National Institute of Neurological Disorders and Stroke

NIH CounterACT Program

Status Epilepticus after Benzodiazepines: Seizures and Improving Long-term Outcomes

February 28 - March 1, 2023

Short and Long-term Effects of Acute Organophosphorus Pesticide Self-poisoning

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Status Epilepticus after Benzodiazepines: Seizures and Improving Long-term Outcomes

Disclaimer

This certifies that the views expressed in this presentation are those of the author and do not reflect the official policy of NIH.

Disclosure

This certifies that I, Nicholas Buckley, have no financial relationship that is relevant to the subject matter of the presentation.

Pesticides & Suicide
(A neglected tropical disease??)

- **World Health Organisation 2006:**

"pesticide poisoning is the single most important global means of suicide"

- **250-370,000 deaths per year**

Africa – 7,800
Americas – 3,105
East Mediterranean – 5,629
Europe – 6,080
SE Asia – 51,050 * (113,000 not counted?)
Western Pacific – 184,570

≈2/3rds are OP anti-cholinesterases

Sri Lanka (~2001)
17000 admissions
35% ICU
10% Die
(20% if symptomatic)

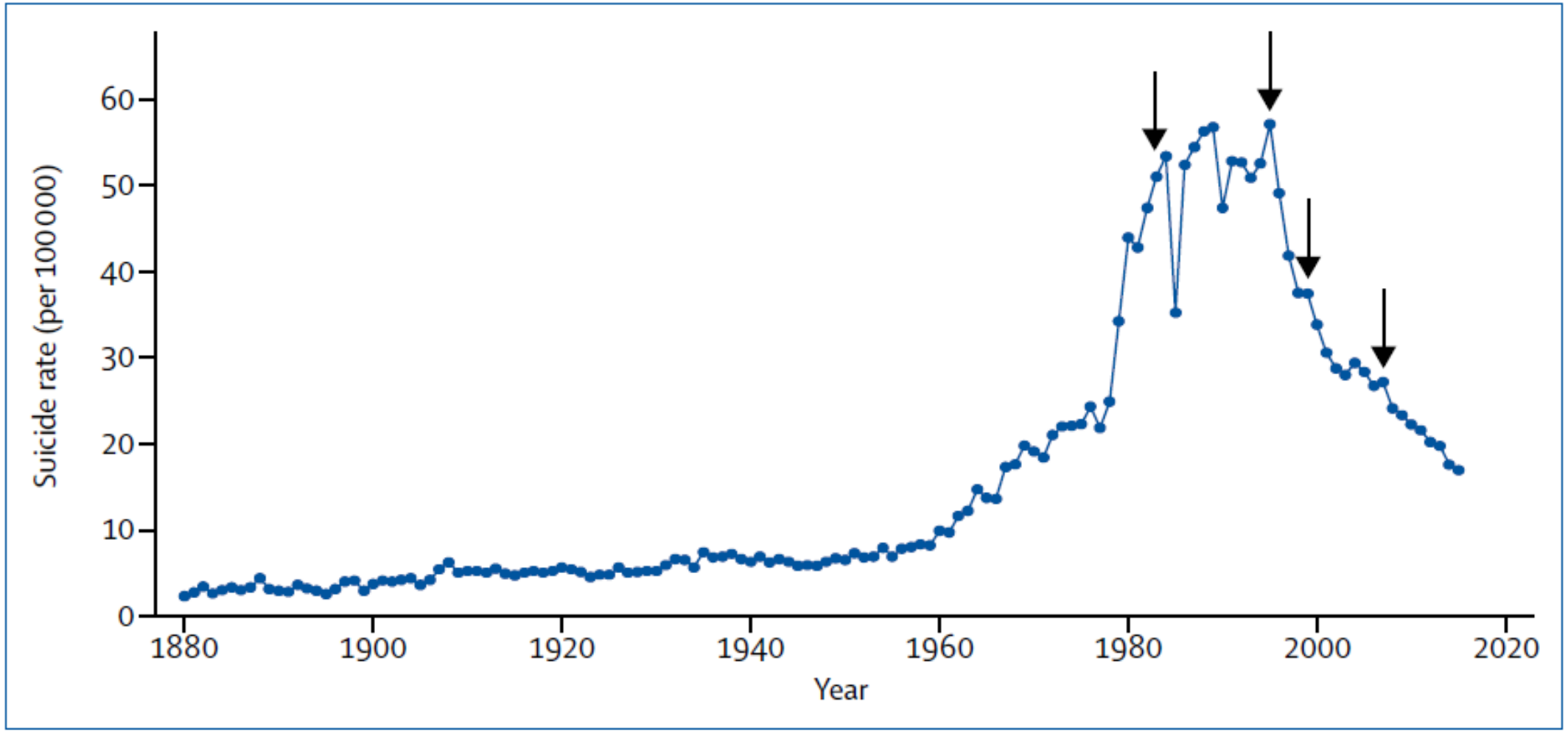
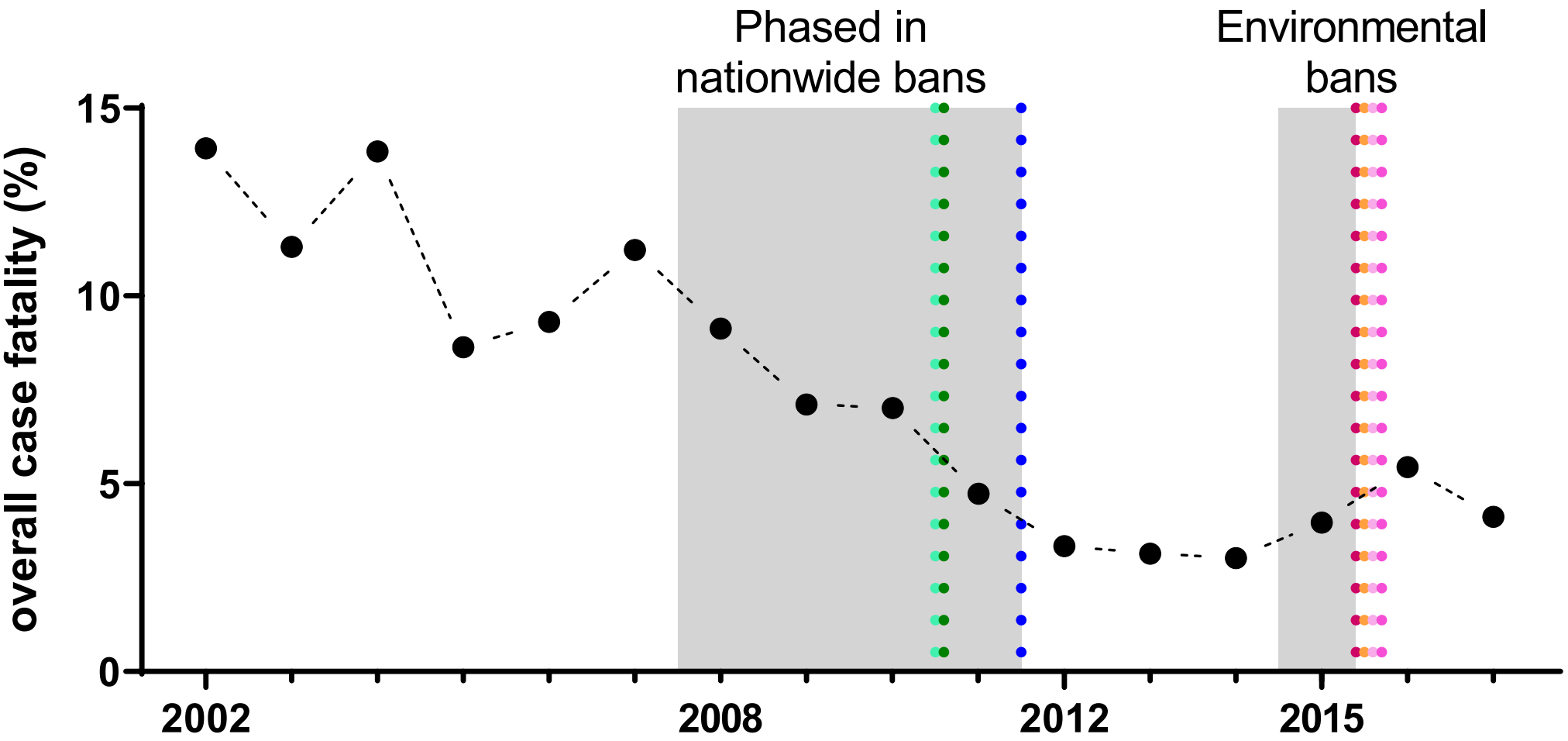


Figure: **Incidence of suicide in Sri Lanka, 1880–2015**

Arrows show timing of pesticide bans (1984: parathion, methylparathion; 1995: all remaining WHO class I toxicity pesticides, including methamidophos and monocrotophos; 1998: endosulfan; 2008: dimethoate, fenthion, paraquat). Suicide data were obtained from police records.

Knipe, D. W., et al. (2017). "Preventing deaths from pesticide self-poisoning-learning from Sri Lanka's success." Lancet Glob. Health **5**(7): e651-e652.

The most recent bans of toxic pesticides



Buckley, N. A., et al. (2021). "Case fatality of agricultural pesticides after self-poisoning in Sri Lanka: a prospective cohort study." Lancet Glob Health **9**(6): e854-e862.

Delayed effects:

Intermediate Syndrome

- NMJ failure
1-4 days post OP poisoning
lasting 1-3 weeks

OPIDN:
OP induced delayed neuropathy

predominantly motor distal neuropathy,
onset 2 to 4 weeks,
may be permanent

Clinical Neurophysiology 120 (2009) 1693–1698

CLINICAL TOXICOLOGY
2021, VOL. 59, NO. 2, 118–130
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CLINICAL RESEARCH

Subacute and chronic neuropsychological sequalae of acute organophosphate pesticide self-poisoning: a prospective cohort study from Sri Lanka

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CLINICAL RESEARCH

Changes of attention-related brain activity over 6 months after acute organophosphate pesticide poisoning: a prospective follow-up study

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CLINICAL TOXICOLOGY
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CLINICAL RESEARCH

Dysfunction in macula, retinal pigment epithelium and post retinal pathway in acute organophosphorus poisoning

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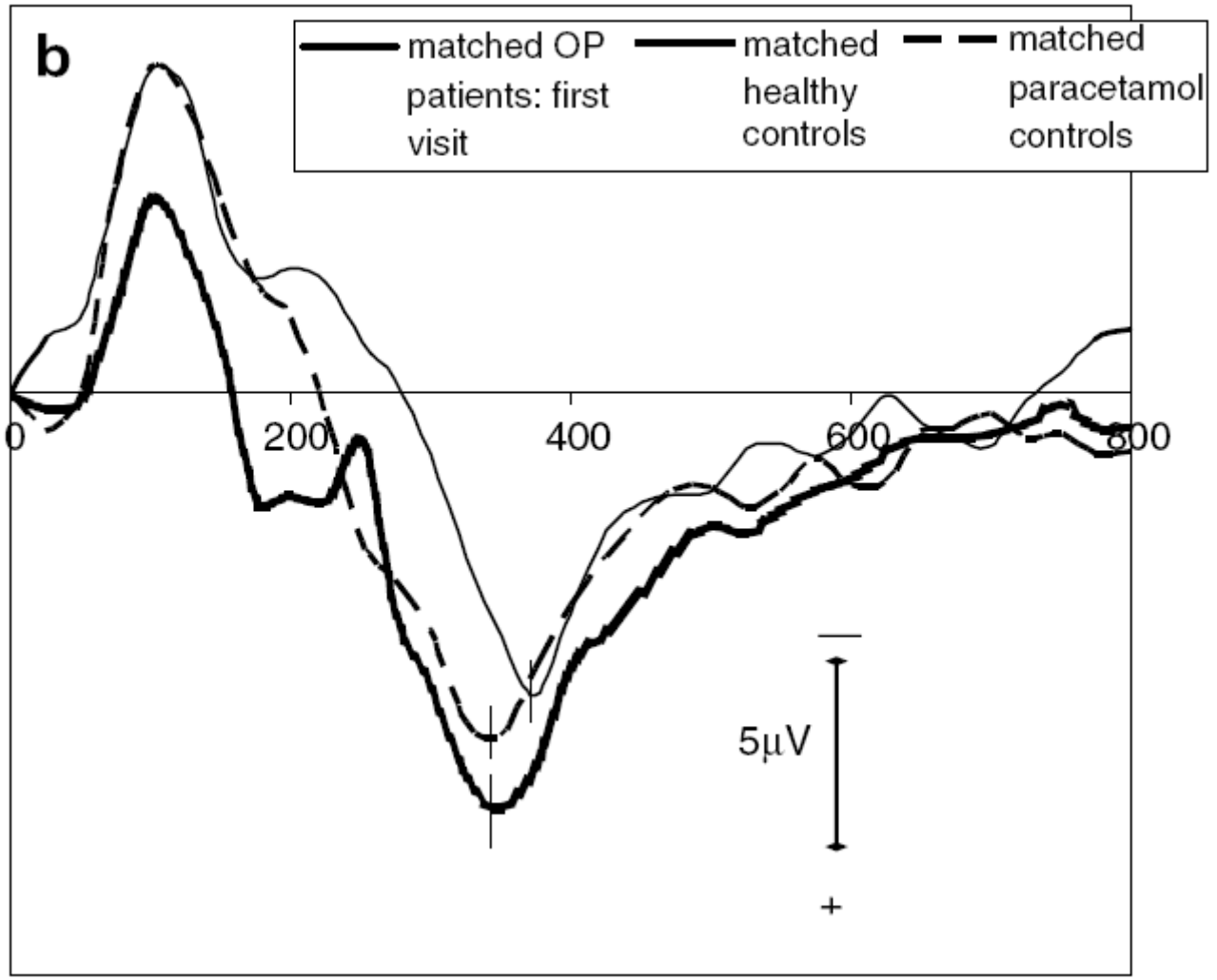
Accepted 24 September 2007



- Prolonged P300 cognitive event-related potential latency in patients with acute OP poisoning after clinical recovery.
- Dassanayake, T., et al. (2008). "Long-term event-related potential changes following organophosphorus insecticide poisoning." Clin. Neurophysiol **119**(1): 144-150.

P300 and chronic OP exposure

- Note: prolonged latency and decreased amplitude of P300 cognitive event-related potential.
- This signifies delay in stimulus evaluation and impairment of allocation of neural resources for cognitive processing.

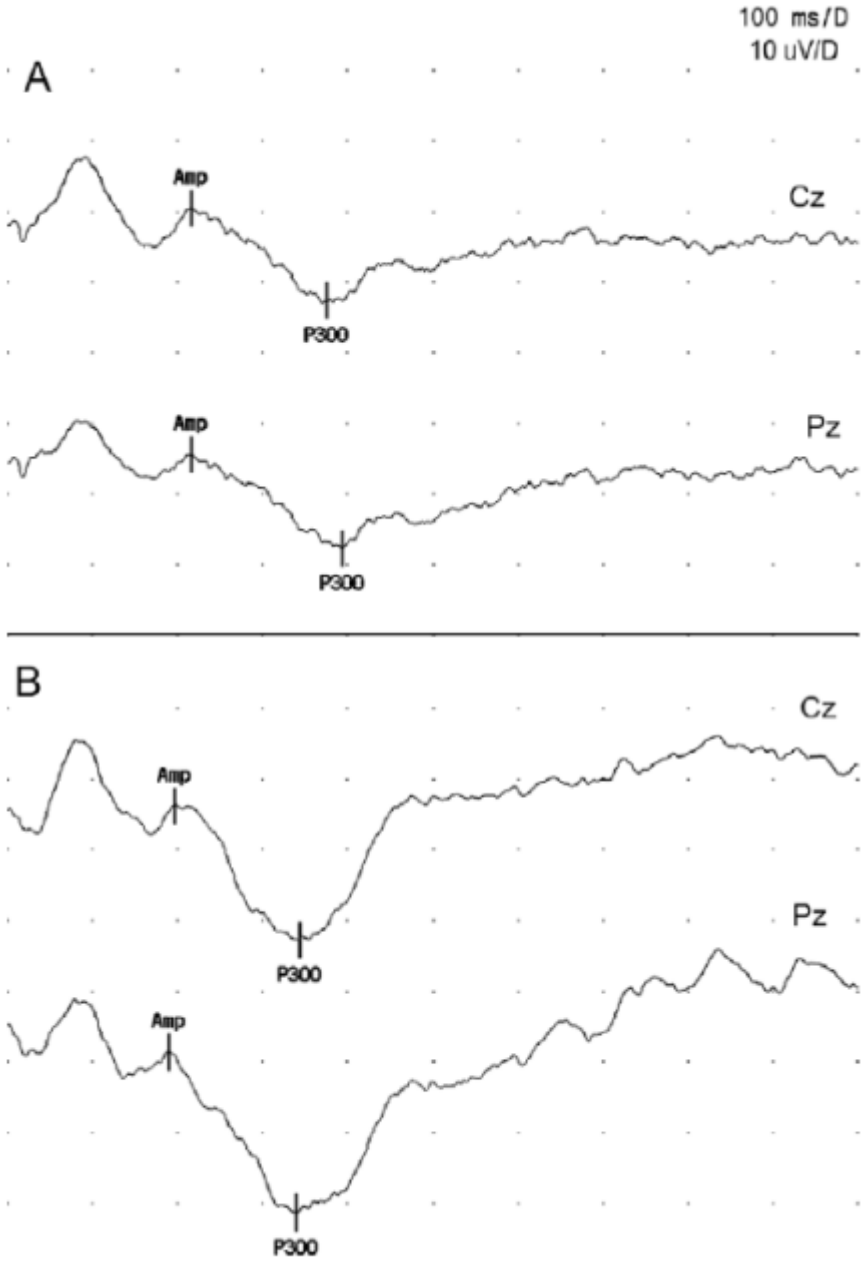
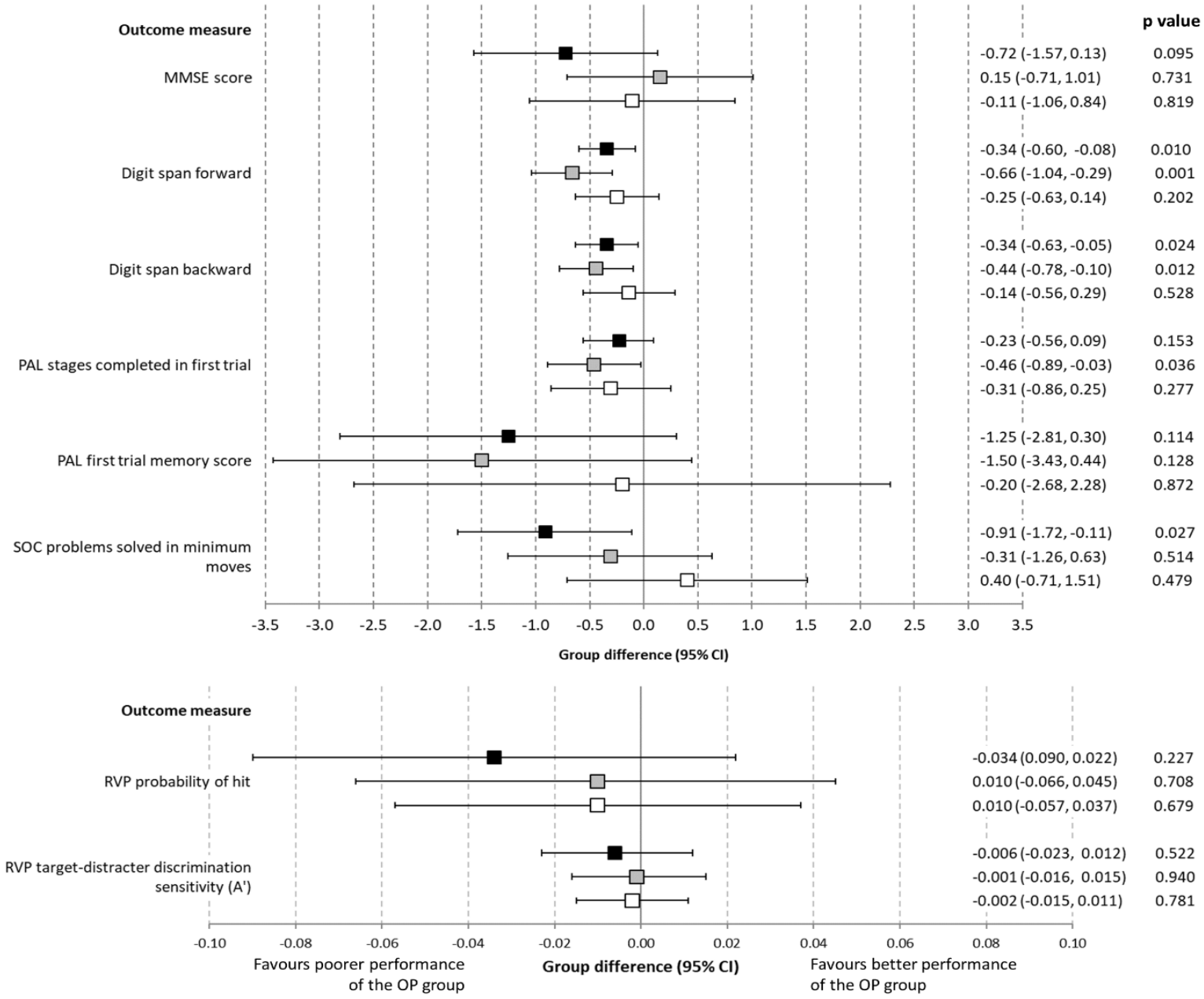


Fig. 1. Sample ERP waveforms for target tones: (A) a vegetable farmer and (B) a control subject.

- Dassanayake, T., et al. (2009). Auditory event-related potential changes in chronic occupational exposure to organophosphate pesticides. Clin Neurophysiol **120**(9): 1693-1698.

Prospective study – post acute OP poisoning neuropsychological testing



post-discharge (n= 193 ■), at 6-weeks (n= 154 ■) and at 6 months (n=119 □)

Dassanayake, T. L., et al. (2021). "Subacute and chronic neuropsychological sequalae of acute organophosphate pesticide self-poisoning: a prospective cohort study from Sri Lanka." Clin Toxicol (Phila) 59(2): 118-130.

Retrospective studies – post acute OP poisoning neuropsychological testing (generally positive at population level) –

Dassanayake, T. L., et al. (2021). "Subacute and chronic neuropsychological sequalae of acute organophosphate pesticide self-poisoning: a prospective cohort study from Sri Lanka." Clin Toxicol (Phila) 59(2): 118-130.

Study / subgroup	Savage et al. 1988	Rosenstock et al. 1991	Steenland et al. 1994 (all poisoned cases)	Steenland et al. 1994 (hospitalized poisoned cases)	Wesseling et al. 2002	Yokoyama et al. 1998	Nishiwaki et al. 2001 (high exposure group)	Nishiwaki et al. 2001 (low exposure group)
Country	USA	Nicaragua	USA	USA	Costa Rica	Japan	Japan	Japan
Study Population	Pesticide poisonings in Colorado & Texas rosters	Men working with pesticides	Men from California pesticide illness records	Men from California pesticide illness records	Banana plantation workers	Victims of 1995 Tokyo subway sarin attack	Rescue workers Tokyo sarin attack	Rescue workers Tokyo sarin attack
Mode of poisoning	Unintentional (?occupational)	Occupational exposure	Occupational exposure	Occupational exposure	Occupational exposure	Accidental exposure	Accidental exposure	Accidental exposure
Control Group	Matched for age, sex, education, social class, socioeconomic status, race.	Age- & sex-matched friends or siblings	Friends not working with pesticides	Friends not working with pesticides	Fellow workers not treated for any pesticide poisoning	Unexposed healthy individuals	Age- and occupation-matched controls	Age- and occupation-matched controls
Exposure and / or severity ascertainment	Retrospective. Symptoms documented by physician.	Retrospective. Hospital records.	Retrospective. Symptoms & RBC-AChE inhibition.	Retrospective. Symptoms & RBC-AChE inhibition.	Retrospective. Medical review, not hospitalized.	Retrospective Cholinergic signs, plasma ChE	Retrospective. Immediate hospitalization.	Retrospective. Attended hospital as outpatients.
Time between exposure and testing	> 3months	> 9 months	Not specified (years)	Not specified (years)	27 months (average)	6-8 months	~3 years	~3 years
Statistical Analysis	Comparison of means	Paired t test	Regression, adjusted for confounders	Regression, adjusted for confounders	Regression, adjusted for confounders	Analysis of covariance adjusted for age, sex.	Univariate comparison and multiple regression	Univariate comparison and multiple regression

Cognitive electrophysiology post acute OP poisoning

Dassanayake, T. L., et al. (2022). "Changes of attention-related brain activity over 6 months after acute organophosphate pesticide poisoning: a prospective follow-up study." Clin Toxicol (Phila) **60**(5): 576-584.

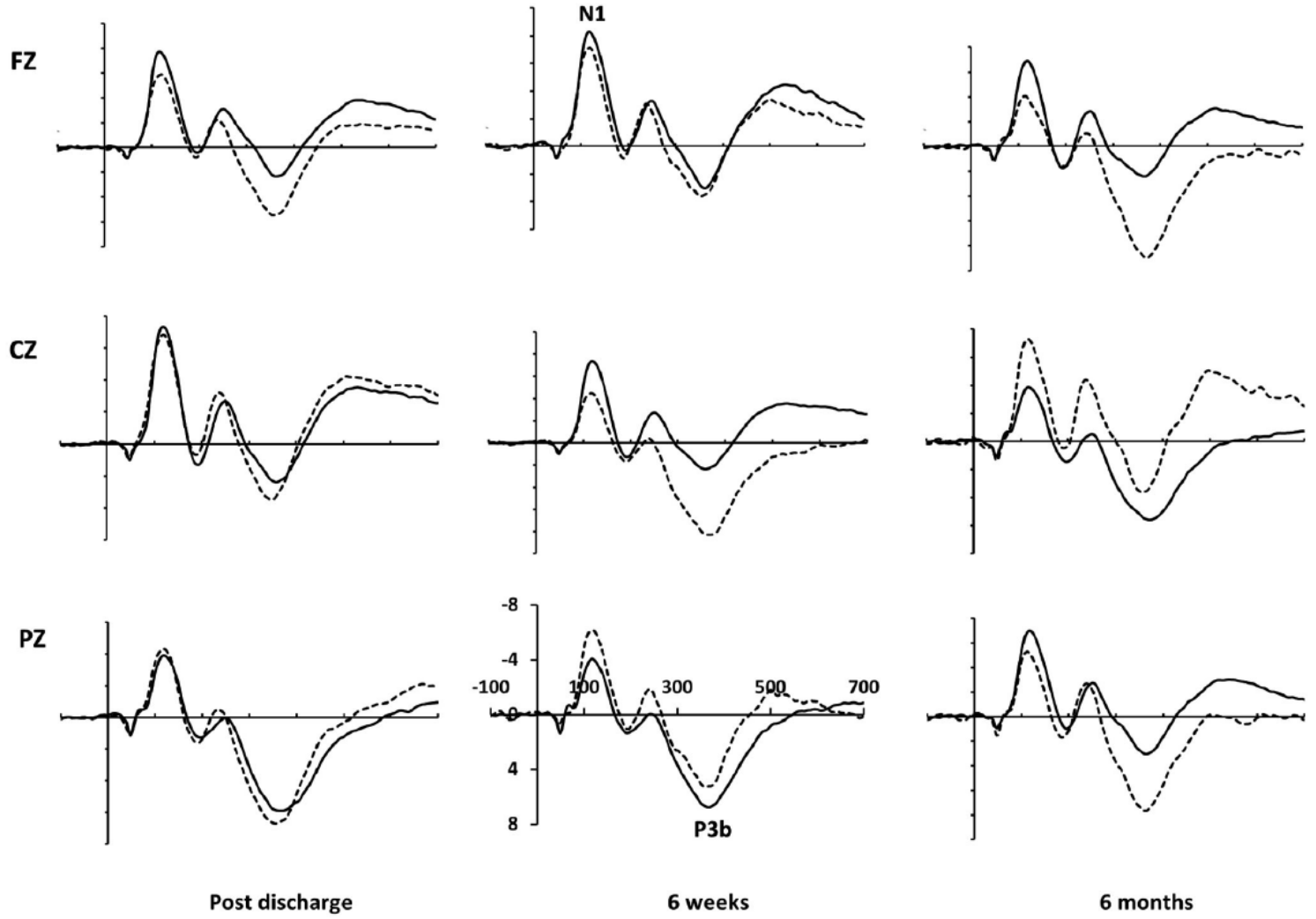


Figure 2. Grand average event-related potential (ERP) waveforms for target stimuli in the OP group (solid line) and the control group (dashed line) in post-discharge, 6-week and 6-month assessments.

Conclusions

- Acute organophosphate poisoning is very much less likely to cause overt seizures than nerve agents……
- Even so, it commonly causes neurotoxicity persisting beyond the acute illness.
  - Some resolution over 6 months
  - Some deficits are very obvious (e.g. severe OPIDN)
  - Many deficits are sub-clinical
    - Only demonstrable for cohorts rather than individuals.
  - There may also be neurotoxicity with chronic OP exposure
  - Objective electrophysiological measures can be designed to detect cognitive deficits to complement traditional neuropsychological testing

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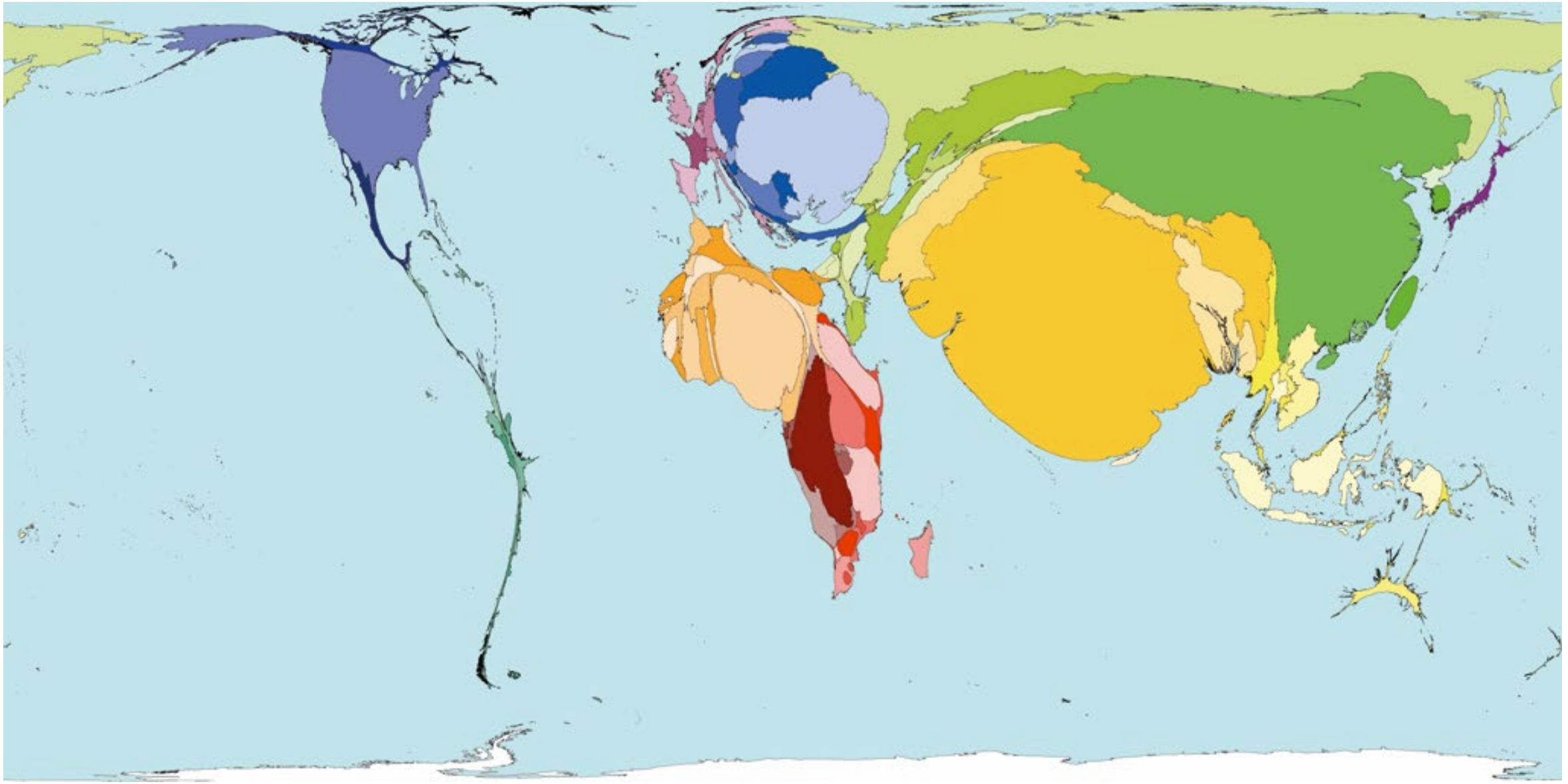
Questions?



Global burden of accidental poisoning deaths (~2010)

www.worldmapper.org