



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)

Rotenone Exposure and PD

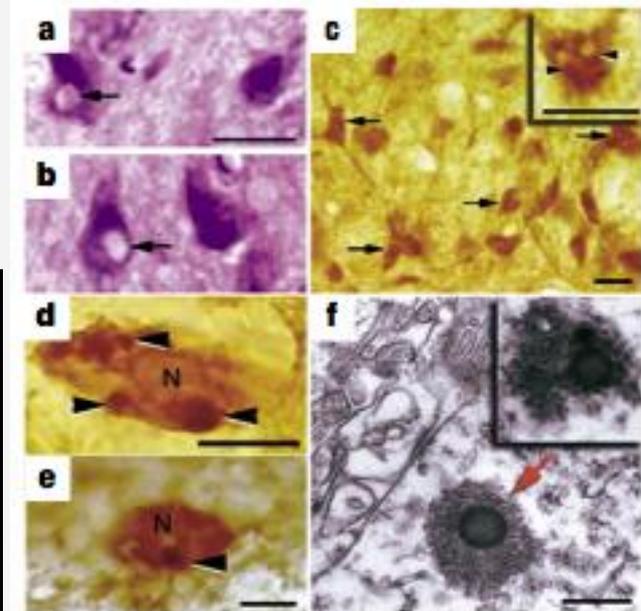
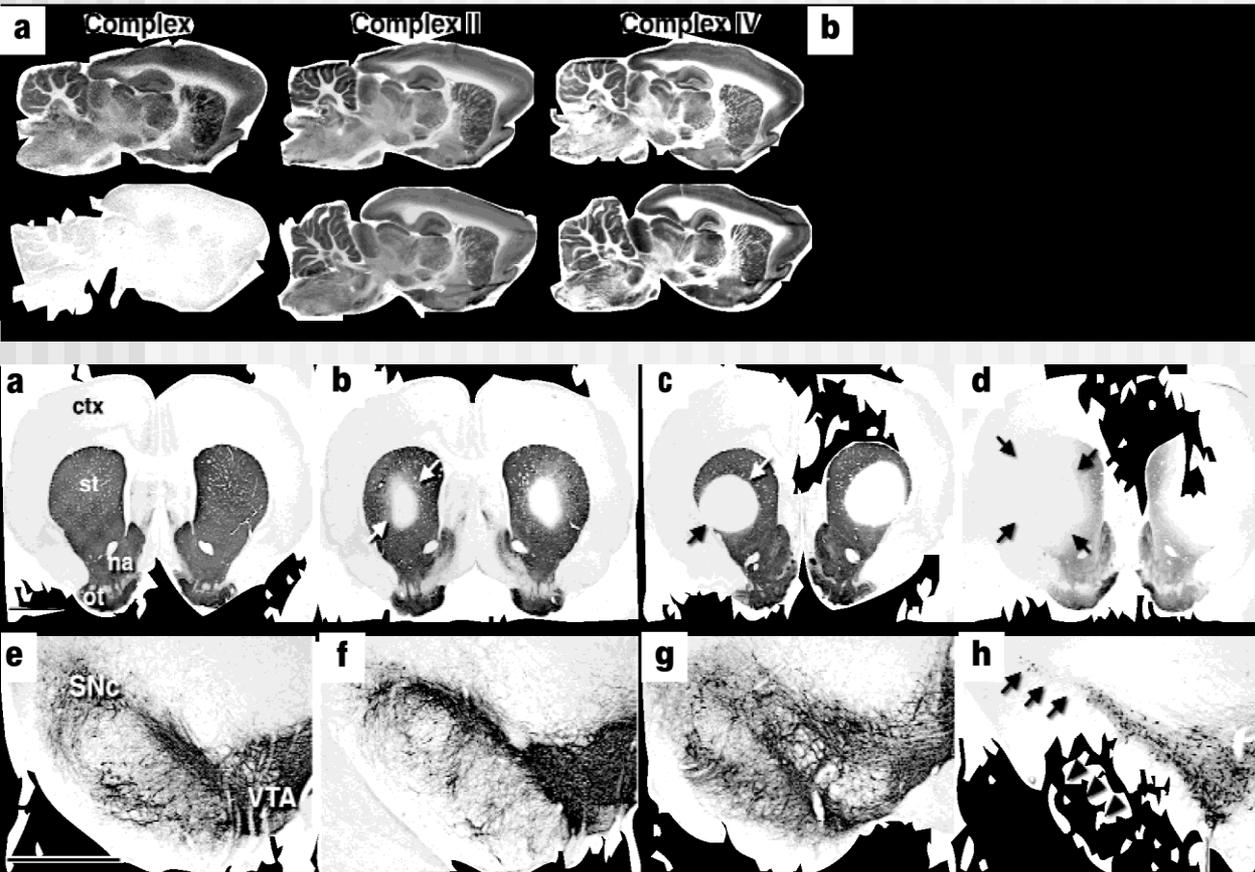
- Residential use more common than commercial use.
- A few case-control studies support increase incidence but not conclusive.
 - Dhillon et al 2008: OR 10.9 (2.5-48)
 - Agriculture Health Study: OR 1.7 (few cases)
 - Anecdotal reports

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

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

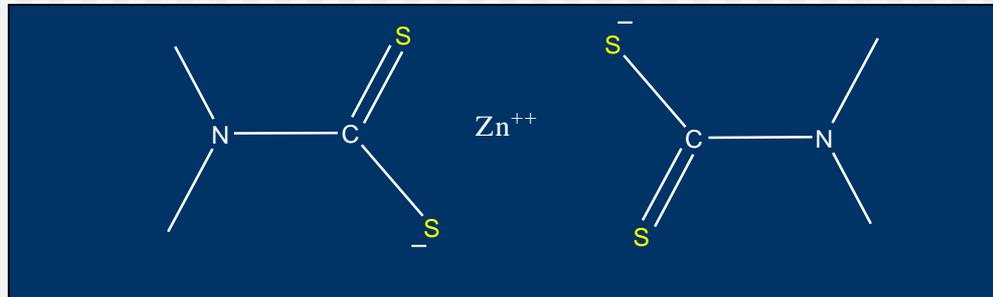
Dieldrin and Endosulfan

Organochlorines (epoxidic)

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.



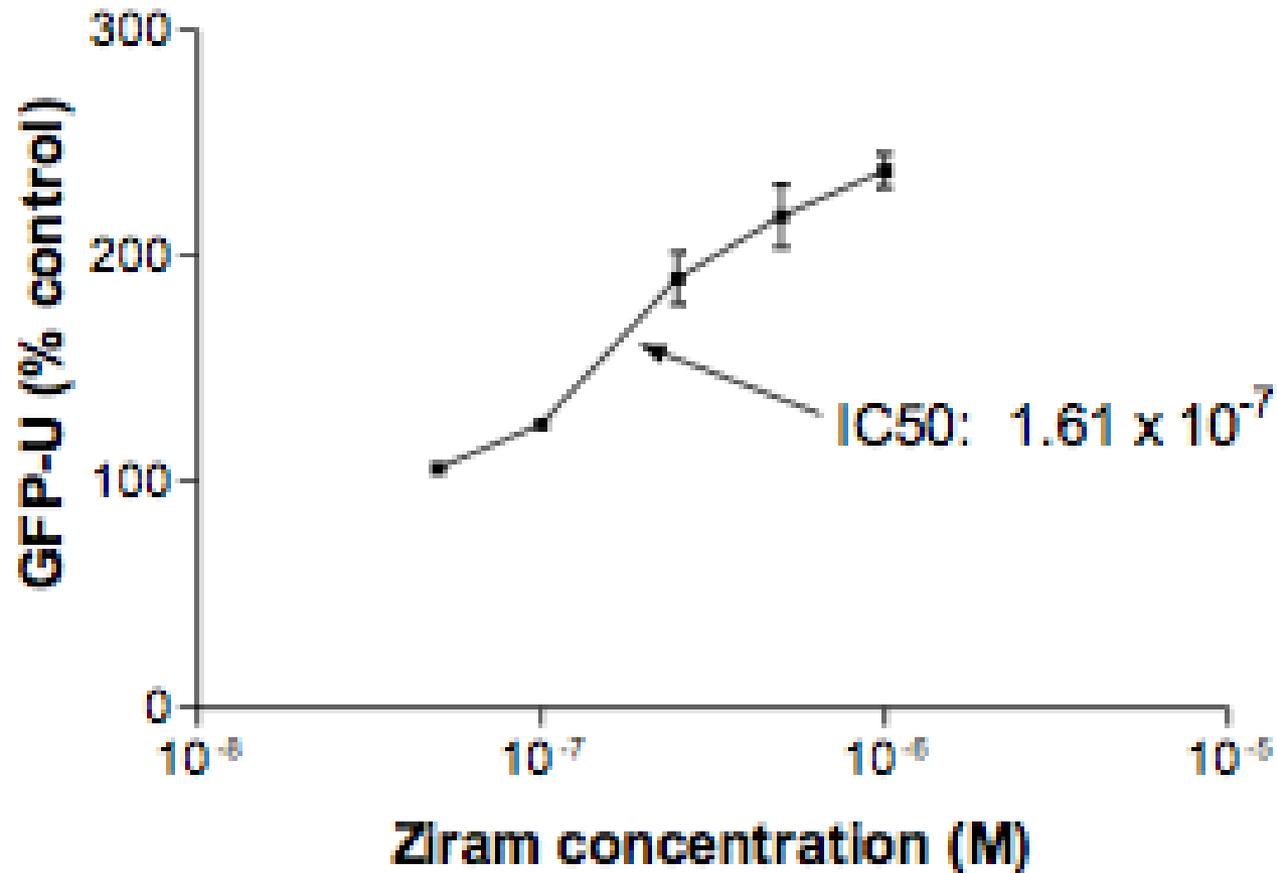
Ziram Exposure and PD (PEG Study)

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

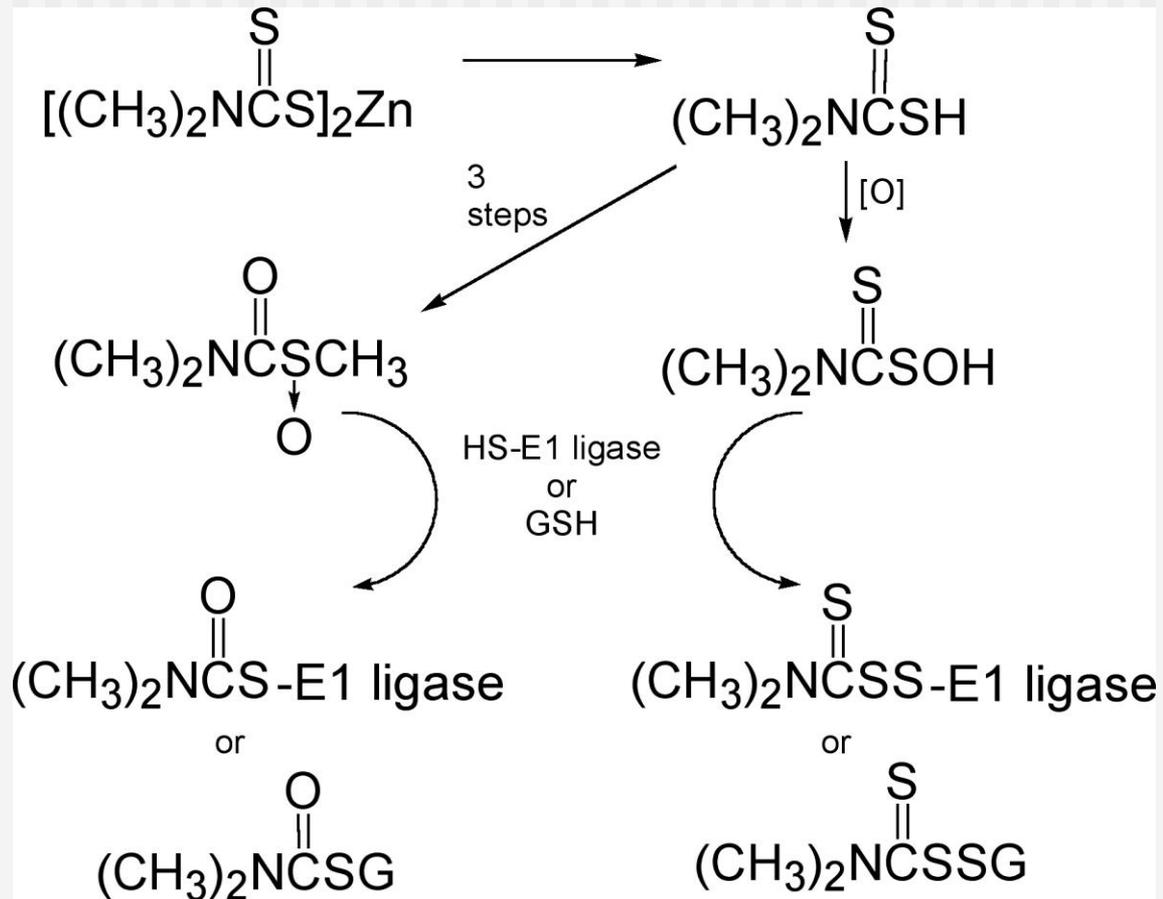
	Occupational**				Residential***			
	Case	Control	OR*	95% CI	Case	Control	OR*	95% CI
Ziram and paraquat exposure								
<u>1974-1999 Time Window</u>								
60 years old or younger								
No exposure to ziram or paraquat	28	53	1.00	ref	21	38	1.00	ref
Ziram or paraquat exp only	30	29	1.90	(0.92,3 .94)	35	37	1.66	(0.80,3 .47)
Ziram and paraquat exp	19	5	5.97	(1.94, 18.33)	21	12	2.76	(1.09,7 .00)
Over 60 years old								
No exposure to ziram or paraquat	137	141	1.00	ref	103	99	1.00	ref
Ziram or paraquat exp only	84	76	1.17	(0.78,1 .76)	113	112	0.88	(0.59,1 .31)
Ziram and paraquat exp	64	37	1.93	(1.18,3 .15)	69	43	1.41	(0.86,2 .29)

Wang A, Costello S, Cockburn M, Zhang X, Bronstein, Ritz B

Ziram Inhibits the 26S UPS

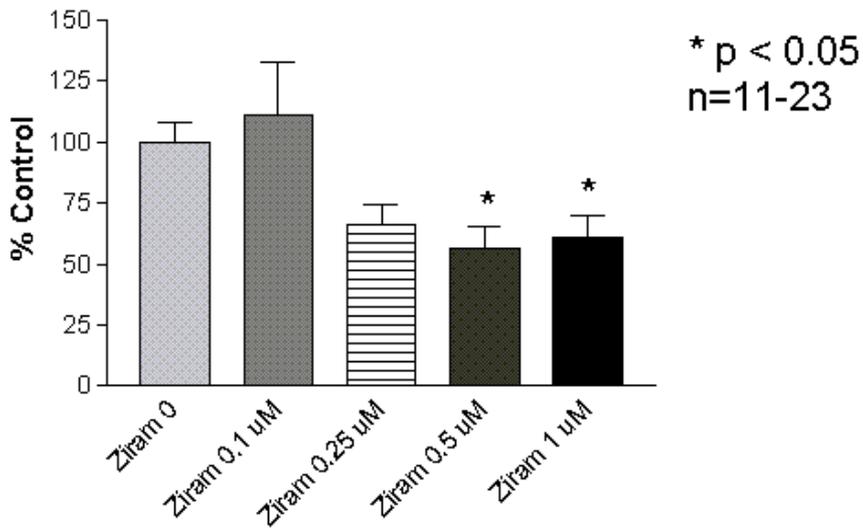


Ziram Inhibits E1 Ligase

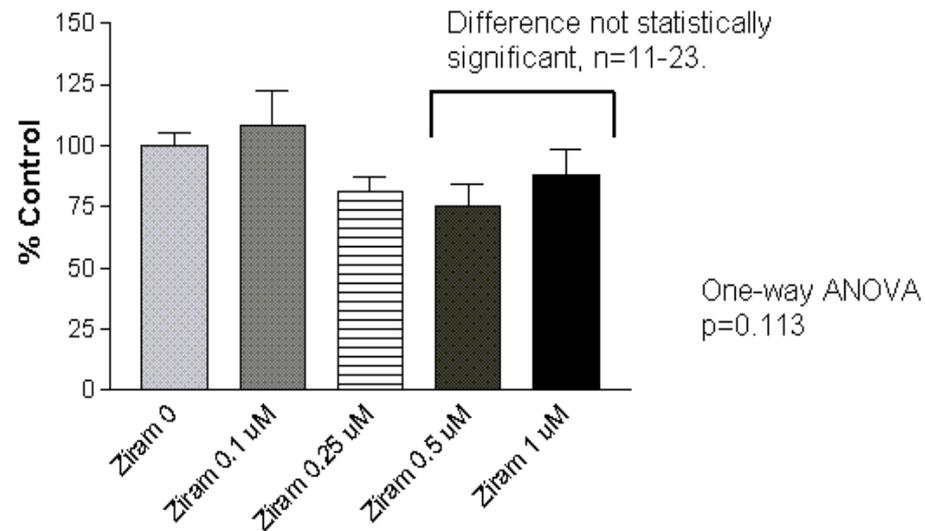


Ziram and Primary Mesencephalic Cultures

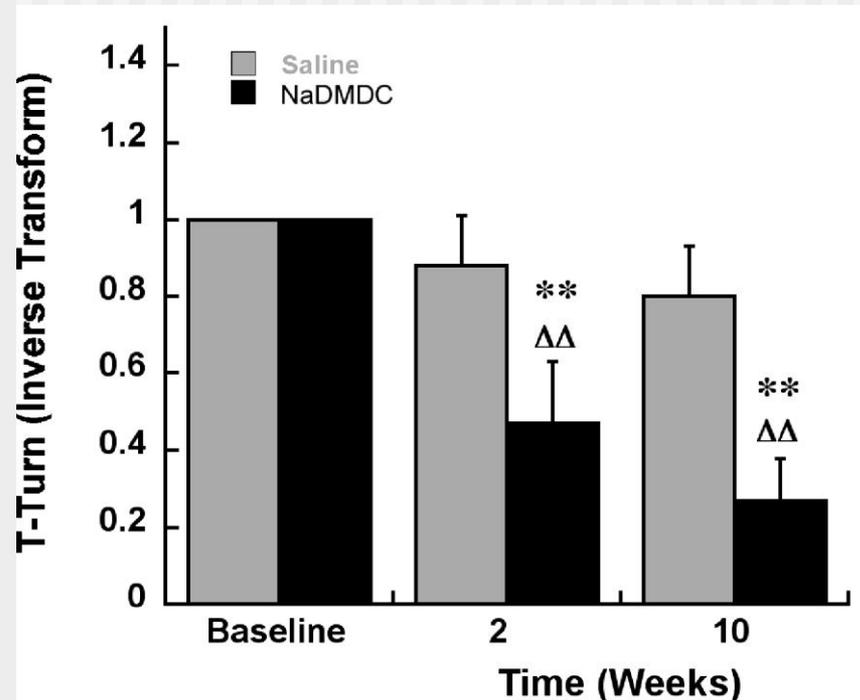
Effects of Ziram on TH+ Cell Number



Effects of Ziram on NeuN+ Cell Number

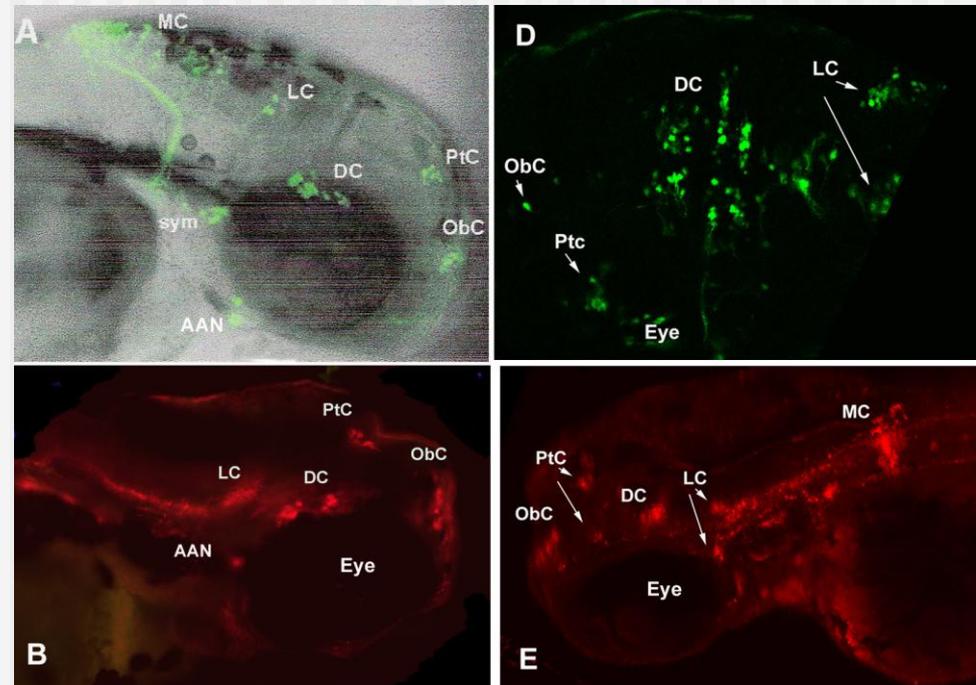


Systemic Administration of DMTC



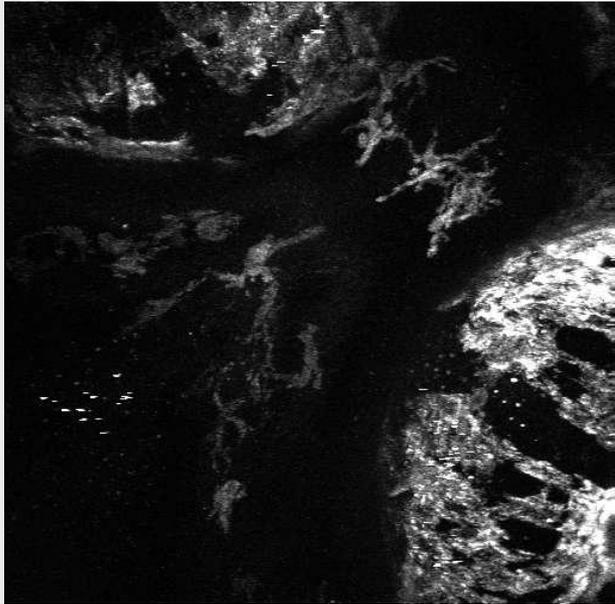
A Zebrafish Model to Study Gene-Environment Interactions in PD

- 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

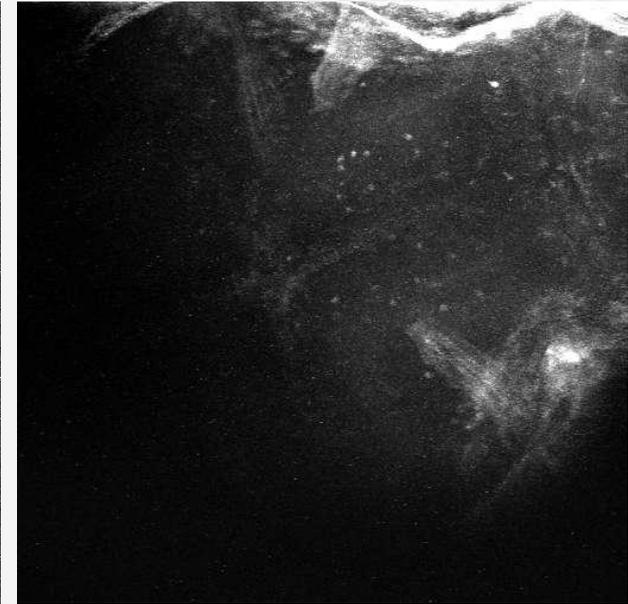
Ziram (1-10 nM) Alters DA Neuron Development



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**

Acknowledgments

UCLA

- Sheldon Wang PhD
- Artie Chou (MSTP Student)
- Sharin Li PhD
- Aswani Kumar Kotagiri PhD
- Arthur Fitzmaurice (PhD student)
- Shubhangi Prabhudesai PhD

- Nigel Maidment PhD
- Kelvin Chiu

- Chris Evans PhD
- MF Chesselet MD, PhD

Beate Ritz MD, PhD

- Yvette Bordelon
- AD Wahner
- S Costello

UC Berkeley

- John Casida PhD
- Rebecka Klintenberg PhD

Funding

- NIEHS (CCPDER and PEG)
- Veterans Administration
(SW PADRECC)