





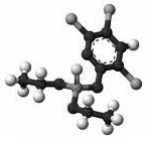
Chronic Neurologic Effects of Pesticides: Results from the Agricultural Health Study

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Pesticides: Definition

- “A pesticide is any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest.” (US EPA)
- Classify by use
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- Classify by chemistry (insecticides)
 - Organophosphates
 - Carbamates
 - Pyrethroids
 - Organochlorines



Pesticide Products

- Formulations: active ingredients plus "inerts"
 - >16,000 formulations
 - >1,000 active ingredients
 - "Inerts" may also be neurotoxic
- 1.2 billion lb active ingredient used annually in US
 - 5.3 billion lb worldwide
- Occupational vs environmental exposure
 - Similar chemicals
 - Formulations or quantities may differ

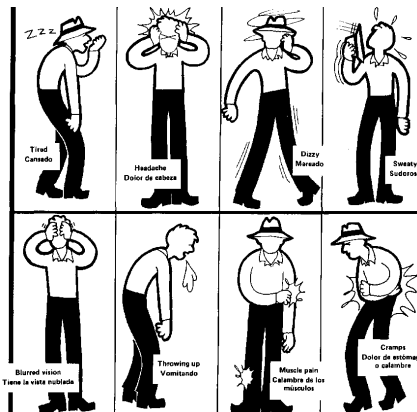


Pesticide Neurotoxicity

- Insecticides designed to be neurotoxicants



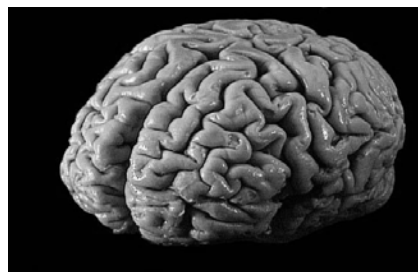
- Acute high-level exposure is neurotoxic in humans
 - Symptoms are obvious and severe (poisoning)
- 1980s – 1990s: poisoning can have long-term sequelae
 - Direct effect of pesticides?



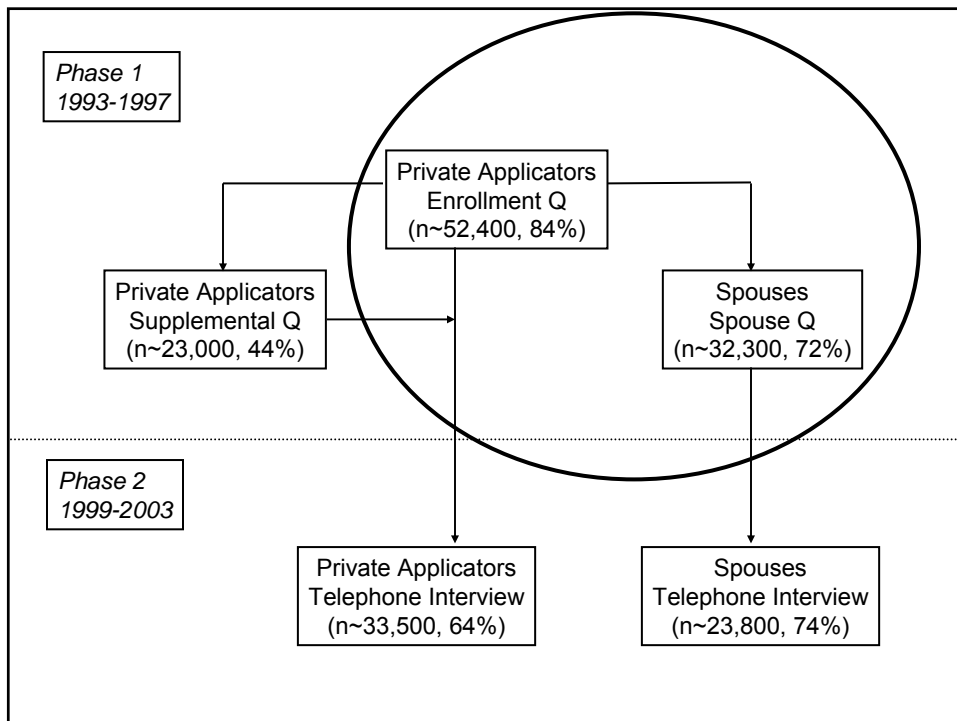
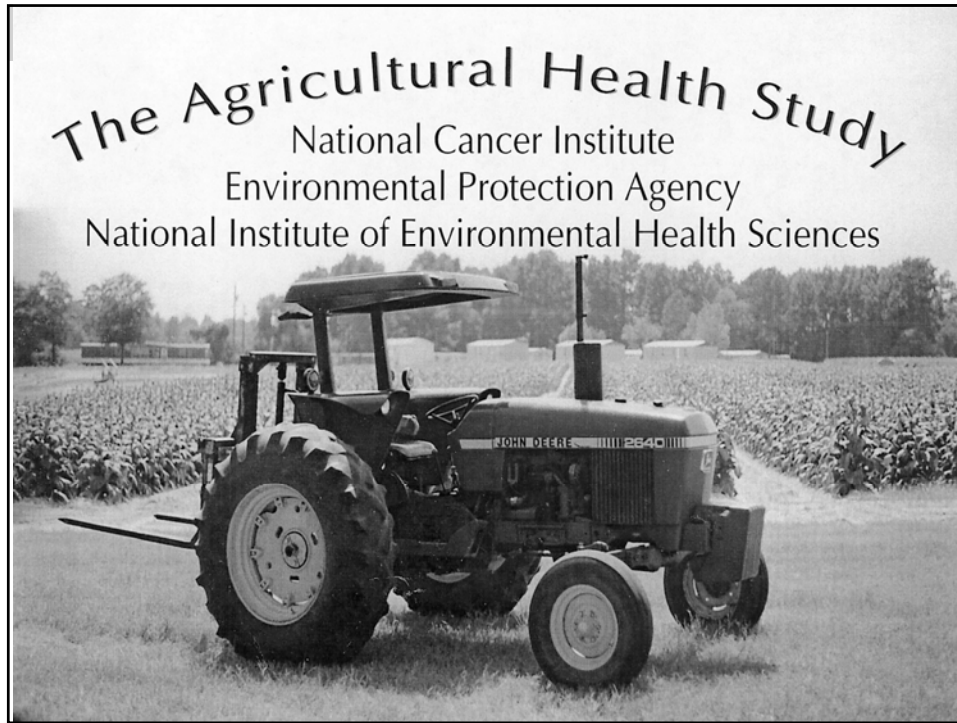
Questions

- Effects of chronic exposure without poisoning?
- Most research on organophosphates -- effects of other chemicals?
- Relevant aspects of exposure?
 - Duration? Intensity?
 - Application methods? Protective equipment?
 - Interaction with other exposures?
- Which outcomes are affected?

Overview



- Agricultural Health Study
 - Design
 - Exposure assessment
- Neurologic dysfunction and disease
 - Neurologic symptoms
 - Macular degeneration
 - Parkinson's disease

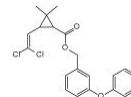
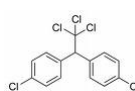
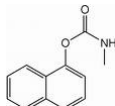
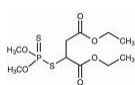


Characteristics of Cohort at Enrollment

	Applicators	Spouses
State (% Iowa)	61	67
Median age (years)	46	40
Gender (% male)	97	1
Race (% white, not Hispanic)	96	98
Education (% >high school)	41	54
Smoking (% ever, lifetime)	47	28
Alcohol use (% ever, previous year)	65	46
Pesticide use (% ever, lifetime)	99	44

Exposure Assessment (Phase 1)

- General pesticide exposure
 - Ever use; duration, intensity
 - Application methods
 - Personal protective equipment
 - Acute high intensity exposure
 - Pesticide-related medical care; poisoning
- 50 specific pesticides



- Level of exposure variable within cohort
- Substudies using biomarkers validate questionnaire data

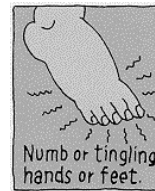
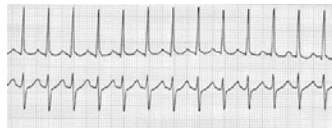
Neurologic Dysfunction and Disease



- Neurologic symptoms
- Macular degeneration
- Parkinson's disease

Neurologic Symptoms

- Early evidence of neurologic dysfunction, before clinical signs are apparent
- Multiple functional domains



Symptom Study Design

- Cross-sectional study based on Phase 1 data
- Applicators who completed take-home questionnaire (n=18,782)
- Outcome: multiple symptoms in year before enrollment
 - Cases: ≥ 10 symptoms (20%)
 - Controls: < 10 symptoms (80%)
- Referent for exposure: internal comparison
 - More exposed vs less exposed applicators

Kamel et al 2005, 2007

High-Exposure Events

	Case (%)	Control (%)	Adjusted OR * (95% CI)
Ever had event involving high personal exposure			
No event	76	88	1.0 (referent)
Mainly dermal exposure	13	8	1.8 (1.6-2.0)
Inhalation, ingestion	11	4	3.0 (2.7-3.5)

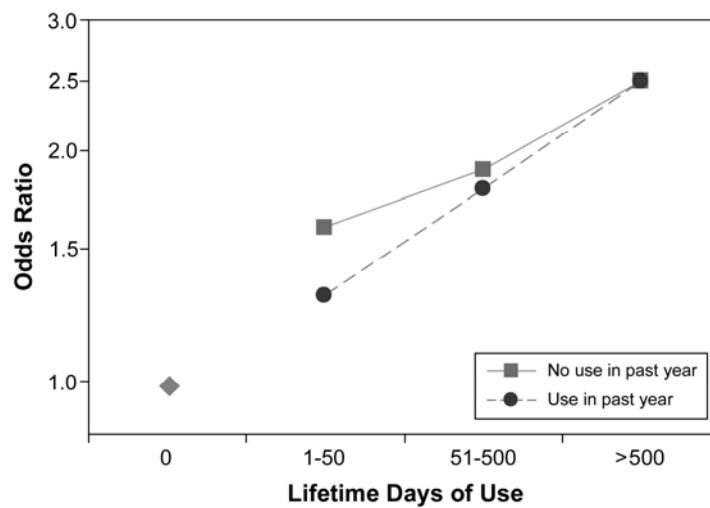
* Adjusted for age, state, education, cigarette smoking and alcohol use

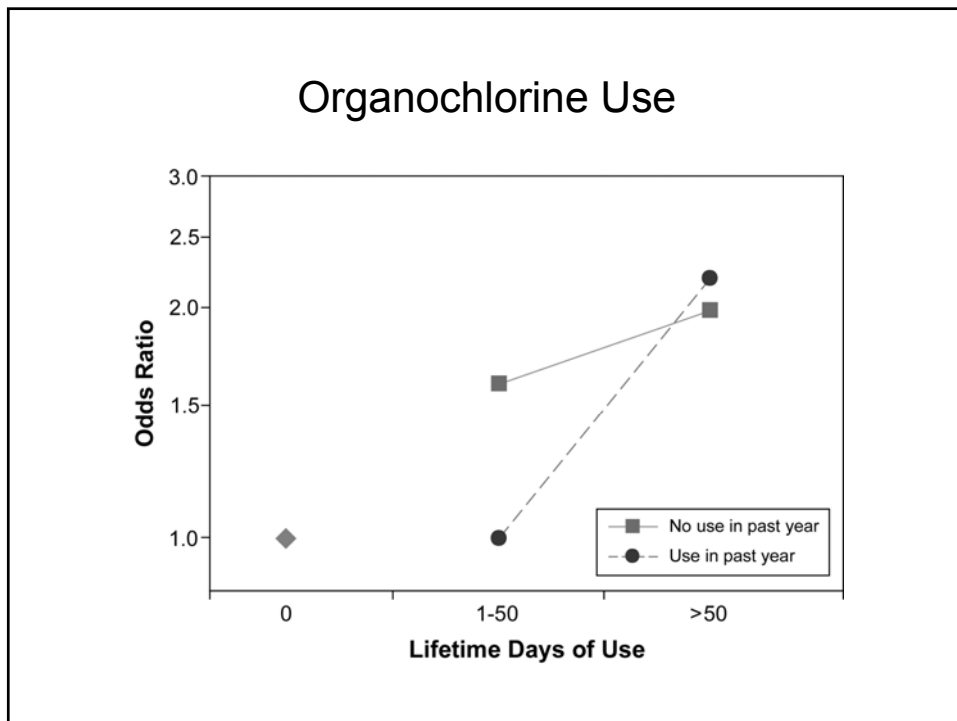
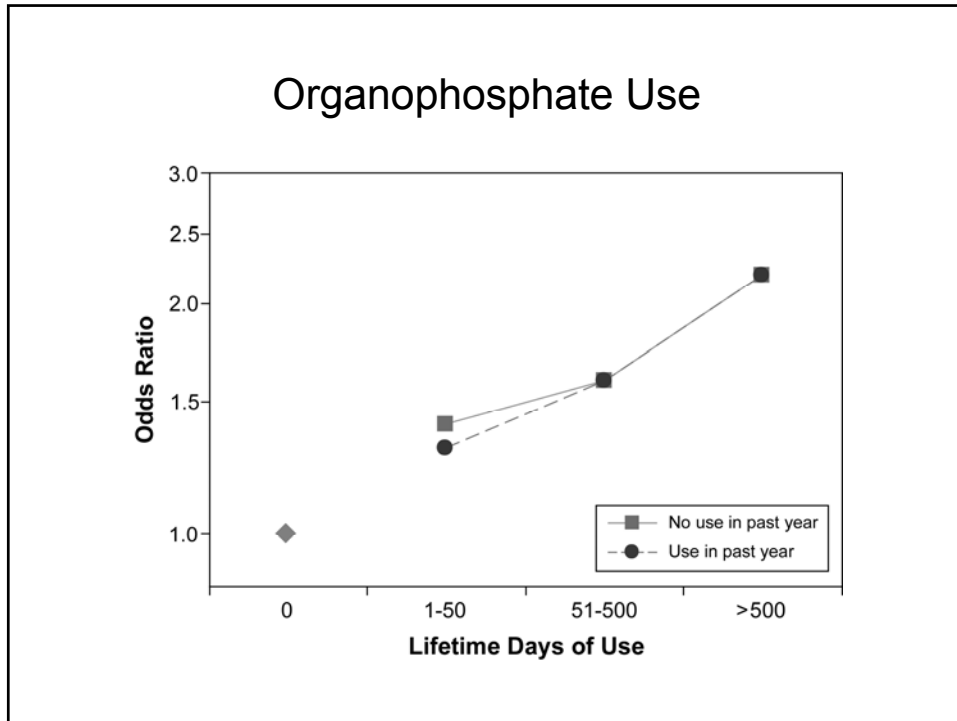
Pesticide-Related Medical Care

	Case (%)	Control (%)	Adjusted OR * (95% CI)
Ever sought medical care for pesticide-related illness			
Never	89	95	1.0 (referent)
Doctor visit	9	4	2.3 (2.0-2.6)
Hospitalized	2	1	2.0 (1.4-2.7)
Ever diagnosed with pesticide poisoning			
No	96	98	1.0 (referent)
Yes	4	2	2.5 (2.0-3.1)

* Adjusted for age, state, education, cigarette smoking, and alcohol use

Insecticide Use





Specific Chemicals

	Number evaluated	Number with OR > 1.5
Organophosphates	10	4
Organochlorines	7	7
Carbamates	3	1
Fungicides	6	0
Fumigants	4	1
Herbicides	18	3

Application Methods

Level of Exposure	Case (%)	Control (%)	Adjusted OR * (95% CI)
Crop insecticides – No	19	20	1.0 (referent)
Low methods only	58	60	1.0 (0.9-1.1)
Low and high	23	20	1.4 (1.2-1.6)
Herbicides – No	4	6	1.0 (referent)
Low methods only	21	31	0.9 (0.7-1.1)
Low and high	74	63	1.5 (1.2-1.8)
Fungicides – No	70	73	1.0 (referent)
Low methods only	16	14	1.3 (1.2-1.4)
Low and high	14	13	1.4 (1.3-1.6)

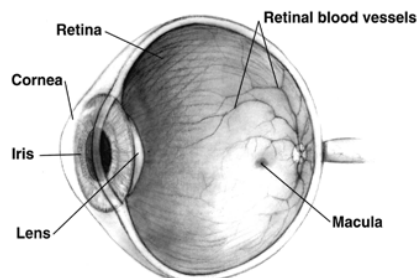
* Adjusted for age, state, education, cigarette smoking, and alcohol use

Summary

- Cumulative lifetime use of insecticides associated with increased risk of having ≥ 10 symptoms in prior year
- Strong and consistent effects for organophosphates and organochlorines
- Accounting for recent pesticide use did not change association with cumulative use
- Effects present in applicators with no history of pesticide poisoning or high exposure events
- Use of high exposure application methods associated with increased risk

Age-Related Macular Degeneration (AMD)

- Leading cause of blindness in older adults in the developed world
- Risk associated with genetic polymorphisms
- Environmental risk factors: smoking



Retinal Degeneration and Pesticides

- Rationale: Animal studies suggest organophosphate exposure damages retina
- Cross-sectional study (Phase 1)
- Case definition: self-reported physician diagnosis of retinal or macular degeneration
- Applicators: 154 cases, 17,804 controls (Kamel et al 2000)
 - Fungicides OR = 1.8 (1.3-2.6)
 - Organophosphates OR = 1.6 (0.9-2.9)
 - Organochlorines OR = 1.5 (1.1-2.2)
 - Carbamates OR = 1.6 (1.1-2.4)
- Spouses: 281 cases, 29,657 controls (Kerrane et al 2005)
 - Fungicides OR = 1.9 (1.2-3.1)

Genes, Environment, and AMD

- Case-control study of incident cases (Phase 2 and 3)
 - Exclude cases from Phase 1
 - Applicators and spouses
- Confirm self-reported macular degeneration using physician questionnaire and retinal fundus photographs
- Controls: remaining cohort
- Exposure data from Phase 1 (prospective)
- Field work completed: ~160 confirmed cases



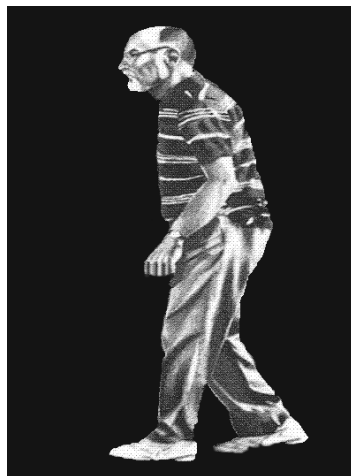
Montgomery et al, in progress

AMD and Pesticides

	Adjusted OR * (95% CI)	
	Men	Women
Organochlorines	2.2 (1.3-3.8)	2.7 (1.5-4.9)
Organophosphates	2.6 (1.1-6.1)	1.8 (1.1-3.2)
Carbamates	1.2 (0.7-1.9)	1.3 (0.8-2.2)
Pyrethroids	1.4 (0.8-2.4)	3.5 (1.5-8.4)
Fungicides	1.4 (0.9-2.2)	1.9 (0.9-4.3)
Fumigants	1.0 (0.6-1.6)	NC
Herbicides	NC	1.2 (0.7-2.0)

* Adjusted for age, state and smoking. NC, not calculated.

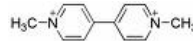
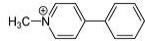
Parkinson's Disease (PD)



- Progressive neurodegenerative disease affecting movement
- Cardinal signs: tremor, slow movement, rigidity, postural instability
- Symptoms: stooped posture, shuffling gait, soft voice, small handwriting
- Genetic variants in early onset PD
- Environmental risk factors: pesticides

PD and Pesticides

- Why pesticides?
 - Rural residence, farming associated with PD
 - MPTP causes parkinsonism -- structurally similar to paraquat



- Over 50 epidemiologic studies of pesticides and PD
 - Meta-analysis: relative risk ~1.9
- Animal and mechanistic studies
- Data sparse, lacking detail



PD and Pesticides in AHS

- Case-control study of incident PD
- Case definition: self-report of physician diagnosis
 - Exclude those with PD in Phase 1
 - Incident PD in Phase 2 (n = 78)
 - Applicators and spouses
- Controls: remaining Phase 2 cohort (n = 55,931)
- Exposure data from Phase 1 (prospective)

PD and High Intensity Exposure

	Case (%)	Control (%)	Adjusted OR* (95% CI)
High exposure event			
None	84	85	1.0 (referent)
Washed within 1 hour	6	9	1.1 (0.3-4.7)
Washed after 1 hour	10	6	1.7 (0.5-5.9)
Pesticide-related medical care			
Never	89	93	1.0 (referent)
Ever	11	7	1.6 (0.7-3.7)

* Adjusted for age and state

PD and Cumulative Lifetime Use

	Case (%)	Control (%)	Adjusted OR* (95% CI)
Days of use			
0-64	28	47	1.0 (referent)
65-200	14	16	1.2 (0.5-2.6)
201-396	23	18	1.7 (0.8-3.5)
397-7000	35	19	2.3 (1.2-4.5)

* Adjusted for age, state, and person

Farming and Movement Evaluation Study

- Collaboration with Carlie Tanner (Parkinson's Institute)
- Address limitations of AHS analysis
 - Self-reported diagnosis
- Nested case-control study
- Diagnosis confirmed by neurologist
- Telephone interview for additional exposure data
- Fieldwork complete
 - N=115 cases, 384 controls
- Data analysis in progress

F A M E



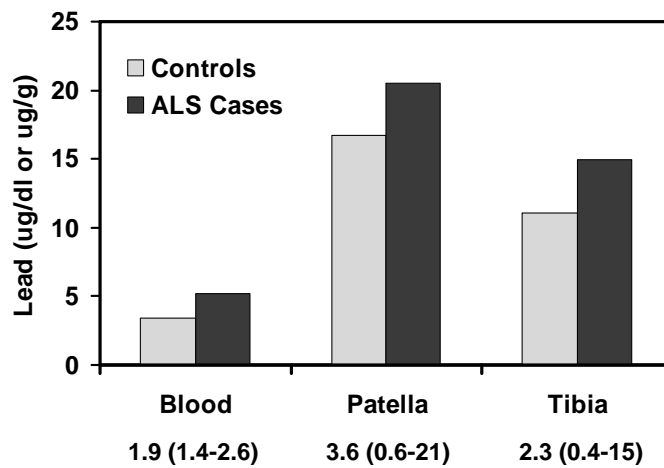
Summary

- AHS provides unique and powerful setting to study neurologic effects of pesticide exposure
- Address fundamental questions
 - Which outcomes are affected
 - Relevant aspects of exposure
 - Role of modifying factors
- Chronic moderate exposure has neurologic effects in humans

ALS and Lead Exposure

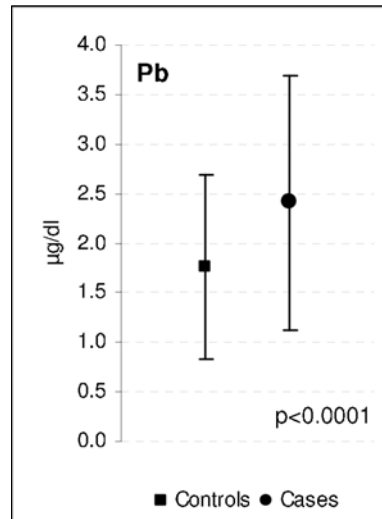
- Long-standing hypothesis, but data are sparse
- New England ALS Study
 - Case-control study, 1993-1996
 - 110 cases and 39 controls (men and women)
 - Blood and bone lead levels
- Veterans with ALS and Lead Exposure (VALE)
 - Case-control study, 2007-2008
 - Based on the National Registry of Veterans with ALS
 - 184 cases and 194 controls (veterans)
 - Blood lead levels
 - Bone turnover biomarkers

New England ALS Study Blood and Bone Lead Levels



Kamel et al 2002

Veterans with ALS and Lead Exposure (VALE) Blood Lead Levels



- Overall OR 1.9 (1.3-2.7)
- Stratified by CTX
 - ≤median: 2.8 (1.4-5.5)
 - >median: 1.6 (1.1-2.4)
- Stratified by ALAD genotype
 - ALAD1-1: 2.0 (1.3-2.9)
 - ALAD2-x: 1.2 (0.4-3.1)

Fang et al, under review

Acknowledgments

- AHS Executive Committee: Michael Alavanja, Aaron Blair, Cindy Hines, Jane Hoppin, Dale Sandler, Kent Thomas
- AHS Staff:
 - Westat: Jack Cahill, Stanley Legum, Marsha Dunn, Kate Torres
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Collaborators

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- Duke University: Silke Schmidt



Symptoms Studied in AHS

Domain	Symptoms (% in year before enrollment)
Affect	Anxiety (52), irritability (37), depression (27)
Cognition	Memory (24), concentration (20)
Sensory	Numbness (27), night vision (12), blurred vision (10), smell/taste (6)
Motor	Twitches (17), weakness (15), balance (12), tremor (11), speech (4)
Autonomic	Nausea (27), appetite (18), sweating (17), heart rate (15)
Other	Headache (68), fatigue (58), insomnia (43), dizziness (28), loss of consciousness (2)

