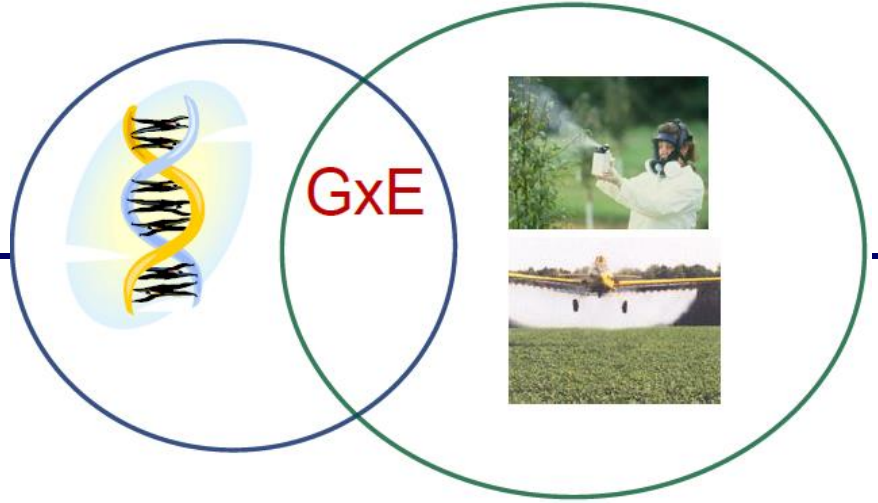


Pesticides and Parkinson's Disease

Beate Ritz, MD PhD

Dept. of Epidemiology and Neurology

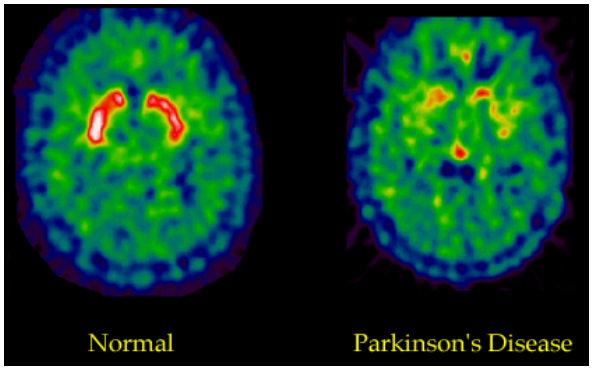
Center for Occupational and Environmental Health

UCLA, Fielding School of Public Health & Geffen School of Medicine

Parkinson's Disease

PD affects 5-10 adults per 1,000 over age of 60

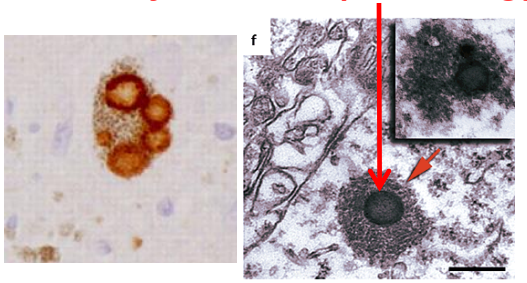
Abnormalities in the neurons in the basal ganglia & loss of dopamine (DA) neurons in the substantia nigra midbrain region

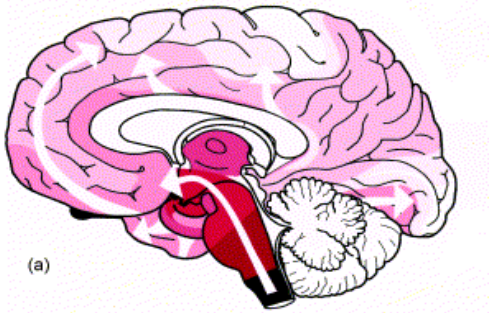


Cardinal clinical **motor** symptoms

- Tremor
- Rigidity
- Akinesia
- Postural reflex impairment

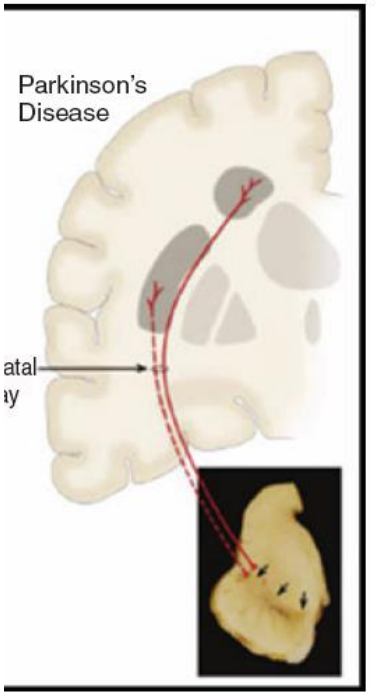
A-synuclein pathology

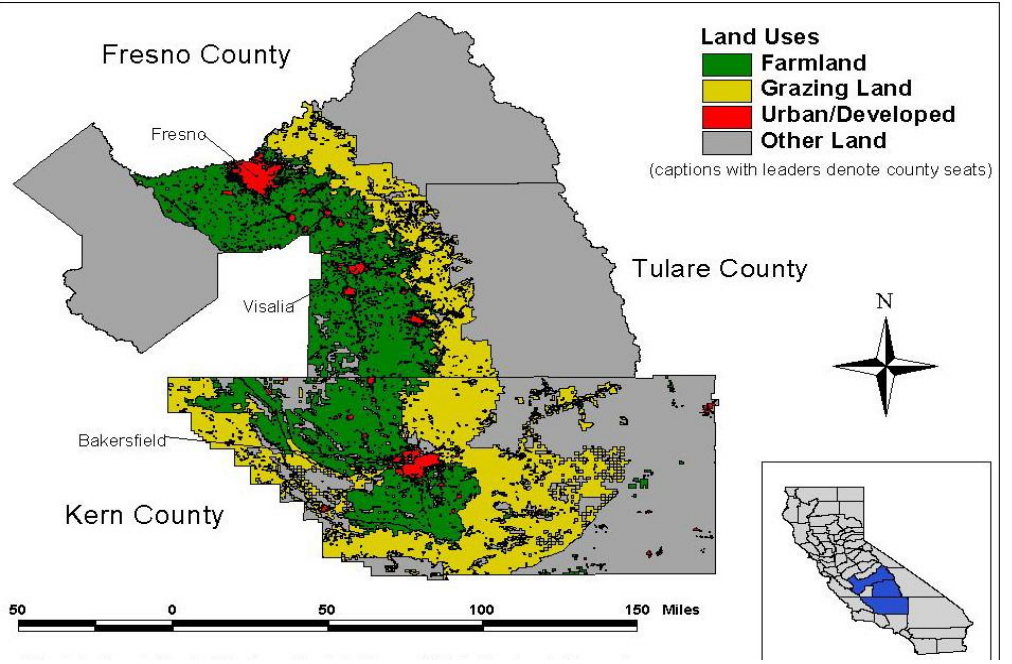




Plus **non-motor** symptoms

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





Parkinson's, Environment and Gene Study (PEG)

(Pesticides and Genes)

funded by
NIH/ National Institute of Environmental Health Sciences
RO1ES10544, 5P01ES016732

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):

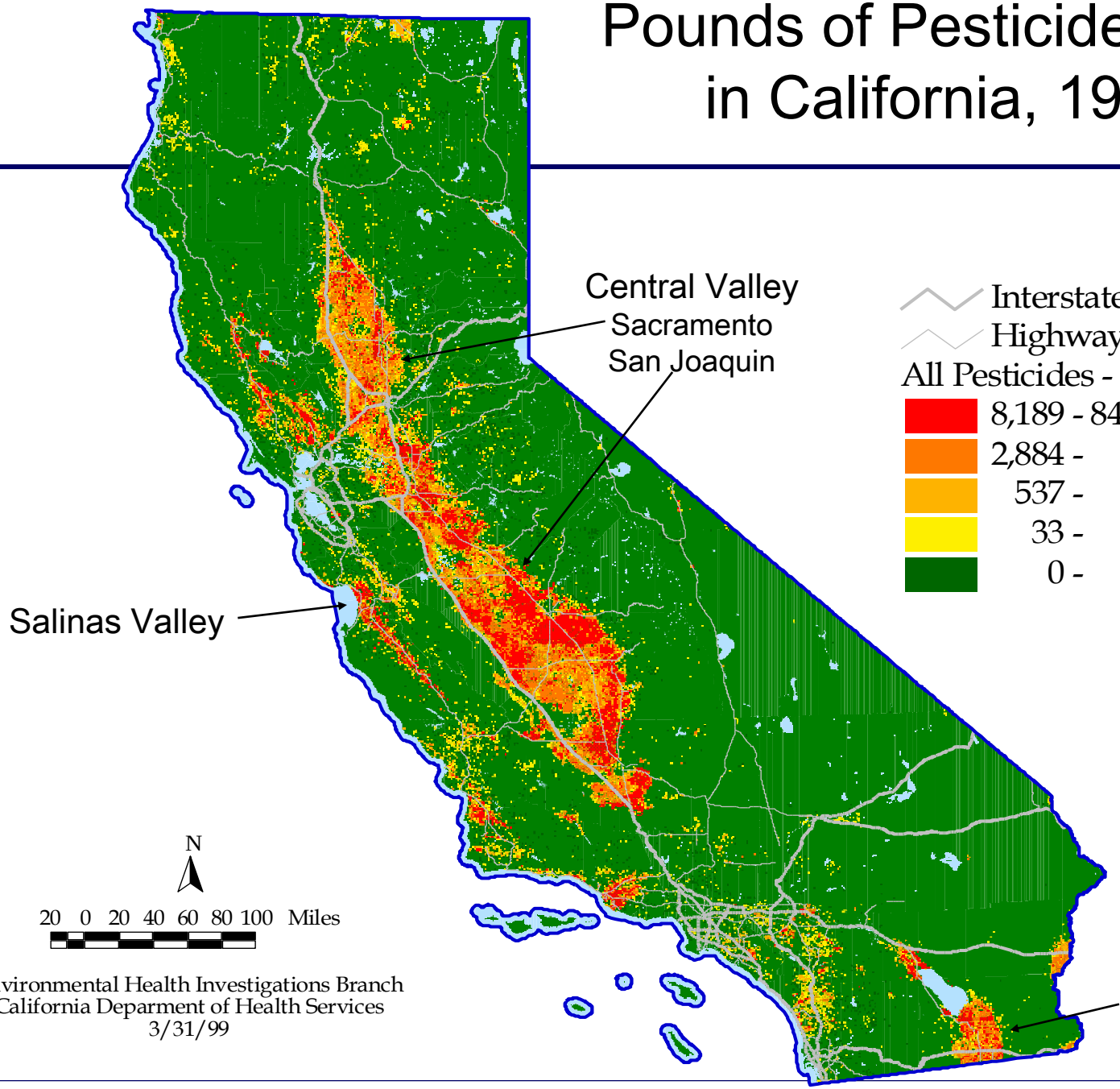
- County: Kern
- Location: 15M28S27E19 (PUR geo-locator)
- Application date: 2/23/1989
- Commodity: 2503 (Grapes)
- Method: Ground
- Treated: 424 acres
- Product applied: 155 gallons
- Chemical: 00459 (*Parathion*)
- Percentage: 80%
- Active Ingredient Pounds: 1,241

Geographic Locators for the PUR are based on Public Land Survey System

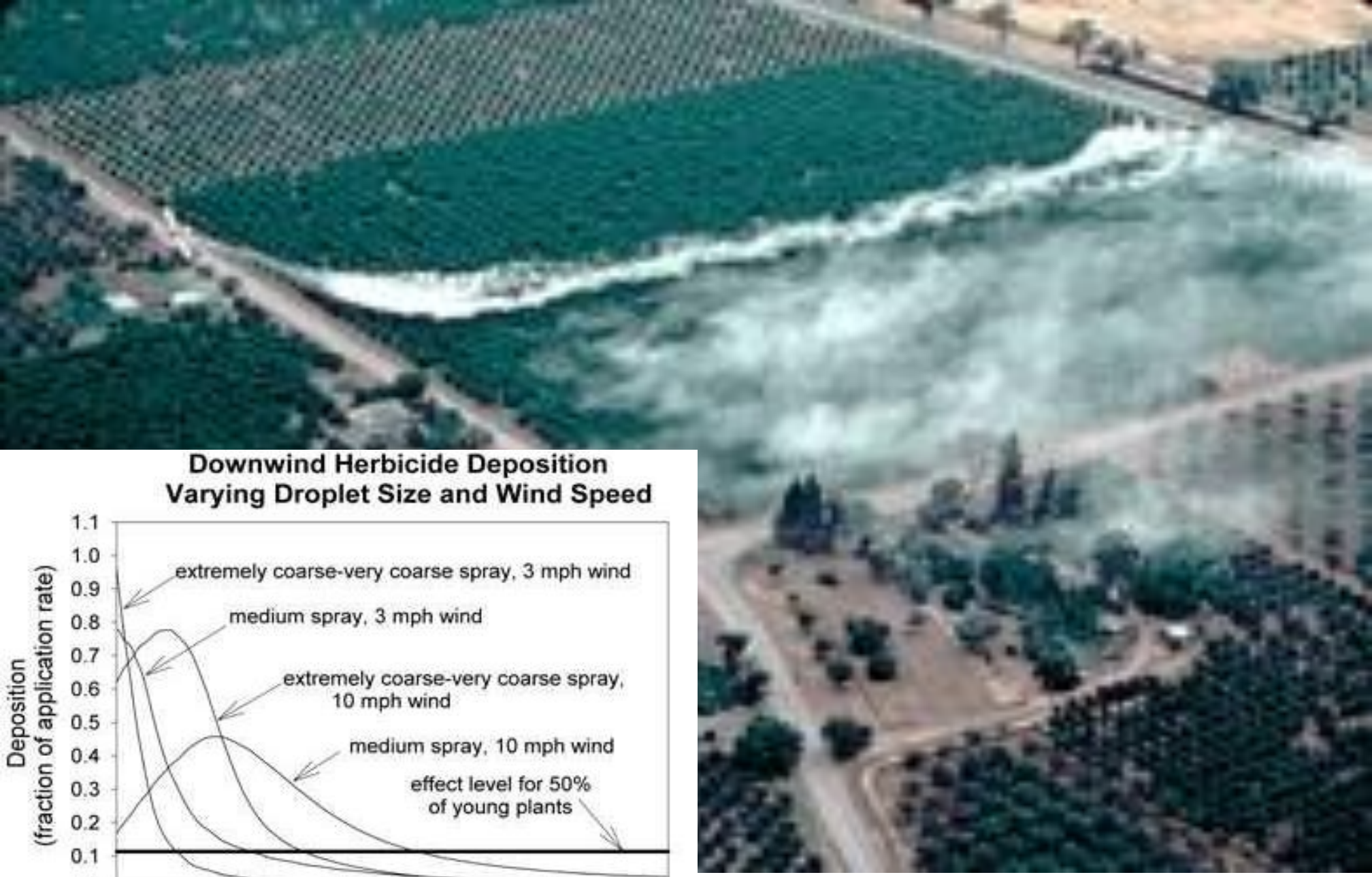
  – limited to 1 PLS section (appr. 640 acres =1 sq.mi)

Thus, we improved the resolution in GIS with CA land-use survey maps (DWR)

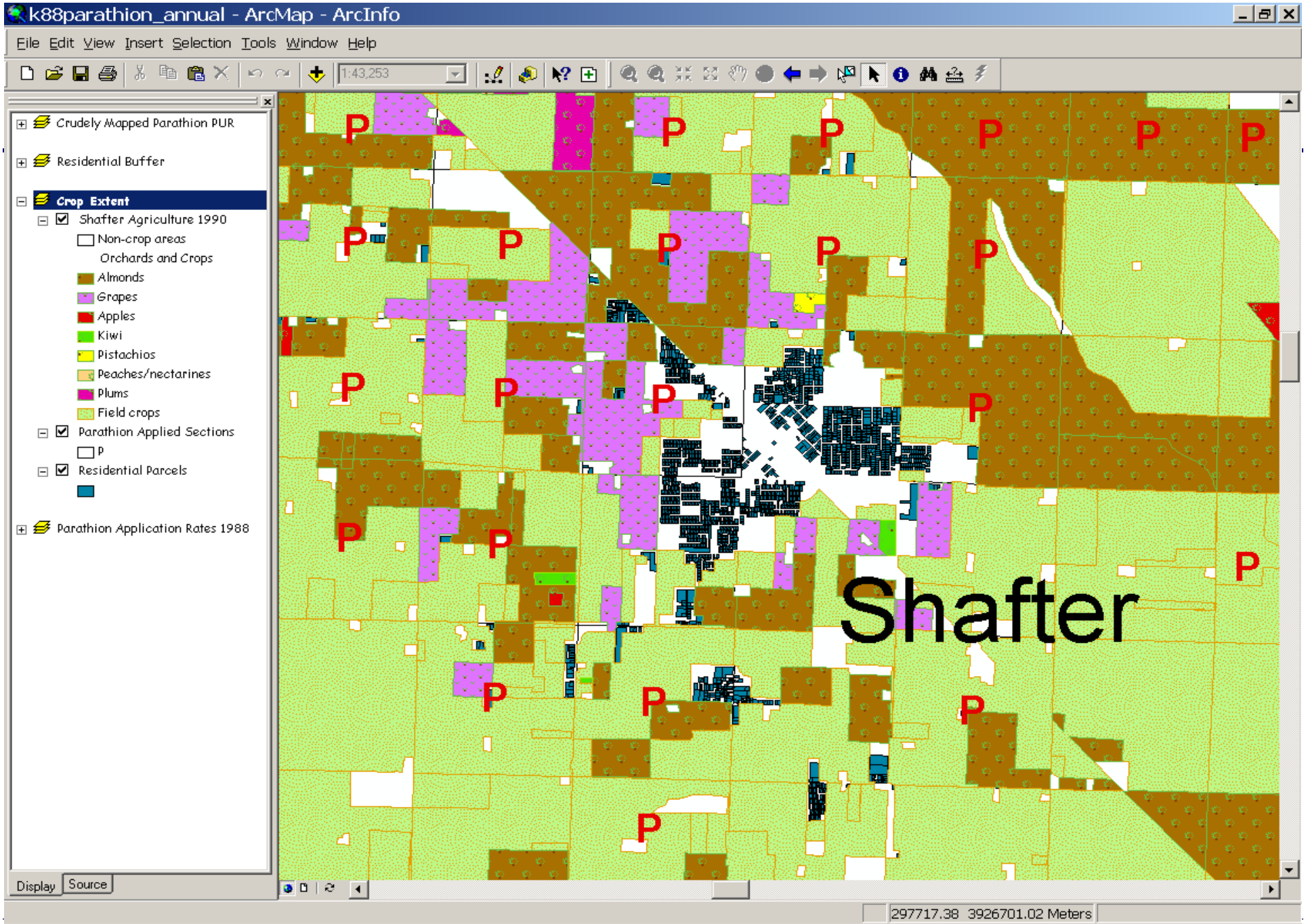
Pounds of Pesticides Applied in California, 1991-94

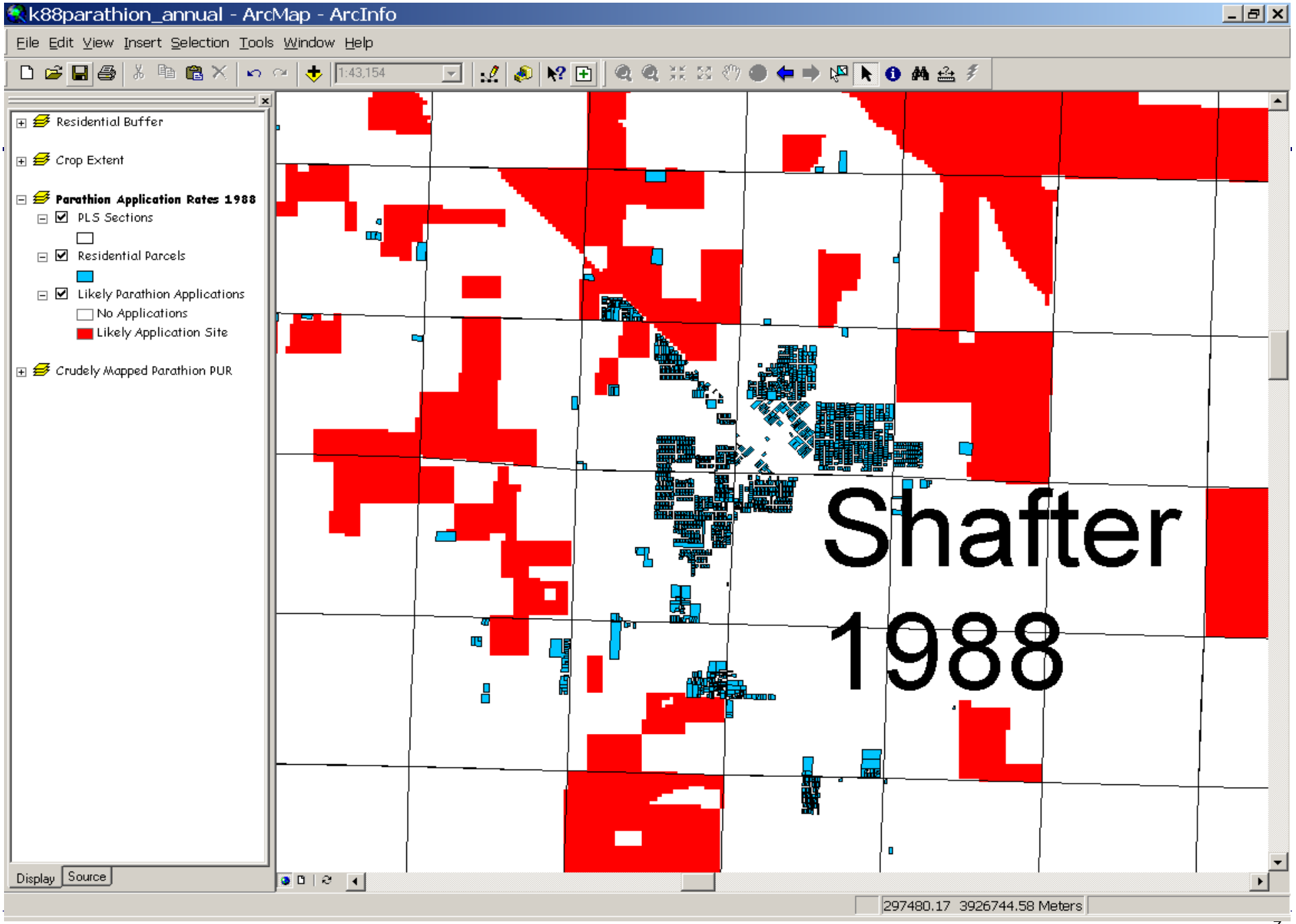


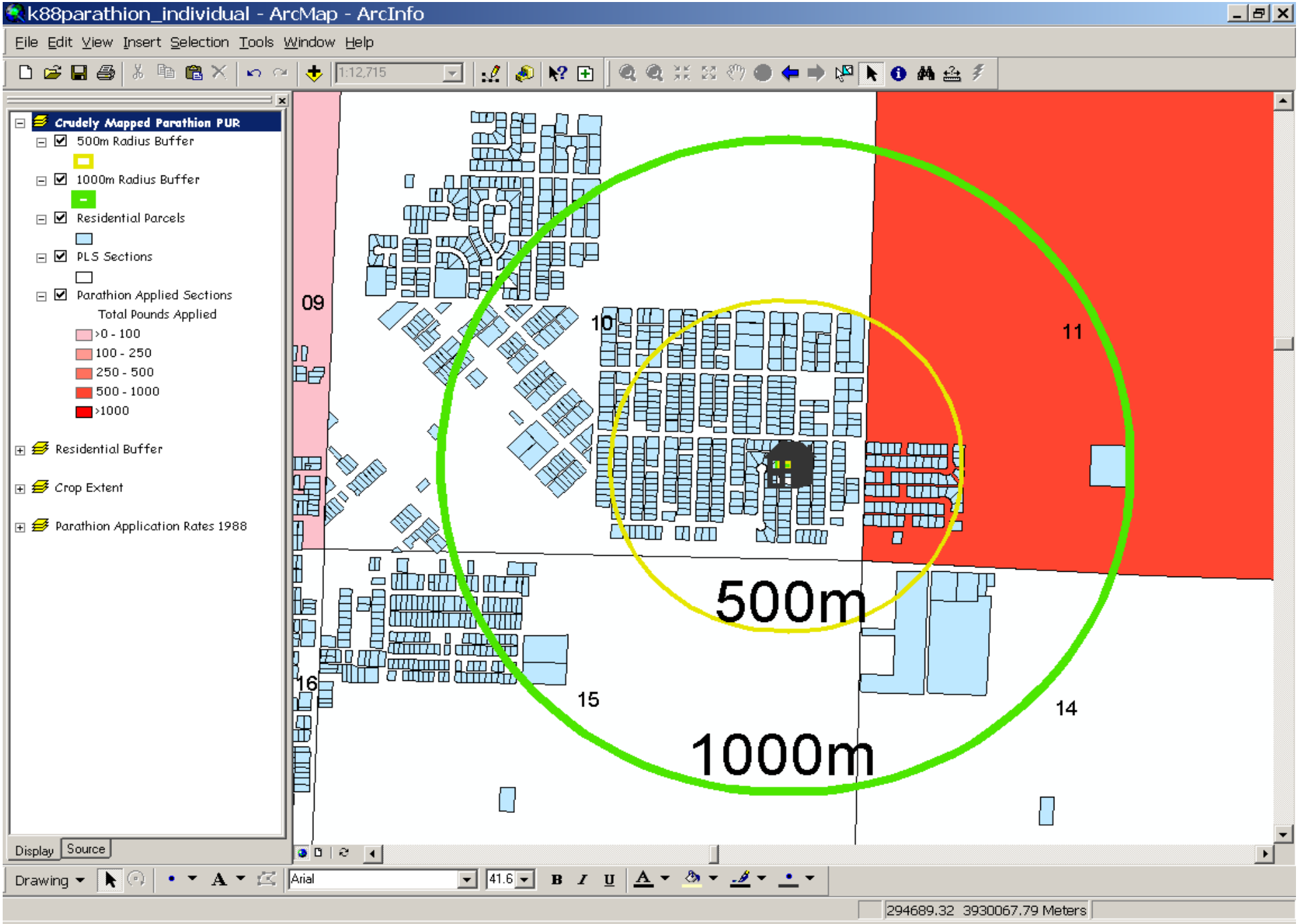
Environmental Health Investigations Branch
California Deparment of Health Services
3/31/99



Downwind Herbicide Deposition
Varying Droplet Size and Wind Speed
Deposition
(fraction of application rate)
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
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
0
200
400
600
800
1000
Downwind distance (ft)


k88parathion_annual - ArcMap - ArcInfo
File Edit View Insert Selection Tools Window Help
1:43,253
Crudely Mapped Parathion PUR
Residential Buffer
Crop Extent
Shafter Agriculture 1990
Non-crop areas
Orchards and Crops
Almonds
Grapes
Apples
Kiwi
Pistachios
Peaches/nectarines
Plums
Field crops
Parathion Applied Sections
P
Residential Parcels
Parathion Application Rates 1988
Display
Source
Shafter
297717.38 3926701.02 Meters


k88parathion_annual - ArcMap - ArcInfo
File Edit View Insert Selection Tools Window Help
1:43,154
Residential Buffer
Crop Extent
Parathion Application Rates 1988
PLS Sections
Residential Parcels
Likely Parathion Applications
No Applications
Likely Application Site
Crudely Mapped Parathion PUR
Display
Source
Shafter
1988
297480.17 3926744.58 Meters

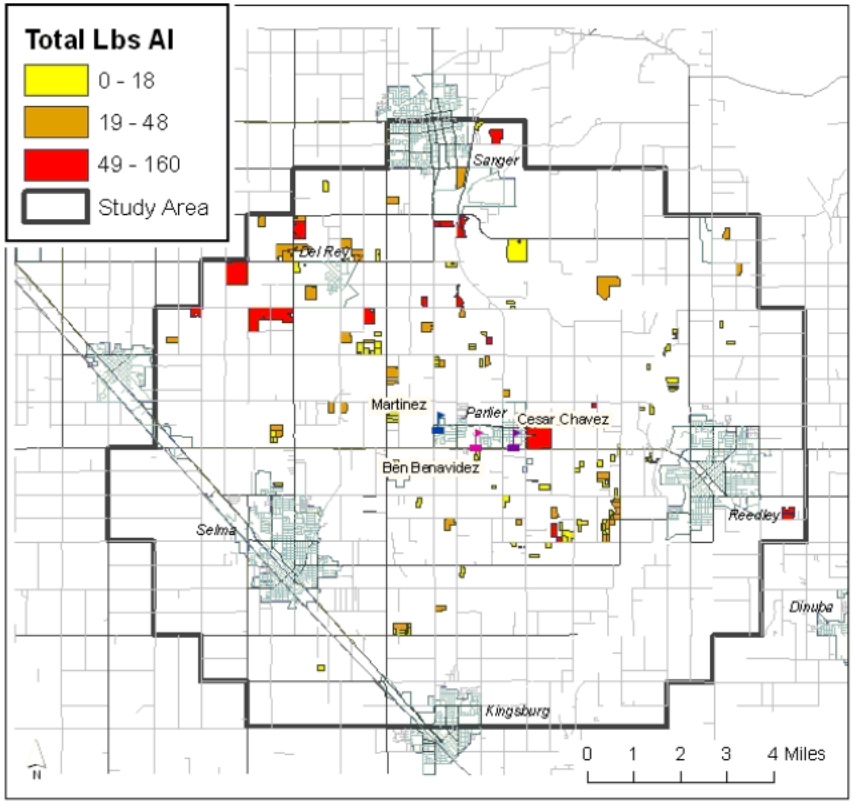

k88parathion_individual - ArcMap - ArcInfo
File Edit View Insert Selection Tools Window Help
1:12,715
Crudely Mapped Parathion PUR
500m Radius Buffer
1000m Radius Buffer
Residential Parcels
PLS Sections
Parathion Applied Sections
Total Pounds Applied
>0 - 100
100 - 250
250 - 500
500 - 1000
>1000
Residential Buffer
Crop Extent
Parathion Application Rates 1988
09
10
11
16
15
14
500m
1000m
Display
Source
Drawing
Arial
41.6
294689.32 3930067.79 Meters

Environ Monit Assess (2014) 186:1355–1370
DOI 10.1007/s10661-013-3394-x

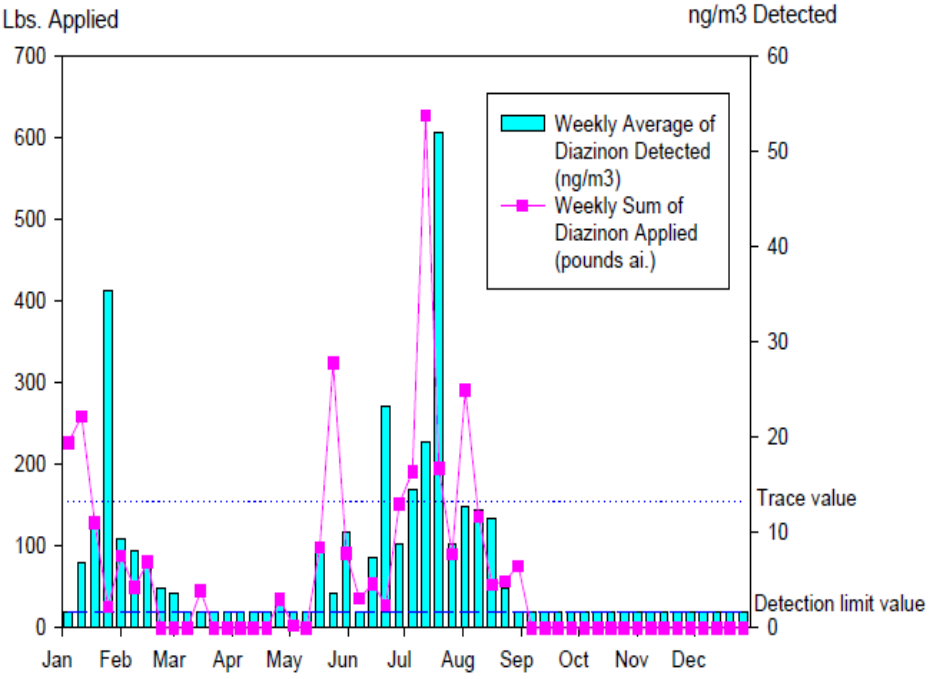
Community air monitoring for pesticides. Part 3: using health-based screening levels to evaluate results collected for a year

Pamela Wofford · Randy Segawa · Jay Schreider · Veda Federighi · Rosemary Neal · Madeline Brattesani

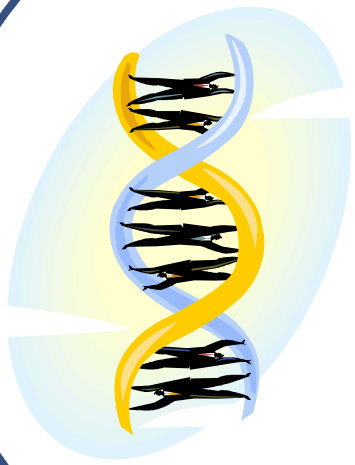
Figure 22. Diazinon: locations of all reported applications in 2006.



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



Gene x Pesticide Interactions



Pesticides

640

GENES

~20,000

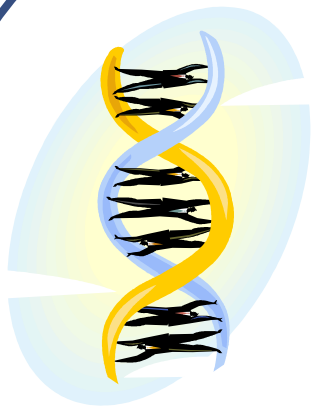
Age

Sex

home and agricultural use

DAT1 and Paraquat/Maneb and PD

Transporter for dopamine involved in dopamine homeostasis



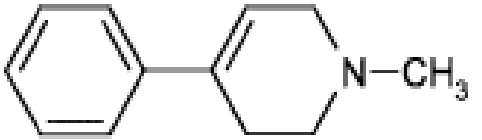
Maneb/
Paraquat
Age
DAT1
Sex

agricultural use

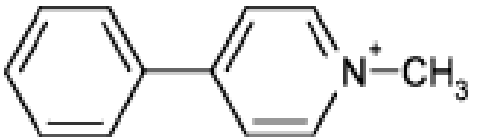
Animal Tox Testing: Paraquat and maneb

Paraquat

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



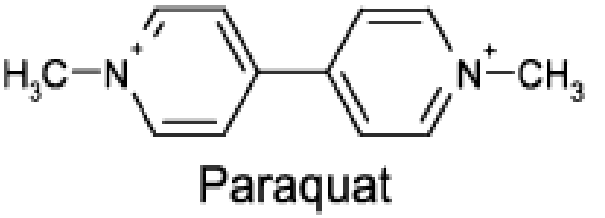
MPTP



MPP+

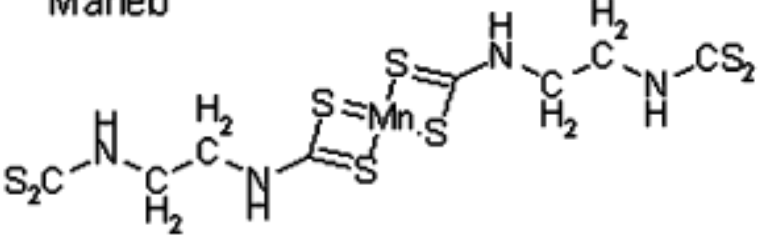
Maneb

- Dithiocarbamate (DTC) fungicide (manganese ethylene-bis-dithiocarbamate (Mn–EBDC))
  - In animal models it potentiates MPP+ effects
  - **Modulates/enhances paraquat toxicity**



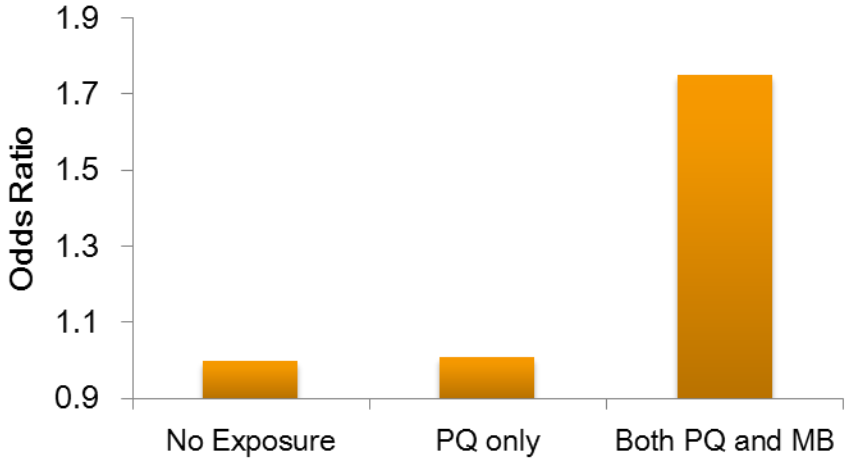
Paraquat

Maneb





Pesticides and PD in PEG study: What happens with combined paraquat & maneb exposure in humans?

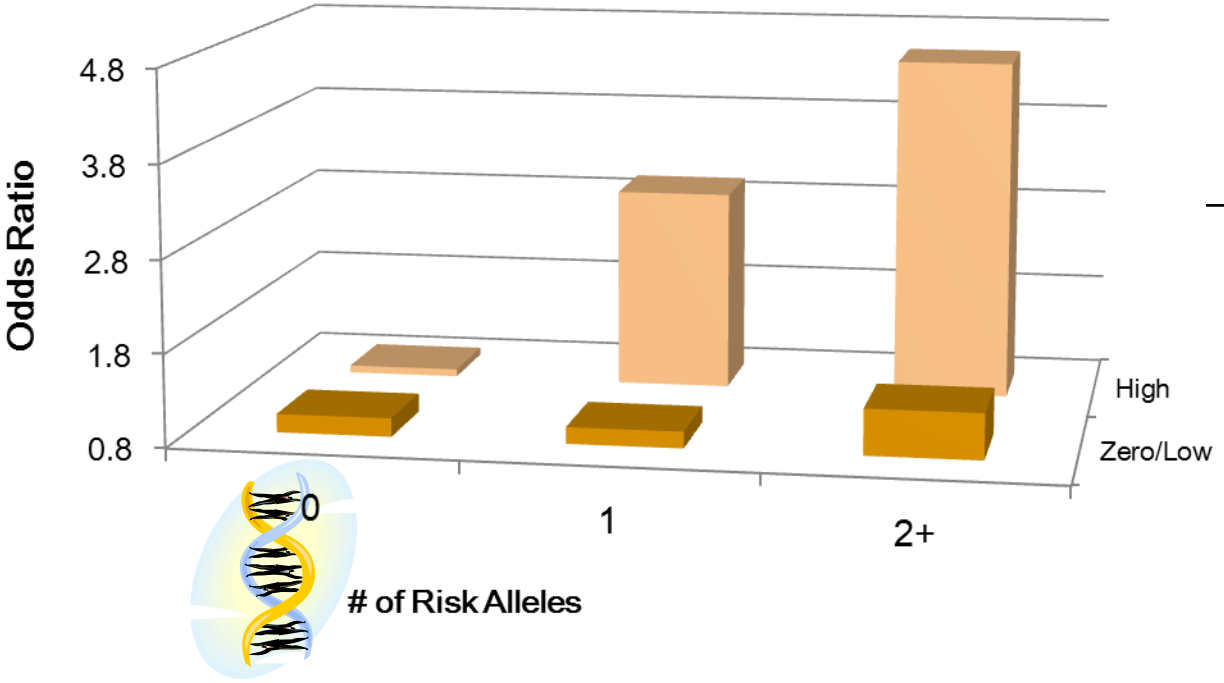


	Cases/ctrls	OR (95% CI)
No exposure	115/126	ref
Paraquat only	149/152	1.01 (0.71, 1.43)
Maneb only	*3/1*	-
Paraquat & maneb	88/49	**1.75 (1.13, 2.73)**

Costello S, Wahner A, Bronstein J, Cockburn M., Zhang X, Ritz B. Paraquat and Maneb exposure and Parkinson's disease in the California Central Valley. Am J Epidemiol. 2009 Apr 15;169(8):919-26.



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



Ambient PESTICIDE EXPOSURES

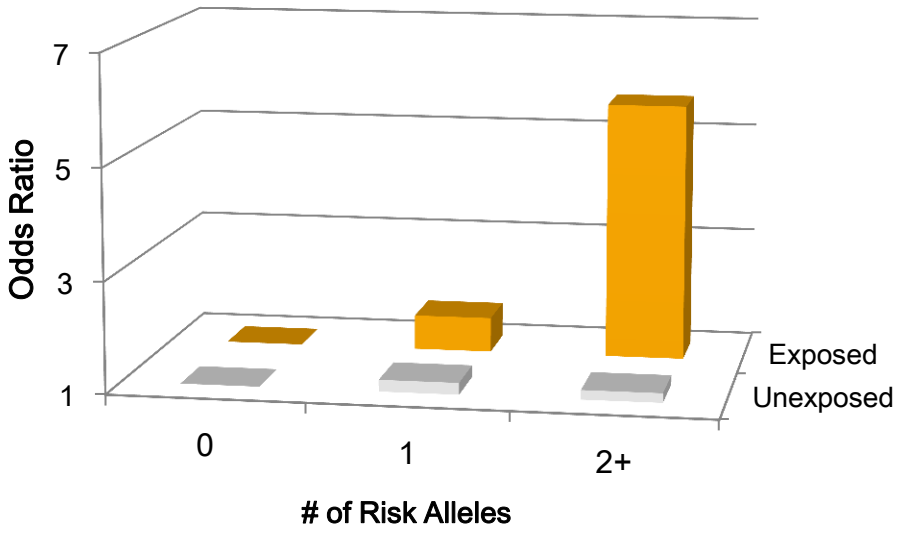
# of Risk Alleles	Zero/Low	High
0	ref	0.88 (0.22, 3.48)
1	0.98 (0.63, 1.52)	2.99 (0.88, 10.21)
2+	1.30 (0.85, 2.00)	4.53 (1.70, 12.09)

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):*

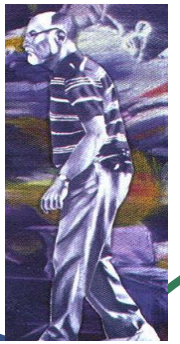


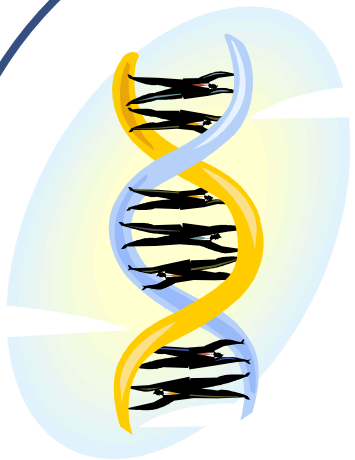
Number of DAT1 risk alleles	Pesticide Unexposed OR (95%)[a]	Pesticide Exposed OR (95%)[a]
0	1 (ref.)	1.0 (ref.)
1	1.21 (0.62–2.36)	1.63 (0.52-5.15)
2+	1.17 (0.62–2.23)	5.66 (1.73-18.53)

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





OP pesticides

Age

PON1

Sex

agricultural and home use

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

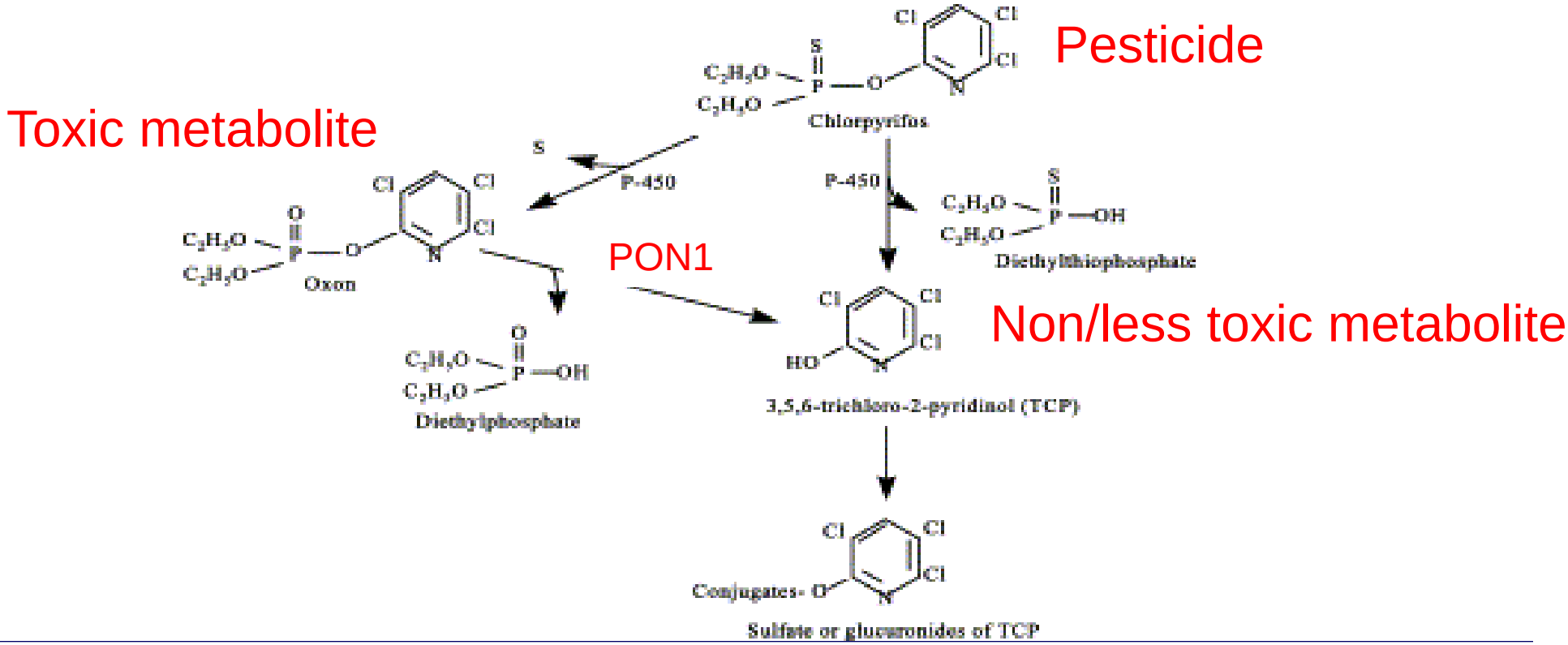
- Chlorpyrifos (TCPY) in more than **96%** samples
- Diazinon (IMPY) in 29% samples

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

Barr et al. Concentrations of selective metabolites of organophosphorus pesticides in the United States population. Environ Res. 2005 Nov;99(3):314-26.

PON1 hydrolyzes toxic organophosphates and carbamate pesticide metabolites



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

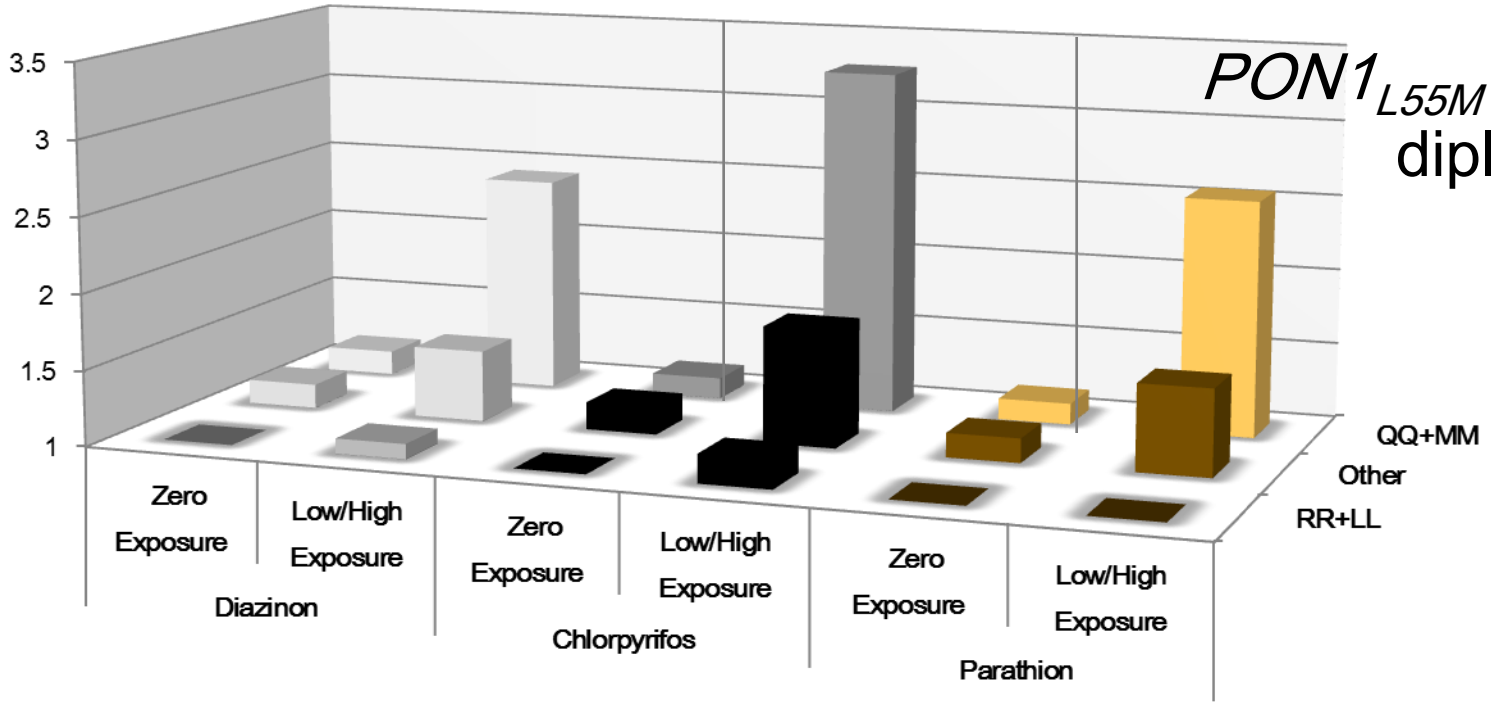
PON1 serum activities for diazoxon (50 mM) by genetic polymorphism: M55L and Q192R
[O'Leary et al. 2006]

PON1 -genotypes	55-LL	55-LM	55-MM
192-QQ	15.6 ± 6.0	11.2 ± 5.0	6.35 ± 1.50
192-QR	18.1 ± 7.7	14.3 ± 2.8	-
192-RR	22.0 ± 9.4	16.4 ± 0.0	-

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,b], Shannon L. Rhodes [a], Janet S. Sinsheimer [c], Jeff Bronstein [d], Beate Ritz [a,d,*]



PON1$_{L55M}$ & *PON1*$_{Q192R}$ diplotypes

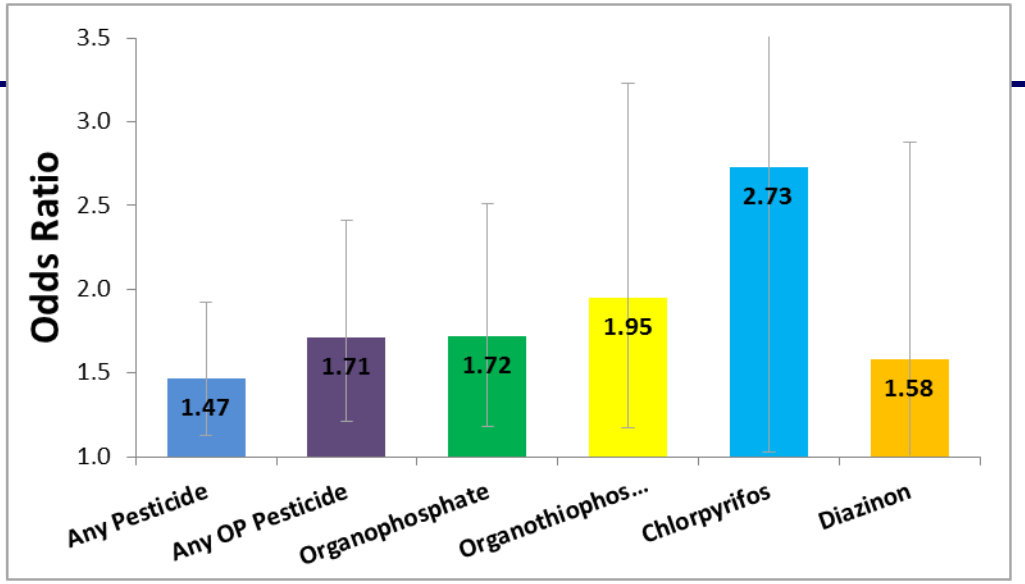
PON1$_{L55M}$ and PON1$_{Q192R}$ diplotypes	Diazinon		Chlorpyrifos		Parathion	
	Zero Exposure	Low/High Exposure	Zero Exposure	Low/High Exposure	Zero Exposure	Low/High Exposure
RR+LL	1	1.10 (0.35-3.47)	1	1.19 (0.36-3.92)	1	0.99 (0.30-3.25)
Other	1.16 (0.41-3.27)	1.47 (0.53-4.05)	1.18 (0.42-3.33)	1.77 (0.64-4.92)	1.16 (0.41-3.28)	1.57 (0.56-4.37)
QQ+MM	1.16 (0.29-4.62)	2.43 (0.78-7.56)	1.14 (0.29-4.58)	3.28 (1.02-10.58)	1.14 (0.28-4.55)	2.56 (0.78-8.39)

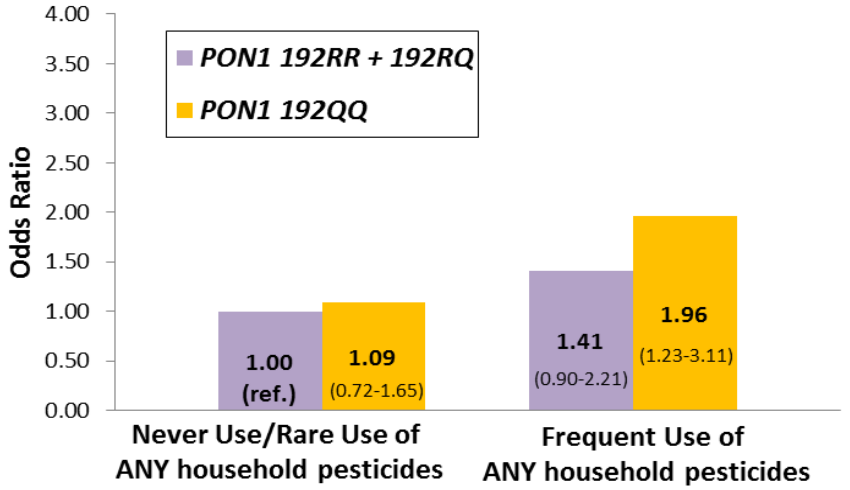
287 cases, 440 controls (Caucasians only)

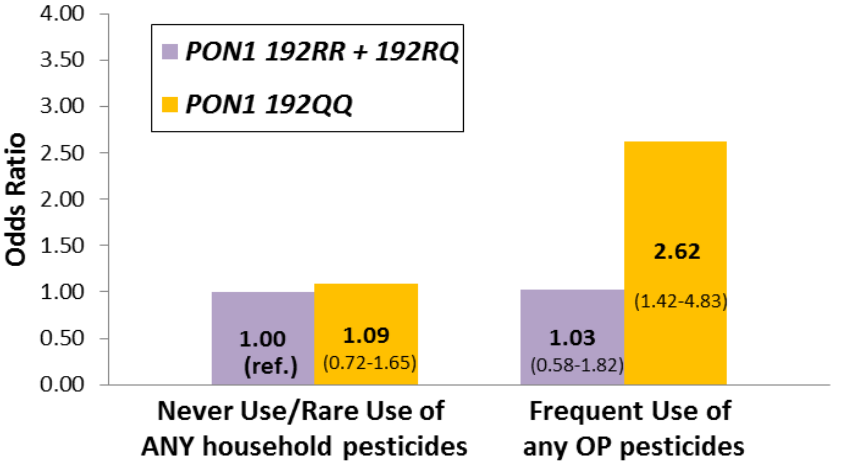
- adjusted for age, gender, smoking status, county, and education level

-reference group of participants is for those unexposed to all three OPs

PON1$_{Q192R}$ and Household Pesticide Usage



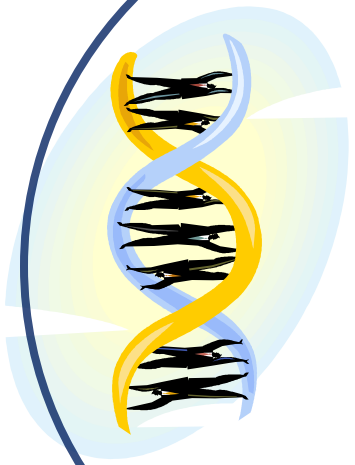




Average usage from age 16 until 10 years prior to age of onset and PD, Caucasians Only; pesticides ingredients identified from list of CA registered chemicals

NOS and OP pesticides and PD

Nitric oxide (NO) is a potent pro-oxidant that can damage dopaminergic neurons



OP pesticides

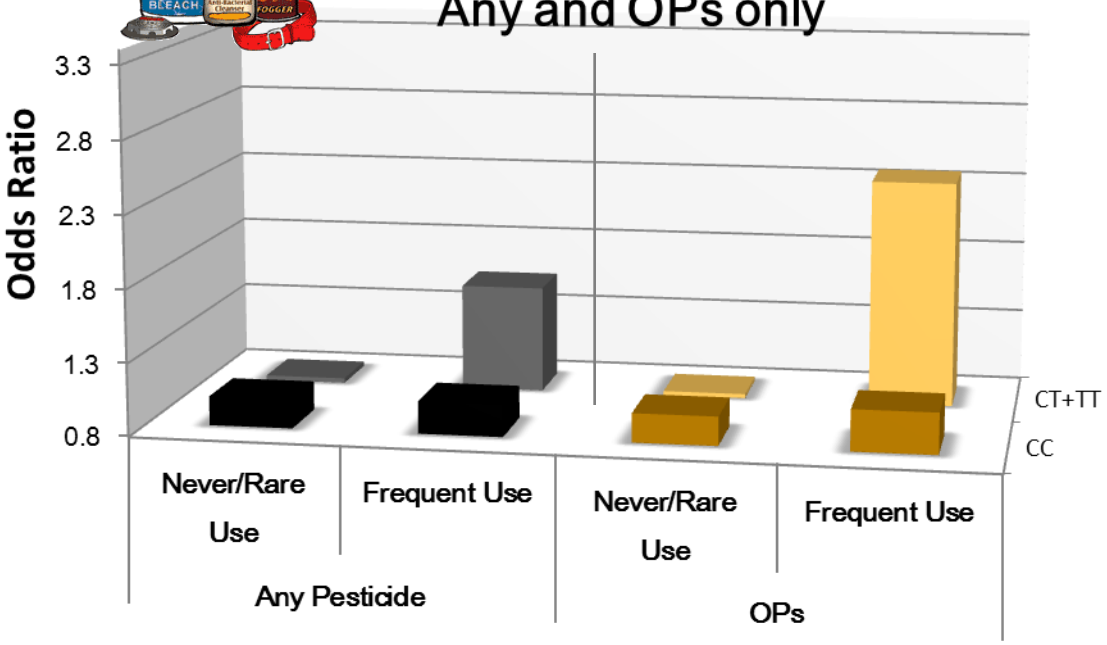
Age

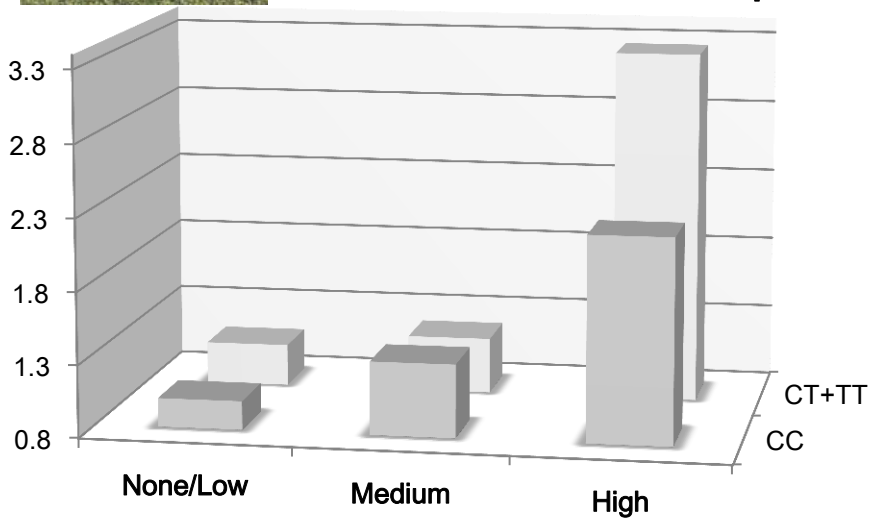
NOS

Sex

home and agricultural use

NOS1 and multiple OP pesticide exposure sources





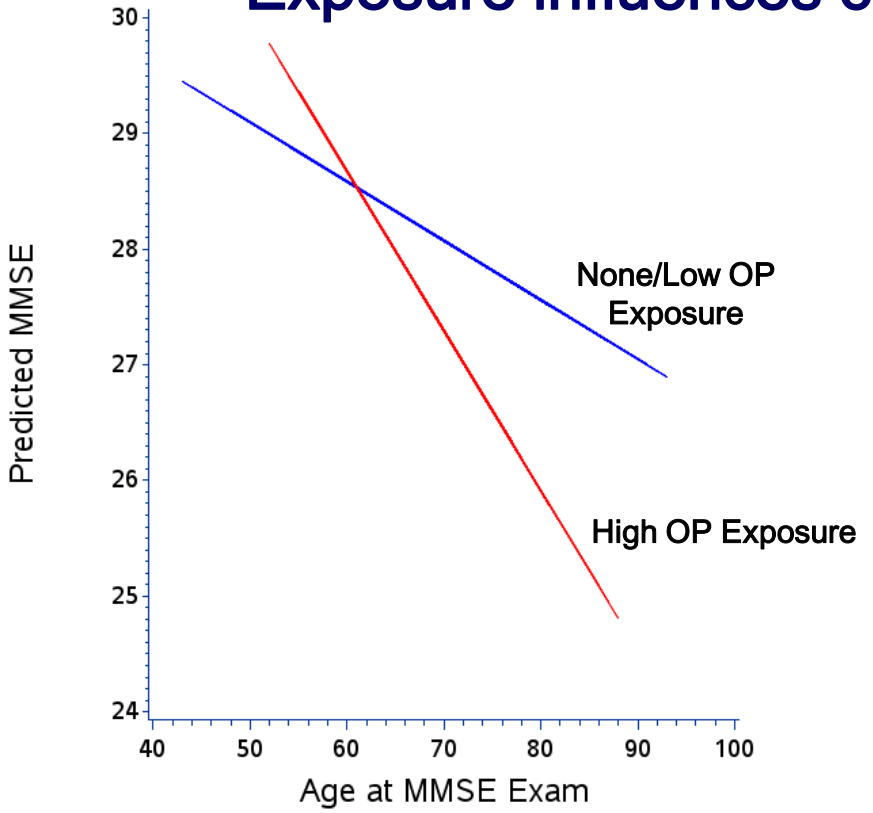
	Any Household Pesticide		Household OP Pesticides		Ambient OP Exposure		
	Never/Rare Use	*Frequent Use*	*Never/Rare Use*	*Frequent Use*	*None/Low*	*Medium*	*High*
CC	1.00	1.02 (0.68-1.55)	1.00	1.09 (0.65-1.82)	1.00	1.31 (0.84-2.04)	2.22 (1.24-3.96)
CT+TT	0.83 (0.58-1.20)	1.54 (1.02-2.33)	0.83 (0.57-1.20)	2.37 (1.34-4.18)	1.09 (0.72-1.65)	1.19 (0.75-1.87)	3.25 (1.73-6.10)
Interaction OR1	1.81 (1.01-3.24)		2.63 (1.23-5.63)				0.83 (0.44-1.56)
Interaction OR2							1.37 (0.58-3.12)

*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

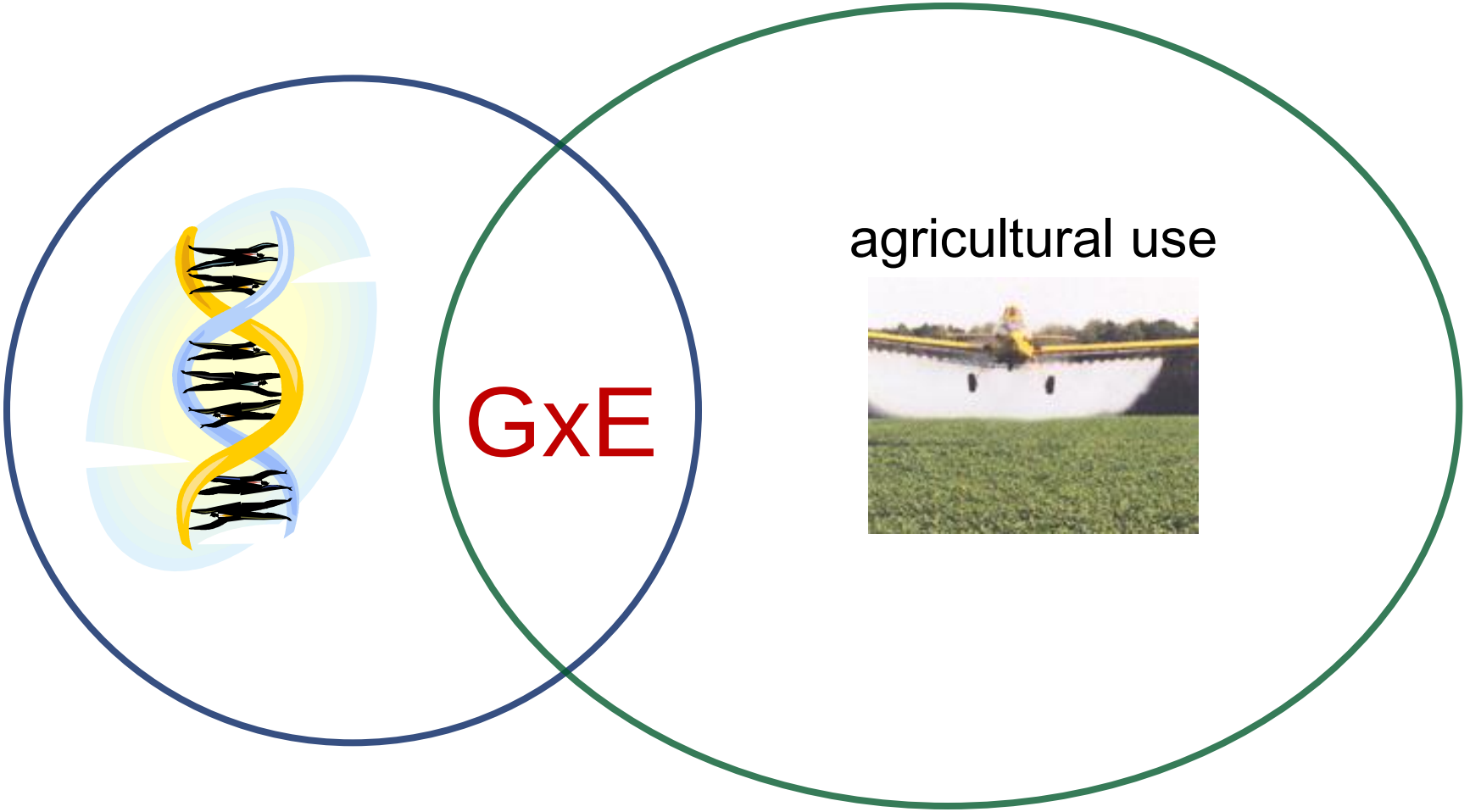


		N=242 n (%)	β	P-value
***OP Exp*:**	**None/Low**	182 (75.2)	0	ref
	High	60 (24.8)	3.92	0.07
***OP x Age*:**	**None/Low x Age**		0	ref
	High OP x Age		-0.06	0.05
Age (continuous)			-0.05	0.003
Sex:	**Female**	104 (43.0)	0	ref
	Male	138 (57.0)	-0.65	0.02
Minority Status:	**White**	194 (80.2)	0	ref
	Non-White	48 (19.8)	-0.80	0.03
School Years (continuous)			0.13	<.0001

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

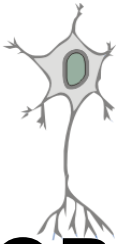
ALDH inhibiting pesticides and PD

ALDH metabolizes DOPAL which is toxic to nigral DA neurons



Aldehyde dehydrogenase (ALDH) enzyme

In DA neurons



Dopamine → DOPAL → DOPAC

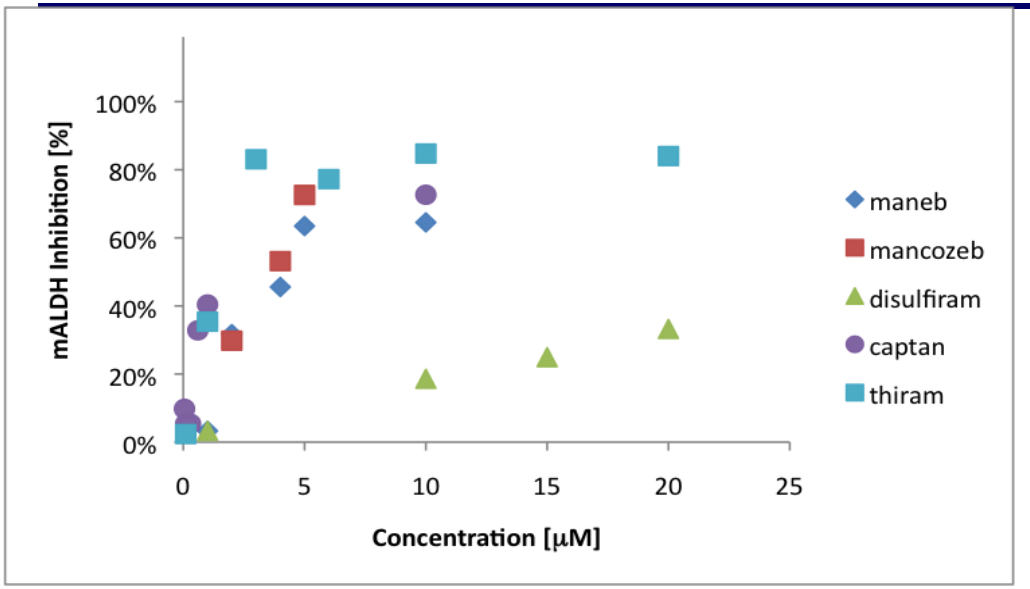
MAO

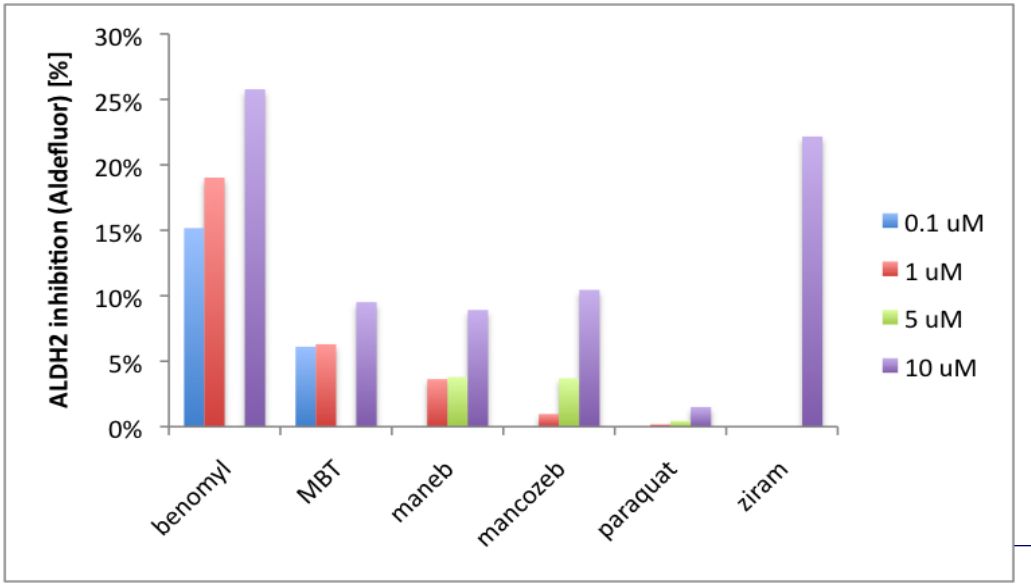
ALDH

5x more toxic to nigral neurons than DA or DOPAC (Burke et al., 2003)

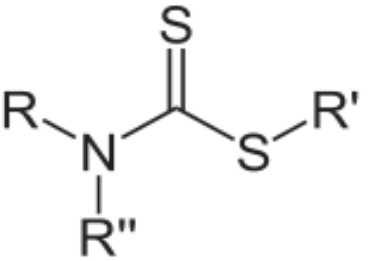
Interferes with NAD^+/NADH balance, mitochondrial activity

Screening in Dr. Bronstein's lab finds dithiocarbamate pesticides inhibit ALDH

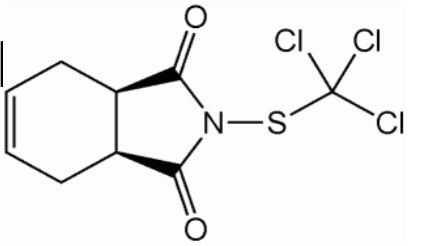




- dithiocarbamates
  - **maneb**
  - mancozeb
  - disulfiram
  - thiram
  - **ziram**



- dicarboxymide/
  - captan



ALDH inhibiting Pesticides X Genetic variants in ALDH and PD

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

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Aldehyde dehydrogenase variation enhances effect of pesticides associated with Parkinson disease

Neurology® 2014;82:419-426

CONCLUSIONS

Gene-environment interactions in human studies are important

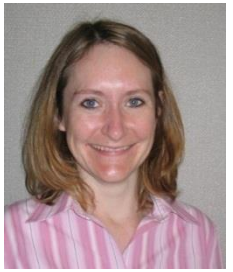
Pesticides put individuals with some **common genetic variant** at much higher risk of developing PD



A strong scientific story is important to justify and stimulate Environmental Regulations



Special Thanks to
NIEHS for the research funding



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