

WASHINGTON STATE UNIVERSITY  
World Class. Face to Face.

**VAPAM HL**  
SOIL FUMIGANT  
A SOIL FUMIGANT SOLUTION FOR ALL CROPS



**Metam Sodium:  
Environmental Chemistry, Toxicology,  
& Fumigant Registration Issues**

Allan Felsot  
Washington State University  
Department of Entomology  
Food & Environmental Quality Lab



**Farming's Amazing Productivity**

Year →	1910	2000
<b>Total Principal Crops (acres)</b>	305,299,000	307,839,000
<b>Potatoes (acres)</b>	3,644,000	1,352,000
<b>Potato Yield Per Acre (cwt)</b>	56	382

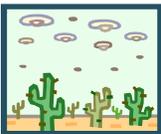
**Pesticides as a Public Menace**

- Pesticide contamination of water is widespread
- Pesticides responsible for ecological problems
- Pesticides responsible for human health problems



**Common Misperceptions**

- Mere detection of a pesticide residue is equal to a hazard
- Exposure to pesticide residues is equal to a hazard
- Desire to manage (for ex., court-mandated buffer zones) means there is a hazard
- EPA registers pesticides without knowing about their risk to the environment or people



**A Letter from a Concerned Citizen to EPA**

- Re: fumigants
  - "I am writing to urge EPA to phase out use of toxic soil fumigants." Fumigants are prone to drift through the air and contaminate ground water."
  - "Many workers and community residents--including children and the elderly--have experienced acute illness from exposure to these chemicals, with symptoms including nausea, vomiting, dizziness, tremors, asthma and severe respiratory irritation."
  - "Chronic illnesses such as cancer, birth defects and permanent neurological damage have been linked to exposure to these chemicals as well."
  - "Continued widespread use of soil fumigants damages human health and the environment and does not move agriculture toward true sustainability."

EPA Docket ID (OPP-2005-0125-0027)  
<http://www.regulations.gov/fdmspublic-re11/component/main>

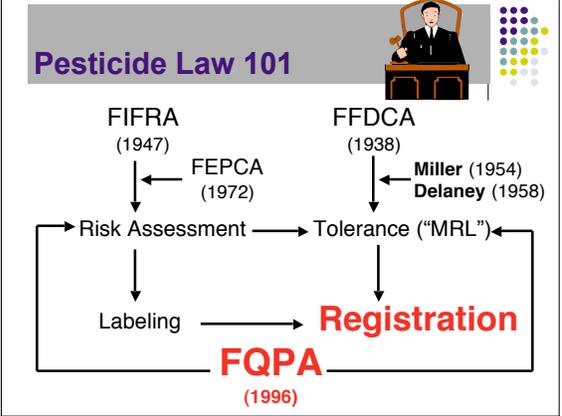
**The Almighty FIFRA**  
(Federal Insecticide Fungicide & Rodenticide Act)



## FIFRA Rules



- Policies, regulations, & standards set under the mandate of the Federal Insecticide, Fungicide & Rodenticide Act govern pesticide use (in the broadest sense--the whole technology)
- Although pesticides are arguably the most intensely scrutinized and regulated chemical technology, the law historically allowed consideration of benefits of use as well as an assessment of risks
  - Currently only applicable to worker protection and ecological effects
  - Only risk considered when protecting consumers

## It Ain't Over Until the EPA Sings



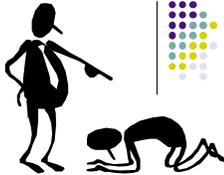
- Under the old amendments to FIFRA as well as the new mandates of FQPA since 1996, all pesticides will continue to be re-reviewed for consideration of continuing registration
- Thus, registration is dynamic, resulting in a continual updating of product labels that reflect the need to protect human health and the environment

## The Pesticide Label It's the Law



- All registered active ingredients formulated into commercial products
  - All individual products must be registered, but registration not given until label developed and approved
- The label is the governing law
  - Identification of active ingredient and contents
  - Legal uses (crops, maybe specific pests)
  - Rates of application; application methods
  - Personal protective equipment
  - Restrictions on use (no drift; no application near water; sometimes region-restricted)
  - Directions for disposal

## The Pesticide Label

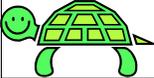


Prime Mechanism of Controlling Pesticide Use

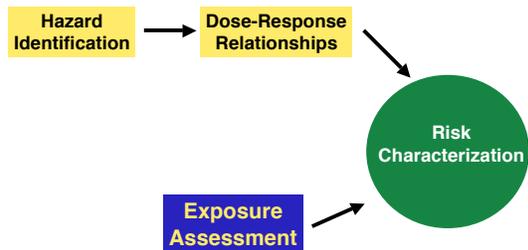



## Controlling Pesticide Use Ensures

Reasonable Certainty of No Harm  
To Human Health & Environment




## Risk Assessment-- Testing the Probability of Harm



## More Than Mere Semantics

- **Hazard:** potential of a substance or activity to cause harm (adverse effects) under a specific set of conditions
  - Do not confuse toxicity with hazard
    - Toxicity is the innate capacity to cause harm
    - Results from the specific 3-D structure and specific biochemical targets
- **Risk:** probability (likelihood) of adverse effects occurring
  - Function of the magnitude of exposure (or contamination)
  - No zero risk

## Separate But Not Equal

- **Risk assessment:** scientific endeavor for determining the likelihood of bad things happening
  - Mandated by statutory and administrative (regulatory) law
  - Mostly science based activity: hypothesis, experiment, observation
- **Risk management:** social endeavor for avoiding bad things
  - Mandated by statutory law
  - Implementation defined by administrative law
  - Influenced by politics, economics, social goals

## EPA Takes Its FQPA Mandate Seriously

- EPA is trying to meet the Congressional deadline of August 2006 to have every active ingredient re-reviewed and re-registered if the chemical meets the revised standards for "safety"
- As part of this process, EPA is tackling all of the fumigants as a cluster in a similar time frame
  - Agency wants to level the playing field and use a consistent method
  - Non availability of use of any fumigant can affect the use of the other fumigants
  - Limited choices in what a grower can use

## My Hypothesis

- Another rationale for assessing risk of fumigants as a cluster of similar compounds
  - Part of the reason is that many have modes of action that are generally unknown but kill the same array of pests
  - Also, the environmental behavior of these chemicals is driven by an extremely high volatility and thus air models can be used to predict residue concentrations during and after application



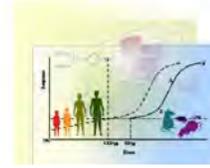
## Registration Eligibility Decision Document (the RED)

- EPA uses REDs to explain the basis for its decision to register new active ingredients and their formulated products or re-register older products
- RED includes
  - Use profile
  - Regulatory history
  - Human Health Risk Assessment
  - Environmental Risk Assessment
  - Risk Mitigation



## HUMAN HEALTH RISK ASSESSMENT

### Metam Sodium



U.S. Environmental Protection Agency  
Office of Pesticide Programs  
Health Effects Division (7509C)  
Sherrie Kinard, Residue Chemist/Risk Assessor  
Bill Smith, Environmental Scientist/Risk Assessor  
Date: June 13, 2005

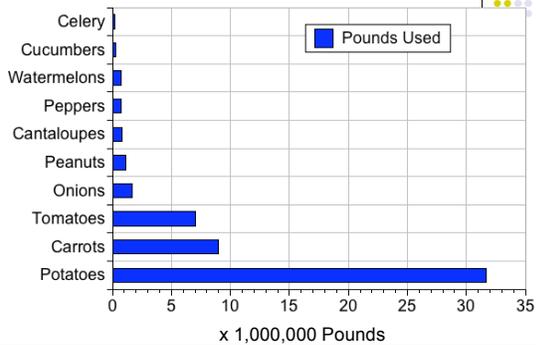


### Metam Sodium Annual Pounds of Active Ingredient Applied 3 Year Average (2002-2004)



### Top Ten Crop Uses for Metam Sodium

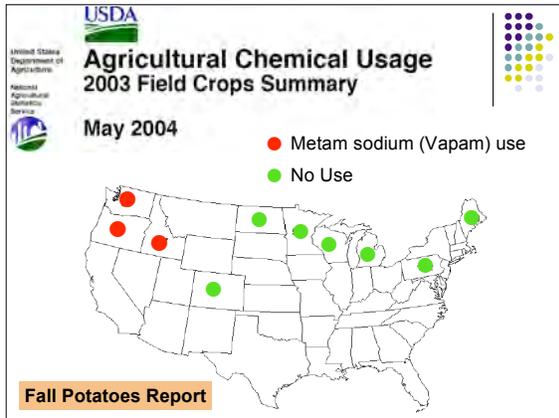
Source: EPA 6/2005



### EPA (2005) Estimates of Metam Usage on Potatoes

- 100 - 150 lbs AI/acre in Colorado, Florida, South Dakota
- 200 - 250 lbs AI/acre in Idaho, Virginia, Washington

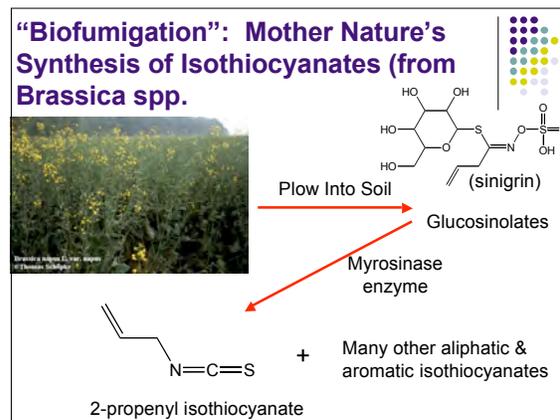
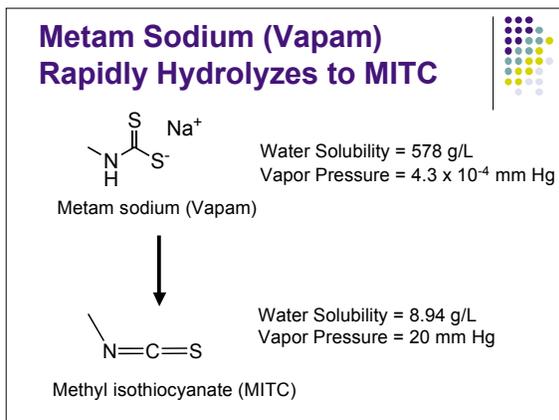




### PNW Potatoes Are the Largest Consumer of Metam Sodium

	All U.S. Potatoes	Idaho	Oregon	Washington
Area Applied (%)	25	33	54	55
Rate per crop yr (lbs/acre)	123	78	123	173
Total Applied (lbs x 1000)	31,758	9,341	2,848	15,527

Source: USDA NASS 2004



### MITC: Biochemical Mode of Action

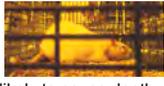
- We know MITC is very active against nematodes, pathogens, and weeds
- But we don't know how its toxicity is manifested biochemically
  - Literature about 20 years ago suggests “interactions with proteins”
- Your guess is as good as mine, but...
  - We do know that a number of isothiocyanates exhibit biological activity (i.e., they can be toxic or they can be therapeutic)

### Ironically,

- Glucosinolates in Brassicae plants are transformed to isothiocyanates by myrosinase enzyme
  - When mustard plant tissues (and related species in Brassicae) are wounded myrosinase is released
  - Microbial flora in the human intestine also releases myrosinase
- Glucosinolate metabolites like the various isothiocyanates have been of research interest for their potential anti-cancer properties (Fahey et al. [2001] Phytochemistry 56:5-51)

## Hazard Identification

- Acute Toxicity
  - Dose rats orally with single doses likely to cause death
- Chronic Toxicity
  - Subchronic oral:
    - 90 days of dietary exposure
    - Dice & slice: tissue pathologies
    - Signs of neurotoxicity
    - Blood parameters
  - Developmental
    - Expose pregnant female via diet on gestation days ~9-15
    - Dice & slice; birth defects; "miscarriage"; fetal death; newborn (neonatal) health



## Hazard Identification

- Chronic Toxicity (continued)
  - Reproductive
    - Several generations of exposure, especially during times of mating; continual exposure after birth
  - Cancer
    - 2 year feeding studies with rats
    - Slice and dice



Note: For all of the tests, neurotoxicity, endocrine system toxicity, and immune system toxicity can be determined directly or inferred from the data

## Narrative Description of Hazards (Signs & Symptoms)

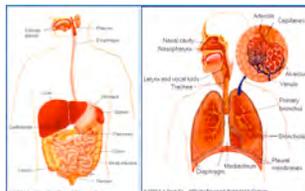
- Rats and humans react similarly
- Air exposures to MITC:
  - Irritation of respiratory tract
  - In humans--
    - Itchy & burning eyes in humans,
    - Rash and burning skin
    - Nausea
    - Scratch throat
    - Salivation
    - Coughing
    - Shortness of breath

## Narrative Description of Hazards (Signs & Symptoms)

- Oral Exposures (rats, mice)
  - Reduced body weight gain & food consumption
  - Hematological parameters affected
  - Liver pathology
  - Reduced motor activity
  - Fetal weight decrements
  - Reduced ossification of various skeletal structures
  - Increased incidence of embryo resorptions

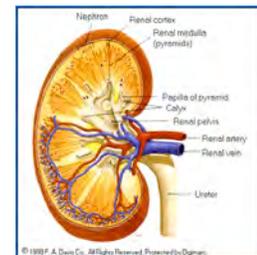
## Pharmacokinetics: (What Happens to It After It Enters the Body)

- Dermal absorption studies indicate only 2.5% is absorbed through the skin into the blood over a 10 h period
- Oral absorption (and by implication inhalational absorption) is very efficient (~100%)



## Pharmacokinetics: (What Happens to It After It Enters the Body)

- 87% of an administered dose of MITC was excreted in the urine within 168 hours
  - Within 24 h, 85% was excreted
  - After 24 h, remaining MITC in blood with a long half-life (~3 days)
- 1.5% excreted in the feces
- ~2% retained in the tissues after 168 hrs



**Pharmacokinetics:**  
(What Happens to It After It Enters the Body)

- Metam sodium is rapidly converted to MITC in the body
- Other metabolites detected (emitted in exhalations) include CS<sub>2</sub>

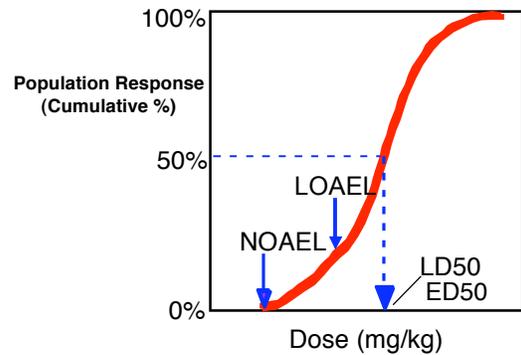
**Dose-Response Assessment**

- How do the adverse effects vary with dose?
- What is the lowest dose that causes an effect?
  - LOAEL (Lowest Observable Adverse Effect Level)
- What is the dose that doesn't cause any effect?
  - NOAEL (No Observable Adverse Effect Level)
- What is the adverse effect that occurs at the lowest dose?
  - This is the dose that becomes the basis for determination of a "safe level of exposure"
  - The toxicological endpoint of concern

*What Is Dose?*

- Dose is the amount of substance per unit of body weight
  - Expressed as mg/kg/day
    - A milligram (mg) is 1/1000 of a gram (g)
    - A gram is 0.03 oz
    - A kilogram (kg) is 2.2 pounds

**"Dose Makes the Poison"**



**MITC Doses Tested to Find Inhalational Hazards**

Toxicity Test	Doses Administered (mg/m <sup>3</sup> )
Subchronic Inhalational (28 day; 6 hr/day; 5 days/week; rats)	0, 5, 20, 100 mg/m <sup>3</sup>
Subchronic Inhalational (90 day; 6 hr/day; 5 days/week; rats)	0, 3.2, 30.7, 137.1 mg/m <sup>3</sup>

**MITC Doses Tested to Find Oral & Dermal Subchronic Exposure Hazards**

Toxicity Test	Doses Administered (mg/kg/day)
90-day Subchronic Toxicity (Dogs; gel capsule exposure)	0, 0.56, 2.8, 5.6
Subchronic dermal (28 day)	0, 1, 10 100
Prenatal Developmental Toxicity (Days 6-17 of pregnancy; gavage)	0, 2.8, 11.2, 33.6
Reproduction & Fertility (2-generations; oral exposure via water)	0, 0.21, 1.01, 4.76

### Metam Sodium Doses Tested to Find Chronic Exposure Hazards

Toxicity Test	Doses Administered (mg/kg/day)
Carcinogenicity Study (rats, drinking water, 104 weeks)	0, 1.3, 3.9, 12
Carcinogenicity Study (mice, drinking water, 104 weeks)	0, 1.6, 6.5, 27.7

### Acute Toxicity Dose-Response

Toxicological Endpoint	Metam Sodium (mg/kg)	MITC (mg/kg)
Acute oral LD50	780	55
Acute dermal LD50	2020	136
Acute Inhalational LD50	2.27 mg/L	0.54 mg/L
Eye Irritation	Slight	Corrosive
Skin Irritation	None	Lethal
Acute Neurotoxicity	LOAEL = 22 NOAEL < 22	--

### Dose-Response Endpoints for Inhalational Risk Characterization (MITC)

Toxicological Endpoint	LOAEL (mg/kg/d)	NOAEL (mg/kg/d)
Subchronic Inhalational (28 day; 6 hr/day; 5 days/week; rats)	19.9 mg/m <sup>3</sup>	5 mg/m <sup>3</sup>
Subchronic Inhalational (90 day; 6 hr/day; 5 days/week; rats)	30.7 mg/m <sup>3</sup>	3.2 mg/m <sup>3</sup>

### Dose-Response Endpoints for Subchronic Risk Characterization (MITC)

Toxicological Endpoint	LOAEL (mg/kg/d)	NOAEL (mg/kg/d)
Subchronic Systemic (90 day; dog; oral capsule exposure)	0.56	<0.56
Subchronic dermal (28 day; rat)	10	1
Prenatal Developmental (11 day; pregnant rat; oral gavage)	11.2	2.8
Reproduction/Fertility (2 generations; water)	>3.4	3.4

### Dose-Response Endpoints for Carcinogenic Risk Characterization (MITC)

Toxicity Test	LOAEL (mg/kg/d)	NOAEL (mg/kg/d)
Carcinogenicity Study (rats, drinking water, 104 weeks)	>12 (No increase in tumors)	12
Carcinogenicity Study (mice, drinking water, 104 weeks)	1.6 (Increased angiosarcomas in males)	<1.6

### EPA's Perspective on Carcinogenic Risk of MITC

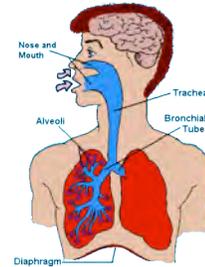
- Despite the negative rat study, the increased incidence of angiosarcoma tumors in the liver of male mice at all doses (but only in females at the highest dose!), EPA classified MITC (actually Metam sodium) as a B2 carcinogen (probable human carcinogen)
  - Pertinently, nearly all tests for mutagenicity were negative (for both MITC and Metam sodium)

## A Human Study with MITC

Toxicological Endpoint	NOAEL (mg/m <sup>3</sup> )
Odor Threshold	5
Eye Irritation	1.764
Eye Blink Rate	0.647

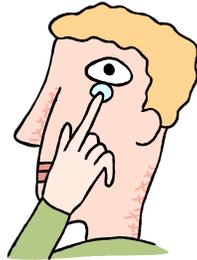
## Exposure Assessment

- EPA says "The primary route of human exposure to MITC is through inhalation in ambient air"
- Metam sodium & MITC have no food tolerances
  - Residues are not expected in food (nor in drinking water)



## Air Residues--Monitored

- Studies in California have measured µg/m<sup>3</sup> levels of MITC
- Recall that 0.647 mg/m<sup>3</sup> was the level for no increase in eye blink rate following human exposure
  - Not considered a toxic effect
  - Rather it's a "biomarker" of exposure



## Risk Characterization for MITC

- Rather than use the traditional Reference Dose (RfD) approach, wherein the animal NOAEL is divided by a safety factor of 100 - 1000,
- EPA invented the Human Equivalent Concentration (HEC) for MITC
  - Animal inhalational NOAELs are mathematically manipulated to account for human exposure factors and pharmacokinetics
    - The safety factor is reduced to 30 (short, intermediate, and long term inhalational exposures for post application volatilized residues)
  - EPA also relied on the human "eye blink" study and thus justified reducing the HEC safety factor to 10 for acute exposures 24 h; (i.e., during application nearby a field)

## Risk Characterization for Metam Sodium

- However, larger safety factors were used for **dermal** occupational short and intermediate term exposure to metam sodium
  - (100 x) applied to rodent NOAEL from dermal tox study
  - (1000 x) applied to LOAEL if no NOAEL
- Similarly, for **inhalational** occupational exposure to metam sodium, a 100 x safety factor was applied to the rodent NOAELs

## Risk Characterization For Bystanders & Workers

- Risk is characterized by determining how large the exposure is relative to the NOAEL
- EPA will conclude that the exposure is safe if the estimated exposure is 100 - 1000 times less than the NOAEL
  - This level of exposure is called the MOE (Margin of Exposure)
- In other words...

$$\text{MOE} = \frac{\text{NOAEL (mg/kg/day)}}{\text{Exposure (mg/kg/day)}}$$

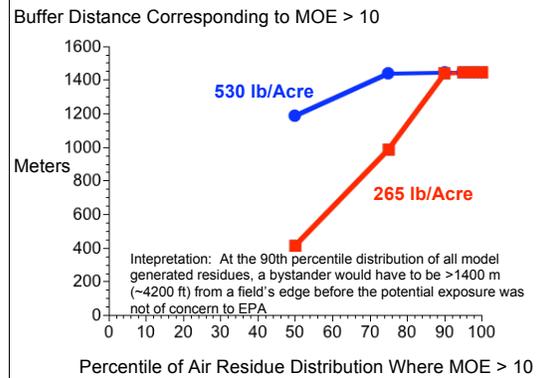
**A-OK if > 100 or 1000**

## How Risky Is an Acute (24 h) Exposure to Bystanders

- EPA used a model (PERFUM; Probabilistic Exposure & Risk Model for Fumigants) to estimate residues in air from a point source field of several sizes and with various meteorological conditions
- The “riskiness” was expressed as a buffer zone wherein the distance downwind represents the point where the exposure would not exceed the Human Equivalent Concentration (HEC), representing the NOAEL from the “blink rate study” and a safety factor of 10X

- In other words, if the MOE > 10, than exposure is A-OK

## One Risk Characterization Scenario Based on PERFUM



## How Risky is Metam Sodium to Workers

- According to EPA's calculations, it is “very risky”
  - I.e., the estimated exposure exceeds the Level of Concern for just about any work scenario
  - The reason is that EPA decided to use animal test data and apply safety factors of at least a 100 and above

## The Guantlet Is Thrown Down

- The manufacturers of metam sodium products (the Metam Sodium Alliance) have paid for their own risk assessment using a private contractor
- Their RA used a different exposure assessment model, i.e., FEMS (Fumigant Exposure Modeling System)
  - Needless to say, their viewpoint is that metam sodium is far less risky than EPA's perspective



## What We Know Now

- EPA has issued a revised Human Health RED Chapter at the end of 2005
- The comment period is over, and the final RED probably will not change much
- However, in the last phase of the RED, EPA defines the risk mitigation
- I suspect a lot of public pressure in California will mandate some label changes such as application methods, weather conditions, or notification buffer zones
- But, should the California data be applicable to us in the PNW???
- I suggest we do our own monitoring and find out!!

## For More Information

- <http://feql.wsu.edu>
  - Food and Environmental Quality Lab
- <http://wsprs.wsu.edu>
  - Washington State Pest Management Resource Center
- <http://aenews.wsu.edu>
  - Agrichemical & Environmental News
- [afelsot@tricity.wsu.edu](mailto:afelsot@tricity.wsu.edu)

