Assessing developmental neurotoxicity due to pyrethroid insecticide exposure in *C. elegans*

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Background

- Pyrethroids are a type of insecticide widely used in agriculture and public health programs.
- These insecticides disrupt neuronal signaling in target insects through voltage-gated sodium channels and have been **linked to cardiovascular and neurological disease in humans**
- The nervous system of the nematode *Caenorhabditis elegans* is fully mapped, and specific behavioral circuits can be tested, making it a powerful model for studying neurotoxicity.
- Because the primary target of pyrethroids is not conserved in *C. elegans*, secondary mechanisms of pyrethroid neurotoxicity can be identified by testing whether specific behavioral circuits are affected.

Significance

- **Assessing behavioral circuits in *C. elegans* is an ethical and cost-effective method to identify conserved secondary mechanisms of pyrethroid neurotoxicity relevant to human health.**

Pyrethroid exposure during larval development

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Developmental Assays

Growth & Survival

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Functional Behavioral Testing

Sensory Detection
Soft- touch response
Behavioral Regulation
Basal slowing response
Motor Output
Locomotory rate
Neuromuscular Signaling
Aldicarb response

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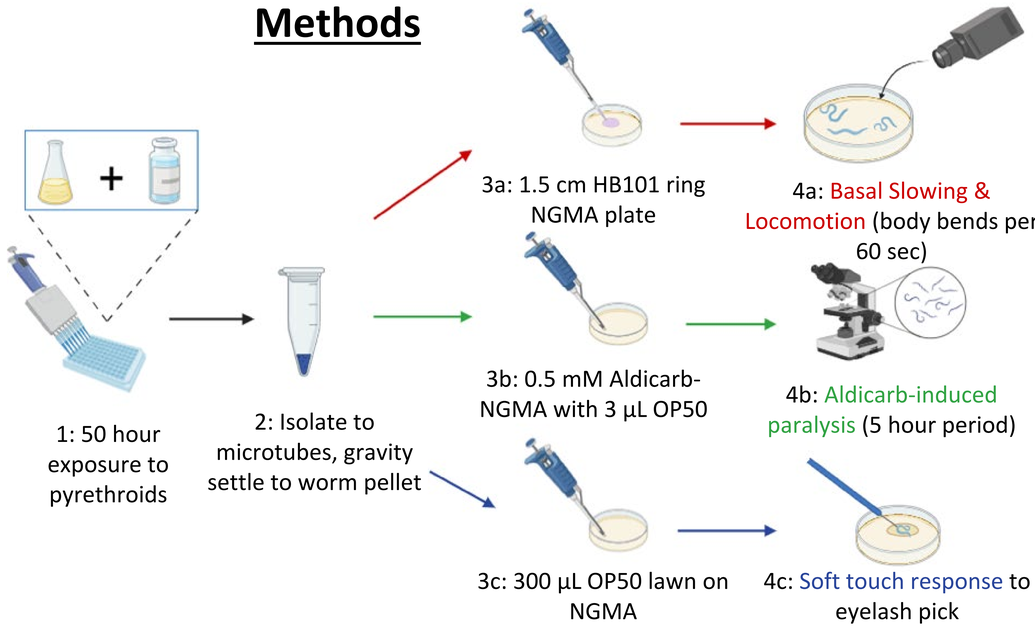
Selective Neural Effects

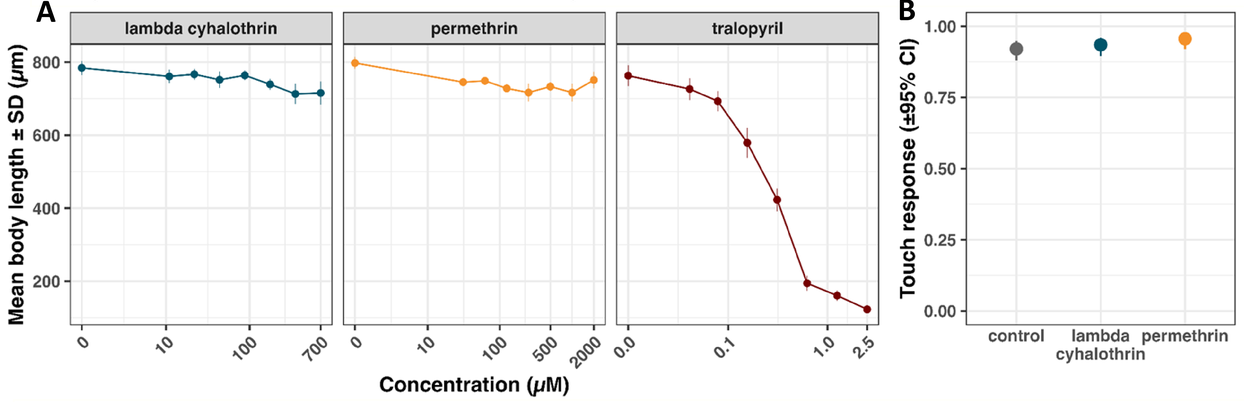
Point to non-canonical, secondary mechanisms of pyrethroid toxicity

Methods



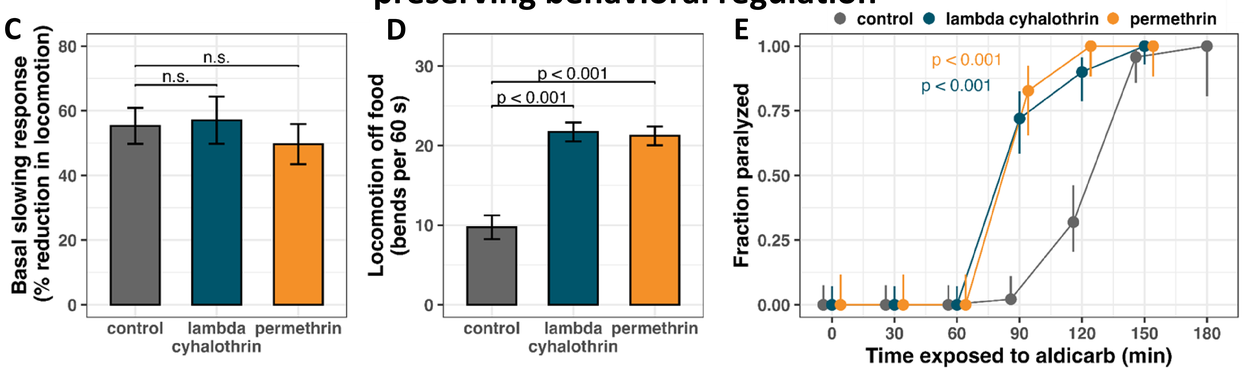
Results

Pyrethroids do not affect development or the soft touch behavioral circuit



(**A**) Body length is shown for worms exposed to two pyrethroids (lambda cyhalothrin & permethrin) or tralopyril, a positive control compound, ~90 worms per data point. (**B**) The fraction of worms exhibiting soft touch response after exposure to either pyrethroid or vehicle control (DMSO). Two independent assays, >20 worms per treatment.

Pyrethroids selectively alter motor output and neuromuscular signaling while preserving behavioral regulation



(**C**) Basal slowing response is shown as the percent reduction in locomotion on food relative to the unfed rate, three independent assays, >15 worms measured per condition (**D**) The unfed locomotion rate in body bends per 60 seconds is shown. (**E**) The time for aldicarb paralysis is shown, points are fraction paralyzed and error bars are standard errors of the marginal means from a binomial generalized linear model.

Conclusions

- Larval-stage pyrethroid exposure **selectively altered** locomotory output and aldicarb sensitivity **without broad impairment** across behavioral circuits.
  ➢These results Indicate disruption of motor circuit function and neuromuscular signaling.
- We propose a model in which pyrethroids disrupt Ca^{2+} dependent synaptic transmission, potentially through effects on voltage-gated Ca^{2+} channels, leading to increased cholinergic signaling at the neuromuscular junction.

Future Directions

- Compare neurotoxic effects between maternal and larval-stage exposures.
- Test mechanisms involving Ca^{2+}-dependent synaptic release, ion channel regulation, and inhibitory signaling, and **evaluate conservation of candidate genes and pathways in humans.**

References

Huayta, J., Seay, S., Laster, J., 3rd, Rivera, N. A., Jr, Joyce, A. S., Ferguson, P. L., Hsu-Kim, H., & Meyer, J. N. (2025). Assessment of developmental neurotoxicology-associated alterations in neuronal architecture and function using Caenorhabditis elegans. *ALTEX*, *42*(4), 591–609. https://doi.org/10.14573/altex.2501151

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