Arysta LifeScience

Introductions

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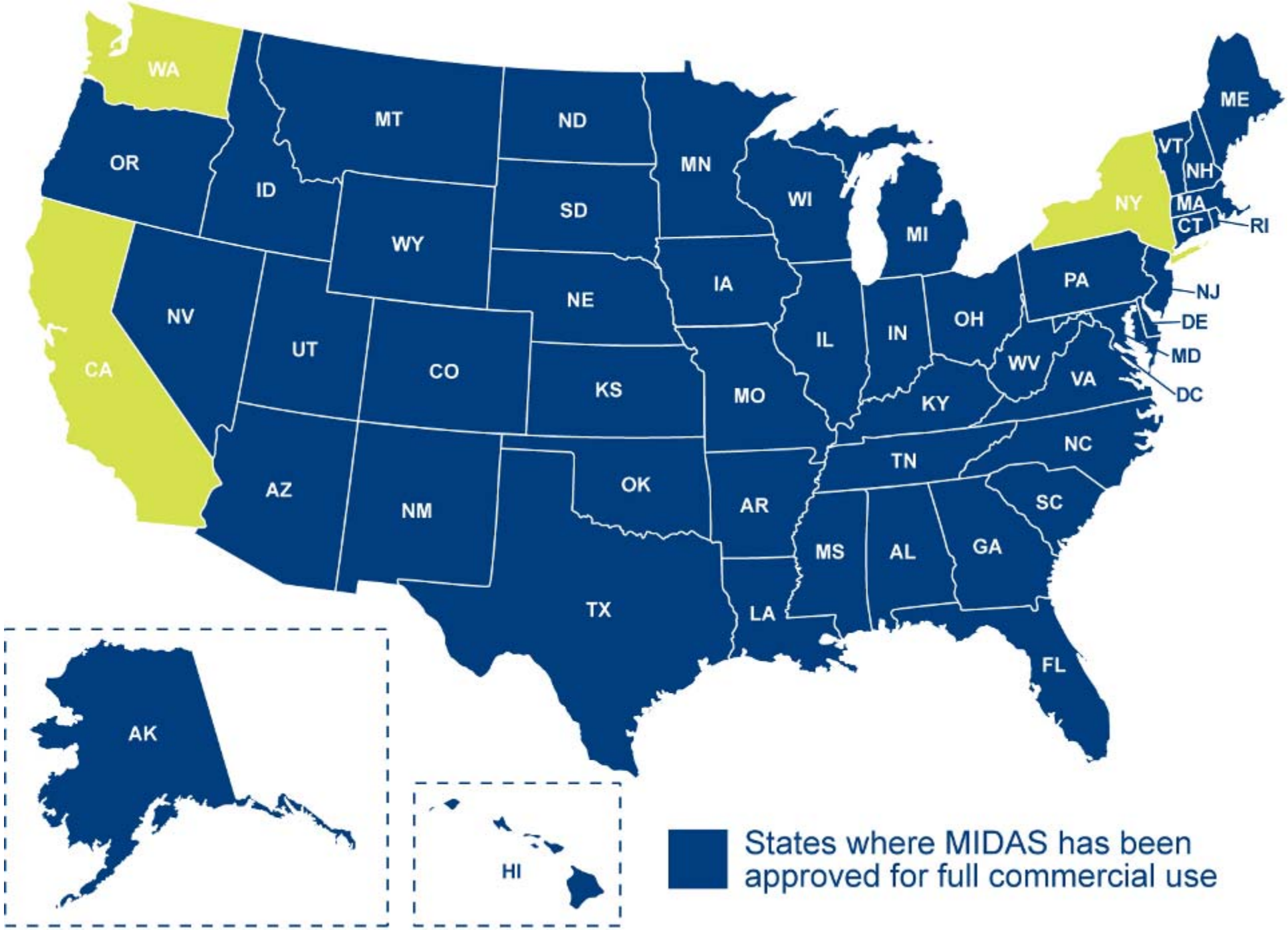
Iodomethane

- Developed as a methyl bromide alternative by the University of California, Riverside
- UC granted license to Arysta
- Awarded prestigious EPA Ozone Layer Protection Award

EPA Review

- Initial data package submitted in 2002 to EPA and to DPR
- Registered in 2007 by the EPA
- Toughest label in the fumigant industry
- Most comprehensive stewardship and in-the-field training program for fumigants
- UC Davis, UC Riverside, University of Florida, University of New Mexico, USDA-ARS
- Nearly 100 scientists from independent laboratories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States where MIDAS has been approved for full commercial use

Usage

- 17,000 acres in Florida, Maine, Michigan, Virginia, North and South Carolina, Georgia
- 30 – 50% less pounds per acre

Application

Arysta's Position

- Shared goal of safe and effective use of iodomethane
- Existing label, as approved by EPA, affords industry-leading protection to workers, bystanders and communities
- DPR's draft RCD is unnecessarily conservative

Key Issues

1. DPR selected the No-Observed Effect Level (NOEL) of 2 ppm in rabbits for the developmental toxicity endpoint instead of the 10 ppm No Observed Adverse Effect Level (NOAEL) as the point of departure

2. DPR did not accept the weight of evidence for the developmental toxicity mode of action (MOA) thereby selecting an inappropriate dose metric for human equivalent concentrations (HECs)

Key Issues

3. DPR recommended uncertainty factor (UF) of 300
   10X more than EPA

4. DPR indicated a developmental neurotoxicity study (DNT) is a data gap. EPA determined available data are adequate

5. DPR used **chronic** oral iodide intake to assess potential risk from **acute** iodomethane exposure

6. DPR used simplistic screening level methods for exposure assessment instead of state-of-the-art probabilistic exposure assessment methods

Considerations for Acute Exposure

Acute Toxicity Endpoint	EPA HEC		DPR HEC	
	Occupational	**Bystander**	**Occupational**	**Bystander**
Nasal lesions	5.8 ppm	4.5 ppm	2.8 ppm	2.2 ppm
Transient Neurotoxicity	10 ppm	10 ppm	3.4 ppm	3.4 ppm
Developmental Toxicity	**23 ppm**	7.4 ppm	**0.22 ppm**	0.24 ppm

Nasal Lesions

Glutathione (GSH) depletion in nasal olfactory epithelium in rats

- EPA dose metric for extrapolation from rats to humans 50% depletion
- DPR dose metric 25% GSH depletion

Acute Toxicity Endpoint	EPA HEC		DPR HEC	
	Occupational	Bystander	Occupational	Bystander
Nasal Lesions	5.8 ppm	4.5 ppm	2.8 ppm	2.2 ppm

Preponderance of data in literature supports EPA conclusion of 50% depletion

Transient Neurotoxicity

Transient neurotoxicity

↓ motor activity ↓ body temperature

Dose metrics

EPA: steady-state brain concentration of iodomethane

DPR: area under the concentration curve (AUC) for brain iodomethane

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Rabbit Developmental Toxicity
EPA Guideline Study

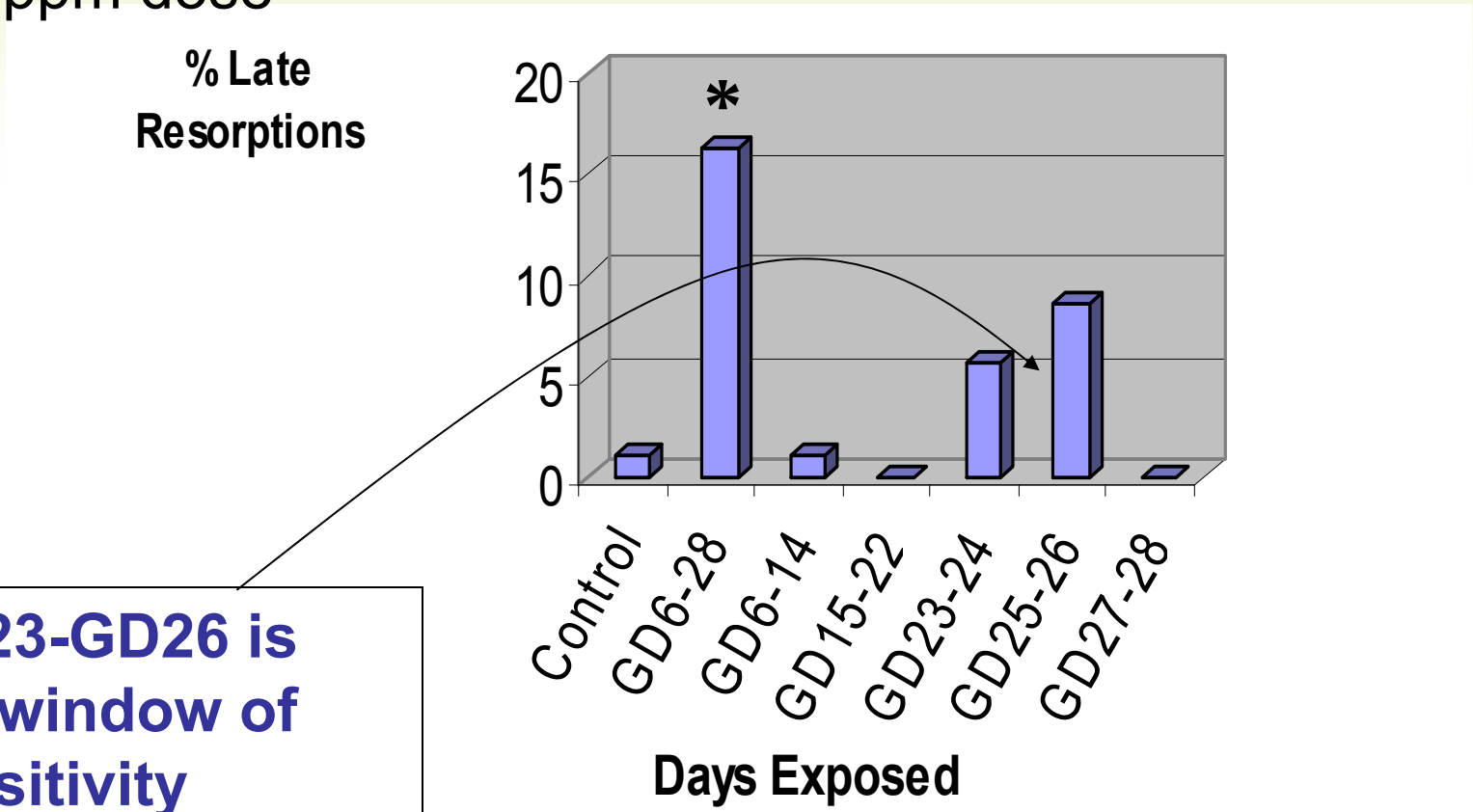
0, 2, 10, and 20 ppm dose on gestation days (GD) 6-28

Findings:

- In the 20 ppm group:
  - a statistically significant increase in late resorptions
  - decreased % viable fetuses per litter
  - increased post-implantation loss
  - reduced offspring body weight compared to control
- In the 10 ppm group:
  - no statistically significant difference in late resorptions
  - no effect on % viable fetuses per litter
  - no effect on post-implantation loss
  - statistically significant decrease in female offspring body weight (only significant effect) described by the study director as equivocal
- Therefore the NOAEL is 10 ppm.

Developmental Toxicity
Phased Rabbit Exposure Study

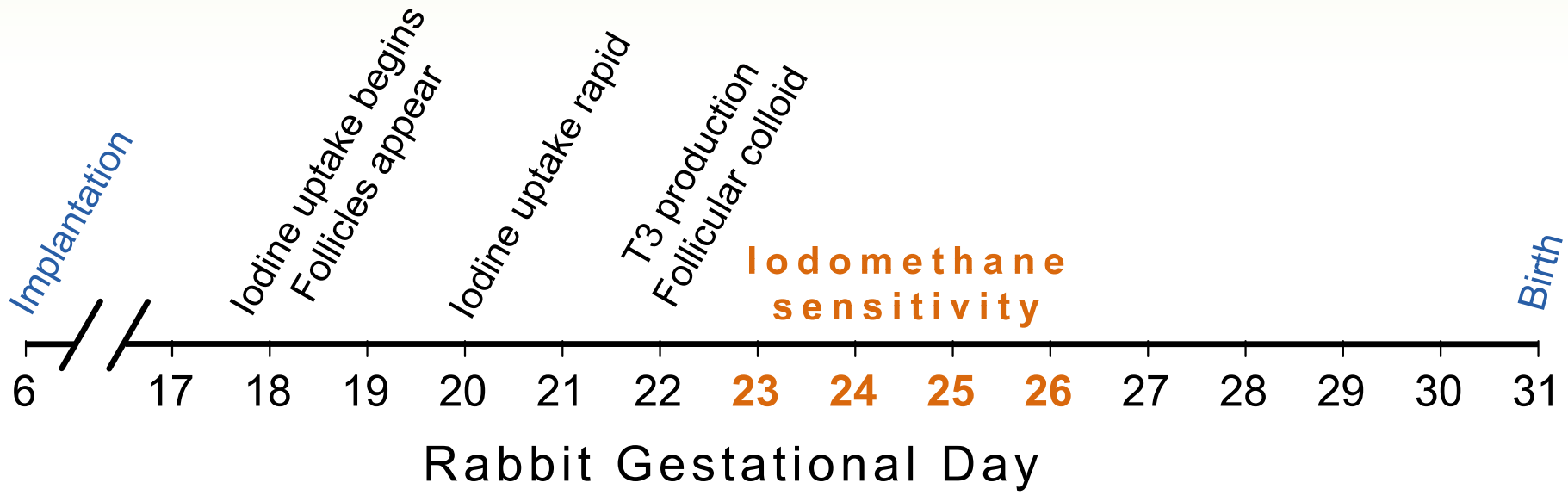
20 ppm dose



GD23-GD26 is the window of sensitivity

*** Different from controls ($p<0.05$)**

Developmental Toxicity
Fetal Rabbit Thyroid Ontogeny



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Developmental Toxicity Postulated Mode of Action

Late resorptions in iodomethane-exposed rabbits are a direct effect of increased ***fetal*** *plasma iodide*

MOA Evaluation
IPCS Framework

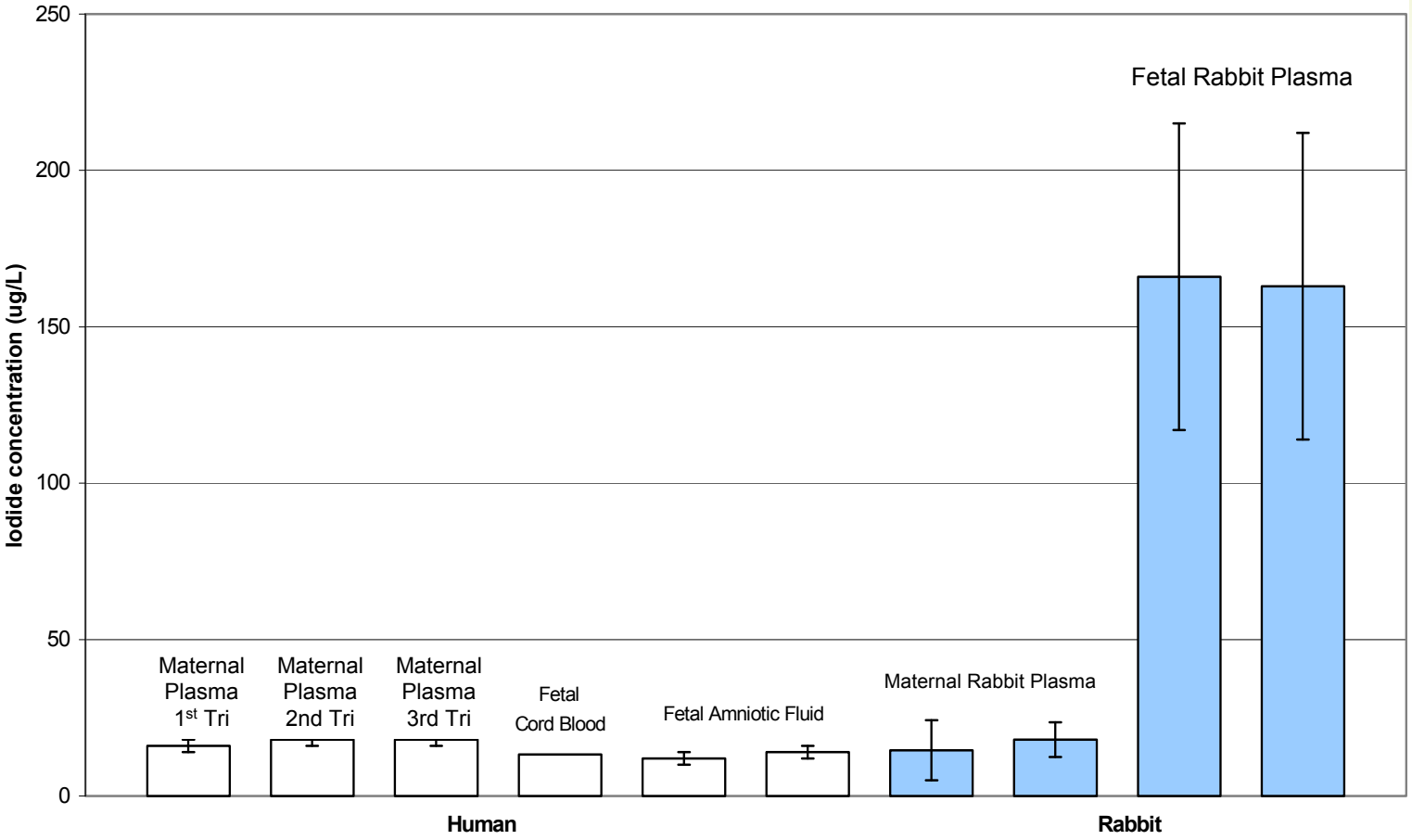
- **Postulated Mode of Action**
- **Key events – critical to induction of effect**
- Concordance of dose-response
- Temporal association
- Strength, consistency and specificity of association of response with key events
- Biological plausibility and coherence
- **Alternative MOAs**
- Uncertainties, inconsistencies,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

MOA Evaluation
Key Events in Developmental Toxicity

- **Iodide is concentrated in fetal rabbits compared to the doe in control and treated**
  - Fetal:maternal plasma iodide ratio
    - ~9 in control rabbits
    - ~6 in iodomethane-treated
  - Fetal rabbits are known to be susceptible to excess iodide, resulting in fetal loss (Literature from the 1960's)

Developmental Toxicity Key Event Evaluation of Iodide Distribution to Fetus

Fetal and Maternal Iodide Concentrations in Unexposed Humans* and Rabbits (Literature)**



* Liberman *et al*. (1998); Herve *et al.* (1997); Mahillon *et al*. (1989)
**Sloter *et al.* (2009)

Developmental Toxicity Key Events
Iodide Effects on Rabbit Thyroid During GD23-26

- **Excess iodide is known to alter thyroid function**
- **Exposure to intravenous iodide or inhaled iodomethane caused the same effects in rabbits**

<u>20 ppm Iodomethane (GD23-26)</u>
- Altered thyroid hormone levels
  - Greater and more consistent in fetal than maternal plasma
- Reduced colloid in fetal thyroid follicles
- Induced follicular cell hypertrophy in fetal thyroid

<u>Sodium iodide (NaI) administered intravenously</u>
- Induced same effects on fetal thyroid structure and function
- Dose resulted in lower plasma iodide levels than iodomethane-exposed, so less severe effects would be expected

Fetal iodide is the most appropriate dose metric for risk assessment

MOA Evaluation
Alternative MOAs Developmental Toxicity

- **DNA Methylation**
- **Glutathione Depletion**
- **Altered Cholesterol Metabolism resulted in 15-16% ↓ in estradiol (E_2) in rabbits exposed to 25 ppm iodomethane (not significant)**

MOA Evaluation
Conclusion

- The developmental toxicity MOA was evaluated and identified using the IPCS Framework
- DPR performed the MOA evaluation and determined the data was insufficient to support the MOA
- EPA and Arysta concluded the weight of evidence supports the MOA for fetal loss in iodomethane-exposed rabbits as a direct effect of increased fetal plasma iodide
- The MOA supports use of fetal plasma iodide as the dose metric for extrapolation from rabbits to humans
- EPA and Arysta use this dose metric for extrapolation, DPR does not use this dose metric for extrapolation

Extrapolation from Rabbits to Humans
Using the PBPK Model and the MOA

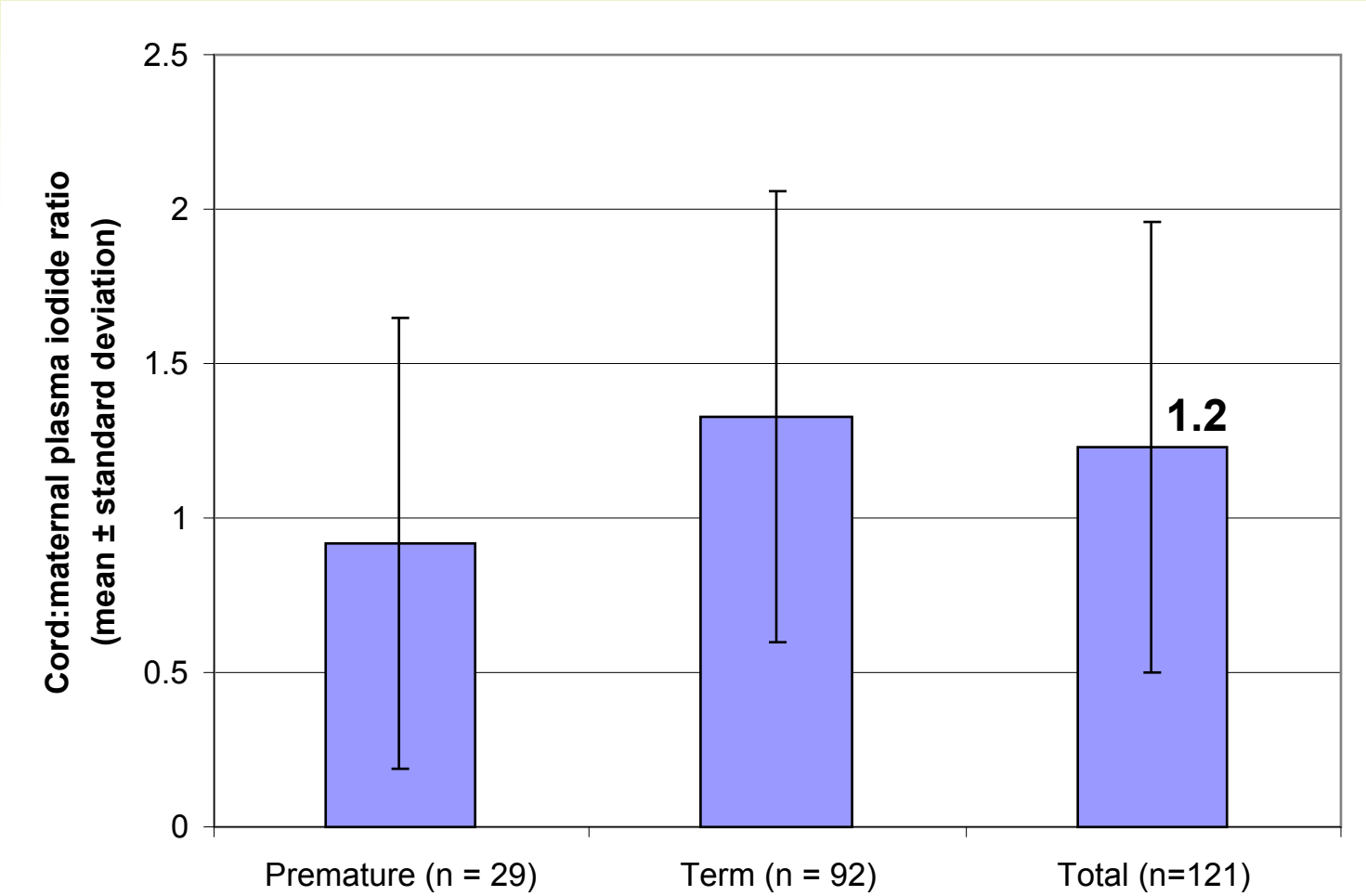
- EPA and Arysta assumed the human fetus is equally sensitive to iodide as the rabbit
- The PBPK model accounts for the difference in fetal iodide concentration between rabbits and humans
- Rabbit fetus does concentrate iodide while human fetus ***does not*** concentrate iodide
  - Human fetal:maternal iodide ratio is ~1 in women exposed to iodide by injection

    (Cottino et al., 1972)
  - Human fetal:maternal iodide ratio is ~1 in unexposed women

    (Rayburn et al., 2008, peer-reviewed publication)

Extrapolation from Rabbits to Humans

Human paired fetal:maternal plasma iodide ratios



Rayburn et al. (2008)

Developmental Toxicity Endpoint HECs

- Arysta and EPA HECs are based on fetal plasma iodide **AUC** and the NOAEL of 10 ppm
- DPR HECs based on maternal plasma iodide AUC and the NOEL of 2 ppm

Acute Toxicity Endpoint	EPA HEC		DPR HEC	
	Occupational	Bystander	Occupational	Bystander
Developmental Toxicity	**23 ppm**	7.4 ppm	**0.22 ppm**	0.24 ppm

DPR based its HEC on maternal plasma iodide level, dismissing the evidence supporting fetal plasma iodide as the appropriate dose metric

Key Issues

3. DPR recommended uncertainty factor (UF) of 300
   10X more than EPA; because…

4. DPR indicated a developmental neurotoxicity study (DNT) is a data gap. EPA determined available data are adequate

5. DPR used **chronic** oral iodide intake to assess potential risk from **acute** iodomethane exposure

6. DPR used simplistic screening level methods for exposure assessment instead of state-of-the-art probabilistic exposure assessment methods

Uncertainty Factor

DPR recommended 300, 10X EPA

DPR indicated a DNT is a data gap

Data submitted and PBPK modeling identify iodomethane exposure levels that do not cause effects on fetal or maternal thyroid

By basing the HEC on the fetal iodide level, the offspring are never exposed to excess iodide thus preventing adverse effects on the thyroid and neurodevelopmental effects from thyroid toxicity

Therefore neurodevelopmental and neurobehavioral effects from excess iodide are prevented.

DNT testing is unnecessary, EPA agrees

Uncertainty Factor

DPR recommended 300; 10X EPA

DPR used **chronic** oral iodide intake to assess potential risk from **acute** iodomethane exposure

- The basis of the NAS tolerable upper intake level (UL) for iodine is increased thyroid stimulating hormone in humans (TSH) after daily oral iodine intake

- "The UL applies to chronic daily use" NAS, 2000

<u>The use of chronic iodine UL for acute exposure to iodomethane is inappropriate</u>

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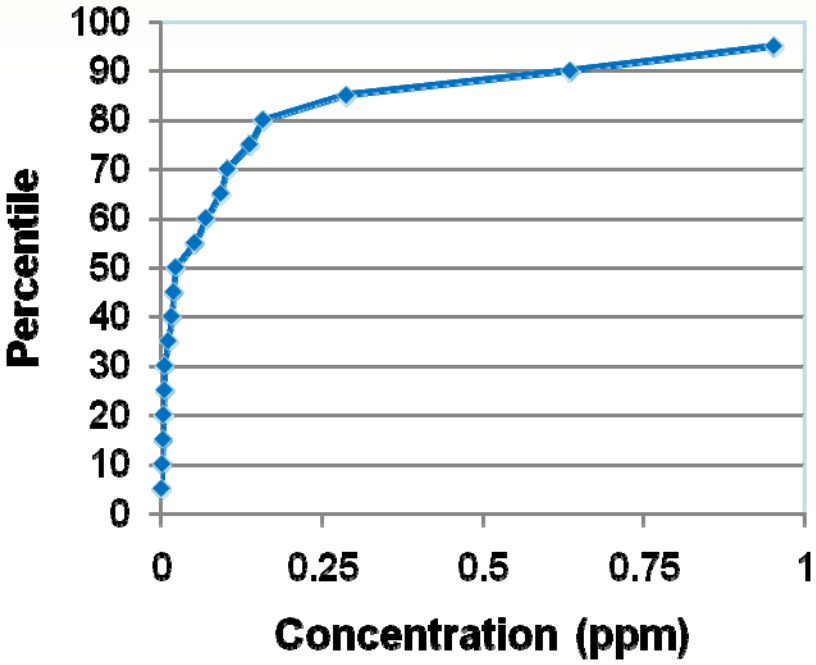
Occupational Exposure Data

Exposure Data

- 39 personal exposure measurements in 6 field trials covering all job categories, application methods
- Range 0.0001 – 1.1 ppm (mean = 0.16 ppm)
- All exposures are acceptable using PPE under EPA's approved label

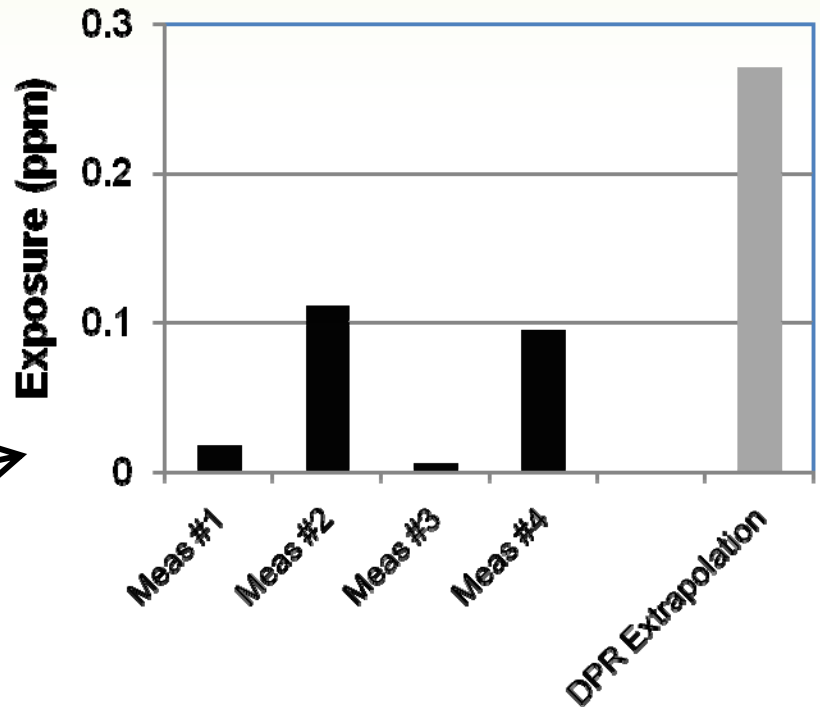
Distribution of Exposure Data



Occupational Exposure Estimates

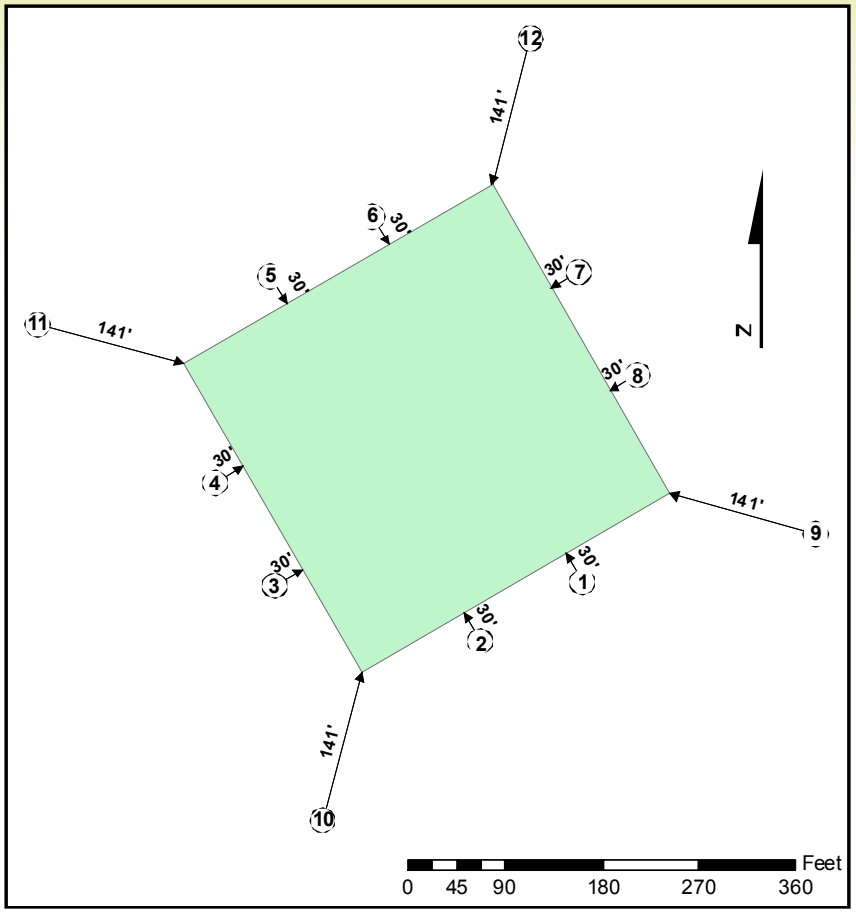
- DPR vs EPA
  - EPA: maximum measured values
  - DPR: maximum + using highly uncertain extrapolation method
- Driver/applicators – broadcast & raised bed
  - Max: 0.11 ppm
  - DPR Extrapolation: 0.27 ppm

Exposures for Drivers/Applicators - (broadcast and raised bed, respiratory protection applied)



Bystander Exposure Studies

- Arysta has performed 11 studies, mostly in California
- Each one provides flux estimates for 2 weeks after the application
- Mass balance shows 80-100% volatilized

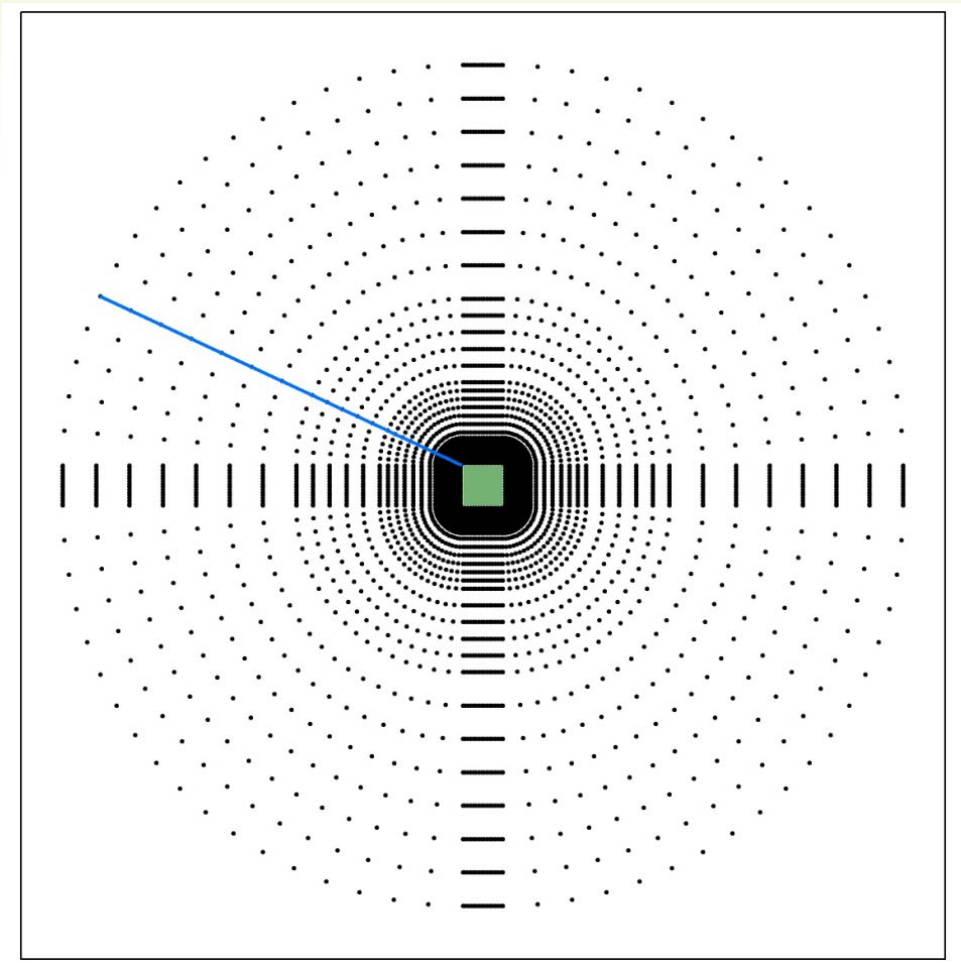


Flux = Mass emitted per area per time

Bystander Exposure Estimates

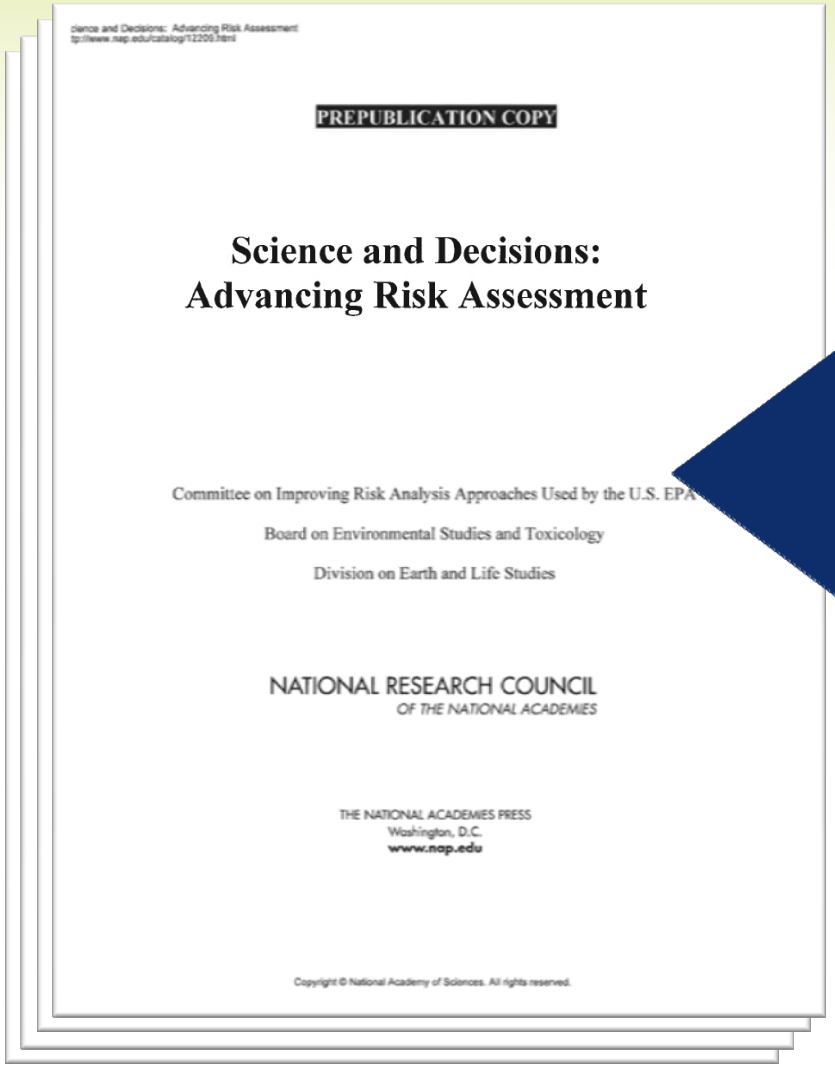
- DPR used simplistic meteorological scenarios (e.g., 24-hr exposure):
  - 1.4 m/sec wind speed
  - “C” class stability
  - Constant wind direction
- Advantages of using PERFUM:
  - Real meteorological data
  - Better representation of reality
  - Allows probabilistic estimates
  - More information for risk management

PERFUM Probabilistic Modeling



Points on diagram = individual air concentration estimated reading

Probabilistic vs. Deterministic Exposure Assessment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Science and Decisions: Advancing Risk Assessment

Committee on Improving Risk Analysis Approaches Used by the U.S. EPA

Board on Environmental Studies and Toxicology

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The risk estimates can be most fully characterized by performing probabilistic analyses when possible and by presenting the range of possible risk estimates rather than by reporting the single point estimates. Risk characterization should provide useful information to risk managers to help them understand the variability and uncertainty in the risk estimates.

National Academy of Sciences (2008)

Carcinogenicity Evaluation

DPR's revised RCD concluded that iodomethane should be considered as a potential human oncogen because of tumor formation in:

- male rat brain (astrocytoma)
- mouse uterus/cervix
- rat and mouse thyroid

Rodent Tumor Data

Malignant Astrocytoma Incidence in Male Crl:CD BR Rats		
Iodomethane (highest incidence group)	Historical Control - Testing laboratory	Historical Control - Breeder
2.9%	0 -3.3% (17 control groups)	0.87 – 4.29% (30 control groups)

Mouse Fibroma	Iodomethane Dose (mg/kg/day)			
	0	10	35	100
Uterus/Cervix Combined	0/50	1/50	0/50	4/50

In both cases, the tumors are not seen to be caused by iodomethane

Rodent Thyroid Results

Iodomethane Rodent Thyroid Tumor Results

- Male rat and mouse benign and malignant follicular cell tumors
- Thyroid hypertrophy (statistically significant dose-related) and hyperplasia
- Plasma TSH levels were elevated in high-dose rats and mice during chronic exposure to iodomethane; T4 hormone levels not increased (decreased in the mouse)

Rodent Thyroid Hormone Levels

Hormone	Control	Low Dose	Medium Dose	High Dose
Rat T4 (µg/dL)	2.25 ±0.7	2.27±0.7	2.24±1.0	2.50±0.6
Rat TSH (µg/mL)	2.38±1.1	3.29±1.6	3.48±1.8	11.29±14.9**
Mouse T4 (µg/dL)	2.68±0.742	2.60±0.976	2.55±0.942	1.87**±0.570
Mouse TSH (µg/mL)	0.45±0.140	0.54±0.210	0.69*±0.277	0.86**±0.468

*Significant at 0.05
** Significant at 0.01

Rodent Thyroid Results

EPA Risk Assessment Forum (RAF) 1998 Rodent Thyroid Tumor Criteria

- Tumors associated with altered thyroid-pituitary function are associated with chronic reduction in thyroid hormones and an increase in TSH
- RAF recommends a threshold method of assessment for thyroid tumors resulting from alteration in thyroid-pituitary function

Genotoxicity Findings

Study Type	Guideline Study Result	Older Published Study Result
Bacterial, Yeast Mutation	One study Negative for mutation	Five studies Mixed results; positives at high test concentrations
In Vitro Mammalian Mutation	One study Negative for mutation	One study Reported as positive for mutation but with high spontaneous background mutation rates
In Vitro Mammalian Clastogenicity	One study Positive for clastogenicity	Five studies Mixed results, mainly positive for clastogenicity
In Vivo Mammalian	One study Negative for clastogenicity	One study Reported as positive for DNA adduct formation; however, interference from de novo synthesis appears to have occurred

Carcinogenicity Evaluation

- EPA evaluation of iodomethane carcinogenicity was performed correctly

- Chronic exposure is not associated with the development of astrocytomas or uterine/cervical fibromas in rodents
  - Astrocytoma formation within historical control range
  - Histopathological confirmation of the spontaneous nature of mouse cervical and uterine cell fibromas

- Thyroid tumors in rodents are the result of alteration of thyroid hormone homeostasis
  - Mechanistic data for thyroid follicular cell tumor formation
  - Genotoxicity studies using current, standardized protocols are negative *in vivo*

Iodomethane does not pose a cancer threat to humans

Iodomethane Fate in Soil and Water

Parameter	Value	Property
Vapor Pressure	405.9 mmHg	**High volatility**
Henry's Law Constant	0.0053 atm-m^3/mol	**High volatility**
Water Solubility	14.2 g/L	**Soluble**
Octanol/water partition coefficient (log k_{ow})	1.51 – 1.69 *(1.1 for MeBr)*	**Low bioaccumulation in aquatic organisms**
Aqueous Photolysis	13 day half-life	**Rapid degradation**
Soil Metabolism • Aerobic • Anaerobic	 2 hour half-life 38 hour half-life	**> 90% volatilized less than 24 hours**
Soil Dissipation	5 day half-life	**~80% volatilization and rapid degradation**
Atmospheric Residence Time	< 12 days *(0.7 yrs for MeBr)*	**Rapid atmospheric degradation**
Ozone Depletion Potential	0.029 *(0.65 for MeBr)*	**Significantly < 0.20 Ozone Depleter threshold**

Iodomethane Fate in Water

	EPA (Estimated Drinking Water Concentrations)	DPR
Surface water	Acute = 1.965 ppb Chronic = 0.0067 ppb *No adverse impact*	Contamination unlikely
Groundwater	60 ng/L (60 ppt) *No adverse impact*	Zero concentration in groundwater

Iodomethane -- No Adverse Impact to Water

DPR Estimate of Iodide Groundwater Concentration

- DPR calculated 18 ppm and described it as an “extremely conservative worst-case estimate”

- DPR estimation highly conservative and does not consider:
  - High volatilization (80-100%) of iodomethane following application
    - *DPR assumes 50%*
  - Formation of other degradates in subsoil
    - *DPR assumes 100% conversion into iodide. Field data indicates max 2.6% conversion into iodide*
  - Iodide interaction with soil organic matter and methylation by micro-organisms
    - *DPR assumes all iodide formed is available for transport*
  - DPR assumes no dispersion, dilution or degradation in water

Scientific Summary

- Developmental NOAEL of 10 ppm is appropriate
- Developmental mode of action is as postulated
- Developmental HEC derived from fetal plasma iodide concentrations
- Workers and bystanders protected by EPA approved label
- Not carcinogenic
- Rapid volatilization…no adverse impact to water

Conclusions

- Overly conservative assumptions, while without benefit, have a cost
  - Extension of the critical use exemptions for Methyl Bromide
  - Increased use of non-fumigant pesticides
  - Loss of production of California crops - small farmers hit the hardest
  - Increased import of fruits and vegetables from countries with minimal health and safety standards and minimal pesticide enforcement

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