August 2009) for Inhalation Exposure Volume I. These responses address only comments related to the concerns regarding the toxicology and risk assessment aspects.

**Comment #1**: [*CDPR] Determining a lower NOAEL for fetal death than USEPA is an improvement, but the more scientifically appropriate method is to use a benchmark dose model. These linear models are much better representations of the dose-response behavior.*

**DPR Response**: As much as the benefit of benchmark dose approach is recognized, it is also well understood that some key determinants for its proper application can be subject to scientific debates of diverse opinion and are database- and endpoint-specific. The reason for DPR's hesitation in applying the BMD approach to fetal death endpoint was stated. However, at the recommendation of the SRC, benchmark dose analysis has been incorporated into the revised document. A discussion on the uncertainty associated with the benchmark dose at the level of benchmark response recommended by the SRC is also included in the revised document.

**Comment #2**: *Rather than using overt health outcomes such as thyroid hormone tumors and fetal death to calculate reference concentrations, CDPR should use the doses that indicate earliest observed adverse endpoints such as the glutathione depletion seen in these experiments.*

**DPR Response**: Glutathione depletion as a toxicity endpoint has been added to the revised document. When its point of departure is compared to those for other acute systemic endpoints, GSH depletion is not the most sensitive endpoint.

**Comment #3**: *There is no safety factor considered or discussion of, background chemical exposures or co-exposure incidences—populations living in agricultural areas are also exposed to other pesticides year-round and these contribute to higher body burdens and increased overt health outcomes in these groups.*

**DPR Response**: This is an issue pertaining to the exposure assessment and should be addressed under Volume II of the MeI Risk Characterization Document.

**Comment #4**: *The formulation of this pesticide is such that is mixed with another highly toxic fumigant, Chlorpicrin.... There is nothing in the risk assessment that addresses the fact there will be simultaneous exposures to both of these chemicals.*

**DPR Response**: We recognize that MeI formulations contain various amounts of chloropicrin, ranging from 25% to 75%. There is a potential for cumulative risk issues as both chemicals have similar effects such as GSH depletion and developmental toxicity. While a discussion about chloropicrin toxicity has been added to the revised document, there is no information on the exposure levels of chloropicrin when MeI formulations are used. Since the concentrations of MeI and chloropicrin are relative in the formulations, there should be greater concern about chloropicrin toxicity when the MeI formulation contains 75% chloropicrin, compared to the one containing 25% chloropicrin. The DPR chloropicrin risk assessment, with 100% chloropicrin as the active ingredient and 2% as a warning agent, is being reviewed by the California Scientific Review Panel. When finalized, information in that risk assessment could be used to determine the potential for cumulative toxicity when both chloropicrin and MeI are used.

# Department of Pesticide Regulation

Mary-Ann Warmerdam
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DATE: January 12, 2010

SUBJECT: Response to Worksafe Comments on the Draft Methyl Iodide Risk Characterization Document (August 2009) for Inhalation Exposure Volume I

---

The following are our responses to Worksafe comments on the Draft Methyl Iodide Risk Characterization Document (August 2009) for Inhalation Exposure Volume I. These responses address only comments related to the concerns regarding the toxicology and risk assessment aspects.

**Worksafe Comment**: *Quantitative adjustments that incorporate greater safety factors are required in any assessment of risk that contemplates exposing children. In addition, the lack of adequate information regarding potential neurotoxic effects across the age span, and especially in high cognitive functioning, is a critical information gap can be partially addressed by a substantial additional margin of safety. To provide adequate protection, it is necessary that research be carried out that can provide assurances of safety. At present there is no research of this type available on Mel so it is not possible to determine whether there is any safe level of exposure to Mel with respect to hormonal and neurological development....*

**DPR Response**: DPR has considered age-related differences in risk. In the absence of data, the human equivalent concentration (HEC) is reduced by a 10-fold factor to account for interindividual differences, which may be age-related. DPR also estimated exposures using age-depended breathing rates. The potential for developmental neurotoxicity from MeI exposure required the use of an additional 10-fold uncertainty factor.

# Department of Pesticide Regulation

Mary-Ann Warmerdam
*Director*

M E M O R A N D U M

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DATE: January 26, 2010

SUBJECT: RESPONSE TO ARYSTA'S COMMENTS ON METHYL IODIDE (MI) EXPOSURE ASSESSMENT DOCUMENT (EAD)

---

Arysta supplied DPR with a series of additional comments regarding the Risk Assessment for methyl iodide in a document dated July 9th, 2009. The only comments specifically addressing potential exposure to methyl iodide (MI) addressed the deterministic approach of using the ISCST3 model to develop screening levels. Arysta compared and contrasted the ISCST3 model with the probabilistic approach using the PERFUM model.

While this is an exposure issue, the Environmental Monitoring Branch is addressing the additional Arysta comments as they pertain to modeling of environmental data.

Department of Pesticide Regulation

Mary-Ann Warmerdam
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# MEMORANDUM

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DATE: January 29, 2010

SUBJECT: RESPONSE TO CALIFORNIA RURAL LEGAL ASSISTANCE FOUNDATION (CRLAF) COMMENTS ON METHYL IODIDE (MI) EXPOSURE ASSESSMENT DOCUMENT (EAD)

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The California Rural Legal Assistance Foundation (CRLAF) supplied DPR with a series of comments regarding the Risk Assessment for methyl iodide in a slide presentation dated September 25th, 2009. A number of exposure issues were raised in the presentation; however, there are no explicitly written explanations of the slides. Consequently, I may not capture all that was meant to be said by CRLA on each of the points they addressed.

First, *CRLA did not feel that a 90% reduced exposure factor was appropriate to use for respiratory protection. Specifically, a slide was presented that indicated a review by Nicas and Neuhaus (2004) indicated that a smaller protection factor was warranted.*

DPR assumes a default protection factor for half-face respirator of 90% when an air-purifying respirator is required (NIOSH, 1987). The level of respiratory protection conveyed by respirators can be a source of uncertainty. The uncertainty may be attributed to improper testing, maintenance, or improper use of these devices. There is no consensus on how to determine the degree of efficacy of respiratory protection for the multitude of industrial and agricultural uses (Campbell *et al*., 2001; Caretti and Gardner, 1999; Cohen *et al*., 2001; Crump, 2007; Doney *et al*., 2005; Greskevith *et al.*, 2007; Janssen *et al.*, 2002; Lawrence *et al.*, 2006; Mitchell and Shenker, 2008; Myers and Zhaung, 1998; Nelson, 1996; Nelson and Colton, 2000; Nelson *et al.*, 2000, 2001; Nicas and Neuhaus, 2004; Reynolds *et al.*, 2007; Zhaung *et al.*, 2005). One review of four studies concerning the degree of protection rendered by air-purifying respirators suggested that 50% might be a more appropriate level of protection (Nicas and Neuhaus, 2004). However, those studies involved chemical canisters that had not been developed specifically for methyl iodide (MI) use, or had problems with maintenance schedules. In the case of MI, the respiratory canisters were specifically designed to absorb MI. The actual protection factor for MI for the half-face respirators, properly fitting, in tests for this chemical resulted in a protection factor between 92-98% (3-M Corporation, 2001, 2005; Wood 1981). Furthermore, the California Code of Regulations Section 6739 identifies the requirements for a pesticide

respiratory protection program. In brief, fit testing, cleaning and disinfecting procedures, employee training, inspection and repair requirements, and end-of-service life change-out requirements (in the case of MI, canisters can only be used once) are spelled out. In light of chemical specific test results and regulatory mandates, DPR believes that a 90% protection factor is reasonable. Uses that do not comply with label or regulatory language will likely result in greater exposures.

Second, *CRLA felt that the duration of exposure could exceed 8 hours/day, and thus the acute exposure of workers does not represent the worst case.*

The availability of reliable work activity durations is sparse at best. Based on communication with growers and industry task forces, DPR assumes that 8-hours is a conservative estimate when defining a single workday. Nonetheless, DPR also believes that under specific conditions and situations, single day durations for worker activities can and do exceed 8 hours. For example, a survey of crop advisors (re-entry workers examining the efficacy of pesticide treatments) indicated that an average workday can be as high as $9.16 \pm 1.15$ hrs/day (Spencer *et al*., 2006). DPR is currently examining the appropriateness of basing exposure estimates on an 8-hour workday. Should the Department determine that longer workdays are warranted for certain activities that will be taken into account when considering potential mitigation measures if MI is registered in California. While longer workdays for acute exposure to MI could result in greater estimated exposures for certain activities, the adjustments in work-day hours would not be expected to alter the current scientific identification of potential hazards. Furthermore as the workday for methyl bromide application is limited to 5-6 hours by California regulations for risk mitigation purposes, DPR assumes that an 8-hour workday for application of its replacement chemical, methyl iodide, is an upper-bound.

Third, *CRLA stated that applicators who travel from county to county can be exposed for a season lasting 5 months or more. Thus, DPR did not calculate the "worst case" seasonal exposure.*

DPR assumed that the use-pattern of methyl iodide would be similar to that of methyl bromide, the pre-plant field fumigant MI is designed to replace. The methyl bromide data indicated that fields are likely to be fumigated only once per year. Use seasons in different counties may overlap, and it is theoretically possible that MI handlers could travel from one county to the next doing applications. Migrant farm workers do travel from one county's harvest season to another county over the course of a year. However, for estimates of repetitive exposures to MI, DPR typically considers the average exposure to be more appropriate than a compilation of worst case exposure scenarios. While upper-bound exposures are anticipated for acute scenarios, DPR assumes an individual will not receive upper-bound exposures on a repetitive basis over the course of a season, year, or lifetime. For example, DPR assumes that it is possible for a pesticide applicator to make applications of MI on 40-acre parcels (the maximum allowable plot per day), at the maximum application rate in order to estimate a single day's exposure. However, DPR

does not assume that this type of exposure would occur, every day throughout a season, and every season throughout a lifetime. DPR also assumes it is unlikely that worker bystanders would be at the edge of the buffer zone of a 40-acre parcel, treated at the maximum application rate, every day of a season, year after year throughout a lifetime. Although continuous upper-bound scenarios are theoretically possible, DPR does not believe that they are realistic, or lend themselves to a credible scientific interpretation.

Fourth, *CRLA stated that the potential for dermal exposure to liquid MI was not considered in the exposure assessment for applicators.*

CRLA indicated that their concern was related to an actual skin exposure to a worker who was wearing improper equipment. The objective of the EAD is to identify potential hazards associated with proper and legal uses of a pesticide. The EAD does not endeavor to identify and estimate exposures resulting from off-label (illegal) and low probability accidents. As one might expect, to do so would generate an unlimited number of possible exposure scenarios with little or no probability of actually occurring. Although DPR is concerned with potential exposures resulting from accidents or illegal uses, those issues are typically addressed more directly by the Department's Enforcement Branch or County Agricultural Commissioners. With respect to MI, DPR considers applicator exposure due to spills highly unlikely. The equipment designed for application of the MI formulations (shank injection and drip irrigation) keeps the liquids away from the individual applicators. Under accidental spill conditions, when applicators need to repair leaking equipment, the limits of the agricultural label ("do not wear chemically protective gloves, clothing or boots to avoid trapping chemical vapors in proximity with the body") do not apply. Under accidental spill conditions, the directions listed on the Material Safety and Data Sheet (MSDS) must be followed. Those directions specify very stringent personal protective equipment (29CFR 1910.133 and 29CFR 1910.134).

Fifth, *CRLA wanted shorter duration sampling times to capture the high air concentrations of MI that may occur episodically*.

DPR agrees that shorter sampling times could be useful in capturing potential peaks.

Sixth, *CRLA was concerned that there was not a concomitant presentation regarding chloropicrin air concentrations*.

Exposure to chloropicrin air concentrations as the result of potential applications of MI formulations would be of significant importance. The Department of Pesticide Regulation is currently assessing the potential risks from exposure to chloropicrin, in a separate risk assessment effort. As part of that effort, a chloropicrin exposure assessment has been presented to the State's Scientific Review Panel for Toxic Air Contaminants. A comprehensive risk assessment is expected to follow.

Seventh, *CRLA was concerned about the potential contamination of groundwater because of MI use as a pre-plant soil fumigant*.

At the present time, there are no data available that indicate potential contamination of groundwater with MI. This is being discussed by the Environmental Monitoring Branch in their response to comments.

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# Department of Pesticide Regulation

Mary-Ann Warmerdam
*Director*

M E M O R A N D U M

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*Governor*

TO: Joseph P. Frank, D.Sc.
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FROM: Roger C. Cochran, Ph.D., D.A.B.T. [*Original signed by R. Cochran*]
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DATE: January 29, 2010

SUBJECT: RESPONSE TO NATIONAL RESOURCES DEFENSE COUNCIL (NRDC) COMMENTS ON METHYL IODIDE (MI) EXPOSURE ASSESSMENT DOCUMENT (EAD)

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The National Resources Defense Council (NRDC) supplied DPR with a series of comments regarding the Risk Assessment for methyl iodide in a document dated September 25th, 2009.

The only comment specifically addressing potential exposure to methyl iodide (MI) contained in document concerns the potential for contamination of groundwater.

At the present time, there are no data available that indicate potential contamination of groundwater with MI. This is being discussed by the Environmental Branch in their response to the comments.

Department of Pesticide Regulation

Mary-Ann Warmerdam
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# MEMORANDUM

TO: Joseph P. Frank, D.Sc.
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SUBJECT: RESPONSE TO PESTICIDE ACTION NETWORK COMMENTS ON MI EAD
THE PESTICIDE ACTION NETWORK (PANNA) SUPPLIED DPR WITH A SERIES OF COMMENTS REGARDING THE RISK ASSESSMENT FOR METHYL IODIDE (MI) IN A DOCUMENT DATED OCTOBER 12, 2009

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They state: "*DPR should carefully review the input parameters used in the ISCST3 exposure model*". Also: "*We request that DPR include the details of the field studies evaluated for use as the basis for the indirect back-calculation of the flux profile for methyl iodide for each application method and clarify how differences in soil temperature are accounted for by the model.*"And: "*The documentation of the exposure model should explicitly describe how and when averaging is used in the data and in the implementation of the model.*"

While this is an exposure issue, the Environmental Monitoring Branch is addressing this comment as it pertains to modeling of environmental data.

PANNA states: "*Averages are also used for the assumed breathing rates to estimate worker exposures. Averaging is again used for worker exposure studies in which ADDs and SADDs are determined from several different studies. The SRP and DPR should evaluate whether this is an appropriate use of averaging as well.*"

DPR acknowledges that for various activities, breathing rates may differ. However, we do not believe that adjusting for differential breathing rates would have a significant impact on the absorbed dose of MI. The respiratory rate used in the EAD for workers and bystanders was a DPR default breathing rate that is used, as a policy, when there are no data to indicate what the actual breathing rates are (Andrews and Patterson, 2000). The rates are based on the inhalation rates ($m^3$/day) and body weights determined by Layton (1993). These rates were estimated from the food-energy intakes of hundreds of individuals sampled in the 1977-1978 National Food Consumption Survey data. At the time of establishing the default, DPR considered this data to be the best available. Currently, DPR is evaluating additional data to ascertain whether the default value should be modified (USEPA, 2008, 2009a,b). The findings of that review are anticipated in the near future. Due to assumptions made in the current exposure assessment, it is

not anticipated that an adjustment to the default breathing rate would increase our concern for MI exposure. Intuitively, one might assume that an increase in breathing rates due to exertion or other activities will automatically result in an increase in the absorbed dose of MI. As it turns out, the relationship is far more complicated. A study conducted by Morgan and Morgan (1967) suggests that increases in breathing rates actually result in decreased retention/absorption. In extreme cases the decrease in retention/absorption of methyl iodide was as high as 15 to 20-fold. This result is consistent with the findings in more than 20 human inhalation studies of various chemical vapors (Frank 2008). Observation of 18 human subjects, indicated that the inhalation retention/absorption of methyl iodide averaged 72% (Morgan and Morgan, 1987). Because of the variability in the study results, DPR adopted a health protective approach and assumed 100% retention absorption. While this likely overestimates the exposure, the data does not lend itself to quantifying the magnitude of the uncertainty. In light of this information, DPR believes that varying the breathing rate for activity would not improve the accuracy of the estimated absorbed dose. However, should our review of the currently available data on breathing rates indicate a change is warranted, DPR will consider any impact on the estimated exposure to MI.

PANNA states: *"Groundwater contamination remains a concern."*

At the present time, there are no data available that indicate potential contamination of groundwater with MI. This is being discussed by the Environmental Monitoring Branch in their response to comments.

PANNA states: *"DPR conducted exposure modeling for a 40-acre field fumigation with a 500-foot buffer zone. In practice, our experience with methyl bromide fumigations indicates that growers will do whatever it takes to reduce the size of the required buffer zone, and few will accept a 500-foot buffer. The alternative is to break the application into smaller application blocks of 5–10 acres and/or use fumigants for which smaller buffer zones are acceptable for the blocks near sensitive sites. The result is that fumigation of the same 40-acre field would occur over a longer time period, such that subchronic exposure becomes a significant issue. Additionally, bystanders are exposed to multiple fumigants, often simultaneously."*

Repetitive exposures of bystanders residing adjacent to a 40-acre field is considered a worst case situation. Smaller fumigated parcels upwind, separated from each other by their respective non-overlapping buffer zones, would likely produce lower air concentrations of MI than the worst case scenario selected. The map shown by PANNA on page 13 does not take into account wind direction, or the label-required, non-overlapping buffer zones which must separate treated fields.

PANNA states: *"Occupational exposures are underestimated."*

PANNA did not provide specifics regarding this comment. A direct response is not considered appropriste.

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# Department of Pesticide Regulation

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DATE: January 29, 2010

SUBJECT: RESPONSE TO DR. AMBER WISE COMMENTS ON METHYL IODIDE (MI) EXPOSURE ASSESSMENT DOCUMENT (EAD)

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Dr. Amber Wise (UCSF) supplied DPR with a series of comments regarding the Risk Assessment for methyl iodide in a document dated October 9th, 2009.

*Dr. Wise was concerned about potential exposures to chloropicrin and other pesticides in conjunction with MI exposure*.

Exposure to chloropicrin air concentrations as the result of potential applications of MI formulations would be of significant importance. The Department of Pesticide Regulation is currently assessing the potential risks from exposure to chloropicrin, in a separate risk assessment effort. As part of that effort, a chloropicrin exposure assessment has been presented to the State's Scientific Review Panel for Toxic Air Contaminants. A comprehensive risk assessment is expected to follow.

*Dr. Wise was also concerned about MI contamination of groundwater*.

At the present time, there are no data available that indicate potential contamination of groundwater with MI. Preliminary sampling of groundwater in Florida, where MI is being used for pre-plant field fumigation, has indicated the presence of iodine, but not methyl iodide. In those samples which do contain iodine, it is not clear what the source of the iodine is. Nonetheless, DPR will continue to encourage the monitoring of groundwater for potential MI contamination.

Mary-Ann Warmerdam
*Director*

# Department of Pesticide Regulation

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

TO: Randy Segawa
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FROM: Terri Barry *Original signed by*
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DATE: January 29, 2010

SUBJECT: Response to public comments on the Methyl Iodide Risk Characterization Document

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**Background**

The Department of Pesticide Regulation (DPR) received comments on the Methyl Iodide (MeI) Risk Characterization Document (RCD) from several outside parties. This memorandum provides responses to comments on the air dispersion modeling and the environmental fate sections.

Comments were received from the following parties: Arysta, Worksafe, National Resource Defense Council (NRDC), Pesticide Action Network North America (PANNA), and K. Collins. Each set of comments will be discussed separately below.

**Responses to Comments**

**Arysta –**

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

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

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

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

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

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

3) The effect of scaling on averaging times is not proportional. For example, the maximum continuous 8-hr concentration during a continuous 24-hr monitoring period will be in the neighborhood of twice the 24-hr concentration. This effect is documented in air dispersion theory literature.

Thus, it is inappropriate to make the direct comparison and calculations such as those made by Arysta. With respect to the DPR air concentration estimates, it is not possible to make simple statements such as "*For a given "maximum" 8-hour average concentration, the corresponding "maximum" 24-hour average concentration should not be less than one-third of the "maximum" 8-hour average concentration."*

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

**Arysta states: *"DPR's methodology for estimating the 2-week average concentration is based on something DPR calls "peak-to-mean" theory. The peak-to-mean theory is based on measurements made in the 1950-1960s of the variability in air pollution at sampling points downwind of contiuously-emitting smoke stacks…"***

The technique is commonly used in the air pollution regulatory community. The memorandum cited (Barry, 2000) is available for reference at the following internet website: http://www.cdpr.ca.gov/docs/emon/pubs/ehapreps/analysis_memos/2000_segawa.pdf. The theoretical foundation of "peak-to-mean" methods dates back to 1921 in the work of G.I. Taylor's concepts of diffusion by continuous motion. The first major paper addressing the peak-to-mean concept was published in 1959 by Gifford. The method was further developed by Hino in 1968 and is referenced specifically by Turner in his 1994 text entitled "Workbook of atmospheric dispersion estimates. Furthermore, the peak-to-mean adjustment concept is used by U.S.EPA in the 1992 document Screening Procedures for Estimating the Air Quality Impact of Stationary Sources, Revised (EPA-454/R-92-019) in the same manner as applied by DPR. This method has been used routinely to obtain long-term averages from shorter averaging time air concentrations.

**Arysta states; "…emission rates for iodomethane dramatically decline after the first 24-hours after the application, as evidenced in all of the flux studies. Therefore, the primary reason for lower concentrations over a 2-week period is the reduction in emission rate. Peak-to-mean theory is used to estimate the impact of variability due to changes in the wind direction and the looping of the plume. Therefore, it was misapplied to estimate season exposures by DPR.**

DPR staff is aware, and agrees that methyl iodide flux declines steeply after the first 24 hours. That is why the effective flux used to estimate the 2 week average air concentration is the 2 week average 24 hr flux. This flux estimate incorporates the form of the flux profile over 2 weeks and is effectively a uniform flux for that period, thus satisfying the continuously emitting assumption of the peak-to-mean theory (see the Arysta comment above). It should be noted that the peak-to-mean theory does not incorporate the looping of an elevated plume. The theory is derived by characterizing the lateral displacement of the plume centerline over one averaging period relative to the averaging period of interest. P.J. Barry in Boundary-Layer Meteorology Vol 2(1971): 122-126 indicates that the basic peak-to-mean ratio holds for any short-period to long-period ratio within the bounds given in his paper. The short period bounds are 5 s to 24 hrs; long period bounds are 6 min and 5 yrs. The ratio can be applied to obtain long to short or short to long adjustments, as discussed in Turner. Peak-to-mean adjustments are routinely used on area sources (e.g. manure piles, sewage treatment plants) in odor abatement.

**Worksafe** – This set of comments pertains only to farm workers. No air dispersion modeling or environmental fate comments were included. Thus, no response is required.

**NRDC** – This set of comments has no comments pertaining to air dispersion modeling and one comment pertaining to environmental fate.

**Comment 9: "MeI is likely to contaminate groundwater resources, which could pose a significant health hazard through contamination of drinking water."**

The assessment by NRDC is that the ground water iodide estimate should be refined and that the issue should be thoroughly studied and resolved before MeI is granted a California registration.

Response: DPR's evaluation indicates that methyl iodide is very unlikely to contaminate groundwater. The potential for the iodide anion breakdown product to contaminate groundwater is unknown. DPR's assessment includes a worst-case estimate of potential groundwater contamination by iodide. In addition, DPR added an alternative estimate of ground water concentrations to its assessment, using bromide ion as a surrogate. The U.S. Geological Survey detected bromide in 246 of 256 wells in California, with concentrations ranging from 0.01 mg/L to 13.3 mg/L, and a mean of 0.30 mg/L. They also detected iodide in 234 of the same 256 wells, with concentrations ranging from 0.001 to 2.4 mg/L, and a mean of 0.08 mg/L. These groundwater concentration estimates are adequate to estimate the health risk of iodide in water.

**A. Wise** – This set of comments references DPR air dispersion modeling and environmental fate analysis but does not suggest changes in either. Thus, no response is required.

**K. Collins** – This set of comments pertains only to toxicology. Thus, no response is required.

**PANNA –** Two documents are included in the PANNA submission: Review of the DPR RCD and Comments submitted to U.S.EPA.

**Page 8. Suggestion that DPR should use AERMOD rather than ISCST3.**
Response: The new algorithms in AERMOD are not implemented for area sources. For similar inputs, similar results will be obtained with both ISCST3 and AERMOD. All previous modeling at DPR has been conducted using ISCST3. For consistency, ISCST3 will continue to be used since switching to AERMOD for area sources has no benefit.

**Page 8. comment on modeling poisoning incidents.**

Response: DPR staff has published five peer reviewed articles on modeling incidents. All four California incidents shown on Page 6, Table 2 of the PANNA comments are subjects of those published peer review articles. Shown below are those articles:

1: Oriel M, Edmiston S, Beauvais S, Barry T, O'Malley M. Illnesses associated with chloropicrin use in California agriculture, 1992-2003. Rev Environ Contam Toxicol. 2009;200:1-31.

2: O'Malley M, Barry T, Ibarra M, Verder-Carlos M, Mehler L. Illnesses related to shank application of metam-sodium, Arvin, California, July 2002. J Agromedicine. 2005;10(4):27-42. Erratum in: J Agromedicine. 2006;11(2):91.

3: Centers for Disease Control and Prevention (CDC). Illness associated with drift of chloropicrin soil fumigant into a residential area--Kern County, California, 2003. MMWR Morb Mortal Wkly Rep. 2004 Aug 20;53(32):740-2.

4: O'Malley M, Barry T, Verder-Carlos M, Rubin A. Modeling of methyl isothiocyanate air concentrations associated with community illnesses following a metam-sodium sprinkler application. Am J Ind Med. 2004 Jul;46(1):1-15.

5: Barry T, Oriel M, Verder-Carlos M, Mehler L, Edmiston S, O’Malley M. Community Exposure Following a Drip-Application of Chloropicrin. Journal of Agromedicine, 15:1–14, 2010

**Pages 8-9. Request that DPR include the detail of field studies…clarify how differences in soil temperature are accounted for by the model.**

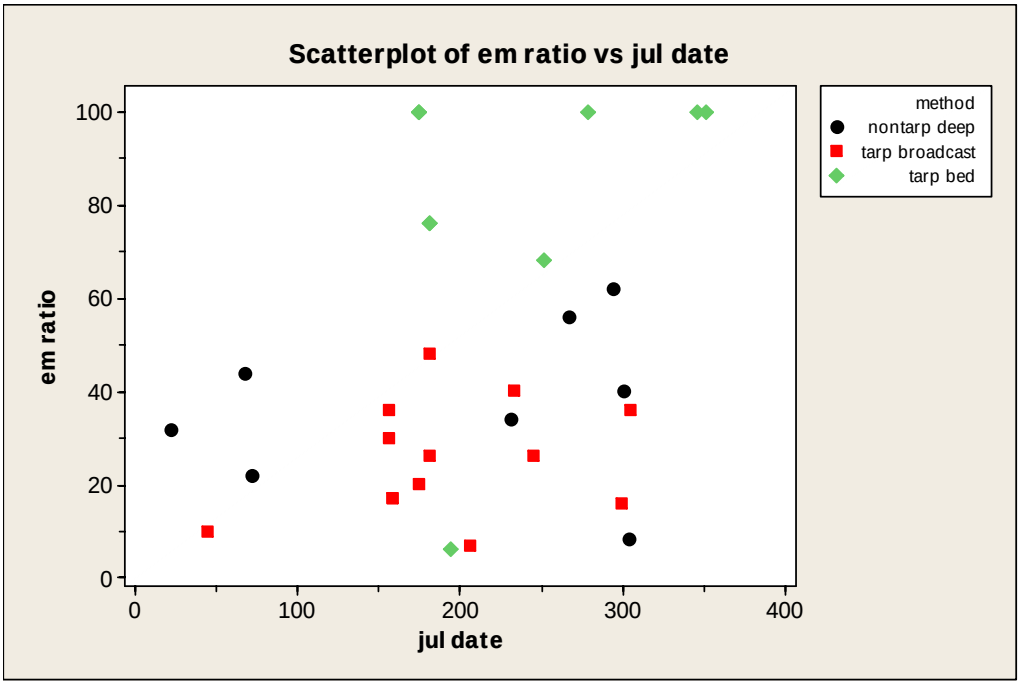
Response: DPR staff agrees in concept that temperature should have some effect on flux. However, other factors also influence flux, such as method of application, soil type, soil moisture, and field preparation procedures. These other factors confound the effect of temperature on flux, so no relationship can be established with existing data. In addition, it's likely that soil temperature at the depth of injection has a greater influence on flux than air temperature. Since most fumigant applications are made at a depth of 12-24 inches, the temperature effect is dampened because the soil temperature varies less than the air temperature.

The relationship between air temperature and flux is not clear. Analysis of MeI flux from 11 field studies by Reiss and Griffin (2007) found no detectable relationship between temperature and flux.

A second example of the lack of demonstrated relationship between air temperature and flux is found for chloropicrin (Beard, 1996). A 33.8% mass loss for chloropicrin was found in a Washington field study. A 36.5% mass loss was found in a Florida field study. These were both broadcast tarp chloropicrin applications. The air temperatures during the Florida study were 15 to 20 degrees F warmer yet the mass loss results are similar to the Washington study.

DPR's work with methyl bromide applications throughout the year found that winter applications can show high flux, high emission ratios (flux expressed as the fraction of amount applied), and high air concentrations. In fact, analysis of the relationship between Julian date of the application (as a surrogate for temperature) and the emission ratio shows no significant relationship between emission ratio and day of application. The regression equations for each application of emission ratio as a function of Julian date had R-square values of 3%, 7%, and 12% for nontarp deep, tarp broadcast, and tarp bed application methods respectively. A measurable temperature effect should be clearly discernable in the regression results. Thus, a simple, clear relationship between temperature and flux is not supported by the DPR methyl bromide database. More likely many factors act together.

A plot of the methyl bromide emission ratios is shown below. Note the complete lack of trend for the tarp broadcast data. In particular, the February 13, 1997 application has an emission ratio of 9.8%. This could be argued to support the low temperature, low flux theory. However, the July 25, 1998 application shows an emission ratio of 6.8%. It is also clear the tarp bed application method shows a high emission ratio no matter when the application is made. In fact, the tarp bed applications in December show a 100% emission ratio, similar to those applications made in June and October. The methyl bromide database is the largest available and likely reflects broad trends in flux and emission ratios for other fumigants. Thus, the relationship between temperature and total mass lost is not clear.




**Page 9. Request that DPR provide clarification of which field studies were used to develop the flux profile and how soil temperatures may differ in those in the study from which the flux profile was determined**

Response:

DPR used 7 flux profiles from the 7 studies available at the time the exposure appraisal was developed. The flux profile that resulted in the highest air concentrations was used from among those 7 flux profiles. See Barry (2008a) for details of how the air concentrations were developed.

**Page 9. Comment 3. Documentation of the exposure model should be explicitly described…**

See Barry(2008a) for details of the exposure modeling.

**Page 12. Comment 5. Subchronic exposure…**

See Barry (2008b) for details of the subchronic air concentration development.

**References**

Barry, T. 2008a. Screening level air concentration estimates for Worker Health and Safety Exposure Appraisals. Memorandum to Randy Segawa dated August 21, 2008. Environmental Monitoring Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA. http://www.cdpr.ca.gov/docs/emon/pubs/ehapreps/analysis_memos/2071_segawa.pdf

Barry, T. 2008b. Development of sub-chronic air concentration estimates associated with a single fumigant application. Memorandum to Randy Segawa dated September 5, 2008Environmental Monitoring, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA. http://www.cdpr.ca.gov/docs/emon/pubs/ehapreps/analysis_memos/2077_segawa.pdf

Beard, K.K., P.G. Murphy, D.D. Fontaine, J.T. Weinberg. 1996. Monitoring of potential worker exposure, field flux and off-site air concentration during chloropicrin field application. HEH 160. Chloropicrin Manufacturers Task Force. DPR Registration Data Volume199-072.

Reiss, R. and J. Griffin. 2007. A review of the flux rate data collected for Iodomethane and Midas® 50:50. DPR Registration Data Volume No. 52875-0140.