Acute Toxicity of Pesticides: An Overview

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Objectives

- To appreciate the complexity of monitoring, managing, preventing acute pesticide exposures
- To briefly focus on specific pesticide classifications of concern for acute exposures

Poison Control Center Statistics

- 2.4 million human exposures reported in 2002
  - 92.3% residential exposures
  - 2.2% of exposures in a workplace
  - 51.6% of cases involved children < 6 years of age
  - 96,112 human exposures to pesticides
    - ~ 4% of total exposures reported to poison centers
      - Most frequently implicated pesticides…

TABLE 17A. Substances Most Frequently Involved in Human Exposures

Substance	No.	%*
Analgesics	256,843	10.8
Cleaning substances	225,578	9.5
Cosmetics and personal care products	219,877	9.2
Foreign bodies	119,323	5.0
Sedatives/hypnotics/antipsychotics	111,001	4.7
Topicals	105,815	4.4
Cough and cold preparations	100,612	4.2
Antidepressants	99,960	4.2
Bites/envenomations	98,585	4.1
Pesticides	96,112	4.0
Plants	84,578	3.6
Food products, food poisoning	75,813	3.2
Alcohols	69,215	2.9
Antihistamines	69,107	2.9
Antimicrobials	63,372	2.7
Cardiovascular drugs	61,056	2.6
Hydrocarbons	59,132	2.5
Chemicals	54,623	2.3

NOTE: Despite a high frequency of involvement, these substances are not necessarily the most toxic, but rather may only be the most readily accessible.

*Percentages are based on the total number of human exposures (2,380,028) rather than the total number of substances.

Watson WA et al., (2003): 2002 Report of the AAPCC, TESS
Am J Emerg Med 21(5)

TABLE 18. Categories with Largest Numbers of Deaths

Category	No.	% of All Exposures in Category
Analgesics	659	.257
Sedative/hypnotics/psychotics	364	.328
Antidepressants	318	.318
Stimulants and street drugs	242	.528
Cardiovascular drugs	181	.296
Alcohols	139	.200
Chemicals	50	.091
Anticonvulsants	65	.181
Gases and fumes	44	.106
Antihistamines	71	.103
Muscle relaxants	52	.260
Hormones and hormone antagonists	33	.062
Cleaning substances	33	.013
Automotive products	30	.213
Cough and cold preparations	22	.022
Pesticides	18	.019

NOTE: Tables 18, 22A and 22B are based on an unlimited number of substances coded per exposure, while Table 21 only includes up to 3 substances per case.

Pesticides implicated in fatal cases (2002):
Sulfuryl fluoride
Paraquat
Strychnine
Brodifacoum
Dinitrophenol(?)
OP's

Strengths, Limitations of Poison Center Data: Acute Pesticide Exposures

- Strengths
  - Number of cases
  - Ease of access
    - 24 hour/day service
    - Toll-free access in U.S.
  - Consistency of reporting mechanism
  - Current initiatives in toxicosurveillance
    - Electronic reporting of acute pesticide exposures from PCC's to State Health Depts.
    - Real-time data uploading and analysis by CDC
      - Temporal, spatial trends
- Limitations
  - May not be capturing occupational exposures
    - High-risk population
  - Limited specificity of reporting
    - Identity of active ingredient
    - EPA Reg. #
    - Details on circumstances surrounding exposure
      - Important for unintentional exposures

BZ Horowitz, S Griffin, CL Thomsen (2002): Pesticide-Related Illnesses: Are Poison Centers Reporting to the State Health Department? *Vet Hum Toxicol*; 44(1):49-51.

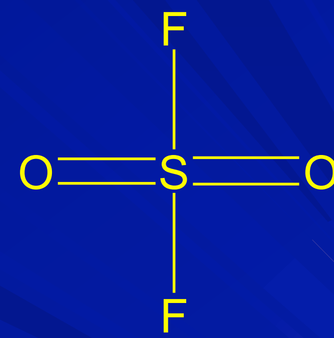
Table 1. Oregon PC Pesticide - Related Calls 1994 - 1998

	1994	1995	1996	1997	1998	Total
Arsenates	13	9	9	9	6	46
Organophosphate	215	183	152	151	168	869
OP + carbamate	10	18	7	18	14	67
OP + chlorinated HC	2	1	2	2	1	8
OP + other substance	9	17	11	15	12	64
OP + carbamate + chlorinated HC	2	0	1	0	0	3
Carbamate	49	42	32	44	33	200
Carbamate + other	11	4	5	5	7	32
Chlorinated HC	45	47	63	75	39	269
Chlorinated HC + other	2	3	4	2	0	11
Borates	69	69	35	50	67	290
Piperonyl butoxide + pyrethrins	82	106	64	84	94	430
Pyrethrins	64	100	64	92	82	402
Rotenone	3	2	1	2	2	10
Metaldehyde	20	18	31	25	42	136
Piperonyl Butoxide	1	3	3	1	2	10
Nicotine	0	1	1	0	0	2
Misc repellents	68	126	67	71	48	380
Other Insecticides	24	17	20	26	25	112
Veterinary insecticide	61	54	41	50	47	253
Unknown	58	56	40	54	60	268
Total Carbamates	65	51	44	50	41	251
Total Organophosphates	238	219	173	186	195	1011
Total OP + carbamates	303	270	217	236	236	1262
Total Insecticides	808	876	653	776	749	3862
Carbamate	5	5	7	1	1	19
Mercurial	0	0	0	0	0	0
Non-mercurial	9	8	8	4	5	34
Unknown	19	13	19	8	13	72
Phthalimide	6	4	2	2	2	16
Total Fungicides	39	30	36	15	21	141
Strychnine	7	5	1	8	5	26
Short-acting anticoagulant	5	5	6	7	7	30
Long-acting anticoagulant	193	130	74	90	119	606
Others	12	8	12	8	7	47
Total Rodenticides	217	148	93	113	138	709
2,4-D or 2,4,5-T	99	112	85	82	112	490
Paraquat	2	2	4	3	6	17
Diquat	2	4	1	2	4	13
Others	113	144	108	138	93	596
Total Herbicides	216	262	198	225	215	1116
Total Pesticides	1280	1316	980	1129	1123	5828

- Over 5-year period, Oregon Poison Center receives ~1,000 calls/year for acute pesticide exposures
- Insecticides most frequently implicated
  - OP's, OP/carbamates, pyrethrin, pyrethroids
- % of OPC cases reported to State Health Department….?

Pesticides of Relevance to Acute Toxicity: Fumigants

- Active ingredient exists as a gas
  - Relevant to inhalation pathways of exposure
- Diverse chemical structures
- Utilized to control pests in enclosed spaces, soil, and structures
- Many are restricted use
- Modern epidemiological data suggest fewer exposure cases than other pesticide classes
- Higher case-severity and case-fatality rate than fungicides
  - Many exposures are accidental
    - Applicators, workers, non-occupational (residential)
- Scenarios of concern: Inadequate ventilation of a treated structure, unanticipated cross-ventilation from a treated structure



Fumigants: Toxicology of Acute Overexposure (Methyl Bromide)

- Highly lipid soluble
  - Well-absorbed via inhalation pathways
- Wide volume of distribution
  - CNS, liver, kidneys are target organs
- Me-Br is strong alkylating agent
  - Cell membrane disruption
  - Inhibition of critical enzyme function
- Metabolism of MeBr occurs rapidly
- Parent compound (MeBr) not usually detectable in tissues
- Management of overexposure is supportive
  - No antidotes are available

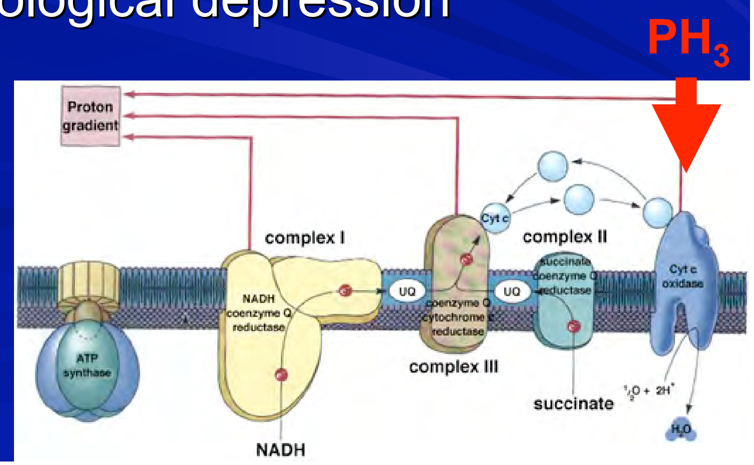
$Br—CH_3$

Fumigants: Toxicology of Acute Overexposure (Phosphides)

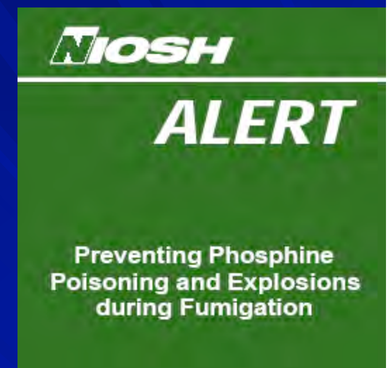
- Decomposition products of phosphide fumigants include phosphine gas, phosphoric acid
- Phosphine inhibits electron transport chain
  - Mechanism similar to cyanide
    - Unlike cyanide, there are no specific antidotes for phosphine gas
    - Reliable biomarkers of exposure are not readily available
- Acute inhalation overexposure
  - Pulmonary injury, cardiogenic shock, neurological depression

$$Al \equiv P \xrightarrow{\text{water, acid}} PH_3$$

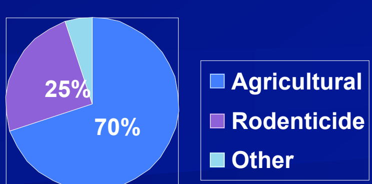
aluminum phosphide → phosphine

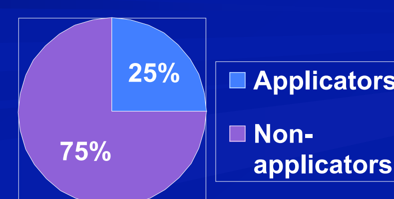


NIOSH Alert: Preventing Phosphine Poisoning and Explosions



- http://www.cdc.gov/niosh/99-126.html
- A review of 205 occupational exposure cases
- Common accidental exposure scenarios
  - Lack of proper handling during fumigant application
  - Failure to monitor air concentrations during application
  - Failure to use appropriate respiratory equipment
  - Improper disposal of unused fumigant products
  - Incidental exposure from nearby fumigant application
- Majority of exposures associated with agricultural applications
- Most symptomatic exposures occurred among non-applicators
  - Workers in proximity to or entering recently treated areas





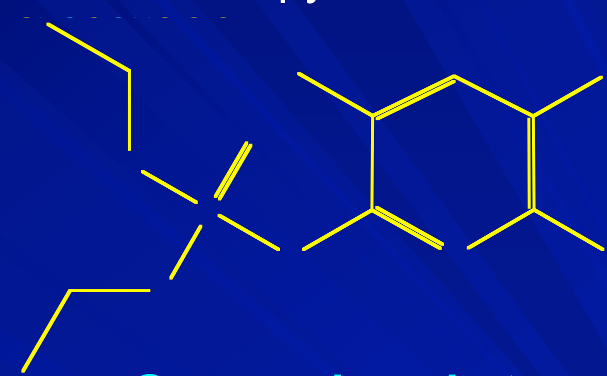
Fumigants and Acute Toxicity

- Inhalation pathways of exposure
- Broad, non-selective mechanisms of toxicity
- Relevance of major morbidity, mortality from accidental exposures
  - Applicators and non-applicators (bystanders)
- In most cases, biomarkers are of limited or no utility
- Specific therapies after overexposure are not available
- **Need for vigilance in prevention**
  - Education, training, engineering controls, and appropriate use of PPE

Insecticides and Acute Toxicity

- Insecticides with a common mechanism of toxicity
  - Inhibitors of acetylcholinesterase
    - Vary in chemical properties, dermal absorption, potency
  - Acute overexposure results in cholinergic signs, symptoms
    - Excess acetylcholine at muscarinic, nicotinic receptors
      - Muscarinic SLUDGE toxidrome: **S**alivation, **L**acrimation, **U**rinary incontinence, **D**iarrhea, **GI** symptoms, **E**yes (miosis)
      - Nicotinic signs
        - Fasiculations, weakness, acute paralysis (in worst-case scenario)

Chlorpyrifos



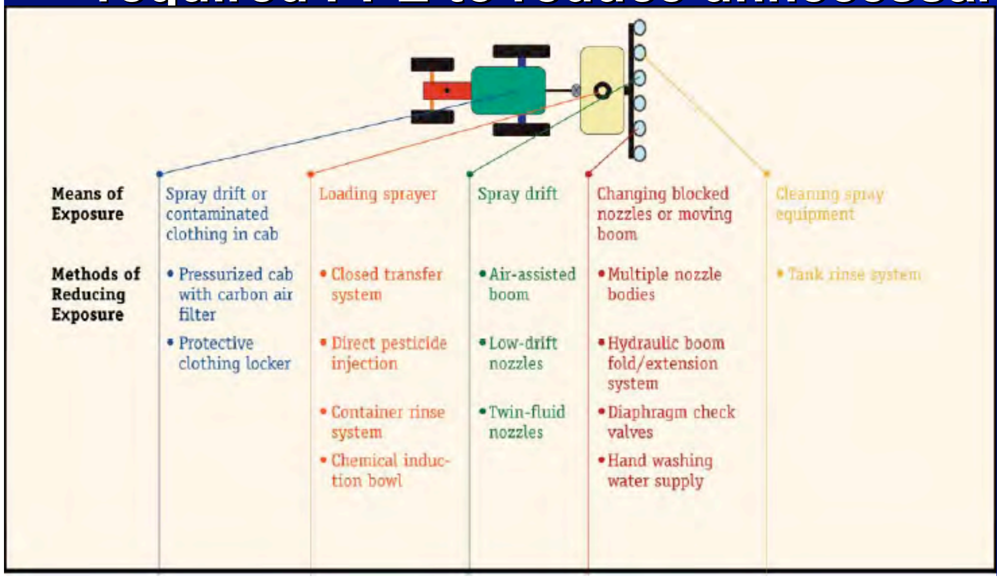
Organophosphate

Carbaryl

N-methyl carbamate

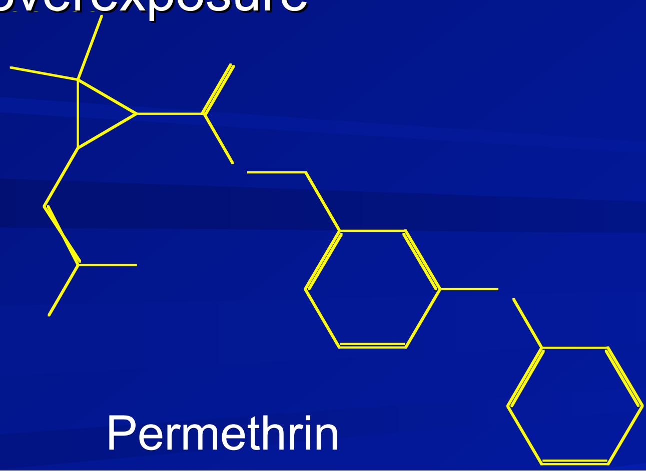
Cholinesterase Inhibitors and Acute Toxicity: Measuring Exposure

- Blood (serum and RBC) monitoring
  - Cholinesterase enzyme activity as a biomarker of effect for OP's, carbamates
- Difficulties, and challenges in cholinesterase monitoring as biomarker
  - Reliability (inter-laboratory)
  - Variation in normal reference ranges
  - Rapid recovery in cholinesterase activity after overexposure to N-methyl carbamates
- **Importance of education, engineering controls, appropriate use of required PPE to reduce unnecessary exposure**

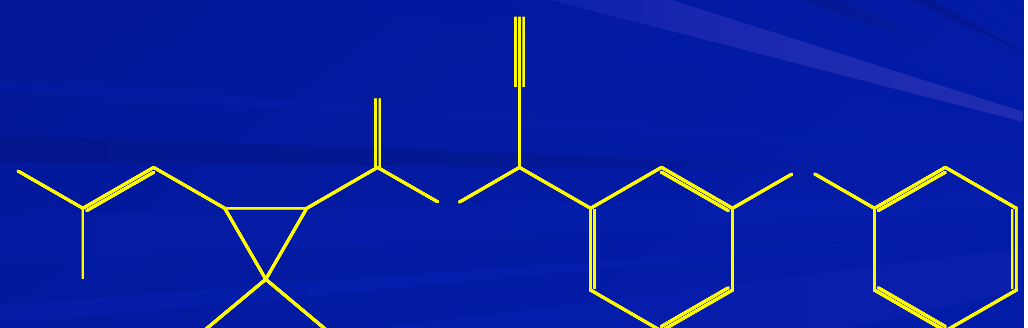


Other Insecticides: Pyrethroids and Acute Toxicity

- Commonly utilized in agriculture, residential settings, public health (vector control)
- Mechanism of toxicity
  - Prolong deactivation of sodium channels, excitation of nerve fibers
- Systemic intoxication is rare
- Local effects from dermal overexposure to concentrated formulations
  - Transient paresthesias (12-24 hours)
  - Usually occur in absence of any signs of skin injury
- Irritant effects (eye, throat, respiratory irritation) from inhalation overexposure



Permethrin



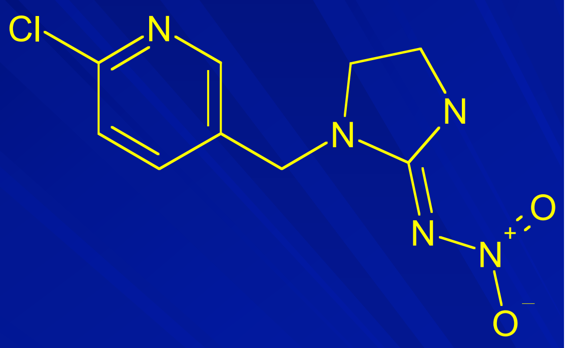
Cypermethrin

Insecticides and Acute Toxicity: Misapplication

- Content of 19 “bug-bombs” released within a 470 sq. foot residence
  - Product label indicated use application for 700 square feet
  - Pilot light ignited the gas that had accumulated, resulting in explosion
- The Label is the Law

Newer Insecticides

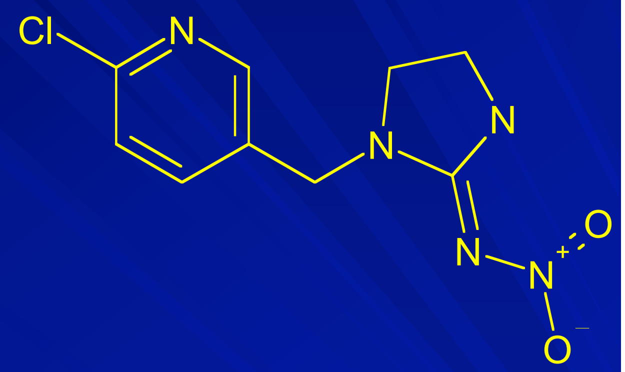
- Imidacloprid
  - Neonicotinoid family of insecticides
  - Selective for the nicotinic acetylcholine receptor of the insect
    - Targets the insect nervous system
  - Poor penetration across blood-brain barrier in mammals
  - Registered applications in agriculture, structural pest control, pet care (topical solution)
  - Experience with human overexposure is very limited



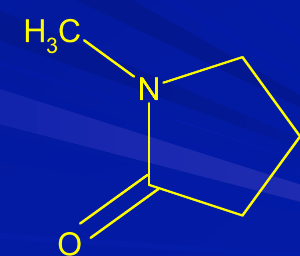
imidacloprid

Newer Insecticides

- A case of intentional (ingestion) poisoning (Wu, 2001)
- Farmer ingested 100 mL of insecticide formulation
  - 9.7% imidacloprid
  - <2 % surfactant
  - Remainder: N-methyl pyrrolidone
- Clinical course: initial drowsiness, dizziness, abdominal pain, vomiting
- GI endoscopy revealed corrosive injury
  - Mainly upper GI tract
- Individual recovered, discharged at 4 days post-ingestion



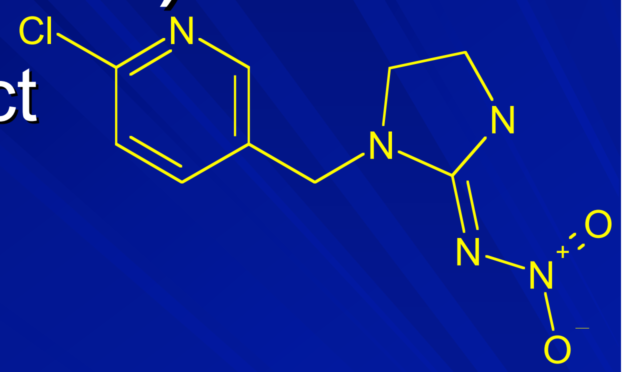
imidacloprid



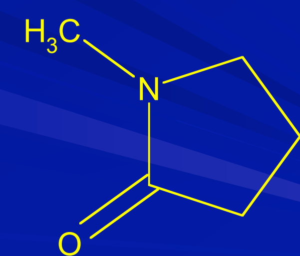
N-methylpyrolidone

A Case of Intentional Insecticide Poisoning (Continued)

- Were most significant effects (GI tract injury) caused by imidacloprid or N-methylpyrolidone?
  - Authors suggest N-methylpyrolidone as more likely explanatory factor
    - dermal, ocular effects from occupational exposures in humans
    - Low potency of imidacloprid as skin, eye irritant in animal studies
- Health care providers need to consider the entire formulation when assessing risks after acute overexposure



imidacloprid



N-methylpyrolidone

Pesticides and Acute Toxicity: Medical Case Profiles at NPIC

- Intended to educate health care providers
  - Importance of exposure history
  - Understanding prevention
    - Engineering controls, PPE, decontamination
  - Clinical assessment
    - Biomarkers of exposure
  - Role of public health surveillance, other State Agencies
- Examples:
  - Pyrethroids and paresthesias
  - Inhalation risks of phosphide fumigants
  - Pesticide incident reporting

npic
NATIONAL PESTICIDE INFORMATION CENTER

Biomarkers of Exposure: Organophosphates

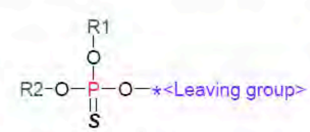
(Medical Case Profile)

Scenario:

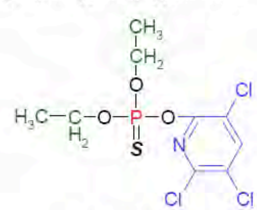
A healthy adult female visits her physician for an annual examination. She has heard reports on television about recent studies that have measured pesticide residues in urine samples taken from the United States population. She would like to know more about testing for exposure to organophosphates, as she has used insecticides containing these active ingredients in the past at her residence. She is seeking information from the physician about testing for exposure to this group of insecticides, and how to interpret the results.

Biomarkers of exposure are important in toxicology, because they are an indicator of internal dose, or the amount of chemical exposure that has resulted in absorption into the body. Significant advances have been made in the development of analytical methods which can detect and/or quantify the presence of many natural or synthetic toxins or their breakdown products (metabolites) in a biological matrix (such as blood or urine). The ability to accurately measure biomarkers of exposure depends upon an adequate understanding of the chemistry and toxicology of the substance under consideration.

Organophosphate insecticides share a common mechanism of toxicity, through inhibitory effects on cholinesterase enzymes in the nervous system.[1] In addition, all organophosphates share some common chemical properties. Organophosphates contain a central phosphorus atom with a double bond to either **sulfur** or **oxygen,** R1 and R2 groups that are either ethyl or methyl in structure, and a leaving group which is specific to the individual organophosphate. The general structure of organophosphates, and a specific example (chlorpyrifos) appear below:



organophosphate (general structure)



chlorpyrifos

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