Public Exposure to Chloropicrin in California

(WHS/DPR Photo)

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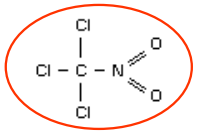
Chloropicrin: Introduction



- Trichloronitromethane
  - Colorless, volatile liquid
- Strongly and rapidly irritating to eyes and respiratory system
- Used as fumigant active ingredient (AI), alone or mixed with other fumigants (e.g., methyl bromide, Telone®)
  - Primarily controls soil fungi and other pathogens, as well as nematodes
  - Controls some weeds
  - Also used as a warning agent

(Photo from Rossopf *et al*, 2005)

(Chloropicrin cylinder & pan with cotton from Cardinal Products)

Warning Agent

- What is a warning agent (WA)?
  - Has **good warning properties**, such as odor or irritation
  - **Ideally,** can detect the warning agent at concentrations below which it and co-applied chemicals are toxic
- Soil fumigations
  - Methyl bromide contains chloropicrin at **≤ 2%** (at higher concentrations, chloropicrin is considered an AI)
- Structural fumigations
  - 2 methyl bromide products with **0.5 - 1%** chloropicrin
  - Sulfuryl fluoride labels require use of chloropicrin, which is added separately to a pan in front of a fan (see photos)

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U.S. EPA Status

- Soil Fumigant Risk Assessments
  - Chloropicrin is one of 5 AIs with risk mitigation measures proposed by EPA in 2008 – amended documents with revised measures released in May 2009
  - Proposed mitigation measures include **buffer zones of 25 ft – ½ mile**, depending on the application method and conditions
- EPA's risk assessment only considered uses supported by the Chloropicrin Manufacturers Task Force (CMTF)
  - Other registrants must submit data to support reregistration of any uses not supported by CMTF
  - (DPR's risk assessment examines current uses)

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Chloropicrin in Reevaluation at DPR

- DPR placed all products containing chloropicrin into reevaluation, based on data submitted under California's Birth Defect Prevention Act
  - DPR required submission of new studies from registrants; all required studies have been submitted
- Chloropicrin is also a candidate to be listed as a Toxic Air Contaminant (full exposure assessment to follow)
  - Focused on public airborne exposures to chloropicrin
  - **Screening estimates** for bystanders to soil, structural, and enclosed space fumigations (if screening estimates are okay, others are, too)

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Chloropicrin Products

Active Ingredient	Number of Products Registered	Chloropicrin Concentration Range (%)	Fumigation Type
Methyl Bromide	25	0.25 – 67	
Chloropicrin – WA	(8)	0.25 – 10.5	Soil/Space/WA in Structural
Chloropicrin – AI	(17)	19.8 – 67	Soil/Space
Methyl Iodide*	0	2 – 75	Soil
1,3-Dichloropropene	13	15 – 60	Soil
Chloropicrin as sole AI	9	94 - 100	Soil/Space/WA in Structural
Total	47		

(Warning agent for sulfuryl fluoride)

- **47** products registered in California
- Registered uses:
  - Soil/space fumigation (also warning agent for structural fumigation)

** Methyl iodide is not currently registered in California*

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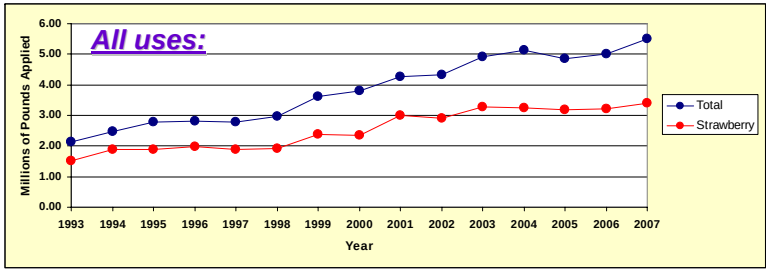
Chloropicrin Use

- Over the past 15 years, an average of **68%** of use (lbs applied) was pre-plant for **strawberries**
  - Other top crops: nursery, tomatoes, berries, melons
  - Use approximately doubled between 1993 and 2003, hovered around 5 million lbs in 2003 – 2006, then increased to nearly 5.5 million in 2007



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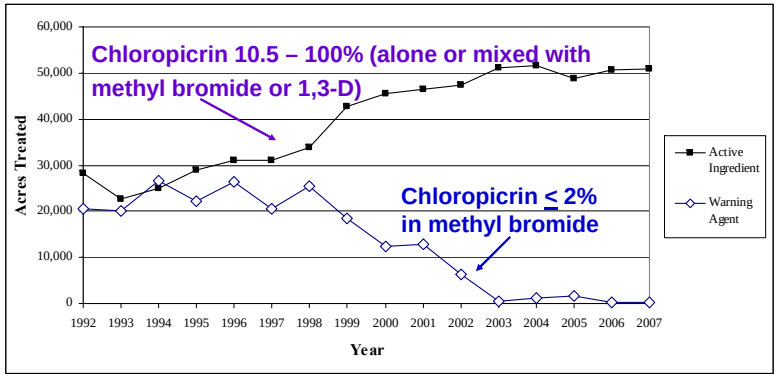
Warning Agent vs. AI in Soil Fumigations

Warning agent use decreased with methyl bromide phase-out

- **Agricultural applications** reported in **acres treated**:



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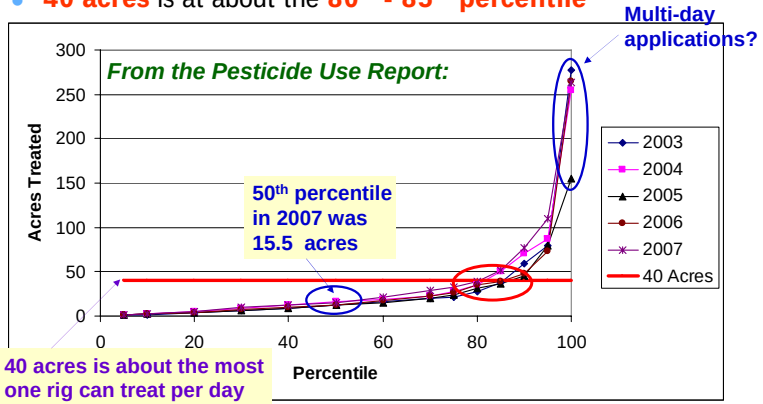
Acres Treated/Day (Reported in PUR)

- Applications reported as acres treated, chloropicrin ≥ 94%
- **40 acres** is at about the **80th - 85th percentile**



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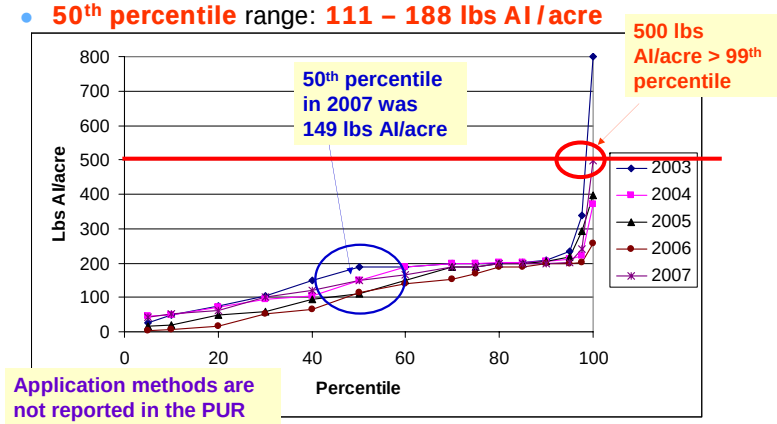
Application Rates (Reported in PUR)

- Applications reported as acres treated, chloropicrin ≥ 94%
- **50th percentile** range: **111 – 188 lbs AI/acre**



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Environmental Fate

- After application, chloropicrin rapidly diffuses through the soil in all directions
- **Volatilization** is the major pathway through which chloropicrin dissipates from soil
  - Over 2-week intervals, on average **61 – 69%** of chloropicrin applied by shank fumigation volatilized; **15%** of chloropicrin applied by tarped drip methods
  - Also degraded through biotic and abiotic reactions, with $T_{1/2}$ ~ 1 to 8 days in field studies
- Volatilized chloropicrin undergoes rapid photolysis by absorbing UV light
  - Predicted $T_{1/2}$ < 1 day in bright sunlight

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Exposure Durations

- **Short-term**
  - Upper-bound estimate: want realistic worst case
  - **1 Hour:** Chloropicrin-associated irritation occurs rapidly
  - **8 Hours:** Occupational bystanders
  - **24 Hours:** Residential bystanders

- **Seasonal**, **Annual** and **Lifetime**
  - In some agricultural areas, repeated exposure may occur from **multiple fumigations**
  - Want typical exposures – over longer intervals, individuals would not consistently have high-end exposures

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Soil Fumigation Air Monitoring

- **California Air Resources Board (ARB)**
  - Ambient air and application off-site monitoring (summarized but not used to estimate exposure)
- **Chloropicrin Manufacturers Task Force (CMTF, registrants)**
  - Application site monitoring, **on-site** & off-site measurements (only **on-site** used to estimate exposure)
  - Two sets of studies (data from both were used):
    - Arizona, Florida and Washington in 1995-1996
    - California in 2003-2004

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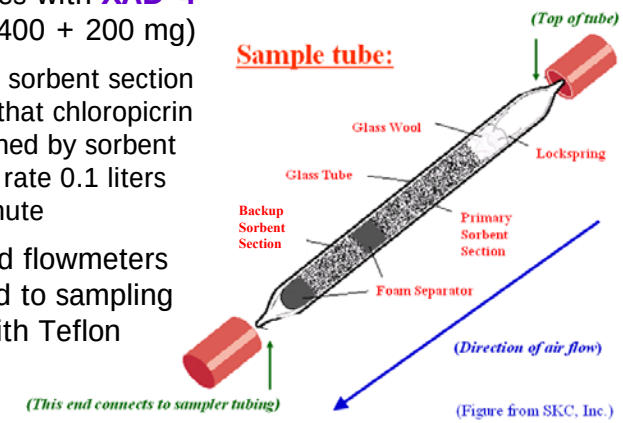
Air Samplers

- Glass tubes with **XAD-4** sorbent (400 + 200 mg)
  - Backup sorbent section shows that chloropicrin is retained by sorbent at flow rate 0.1 liters per minute
- Tubes and flowmeters connected to sampling pumps with Teflon tubing



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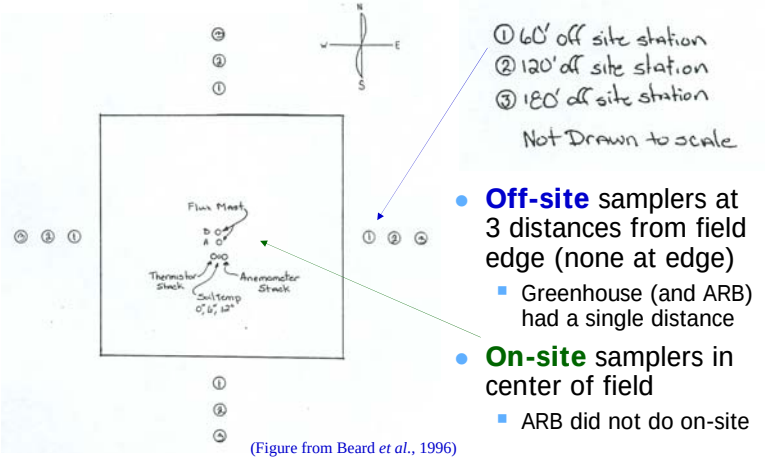
CMTF: Sampler Locations



(Figure from Beard *et al.*, 1996)

- **Off-site** samplers at 3 distances from field edge (none at edge)
  - Greenhouse (and ARB) had a single distance
- **On-site** samplers in center of field
  - ARB did not do on-site

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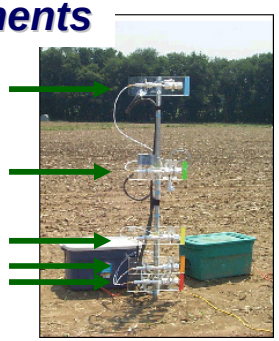
CMTF: *On-Site* Measurements

- Series of **air samplers** on a sampling mast at the field center
- Changes in air concentration, temperature, and wind speed with height used to calculate flux (Barry, 2008a)
- **Flux** is the amount of chemical emitted per unit area and time
  - Field volatility or emission rate



(USDA Photo from McConnell *et al.*)

- **Flux** can be used to calculate off-site concentrations
  - Results in more health-protective exposure estimates than obtained from off-site monitoring

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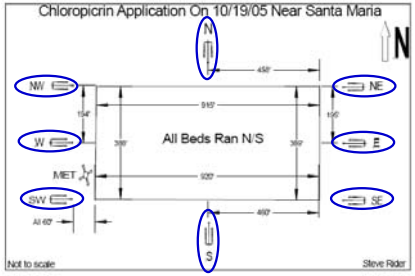
Air Monitoring Considerations



(Figure from ARB, 2006)

(wind, temperature, field size, etc.)

- Any one sampler might not be in the plume center for a full monitoring interval
  - Even if a sampler is at the plume center during an interval, conditions might not produce the highest possible concentrations during that interval
- **Field sizes** monitored ranged **~ 5 – 8 acres**
  - **Larger applications** are possible and would give **higher concentrations** for bystanders

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Health-Protective Estimates

- Considerations for chloropicrin exposures
  - Chloropicrin is a volatile compound
  - Irritation occurs rapidly
  - Bystanders may be closer to application than samplers were
    - Chloropicrin-only products presently have no statewide requirements for buffer zones
- Modeling is used to address these issues

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Air Dispersion Modeling

- Air dispersion models use emission information from one or more sources to estimate chemical air concentrations
- Gaussian Plume Model
- Gaussian Plume Model inputs:
  - **Field volatility** (**emission rate** or **flux**)
  - Dimensions and orientation of treated field, distance from field, urban or rural dispersion pattern
  - Temperature, wind speed, atmospheric stability
- Gaussian Plume Model Screening mode:
  - Model predicts the reasonable worst case **downwind** ground level concentrations that may occur off-site by examining a full range of meteorological conditions across all stability classes and wind speeds.

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Off-Site Movement: Plume

Plume movement away from the field is affected by wind speed and direction, etc.

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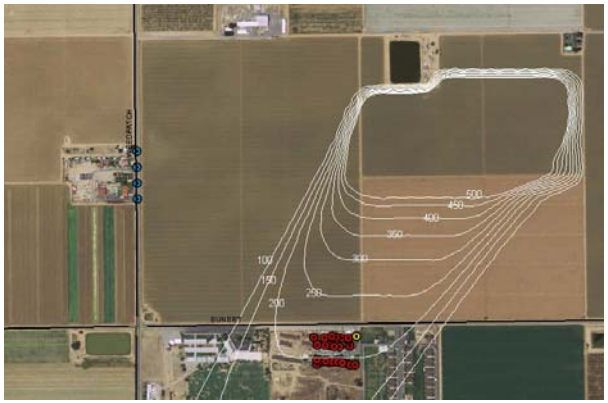
Off-Site Movement: Plume



The fumigant volatilizes, mixes with air and moves downwind.

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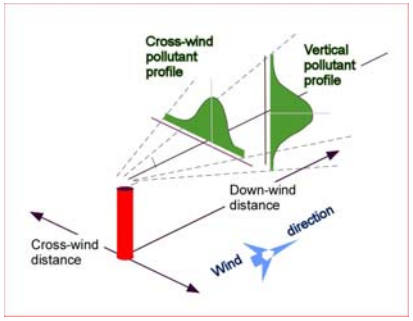
DPR Uses the ISCST3 Model

Industrial Source Complex—Short Term, Version 3



(Figure from Univ of Colorado)

Features of ISCST3 model

- **Steady-state:** conditions do not change within a unit of time (e.g., 1 hour)
- **Gaussian plume:** chemical concentrations peak at center of plume, taper toward edges
  - Calculate concentrations along plume centerline

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Computer Modeling

- Industrial Source Complex Short Term (ISCST3)
- Primary model used by DPR since 1992
- Gaussian plume model developed by U.S. EPA

$C = F \times M$

C = concentration (ug/m^3)

F = flux (ug/m^2s)

M = Function of x,y,z,meteorology (s/m)

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Computer Modeling

- Screening methods produce reasonable worst case air concentration estimates
- The averaging time of the air concentration is directly related to the averaging time that produced the flux estimate
- The meteorological data is considered the predominant condition for that averaging time
  - Screening meteorological conditions can and do occur in the environment
  - The wind direction is interpreted as the predominant (average) direction for the averaging time

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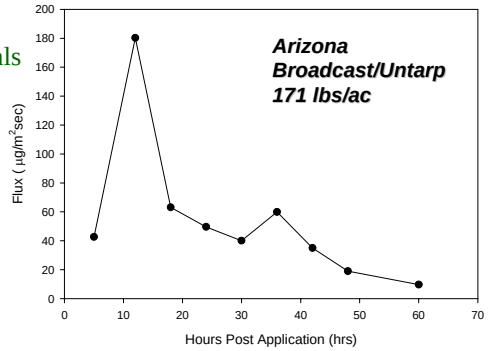
Example Flux Profile

First 9 Sampling Intervals

Each Interval = 6 hrs



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Estimating 1-Hour Concentrations

- Shortest monitoring interval for flux in any chloropicrin study was **6 hours** (used for 8-hour exposure estimate)
- **1-hour** concentrations were estimated from the **6-hour** concentrations by employing a **peak-to-mean ratio** using the following equation (Barry, 2000):
  - $C_p = C_m(t_p/t_m)^{-1/2}$

C_p = peak concentration over period of interest

C_m = mean concentration over measurement period

t_p = duration of peak period of interest (1-hour)

t_m = duration of mean measurement period (6 hours)

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Bystanders to Soil Fumigation

- **Short-term screening exposure estimates**: highest modeled concentration for each interval
- Assumptions: **40 acres** & **maximum** allowed application rate on current product labels (**500 lbs AI / acre**)

Duration	Concentration ($\mu g / m^3$)	Concentration (ppb)
1 Hour	110,000	16,000
8 Hours	44,000	6,500
24 Hours	7,400	1,100

For chloropicrin, ppb = (0.1487) x ($\mu g / m^3$)

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For Context: 50th Percentile Exposures

- Highest modeled concentration per interval for bystanders **45 feet (15 m)** downwind from field edge
- Assumptions: **2007 - 50th percentile** application rate (**150 lbs AI / acre**) & acres treated (**15 acres**)

Duration	Concentration ($\mu g / m^3$)	Concentration (ppb)
1 Hour	30,000	4,500
8 Hours	12,000	1,800
24 Hours	2,500	370

Concentrations summarized in Appendix 3

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For Context: 50th %ile, ½-Mile Away

- Highest modeled concentration per interval for bystanders **½ mi (760 m)** downwind from field edge
- Assumptions: **2007 - 50th percentile** application rate (**150 lbs AI/acre**) & acres treated (**15 acres**)

Duration	Concentration ($\mu g/m^3$)	Concentration (ppb)
1 Hour	7,400	1,100
8 Hours	3,000	450
24 Hours	250	37

Concentrations summarized in Appendix 3

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Exposure Appraisal

Assumptions

- **40 acres** treated/day is a practical maximum
  - If more than one rig is used, can treat more acres
  - PUR data suggest that 40 acres/day is about the 80th to 85th percentile of all applications (some of the applications reported in the PUR probably spanned multiple days)
- Adjustments for application rate assume that flux and concentrations are proportional to rate
  - Adjusted concentrations are outside measured range

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Seasonal, Annual, Lifetime Exposures

- Monitoring in several of the CMTF studies spanned 2 weeks
  - Average 24-hour flux calculated over 2 weeks (Barry, 2008c)
  - Because wind direction is not constant over longer intervals, concentrations were adjusted with a time-scaling factor derived using peak-to-mean theory (Barry, 2008c)
  - Concentrations **not** adjusted for maximum rate
- Length of season approximated using PUR data from Monterey County

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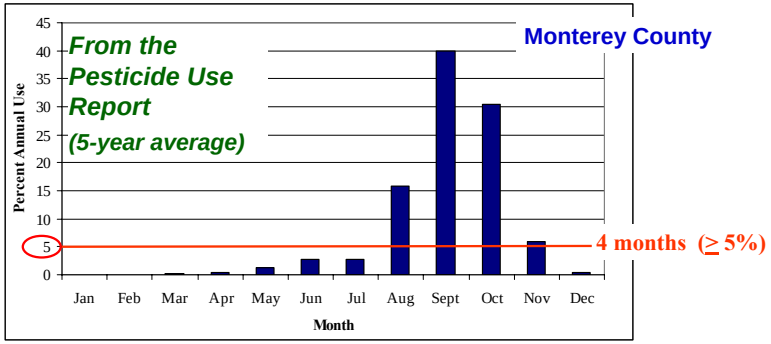
Chloropicrin Use Pattern for Seasonal & Annual Bystander Exposures

- **Assumption:** Exposures are **less likely** during months when little use occurs (e.g., < 5% of total use each year)



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Bystanders to Soil Fumigation

- **Intermediate- and long-term exposure estimates**: Seasonal exposure includes intervals of 1 week – 1 year
- Assumptions: **40 acres** treated & that applications occur about **every 2 weeks** over **4 months** each year
- Annual concentration = Seasonal concentration x (4/12 months)

Supported by registrants

Duration	Assumed Application Rate	Conc. ($\mu g/m^3$)	Conc. (ppb)
Seasonal	350 lbs AI/acre	490	73
Annual	350 lbs AI/acre	160	24
Lifetime	150 lbs AI/acre	70	10

50th percentile

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Exposure Appraisal

Assumptions

- With the exception of application rate, assumptions of modeling are the same as for short-term estimates
  - 40 acres/day, distance from field, etc.
  - Not adjusted for maximum application rate, assuming that upper-bound exposures are less likely over a longer interval
- Multiple applications are possible, at least in 1-mi^2 sections
  - Frequent applications occur in some sections in Monterey County, as much as 38 days/year over a 4-month interval
  - PUR data only reported at section level; no data with better resolution are available

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Structural Fumigation

- Exposure estimates are based on **measured** rather than **modeled** concentrations
  - Samplers surround house

(Photos from Texas A&M and Cardinal Products websites)

- Amount of chloropicrin used is much lower for structural than soil fumigations
  - Chloropicrin is used only as a warning agent for structural fumigations
  - Smaller areas treated
  - Off-site concentrations in ARB studies were < LOQ within 6 hours after aeration begun

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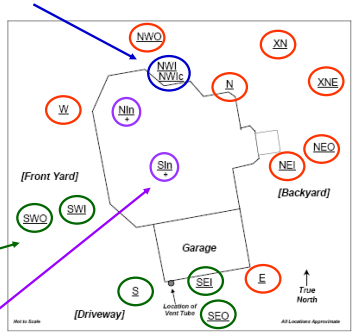
ARB Monitoring of Chloropicrin

43.3 µg/m³ (1.5-hour sample, start of aeration) at sampler located 5 feet from edge of house

- Among 3 fumigations monitored by ARB, highest concentrations were during a 2004 fumigation of a house in Grass Valley, ~ 81,000-ft³ (2,300-m³)
- Highest concentration at this site occurred at **NW inner (NWI)** sampler
- Five samplers yielded all non-detects



(Figure from ARB, 2005a)

Also indoor samples post-aeration

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Bystanders to Structural Fumigation

- Results were adjusted for field spike recoveries and for the maximum rate at which chloropicrin is used as a warning agent in structural fumigation
- Seasonal, annual, or lifetime exposures are not anticipated

Duration	Concentration ($\mu g/m^3$)	Concentration (ppb)
1 Hour	73	11
8 Hours	16	2.4
24 Hours	6.2	0.92

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Bystanders to Space Fumigation

- Chloropicrin can be used as an active ingredient to fumigate enclosed spaces
  - One product gives directions for use in fumigating empty potato storages and empty grain bins
  - U.S. EPA has received requests to cancel the space fumigation uses
- Maximum application rate: 0.7 lbs/1,000 ft^3 (0.3 kg/28 m^3)
- Assume twice per year: storage fumigated between crops, two crops per year
  - Annual = 24-hour concentration x (2 days/365 days)

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Bystanders to Space Fumigation

- Short-term, annual and lifetime exposures estimated
- No seasonal exposures (i.e., no durations 1 week - 1 year)

Duration	Concentration ($\mu g/m^3$)	Concentration (ppb)
1 Hour	2,400	360
8 Hours	680	100
24 Hours	210	31
Annual	1.2	0.18
Lifetime	1.2	0.18

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Exposure Appraisal

Bystander Exposures Associated with Structural/Space Fumigation

- Concentrations were based on measured off-site data, not modeling; measured concentrations are expected to be health-protective
  - Samplers were about as close to application as nearest likely bystander would be – as close as 5 feet (1.5 m)
  - Off-site chloropicrin concentrations quickly decreased following aeration, and all were < LOQ after 6-hours post-aeration
- Corrected for field spike recovery and adjusted for maximum application rate
  - No adjustment for application size, but house size was on larger end of range (~ 4,000 – 5,000 ft^2)

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Indoor Air Concentrations

- Samples were collected for 24-hour **post-aeration**: represent **residents in a treated structure**
- Results were adjusted for field spike recoveries and for the maximum rate at which chloropicrin is used as a warning agent in structural fumigation
- Seasonal, annual, and lifetime exposures are not anticipated

Duration	Concentration ($\mu g / m^3$)	Concentration (ppb)
24 Hours	**140**	**21**

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Questions?

(WHS/DPR Photo)

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Evaluation of Chloropicrin as a Toxic Air Contaminant

Part B Human Health Assessment

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Department of Pesticide Regulation
Cal/EPA

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Historical Background

- Chloropicrin was used as a war gas in WWI
- First used as a fumigant in flour mills in 1926
- NIOSH's IDLH – 2 ppm
- ACGIH TWA-TLV – 0.1 ppm
- DPR placed chloropicrin into reevaluation based on air monitoring data with levels greater than TLV

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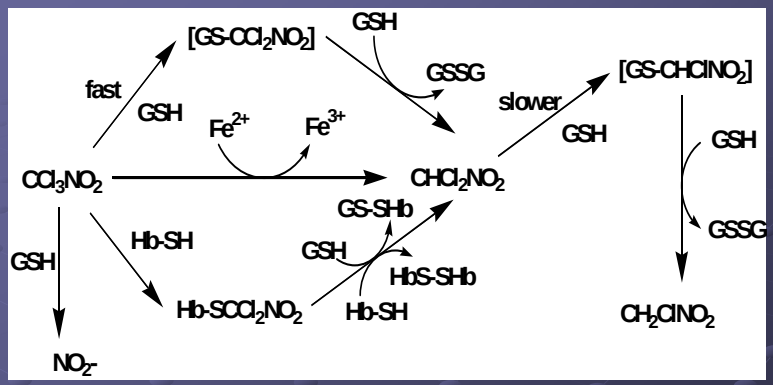

Figure 1. Proposed pathways for reaction of chloropicrin with glutathione and hemoglobin

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Acute Toxicity – 1 Hour Exposure

Human sensory irritation study (Cain, 2004)

- Three phases
  - Phase 1 – Brief inhalation exposures (seconds)
  - Phase 2 – 20 minute exposure
  - Phase 3 – 1 hour exposure on 4 consecutive days
- DPR found this study acceptable
  - Conducted in accordance with GLP regulations and protocol approved by the IRB at U.C. San Diego
  - Protocol was reviewed by biostatistician to ensure there was sufficient statistical power
  - Approved by U.S. EPA's HSRB

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Acute Toxicity – 1 Hour Exposure (cont.)

Human Sensory Irritation Study, Phase 3

- 32 Young adult subjects – 15 males and 17 females
- Subjects exposed to 0, 100 or 150 ppb for 1 hour on 4 consecutive days
- Rated eye, nose and throat irritation on scale of 0 to 3 every minute during their 1-hour exposures
  - No nasal or throat irritation reported
  - Eye irritation at 100 and 150 ppb

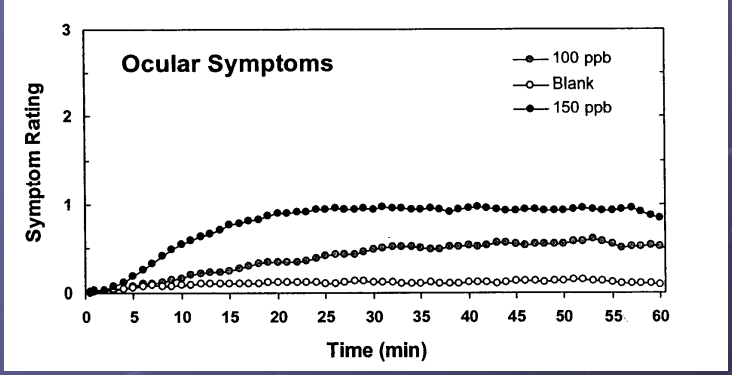

Figure 2. Average rated severity of ocular irritation during 1-hour exposures during phase 3 of the human sensory irritation study for chloropicrin*

* (n = 32, males and females combined).

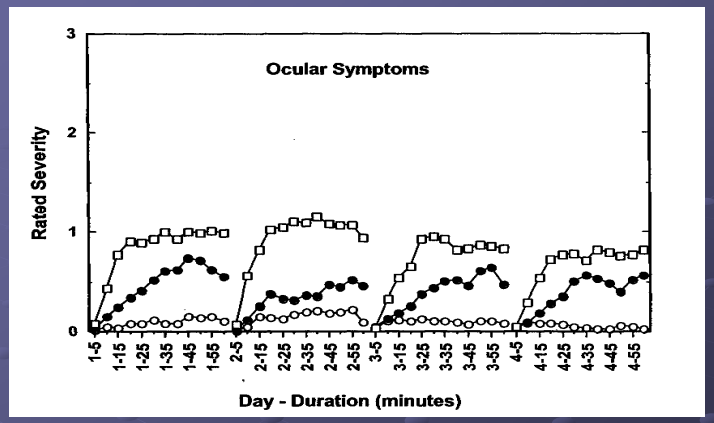

Figure 3. Average rated severity of ocular irritation by day of exposure in phase 3 of the human sensory irritation study for chloropicrin*

*(n = 32, males and females combined; blank = open circles, 100 ppb = solid circles; 150 = open squares)

Acute Toxicity - Human Sensory Irritation Study (cont.)

- Other respiratory variables evaluated in Phase 3
  - Lower respiratory variables unaffected
    - Nitric oxide (NO) concentration in expired pulmonary air
    - Pulmonary function (FVC and FEV_1)
  - Upper respiratory variables affected
    - Nasal air flow reduced at 150 ppb
    - Elevated NO concentration in expired nasal air at 100 and 150 ppb

Table 1. Ocular and Nasal Irritation in Human Subjects Exposed to Chloropicrin for One Hour over Four Consecutive Days[a]

	Dose Level (ppm)		
	0	100	150
Ocular irritation			
Average score, overall[b]	0.10±0.19[c]	0.39±0.39	0.76±0.71
Average score, plateau[d]	0.12±0.22	0.54±0.51	0.90±0.86
Nasal Irritation			
Average increase in NO[e] in expired nasal air	1.6±15.6	12.0±11.9	12.7±16.6

a Cain, 2004.

b Average severity score reported for every minute of 1 hour exposure for all four days of exposure. Severity score range from 0 (no irritation) to 3 (severe – hard to tolerate and can interfere with activities of daily living)

c mean ± standard deviation n = 32, males and females combined since no significant gender differences

d Plateau period was defined as minutes 30 to 55 when the maximum scores were observed.

e The average difference in nitric oxide (NO) concentration (ppb) in expired nasal air before and after exposure for each individual for all four days of exposure.

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Benchmark Dose Analysis for Human Study

- Threshold for identifying responders was estimated using the standard deviation in the control group
- Benchmark Concentration at the 10% response level (BMC_{10}) was used rather than the default of 5% because these effects were mild and reversible
- BMC_{10} for eye irritation was 26 ppb
- BMC_{10} for increased NO in nasal air was 75 ppb

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Acute Toxicity – 8 and 24 Hour Exposures

Rabbit Developmental Toxicity Study

- Pregnant rabbits exposed to vapors 6 hrs/day from GDs 7-21
- Maternal effects observed in first few days of exposure were considered acute
  - Deaths
  - Red discolored lungs and pulmonary edema
  - Clinical signs of sensory and respiratory irritation
  - Reduced body weights and food consumption
- Acute NOEL = 0.4 ppm
  (8 hr HEC – 270 ppb; 24 hr HEC – 92 ppb)

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Subchronic Toxicity

90-Day Inhalation Toxicity Studies with Rats and Mice

- Exposure for 6 hrs/day, 5 days/wk for 13 weeks
- Effects at 1.03 ppm and higher
  - Mortalities and clinical signs
  - Reduced body weights and food consumption
  - Increased lung weights and pathological lesions in nasal cavity and lungs
- Benchmark dose analysis performed to determine most sensitive endpoint
  - Default 5% response level used since frank effects
- The most sensitive endpoint was rhinitis in female rats with a BMC_{05} of 120 ppb (HEC – 35 ppb)

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Chronic Toxicity

Chronic Inhalation Studies with Rats and Mice

- Exposed for 6 hrs/day, 5 days/wk for 78 weeks (mice) or 107 weeks (rats)
  - Effects in mice at 0.5 ppm and higher
    - Reduced body weights and food consumption
    - Pathological lesions in nasal cavity and lungs
  - Effects in rats at 0.5 ppm or higher
    - Reduced survival and clinical signs
    - Reduced body weights
    - Increased lung weights and rhinitis
- BMD analysis performed to determine the most sensitive endpoint
- The most sensitive endpoint was bronchiectasis in female mice with a BMC_{05} of 59 ppb (HEC – 32 ppb)

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Weight of Evidence - Carcinogenicity

Genotoxicity Studies

- Numerous positive assays
  - 8 Reverse mutation assays with *S. typhimurium* ± S-9
  - *In vitro* chromosomal aberrations with CHO cells
  - Sister chromatid exchanges in human lymphocytes
- Some negative assays
  - Forward mutation assay with mouse lymphoma cells
  - *In vitro* chromosomal aberrations with human lymphocytes
- Based on these data, DPR concluded that a genotoxic mode of action for tumor formation may be possible

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Weight of Evidence – Carcinogenicity (cont.)

Carcinogenicity Studies in Animals

- Inhalation Studies
  - Significant increase in the combined incidence of adenomas and carcinomas in the lungs of female mice if adjusted for survival
    - Dose-related increase in the multiplicity of the tumors
    - Slight shortening of time-to-tumor at high dose
- Oral Studies
  - Significant increase in fibroadenomas of female rats
- DPR concluded that the evidence was sufficient to warrant a quantitative assessment of carcinogenicity
- Cancer potency estimated to be 2.2 $(mg/kg/day)^{-1}$ based on lung tumors in female mice

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Table 2. DPR Critical Endpoints for Chloropicrin Risk Assessment

Exposure Scenario	NOEL/BMC	Effects at LOEL
Acute 1 hr	26 ppb	Ocular irritation in humans
Acute 8 & 24 hr	400 ppb	Mortalities, nasal discharge, ↓ body wts. & food consumption, red discoloration of lungs of pregnant rabbits
Seasonal	120 ppb	Rhinitis in female rats
Chronic	59 ppb	Bronchiectasis in female mice
Lifetime	Potency = 2.2 $(mg/kg/day)^{-1}$	Lung tumors in female mice

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TAC Listing Criteria

$$Margin\ of\ Exposure = \frac{HEC\ (ppb)}{Air\ Concentration\ (ppb)}$$

- Generally, a MOE > 100 is considered protective of human health based on the following assumptions:
  - Humans are 10 times more sensitive than animals
  - 10-fold variation in sensitivity in the human population
- To not list as TAC, MOE > 1,000
  - For sensory irritation MOE > 30
    - No interspecies UF
    - Intraspecies UF = 3 since toxicokinetic differences not expected with direct-acting mechanism of toxicity

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TAC Listing Criteria

$$Risk = Potency\ (mg/kg/day)^{-1}\ X\ Exposure\ (mg/kg/day)$$

Carcinogenicity

- Risk < 10^{-6} is generally considered negligible
- To not list a TAC : Risk < 10^{-7}

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Table 3. Worse Case Margins of Exposure for Bystanders Following Soil Fumigation with Chloropicrin

Exposure Duration	Margin of Exposure[a]	
	Children	Adult
Acute – 1 hour Eye Irritation/human	0.0016	0.0016
Acute – 8 hour Deaths, lung path/rabbit	0.042	0.088
Acute – 24 hour Deaths, lung path/rabbit	0.084	0.18
Seasonal Rhinitis/rat	0.48	1.0
Annual Bronchiectasis/mice	1.3	2.8

a Margin of Exposure (MOE) = HEC / Air Concentration. HEC = Human Equivalent Concentration. For TAC listing, target MOE > 30 when based on eye irritation in human study and > 1,000 when based on effects in animal study. Only MOEs for the application method with the highest worse case estimate is shown for each exposure duration.

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Table 4. Margins of Exposure for Bystanders Following Soil Fumigation with Chloropicrin Using 50th Percentile

Exposure Duration	Margin of Exposure[a]	
	Children	Adults
Acute – 1 hour Eye irritation/human	0.0060	0.0060
Acute – 8 hour Deaths, lung path./rabbits	0.15	0.32
Acute – 24 hour Deaths, lung path./rabbits	0.25	0.52

a Margin of Exposure (MOE) = HEC / Air Concentration. HEC = Human Equivalent Concentration. For TAC listing, target MOE > 30 when based on eye irritation in human study and > 1,000 when based on effects in animal study

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Table 5. Margins of Exposure for Bystanders Following Soil Fumigation with Chloropicrin Using 50th Percentile and Half-Mile from Field Edge

Exposure Duration	Margin of Exposure[a]	
	Children	Adults
Acute – 1 hour Eye irritation/human	0.024	0.024
Acute – 8 hour Deaths, lung path./rabbits	0.62	1.3
Acute – 24 hour Deaths, lung path./rabbits	2.5	5.2

a Margin of Exposure (MOE) = HEC / Air Concentration. HEC = Human Equivalent Concentration. For TAC listing, target MOE > 30 when based on eye irritation in human study and > 1,000 when based on effects in animal study.

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Table 6. Estimated Cancer Risks for Bystanders Exposed to Chloropicrin Following Soil Fumigation

Application Method	Residential		Occupational	
	MLE	95% UB	MLE	95% UB
Bedded, tarped	2.5×10^{-2}	4.3×10^{-2}	1.5×10^{-2}	2.5×10^{-2}

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Table 7. Margins of Exposure for Bystanders Following Structural Fumigation with Chloropicrin

Exposure Duration	Margin of Exposure[a]	
	Children	Adult
Acute – 1 hour Eye irritation/human	2.4	2.4
Acute – 8 hour Deaths, lung path./rabbits	110	240
Acute – 24 hour Deaths, lung path./rabbits	100	210

a Margin of Exposure (MOE) = HEC / Air Concentration. HEC = Human Equivalent Concentration. For TAC listing, target MOE > 30 when based on eye irritation in human study and > 1,000 when based on effects in animal study

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Table 8. Margins of Exposure for Indoor Air Following Structural Fumigation with Chloropicrin

Exposure Duration	Margin of Exposure[a]	
	Children	Adult
Acute – 24 hour Deaths, lung path./rabbits	4.4	9.0

a Margin of Exposure (MOE) = HEC / Air Concentration. HEC = Human Equivalent Concentration. Only for the application method with the highest worse case estimate is shown. Tor TAC listing, target MOE > 1,000 based on effects in animal study

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Table 9. Margins of Exposure for Bystanders Following Enclosed Space Fumigation with Chloropicrin

Exposure Duration	Margin of Exposure[a]	
	Children	Adult
Acute – 1 hour Eye irritation/human	0.072	0.072
Acute – 8 hour Deaths, lung path./rabbits	2.8	5.8
Acute – 24 hour Deaths, lung path./rabbits	3.0	6.2
Annual Bronchiectasis/mice	180	380

a Margin of Exposure (MOE) = HEC / Air Concentration. HEC = Human Equivalent Concentration. For TAC listing, target MOE > 30 when based on eye irritation in human study and > 1,000 when based on effects in animal study.

Table 10. Estimated Cancer Risk for Bystanders Exposed to Chloropicrin Following Enclosed Space Fumigation

Exposure Scenario	MLE	95% UB
Enclosed Space Fumigation	1.9×10^{-4}	3.2×10^{-4}

FQPA Issues

- Prenatal and Postnatal Sensitivity
  - Fetal NOELs ≥ maternal NOELs in developmental toxicity studies in rats and rabbits
    - Fetal effects were nonspecific signs, possibly secondary to maternal toxicity
  - Pup NOEL ≥ parental NOEL in rat reproductive toxicity study
    - Neonates were not exposed directly
  - Significant amounts of chloropicrin are not expected in the maternal blood stream due to its rapid reaction at the site of first contact
- Endocrine effects
  - Some reproductive effects, but unclear if endocrine-related
    - Reduced number of implantation sites
    - Increased pre- and post-implantation losses
    - Late-term abortions

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Conclusions

Soil fumigation
- All of the bystander MOEs are significantly less than the target MOEs
- The cancer risk estimates are significantly greater than the target risk level of 10^{-7}
- Clearly meets criteria for listing as a TAC

Structural fumigation
- All of the bystander MOEs less than their target MOEs
- MOEs for indoor air are less than target MOE
- Air concentrations high enough to meet criteria for listing

Enclosed space fumigation
- Bystander MOEs are significantly less than target MOEs
- The cancer risk estimates are greater than the target risk level
- Clearly meets the criteria for listing as a TAC

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