Pesticides and Parkinson’s Disease

Beate Ritz, MD PhD
Dept. of Epidemiology and Neurology
Center for Occupational and Environmental Health
UCLA, Fielding School of Public Health & Geffen School of Medicine
Abnormalities in the neurons in the basal ganglia & loss of dopamine (DA) neurons in the substantia nigra midbrain region

Cardinal clinical motor symptoms
- Tremor
- Rigidity
- Akinesia
- Postural reflex impairment

Plus non-motor symptoms
- autonomic dysfunction, sleep disorders, GI tract, bladder and heart problems
- depression, dementia etc.

A-synuclein pathology

Parkinson’s Disease
PD affects 5-10 adults per 1,000 over age of 60
Identified and enroll newly diagnosed cases of PD since Jan 2001 in three rural California counties:

- >800 PD cases were clinically evaluated by a study movement disorder neurologist at least once and confirmed as idiopathic PD

- 803 population controls and 193 (unaffected) sibling controls interviewed and DNA samples collected (Jan 2001-Dec 2012)
Since 1972, CA law requires commercial pesticide users to report to a statewide registry (PUR)

Information collected includes (example):

• County: Kern
• Location: 15M28S27E19 (PUR geo-locator)
• Application date: 2/23/1989
• Commodity: 2503 (Grapes)
• Method: Ground
• Treated: 424 acres
• Product applied: 155 gallons
• Chemical: 00459 (*Parathion*)
• Percentage: 80%
• Active Ingredient Pounds: 1,241

Geographic Locators for the PUR are based on Public Land Survey System
  - limited to 1 PLS section (appr. 640 acres =1 sq.mi)

Thus, we improved the resolution in GIS with CA land-use survey maps (DWR)
Downwind Herbicide Deposition
Varying Droplet Size and Wind Speed

Deposition (fraction of application rate)

Extremely coarse—very coarse spray, 3 mph wind
Medium spray, 3 mph wind
Extremely coarse—very coarse spray, 10 mph wind
Medium spray, 10 mph wind
Effect level for 50% of young plants

Downwind distance (ft)
Figure 22. Diazinon: locations of all reported applications in 2006.

Diazinon detected in 32% of all air samples (468) in 2006 applied 1,565 kg, # applications: 222
Gene x Pesticide Interactions

- Pesticides
- Age
- Sex
- GENES
- ~20,000

home and agricultural use
DAT1 and Paraquat/Maneb and PD

Transporter for dopamine involved in dopamine homeostasis
Animal Tox Testing: Paraquat and manebr

**Paraquat**
- Systemic and repeated administration of paraquat to mice results in a specific loss of tyrosine hydroxylase-positive neurons of the SNc

**Manebr**
- Dithiocarbamate (DTC) fungicide (manganese ethylene-bis-dithiocarbamate (Mn–EBDC))
  - In animal models it potentiates MPP+ effects
  - Modulates/enhances paraquat toxicity
Pesticides and PD in PEG study: What happens with combined paraquat & maneb exposure in humans?

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Cases/ctrls</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No exposure</td>
<td>115/126</td>
<td>ref</td>
</tr>
<tr>
<td>Paraquat only</td>
<td>149/152</td>
<td>1.01 (0.71, 1.43)</td>
</tr>
<tr>
<td>Maneb only</td>
<td>3/1</td>
<td>-</td>
</tr>
<tr>
<td>Paraquat &amp; maneb</td>
<td>88/49</td>
<td>1.75 (1.13, 2.73)</td>
</tr>
</tbody>
</table>

**DAT1** increases risk for PD with ambient paraquat & maneb exposures at residences (PEG study; Ritz et al 2009):

<table>
<thead>
<tr>
<th># of Risk Alleles</th>
<th>Ambient PESTICIDE EXPOSURES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zero/Low</td>
</tr>
<tr>
<td>0</td>
<td>ref</td>
</tr>
<tr>
<td>1</td>
<td>0.98 (0.63, 1.52)</td>
</tr>
<tr>
<td>2+</td>
<td>1.30 (0.85, 2.00)</td>
</tr>
</tbody>
</table>

p-trend (across all categories) = 0.0006

a. Risk alleles defined as 5’A’ clade & 3’ VNTR 9-repeat allele, Odds Ratio (OR) adjusted for age (continuous), race/ethnicity, education (<12,12,>12 years), smoking (ever/never), occupational pesticide exposures (JEM)
PEG results corroborated results for PD and Pesticide Exposure in Washington State (Kelada et al 2006):

<table>
<thead>
<tr>
<th># of Risk Alleles</th>
<th>Number of DAT1 risk alleles</th>
<th>Pesticide Unexposed OR (95%)a</th>
<th>Pesticide Exposed OR (95%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1 (ref.)</td>
<td>1.0 (ref.)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.21 (0.62–2.36)</td>
<td>1.63 (0.52–5.15)</td>
<td></td>
</tr>
<tr>
<td>2+</td>
<td>1.17 (0.62–2.23)</td>
<td>5.66 (1.73–18.53)</td>
<td></td>
</tr>
</tbody>
</table>

a. Risk alleles defined as 5’A’ clade & 3’ VNTR 9-repeat allele, Odds Ratio (OR) adjusted for age (<60, >60, education (quintiles) and smoking status (ever/never).
PON1 and OP pesticides and PD

Metabolizing/detoxifying proteins for OP pesticides
Organophosphate pesticides, why we care:
Widely used in US agriculture, and known for acute neurotoxicity

BUT also in 1999-2000 NHANES (US population survey, participants aged 6-59) in urine pesticide metabolites: were detected for

• Chlorpyrifos (TCPY) in more than 96% samples
• Diazinon (IMPY) in 29% samples

Both are among the top 20 toxic air contaminants in CA according to CDPR
Chlorpyrifos banned for **indoor use** by EPA in 2000, but still used outdoors and reconsidered for indoor use

PON1 hydrolyzes toxic organophosphates and carbamate pesticide metabolites

Pesticide

Toxic metabolite

PON1

Non/less toxic metabolite
PON1 enzyme function depends on genotypes

10- to 40-fold inherited differences in PON1 enzyme activity in serum - 2 common polymorphisms in the PON1 gene contribute to this difference

PON1 serum activities for diazoxon (50 mM) by genetic polymorphism: M55L and Q192R [O’Leary et al. 2006]

<table>
<thead>
<tr>
<th>PON1 -genotypes</th>
<th>55-LL</th>
<th>55-LM</th>
<th>55-MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>192-QQ</td>
<td>15.6 ± 6.0</td>
<td>11.2 ± 5.0</td>
<td>6.35 ± 1.50</td>
</tr>
<tr>
<td>192-QR</td>
<td>18.1 ± 7.7</td>
<td>14.3 ± 2.8</td>
<td>-</td>
</tr>
<tr>
<td>192-RR</td>
<td>22.0 ± 9.4</td>
<td>16.4 ± 0.0</td>
<td>-</td>
</tr>
</tbody>
</table>
Agricultural use resulting in exposures at residences and workplaces

Functional paraoxonase 1 variants modify the risk of Parkinson's disease due to organophosphate exposure

Pei-Chen Lee a, Shannon L. Rhodes a, Janet S. Sinsheimer c, Jeff Bronstein d, Beate Ritz a,d,*

PON1L55M & PON1Q192R diplotypes

<table>
<thead>
<tr>
<th>PON1L55M and PON1Q192R diplotypes</th>
<th>Diazinon</th>
<th>Chlorpyrifos</th>
<th>Parathion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zero Exposure</td>
<td>Low/High Exposure</td>
<td>Zero Exposure</td>
</tr>
<tr>
<td>RR+LL</td>
<td>1</td>
<td>1.10 (0.35-3.47)</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>1.16 (0.41-3.27)</td>
<td>1.47 (0.53-4.05)</td>
<td>1.18 (0.42-3.33)</td>
</tr>
<tr>
<td>QQ+MM</td>
<td>1.16 (0.29-4.62)</td>
<td>2.43 (0.78-7.56)</td>
<td>1.14 (0.29-4.58)</td>
</tr>
</tbody>
</table>

287 cases, 440 controls (Caucasians only)

- adjusted for age, gender, smoking status, county, and education level

-reference group of participants is for those unexposed to all three OPs
Average usage from age 16 until 10 years prior to age of onset and PD, Caucasians Only; pesticides ingredients identified from list of CA registered chemicals
NOS and OP pesticides and PD

Nitric oxide (NO) is a potent pro-oxidant that can damage dopaminergic neurons.
**NOS1** and multiple OP pesticide exposure sources

Any Household Pesticide

<table>
<thead>
<tr>
<th>Pesticide Use</th>
<th>CC</th>
<th>CT+TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never/Rare Use</td>
<td>1.00</td>
<td>0.83 (0.58-1.20)</td>
</tr>
<tr>
<td>Frequent Use</td>
<td>1.02 (0.68-1.55)</td>
<td>1.54 (1.02-2.33)</td>
</tr>
</tbody>
</table>

Household OP Pesticides

<table>
<thead>
<tr>
<th>Pesticide Use</th>
<th>CC</th>
<th>CT+TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never/Rare Use</td>
<td>1.00</td>
<td>0.83 (0.57-1.20)</td>
</tr>
<tr>
<td>Frequent Use</td>
<td>1.09 (0.65-1.82)</td>
<td>2.37 (1.34-4.18)</td>
</tr>
</tbody>
</table>

Ambient OP Exposure at Residences and Workplaces

<table>
<thead>
<tr>
<th>Exposure Level</th>
<th>CC</th>
<th>CT+TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>None/Low</td>
<td>1.00</td>
<td>1.09 (0.72-1.65)</td>
</tr>
<tr>
<td>Medium</td>
<td>1.31 (0.84-2.04)</td>
<td>1.19 (0.75-1.87)</td>
</tr>
<tr>
<td>High</td>
<td>2.22 (1.24-3.96)</td>
<td>3.25 (1.73-6.10)</td>
</tr>
</tbody>
</table>

*Mutually adjusting for household pesticide use, ambient exposures and occupational exposures to pesticides did not change results.*
Ambient Organophosphate Exposure and Cognition: Exposure influences cognitive decline in PD patients

Results from linear mixed model, using repeated measures, modeling age as random effect and adjusted for age, sex, race, education.
ALDH inhibiting pesticides and PD

ALDH metabolizes DOPAL which is toxic to nigral DA neurons
Aldehyde dehydrogenase (ALDH) enzyme

In DA neurons

Dopamine \rightarrow \text{DOPAL} \quad \begin{array}{c} \text{MAO} \end{array} \quad \text{DOPAC}

5x more toxic to nigral neurons than DA or DOPAC \quad \text{(Burke et al., 2003)}

\text{Interferes with NAD}^+/\text{NADH balance, mitochondrial activity
Screening in Dr. Bronstein’s lab finds dithiocarbamate pesticides inhibit ALDH

- dithiocarbamates
  - maneb
  - mancozeb
  - disulfiram
  - thiram
  - ziram

- dicarboxymide/
  - captan
ALDH inhibiting Pesticides X Genetic variants in ALDH and PD

<table>
<thead>
<tr>
<th>Exposure level</th>
<th>ALDH2 clade 1/1 Cases/controls</th>
<th>OR(^b) (95% CI)</th>
<th>ALDH2 clade 1/2 or 2/2 Cases/controls</th>
<th>OR(^b) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexposed to all ALDH-inhibiting pesticides</td>
<td>76/124</td>
<td>1.00</td>
<td>92/160</td>
<td>1.00</td>
</tr>
<tr>
<td>Exposed to any number of pesticides at residence but unexposed at workplace</td>
<td>29/38</td>
<td>1.17 (0.65-2.10)</td>
<td>20/49</td>
<td>0.73 (0.41-1.32)</td>
</tr>
<tr>
<td>Exposed to any number of pesticides at workplace but unexposed at residence</td>
<td>24/33</td>
<td>1.16 (0.63-2.16)</td>
<td>29/46</td>
<td>1.14 (0.66-1.95)</td>
</tr>
<tr>
<td>Exposed to 1 or 2 pesticides at each residence and workplace</td>
<td>22/23</td>
<td>1.58 (0.80-3.10)</td>
<td>17/13</td>
<td>2.21 (1.01-4.82)</td>
</tr>
<tr>
<td>Exposed to ≥3 pesticides at residence but only 1 or 2 at workplace</td>
<td>5/6</td>
<td>1.21 (0.35-4.23)</td>
<td>8/7</td>
<td>1.74 (0.61-5.03)</td>
</tr>
<tr>
<td>Exposed to ≥3 pesticides at workplace but only 1 or 2 at residence</td>
<td>4/7</td>
<td>0.92 (0.25-3.43)</td>
<td>7/4</td>
<td>2.80 (0.78-10.0)</td>
</tr>
<tr>
<td>Exposed to ≥3 pesticides at each residence and workplace</td>
<td>9/5</td>
<td>2.47 (0.78-7.82)</td>
<td>11/3</td>
<td>5.30 (1.42-19.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.1285</td>
<td>0.0010</td>
<td></td>
</tr>
</tbody>
</table>

\(p\) Trend

Aldehyde dehydrogenase variation enhances effect of pesticides associated with Parkinson disease

Arthur G. Fitzmaurice, PhD*
Shannon L. Rhodes, PhD*
Myles Cockburn, PhD
Beate Ritz, MD, PhD
Jeff M. Bronstein, MD, PhD

*Corresponding author
CONCLUSIONS

Gene-environment interactions in human studies are important.

**Pesticides** put individuals with some *common genetic variant* at much higher risk of developing PD.
A strong scientific story is important to justify and stimulate Environmental Regulations.
Special Thanks to NIEHS for the research funding
UCLA Movement Disorder Specialists:
Yvette Bordelon, MD PhD & Jeff Bronstein, MD PhD
and multiple UCLA PEG Study Teams, Students, and Postdocs