Acute Toxicity of Pesticides: An Overview

Daniel L. Sudakin, M.D., M.P.H.
Assistant Professor, Department of Environmental and Molecular Toxicology
Oregon State University
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**

<table>
<thead>
<tr>
<th>Substance</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics</td>
<td>256,843</td>
<td>10.8</td>
</tr>
<tr>
<td>Cleaning substances</td>
<td>225,578</td>
<td>9.5</td>
</tr>
<tr>
<td>Cosmetics and personal care products</td>
<td>219,877</td>
<td>9.2</td>
</tr>
<tr>
<td>Foreign bodies</td>
<td>119,323</td>
<td>5.0</td>
</tr>
<tr>
<td>Sedatives/hypnotics/antipsychotics</td>
<td>111,001</td>
<td>4.7</td>
</tr>
<tr>
<td>Topicals</td>
<td>105,815</td>
<td>4.4</td>
</tr>
<tr>
<td>Cough and cold preparations</td>
<td>100,612</td>
<td>4.2</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>96,860</td>
<td>4.2</td>
</tr>
<tr>
<td>Bites/envenomations</td>
<td>98,585</td>
<td>4.1</td>
</tr>
<tr>
<td>Pesticides</td>
<td>96,112</td>
<td>4.0</td>
</tr>
<tr>
<td>Plants</td>
<td>84,578</td>
<td>3.6</td>
</tr>
<tr>
<td>Food products, food poisoning</td>
<td>75,812</td>
<td>3.2</td>
</tr>
<tr>
<td>Alcohols</td>
<td>69,215</td>
<td>2.9</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>69,107</td>
<td>2.9</td>
</tr>
<tr>
<td>Antimicrobials</td>
<td>63,372</td>
<td>2.7</td>
</tr>
<tr>
<td>Cardiovascular drugs</td>
<td>61,056</td>
<td>2.6</td>
</tr>
<tr>
<td>Hydrocarbons</td>
<td>59,132</td>
<td>2.5</td>
</tr>
<tr>
<td>Chemicals</td>
<td>54,623</td>
<td>2.3</td>
</tr>
</tbody>
</table>

**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.*
TABLE 18: Categories with Largest Numbers of Deaths

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

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
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

\[
\text{Br} \quad \text{CH}_3
\]
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

\[ \text{AlP} + \text{water, acid} \rightarrow \text{PH}_3 \]

aluminum phosphide    phosphine
NIOSH Alert: Preventing Phosphine Poisoning and Explosions


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: Salivation, Lacrimation, Urinary incontinence, Diarrhea, GI symptoms, Eyes (miosis)
    - Nicotinic signs
      - Fasiculations, weakness, acute paralysis (in worst-case scenario)
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
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
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
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

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. 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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Daniel L. Sudakin, M.D., M.P.H.
Assistant Professor
Department of Environmental and Molecular Toxicology
Oregon State University
sudakind@ace.orst.edu
NPIC: http://www.npic.orst.edu/