Iodomethane Risk Assessment Overview

Methyl Iodide External Peer Review Panel Workshop
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EPA Current Position on Iodomethane

- Depending on the outcome of California's external peer review and final risk assessment, EPA may choose to initiate reevaluation of the methyl iodide registration.

- If the scientific review panel provides new information that would alter or change EPA's scientific analysis, we will include that information in this reevaluation decision.

Risk Assessment

Wind

Worker Risks

Bystander Risks

Other potential exposures considered (food, drinking water)

EPA Risk assessment completed on 8/23/07 and it is available at www.regulations.gov (Docket: EPA-HQ-OPP-2005-0252-0051)

Risk Assessment

Risks evaluated under many conditions

- Lifestages
- Durations of exposure
- Common application methods
- Emissions under typical and barrier films
- Weather sources from inland/coastal California and Florida, Michigan, PNW

Risk Assessment

Peer reviewed methods under FACA

- SAB on inhalation risk methodology used to calculate Human Equivalent Concentrations (HECs) (1998)
  http://yosemite.epa.gov/sab/sabproduct.nsf/5C8DAE43A736B06E8525718F0062FDC1/$File/ehc9905.pdf
- SAP on distributional exposure modeling for determining buffer zone estimates (2004)

http://www.epa.gov/scipoly/sap/meetings/2004/august1/august2425minutes.pdf

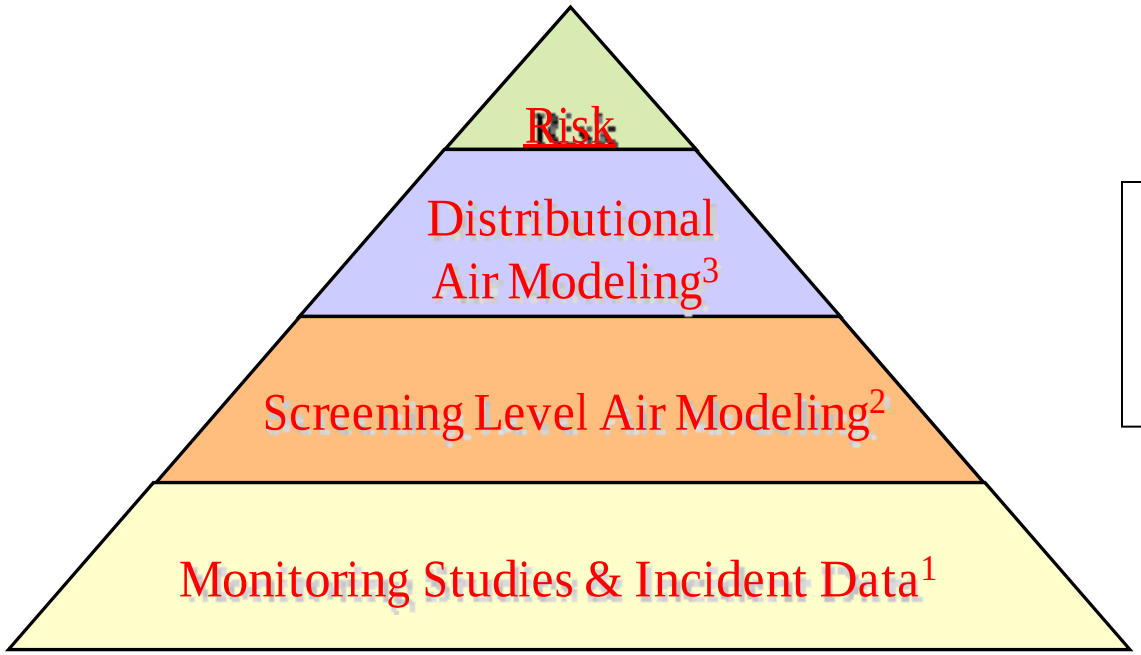
Significant collaboration with other scientists (e.g., EPA/ORD, DPR, USDA)

Exposure Assessment

Worker Exposure Results

- Common tasks monitored during actual methyl iodide applications
- All data meet ethics criteria
- Risks calculated for all endpoints
- Exposure monitoring reflects emission profile of iodomethane (e.g., planter exposures)
- Risks were identified for high exposure tasks

Bystander Exposure Assessment
An Integrated Approach



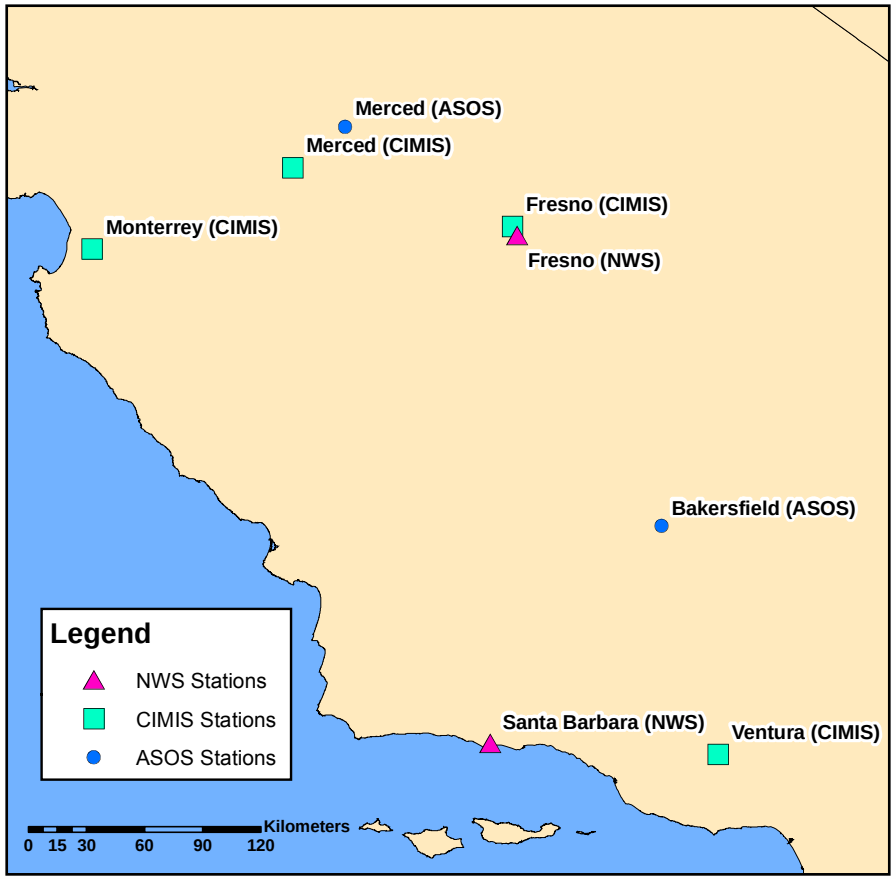
1	11 Monitoring studies & no incidents to date (17K acres);
2	ISCST3 air model (2003/2004)
3	PERFUM development & SAP air model review (2004)

Varied Conditions Examined

Weather Station Location	Flux Study Summary With Commonly Used Polyethylene Tarps							
	Watsonville CA Flat Fume	Manteca CA Flat Fume	Plant City FL Raised Bed	Oxnard CA Raised Bed	Guadalupe CA Raised Bed	La Selva CA Drip Irrigation	Camarillo CA Drip Irrigation	Guadalupe CA Drip Irrigation
Ventura CA	X	X	NA	X	X	X	X	X
Bakersfield CA	X	X	NA	X	X	X	X	X
Flint MI	X	X	X	X	X	X	X	X
Tallahassee FL	X	X	X	NA	NA	X	X	X
Bradenton FL	X	X	X	NA	NA	X	X	X
Analyses completed using all endpoints of concern.								

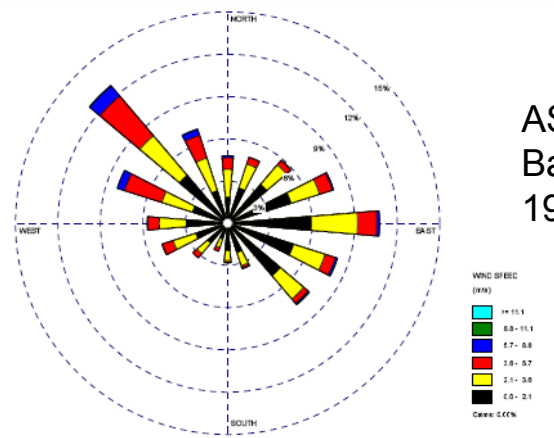
Additional analyses also completed using same weather data & 3 additional flux studies which utilized higher barrier tarps

Weather Data



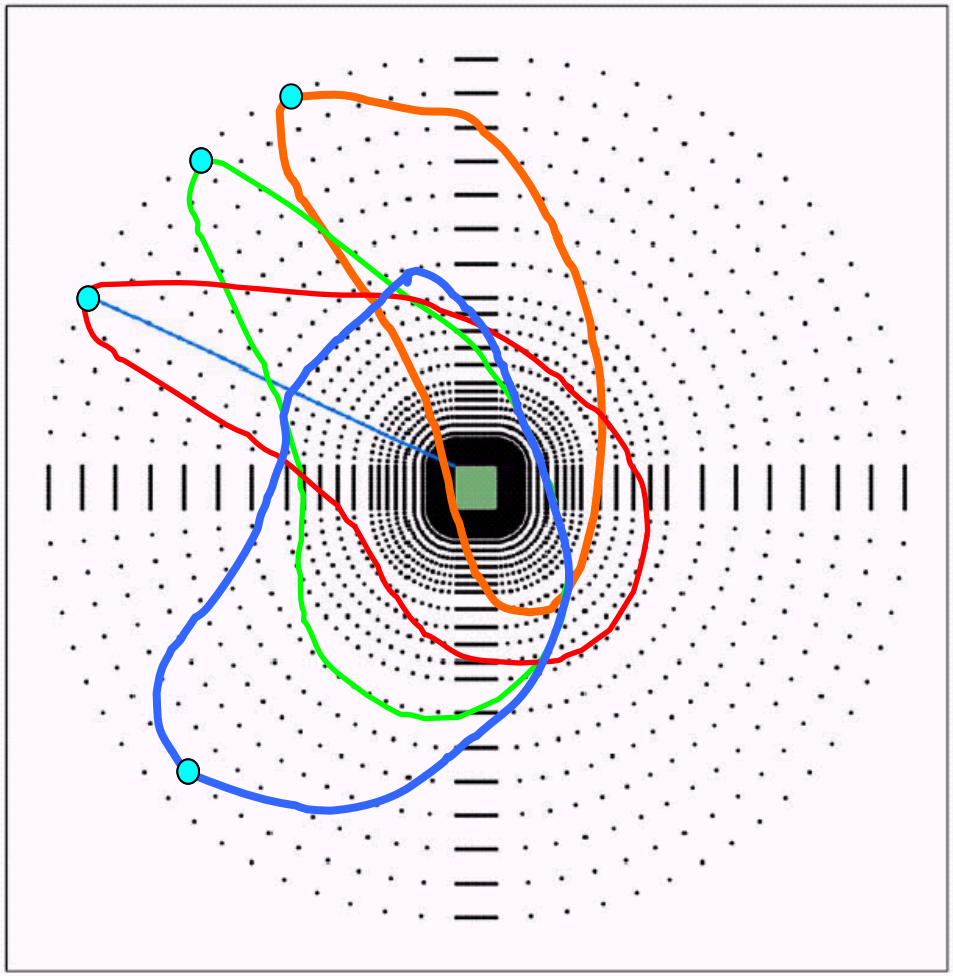
5 Years of Weather Data Used

- 6 stations (CA, FL, MI, WA)
- 2 stations in California
  - Coastal – Ventura
  - Inland – Bakersfield
- Bradenton FL – consistently predicted farthest distances



ASOS
Bakersfield CA
1999-2003

Risk Assessment Outputs



Various Ways of Presenting Outputs

- Each contour represents the distance from a field where an air concentration of concern is achieved for a day
- 5 years of daily outputs for each weather/flux profile analysis
- 3 distinct methods for compiling the results, all considered for methyl iodide

Whole Field: Uses all points around each day for 5 years

Maximum Buffer: Uses only the farthest point for each day

[Ring]: distribution of air concentrations at specific perimeter distances

Factors Which Influence Emissions

- Many factors were examined

(EPA-HQ-OPP-2005-0123-0467 at http://www.regulations.gov/)

- Key parameters include:
  - tarp type
  - field conditions
  - soil amendments
  - application methods
- Currently undergoing revision
    - soil data, comments, model options, MTCs

Other Types of Bystander Exposures

- Longer-term exposures
  - Used ambient air data for methyl bromide
    - Shorter ½ life and lower amounts used
  - Currently investigating additional approaches
    - Modeling approaches
      - Peak to mean techniques
      - December 2009 FIFRA SAP for non-fumigants
      - Airshed modeling approaches (e.g., CALPUFF)
    - Monitoring data

Lack of Incidents

- ~17,000 acres treated, mostly in Florida
- At least 425 application events
- No incidents

EPA Ongoing Activities

- Revisions to factors analysis
- Implementation of integrated study protocol which links soil phenomena to emissions
- EPA tarp permeability testing project

Hazard Assessment

Hazard Overview

- Extensive toxicology database
  - Core studies required by 40CFR§158 *via* inhalation route
  - Mechanistic studies
  - PBPK model
  - Observational Human Study
- Hazard assessment conducted for all durations of exposure
  - Emphasis on acute bystander assessment

Hazard Overview

- Used RfC methodology to derive human equivalent concentrations (HECs) for all but acute scenarios
- Dose metrics and parameters derived using a Physiologically Based Pharmacokinetic Model (PBPK) for acute scenario
- No requirement for a developmental neurotoxicity study (DNT)
- Not likely to be carcinogenic in humans at doses which do not alter thyroid hormone homeostasis

Acute Hazard Assessment

- Three effects of concern identified
  - Nasal lesions
  - Neurotoxicity
  - Fetal loss
- PBPK model used to derive Human Equivalent Concentrations (HECs)

Effect: Nasal Lesions

- Subchronic Inhalation Toxicity Study
  - Degeneration of olfactory epithelium
    - Likely occurred after more than one exposure
  - HEC = 4.5 ppm (bystander) or 5.8 ppm (occupational)
- PBPK model used GSH depletion as dose metric to derive HEC
  - Preventing excessive GSH depletion would be protective of olfactory epithelial damage
  - 50% depletion commonly cited in the literature as critical for development of nasal histopathology
  - Model likely overestimates extent of GSH depletion
  - GSH depletion during time of peak emissions ≈ 38%

Effect: Fetal Loss

- Pre-Natal Developmental Study in Rabbits
  - Fetal loss
    - After two days of exposure
    - Coincides with period of fetal thyroid development in rabbit
  - HEC = 7.4 ppm (bystander) or 23 ppm (occupational)
  - PBPK model used AUC fetal serum inorganic iodide as dose metric

Effect: Neurotoxicity

- Acute Neurotoxicity Study
  - Clonic convulsions, decreased body temperature, and decreased motor activity
  - HEC = 10 ppm (bystander & occupational)
- PBPK model used steady state MeI concentration in brain as dose metric to derive HECs
  - Steady state reached within 8 hours of exposure

Effect: Neurotoxicity (2)

- Developmental Neurotoxicity (DNT) Study not required
  - DNT conducted in less responsive species (rats)
    - MeI thyroid toxicity more sensitive in rabbits than rats
  - Disruption of thyroid hormone homeostasis initial and critical effect leading to adverse effects on the developing nervous system
    - Apical measures in DNT less sensitive than this mechanistic measure
    - Thyroid hormone perturbations most sensitive systemic effect caused by iodomethane

Protecting for thyroid hormone perturbations results in protection for development of the nervous system

Effect: Carcinogenesis

- Increased incidence follicular cell tumors in the Combined Chronic/Carcinogenicity Study in rats and the Oncogenicity Study in Mice
  - Key event: sustained stimulation of cell proliferation by TSH, consistent with the increase in thyroid follicular cell tumors
    - Rats more sensitive than humans to the development of thyroid follicular cell tumors in response to thyroid hormone imbalance
      - Thyroid hormone half-life much shorter in rats than humans (12 hrs *vs* 5-9 days)
      - Larger thyroid hormone reserve in the human than rat
      - Constitutive TSH levels are approximately 25 times higher in rats than in humans
      - Modest changes in thyroid hormone homeostasis may promote tumor formation in rats
      - Data in humans suggest that prolonged TSH stimulation of the thyroid gland poses a negligible risk of thyroid carcinogenesis
        - Causes of cancer on 9.6 million individuals investigated using the Nationwide Swedish Family-Cancer Database found the environment did not appear to play a principal causative role in thyroid cancer
        - The only known human thyroid carcinogen is x-irradiation

MOA extensively described and widely recognized by WHO & International Agency For Research on Cancer

Effect: Mutagenic MOA

- Not considered operative MOA for thyroid tumors
- Except for thyroid, no indication of carcinogenicity in any tissue after chronic exposures

Short-, Intermediate-, and Long-Term Hazard Assessments

Duration	Toxicity Endpoint	NOAEL[a]	Human Equivalent Concentrations (HECs)	
			Bystander	Occupational
Intermediate/ Subchronic term	↓pup weight, ↓pup weight gain, ↓ thymus weight, delayed vaginal patency acquisition	5 ppm	1.25 ppm	N.A.
	Degeneration of the olfactory epithelium	21 ppm	N.A.	3.7 ppm
	↑ relative liver wt., ↓ body weight gain	21 ppm	N.A.	N.A.
Chronic	↑ salivary gland squamous cell metaplasia	5 ppm	0.89 ppm	3.75 ppm
Lifetime	Thyroid tumors	20 ppm	Not likely to be carcinogenic to humans at doses that do not alter rat thyroid hormone homeostasis	

Summary

- Robust and extensively evaluated toxicity database
- Three acute HECs calculated
  - Nasal lesions HEC = 4.5 ppm (bystander) 5.8 ppm (occupational)
  - Fetal loss HEC = 7.4 ppm (bystander) 23 ppm (occupational)
  - Neurotoxicity HEC = 10 ppm (bystander & occupational)
- Not likely to be carcinogenic to humans at doses that do not alter thyroid hormone homeostasis

EPA Risk Management

- Restricted use pesticide status with enhanced responsibility for applicators
- Buffer zones and prohibition of ¼ mile minimum if sensitive sites are present
- Credits for emission reduction measures
- Protections for workers
- Daily use limited to 40 acres