

Parkinson's Disease: the Pesticide Link



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PD and Pesticides

Questions to be addressed

- 1. What is the evidence linking pesticides and PD?**
- 2. What specific pesticide compounds are implicated?**
- 3. What is the relevance of the PD and pesticide link to veterans with PD and their families?**

The New York Times

October 12, 2009



- “...the Department of Veterans Affairs plans to add Parkinson’s disease, ischemic heart disease and hairy-cell leukemia to the growing list of illnesses presumed to have been caused by Agent Orange, the toxic defoliant used widely in Vietnam.”

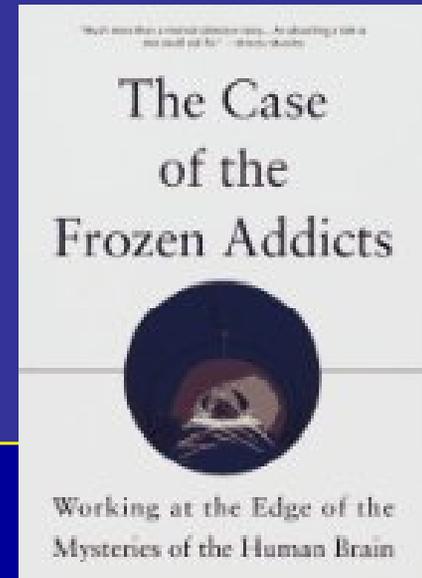
Agent Orange

- Code name for a defoliant herbicide used during the Vietnam War.
- Name derived from orange drums it is shipped in
- Mixture of 2 herbicides:
 - 2,4-dichlorophenoxyacetic acid (2,4-D)
 - 2,4,5-trichlorophenoxyacetic acid (2,4,5-T).



PD and Pesticides: What is the evidence?

- **MPTP-induced parkinsonism**
 - **1983: Langston, Tetrad and colleagues described a cluster of rapid onset parkinsonism in narcotic addicts living in the Bay Area**
 - **traced to 1-methyl-4 phenyl-1,2,3,6-tetrahydropyridine (MPTP)**
 - **parkinsonism syndrome indistinguishable from PD including good response to levodopa**



MPTP as a model neurotoxin

- **Causes selective loss of dopamine producing neurons**
- **structural similarity to known pesticides such paraquat**
- **toxic mechanism, interference with energy production by mitochondria in the cells, is similar to known pesticides such as rotenone**

MPTP AND STRUCTURALLY-RELATED COMPOUNDS



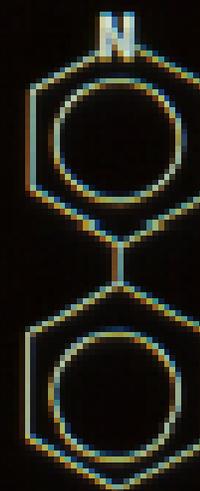
MPTP



MPP+
(CYPERQUAT)



PARAQUAT



**4-PHENYL
PYRIDINE**

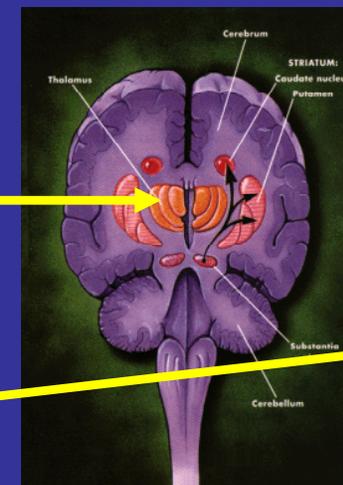
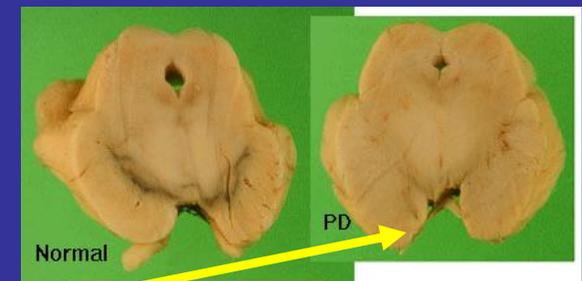
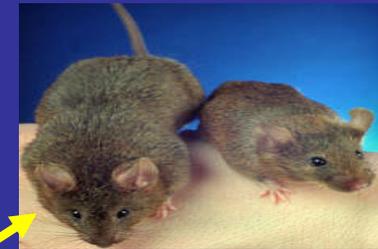
Pesticides and PD Link: Indirect evidence

- **In research comparing persons with PD to similarly aged persons without PD (case control study) those with PD:**
 - **Live more often in rural areas**
 - **Work more often in agricultural occupations**
 - **Drink well water**

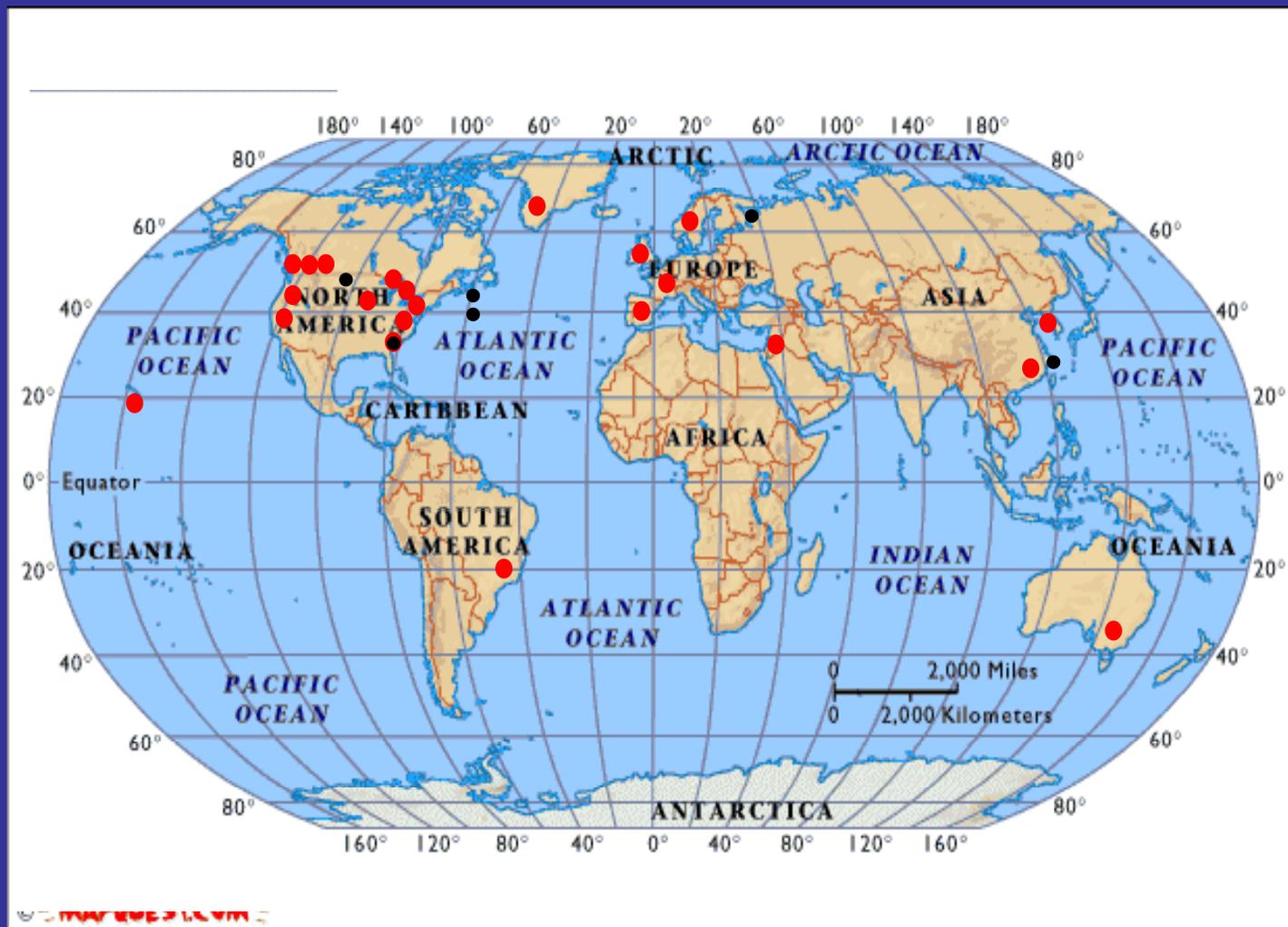
Are these factors surrogates for exposure to pesticides??

Pesticides and PD Link: Research with animal models

- **Exposure of laboratory animals to MPTP, paraquat and maneb, dieldrin, and rotenone causes:**
 - Behavior suggestive of parkinsonism
 - Destruction of pigmented neurons in the substantia nigra
 - Loss of dopamine in the striatum
 - Lewy body like inclusions in some



- In a recent review, over 24 of 31 case-control studies have shown an association of PD and pesticides.
- PD risk is 1.6 to 7 times higher in pesticide exposed
- The higher the exposure the greater the risk



BUT

- Broad chemical categories
- Few specific agents identified

Brown et al, 2006

The Agricultural Health Study

National Cancer Institute

Environmental Protection Agency

National Institute of Environmental Health Sciences

- **Prospective cohort study examining relationship between pesticide use and human disease**
- **52,000 pesticide applicators and 32,000 spouses from Iowa and N. Carolina enrolled 1993-97**
- **Detailed pesticide use information**
- **PD participants almost twice as likely to be exposed to 2,4,5-T and to trifluralin than non-PD (control) participants**

Kamel et al, 2007

Pesticides and PD Link: Central valley of California Costello et al, 2009



- **368 persons with PD and 341 without PD from the Central Valley of California.**
- **Assessed exposure to specific pesticides based on proximity to pesticide use in the residential environment.**
- **Exposure to maneb and paraquat increased PD risk by 75%.**

Pesticides and PD Link:

Study of environmental association and risk of PD

Tanner et al, 2009

- **519 PD participant and 511 non-PD controls from 8 centers in North America**
- **Telephone interviews to determine exposures to specific pesticides.**
- **Risk of parkinsonism in pesticide exposed was 1.8 times that of unexposed**
- **Those exposed to 2,4-D were 2.6 times more likely to have parkinsonism**

Pesticides and PD Link: Organochlorine insecticides

- French study found that PD participants were 2.4 times more likely to have been exposed to organochlorines than non-PD controls. (Elbaz et al, 2009)**
- Two studies have found higher levels of organochlorines (dieldrin and lindane) in brains of deceased persons with PD compared to non-PD controls (Fleming et al, 1994; Corrigan et al, 2000)**

Pesticides and PD Link: Summary

- Preponderance of evidence indicates that pesticide exposure is associated with higher PD risk.
- Specific pesticides implicated include:
 - Paraquat – commonly used herbicide
 - Maneb – commonly used fungicide
 - Rotenone – widely used in home gardening, pest control, fish poison, and commercial insecticide
 - Dieldrin - organochlorine
 - 2,4-D - constituent of agent orange
 - 2,4,5-T - constituent of agent orange

However....

**Association does not
prove cause and
effect!**

**The evidence that
pesticides cause PD
is not definitive.**

Nevertheless....



***Are you sure about this? It seems odd that a
pointy head and long beak is what makes birds fly.***

Pesticides and PD Link: Relevance to Vietnam veterans

- National Academy of Sciences Institute Of Medicine determined that “there is limited or suggestive evidence of an association between exposure to the compounds of interest and PD”
- October, 2009: Sec. Shinseki declared that PD will receive a presumption of service connection for Vietnam veterans with PD
- Much work still to be done:
 - Studies of PD among Vietnam veterans still needed
 - More research is needed related to the biological mechanism by which agent orange may lead to PD

Agent Orange and PD claims

- **Is Parkinson's disease a service connected disability for Vietnam veterans?**
 - **Secretary Shinseki has said yes.**
 - **Final decision remains in the rulemaking process**
- **Who will be is eligible?**
 - **Vietnam veterans who served in country (exposed to agent orange).**
- **What is the process to open a claim?**
 - **Veteran Benefits Administration is accepting claims**
 - **Presently, claims are being held pending final rulemaking**

Thank you for your attention