Methyl Iodide:
DPR Risk Characterization

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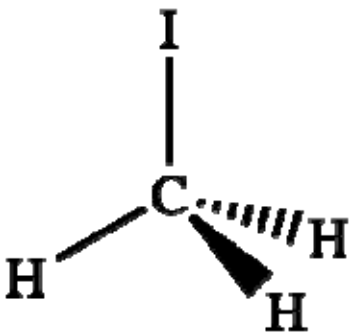
Overview

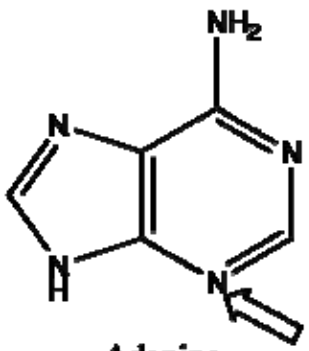
- Chemical profile
- CA fumigant use trends
- Comments on human health risk assessment
- Comments on exposure assessment

Chemical Reactivity of Methyl Iodide

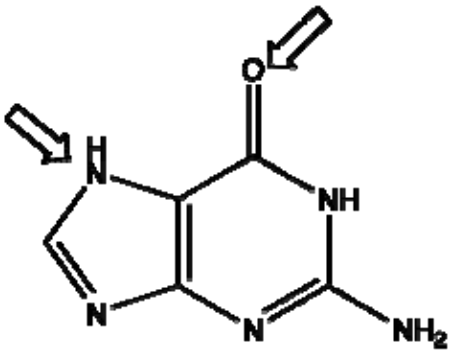
- Electrophilic carbon: Undergoes S_N2 substitution reactions

- DNA methylating agent: Both N- and O-alkylation of DNA bases





Adenine

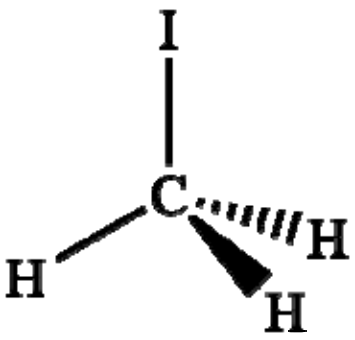


Guanine

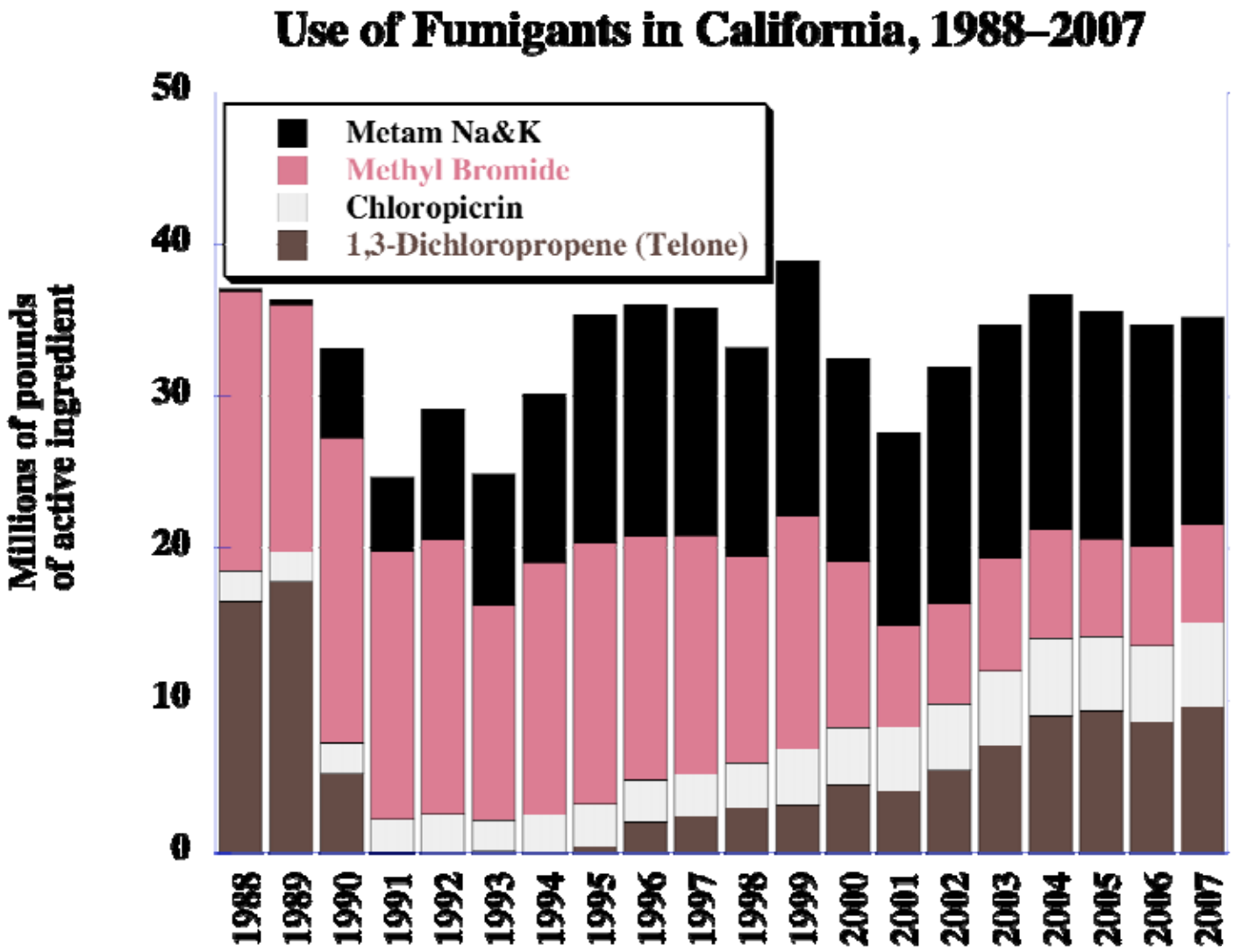
Gansewendt, Xu, Foest, *et al.* DNA binding of methyl iodide in male and female F3445 rats. *Carcinogenesis* 1991 12(3):463–467.

Regulatory Facts about Methyl Iodide

- CA Proposition 65 Carcinogen
  - Listed in 1988
- NIOSH Potential Occupational Carcinogen
- US EPA Hazardous Air Pollutant
  - Substantial paperwork required for release into the environment from academic and industrial labs or manufacturing facilities



California Fumigant Use Trends



Large-Scale Community Poisonings Caused by 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

DPR’s Risk Assessment

- Comprehensive, thorough, well-documented
- Science-based, with decisions justified by scientific observations and/or principles
- General agreement with most of DPR’s analysis
- Several areas where risk assessment could be improved

Human Health Risk Assessment: Issues for the SRP to Consider

- Carcinogenicity assessment
- Concerns about inhalation studies
- The role of glutathione
- Mode of action for fetal loss
- Special vulnerability of children

Issues with Rat Carcinogenicity Study

- Rat chronic/carcinogenicity study validity in question
  - Survival rate of control groups (38–39%) lower than that of the treated groups (43–51%)
  - "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."
  - Not clear if all animals were examined and all tumors reported in the study, particularly for those that died before termination—pituitary adenomas and "undetermined" accounted for nearly all early deaths

Evidence for Non-Threshold Mechanism of Carcinogenicity

- EPA cancer rating based on perturbation of thyroid function, postulating a threshold mechanism
  - Thyroid tumors and thyroid follicular cell hyperplasia.
- Other data suggest this explanation may not be correct—a genotoxic mode of action better explains:
  - Lung tumors in mice injected with MeI, even those receiving only a single injection
  - Astrocytomas in rats and benign uterine and cervical fibromas in mice
  - Mutagenicity in *in vitro* studies w/bacteria, yeast, mammalian cells
- Supporting data: Dosing 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

Relative Cancer Potencies and Multiple Exposures

- The cancer potency (Q_1*) of a chemical is a measure of how much exposure would be required over a lifetime to increase the number of cancers caused by that chemical. Larger Q_1* values mean higher potency.

	Inhalation Q_1* in $(mg/kg\text{-}day)^{-1}$
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(OEHHA, 2005)
Benzidine	500 (OEHHA, 2005)
Methylene chloride	0.0035 (OEHHA, 2005)

Cancer Potency Factors, OEHHA, May 2005, www.oehha.ca.gov/air/hot_spots/index.html

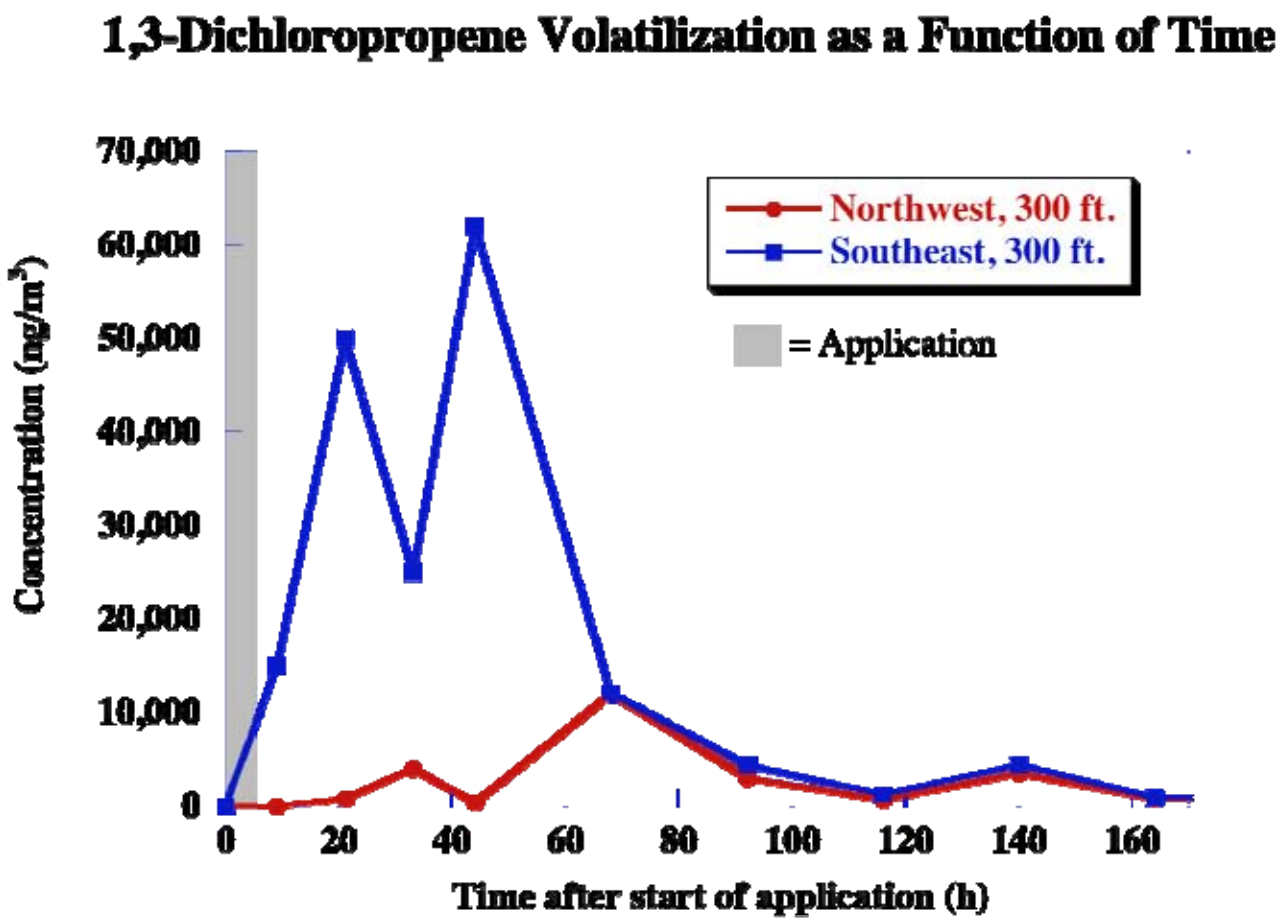
General Concerns About Inhalation Studies

- Dosing patterns are not representative of actual exposure patterns
  - Rats: 6 hr/day, 5 days/week

  - During “rest” phases
    - Glutathione replenished
    - Iodide excreted
    - Cellular repair occurs

General Concerns About Inhalation Studies

- Humans



The Role of Glutathione

- Agree with OEHHA that glutathione depletion an endpoint in itself, like cholinesterase inhibition
  - mitochondrial impairment
  - increased risk of lung damage and disease
  - neuronal loss may be initiated by GSH depletion
  - Glutathione depletion in olfactory epithelium used as an endpoint for acute exposure. Assumptions to check:
    - Damaged nasal epithelial tissue produces the same amount of GSH as healthy tissue. Yet "overall incidence of olfactory epithelium degeneration was 90% for males and 75% for females after 1 year and 100% for both sexes after 2 years."
    - Smoking or other glutathione-depleting exposures are not significant contributors to overall glutathione decreases.

Mode of Action for Fetal Loss

- EPA: Thyroid toxicity from excess iodide
- DPR:
  - Thyroid toxicity from excess iodide
  - Methyl iodide alkylation reactions
  - Glutathione depletion
  - Altered cholesterol homeostasis
- These other mechanisms may have a variety of observable endpoints, including developmental neurotoxicity (not evaluated by DPR or EPA)

NOAEL for Fetal Loss Could Be Lower Than 2 ppm

- From DPR Aug 2009 RCD, Volume 1, p. 120

Table 55: Rabbit fetal late resorption and death data from MeI treatment.[a]

MeI		Viable	Late Resorption		
ppm	GD	fetus	% Fetus/Litter[b]	Litter Affected[b]	Fetus Affected[c]
Study: Nemec 2002d (n=19-22)					
0	NA	6.1±2.6	1.8 ± 6.4	2/22 (9%)*	3/143 (2%)*
2	6-28	5.5±2.6	3.3 ± 10.9	2/19 (11%)	6/115 (5%)
10	6-28	4.6±2.6	11.1 ± 21.2	6/20 (30%)	18/109 (17%)**
20	6-28	3.6±2.2**	22.5 ± 27.2**	11/20 (55%)**	34/110 (31%)**

a/ The estimated dose at 2, 10, and 20 ppm MeI was 1.5, 8, and 15 mg/kg/day MeI. In both studies, fetal observations were made on GD 29. *, ** for statistical significance at $p<0.05$ and <0.01, respectively. Viable fetus = number of viable fetus per litter. % Dead fetus/Litter = average percent of "late resorption" per litter. Litter Affected = number of litter with fetal death/total litter. Fetus Affected = total number of dead fetus/total fetus

b/ Litters with 100% early resorption were excluded

c/ Per total fetus at risk (minus early resorption).

Exposure Assessment: Issues for the SRP to Consider

- PERFUM vs ISCST3
- Inversion conditions and applicator error
- Ground water contamination potential
- Subchronic exposure

EPA SAP Concerns About PERFUM

- PERFUM was reviewed by SAP, but SAP had concerns—were those concerns addressed?
  - **Many different types of uncertainty in the model:** "The Panel thought that representing emission flux as a probability distribution to address uncertainty and real variation is a worthy objective. There should be a distinction between uncertainty arising from measurements, uncertainty from the limited sampling, uncertainty from measuring emission flux from back calculations by the dispersion model, and uncertainty from the actual variability of emissions."

    Factors contributing to uncertainty: the flux emission estimate/profile, soil properties, temperature, meteorological data, anemometer height, calms processing, non-meteorological environmental factors, "Gaussian formulated" model-model comparisons, indoor exposure, human activity patterns, coincidental temporally/spatially close multi-field applications, seasonality, and horizontal placement of monitors during field studies for flux estimation. The uncertainty associated with these factors should be considered in an integrated manner.
  - **Important variables left out of the model: "**Application method, injection depth, tarp type and thickness, soil properties, and the physical/chemical properties of iodomethane. . . many soil, environmental, and application factors have a significant effect on volatilization rates."
  - **Generalizing the use of PERFUM to regional or state scale:** ""Not appropriate if the emission data were collected at a single (or relatively few) location(s)."
  - **Concurrent applications:** May increase the background concentrations and may affect the buffer zone.

EPA SAP Concerns About PERFUM

- "There is a flux of material in the real plume unaccounted for by the modeled plume . . . [this] indicates that the flux will be underestimated because there is a flux of material in the real plume that cannot be captured in the modeled plume."

- Complex terrain and buildings cause changes in flux estimates.

- SAP preferred AERMOD model: ". . . any of the limitations in the ISCST3 model (the core of PERFUM) would be alleviated when the Agency adopts AERMOD. The Panel thought approving the AERMOD model should be a high priority of the Agency."

- DPR's use of ISCST3 over PERFUM is appropriate
  - Accounts for a downwind "worst-case" scenario, unlike the "whole-field" method used in the PERFUM model

Inversion Conditions and Applicator Error

- Inversion conditions
  - Weather data and prevalence of inversions
  - Failure of ISCT3 and PERFUM to account for calms during inversions
  - Failure of PERFUM model to utilize contiguous weather hours
- Perfect applicator behavior assumed

Incident

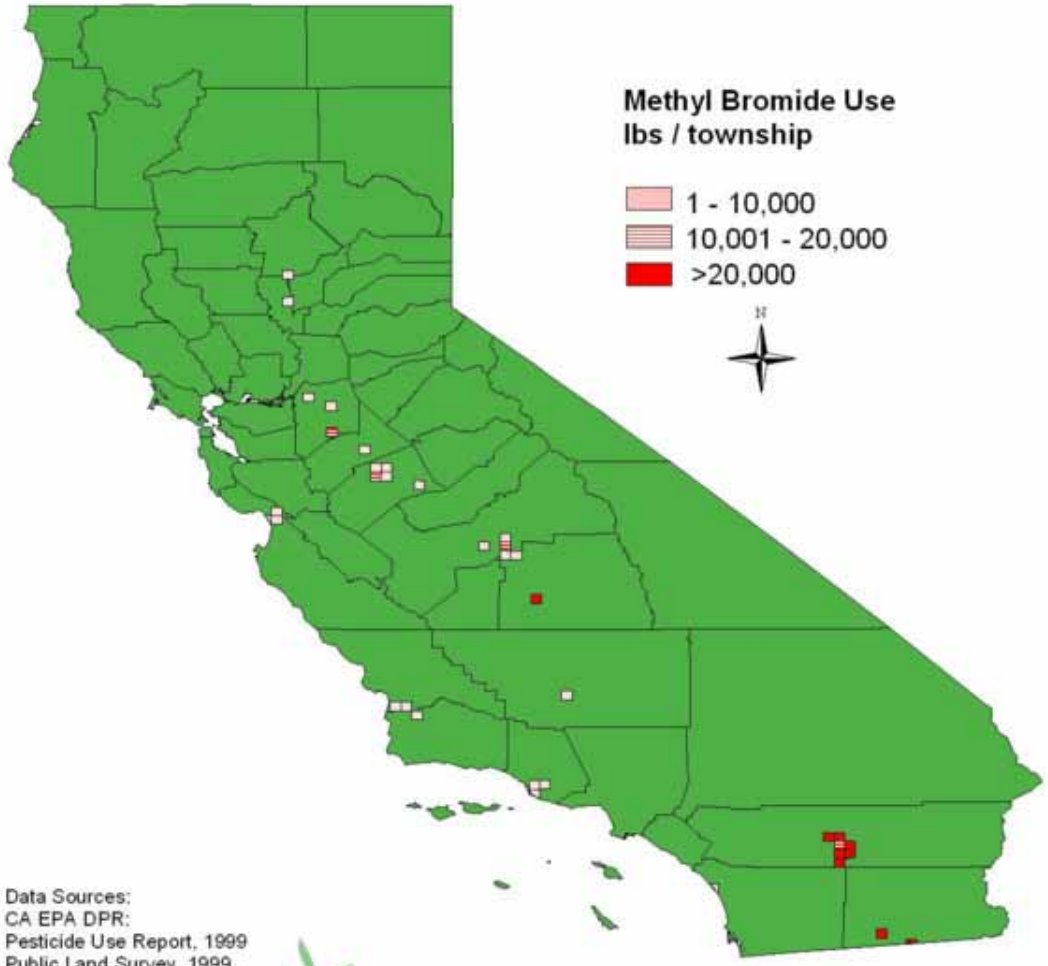
- Monterey 2007 (62-mon-07). A family felt irritant symptoms one evening and called 911. Responding firefighters detected no problem, but notified the agricultural commissioner of a suspected fumigant release. The agricultural commissioner's staff identified a field fumigated with methyl bromide and chloropicrin earlier that day about **150 yards** from the affected area. The ag PCO fumigated 13 acres, three more than allowed by the permit conditions. The investigators also visited the treated field, where they felt symptoms themselves. The grower acknowledged the fumigant off-gassing from the field, but did not know what went wrong. The fumigation itself had gone smoothly. Irritated eyes, nose and lips, sore throat, nausea, dizziness. Nausea and dizziness were among symptoms 27 people experienced.

Other Exposure Assessment Issues

- USDA, UCR studies show potential for leaching of MeI to groundwater

- Subchronic exposure an issue if acres permitted to be treated simultaneously are reduced. Lower average concentrations, but longer exposure time period as a fraction of a year. What will be the effects on children and adults: Thyroid disease? Nervous system disorders? Cancer risks?

Methyl Bromide Use in California
January 2000



Data Sources:
CA EPA DPR:
Pesticide Use Report, 1999
Public Land Survey, 1999
Datamocracy:
Road, Water, County
and City Coverages
Produced with:
ESRI ArcView 3.2a

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Methyl Bromide Use in California
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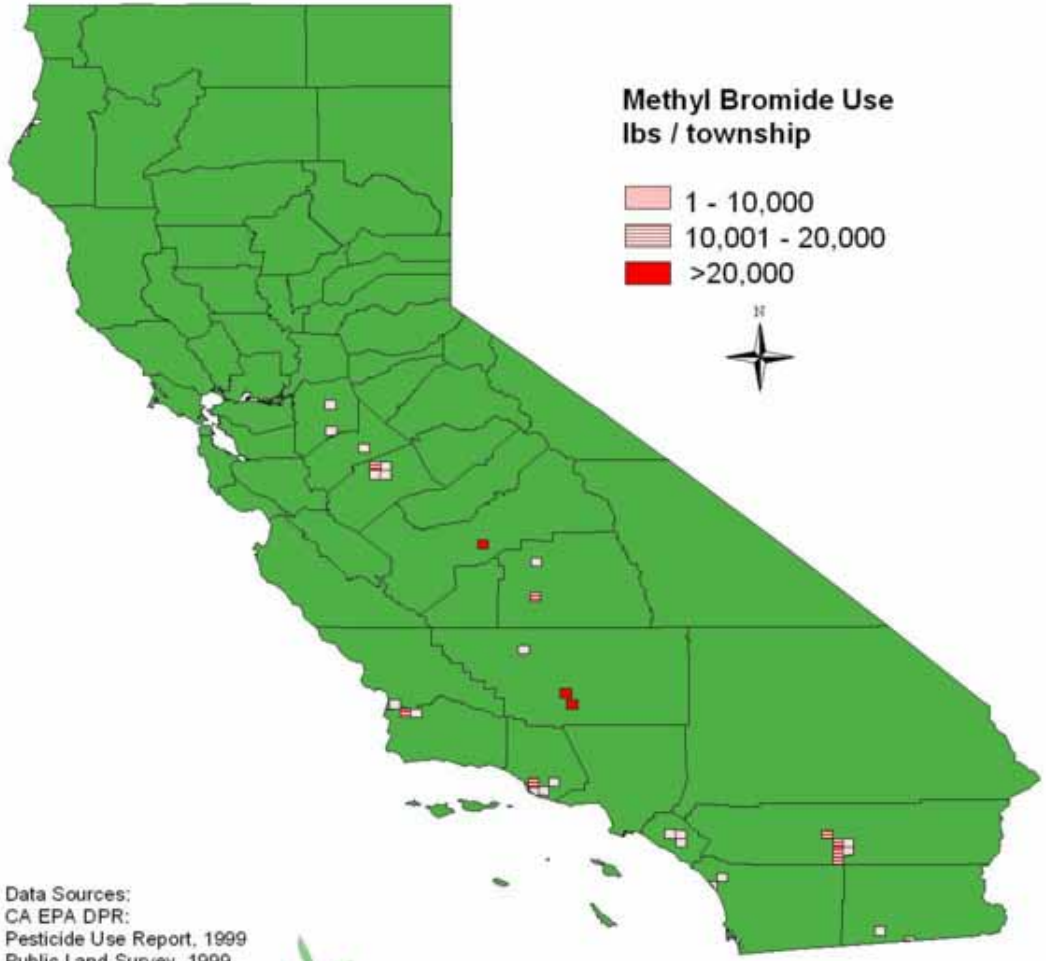

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Methyl Bromide Use in California
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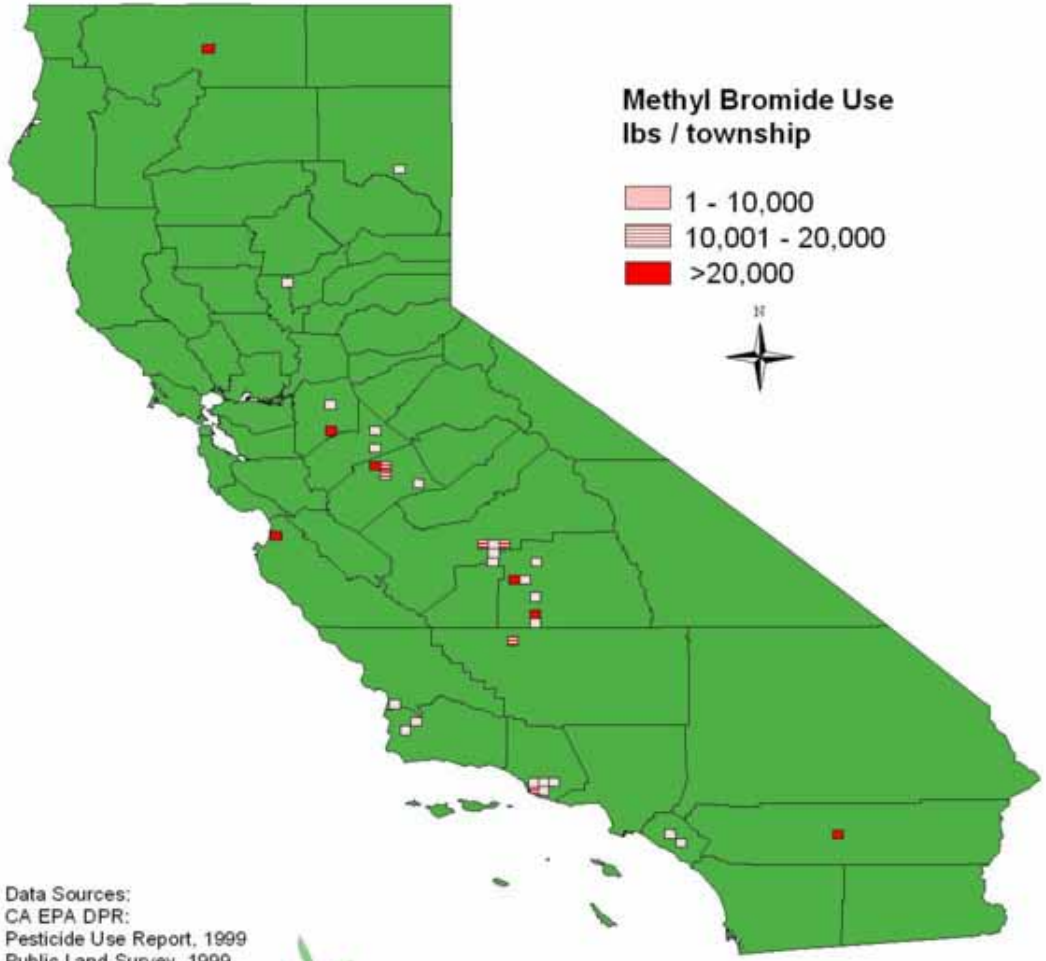

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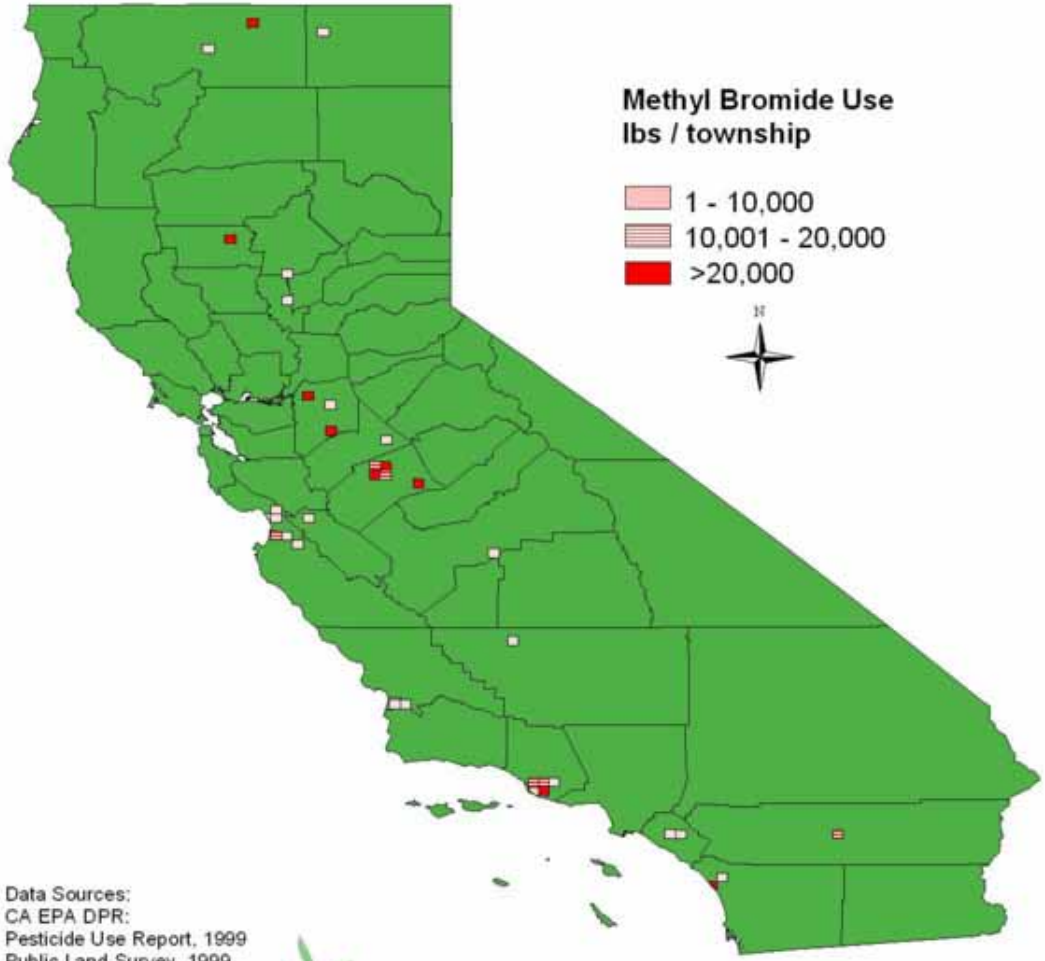

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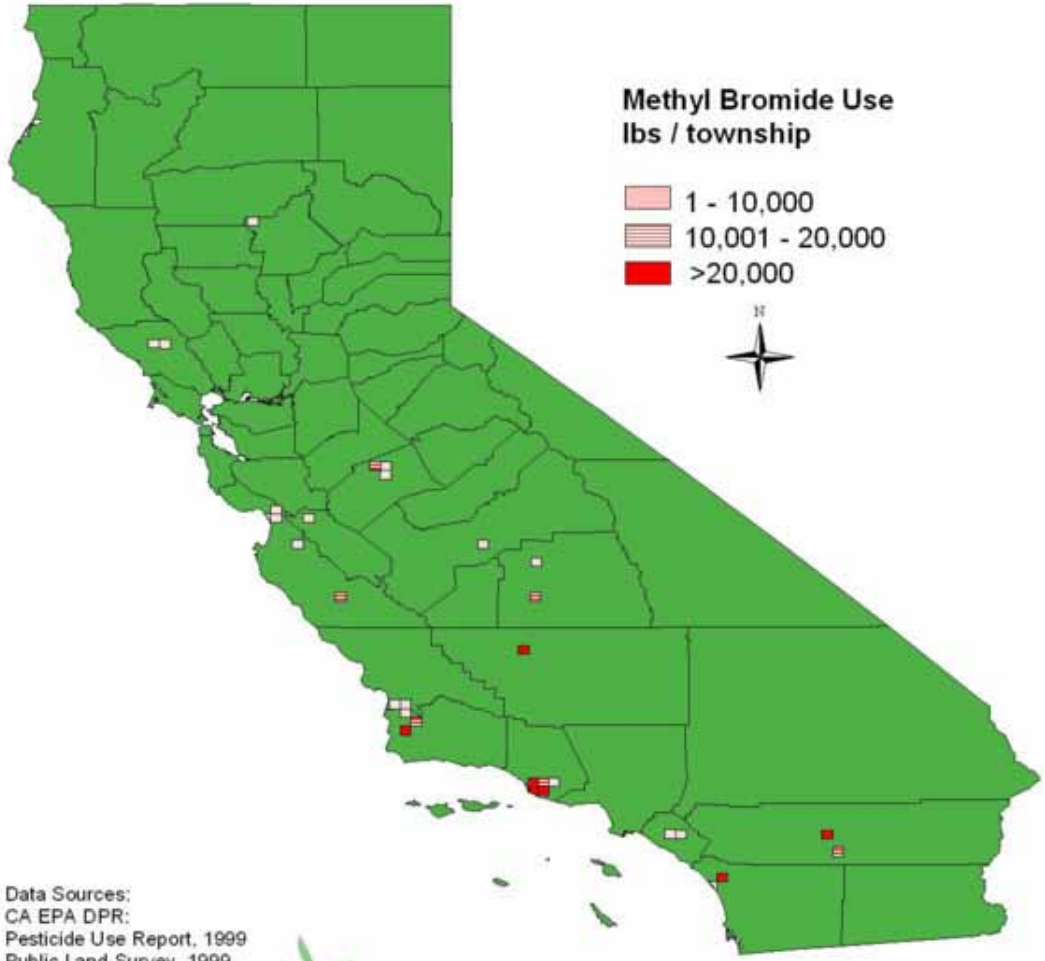

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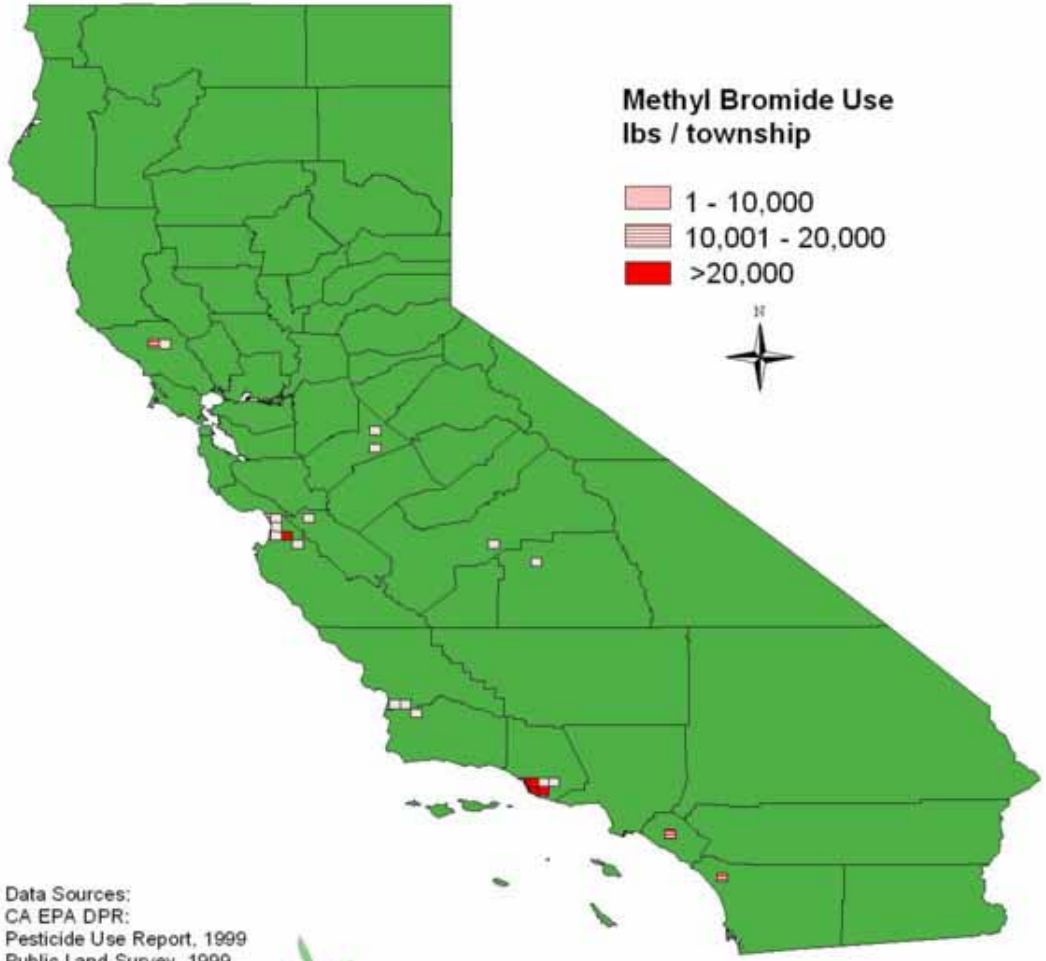
June 2000



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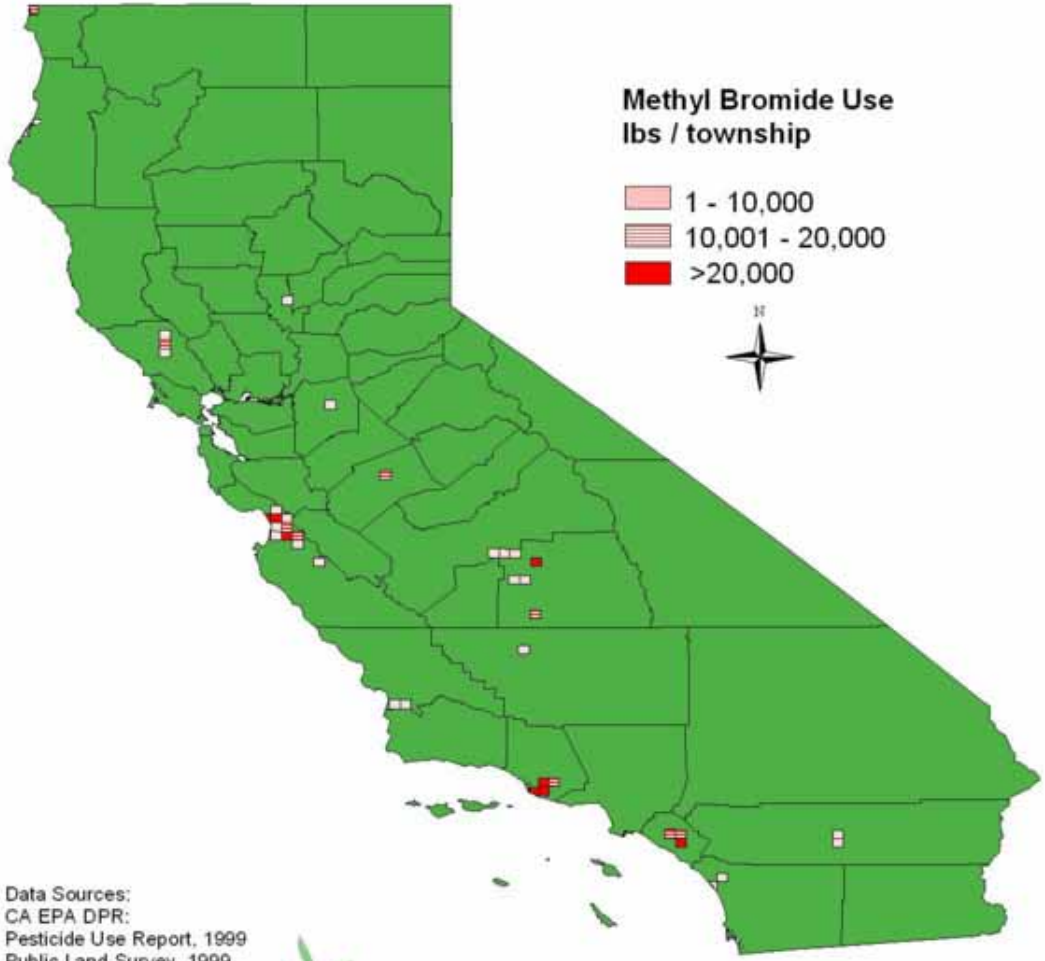
Methyl Bromide Use in California
July 2000



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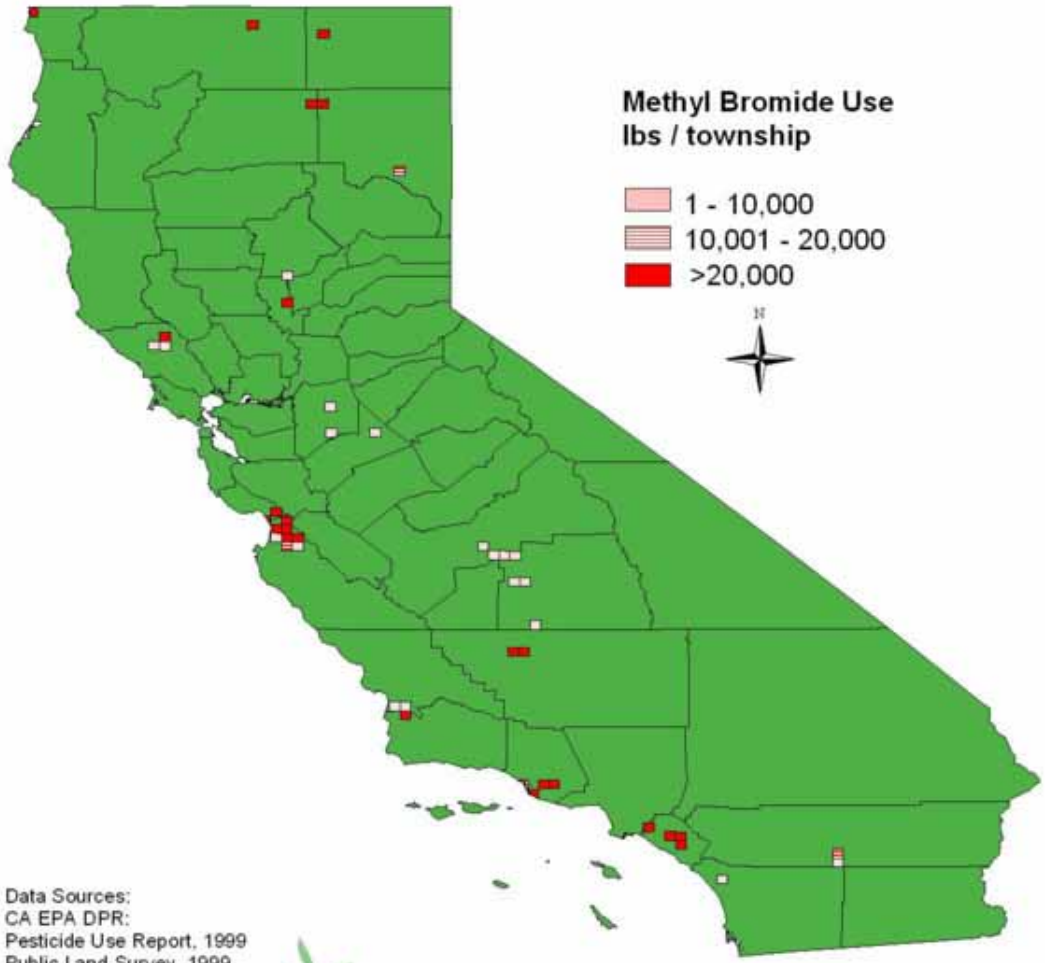
August 2000



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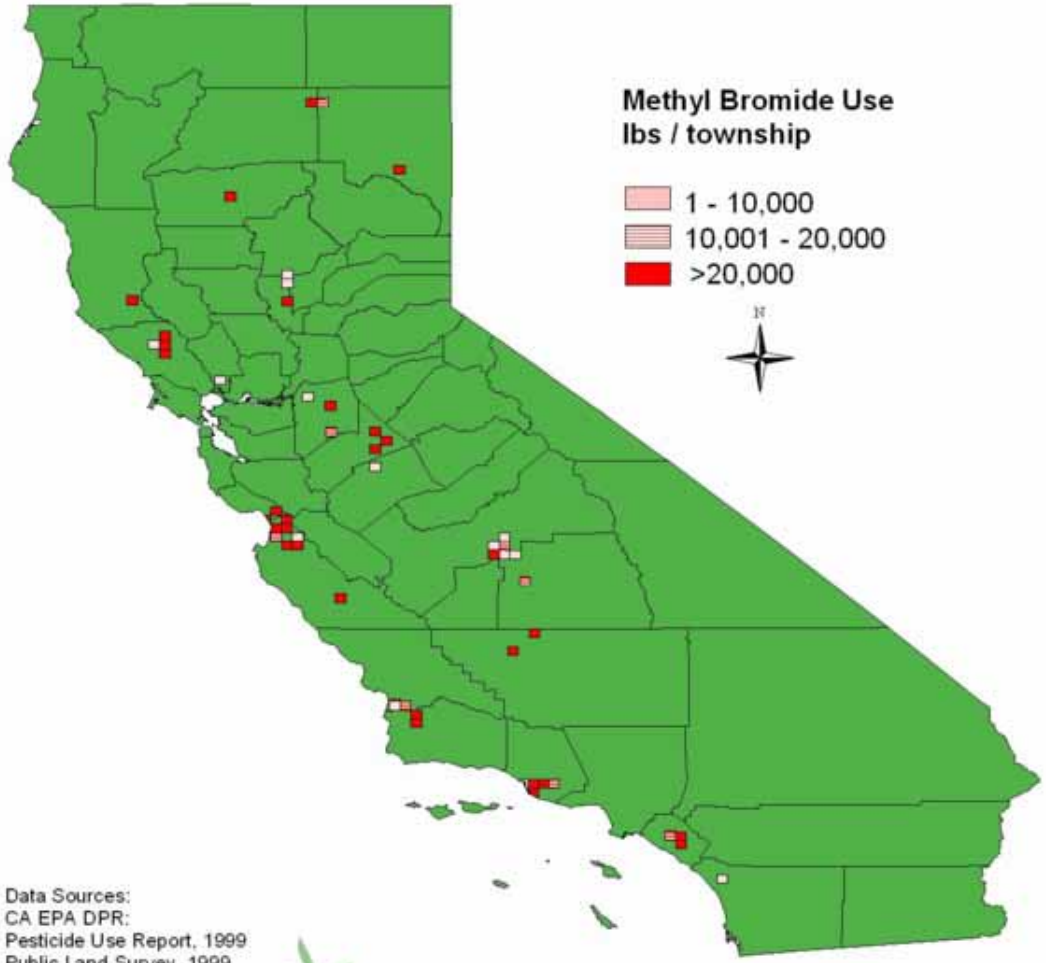

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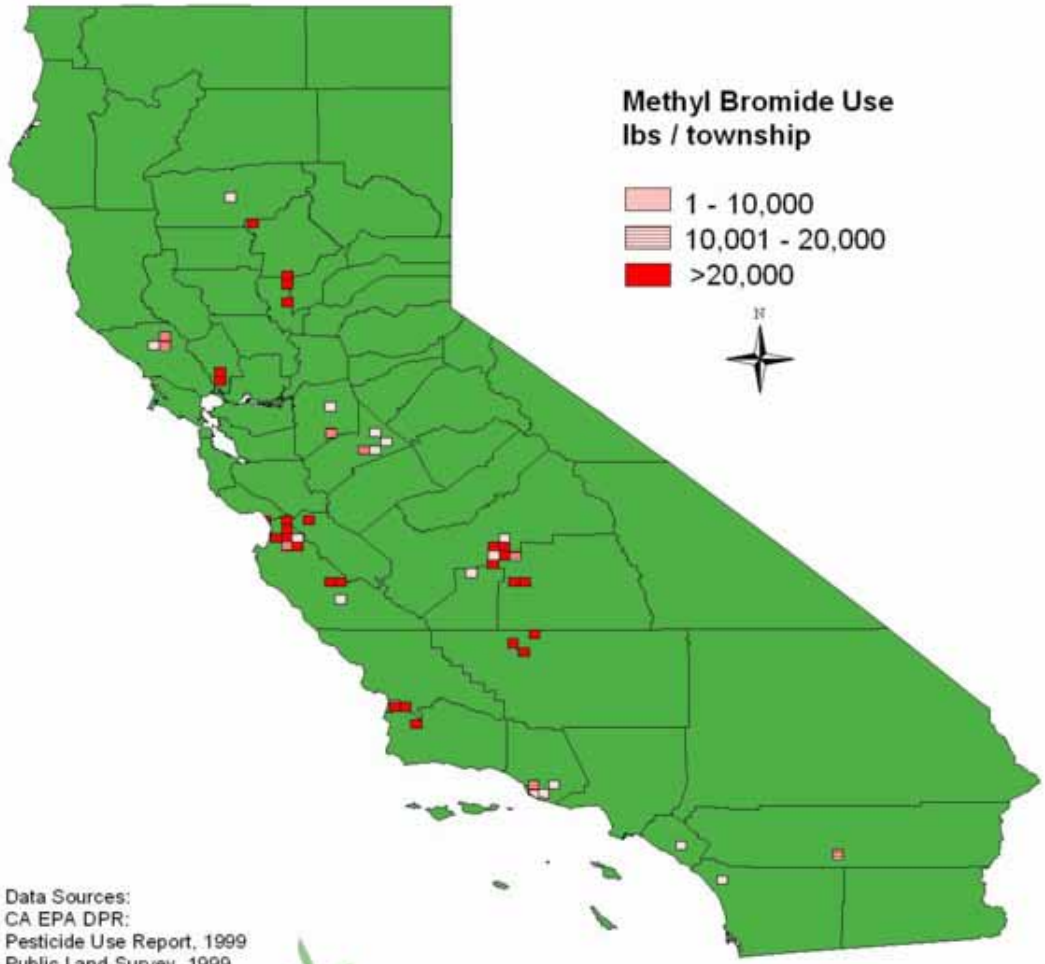

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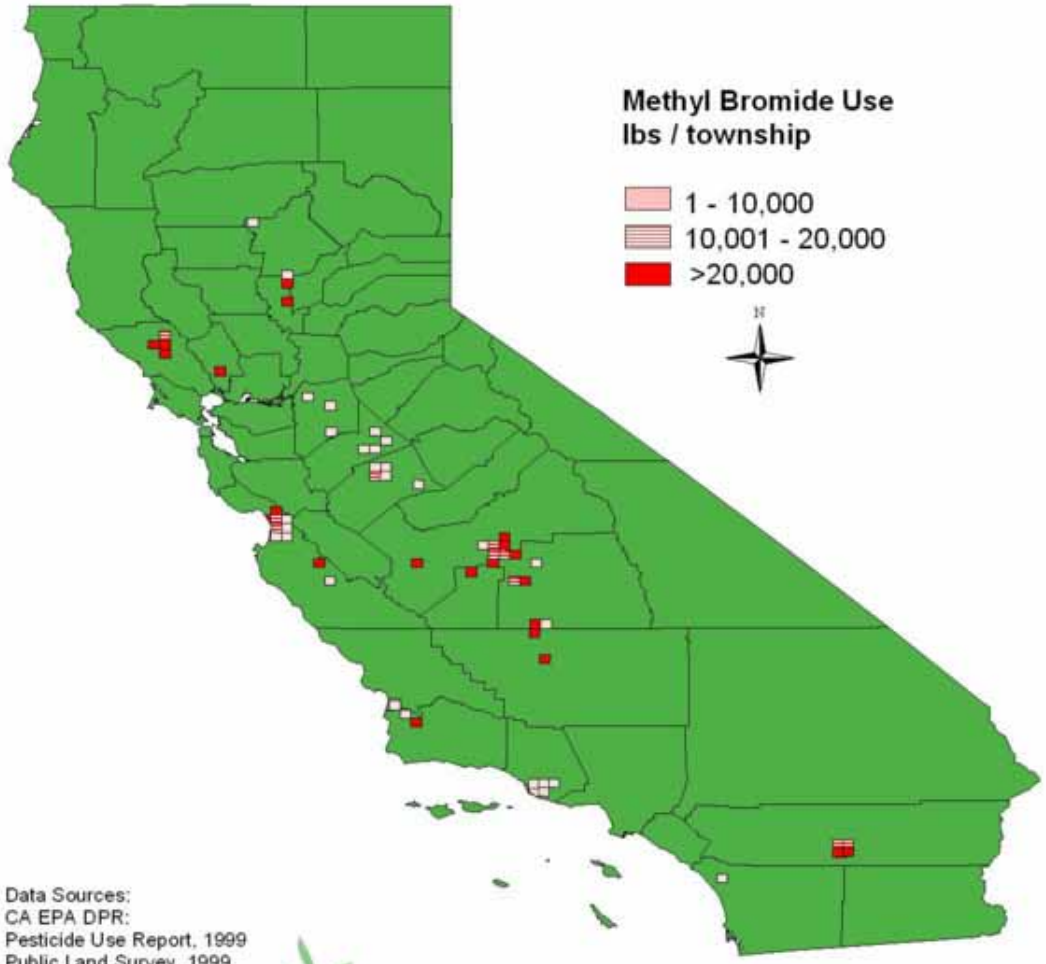

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Methyl Bromide Use in California
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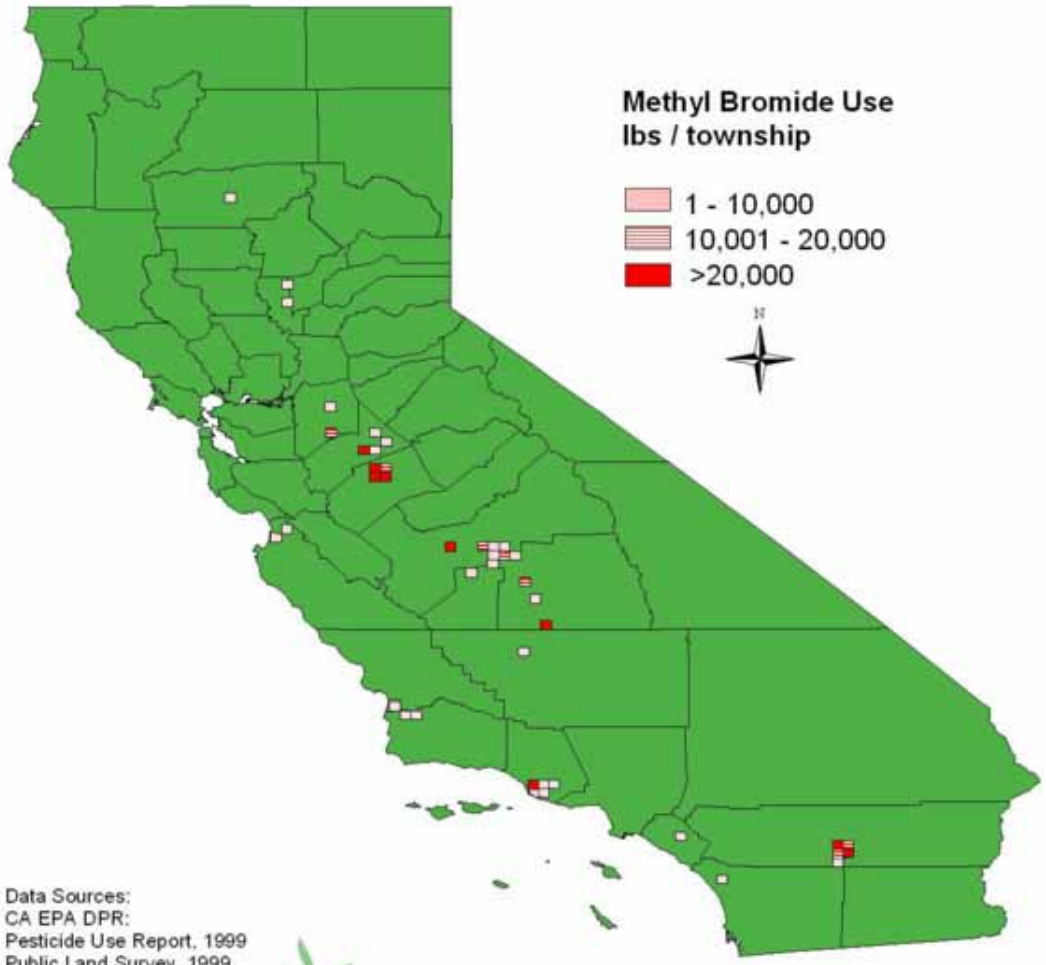

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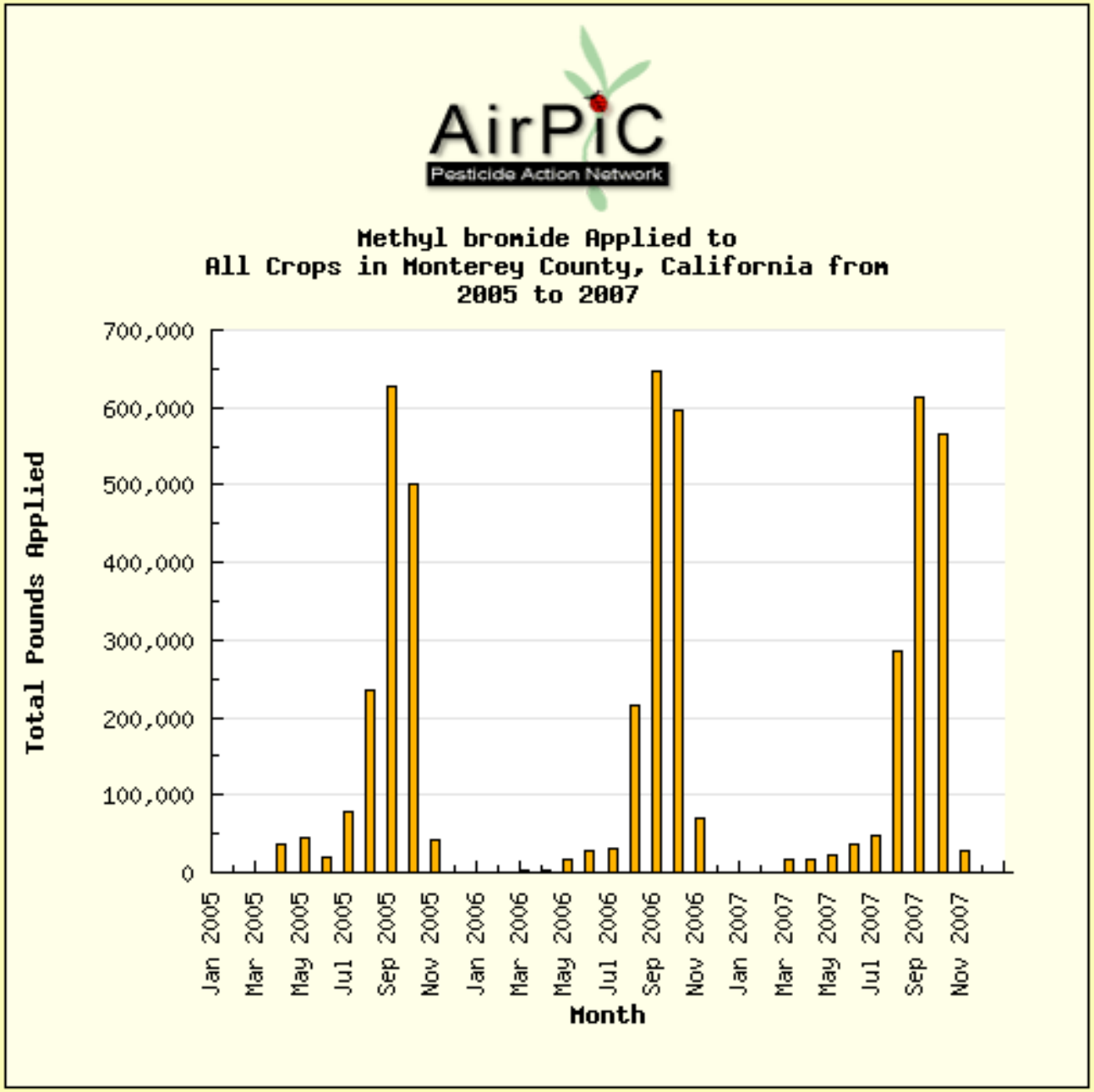
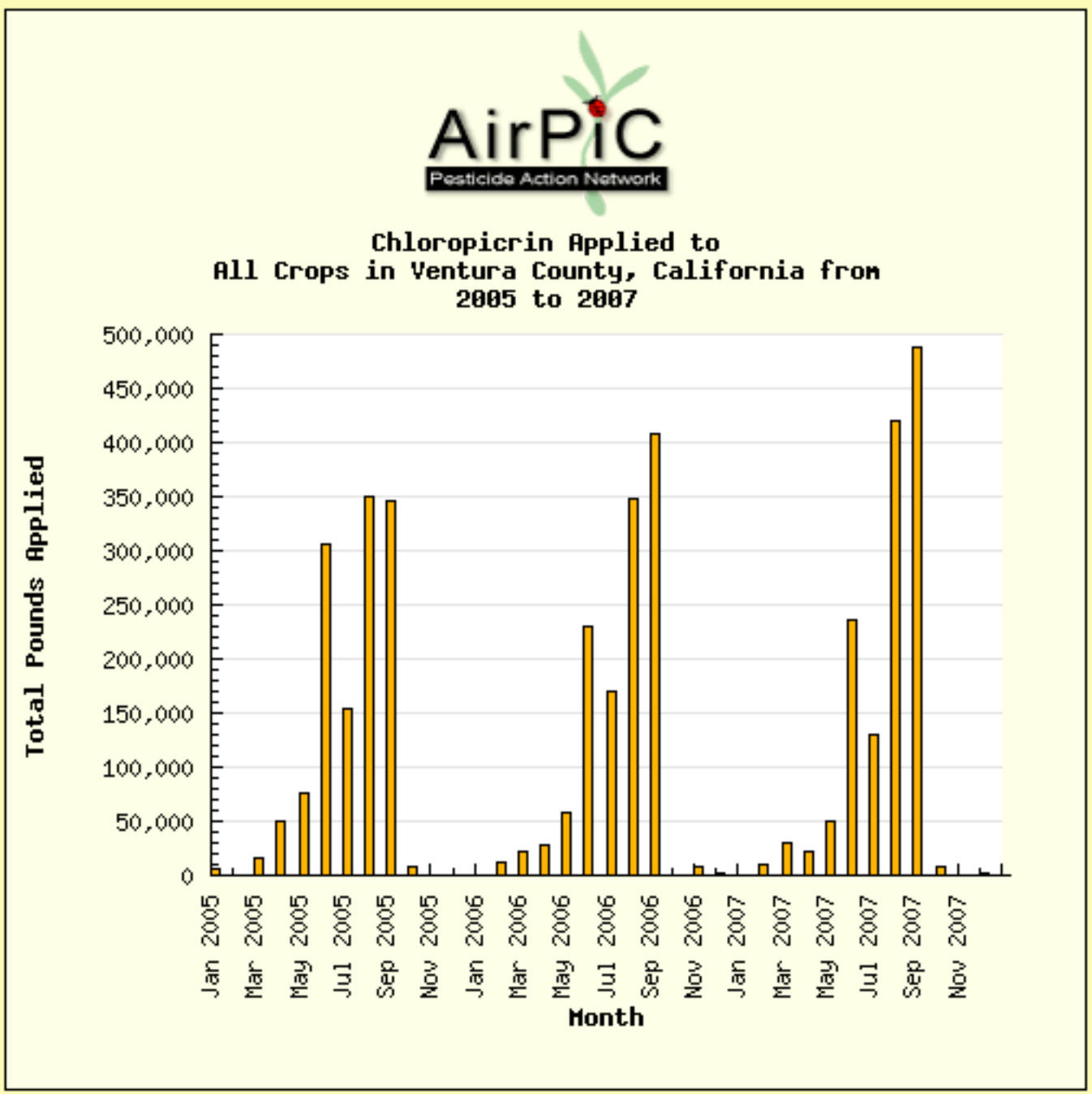

AirPiC
Pesticide Action Network
Methyl bromide Applied to
All Crops in Monterey County, California from
2005 to 2007
Total Pounds Applied
700,000
600,000
500,000
400,000
300,000
200,000
100,000
0
Jan 2005
Mar 2005
May 2005
Jul 2005
Sep 2005
Nov 2005
Jan 2006
Mar 2006
May 2006
Jul 2006
Sep 2006
Nov 2006
Jan 2007
Mar 2007
May 2007
Jul 2007
Sep 2007
Nov 2007
Month


AirPiC
Pesticide Action Network
Chloropicrin Applied to
All Crops in Ventura County, California from
2005 to 2007
Total Pounds Applied
500,000
450,000
400,000
350,000
300,000
250,000
200,000
150,000
100,000
50,000
0
Jan 2005
Mar 2005
May 2005
Jul 2005
Sep 2005
Nov 2005
Jan 2006
Mar 2006
May 2006
Jul 2006
Sep 2006
Nov 2006
Jan 2007
Mar 2007
May 2007
Jul 2007
Sep 2007
Nov 2007
Month

54 Acres:
Two Months To Complete Fumigations

Summary: Science Supports DPR's Decisions Regarding

- Reduction from 50% to 25% glutathione depletion as an endpoint for olfactory epithelium degeneration
- Use of a 2 ppm endpoint for fetal loss instead of a 10 ppm endpoint—possibly <2 ppm is more appropriate
- Additional UF of 10
  - Inadequacy of toxicity testing on young animals
  - Potential toxicity from additional iodide
- Correction for charcoal trapping efficiency in monitoring studies
- Use of ISCST3 instead of PERFUM for exposure assessment and worst-case downwind plume modeling scenario. AERMOD might be better.

Remaining Concerns/Questions

- ISCST3 model
  - Does it handle “calms” adequately? 10% of the total hours are calms in CA
  - Flux changes with temperature should be included in the model, since many fumigations occur in the hot summer months
  - Evaluation of 1-hr and 4-hr peak flux/concentrations. Only 8-hr & 24-hr done.
  - 8-hour and 24-hour averages not reflective of concentration spikes
- Perfect applicator behavior assumed, yet application conditions are complex and enforcement is weak
- What would be the effect of multiple back-to-back applications on cancer risk? Fetal death risk? Thyroid disease risk? Nervous system toxicity?
- Uncertainty factor of 10 may be too low
  - Potential effects from lipid level disturbances
  - No information on developmental neurotoxicity for a neurotoxicant
  - Multiple, back-to-back applications
  - Co-applications with chloropicrin, a strong irritant & carcinogen
  - Human error will occur

Beware of Averaging!

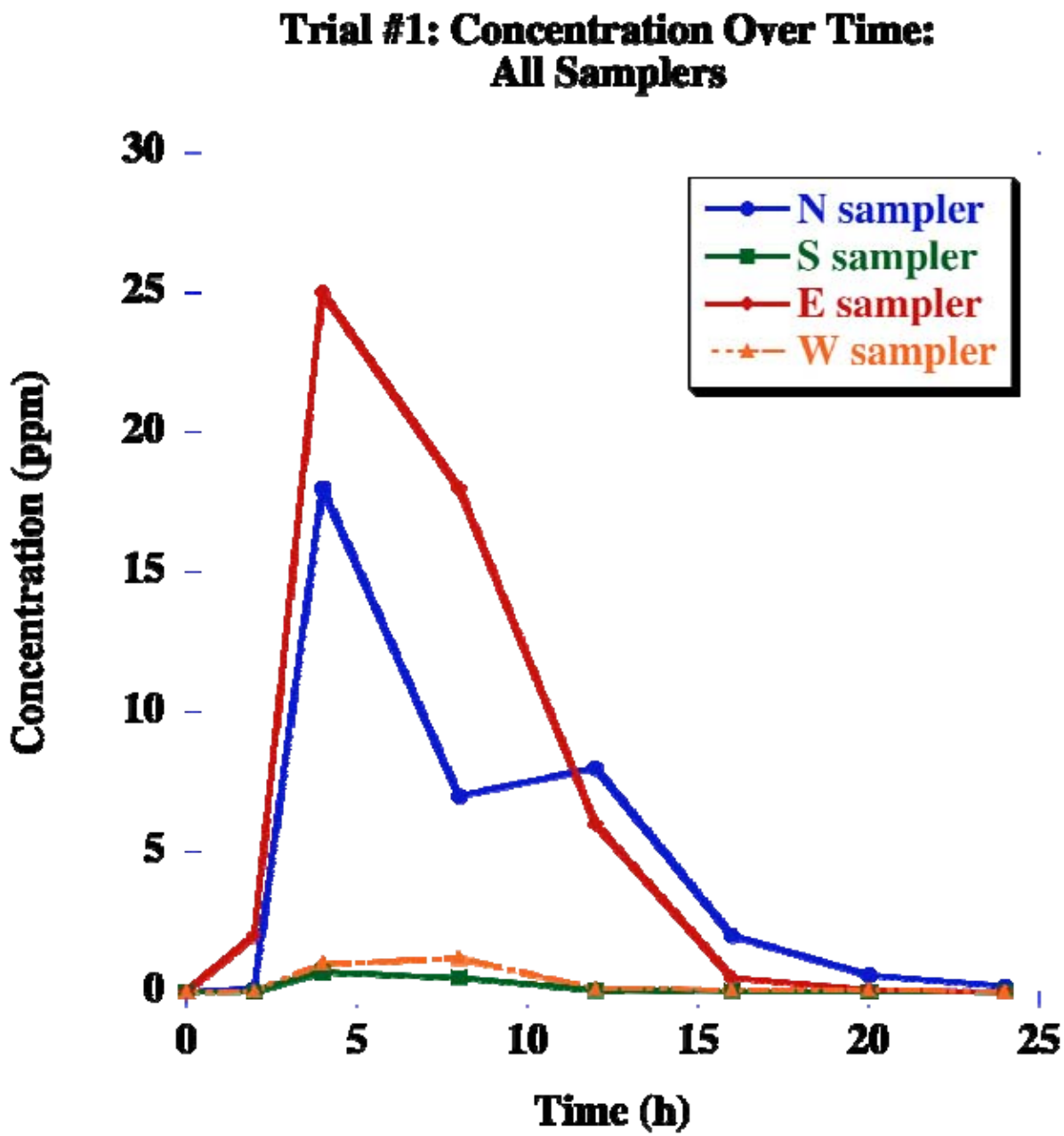
- TWA of flux over 8 hours or 24 hours
- Average daily air concentration calculated
  - Calculated 24-hour average conc. was 0.83 ppm
  - Need to recall that: “At 25 ppm MeI, maximal GSH depletion (40 to 50% of control) was measured in the nasal epithelium, and about 30% in the other tissues, 3 to 6 hours after initiation of exposure”
  - How would a 4-8-hour spike in concentration affect GSH?
- EPA averages concentrations around the field “whole field” method
- Average (low) breathing rate for workers
- Average ADDs and SADDs from all studies

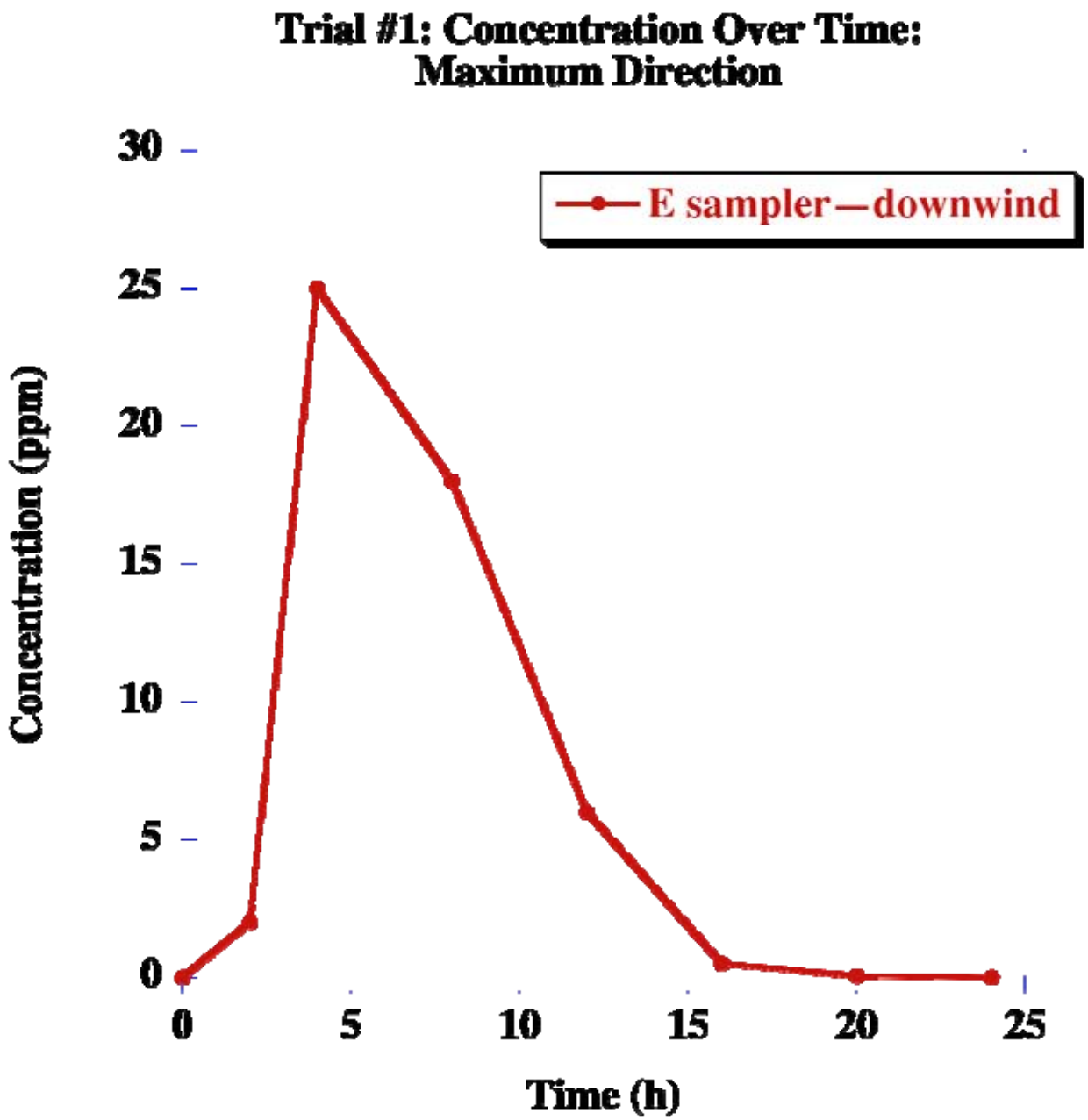
Twenty-four-hour air concentrations of methyl iodide at various distances from a 40-acre field treated at 175 lb/acre

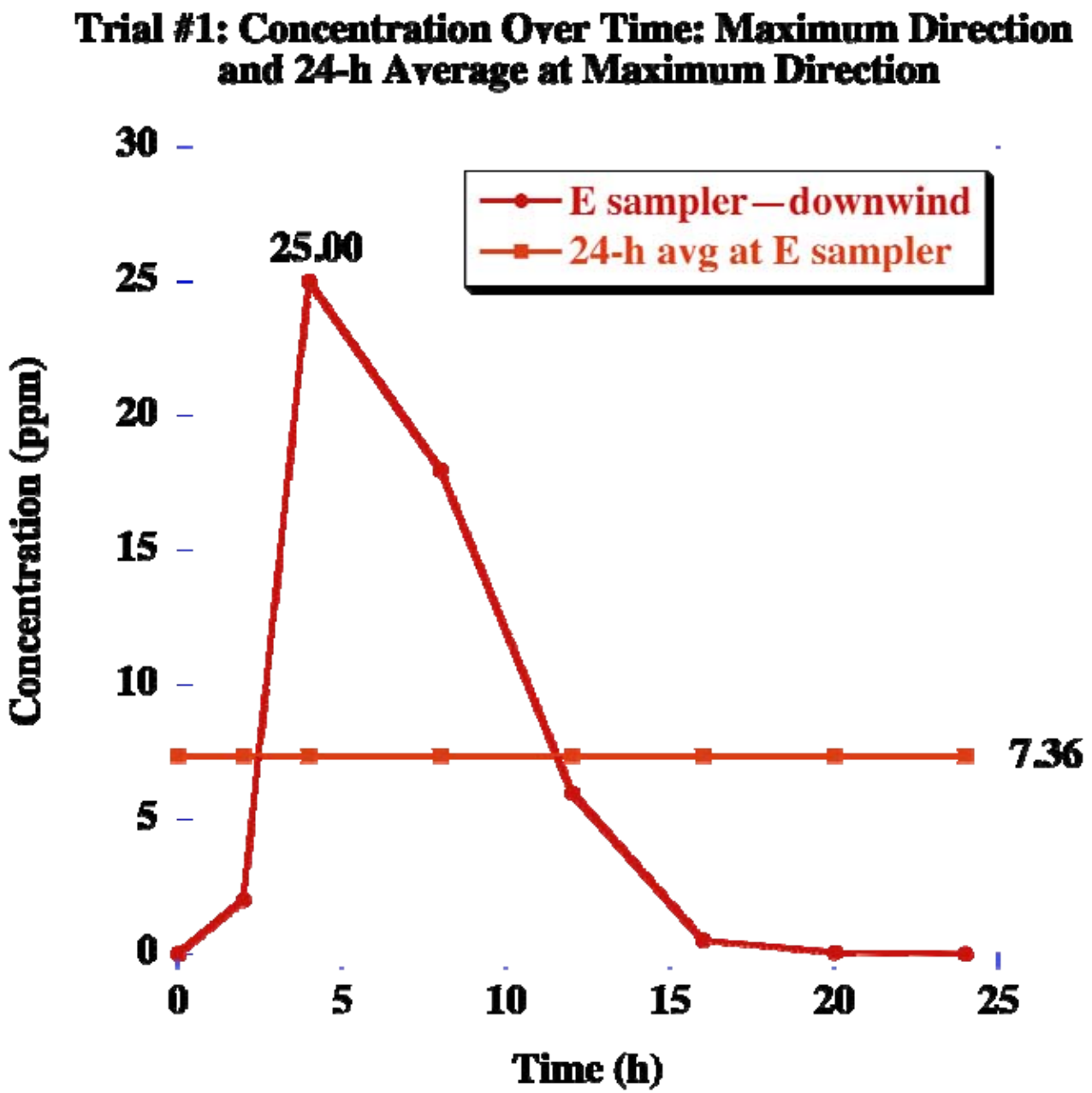
Table 5. Volume 2, Exposure Assessment, p. 71.

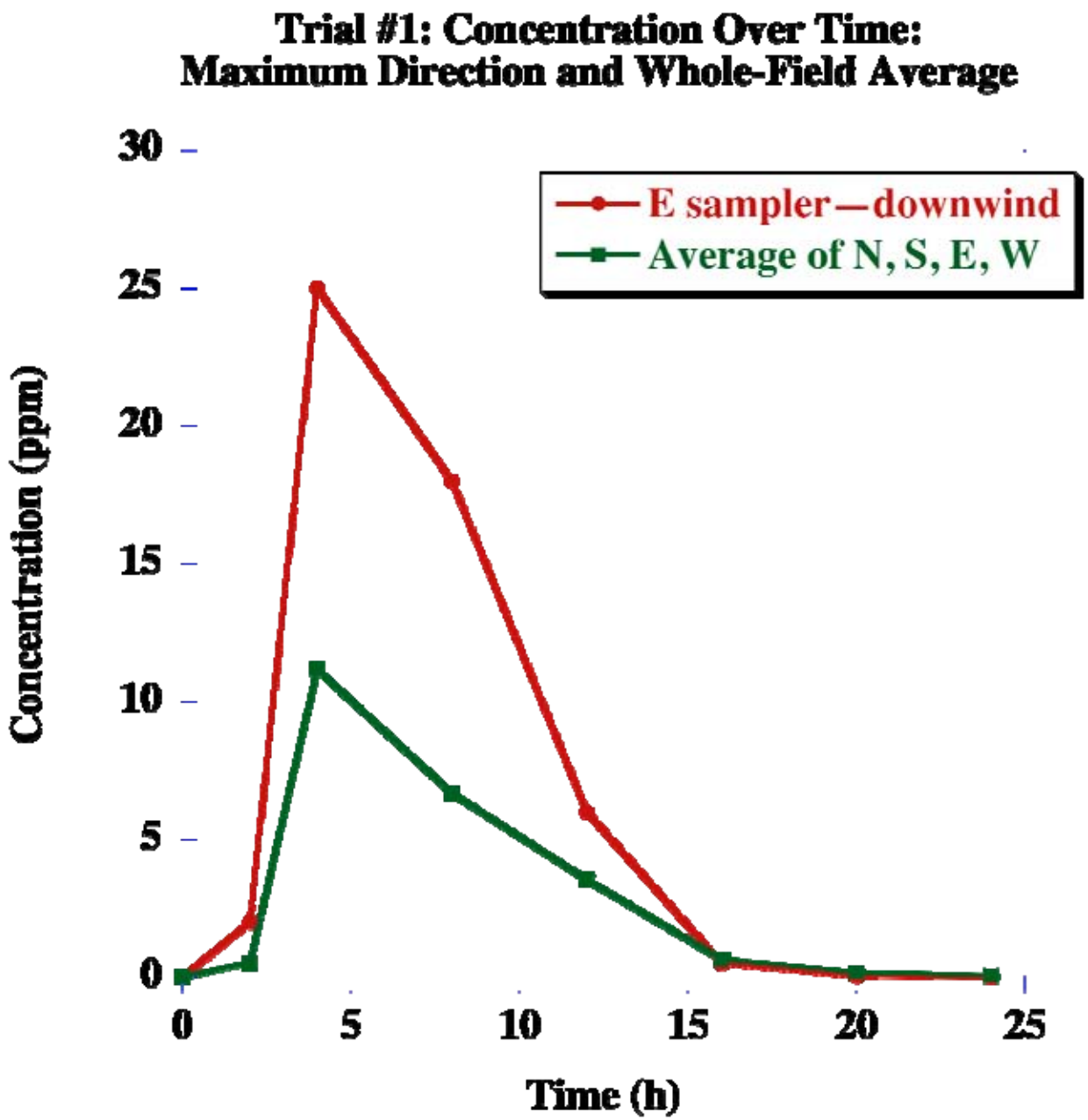
Distance (m)	Guadalupe Shank/Bed/Tarp (µg/L)	Watsonville Shank/Broadcast/Tarp (µg/L)	Manteca Shank/Broadcast/Tarp (µg/L)	Oxnard Shank/Bed/Tarp (µg/L)
3	3.7	2.2	3.0	4.9
15	3.4	2.0	2.7	4.5
30	2.9	1.7	2.3	3.8
91	2.0	1.1	1.6	2.6
152	1.6	0.9	1.2	2.1
760	0.5	0.3	0.4	0.7

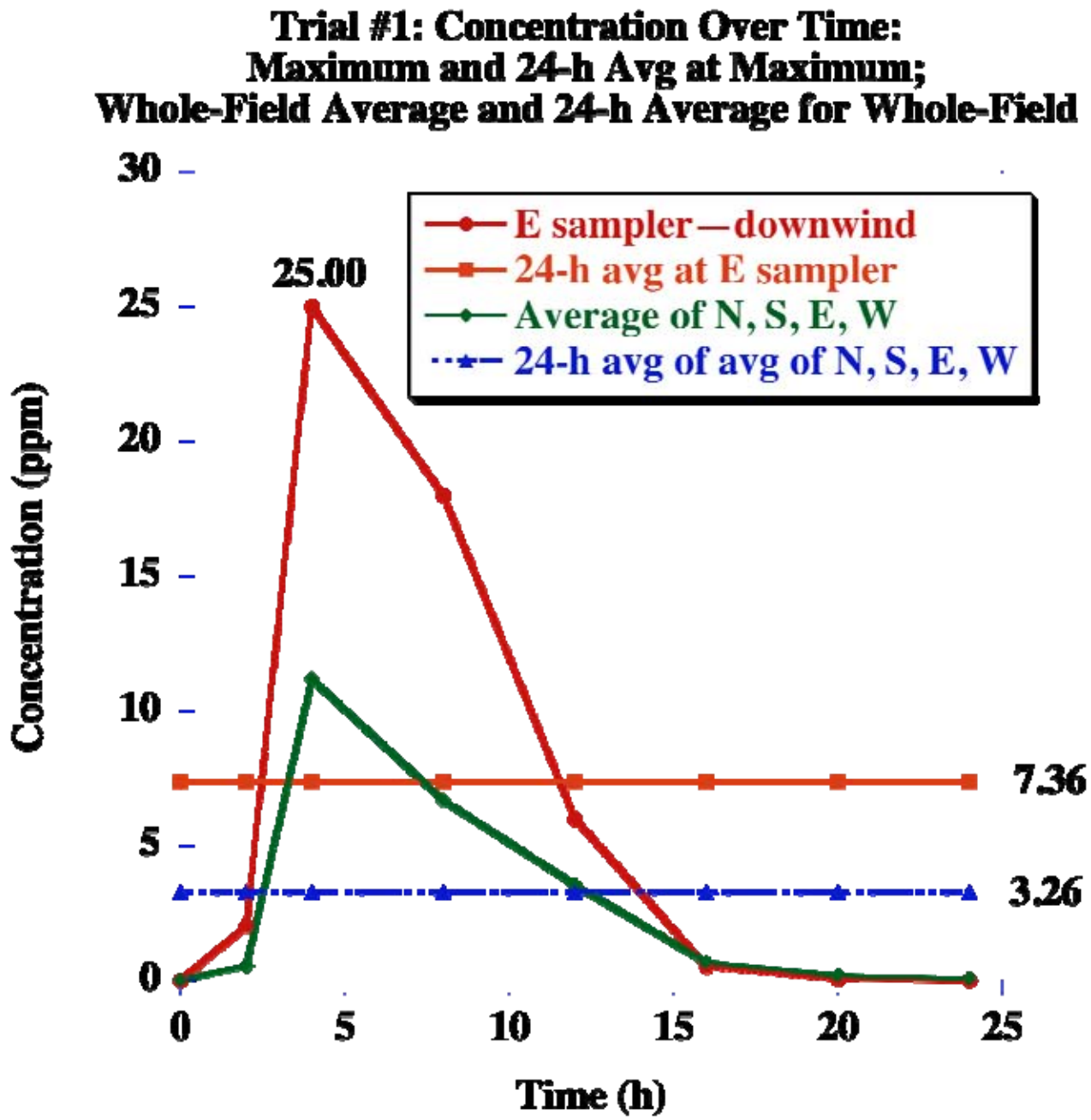
An Example, Using Imaginary, but Realistic Data




Trial #1: Concentration Over Time:
Maximum Direction
E sampler—downwind
Concentration (ppm)
30
25
20
15
10
5
0
0
5
10
15
20
25
Time (h)


Trial #1: Concentration Over Time: Maximum Direction and 24-h Average at Maximum Direction
E sampler—downwind
24-h avg at E sampler
25.00
7.36
Concentration (ppm)
Time (h)
30
25
20
15
10
5
0
0
5
10
15
20
25


Trial #1: Concentration Over Time:
Maximum Direction and Whole-Field Average
E sampler—downwind
Average of N, S, E, W
Concentration (ppm)
30
25
20
15
10
5
0
0
5
10
15
20
25
Time (h)


Trial #1: Concentration Over Time:
Maximum and 24-h Avg at Maximum;
Whole-Field Average and 24-h Average for Whole-Field
E sampler—downwind
24-h avg at E sampler
Average of N, S, E, W
24-h avg of avg of N, S, E, W
25.00
7.36
3.26
Concentration (ppm)
Time (h)
0
5
10
15
20
25
30

Recommendations to DPR

- All available data indicated that MeI is a high toxicity chemical in many ways. Any additional data collected would not likely exonerate the chemical.
- Use would result in exposures for workers and bystanders far above levels of concern
- Mitigations that might include reduced application blocks would lead to longer periods of sub-chronic exposure
- Application conditions are too complex for applicators to reliably perform without error, even with additional training
- SB 950 (CA Birth Defects Prevention Act) indicates the DPR Director has a responsibility 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.