Do Pesticides Cause PD?

Jeff Bronstein MD, PhD
Director SW PADRECC and UCLA Movement Disorders
How can we prove that a toxin contributes to the pathogenesis of PD?

- A plausible mechanism of action.
- Association between a toxin and PD in epidemiological studies.
- Recapitulation of behavioral and pathological features in cellular and animal models.
Mitochondrial Dysfunction and PD

- MPTP is a complex I inhibitor
- Decreased complex I and II in brains and peripheral platelets in PD
- Mitochondrial-associated genes and PD (PINK1, DJ1, POLG, cybrids)
Residential use more common than commercial use.

A few case-control studies support increase incidence but not conclusive.
- Dhillon et al 2008: OR 10.9 (2.5-48)
- Agriculture Health Study: OR 1.7 (few cases)
- Anecdotal reports
Mechanisms of Rotenone Toxicity

- Complex I inhibition leads to oxidative stress and energy failure at low concentrations
- Proteasome inhibition
- Microtubule inhibition
Chronic systemic pesticide exposure reproduces features of Parkinson’s disease

Ranjita Betarbet, Todd B. Sherer, Gillian MacKenzie, Monica Garcia-Osuna, Alexander V. Panov and J. Timothy Greenamyre
Progression of Parkinson's Disease Pathology Is Reproduced by Intragastric Administration of Rotenone in Mice

Francisco Pan-Montojo et al.  PLOS One 2010
Proteasome Dysfunction

- Proteasome-associated genes and PD (Parkin, UCH L1)
- Decreased activity in brains and blood in PD
- Alpha-synuclein is at least partially degraded by the proteasome.
Pesticides that Lead to UPS Inhibition

**Rotenone**
- Complex I inhibitor

**Ziram and other dithiocarbamates**
- Fungicide
- Multivalent interactions

**Benomyl**
- Fungicide (Benzimidazole)
- Binds to tubulin

**Dieldrin and Endosulfan**
- Organochlorines (epoxicide)
- Inhibits GABA-gated chloride channels
Ziram and Related Compounds

- Dimethyl- and diethyldithiocarbamates
- Widely used fungicides on fruits and nuts.
- Approximately 15 million lbs were used in the US in 2002.
Ziram Exposure and PD (PEG Study)

Table 3. Ambient Occupational and Residential Maneb, Ziram, and Paraquat Exposure by Time Window of Exposure and Age of Central Valley of California Study Population

<table>
<thead>
<tr>
<th>Ziram and paraquat exposure</th>
<th>Occupational **</th>
<th></th>
<th>Residential ***</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case</td>
<td>Contro l</td>
<td>OR*</td>
<td>95% CI</td>
</tr>
<tr>
<td>1974-1999 Time Window</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 years old or younger</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No exposure to ziram or paraquat</td>
<td>28</td>
<td>53</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>Ziram or paraquat exposure</td>
<td>30</td>
<td>29</td>
<td>1.90</td>
<td>(0.92, 3.94)</td>
</tr>
<tr>
<td>Ziram and paraquat exposure</td>
<td>19</td>
<td>5</td>
<td>5.97</td>
<td>(1.94, 18.33)</td>
</tr>
<tr>
<td>Over 60 years old</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No exposure to ziram or paraquat</td>
<td>137</td>
<td>141</td>
<td>1.00</td>
<td>ref</td>
</tr>
<tr>
<td>Ziram or paraquat exposure</td>
<td>84</td>
<td>76</td>
<td>1.17</td>
<td>(0.78, 1.76)</td>
</tr>
<tr>
<td>Ziram and paraquat exposure</td>
<td>64</td>
<td>37</td>
<td>1.93</td>
<td>(1.18, 3.15)</td>
</tr>
</tbody>
</table>

Wang A, Costello S, Cockburn M, Zhang X, Bronstein, Ritz B
Ziram Inhibits the 26S UPS

IC50: $1.61 \times 10^{-7}$
Ziram Inhibits E1 Ligase
Ziram and Primary Mesencephalic Cultures

**Effects of Ziram on TH+ Cell Number**

* p < 0.05
n=11-23

**Effects of Ziram on NeuN+ Cell Number**

Difference not statistically significant, n=11-23.

One-way ANOVA
p=0.113
Systemic Administration of DMTC

Chou et al, 2009
A Zebrafish Model to Study Gene-Environment Interactions in PD

- Vertebrates with short life span
- Easy to insert genes
- Transparent to image gene expression
- Behavior easily measured
- Well developed DA system
Transgenic TH-GFP Zebrafish
Ziram (1-10 nM) Alters DA Neuron Development

Control                                MPTP                      Ziram (20 nM)
Other Pesticides

- **Paraquat**
  - Associated with increased risk of PD (in combination with maneb and ziram)
  - Mechanism: Redox-cycling?
  - Animal model; DA cell loss and behavior

- **Benomyl**
  - Associated with increased risk of PD (PEG and Ag Health)
  - Mechanisms: UPS-I, ALDH-I, and MT-I
  - Primary culture DA loss but no animal models
How can we prove that a toxin contributes to the pathogenesis of PD?

- A plausible mechanism of action. **YES**
- Association between a toxin and PD in epidemiological studies. **YES**
- Recapitulation of behavioral and pathological features in cellular and animal models. **YES**
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