The Toxicology and Regulation of Chlorphenapryl, Fipronil, Imidacloprid, and Thiamethoxam

Bob Krieger
Personal Chemical Exposure Program
Helen Vega, Administrative Assistant
Today’s Menu

• Chemicals and Public Perceptions
• General Pesticide Science
• Advanced Pesticide Science
• Health Records
• Regulate: Margin-of-Exposure
• Safe Pesticide Use

Sign-up Envelope: Quiz will be on internet Monday a.m. 4-digit Number on Zip-Scan, 35 questions/pencil; postmark on or before 4/6/06. $40 Lottery from all completed returns (Survey & Z-Scan)
Chemicals *are* our everywhere. ...the environment!
Chemicals are our everywhere....the environment

- Food (residues)
- Water (contaminants)
- Air (pollutants)
- Home (residues)
Individual Views of Chemical Exposures

“How little is OK?”  “How much is too much?”

“Dose makes the poison”  “All-or-none”

Amount

Safe levels of everything  Small exposures--certain harm

Laboratory Studies

Response

Awareness of limitations of testing in animals  Little confidence in relevance of testing
Active Ingredients vs Products
Primary Flavor Constituents (>2 FU)

All Beers
- Ethanol
- Hop bittering compounds
- Carbon dioxide

Specialty Beers
- Hop aroma compounds
- Caramel and roasted flavor compounds
- Esters and alcohols (high gravity beers)
- Short-chain acids

Defective Beers
- 2-trans-Nonenal (oxidation)
- Vicinal diketones (diacetyl)
- Sulfur compounds (H₂S, DMS)
- Acetic acid (contamination)
- 3-Methyl-2-butene-1-thiol (lightstruck)
- Others (contamination)
Specialty Beers

• “No Alcohol” beers contain 0.3-0.7% EtOH
• Cobalt head stabilizer killed alcoholics in U.S. and Canada in 1960s (heart; 40-140 ug/kg-day)
• *NicoShot* beer (Germany) contains 6.3% ethanol and 3 mg nicotine/250 ml “shot” can—3 cans (≈1 pack cigarettes) will make you illegal behind the wheel in all 50 states!
Primary Flavor Constituents (>2 FU)

All Beers
- Ethanol
- Hop bittering compounds
- Carbon dioxide

Specialty Beers
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- 2-trans-nonenal (oxidation)
- Vicinal diketones (diacetyl)
- Sulfur compounds (H2S, DMS)
- Acetic acid (contamination)
- 3-Methyl-2-butene-1-thiol (lightstruck)
- Others (contamination)

Secondary Flavor Constituents (0.5-2 FU)

Volatile
- Banana esters (e.g., isoamyl acetate)
- Apple esters (e.g., ethyl hexanoate)
- Fusel alcohols (e.g., isoamyl alcohol)
- C6, C8, C10 aliphatic acids
- Ethyl acetate
- Butyric and isovaleric acids
- Phenylacetic acid

Nonvolatile
- Polyphenols
- Various acids, sugars, and hop compounds

Tertiary Flavor Constituents (0.1-0.5 FU)

- 2-Penethyl acetate, o-amino acetophenone
- Isovaleraldehyde, methional, acetoin
- 4-Ethylguaiaicol, g-valerolactone

Background Flavor Constituents (<0.1 FU)
- Remaining chemicals of more than 1,000
The Beer Flavor Wheel

Meilgaard, 1970
BEER
Properties

• Appearance: tan, brown, amber, light yellow, light tan

• Water solubility: low (relative to salt)

• Vapor pressure: low \(10^{-7} \text{ to } 10^{-12} \text{ mm Hg}\)

• Odor: mild
Pesticides Are Chemical Mixtures

- Formulation: Solid, Liquid, Gas
- Active ingredient
- Inert (preferably “Other”) ingredients
  - Solubility
  - Acid/Base
  - Chemical stability
  - Spreaders
  - Stickers

a Almost everything is!
Formulations: Use specific

- Inert ingredients
- Or
- Other ingredients

Propylene glycol
Diatomaceous earth
Crystalline silica (quartz)
Starch
etc, etc, etc
Ingredient 1611
“Trade secret”
Adverse Effects: Toxicity

- Dosage (mg chemical/kg bw)
- Time
- ↑↓ Natural organic processes
- “There is a safe level of everything.”
Minimize Your Exposures

• Labeled or not!
• Use best judgment
• Share experience!

Recommendations
• respirator/dust
• eye protection
• WPS + gloves
• ventilation
2006 Advanced Pesticide Science

√ Chlorfenapryl
>
Fipronil
>
Imidaclorpid
>
Thiamethoxam
<table>
<thead>
<tr>
<th>Pesticides</th>
<th>C</th>
<th>H</th>
<th>F</th>
<th>Cl</th>
<th>Br</th>
<th>N</th>
<th>O</th>
<th>P</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorfenapyrl</td>
<td>15</td>
<td>11</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fipronil</td>
<td>12</td>
<td>4</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Imidacloprid</td>
<td>9</td>
<td>10</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thiamethoxam</td>
<td>8</td>
<td>11</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>1</td>
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</tbody>
</table>
Receptors and Responses

Differential receptors

Single-analyte pattern

Readout
Toxicity: Adverse Effects

LD50
ED50
LOAEL

NOAEL

Reference Dose
6-Pack Toxicology

Pesticides
- Chlorfenapryl
- Fipronil
- Imidacloprid
- Thiamethoxam

DANGER
Warning
Caution
**Toxicology**

### Chlorfenapyr

![Chemical structure of Chlorfenapyr]

**Appearance:** Tan liquid

**Volatile:** low (10⁻⁷ mm)

**Odor:** mild “sweet”

**Phantom® termiticide insecticide**

### Pyrrole  mw 408

**Appearance:** Tan liquid

**Volatile:** low (10⁻⁷ mm)

**Odor:** mild “sweet”

**Phantom® termiticide insecticide**

**Persistence & Availability**

**Signal word:** DANGER

*Metabolic activation*
<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Rat oral LD50</td>
<td>560-7 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$I_{w}$</td>
</tr>
<tr>
<td>2.</td>
<td>Mouse, oral LD50</td>
<td>45 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$I_{D}$</td>
</tr>
<tr>
<td>3.</td>
<td>Rat, skin LD50</td>
<td>more than 2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$I_{l}$</td>
</tr>
<tr>
<td>4.</td>
<td>Rat, inhalation LC50</td>
<td>0.6 mg/l</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$I_{l}$</td>
</tr>
<tr>
<td>5.</td>
<td>Rabbit, eye irritation</td>
<td>slight</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$I_{l}$</td>
</tr>
<tr>
<td>6.</td>
<td>Rabbit, skin irritation</td>
<td>slight</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV</td>
</tr>
<tr>
<td>7.</td>
<td>Guinea pig, no skin sensitization</td>
<td></td>
</tr>
</tbody>
</table>
Energetics: ATP

Energy $\rightarrow$ Life

ATP

Food + O$_2$
Neurotoxicity

What?
Toxicology

Thiamethoxam

Synonyms

05598 (CA DPR Chem Code), 060109 (US EPA PC Code), 153719-23-4 (CAS Number), 153719234, 153719234 (CAS Number), 4H-1,3,5-Oxadiazin-4-imine, 3-(2-chloro-5-thiazolyl)methyltetrahydro-5-methyl-N-nitro-, 4H-1,3,5-Oxadiazin-4-imine, 3-δ(2-chloro-5-thiazolyl)methyl, 4H-1,3,5-Oxadiazin-4-imine, 3-([2-chloro-5-thiazolyl)methyl]tetrahydro-5-methyl-N-nitro-, 5598 (CA DPR Chem Code), hiamethoxam, Thiamethoxam, Thiamethoxam (ISO proposed common name), Thiametoxam, Tiametoxam, 05598 (CA DPR Chem Code), 060109 (US EPA PC Code), 153719-23-4 (CAS Number), 153719234, 153719234 (CAS Number), 4H-1,3,5-Oxadiazin-4-imine, 3-(2-chloro-5-thiazolyl)methyltetrahydro-5-methyl-N-nitro-, 4H-1,3,5-Oxadiazin-4-imine, 3-δ(2-chloro-5-thiazolyl)methyl, 4H-1,3,5-Oxadiazin-4-imine, 3-([2-chloro-5-thiazolyl)methyl]tetrahydro-5-methyl-N-nitro-, 5598 (CA DPR Chem Code), hiamethoxam, Thiamethoxam, Thiamethoxam (ISO proposed common name), Thiametoxam, Tiametoxam
Toxicology

Fipronil

NOAEL: short term
skin 5 mg/kg
absorption 1%
 ingest 0.05 mg/kg

↓ weight gain
↓ food consumption

Neurotoxicity
Imidacloprid

NOAEL: chronic
2-year dietary
5.7 ♀ 7.6 ♂ mg/kg-d
↓ weight gain

Subchronic (6-16 d)
8 mg/kg
reproductive (↓ pup wgt)
24 mg/kg
developmental (skeletal abs)
Toxicology

Neurotoxin: Nicotinic Receptor block  
↑ Acetylcholine

Signs & Symptoms

• Fatigue
• Twitching
• Cramps
• Muscle weakness
• Difficult breathing
Safety and Evaluation — Consider Pesticide Effectiveness

Best Guess
Misuse can result in illnesses and deaths.

Check the records…
Health Impact Records

- Occupational: Numbers & Rates
- Causes including poisoning
- California Illnesses and Injuries
- Poison Control Centers
Table 1. Unintentional Injuries at Work by Industry in the U.S.

<table>
<thead>
<tr>
<th>Injury Division</th>
<th>Workers x 10^3</th>
<th>Deaths 2003</th>
<th>Deaths per 10^5 Workers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agriculture</td>
<td>3,340</td>
<td>710</td>
<td>20.9</td>
</tr>
<tr>
<td>Mining</td>
<td>539</td>
<td>120</td>
<td>22.3</td>
</tr>
<tr>
<td>Construction</td>
<td>9,268</td>
<td>1,060</td>
<td>11.4</td>
</tr>
<tr>
<td>Manufacturing</td>
<td>17,708</td>
<td>490</td>
<td>2.8</td>
</tr>
<tr>
<td>All industries</td>
<td>138,988</td>
<td>4,500</td>
<td>3.2</td>
</tr>
</tbody>
</table>

National Safety Council, 2004
The four most frequent work-related fatal events, 1992-2004

Number of fatalities

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,158</td>
<td>1,242</td>
<td>1,343</td>
<td>1,346</td>
<td>1,346</td>
<td>1,393</td>
<td>1,442</td>
<td>1,496</td>
<td>1,409</td>
<td>1,365</td>
<td>1,373</td>
<td>1,353</td>
<td>1,374</td>
</tr>
<tr>
<td></td>
<td>1,044</td>
<td>1,074</td>
<td>1,080</td>
<td>1,036</td>
<td>937</td>
<td>860</td>
<td>714</td>
<td>721</td>
<td>734</td>
<td>810</td>
<td>819</td>
<td>816</td>
<td>815</td>
</tr>
</tbody>
</table>

- Highway incidents
- Homicides
- Falls
- Struck by object

NOTE: Data from 2001 exclude fatalities resulting from the September 11 terrorist attacks.

Table 2. Leading Causes of Death in the U.S.: Unintentional Injuries Including Poisoning

<table>
<thead>
<tr>
<th>Cause</th>
<th>Number</th>
<th>Deaths per 10^5 Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>All unintentional injuries</td>
<td>101,537</td>
<td>35.6</td>
</tr>
<tr>
<td>Motor-vehicle</td>
<td>43,788</td>
<td>15.4</td>
</tr>
<tr>
<td>Falls</td>
<td>15,019</td>
<td>5.3</td>
</tr>
<tr>
<td>Poisoning</td>
<td>14,078</td>
<td>4.9</td>
</tr>
<tr>
<td>Pesticide</td>
<td>7</td>
<td>0.0025</td>
</tr>
<tr>
<td>Choking</td>
<td>4,185</td>
<td>1.5</td>
</tr>
<tr>
<td>Drowning</td>
<td>3,281</td>
<td>1.2</td>
</tr>
<tr>
<td>All other</td>
<td>21,186</td>
<td>7.4</td>
</tr>
</tbody>
</table>

National Safety Council, 2004
Table 3. 5-Year Summary of California Pesticide Illness and Injury

<table>
<thead>
<tr>
<th>Year</th>
<th>Total cases</th>
<th>Relationship of Illness or Injury to Pesticide Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Definitely or Probably</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cases</td>
</tr>
<tr>
<td>1999</td>
<td>1,629</td>
<td>830</td>
</tr>
<tr>
<td>2000</td>
<td>1,144</td>
<td>637</td>
</tr>
<tr>
<td>2001</td>
<td>979</td>
<td>430</td>
</tr>
<tr>
<td>2002</td>
<td>1,859</td>
<td>924</td>
</tr>
<tr>
<td>2003</td>
<td>1,232</td>
<td>614</td>
</tr>
</tbody>
</table>

1Definite: Signs and symptoms would be expected from exposure described. Probable: Close correspondence. Possible: Some correspondence.
Table 3. Five Year Summary of California Pesticide Illness and Injury Data

Rate Exposures Relationship to Effect

- **Definite**
  - Probable
  - Possible
Table 4-1. Top 5 Substances Most Frequently Involved Children Under 6

<table>
<thead>
<tr>
<th>Substance</th>
<th>Number x $10^5$</th>
<th>Per Cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cosmetics and personal care products</td>
<td>1.7</td>
<td>13.4</td>
</tr>
<tr>
<td>Cleaning substances</td>
<td>1.2</td>
<td>9.7</td>
</tr>
<tr>
<td>Analgesics</td>
<td>1.0</td>
<td>7.8</td>
</tr>
<tr>
<td>Foreign bodies</td>
<td>0.92</td>
<td>7.4</td>
</tr>
<tr>
<td>Topicals</td>
<td>0.92</td>
<td>7.4</td>
</tr>
</tbody>
</table>

American Association of Poison Control Centers, 2003
Table 4-2. Next 6-10 Substances Children Under 6

<table>
<thead>
<tr>
<th>Substance</th>
<th>Number x 10^5</th>
<th>Per Cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough and cold preparations</td>
<td>0.68</td>
<td>5.5</td>
</tr>
<tr>
<td>Plants</td>
<td>0.58</td>
<td>4.6</td>
</tr>
<tr>
<td><strong>Pesticides</strong></td>
<td><strong>0.51</strong></td>
<td><strong>4.1</strong></td>
</tr>
<tr>
<td>Vitamins</td>
<td>0.45</td>
<td>3.6</td>
</tr>
<tr>
<td>Antimicrobials</td>
<td>0.35</td>
<td>2.8</td>
</tr>
<tr>
<td>All other</td>
<td>1.5</td>
<td>11.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>12.5</strong></td>
<td>--</td>
</tr>
</tbody>
</table>

American Association of Poison Control Centers, 2003
Primary Regulatory Strategy
Margin-of-Exposure

Reference Dose

Exposure (ADD)
Environmental Justice
or
Advocate Blackmail?

Pesticide Regulation
Regulate!

- An alarmed, chemically naïve public
- Extremely low chemical contacts
- NOAELs become illness thresholds!
Everyone *knows* how bad they are!

Rachel Carson and followers like EDF, NRDC, PAN, Jane Seymour, Martin Sheen, Meryl Streep, Riverside’s *Press Enterprise*, *LA Times*, CBS, PBS, etc.
“Analysts at the Institute have just announced—

“We can now find a flea in a line of 100 full-grown, circus elephants!”

1 Flea $\approx$ millimeter
Elephant $\approx$ 10 meters
Anecdotes Focus Actions

*(Good News is not News!)*

- Birth defects, Collier Co., FL (now NC)
- “They have to stop spraying!”
- Moms within 200 ft of field sprays
  (in NC it’s early field entry)
  - Phocomelia
  - Deformed jaw
  - 3d Death, deformities

“That doesn’t rule it out. It’s just that we couldn’t make the link.” Collier Co. Health Dept

*a 60 MINUTES* and Ed Bradley can’t be far behind!
The plural of anecdotal is not evidence!
--the sky is falling!
Strive For Balance
Safe Use!

Read and Heed Labels
Recognize Realities of Exposure
Use Best Judgment!
Hazards are not *risks*

unless a sensitive population

is exposed and exposure

produces an adverse effect.
Safe Pesticide Use?

• Label developed by scientific studies and effective pest management
• Continuing use in agricultural and residential pest management
• Exposures occur time to time at low levels relative to harmful amounts
• Illness data reveal *mis*conceptions about health impacts of pesticides
"It's not what we don't know that hurts us," said Will Rogers. 
"It's what we know that ain't so."
Safe use?
Yes, it’s up to you!
Just do it!

Bob Krieger, Ph. D.
PCEP Entomology
UC Riverside, 2006
Follow-up Dessert

- Chemicals and Public Perceptions
- General Pesticide Science
- Advanced Pesticide Science
- Health Records
- Regulate: Margin-of-Exposure
- Safe Pesticide Use

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$40 Lottery from **all** completed returns (Survey & Z-Scan)