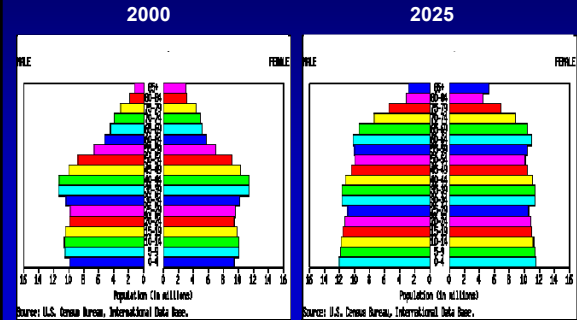


Chemical Toxicant Exposures and Risk of Parkinson's Disease

Marc Weisskopf, PhD, ScD

Depts. of Environmental Health & Epidemiology
Harvard School of Public Health

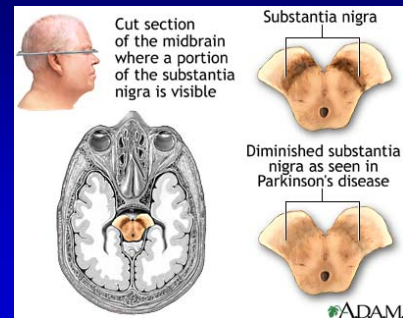
Aging of the US Population



Parkinson's Disease

- Primary Symptoms
 - ▶ Rigidity
 - ▶ Tremor
 - ▶ Bradykinesia
 - ▶ Postural Instability
- Pathophysiology
 - ▶ Selective, pronounced loss of dopamine-producing neurons in the substantia nigra pars compacta (SNpc)
 - ▶ Drastic depletion of dopamine in the striatum (projection site of SNpc)

PD Neuropathology



Parkinson's Disease Epidemiology

- Second most common progressive neurodegenerative disorder
 - ▶ ~50,000 new cases each year
 - ▶ 1-1.5 million PD patients in North America
 - ▶ 1% of people age 60+
 - ▶ 2% of people age 70+
- Peak onset at 60 years
 - ▶ Progresses from diagnosis to major disability over 10 - 20 years.
- ~85% of PD patients are older than 50 years
- Affects men more than women: ~55/45

Parkinson's Disease Are Environmental Factors Important?

- Frozen addicts and MPTP (1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine)
 - ▶ Langston et al., Science, 219:979, 1983
- 7 users of the synthetic opioid MPPP
- Responded to levodopa
- MPTP found to induce parkinsonism in monkeys
 - ▶ Not rats
- 2/7 addicts successfully treated with stem cells

Parkinson's Disease Twin Studies

Tanner, JAMA, 281(4):341, 1999 (World War II Veteran Twins Registry)

- Concordance
 - ≤50 y/o: MZ=1.0 (n=4); DZ=0.167 (n=12)
 - >50 y/o: MZ=0.108 (n=65); DZ=0.105 (n=76)

Wirdefeldt, Neurology, 63(2):305, 2004 (Swedish twin study)

- Concordance (broad-definition PD)
 - MZ=0.11 (n=107); DZ=0.08 (n=190)

Parkinson's Disease

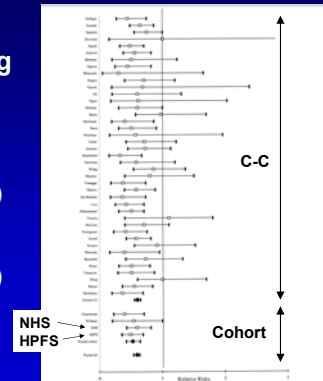
Meta-Analysis of Cigarette Smoking

Pooled RR

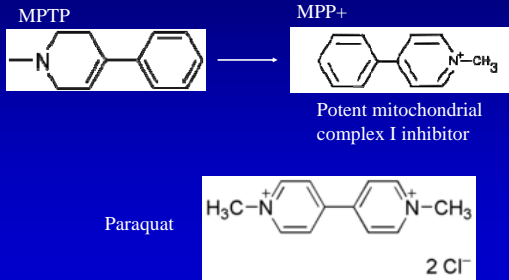
Case-Control: 0.59 (0.55-0.65)

Cohort: 0.52 (0.42-0.64)

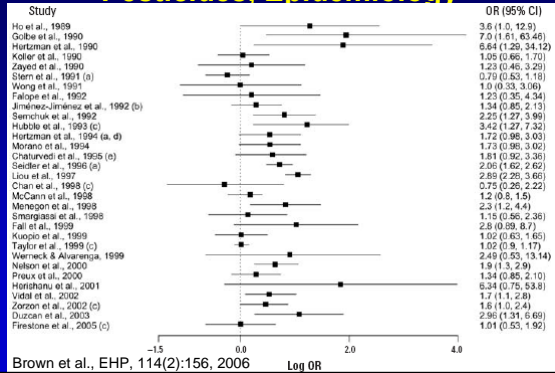
Herman et al., Ann Neurol, 52(3):276, 2002



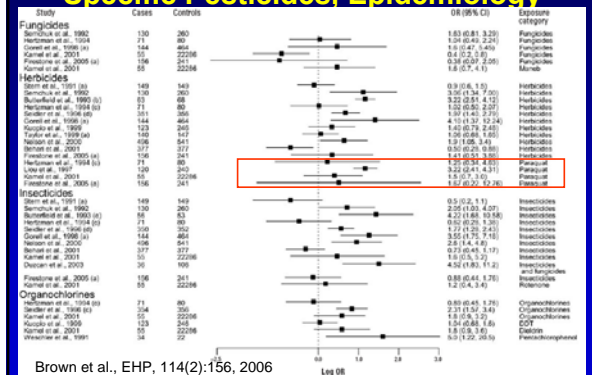
Parkinson's Disease MPTP



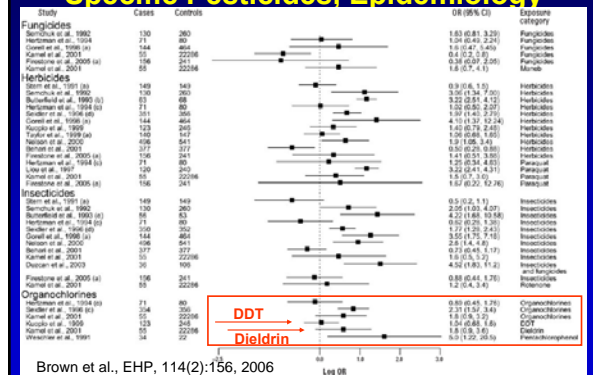
Parkinson's Disease Pesticides, Epidemiology



Parkinson's Disease Specific Pesticides, Epidemiology



Parkinson's Disease Specific Pesticides, Epidemiology



Parkinson's Disease Pesticides, Epidemiology

Meta-analyses of case-control studies

- Priyadarshi et al., Neurotoxicology, 21:435, 2000
 - ▶ Pesticide combined OR=1.94 (95% CI: 1.49-2.53)
 - ▶ Similar across continents
- Priyadarshi et al., Environ Res, 86:122, 2001
 - ▶ Well-water: 1.26 (0.96-1.64)
 - ▶ Farming: 1.42 (1.05-1.91)

Parkinson's Disease Pesticides, Epidemiology

Table 3. Incidence of PD (Rate per 10 000 Person-years) According to Number of Years Worked on a Plantation and Years of Exposure to Pesticides

Duration, y	Sample Size	No. of PD Cases	Unadjusted	Age-Adjusted
Self-reported Plantation Work, 1965-1968				
0	5365	73	5.7	5.8
1-10	1843	24	5.5	5.4
11-20	315	7	9.6	9.2
>20	466	12	11.3*	10.3
Test for trend†	P=.002	P=.01
Overall	7966	116	6.1	...
Self-reported Exposure to Pesticides, 1971-1974				
0	3154	46	7.9	7.8
1	2669	33	6.5	6.5
2-3	587	9	8.1	8.2
>3	450	11	12.9	12.7
Test for trend†	P=.08	P=.10
Overall	6854	99	7.7	...

*Value indicates a significant excess risk of Parkinson disease (PD) compared with men who never worked on a plantation (P=.02).
†Test for trend is based on modeling the number of years worked on a plantation and the number of years of pesticide exposure as continuous variables.

Petrovitch et al., Arch Neurol., 59:1787, 2002

Objective

To assess the association between biomarkers of organochlorine pesticide exposure—measured in prospectively collected serum—and the risk of PD

Finnish Mobile Health Clinic

- Recruited throughout Finland in 1966-1972
- 62,440 adults aged 15 years or more
 - ▶ 82.5% participation
- Serum samples frozen and stored at -20°C
- Eligibility for PD study; at baseline:
 - ▶ No PD or psychosis
 - ▶ 20-79 years old



Case and Controls

PD Cases

- Identified through the Social Insurance Institution's nationwide registry of patients receiving medication reimbursement
- Medical records obtained for 126 of 196 cases for review by study neurologist
 - ▶ 25 deemed not PD

Controls

- Randomly selected
- Individually matched on
 - ▶ age, sex, and municipality
- Alive and free from PD when matched PD case identified

Exposure assessment

- Serum samples
 - ▶ processed and stored in same manner
 - ▶ sent in random order
 - ▶ blinded to disease status
- Organochlorine analysis with gas chromatography
 - ▶ QA/QC: procedural blank, matrix spike samples, laboratory control sample and standard reference material sample
- Cholesterol and triglycerides measurements done enzymatically
- Covariates from baseline FMC questionnaire

Statistical Analysis

- Conditional logistic regression to estimate rate ratios (RR) for PD
- Organochlorines in quintiles based on control distribution
- Additional adjustment for
 - ▶ cigarette smoking, body mass index, blood pressure, serum lipids

Baseline Characteristics

	Cases (n=171)	Controls (n=310)
Age, mean years (sd)	53.7 (10.2)	53.4 (10.3)
Years to PD, mean (sd)	22 (4)	--
BMI, mean (sd)	27 (4)	26 (4)
SBP, mean (sd)	151 (25)	148 (26)
DBP, mean (sd)	86 (12)	83 (12)
Serum cholesterol, mean (sd)	268 (49)	274 (53)
Serum triglycerides*, mean (sd)	133 (62)	134 (73)
Male, n (%)	88 (52)	168 (54)
Never smokers, n (%)	110 (64)	171 (55)

* Measured in 2005-2007

Organochlorine Concentrations* Among Controls

	FMC	NHANES
	90 th %ile (median)	90 th %ile
Aldrin	0.002 (0)	0
Dieldrin	0.660 (0.32)	0.117
Hexachlorobenzene (HCB)	0.775 (0.370)	0
β-hexachlorocyclohexane (β-HCH)	1.29 (0.69)	0.175
p,p'-DDT	3.71 (2.02)	0.201 [†]
p,p'-DDE	17.94 (8.43)	9.75

* ng/g serum or ppb

[†] 95th %ile

Organochlorine Concentrations* Among Controls

	FMC	NHANES
	90 th %ile (median)	90 th %ile
Mirex	0.017 (0.008)	0.137
Heptachlor	0.013 (0)	--
Oxychlorthane	0.103 (0.044)	0.267
Trans-nonachlor	0.170 (0.089)	0.418
Heptachlor Epoxide	0.060 (0.021)	0.107

* ng/g serum or ppb

Rate Ratio for PD by OC Quintile

	Organochlorine quintile				
	Q1	Q2	Q3	Q4	Q5
Dieldrin	Ref	1.5 (0.8-2.8)	1.4 (0.7-2.9)	0.7 (0.3-1.4)	1.1 (0.5-2.6)
HCB	Ref	1.3 (0.7-2.5)	0.8 (0.4-1.5)	1.3 (0.6-2.7)	0.2 (0.5-3.1)
β-HCH	Ref	1.0 (0.6-1.9)	0.9 (0.4-1.7)	0.9 (0.5-1.8)	0.7 (0.3-1.6)
p,p'-DDT	Ref	0.8 (0.4-1.5)	0.8 (0.5-1.5)	0.6 (0.3-1.3)	0.7 (0.3-1.4)
p,p'-DDE	Ref	1.0 (0.6-1.8)	0.8 (0.4-1.5)	0.9 (0.5-1.7)	0.7 (0.4-1.5)

Aldrin: 1.30 (0.70-2.43)

Rate Ratio for PD by OC Quintile

	Organochlorine quintile				
	Q1	Q2	Q3	Q4	Q5
Mirex	Ref	0.9 (0.5-1.7)	1.1 (0.5-2.4)	1.0 (0.5-2.3)	1.5 (0.7-3.1)
Oxychlorthane	Ref	1.7 (0.9-3.3)	1.1 (0.5-2.4)	1.2 (0.6-2.5)	1.0 (0.4-2.2)
Trans-nonachlor	Ref	1.2 (0.7-2.2)	0.9 (0.5-1.6)	0.7 (0.4-1.4)	1.0 (0.5-2.0)
Heptachlor Epoxide	Ref	1.0 (0.5-1.9)	0.9 (0.4-1.8)	1.0 (0.5-2.2)	0.8 (0.3-1.8)

Heptachlor: 0.78 (0.36-1.70)

Rate Ratio for PD by OC Quintile Never Smokers Only (n=109 cases)

	Organochlorine quintile				
	Q1	Q2	Q3	Q4	Q5
Dieldrin*	Ref	1.7 (0.7-4.3)	1.6 (0.5-4.6)	0.8 (0.2-2.4)	2.5 (0.7-9.0)
HCB	Ref	0.9 (0.3-2.4)	0.9 (0.3-2.7)	1.9 (0.5-6.7)	4.7 (1.0-2.2)
β-HCH	Ref	0.5 (0.2-1.4)	0.5 (0.2-1.4)	0.7 (0.2-2.4)	0.5 (0.1-2.0)
p,p'-DDT	Ref	1.3 (0.5-3.5)	0.9 (0.4-2.3)	0.7 (0.2-1.9)	0.7 (0.2-1.9)
p,p'-DDE	Ref	1.3 (0.6-2.8)	0.9 (0.4-2.3)	1.2 (0.5-2.9)	1.3 (0.4-4.1)
Aldrin:	0.90 (0.28-2.94)				

* Continuous p=0.09; when restricted to 101 confirmed cases, continuous p=0.03, RR=2.0 (1.5-2.8) per sd

Rate Ratio for PD by OC Quintile Never Smokers Only (n=109 cases)

	Organochlorine quintile				
	Q1	Q2	Q3	Q4	Q5
Mirex	Ref	1.0 (0.4-2.4)	1.2 (0.4-3.5)	1.6 (0.6-4.5)	0.8 (0.2-3.0)
Heptachlor Epoxide	Ref	1.7 (0.6-4.7)	1.8 (0.6-5.2)	3.6 (1.0-13)	3.2 (0.7-15)
Oxychlorthane	Ref	1.5 (0.6-3.5)	2.0 (0.7-5.4)	1.6 (0.5-4.5)	0.7 (0.2-2.7)
Trans-nonachlor	Ref	1.3 (0.6-3.0)	0.8 (0.3-2.0)	0.7 (0.2-1.9)	1.4 (0.4-4.7)

Heptachlor: 0.33 (0.08-1.35)

Additional Results

- Similar results when analyses restricted to neurologist confirmed cases
 - ▶ Dieldrin trend: p=0.03
- Most correlations between OCs Spearman r: 0.3-0.5
- Little correlation between OCs and age
 - ▶ Highest=0.17 (Heptachlor)

Limitations

- Not physical PD exam
 - ▶ Clinical diagnoses about 90% accurate
 - ▶ Errors likely unrelated to OC exposure
- Only persistent compounds could be analyzed
- Single OC measure
 - ▶ Repeated measures over time would better represent long-term average
 - ▶ Changing pesticide use patterns over time
 - ▶ Any bias likely towards null
- No follow-up data for confounders like smoking

Dieldrin, Heptachlor Epoxide, HCB

- Dieldrin
 - ▶ Insecticide widely used on, e.g., corn, cotton
 - ▶ Banned in US in 1974
- Heptachlor (epoxide is breakdown product)
 - ▶ Insect control in homes, buildings, and on food crops
 - ▶ Mostly banned in US in 1988
 - ▶ Can now only be used for fire ant control in underground power transformers
- Hexachlorobenzene (HCB)
 - ▶ Fungicide to protect the seeds of onions and sorghum, wheat, and other grains
 - ▶ Used to make fireworks, ammunition, and synthetic rubber
 - ▶ No current commercial uses

Dieldrin, Heptachlor Epoxide, HCB and PD

- Dieldrin
 - ▶ Elevated in 2 small studies of post-mortem PD brains
 - ▶ Induces α-synuclein fibrillation
 - ▶ DA toxicity via ROS induction
 - ▶ Inhibits proteasome activity
- Heptachlor Epoxide & HCB
 - ▶ No direct studies related to PD

Summary

- Support for increased risk of PD with increasing exposure to
 - ▶ Dieldrin
 - ▶ Hexachlorobenzene
 - ▶ Heptachlor epoxide
- Can't rule out correlation with other less persistent pesticides
- No association with DDT/DDE

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<http://www.hsph.harvard.edu/research/neuroepi/>

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PD review

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Pesticides and PD, reviews

- Hatcher et al., Trends Pharmacol Sci, 29(6):322, 2008
- Elbaz and Tranchant, J Neurol Sci, 262(1-2):37, 2007

Pesticides and PD

- Kuopio et al., Mov Disord, 14(6):928, 1999
- Kamel et al., Am J Epidemiol, 165(4):364, 2007

Finnish Mobile Health Clinic

- Sääksjärvi K, et al. Eur J Clin Nutr, 62: 908, 2008

Resources

<http://www.michaeljfox.org/>
<http://www.parkinson.org/>
<http://www.pdf.org/>
<http://www.apdaparkinson.org/>
<http://www.parkinsonsaction.org/>

http://www.ninds.nih.gov/disorders/parkinsons_disease/parkinsons_disease.htm

<http://www.cdc.gov/ExposureReport/pdf/thirdreport.pdf>

Parkinson's Disease Pesticides, Animal Experiments

- Paraquat (herbicide)
 - ▶ BBB permeability?
 - ▶ Somewhat conflicting neurotox data
 - ▶ SN cell loss, ↑ α -synuclein
- Paraquat & Maneb (herbicide) in mice
 - ▶ Geographic overlap
 - ▶ Synergistic effects: motor, dopaminergic
 - ▶ Early, even prenatal, exposures render more susceptible to later exposures (singly or combined)

Parkinson's Disease Pesticides, Animal Experiments

- Rotenone (insecticide) infusion in rats
 - ▶ Nigrostriatal dopaminergic lesions
 - ▶ α -synuclein inclusions
 - ▶ Motor and postural deficits
- Inflammation
 - ▶ Lipopolysaccharide (LPS) in utero
 - ▶ Increases susceptibility to later toxicant exposures

PD Neuropathology

