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TITLE: Role of Military-Relevant Chlorpyrifos Exposure in Parkinson's Disease-Relevant Dopaminergic Neurotoxicity

PRINCIPAL INVESTIGATOR: Jason Cannon

CONTRACTING ORGANIZATION: Purdue University, West Lafayette, IN

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		5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Purdue University 155 S Grant St West Lafayette, IN 47907 University of Iowa, Iowa City, IA 52242 Richard L. Roudebush VA Medical Center 1481 W. 10th St. Indianapolis, IN 46202		8. PERFORMING ORGANIZATION REPORT NUMBER
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13. SUPPLEMENTARY NOTES A MPI plan was submitted with the original award. Drs. Jason Cannon and Ellen Wells co-lead this effort.		
14. ABSTRACT Given emergent data on chlorpyrifos induced dopaminergic neurotoxicity that may bear relevance to PD, we believe it is critical to understand whether prior military chlorpyrifos exposure may influence PD risk. Thus, we aim to test the following central hypotheses: Military relevant chlorpyrifos exposure causes dopaminergic neurotoxicity and increased risk for Parkinson's disease. We will test our hypothesis through the use of multiple model systems to increase translational value alongside human studies to determine whether likely organophosphate exposure during military service is a risk factor for PD. In testing our hypothesis, we will also explore the basic biology of gene-environment interactions that may potentiate or mitigate the severity and progression of PD-relevant neurotoxicity.		

15. SUBJECT TERMS None listed.					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Unclassified	18. NUMBER OF PAGES 64	19a. NAME OF RESPONSIBLE PERSON USAMRDC
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1. Introduction

The overarching goal is to determine whether military relevant chlorpyrifos exposure may influence PD. To do so, we will conduct a mix of both human and laboratory studies. The inclusion of both types of studies is critical to determine whether there is a plausible link. Human studies will utilize epidemiological approaches to determine if long-term OP exposure is higher among those with PD, or whether such exposures influence disease onset (are those exposed diagnosed at earlier ages?) and severity. We will examine whether exposure may produce atypical disease or the impact of exposure is influenced by genetics (are some people at higher risk due to genetics?). In laboratory-based studies, we will use a variety of model systems that allow us to test precise doses to determine if exposure reproduces key features of PD. These systems will also allow us to test gene-environment interactions and possible therapeutic approaches.

2. Keywords

Parkinson's disease, chlorpyrifos, dopamine

3. Accomplishments

What were the major goals of the project?

Specific Aim 1: Determine if Parkinson's disease or its severity is associated with military-relevant chlorpyrifos exposure among US military veterans.	Timeline	Site 1 (Drs. Cannon and Wells; responsible co-PI indicated for each Major Task)	Site 2 Dr. Doorn	Site 3 Dr. Rattray	% complete/ comments
Major Task 1: Finalization of study protocols and study materials (responsible co-PI – Dr. Wells)	Months				
Subtask 1: Finalize all study protocols Participating teams: • Dr. Wells's laboratory will take the lead on drafting study protocol documentation and materials • Dr. Rattray and colleagues will provide advice and recommendations throughout the process and approve the final materials. • Request employee without pay designations for key Purdue personnel (Wells, study coordinator, graduate student)	1-2	X		X	100
Subtask 2: Obtain local IRB approvals (Purdue University and VA) • Draft IRB application at Purdue (study coordinator) • Submit IRB application to Purdue; revise as needed until approved	3-4	X		X	100

Following approval at Purdue; VA staff will submit the IRB to the VA for approval; will revise as needed					
Subtask 3: Obtain DoD IRB approval Submit IRB documentation to the DoD IRB for approval; IRB approval for all institutions will be obtained prior to initiating any study activities.	5-6	X			100
<i>Milestone #1: All IRB approvals obtained</i>	6	X			100
Major Task 2: Recruit and enroll study participants (responsible co-PI – Dr. Wells)					
Subtask 1: Identify list of potential participants Study participants will be identified using the VA healthcare utilization database; this process will be overseen by VA study staff.	6-7			X	25/modest delay due to delay in VA subaward
Subtask 2: Recruit participants to study - Purdue staff will contact potentially eligible study participants and invite them to participate in the study; - Participants who agree to participate will be send informed consent documentation and have a study interview scheduled. - VA staff will provide assistance/advice as needed	6-24	X (N=500)		X	10/ recruitment underway
<i>Milestone #2: Study enrollment goals (N=500) achieved</i>		X			For next reporting period
Major Task 3: Collect study data (responsible co-PI – Dr. Wells)					
Subtask 1: Conduct study interviews Purdue staff (grad student, study coordinator) will conduct study interviews with all participants	6-24	X		X	10
Subtask 2: Develop and maintain databases Purdue staff (grad student, study coordinator) will develop and maintain databases with interview data	6-24	X			10
<i>Milestone #3: Complete interviews (N=500)</i>	24	X			For next reporting period
Major Task 4: Analyze and present results (responsible co-PI – Dr. Wells)					
Subtask 1: Develop exposure assessment models - Dr. Wells and her graduate student will develop exposure assessment models based on data from initial enrolled participants - Apply exposure assessment model to other participants as they complete study interviews	12-24	X			For next reporting period
Subtask 2: Extract medical outcome data from VA database	25-26			X	For later reporting period

VA staff will take the lead in extracting data related to PD diagnosis and severity from the VA database.					
Subtask 3: Analyze saliva samples for PON1 genotype Saliva samples (send by participants to Purdue via mail) will be processed and analyzed for PON1 genotype at the Purdue Genomics Core Facility (see letter of support)	25-26	X			For later reporting period
Subtask 3: Complete analyses of chlorpyrifos exposure with PD occurrence or severity Purdue staff (grad student) will develop and maintain databases with interview data	27-31	X		X	For later reporting period
Subtask 4: Prepare and submit manuscripts - Prepare and submit manuscript regarding exposure assessment methodology - Prepare and submit manuscript with case-control study results (Aim A1) - Prepare and submit manuscript regarding cross-sectional study results (Aim A2) - Prepare and submit manuscript on potential effect modifiers of pesticide exposure with PD (Aim A3)	32-36	X		X	For later reporting period
<i>Milestone #4: Co-author at least three manuscripts related to Aim 1</i>	36	X		X	For later reporting period
Specific Aim 2: Determine if chlorpyrifos produces selective dopaminergic neurotoxicity in translational models.					
Major Task 5: Conduct neurotoxicity experiments in hIPSCs (responsible co-PI – Dr. Cannon, in collaboration with Dr. Bowman)					
Subtask 1: hIPSC culture and differentiation (using lines already at Purdue). 3 time-frames are given due to 3 independent replicates.	1-3, 6-9, 13-15	X			Exposures underway
Subtask 2: hIPSC chlorpyrifos neurotoxicity exposure experiments. Dose-response studies. 3 time-frames are given due to 3 independent replicates.	4-6, 10-12, 16-18	X			Exposures underway
Subtask 3: Mechanistic exposure studies. Culture, along with assays. Cell death, bioenergetic and mitochondrial function analyzed. 3 time-frames are given due to 3 independent replicates.	19-24, 25-30, 30-35	X			Exposures underway
<i>Milestone #5: Co-author manuscript on chlorpyrifos neurotoxicity in hIPSCs.</i>	35-36	X	X		For later reporting period
Major Task 6: Conduct in vivo chlorpyrifos neurotoxicity experiments (responsible co-PI – Dr. Cannon)					
Subtask 1: Local IACUC approval	1	X			100
Subtask 2: ACURO approval	1-3	X			100
Subtask 3: Transgenic rat generation (at Purdue Transgenic and Genome Editing Facility), validation, and breeding colony propagation (PON1 knockout or wildtype, backcrossed in Lewis strain)	4-9	X			75/most tasks completed, propagation somewhat slower than planned

Subtask 4: Chlorpyrifos exposure (exposure time is 2 months, 3 exposure sets expected to achieve desired number: (3 groups x 2 genotypes x 8 animals/group x 2 sexes x 2 exposure scenarios). Neurobehavioral analysis also conducted during this time.	10-15	X (n=192)			Exposures underway
Subtask 5: Animal sampling (immediate onset group at end of exposure and delayed onset – 7 months after exposure)	16-22	X			For next reporting period
Subtask 6: Neurotoxicological analyses: neurotransmitter measurement, neuropathology: staining and quantitative analyses	23-34	X			For later reporting period
<i>Milestone #6: Manuscript on chlorpyrifos-induced neurotoxicity in rats</i>	34-36	X	X		For later reporting period
Major Task 7: Conduct neuroprotection experiments (conducted in N27 cells, minimum n=3/experiment) (responsible co-PI – Dr. Cannon in collaboration with Dr. Doorn)					
Subtask 1: Dopamine metabolism experiments: target dopamine metabolism as a neuroprotective mechanisms and measure dopamine metabolites.	1-6		X		
Subtask 2: ROS measurement as a key indicator of neurotoxicity and ability of neuroprotective strategies to ameliorate ROS	7-12		X		
Subtask 3: Dopamine-mediated protein modification measurement as a key adverse outcome and ability of neuroprotective strategies to prevent such modifications	13-18		X		For next reporting period
Subtask 4: Parkin siRNA efficacy and validation	19-21		X		For later reporting period
Subtask 5: Parkin-targeted neuroprotective experiments (gene targeted neuroprotective strategies, or alternate therapeutic approaches) – endpoints assessed as in subtasks 1-3, along similar timelines.	22-34		X		For later reporting period
Milestone #7: Manuscript on neuroprotective strategies	35-36	X	X		For later reporting period

What was accomplished under these goals?

Initiation of human studies. We have completed the human subjects and similar approvals from the following organizations: Purdue University, IU School of Medicine, Roudebush Veteran's Administration, and the DOD grants management. We also completed the formal subaward contract with the VA Roudebush.

Recruitment material have been completed and initial recruitment and data collection from study participants has begun.

Newly developed recruitment materials. Exemplar recruiting documents are shown.

Figure 1A. Recruiting materials (page 1).

What the study is about

We are conducting the study to learn more about what can cause Parkinson's disease. We are specifically interested in understanding whether exposure to pesticides in the military may lead to Parkinson's disease.

We are looking for US veterans interested in participating in this study!

Who can participate?

We are recruiting US veterans who use the VA medical system. We are recruiting veterans who have Parkinson's disease and we are also recruiting veterans who do not have Parkinson's disease.

Veterans with a neurodegenerative condition other than Parkinson's disease or who have prior moderate or severe head trauma are not eligible to participate.

Contact Us

For more information or to volunteer for the study, contact

pesticidesandparkinsons@purdue.edu
765-496-4823

Study Principal Investigators:

Dr. Nicolas Rattray, Roudebush VA Medical Center
Nicholas.Rattray@VA.Gov
317-988-9762

Dr. Ellen M. Wells, Purdue University
wells54@purdue.edu
765-496-3535



Research study on pesticides & Parkinson's disease

Roudebush VA Medical Center and Purdue University



Causes of Parkinson's disease are not well understood, and there is no cure.

What would happen if you participate?

Our staff will contact you by phone to confirm whether you are eligible and interested in participating in the study.

One of our staff will contact you via phone or videoconference to complete a questionnaire. The questionnaire will have questions about your lifestyle, medical history, and military experiences. We think this will take about an hour to complete.

We will also mail you a saliva collection kit, ask you to provide a saliva sample, and return it to us via mail. We will analyze the saliva for specific genetic patterns which might affect how pesticides affect the brain.

Study staff will also look through your VA medical record to collect data related to brain health and Parkinson's disease.



Approximately one million people in the US have Parkinson's disease.

Additional information

We are conducting the entire study via phone, videoconference, or mail. You would not need to travel anywhere to participate in the study.

There will be no costs to you as a part of participating in this study.

All data collected for the study will be stored and secured according to the VA standards for data protection.

Those who complete all parts of the study will receive \$40.

Veterans may have high pesticide exposure due to their military experiences.

Figure 1B. Recruiting materials (page 2).



DEPARTMENT OF VETERANS AFFAIRS
RICHARD L. ROUDEBUSH VA MEDICAL CENTER
1481 WEST 10th STREET
INDIANAPOLIS, IN 46202

Dear

The Veteran's Administration and Purdue University are conducting a research study on pesticides and their possible relationship with Parkinson's disease. The study has been funded by the Department of Defense. We would like you to consider participating in this study.

If you choose to be in the study, we would ask you to complete a several questionnaires either virtually or by phone with a study team member. The questions will be about your experiences in the military, possible exposure to pesticides, and health status. We expect this to take about 1 to 1 and a half hours. We will also collect selected data from your VA medical records if you choose to be part of this study. We would also ask you to send us a sample of your saliva in a provided kit; we will test the saliva for genetic factor related to Parkinson's disease.

We think this study is very important; it is important to understand what could cause Parkinson's in order to prevent the disease. The results might help protect future military personnel. One of our staff members will call you in the next few weeks to talk with you about the study. If you have any questions or concerns about the study, feel free to reach out to Dr. Rattray (317-988-9762, Nicholas.rattray@va.gov) or Dr. Wells (765-496-3535, wells54@purdue.edu).

More information about the study can also be found at <https://pesticidesparkinsonstudy.my.canva.site/>.

We hope you decide to participate!

Sincerely,

Handwritten signature of Nicholas Rattray, PhD.

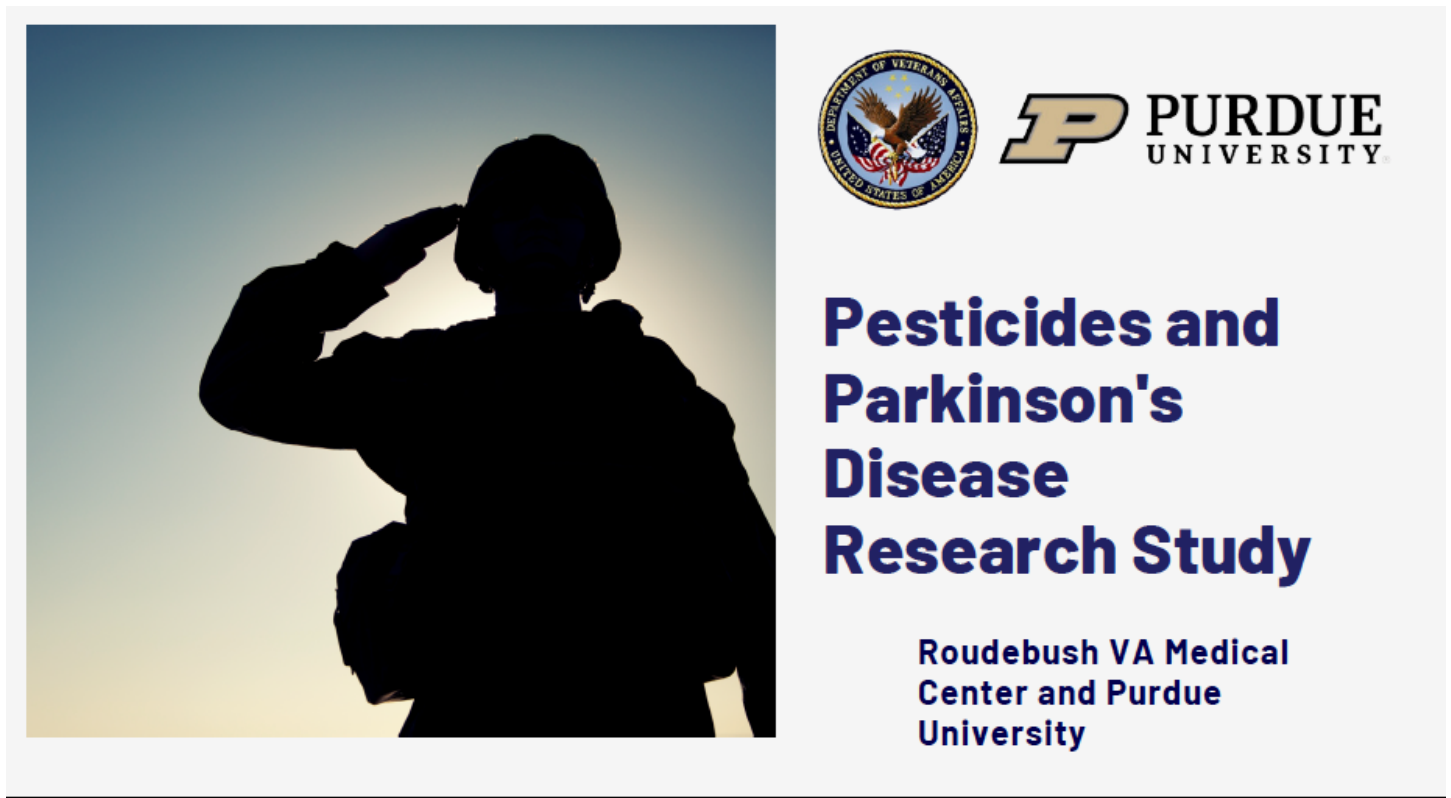
Dr. Nicholas Rattray
Roudebush VA Medical Center

Handwritten signature of Ellen Wells.

Dr. Ellen Wells
Purdue University

Figure 3. Recruitment letter.

Newly developed recruitment website:



The recruitment website banner features a large image on the left showing the silhouette of a soldier in a combat helmet saluting against a bright, hazy sky. To the right of the image, the Department of Veterans Affairs seal and the Purdue University logo are displayed. Below the logos, the title "Pesticides and Parkinson's Disease Research Study" is written in a large, bold, dark blue font. At the bottom right, the text "Roudebush VA Medical Center and Purdue University" is written in a smaller, dark blue font.

Pesticides and Parkinson's Disease Research Study

Roudebush VA Medical Center and Purdue University

Newly developed reminder postcard:



The reminder postcard is divided into two main sections. The left section features a photograph of a soldier in camouflage gear holding a smartphone, with a vertical orange bar to its right. The right section has a white background with the text "We're waiting for your call!" in a large, bold, dark blue font. Below this, the text "Research study on pesticides & Parkinson's disease" is written in a smaller, dark blue font. At the bottom, the text "Roudebush VA Medical Center and Purdue University" is written in a small, dark blue font, followed by the Department of Veterans Affairs seal and the Purdue University logo.

We're waiting for your call!

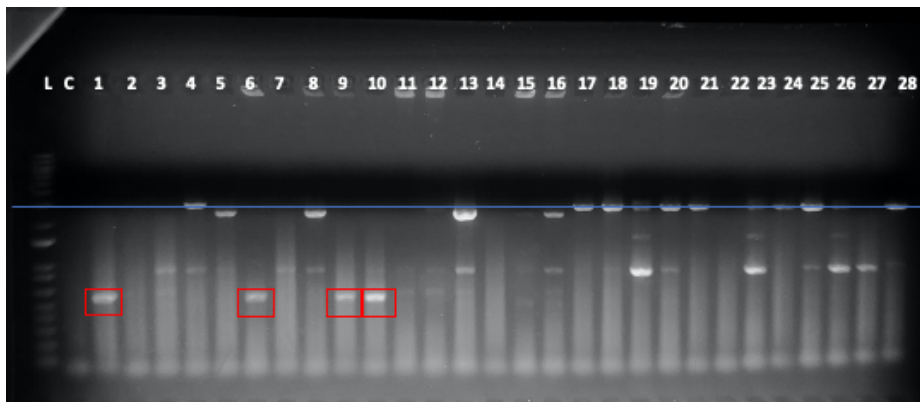
Research study on pesticides & Parkinson's disease

Roudebush VA Medical Center
and Purdue University

Figure 4. Recruitment website and postcard.

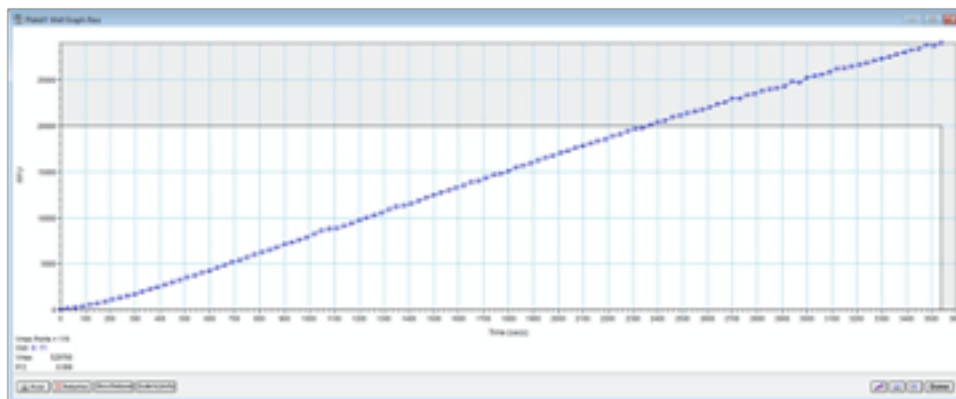
Transgenic animal studies. This project aims to compare the neurotoxic response to chlorpyrifos in wild-type and transgenic (PON1 knockout) rats.



Homozygous deletion: #1,6,9,10

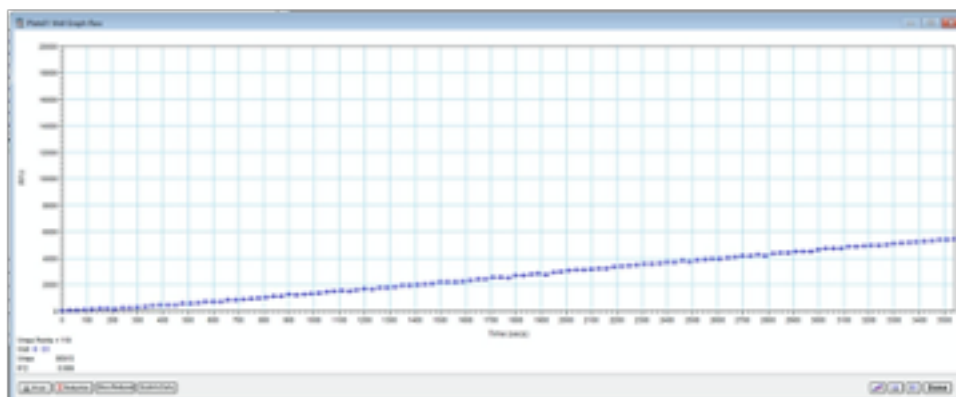
Figure 5. WT/PON1 knockout (truncation) confirmed by PCR assay (exemplar shown below), with selected animals also confirmed by genomic screening.

Wild Type (28)



Peak ~30000

Homozygous deletion(59)



Peak ~5800

Figure 6. Example serum PON1 activity assay shows a substantial decrease in PON1 activity, substantiating the efficacy of PON1 knockout and utility in studying the targeted gene-environment interaction.

Cellular studies on glutamatergic system.

Chlorpyrifos (CP) is an organophosphate pesticide and insecticide developed for agricultural and household settings. Chlorpyrifos, or its more toxic metabolite CP-oxon (CPO), causes a wide range of health complications such as neurological dysfunction, immunotoxicity, developmental issues, and cardiovascular damage. The primary target of CP neurotoxicity is typically thought to be acetylcholinesterase inhibition at high doses, though emergent data suggest that other neurotransmitter systems are affected at lower doses. Currently, little is known about how CP(O) affects the glutamatergic (GLUergic) system. The aim of this study is to determine the neurotoxic effects of CP and CPO on glutamate (GLU) release, characterize baseline GLU dynamics in human GLUergic cortical neurons, and address a gap in neurotransmitter monitoring using novel biosensors.

GLUergic cortical cultures were differentiated via dual-SMAD inhibition from human induced pluripotent stem cells (hiPSCs). Upon maturation (>D90), a baseline collection (in HBSS) for extracellular GLU was performed followed by a 24-h sub-cytotoxic exposure to CP (3 μM – 300 μM) or CPO (0.1 μM – 10 μM) (**Figure 7**). Following exposure, cells recovered for 24 h with an additional GLU collection. After the recovery period, whole-cell protein lysates were harvested to correct measured GLU release for cell density by total protein. All collections were analyzed using a commercial GLU assay kit. Cells exposed to CP demonstrated a concentration-dependent increase in net GLU release, while cells exposed to CPO presented no significant effect. The upregulation persisted over 24 h. Thus, it is shown that in addition to altering the acetylcholinergic system, CP and CPO may have unexpected effects on neuronal GLU homeostasis. An additional set of collections with vehicle exposure was performed at 10-min intervals over 60 min to monitor GLU efflux kinetics. GLU release was identified to sharply increase over 0 - 15 min and plateau after 20 min, which is likely to restore extracellular GLU levels. Newly developed enzymatic electrochemical biosensor arrays with cell culture compatibility were utilized to further characterize these findings. The biosensors were created using direct ink writing robotic printing combined with thin film processing and designed for sample delivery via injection or cell culture. Media samples with L-Glutamic Acid (60 μM) were dispensed on cultured cells and collected after 1 – 60 min for combined evaluation through sensors and enzymatic assays. In addition, GLU standards spiked with L-Glutamic Acid (0 μM - 60 μM) were prepared in HBSS, PBS, and BrainPhys for further testing. The novel biosensors confirmed

earlier GLU-kinetics findings and accurately measured extracellular GLU release in a variety of media types. Finally, multi-electrode array (MEA) analysis was performed to determine if acute CP exposure resulted in a detectable change in overall neuronal circuit activity as a functional outcome measure of GLUergic signaling. We observed (**Figure 8**) changes in several key measures by MEA, including Spikes (summed change in local field potential on a given electrode), Bursts (multiple spikes in temporal proximity on a given electrode), and Network bursts (bursts occurring simultaneously across multiple electrodes). We observed Overall, this study reveals a potential new mechanism for neurotoxicity, establishes a better understanding of GLU dynamics in vitro, and introduces innovative sensor technology.

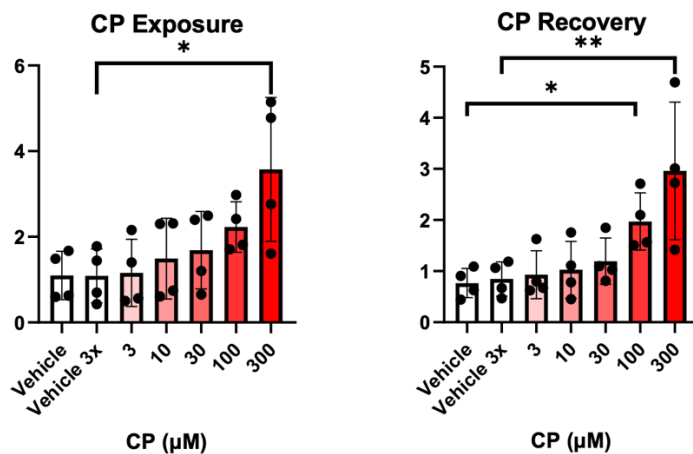


Figure 7. 24-hour CP exposure increases steady state extracellular glutamate levels. Extracellular glutamate concentrations following a 30-minute incubation in HBSS buffer with no added glutamate were measured to determine the steady-state level of glutamate following release from cells. Cells were analyzed after a 24-hour exposure to CP at the indicated concentrations (CP Exposure), then measured again after a 24 hour recovery period in normal neuronal culture media (CP Recovery). We observed a significant increase in extracellular glutamate levels with CP exposure that did not recover even 24 hours after exposure was removed.

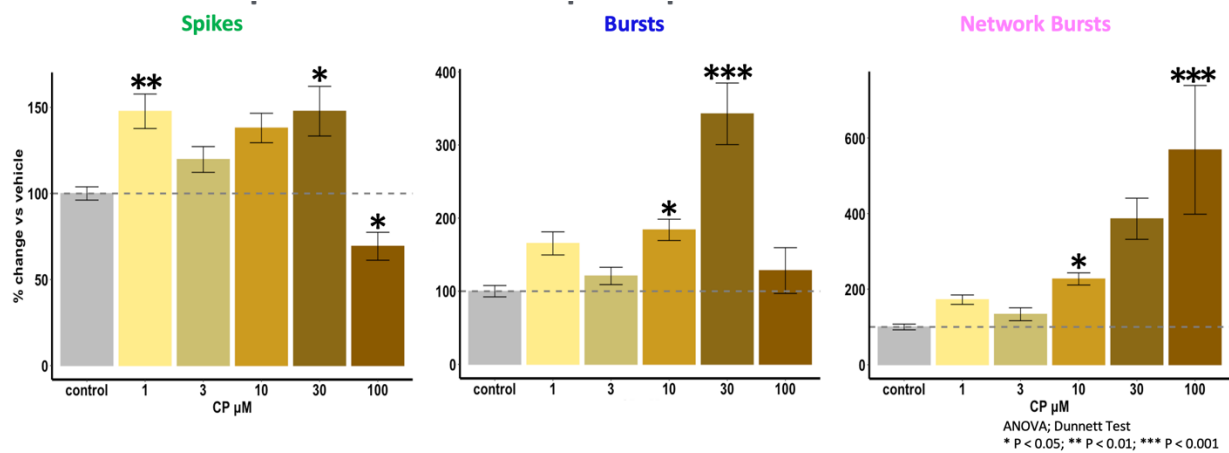


Figure 8. Acute CP exposure alters human cortical neural culture electrical activity. Acute CP Multielectrode array analysis of human stem cell derived cortical neurons exposed to CPF for 15 minutes, then recorded for 15-30 minutes. Mean number of spikes, bursts and network bursts were compared relative to CP exposure level. We observed significant changes in neuronal activity after acute exposure as low as 1 μ M CP.

Studies on a dopaminergic cell line.

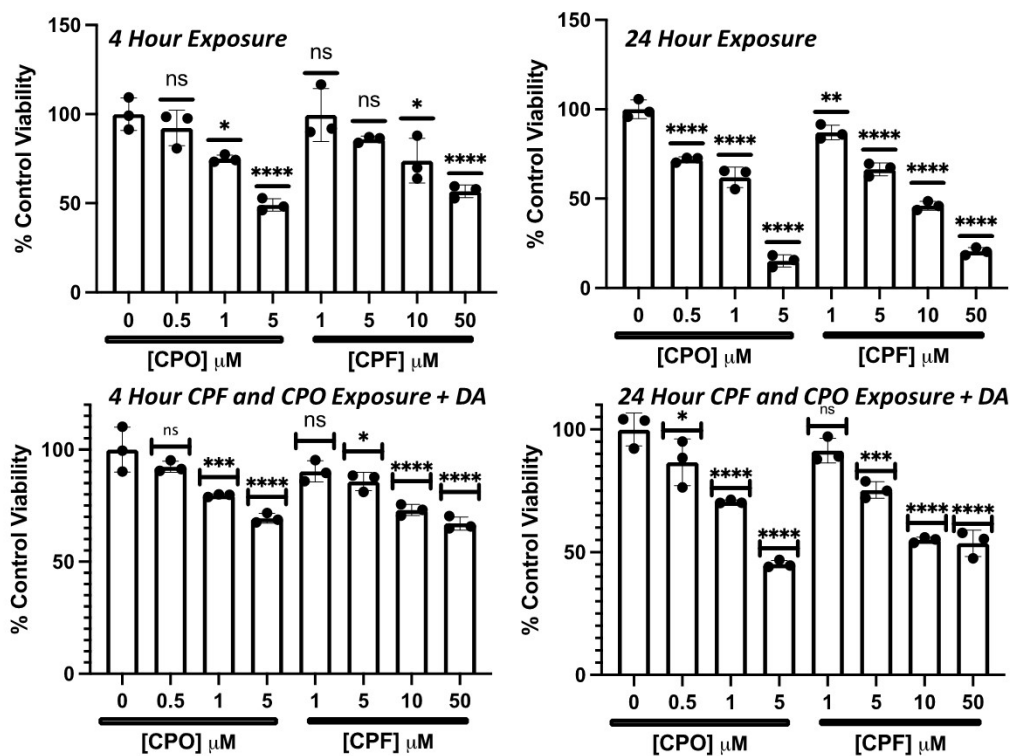


Figure 9. Cellular viability after chlorpyrifos. The University of Iowa team's work has focused on the impact of organophosphates, namely chlorpyrifos (CPF) and its active metabolite (CPO) on dopaminergic cells. Interestingly, they found that inclusion of dopamine (DA' at 100 μM) offered some measure of protection for the dopaminergic PC12 cells at the 4hr and 24hr time-points (MTT assay). The data for 4hr toxicity and influence of DA was verified using the Cell Titer Glo Assay, producing similar results (data not shown).

Table 1. Dopaminergic metabolite changes. It was determined that the treatment with CPF and CPO yielded changes in DA metabolites as shown in the table below: 3,4-dihydroxyphenylacetaldehyde (DOPAL), 3,4-dihydroxyphenylacetic acid (DOPAC), 3,4-dihydroxyphenylethanol (DOPET).

	Treatment (12hrs) Yielding Fold Change in DA Metabolites			
	CPF 1 μM	CPF 5 μM	CPO 0.5 μM	CPO 1 μM
DOPAL	1.20	1.75	1.46	2.01
DOPAC	0.83	0.61	0.32	0.24
DOPET	1.0	0.46	1.54	2.50

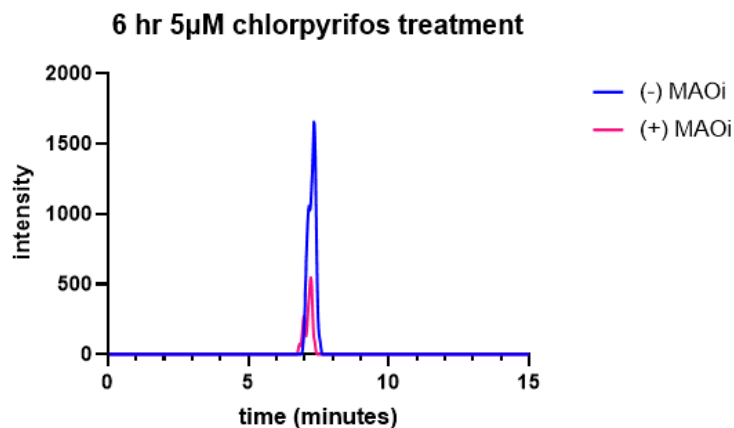


Figure 10. Dopaminergic metabolite – chlorpyrifos conjugate formation. It was found that the treatment of dopaminergic PC12 cells with CPF for 6hrs yielded production of a L-Cys amino acid conjugate with DOPAL, which may represent a stable biomarker for the disruption of DA homeostasis. Treatment with MAO inhibitor inhibitors (10µM clorgyline/pargyline) yielded a decrease in the conjugate formation, demonstrating MAO-dependence and the LCys conjugate includes DOPAL.

What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

- Continue recruitment and analyses of human data points.
- Increase number of technical and biological replicates of cellular studies and advance understanding of mechanism of neurotoxic action.
- Advance animal studies through planned phenotypic analyses, including neurobehavioral and histological endpoints.

4. Impact

What was the impact on the development of the principal discipline(s) of the project?

- The advancement of a new PON1 knockout rat will be useful in understanding how gene-environment interactions influence neurotoxic responses to organophosphates.
- The results on chlorpyrifos induced changes to glutamate neurotransmission suggest that organophosphate neurotoxicity may extend beyond catecholaminergic and dopaminergic targets.
- The results from dopaminergic cell lines suggest specific mechanisms of interaction between organophosphate metabolism and dopaminergic metabolites, also suggesting a possible biomarker of toxicity.

What was the impact on other disciplines?

- Nothing to report

What was the impact on technology transfer?

- Nothing to report

What was the impact on society beyond science and technology?

- In this first reporting period, the primary impact in this area is engagement of veterans in a project that may raise awareness

5. Changes/Problems

The only applicable problems are longer than required execution of subaward agreements and propagation of the animal colony, which have modestly slowed progress in some areas (as noted in Accomplishments). Most milestones are on track and work on animal and human studies are accelerating. No significant changes in animal or human studies, nor related to other items in item 5 instructions.

6. Products

• Publications, conference papers, and presentations

- Journal publications. Nothing to report.
- Books or other non-periodical, one-time publications. Nothing to report.
- Other publications, conference papers, and presentations.

Published Society of Toxicology Abstract and presented in poster form: Rubinchik, A. B., Tukker, A. M., Nolan, J. K., Gupta, K., Lake-Speers, M. A., Sammi, S. R., Cannon, J. R., Wereley, S. T., Lee, H., Bowman, A. B., 2023. Chlorpyrifos and Chlorpyrifos-Oxon Exposures Lead to the Dysregulation of Basal Glutamate Release in Human-Induced Pluripotent Stem Cell-Derived Glutamatergic Neurons. The Toxicologist. 192, 2017.

- *Purdue Spring Undergraduate Research Conference 2022 (Oral Presentaion)*

Same poster

- *CEREBBRAL Symposium Spring 2022 (Poster)*

Same poster

SOT 2023 conference (oral platform presentation)

Chlorpyrifos and chlorpyrifos-oxon exposures lead to the dysregulation of basal glutamate release in human-induced pluripotent stem cell-derived glutamatergic neurons

Adam Barmash Rubinchik¹, Anke M. Tukker¹, James K. Nolan², Kshitiz Gupta³, Melinda A. Lake³, Shrees R. Sammi¹, Jason R. Cannon¹, Steven T. Wereley³, Hyowon Lee², Aaron B. Bowman¹

School of Health Sciences¹, Weldon School of Biomedical Engineering², School of Mechanical Engineering³, Purdue University, West Lafayette, Indiana 47907-2051, USA

- *Purdue Spring Undergraduate Research Conference 2023 (Oral Presentation)*

Same presentation as SOT 2023

- Website(s) or other Internet site(s). Nothing to report.
- Technologies or techniques. Nothing to report.
- Inventions, patent applications, and/or licenses. Nothing to report.
- Other Products. Nothing to report.

7. Participants & Other Collaborating Organizations

What individuals have worked on the project?

Individuals with no change from initial submission:

Jason Cannon
Ellen Wells
Aaron Bowman
Jonathan Doorn
Nicholas Rattray

Other contributing individuals

Name:	Dr. Tauqeer Syeda
Project Role:	Postdoc
Researcher Identifier (e.g. ORCID ID):	<i>ORCID ID: 0000-0001-6673-577X</i>
Nearest person month worked:	3
Contribution to Project:	Dr. Syeda had a key role in propagation and characterization of PON1 animal colony
Funding Support:	From current award and NIH.

Name:	Josephine Brown-Leung
Project Role:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	<i>ORCID ID: 0000-0002-2346-6810</i>
Nearest person month worked:	6
Contribution to Project:	Mrs. Brown-Leung assistants with neurochemical and neurodegeneration assays.
Funding Support:	From current award and NIH.

Name:	Reeya Tanwar
Project Role:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	<i>ORCID ID: N/A – in process</i>
Nearest person month worked:	6
Contribution to Project:	Ms. Tanwar is now responsible for all proposed animal studies, which are ongoing.
Funding Support:	From current award and NIH.

Name:	Dr. S Elizabeth Zauber
Project Role:	Consultant
Researcher Identifier (e.g. ORCID ID):	<i>ORCID ID: 0000-0001-9003-4666</i>
Nearest person month worked:	0.1
Contribution to Project:	Dr. Zauber is a clinician specializing in movement disorders, including Parkinson's disease. She has contributed to all study questions/protocols relevant to clinical aspects of Parkinson's.
Funding Support:	From current award.

Name:	Alison Doepker
Project Role:	<i>Graduate Student</i>
Researcher Identifier (e.g. ORCID ID):	<i>ORCID ID: 0000-0003-4654-9149</i>
Nearest person month worked:	6
Contribution to Project:	Ms. Doepker has contributed to the development of questionnaires and other protocols for the study, supervision/training of undergraduate students working on the project, and will contribute to data collection.
Funding Support:	Through 8/15/2023: funding from NIOSH training grant, T03 OH008615.

Name:	Hannah Bard
Project Role:	<i>Undergraduate Student</i>
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	0.25
Contribution to Project:	Ms. Bard has contributed to the development of questionnaires and other protocols for the study and will contribute to data collection.
Funding Support:	Unfunded.

Name:	Perry Curtis
Project Role:	<i>Undergraduate Student</i>
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	0.25
Contribution to Project:	Mr. Curtis has contributed to the development of questionnaires and other protocols for the study and will contribute to data collection.
Funding Support:	Unfunded

Name:	Tamia Austin
Project Role:	<i>Undergraduate Student</i>
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	0.25
Contribution to Project:	Ms. Austin has contributed to the development of questionnaires and other protocols for the study and will contribute to data collection.
Funding Support:	Unfunded

Name:	<i>Anke Tukker</i>
Project Role:	<i>Postdoc</i>
Researcher Identifier (e.g. ORCID ID):	<i>eRA commons: attukker</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Dr. Tukker provided direct supervision of experiments related to chlorpyrifos exposures in human neurons.</i>
Funding Support:	

Name:	<i>Adam Barmash Rubinchik</i>
Project Role:	<i>Undergraduate student</i>
Researcher Identifier (e.g. ORCID ID):	<i>eRA commons: abarmash</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Mr. Rubinchik performed experiments alongside Dr. Tukker in human neurons.</i>
Funding Support:	

Name:	<i>Xueqi Tang</i>
Project Role:	<i>Graduate student</i>
Researcher Identifier (e.g. ORCID ID):	<i>eRA commons: tang484</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Ms. Tang generated neurons utilized for this study.</i>
Funding Support:	

Name:	David Yi
Project Role:	<i>Research Technician</i>
Researcher Identifier (e.g. ORCID ID):	<i>none</i>
Nearest person month worked:	<i>1</i>
Contribution to Project:	<i>Mr. Yi provided technical assistance to the project in the area of stem cell maintenance and differentiation.</i>
Funding Support:	

Name:	Anna E. Bartman
Project Role:	Graduate Student
Researcher Identifier (ORCID ID):	0000-0002-8986-7860
Nearest person month worked:	3
Contribution to Project:	<i>Ms. Bartman performed experiments relevant to Aim 2 to pinpoint mechanism via which organophosphates cause damage to dopaminergic cells.</i>
Funding Support:	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Current and pending other support for those with new submissions/funding. None of these new grants have an overlapping focus with the present funding.

DOD Current and Pending

Cannon, Jason R

Completed

Title: Mechanisms Of Phip-Mediated Neurotoxicity And Relevance To Parkinson'S Disease

PI: Cannon, Jason R
Time Commitments: Academic Month: 0
Summer Month: 1
Agency: Showalter Trust
Agency Address: No Address in Rolodex
Performance Period: 07/01/2013 - 06/30/2017
Funding:

Title: Imaging Mitochondrial Oxidative Stress In Parkinson'S Disease

PI: Tantama, Mathew C
Time Commitments: Academic Month: 0
Summer Month: 0.39
Agency: Showalter Trust
Agency Address: No Address in Rolodex
Performance Period: 07/01/2015 - 06/30/2018
Funding:

Title: Membrane-Induced Asyn Aggregation In Parkinson'S Disease

PI: Rochet, Jean-Christophe
Time Commitments: Academic Month: 0.18
Summer Month: 0
Agency: Purdue University
Agency Address: No Address in Rolodex
Performance Period: 05/01/2015 - 06/30/2017
Funding:

Title: Vesicle Permeabilization Associated With Membrane-Induced Asyn Aggregation: Role In Parkinson'S Disease

PI: Rochet, Jean-Christophe
Time Commitments: Academic Month: 0
Summer Month: 0.30
Agency: Branfman Family Foundation
Agency Address: 418 Queen Ann Rd,Cherry Hill,NJ 08003
Performance Period: 08/01/2015 - 01/31/2018
Funding:

Title:	16 Prf
PI:	Cannon, Jason R
Time Commitments:	Academic Month: 0.18 Summer Month: 0
Agency:	Purdue Research Foundation
Agency Address:	Office of Technology CommercializationPurdue Technology Center (PTC)3000 Kent Avenue,West Lafayette,IN 47906
Performance Period:	06/01/2015 - 05/31/2018
Funding:	
Title:	Fy1617 Prf Research Grants
PI:	Cannon, Jason R
Time Commitments:	Academic Month: 0.18 Summer Month: 0
Agency:	Purdue Research Foundation
Agency Address:	Office of Technology CommercializationPurdue Technology Center (PTC)3000 Kent Avenue,West Lafayette,IN 47906
Performance Period:	06/01/2016 - 06/30/2019
Funding:	
Title:	Neuroprotective Effects Of Endosulfine-Alpha In Pd Models
PI:	Rochet, Jean-Christophe
Time Commitments:	Academic Month: 0.18 Summer Month: 0.06
Agency:	Michael J. Fox Foundation
Agency Address:	Global Clinical Studies, c/o Box 4111, New York, NY 10163
Performance Period:	03/03/2017 - 06/30/2019
Funding:	
Title:	In Vivo Optical Imaging Of Alpha-Synuclein Aggregation
PI:	Webb, Kevin J
Time Commitments:	Academic Month: 0.45 Summer Month: 0
Agency:	Phs-Nih Nat Inst Neuro Disorders,Strokes
Agency Address:	Room 3201, MSC 95296001 Executive Boulevard,Rockville,MD 20852
Performance Period:	09/30/2018 - 08/31/2021
Funding:	
Title:	Lrk2 Kinase Activity And Mitochondrial Oxidative Stress

PI:	Tantama, Mathew C
Time Commitments:	Academic Month: 0.32 Summer Month: 0.10
Agency:	Phs-Nih Nat Inst Neuro Disorders,Strokes
Agency Address:	Room 3201, MSC 95296001 Executive Boulevard,Rockville,MD 20852
Performance Period:	09/15/2018 - 08/30/2019
Funding:	
Title:	Wise, John

PI:	Cannon, Jason R
Time Commitments:	Academic Month: 0.18 Summer Month: 0
Agency:	Bilsland, Winifred B. Endowment
Agency Address:	No Address in Rolodex
Performance Period:	05/01/2017 - 07/31/2020
Funding:	
Title:	Neuroprotective Effects Of Nfe2l1 In Pd Models

PI:	Rochet, Jean-Christophe
Time Commitments:	Academic Month: 0.18 Summer Month: 0.05
Agency:	Michael J. Fox Foundation
Agency Address:	Grand Central Station P.O. Box 4111, New York, NY 10163
Performance Period:	08/08/2018 - 08/31/2020
Funding:	
Title:	Role Of Alpha-Synuclein-Mediated Membrane Permeabilization In The Propagation Of Pd Neuropathology

PI:	Rochet, Jean-Christophe
Time Commitments:	Academic Month: 0 Summer Month: 0.27
Agency:	Branfman Family Foundation
Agency Address:	418 Queen Ann Rd, Cherry Hill, NJ 08003
Performance Period:	09/01/2018 - 02/29/2020
Funding:	
Title:	Lrrk2 Kinase Activity And Mitochondrial Oxidative Stress

PI:	Lyon, Angeline M
Time Commitments:	Academic Month: 0.32 Summer Month: 0.10

Agency:	Wellesley College
Agency Address:	108 Central Street,Wellesley,MA 02481
Performance Period:	09/01/2019 - 08/31/2020
Funding:	
 Title:	 Role Of A-Synuclein-Mediated Membrane Permeabilization In The Prion-Like Transmission Of Pd Neuropathology
PI:	Rochet, Jean-Christophe
Time Commitments:	Academic Month: 0 Summer Month: 0.60
Agency:	Branfman Family Foundation
Agency Address:	418 Queen Ann Rd,Cherry Hill,NJ 08003
Performance Period:	08/01/2019 - 12/31/2020
Funding:	

Current

Title:	Super-resolution in vivo optical imaging as a window to Parkinson's disease pathogenesis
PI:	Webb, Kevin J
Time Commitments:	Academic Month: 0 Summer Month: 0.23
Agency:	National Science Foundation
Agency Address:	4201 Wilson Boulevard,Arlington,VA 22230
Agency's Contact/Contracting/Grants Officer:	
Performance Period:	Aleksandr L Simonian 02/15/2020 - 12/31/2023
Funding:	
Objectives:	To utilize novel imaging techniques to discover key aspects of Parkinson's disease pathogenesis.
Overlap:	None
 Title:	 Role of endosulfine- α expression and phosphorylation in Parkinson's disease
PI:	Rochet, Jean-Christophe
Time Commitments:	Academic Month: 0.14 Summer Month: 0.05
Agency:	Phs-Nih Nat Inst Neuro Disorders,Strokes
Agency Address:	Room 3201, MSC 95296001 Executive Boulevard,Rockville,MD 20852
Agency's Contact/Contracting/Grants Officer:	
Performance Period:	Karen Molina 05/15/2020 - 10/31/2023

Funding:	To study the role of endosulphine-alpha in the pathogenesis of Parkinson's disease.
Objectives:	
Overlap:	None
Title:	Modeling functional genomics of susceptibility to the persistent effects of environmental toxins in an elderly rural Indiana neurodegenerative cohort
PI:	Bowman, Aaron B
Time Commitments:	Academic Month: 0.09 Summer Month: 0.03
Agency:	Phs-Nih National Institute On Aging
Agency Address:	31 Center Dr, MSC 2292, Bldg 31, Room 5C27, Bethesda, MD 20892
Agency's Contact/Contracting/Grants Officer:	
Performance Period:	Mirosław Mackiewicz 09/15/2022 - 05/31/2024
Funding:	
Objectives:	The major goals are to advance understanding of how gene environment interactions influence neurodegeneration, especially in a rural cohort.
Overlap:	None
Title:	BI: Emergent Mechanisms in Biology of Robustness, Integration, & Organization (EMBRIO)
PI:	Umulis, David M
Time Commitments:	Academic Month: 0 Summer Month: 0
Agency:	National Science Foundation
Agency Address:	4201 Wilson Boulevard, Arlington, VA 22230
Agency's Contact/Contracting/Grants Officer:	
Performance Period:	Wilson Francisco 09/01/2021 - 08/31/2026
Funding:	
Objectives:	Create an institute that advances understanding of basic biology.
Overlap:	None
Title:	Mechanisms of PhIP-induced dopaminergic neurotoxicity

PI:	Cannon, Jason R
Time Commitments:	Academic Month: 0.99 Summer Month: 3
Agency:	Phs-Nih Nat Inst Of Environment Hlth Sci
Agency Address:	No Address in Rolodex
Agency's Contact/Contracting/Grants Officer:	
Performance Period:	Jonathan Hollander 09/15/2023 - 08/31/2026
Funding:	
Objectives:	To advance understanding of heterocyclic aromatic amine neurotoxicity.
Overlap:	None
Title:	Role of Comorbid Military-Relevant Stressors in Osteoarthritis
PI:	Little, Dianne
Time Commitments:	Academic Month: 0.50 Summer Month: 0.50
Agency:	Army Medical Research Acquisition Activ
Agency Address:	No Address in Rolodex
Agency's Contact/Contracting/Grants Officer:	Jesse Trump MA Office: 301-613-3698 Email: jesse.r.trump.civ@health.mil
Performance Period:	09/15/2022 - 09/14/2026
Funding:	
Objectives:	The goals are to understand the interactions between development of knee osteoarthritis and various military relevant stressors.
Overlap:	This is the project for which this annual report is being prepared for
Title:	Role of military relevant chlorpyrifos exposure in Parkinson's disease relevant dopaminergic neurotoxicity
PI:	Cannon, Jason R
Time Commitments:	Academic Month: 0 Summer Month: 1.80
Agency:	Army Medical Res & Development Command
Agency Address:	No Address in Rolodex
Agency's Contact/Contracting/Grants Officer:	
Performance Period:	Stephen Grate 09/30/2022 - 09/29/2025
Funding:	

Objectives: Understand whether military related chlorpyrifos exposure may influence PD risk.

Overlap:

None

Title: FY24 - SHOWALTER AWARDS YOUNG INVESTIGATOR

PI: Baloni, Priyanka

Time Commitments: Academic Month: 0

Summer Month: 0

Agency: Showalter Trust

Agency Address: No Address in Rolodex

Agency's Contact/Contracting/Grants Officer:

Unknown

Performance Period: 07/01/2023 - 07/31/2024

Funding:

Objectives: Discover metabolic and genomic changes associated with PFAS exposure.

Overlap:

None

Pending

Title: Central and peripheral mechanisms of aerodigestive discoordination in an animal pesticide model of Parkinson's disease

PI: Cannon, Jason R

Time Commitments: Academic Month: 0

Summer Month: 0

Agency: Rowan University

Agency Address: 201 Mullica Hill Road, Glassboro, NJ 08028

Agency's Contact/Contracting/Grants Officer:

Unknown

Performance Period: 12/01/2023 - 11/30/2028

Funding:

Objectives: The goal is to discover pathogenic pathways responsible for PD swallowing disorder.

Overlap:

None

Title: PFAS induced alterations in reward processing

PI: Cannon, Jason R

Time Commitments:

Academic Month: 0
Summer Month: 0
National Institutes Of Health
No Address in Rolodex

Agency:
Agency Address:
Agency's Contact/Contracting/Grants Officer:

Jonathan Hollander
08/01/2023 - 08/31/2028

Performance Period:
Funding:

Objectives:

The goal is to translationally address the role of PFAS exposures in adverse mental health outcomes, utilizing cellular, animal, and human studies.

Overlap:

None

Title:

Optimization of small molecule SERCA2b activators to inhibit neuron loss in Alzheimer's disease

PI:
Time Commitments:

Koss, Wendy Ann
Academic Month: 0.45
Summer Month: 0

Agency:
Agency Address:
Agency's Contact/Contracting/Grants Officer:

Neurodon
9800 Connecticut Drive, Crown Point, IN 46307

Performance Period:
Funding:

Unknown
08/01/2023 - 08/31/2028

Objectives:

The goal is to test new therapeutic approaches in an AD mouse model.

Overlap:

None

Title:

Toxicology training in bidirectional translation across biological scale

PI:
Time Commitments:

Cannon, Jason R
Academic Month: 0.18
Summer Month: 0
Phs-Nih Nat Inst Of Environment Hlth Sci
No Address in Rolodex

Agency:
Agency Address:
Agency's Contact/Contracting/Grants Officer:

Carol Shreffler
08/01/2024 - 07/31/2029

Performance Period:
Funding:

Objectives:	The goal is to innovatively train the next generation of toxicologists.
Overlap:	
	None
Title:	Metabolic signatures associated with PFAS exposure and their neurotoxicity effects
PI:	Baloni, Priyanka
Time Commitments:	Academic Month: 0 Summer Month: 2
Agency:	National Institutes Of Health
Agency Address:	No Address in Rolodex
Agency's Contact/Contracting/Grants Officer:	Unknown
Performance Period:	07/01/2024 - 06/30/2029
Funding:	
Objectives:	
Overlap:	

None

Title:	Center for Health Impacts and Remediation of PFAS (CHIRP) in the Great Lakes
PI:	Sepulveda, Maria Soledad
Time Commitments:	Academic Month: 0.18 Summer Month: 0
Agency:	National Institutes Of Health
Agency Address:	No Address in Rolodex
Agency's Contact/Contracting/Grants Officer:	Not yet assigned
Performance Period:	07/01/2024-06/30/2029
Funding:	
Objectives:	To translationally identify and reduce the risk of adverse neurological outcomes from PFAS exposure.
Overlap:	None

DOD Current and Pending

Wells, Ellen M

Completed

Title: Occupational Safety and Health Training Grant

PI: Wells, Ellen M

Time Commitments: Academic Month: 1.20

Summer Month: 0.48

Agency: Phs-Cdc Natnl Inst Of Occup,Safety,Hlth

Agency Address: NIOSH / CDC / PGOBUILDING 140 - MS P05626
COCHRANS MILL ROAD,PITTSBURGE,PA 15236-0070

Performance Period: 07/01/2017 - 06/30/2022

Funding:

Title: 1718 Summer Research Grant Assistantships -
Graduate School

PI: Wells, Ellen M

Time Commitments: Academic Month: 0

Summer Month: 0

Agency: Prf Summer Research Grants

Agency Address: 610 Purdue Mall,West Lafayette,IN 47907

Performance Period: 05/01/2017 - 08/30/2020

Funding:

Title: FY 18-19 Showalter Awards Young Investigator

PI: Wells, Ellen M

Time Commitments: Academic Month: 0.18

Summer Month: 0

Agency: Showalter Trust

Agency Address: No Address in Rolodex

Performance Period: 07/01/2018 - 08/31/2021

Funding:

Title: Practical Training for Dublin Institute of Technology
Students

PI: Wells, Ellen M

Time Commitments: Academic Month: 0

Summer Month: 0

Agency: Tippecanoe County Board Of Commissioners

Agency Address: No Address in Rolodex

Performance Period: 01/23/2023 - 04/28/2023

Funding.

Current

Title:	Neuroimaging of Manganese Toxicity
PI:	Dydak, Ulrike
Time Commitments:	Academic Month: 0.50 Summer Month: 1
Agency:	Phs-Nih Nat Inst Of Environment Hlth Sci
Agency Address:	No Address in Rolodex
Agency's Contact/Contracting/Grants Officer:	Jonathan Hollander
Performance Period:	09/01/2020 - 08/31/2025
Funding:	
Objectives:	To evaluate the impact of Mn exposure in welders on neurological outcomes, as assessed by MRI
Overlap:	None.
Title:	Community-academic partnership to address environmental contamination and health
PI:	Wells, Ellen M
Time Commitments:	Academic Month: 0.45 Summer Month: 2
Agency:	Phs-Nih Nat Inst Of Environment Hlth Sci
Agency Address:	No Address in Rolodex
Agency's Contact/Contracting/Grants Officer:	Lindsey Martin
Performance Period:	09/20/2022 - 07/31/2027
Funding:	
Objectives:	Use a community-based research approach to assess environmental exposures (metals, volatile organic compounds) in northern Lake County, Indiana and determine the association of these exposures with indicators of neurological health.
Overlap:	None.
Title:	Distance Education and Training on Emerging Contaminants and Technologies (DETECT)
PI:	Wells, Ellen M

Time Commitments:

Academic Month: 0

Summer Month: 1.20

Agency:

Phs-Nih Nat Inst Of Environment Hlth Sci

Agency Address:

No Address in Rolodex

Agency's Contact/Contracting/Grants Officer:

Danielle Carlin

Performance Period:

09/22/2021 - 08/31/2028

Funding:**Objectives:**

Create a consortium of universities with established industrial hygiene training programs (Purdue University, University of Toledo, Air Force Institute of Technology, and University of South Florida) to establish a training program on emerging contaminants and technologies, incorporating non-credit online coursework, development of online laboratories, and hosting in-person summer research sessions.

Overlap:

None.

Title:

Modeling functional genomics of susceptibility to the persistent effects of environmental toxins in an elderly rural Indiana neurodegenerative cohort

PI:

Bowman, Aaron B

Time Commitments:

Academic Month: 1.35

Summer Month: 0.42

Agency:

Phs-Nih National Institute On Aging

Agency Address:

31 Center Dr, MSC 2282, Bldg 31, Room
5C27, Bethesda, MD 20892

Agency's Contact/Contracting/Grants Officer:

N/A

Performance Period:

09/15/2022 - 05/31/2024

Funding:

Objectives:	The goal for this project is to test the hypothesis that persistent neurotoxicity is due to exposures altering self-perpetuating homeostatic processes that give the resiliency and perpetuity to the adverse toxicological processes by either genetic and/or epigenetic means. Specifically, we will collect samples from same-sex siblings in northern Indiana that phenotypically differ in AD/ABR/AD relevant cognitive and motor dysfunction phenotypes; reprogram blood cells into human induced pluripotent stem cells (hiPSCs); differentiate them into cortical and midbrain lineages; and characterize their vulnerability to induction of a persistent neurotoxic state caused by neurodevelopmental exposures to environmental hazard/toxicants relevant to this region and history.
Overlap:	None.
Title:	Rural Environmental Health Assessment and Neighborhood-Specific Public Health Plan for Hartford City Using a Community-Engaged Approach
PI:	Wells, Ellen M
Time Commitments:	Academic Month: 0.18 Summer Month: 0
Agency:	IN Clinical & Translational Sci Inst
Agency Address:	410 W 10th St, Indianapolis, IN 46202
Agency's Contact/Contracting/Grants Officer:	N/A
Performance Period:	10/01/2021 - 12/31/2023
Funding:	--
Objectives:	Characterize the extent of environmental contamination and community members' exposure in the Commercial-Main neighborhood. Conduct a comprehensive health survey and determine the relationship between environmental contaminants with health outcomes. Engage community and develop a neighborhood-specific public health action plan to reduce the exposure and improve health equity.
Overlap:	None.
Title:	Role of military relevant chlorpyrifos exposure in Parkinson's disease relevant dopaminergic neurotoxicity
PI:	Cannon, Jason R

Time Commitments:	Academic Month: 0.00 Summer Month: 1
Agency:	Army Medical Res & Development Command
Agency Address:	No Address in Rolodex
Agency's Contact/Contracting/Grants Officer:	
Performance Period:	N/A
Funding:	09/30/2022 - 09/29/2025
Objectives:	The goal for the project is to evaluate the impact of the organophosphate pesticide chlorpyrifos on Parkinson's disease using parallel studies in mice and humans (military veterans). Dr. Wells will direct the human studies components of this project.
Overlap:	
	This is the project being reviewed.
Title:	Occupational Safety and Health Training Grant
PI:	Wells, Ellen M
Time Commitments:	Academic Month: 0.60 Summer Month: 0.43
Agency:	Phs-Cdc Natnl Inst Of Occup,Safety,Hlth
Agency Address:	NIOSH / CDC / PGOBUILDING 140 - MS P05626 COCHRANS MILL ROAD,PITTSBURGE,PA 15236-0070
Agency's Contact/Contracting/Grants Officer:	
Performance Period:	Elizabeth Maples
Funding:	07/01/2022 - 06/30/2024
Objectives:	To train the next generation of occupational and environmental health scientists.
Overlap:	
	None.

Pending

Title:	PFAS induced alterations in reward processing
PI:	Cannon, Jason R
Time Commitments:	Academic Month: 0 Summer Month: 0
Agency:	National Institutes Of Health

Agency Address:
Agency's Contact/Contracting/Grants Officer:

No Address in Rolodex

Performance Period:
Funding:

N/A
08/01/2023 - 08/31/2028

Objectives:

Advance understanding of how environmental exposures impact the neurobiology of psychiatric disorders, where in humans we aim to identify specific exposures/exposure levels linked to psychiatric disorders. We will integrate animal and human data in a way that will ultimately make a meaningful impact on public health. We will identify both persistent and emergent exposures that may impact mental health.

Overlap:

None.

Title:

Highly Sensitive Novel Neutron Activation Analysis (NAA) Technology to Quantify Multiple Metals in Human Bone In Vivo

PI:
Time Commitments:

Nie, Linda H
Academic Month: 0
Summer Month: 0.50
National Institutes Of Health
No Address in Rolodex

Agency:
Agency Address:
Agency's Contact/Contracting/Grants Officer:

Performance Period:
Funding:

N/A
12/01/2023 - 11/30/2027

Objectives:

IVNAA technology will be validated using models that are closely related to future applications. In addition, novel Na analysis methods, advanced spectral analysis software, and novel system calibration methods will be developed.

Overlap:

None.

Title:

Center for Health Impacts and Remediation of PFAS (CHIRP)

PI:
Time Commitments:

Sepulveda, Maria Soledad
Academic Month: 0.18
Summer Month: 0
National Institutes of Health

Agency:
Agency Address:
Agency's Contact/Contracting/Grants

Officer:

Not Available

Performance Period:

07/01/2023-06/30/2029

Funding:

Objectives:

To translationally identify and reduce the risk of adverse neurological outcomes stemming from PFAS exposure.

Overlap:

None

Many federal agencies are revising their instructions regarding Other Support. They requested similar, though not uniform, information and provide somewhat Current and Pending/Other Support documents provided by Sponsored Program draft documents including only the data available within Sponsored Program Additional support should be added as described on the Pre-Award Services

https://www.purdue.edu/business/sps/preaward/menu/2.proposalprepare/basic_elem

****NEW**** Outside Activity Disclosures from the most recent FY are included in the second sheet of this file for your convenience.

Investigator Expectations Regarding Completion of Other/Current and Pending
Consistent with federal agency expectations, Purdue University requires that every disclosure to an external funding agency of an investigator's active, pending, or and other sponsored activities be true, complete, and accurate to the best of the This requirement applies regardless of the source of support, whether or not Purdue University is the recipient of the support.

For example, if an investigator with a joint appointment is listed as a PI on an award to another institution, that must be disclosed in other support.

The requirement for disclosure applies at the time of proposal submission, prior to award acceptance, and as part of the annual progress report.

It is the investigator's responsibility to ensure the accuracy of other support documents, in accord with the application guidelines or the sponsor's instructions. False, fictitious, or fraudulent statements or claims (including intentional omissions) in violation of this policy may result in University and sponsor administrative, civil,

Text above this line and any red text below will be removed prior to
As the PI, you will need to complete the areas below highlighted in

DOD Current and Pending

Bowman, Aaron B

Completed

Title:	Mechanisms of Methylmercury Induced Neuronal Toxicity	19013632
PI:	Bowman, Aaron B	
Time Commitments:	Academic Month: 1.20 Summer Month: 0	
Agency:	Albert Einstein College of Medicine	
Agency Address:	1300 Morris Park Avenue, Bronx, NY 10461	
Performance Period:	08/01/2018 - 05/31/2019	
Funding:		
Title:	Mechanisms of Manganese Neurotoxicity	19013656
PI:	Bowman, Aaron B	
Time Commitments:	Calendar Month: 1.60 Summer Month: 0	
Agency:	Albert Einstein College of Medicine	

Agency Address:	1300 Morris Park Avenue,Bronx,NY 10461	
Performance Period:	08/01/2018 - 03/31/2019	
Funding:		
Title:	Gene-Neurotoxicant Interactions in Huntington Disease	19025043
PI:	Bowman, Aaron B	
Time Commitments:	Calendar Month: 1.75 Summer Month: 0	
Agency:	Phs-Nih Nat Inst Of Environment Hlth Sci	
Agency Address:	No Address in Rolodex	
Performance Period:	08/29/2018 - 02/28/2020	
Funding:		
Title:	Hair Manganese accumulation as a novel biomarker for external Mn exposure	19025074
PI:	Bowman, Aaron B	
Time Commitments:	Calendar Month: 0.36 Summer Month: 0	
Agency:	International Manganese Institute	
Agency Address:		
Performance Period:	09/01/2018 - 08/31/2020	
Funding:		
Title:	Mechanisms of Manganese Neurotoxicity	19089391
PI:	Bowman, Aaron B	
Time Commitments:	Calendar Month: 2.40 Summer Month: 0	
Agency:	Albert Einstein College of Medicine	
Agency Address:	1300 Morris Park Avenue,Bronx,NY 10461	
Performance Period:	04/01/2019 - 03/31/2020	
Funding:		
Title:	Mechanisms of Methylmercury Induced Neuronal Toxicity	19100532
PI:	Bowman, Aaron B	
Time Commitments:	Calendar Month: 1.44 Summer Month: 0	
Agency:	Albert Einstein College of Medicine	
Agency Address:	1300 Morris Park Avenue,Bronx,NY 10461	
Performance Period:	06/01/2019 - 05/31/2020	
Funding:		
Title:	Drug development for tuberous sclerosis complex and other pediatric epileptogenic diseases using neurovascular and cardiac microphysiological models	19100951
PI:	Bowman, Aaron B	

Time Commitments:	Calendar Month: 0.24 Summer Month: 0	
Agency:	Vanderbilt University	
Agency Address:	No Address in Rolodex	
Performance Period:	08/01/2018 - 06/30/2019	
Funding:		
Title:	Mechanisms of Manganese Neurotoxicity	20078985
PI:	Bowman, Aaron B	
Time Commitments:	Calendar Month: 1.92 Summer Month: 0	
Agency:	Albert Einstein College of Medicine	
Agency Address:	1300 Morris Park Avenue, Bronx, NY 10461	
Performance Period:	04/01/2020 - 03/31/2021	
Funding:		
Title:	Mechanisms of Methylmercury Induced Neuronal Toxicity	20101594
PI:	Bowman, Aaron B	
Time Commitments:	Calendar Month: 1.44 Summer Month: 0	
Agency:	Albert Einstein College of Medicine	
Agency Address:	1300 Morris Park Avenue, Bronx, NY 10461	
Performance Period:	06/01/2019 - 02/14/2022	
Funding:		
Title:	Mechanisms of Methylmercury Induced Neuronal Toxicity	21035379
PI:	Bowman, Aaron B	
Time Commitments:	Calendar Month: 1.52 Summer Month: 0	
Agency:	Albert Einstein College of Medicine	
Agency Address:	1300 Morris Park Avenue, Bronx, NY 10461	
Performance Period:	02/15/2022 - 11/30/2023	
Funding:		
Title:	Mechanisms of Manganese Neurotoxicity	21090363
PI:	Bowman, Aaron B	
Time Commitments:	Calendar Month: 1.92 Summer Month: 0	
Agency:	Albert Einstein College of Medicine	
Agency Address:	1300 Morris Park Avenue, Bronx, NY 10461	
Performance Period:	04/01/2021 - 03/31/2022	
Funding:		

Current

Title:	Manganese exposure susceptibility as a modifier of excitotoxicity in Alzheimer's Disease	20057345
PI:	Bowman, Aaron B	
Time Commitments:	Calendar Month: 1.20 Summer Month: 0	
Agency:	Vanderbilt University Medical Center	
Agency Address:	No Address in Rolodex	
Agency's Contact/Contracting/Grants Officer:	Jonathan Hollander, Program Officer	
Performance Period:	02/01/2020 - 10/31/2024	
Funding:	NIH/NIEHS Sub-award to Purdue University from Vanderbilt University Medical Center. To test the central hypothesis is that chronic elevated manganese (Mn) exposure drives cognitive decline through impaired glutamate homeostasis. Our long-term objectives are to isolate the direct link(s) between Mn and cognitive decline by demonstrating how chronic Mn exposure affects altered glutamate clearance and other pathologies to a greater extent in mouse and human stem cell models of AD than in controls	
Objectives:		
Overlap:	None	
Title:	Neuroimaging of Manganese Toxicity	20089173
PI:	Dydak, Ulrike	
Time Commitments:	Academic Month: 0.12 Summer Month: 0	
Agency:	Phs-Nih Nat Inst Of Environment Hlth Sci	
Agency Address:	No Address in Rolodex	
Agency's Contact/Contracting/Grants Officer:	Jonathan Hollander, Program Officer	
Performance Period:	09/01/2020 - 08/31/2025	
Funding:	To use novel MRI and MRS techniques to define the spatio-temporal dynamics of uptake and elimination of brain Mn, as well as markers of oxidative stress in welders exposed to manganese.	
Objectives:		
Overlap:	None	
Title:	Purdue University Health Physics Faculty Development Plan	20111852

PI:	Harris, Jason T	
Time Commitments:	Academic Month: 0.01 Summer Month: 0	
Agency:	Nuclear Regulatory Commission	
Agency Address:	No Address in Rolodex	
Agency's Contact/Contracting/Grants Officer:		
Performance Period:	M'Lita R. Carr, Contracting/Grant Officer 04/12/2021 - 04/11/2024	
Funding:		
Objectives:	To create a new faculty position in Health Physics by leveraging US NRC and matching funds from Purdue University.	
Overlap:	None	
Title:	Modeling functional genomics of susceptibility to the persistent effects of environmental toxins in an elderly rural Indiana neurodegenerative cohort	21080149
PI:	Bowman, Aaron B	
Time Commitments:	Calendar Month: 0.60 Summer Month: 0	
Agency:	Phs-Nih National Institute On Aging	
Agency Address:	31 Center Dr, MSC 2292, Bldg 31, Room 5C27, Bethesda, MD 20892	
Agency's Contact/Contracting/Grants Officer:		
Performance Period:	Alison Q. Tao, Senior Program Officer 09/15/2022 - 05/31/2027	
Funding:		
Objectives:	This R01 study aims to (1) identify subject by toxicant interactions using subject derived cells, (2) identify genetic pathways associated with persistent effects, and (3) validate mechanisms in in vivo model systems.	
Overlap:	None	
Title:	Role of endosulfine-alpha expression and phosphorylation in Parkinson's disease	21112270
PI:	Rochet, Jean-Christophe	
Time Commitments:	Calendar Month: 0.09 Summer Month: 0	
Agency:	Phs-Nih Nat Inst Neuro Disorders, Strokes	
Agency Address:	Room 3201, MSC 95296001 Executive Boulevard, Rockville, MD 20852	
Agency's Contact/Contracting/Grants Officer:	Tom Cheever, Program Officer	

Performance Period:	05/15/2020 - 10/31/2023	
Funding:		
Objectives:	The goals of this project are to (i) determine the effect of ENSA knockout on neuron activity in a cellular DS model; and (ii) determine the relative abundance of pS109-ENSA in DS brains.	
Overlap:	None	
Title:	Role of military relevant chlorpyrifos exposure in Parkinson's disease relevant dopaminergic neurotoxicity	22036362
PI:	Cannon, Jason R	
Time Commitments:	Calendar Month: 0.50 Summer Month: 0	
Agency:	Army Medical Res & Development Command	
Agency Address:	No Address in Rolodex	
Agency's Contact/Contracting/Grants Officer:		
Performance Period:	This award 09/30/2022 - 09/29/2025	
Funding:		
Objectives:	Assess if PD is associated with organophosphate exposure in US military vets, and if chlorpyrifos produces selective dopaminergic neurotoxicity in translational models.	
Overlap:	None	
Title:	Mechanisms of Manganese Neurotoxicity	22089248
PI:	Bowman, Aaron B	
Time Commitments:	Calendar Month: 1.92 Summer Month: 0	
Agency:	Albert Einstein College of Medicine	
Agency Address:	1300 Morris Park Avenue, Bronx, NY 10461	
Agency's Contact/Contracting/Grants Officer:		
Performance Period:	Jonathan Hollander, Program Officer 04/01/2022 - 03/31/2024	
Funding:		
Objectives:	In the third competitive renewal, this program is testing the hypothesis that threshold-level Mn neurotoxicity occurs via alteration of Mn-dependent/-activated biological functions such as insulin/insulin-like growth factor and related metabolic signaling pathways and dopamine neuronal function in worms and mammalian systems.	
Overlap:		

	None	
Title:	Mechanisms of Methylmercury Induced Neuronal Toxicity	23035944
PI:	Bowman, Aaron B	
Time Commitments:	Calendar Month: 1.20 Summer Month: 0	
Agency:	Albert Einstein College of Medicine	
Agency Address:	1300 Morris Park Avenue, Bronx, NY 10461	
Agency's Contact/Contracting/Grants Officer:	Jonathan Hollander, Program Officer	
Performance Period:	12/01/2022 - 11/30/2023	
Funding:		
Objectives:	NIH/NIEHS Sub-award to Purdue Univ. from Albert Einstein College of Medicine. Here we seek to identify and understand persistent and latent effects of methylmercury toxicity on biological pathways impacted by methylmercury toxicity. We aim to determine if it is formally possible that latent neurotoxicity can be stopped before neurological signs appear or that established persistent effects that continue long after exposure has ceased could be reversed.	
Overlap:	None	

Pending

Title:	Mechanisms of Manganese Neurotoxicity	23035934
PI:	Bowman, Aaron B	
Time Commitments:	Calendar Month: 2.40 Summer Month: 0	
Agency:	Phs-Nih Nat Inst Of Environment Hlth Sci	
Agency Address:	No Address in Rolodex	
Agency's Contact/Contracting/Grants Officer:	Jonathan Hollander, Program Officer	
Performance Period:	09/01/2023 - 08/31/2028	
Funding:		

Objectives: Overlap:	NIH/NIEHS competitive renewal, with change of primary institution to Purdue University. The proposed studies will (1) compare biological pathways and functional phenotypes altered by chronic vs acute Mn exposure, (2) identify persistent vs transient effects of chronic Mn exposure, and (3) explore the mechanistic basis of chronic and persistent Mn neurotoxicity. We test the hypothesis that chronic Mn neurotoxicity is caused by a response to the impact of acute elevated Mn on neuronal cell signaling systems for which Mn normally acts as an essential co-factor. None
Title: PI: Time Commitments: Agency: Agency Address: Agency's Contact/Contracting/Grants Officer: Performance Period: Funding: Objectives: Overlap:	Manganese exposure and genetic diversity in risk mechanisms for neurodevelopmental disorders 23056838 Bowman, Aaron B Calendar Month: 1.20 Summer Month: 0 Vanderbilt University Medical Center No Address in Rolodex Jonathan Hollander, Program Officer 04/01/2024 - 03/31/2029 The broad, long-term objectives of the grant are to increase our understanding of the mechanisms underlying the gene x environment interactions that link developmental manganese (Mn) exposure, dopamine (DA) dysregulation and increased frequency of ADHD diagnoses. Aim 1 is to determine the role of sex and genetic background on Mn exposure-induced behavioral change and DAergic transport deficits. Aim 2 will test whether Mn modifies pharmacological modulation of DA transport in vivo. Aim 3 will determine whether Mn has an ADHD-related differential impact on DA functional characteristics of human induced pluripotent stem cell (hiPSC)-derived DAergic neurons. None
Title:	Alzheimer's disease pathology and abnormal protein N-terminal acetylation in extracellular vesicles 23089004

PI:	Tao, Weiguo Andy	
Time Commitments:	Calendar Month: 0.60 Summer Month: 0	
Agency:	National Institutes Of Health	
Agency Address:	No Address in Rolodex	
Agency's Contact/Contracting/Grants Officer:		
Performance Period:	Unknown, unassigned	
Funding:	01/01/2024 - 12/31/2028	
Objectives:	To understand the role of extracellular vesicle protein modifications in the development of AD	
Overlap:		
	None	
Title:	Biobehavioral responses to chronic developmental manganese exposure	23089676
PI:	Bowman, Aaron B	
Time Commitments:	Calendar Month: 0.60 Summer Month: 0	
Agency:	Vanderbilt University Medical Center	
Agency Address:	No Address in Rolodex	
Agency's Contact/Contracting/Grants Officer:		
Performance Period:	Jonathan Hollander, Program Officer	
Funding:	12/01/2023 - 11/30/2028	
Objectives:	Determine the brain regions impacted by chronic Manganese exposure and the behavioral outputs of that exposure	
Overlap:		
	None	
Title:	Toxicology training in bidirectional translation across biological scale	23123079
PI:	Cannon, Jason R	
Time Commitments:	Academic Month: 0.18 Summer Month: 0	
Agency:	Phs-Nih Nat Inst Of Environment Hlth Sci	
Agency Address:	No Address in Rolodex	
Agency's Contact/Contracting/Grants Officer:		
Performance Period:	Unknown, unassigned	
Funding:	08/01/2024 - 07/31/2029	

Objectives:	The Toxicology Training Program at Purdue University aims to innovatively train our graduate students and postdoctoral fellows in bidirectional translation. Our T32 trainees will be uniquely positioned to address the most important problems facing all sectors of toxicology and rapidly pivot to address emergent problems in the field.		
Overlap:	None		
Title:	Mechanisms of Methylmercury Induced Neuronal Toxicity	24035809	
PI:	Bowman, Aaron B		
Time Commitments:	Calendar Month: 2.40 Summer Month: 0		
Agency:	Albert Einstein College Of Medicine		
Agency Address:	1300 Morris Park Avenue,Bronx,NY 10461		
Agency's Contact/Contracting/Grants Officer:	Jonathan Hollander, Program Officer		
Performance Period:	12/01/2023 - 11/30/2024		
Funding:	NIH/NIEHS Sub-award to Purdue Univ. from Albert Einstein College of Medicine. Here we seek to identify and understand persistent and latent effects of methylmercury toxicity on biological pathways impacted by methylmercury toxicity. We aim to determine if it is formally possible that latent neurotoxicity can be stopped before neurological signs appear or that established persistent effects that continue long after exposure has ceased could be reversed.		
Objectives:			
Overlap:	None		
Title:	Modeling functional genomics of susceptibility to the persistent effects of environmental toxins in an elderly rural Indiana neurodegenerative cohort	23111462	
PI:	Bowman, Aaron B		
Time Commitments:	Calendar Month: 0.60 Summer Month: 0		
Agency:	National Institutes Of Health		
Agency Address:	No Address in Rolodex		
Agency's Contact/Contracting/Grants Officer:	Allison Q. Tao, Senior Program Officer		
Performance Period:	09/01/2023 - 08/31/2024		
Funding:			

Objectives:

Supplement application to apply the novel machine learning methods for gene regulatory network construction proposed in our parent R01 to single-cell data from healthy individuals and patients with ADRD. Results from these analyses will augment the power of the statistical analysis in our funded R01 study; and collectively facilitate the development of new strategies to prevent, delay, and treat ADRD.

Overlap:

None

DOD Current and Pending**Nick Rattray****Completed**

Title:	From Military to Community Life: Reintegrating Veterans with Invisible Injuries
PI:	Rattray, Nicholas
Time Commitments:	Person months: 12.0 calendar
Agency:	Veteran Affairs, Rehabilitation Research and Development
Agency Address:	Department of Veterans Affairs (14RDR), 810 Vermont Avenue NW, Washington, DC 20420
Performance Period:	10/01/2018 – 09/30/2023
Funding:	

Current

Title:	Role of military relevant chlorpyrifos exposure in Parkinson's Disease relevant dopaminergic neurotoxicity
PI:	Cannon, Jason
Time Commitments:	Person months .036 calendar
Agency:	Army Medical Res & Development Command
Agency Address:	
Agency's Contact/Contracting/Grants Officer:	
Performance Period:	10/01/2022 – 09/30/2025
Funding:	
Objectives:	
Objectives:	The goal for the project is to evaluate the impact of the organophosphate pesticide chlorpyrifos on Parkinson's disease using parallel studies in mice and humans (military veterans). Dr. Wells will direct the human studies components of this project.
Overlap:	This is the project being reviewed.

Title:	Mobilizing Rural Communities to Improve Quality of Life And Promote Opioid Prevention Among High-Need, Low-Resource Veterans And Their Families
PI:	Shelley MacDermid Wadsworth
Time Commitments:	Person months: contributed
Agency:	US Department of Agriculture
Agency Address:	
Agency's Contact/Contracting/Grants Officer:	
Performance Period:	10/1/2021 — 9/30/2023
Funding:	
Objectives:	The project team is evaluating the effectiveness of a service program for veterans, Reaching Rural Veterans (RRV). RRV uses food insecurity as a gateway for addressing other needs including, social isolation and connections to services and benefits among low-resource veterans living in rural areas.
Overlap:	None.

Title:	EXTEND: Expanding Expertise through e-Health Networks
PI:	Damush, Teresa
Time Commitments:	Person months: 2.4
Agency:	VA Health Services Research and Development
Agency Address:	
Agency's Contact/Contracting/Grants Officer:	
Performance Period:	10/01/2020 – 09/30/2025
Funding:	
Overlap:	None.
Title:	VA Office of Specialty Care Neurology – Headache Centers of Excellence
PI:	Jason Sico
Time Commitments:	Person Months: 3.0
Agency:	Congressional Funding – VA Office of Specialty Care Neurology
Agency Address:	
Agency's Contact/Contracting/Grants Officer:	
Performance Period:	N/A
Funding:	09/01/2023-09/30/2024
Objectives:	The project will conduct a formative evaluation with both Vetreran patients with PTSD chronic headaches and their VA providers and Community Care providers available and in need. We will also evaluate the implementation of the VA Headache Centers of Excellence.
Overlap:	None.
Title:	Role of military relevant chlorpyrifos exposure in Parkinson's disease relevant dopaminergic neurotoxicity
PI:	Cannon, Jason R
Time Commitments:	Academic Month: 0.80 Summer Month: 1
Agency:	
Agency Address:	No Address in Rolodex
Agency's Contact/Contracting/Grants Officer:	
Performance Period:	N/A
Funding:	09/30/2022 - 09/29/2025
Objectives:	The goal for the project is to evaluate the impact of the organophosphate pesticide chlorpyrifos on Parkinson's disease using parallel studies in mice and humans (military veterans). Dr. Wells will direct the human studies components of this project.
Overlap:	This is the project being reviewed.

**PREVIOUS/CURRENT/PENDING SUPPORT
JONATHON DOORN; UNIVERSITY OF IOWA**

Current Positions and Scientific Appointments

1997	Summer Intern, Dept. of Drug Delivery, Pharmacia and Upjohn, Kalamazoo, MI
1998-2001	Graduate Student/NIH Trainee, Toxicology Program, University of Michigan
2001-2002	Postdoctoral Fellow/NIH Trainee, Dept. of Pharmacology, University of Colorado HSC
2002-2004	Postdoctoral/NRSA Fellow, Dept. of Pharmaceutical Sciences, University of Colorado HSC
2004-2010	Assistant Professor of Medicinal and Natural Products Chemistry, University of Iowa 2004- Member, Center for Biocatalysis and Bioprocessing, University of Iowa
2005-	Member, Environmental Health Sciences Research Center, Oxidative Stress and Metabolism Research Core, University of Iowa
2006-	Member, Human Toxicology and Bioscience Training Program, University of Iowa
2010-2019	Associate Professor of Medicinal and Natural Products Chemistry, University of Iowa
2015-	Division Chair, Medicinal and Natural Products Chemistry, University of Iowa
2019	Member, Interdisciplinary Graduate Program in Neuroscience, University of Iowa
2019-	Professor of Medicinal and Natural Products Chemistry, University of Iowa

Current

Title: Pesticide-Mediated Generation of a Toxic Neurotransmitter Metabolite

Time Commitment/Role: 2.4 calendar months/PI

Supporting Agency: NIH/NIEHS

Address: 1101 Wootton Parkway, Ste 200, Rockville MA, 20852

Contracting/Grants Officer: Jonathon Hollander

Performance Period: 09/30/2018 – 08/31/2023

Level of funding:

Project Goals/Aims: The goal of this work is to determine the contribution of reactive neurotransmitter metabolites in the neurotoxicity of pesticides, relevant to neurodegenerative disease, specifically focusing on the role of biogenic aldehydes, aldehyde metabolism and glial cells.

Overlap: There is no scientific or budgetary overlap.

Title: Airborne PCBs: Sources, Exposures, Toxicities, Remediation

Time Commitment/Role: 1.2 Calendar Months/Co-I

Supporting Agency: NIH/NIEHS

Address: 1101 Wootton Parkway, Ste 200, Rockville MA, 20852

Contracting/Grants Officer: Michelle Victalino

Performance Period: 04/01/2020 – 03/31/2024

Level of funding:

Project Goals/Aims: The goal of this work is to elucidate the contributions of airborne PCBs and their metabolites to, and their mechanisms of action in, neurotoxic responses relevant to neurodevelopmental outcomes.

Overlap: There is no scientific or budgetary overlap.

Title: Environmental Health Sciences Research Center (EHSRC)

Time Commitment/Role: 0.36 calendar months/Co-I

Supporting Agency: NIH

Address: 1101 Wootton Parkway, Ste 200, Rockville MA, 20852

Contracting/Grants Officer: Barbara Gittleman

Performance Period: 04/01/1997 – 03/31/2027

Level of funding:

Project Goals/Aims: The goal of the EHSRC is to promote research interactions among environmental health researchers at the UI, enhancing ongoing environmental health research and facilitating initiation of new collaborative and interdisciplinary environmental health research focused on rural populations.

Overlap: There is no scientific or budgetary overlap.

Title: Role of military relevant chlorpyrifos exposure in Parkinson's disease relevant dopaminergic neurotoxicity

Time Commitment/Role: 0.30 calendar months/Co-I

Supporting Agency: DOD

Address: The Pentagon, Washington DC, 20301

Contracting/Grants Officer: unknown

Performance Period: 09/30/2022 – 09/30/2025

Level of funding:

Project Goals/Aims: Aim 2C. Test therapeutic interventions for chlorpyrifos damaged dopaminergic neurons, including agents that modulate dopaminergic transmission. Dr. Doorn's lab will maintain cell culture and perform experiments to measure viability of dopaminergic cells following exposure to chlorpyrifos and its oxon and the various treatments to modulate dopamine homeostasis. Dr. Doorn's lab will also determine levels of dopamine and metabolites, production of reactive oxygen species and protein modification by catechols.

Overlap: There is no scientific or budgetary overlap.

Pending

Title: Adolescent Insecticide Exposure and ADHD Risk: Mechanisms of Immediate Effects and Long-term Vulnerability

Time Commitment/Role: 0.6 calendar months/Co-I

Supporting Agency: NIH

Address:

Contracting/Grants Officer: Jonathon Hollander

Performance Period: 12/01/2023 – 11/30/2026

Level of funding:

Project Goals/Aims: Adolescent Insecticide Exposure and ADHD Risk: Mechanisms of Immediate Effects and Long-term Vulnerability

Overlap: There is no scientific or budgetary overlap.

Previous

Title: Toxic Neurotransmitter Metabolites in Aged and Diabetic Human Myocardium

Time Commitment/Role: 0.6 calendar months/Co-I

Supporting Agency: NIH/NIA

Address: PO Box 8057, Gaithersburg MD, 20898

Contracting/Grants Officer: Susan Zieman

Performance Period: 09/01/2017 – 05/31/2021

Level of funding:

Project Goal/Aims: The goals of this work are to: 1) determine mechanisms for the production of toxic neurotransmitter metabolites of dopamine and norepinephrine in human atrial myocardium, relevant to cardiovascular complications, and 2) develop a sensitive assay to quantify production of these toxic neurotransmitter metabolites in human blood and tissues as a biomarker for pathological mechanisms.

Overlap: There is no scientific or budgetary overlap.

Overlap: No overlap exists between previously funded research and OR230035.

I, PD/PI or other senior/key personnel, certify that the support information provided herein is current, accurate, and complete to the best of my knowledge, and accept the obligation to comply with the terms and conditions if a grant is awarded as a result of this application, per Section 223(a) of the William M. (Mac) Thornberry National Defense Authorization Act for Fiscal Year 2021. I agree to update such disclosure at the request of the agency prior to the award of support and at any subsequent time the agency determines appropriate during the term of the award. I have been made aware of the requirements under Section 223(a)(1) of this Act. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties (U.S. Code, Title 218, Section 1001).

*Signature:  787EE70A623C4C2

Date: 10/25/2023

PHS Inclusion Enrollment Report

1. * Inclusion Enrollment Report Title

Role of military relevant chlorpyrifos exposure in Parkinson's disease relevant dopaminergic neurotoxicity

2. * Using an Existing Dataset or Resource

☐ Yes ☒ No

3. * Enrollment Location Type

☒ Domestic ☐ Foreign

4. Enrollment Country(ies)

x

USA: UNITED STATES

Add New Country

5. Enrollment Location(s)

United States

6. Comments

Enrollment/participation is conducted remotely (online, mail, phone).

Planned

Racial Categories	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/ Alaska Native	5	5	0	0	10
Asian	5	5	0	0	10
Native Hawaiian or Other Pacific Islander	5	5	0	0	10
Black or African American	20	80	20	40	160
White	30	100	20	40	190
More than One Race	20	60	20	20	120
Total	85	255	60	100	500

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	0	0	1	0	1
White	1	28	1	0	0	0	0	0	0	30
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	1	0	0	0	0	1
Total	1	28	1	0	1	0	0	1	0	32

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Role of military relevant chlorpyrifos exposure in Parkinson's disease relevant dopaminergic neurotoxicity

PD210037

W81XWH-22-1-1025

PI: Jason Cannon and Ellen Wells

Org: Purdue University

Award Amount: \$1,199,999

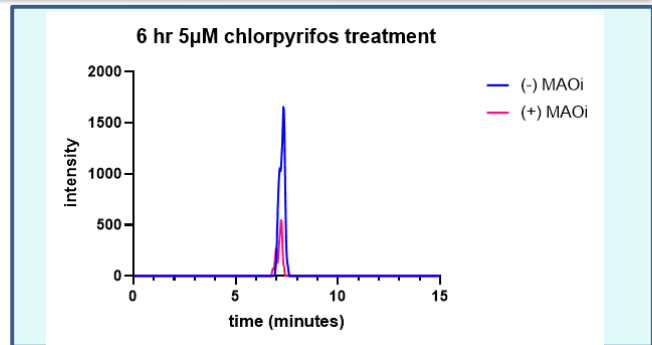


Study/Product Aim(s)

- 1. Determine if Parkinson's disease (PD) is associated with organophosphate (OP) exposure among US military veterans.
- 2. Determine if chlorpyrifos produces selective dopaminergic neurotoxicity in translational models.

Approach

We will address the potential role of military relevant chlorpyrifos exposure to increase PD risk. We will compare PD status with previous exposure to OPs and assess whether indicators of PD severity are associated with higher OP exposure. We will determine if dopamine neurons exhibit heightened sensitivity; determine if chlorpyrifos produces neurobehavioral, neurochemical, and neuropathological alterations indicative of a PD phenotype in rats, and test therapeutic interventions.



Chlorpyrifos (CPF) treatment in PC12 cells (6hrs) produced L-Cys amino acid DOPAL conjugate (biomarker of dopamine dyshomeostasis). Monoamine oxidase inhibitors (10µM clorgyline/pargyline) decreased conjugate formation

Timeline and Cost (updated 04/01/2024)

Activity	Calendar Year (CY)			
	23	24	25	26
Patient recruitment, cellular studies and pilot animal studies				
Patient recruitment/analyses, cell/animal model studies				
Data analyses, neuropathology, and publications				
Estimated Budget (\$K)	\$420	\$408	\$373	\$000

- Use the green horizontal bars to indicate the durations of activities

- (Only applicable to existing awards) Use the purple vertical bar to indicate the current status of activities

Goals/Milestones (Example)

CY23 Goal – System demonstration

- ☒ Initiate patient recruitment
- ☒ Preliminary cellular studies and pilot animal studies

CY24 Goals – System validation

- ☐ Patient recruitment/analyses,
- ☐ Conduct cell/animal model studies

CY25 Goal – Production readiness

- ☐ Patient data analyses,
- ☐ Conduct cell/animal model studies; neuropathology.
- ☐ Publications

Comments/Challenges/Issues/Concerns

- Revised report – expenditures below through March, 2024 (projections adjusted for this timeline). Expenditures less than expected due to contracting delays.

Budget Expenditure to Date

Projected Expenditure: \$555,263

Actual Expenditure: \$350,610

What other organizations were involved as partners?

N/A beyond the subawards as planned and already reported throughout this document.

8. Special Reporting Requirements

N/A

9. Appendices

- Full abstract from the 2023 Society of Toxicology Meeting extracted and included here (#2017)

Together, our study shed light on the role of ARMMs - a novel way of examining - in metal neurotoxicity. *This research was funded by the MEMCARE Superfund Research Center grant (P42ES030990).*

PL 2015 Mitochondrial Metabolism in Astrocytes Is Essential for Their Survival against Inorganic Arsenic Exposure

R. Franco. *University of Nebraska Lincoln, Lincoln, NE.*

Astrocytes are the first line of defense against xenobiotics crossing into the brain. As primarily glycolytic cells, mitochondrial metabolism in astrocytes is not required for their survival. However, in this work, we demonstrated that astrocytic mitochondrial metabolism is essential for their survival against neurotoxic electrophiles such as inorganic arsenic (iAs). Subtoxic iAs exposure induced an increase in *de novo* glutathione (GSH) synthesis and a reduced intracellular environment in primary cortical astrocytes. iAs toxicity was potentiated by inhibition of *de novo* GSH synthesis, and blockage of multi-drug resistance associated proteins (MRPs), which enhanced arsenic accumulation. NMR metabolomics revealed that iAs induced the cataplerotic generation of glutamate via the tricarboxylic acid (TCA) cycle, which contributed to *de novo* GSH synthesis. iAs exposure increased the dependency of mitochondrial oxygen consumption on fatty acid oxidation (FAO). Interestingly, while inhibition of mitochondrial pyruvate transport (MPC1), the electron transport chain (ETC) or FAO had no effect on astrocyte viability, it enhanced arsenic accumulation and iAs toxicity while inducing a moderate decrease in cellular bioenergetics. This demonstrated that mitochondrial metabolism is important for xenobiotic detoxification. iAs exposure led to a substantial accumulation of extracellular glutamate that was mediated by the reversal of excitatory amino acid transporters EAAT1/2. Accordingly, inhibition of glutamate transport enhanced iAs toxicity. NMR-metabolomics also demonstrated that extracellular glutamate uptake and metabolism is required for *de novo* GSH synthesis upon iAs exposure. These results revealed that astrocytic mitochondrial metabolism support detoxification of neurotoxic electrophiles by GSH, via the synthesis of its precursors. Furthermore, they suggest that mitochondrial-dependent glutamate synthesis compensates for intracellular glutamate depletion triggered by astrocytic glutamate transport reversal upon iAs exposure.

PL 2016 Glyphosate and Roundup Exposure during Neurodevelopment Effects Gene Expression, Neurogenesis, and Behavior in Zebrafish Larvae

R. Lacroix, S. McKenzie, M. Armstrong, and D. Kurrasch. *University of Calgary, Calgary, AB, Canada.*

N-(phosphonomethyl) glycine (glyphosate) is the number one agricultural chemical used globally, with estimated spray rates of ~1.6 billion pounds annually. Glyphosate blocks an enzyme unique to plants and microorganisms, thus glyphosate is postulated to be safe in animals since they lack this molecular pathway. However, the chemical's widespread use and increasing scientific evidence for off-target effects has spurred a renewed need to study effects of this chemical in animal models. Here, using zebrafish, we investigate how glyphosate or the commercial glyphosate formulation RoundUp, effect neurodevelopment. To start, we performed RNA-Seq on larvae zebrafish heads exposed to an environmental dose of glyphosate (10 µg/L) during critical window of brain development (10-48 hours post-fertilization (hpf)) and uncovered 39 differentially expressed genes. Gene ontology analyses show regulation of metabolic processes and mRNA splicing and processing as the top dysregulated categories, processes critical for neurodevelopmental programs. Next, using 5-ethynyl-2-deoxyuridine, we tested whether the timing of neuronal birth was affected by exposure to glyphosate or RoundUp from 10-48 hpf, a time point encompassing larval neurogenesis. We showed that glyphosate and RoundUp effect the timing of neuronal birth, suggesting glyphosate exposure can cause precocious neurogenesis. Lastly, using ZebraBox® and ZebraCube® apparatuses to measure behaviour, we determined that glyphosate and RoundUp have opposite effects on locomotive behaviours, suggesting the active ingredient and the proprietary formulation have different mechanisms of action. This research starts to shed insights into whether embryonic exposure to glyphosate affects neurodevelopment in zebrafish.

PL 2017 Chlorpyrifos and Chlorpyrifos-Oxon Exposures Lead to the Dysregulation of Basal Glutamate Release in Human-Induced Pluripotent Stem Cell-Derived Glutamatergic Neurons

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Chlorpyrifos (CP) is an organophosphate pesticide and insecticide developed for agricultural and household settings. Chlorpyrifos, or its more toxic metabolite CP-oxon (CPO), causes a wide range of health complications such as neurological dysfunction, immunotoxicity, developmental issues, and cardiovascular damage. The primary target of CP neurotoxicity is typically thought to be acetylcholinesterase

inhibition, though emergent data suggest that other neurotransmitter systems can be affected at low doses. Currently, little is known about how CP(O) affects the glutamatergic (GLUergic) system. The aim of this study is to determine the neurotoxic effects of CP and CPO on glutamate (GLU) release, characterize baseline GLU dynamics in human GLUergic cortical neurons, and address a gap in neurotransmitter monitoring using novel biosensors. GLUergic cortical cultures were differentiated via dual-SMAD inhibition from human induced pluripotent stem cells (hiPSCs). Upon maturation (>D90), a baseline collection (in HBSS) for extracellular GLU was performed followed by a 24-h sub-cytotoxic exposure to CP (3 µM - 300 µM) or CPO (0.1 µM - 10 µM). Following exposure, cells recovered for 24 h with an additional GLU collection. After the recovery period, whole-cell protein lysates were harvested to correct measured GLU release for cell density by total protein. All collections were analyzed using a commercial GLU assay kit. Cells exposed to CP demonstrated a concentration-dependent increase in net GLU release, while cells exposed to CPO presented no significant effect. The upregulation persisted over 24 h. Thus, it is shown that in addition to altering the acetylcholinergic system, CP and CPO may have unexpected effects on neuronal GLU homeostasis. An additional set of collections with vehicle exposure was performed at 10-min intervals over 60 min to monitor GLU efflux kinetics. GLU release was identified to sharply increase over 0 - 15 min and plateau after 20 min, which is likely to restore extracellular GLU levels. Newly developed enzymatic electrochemical biosensor arrays with cell culture compatibility were utilized to further characterize these findings. The biosensors were created using direct ink writing robotic printing combined with thin film processing and designed for sample delivery via injection or cell culture. Media samples with L-Glutamic Acid (60 µM) were dispensed on cultured cells and collected after 1 - 60 min for combined evaluation through sensors and enzymatic assays. In addition, GLU standards spiked with L-Glutamic Acid (0 µM - 60 µM) were prepared in HBSS, PBS, and BrainPhys for further testing. The novel biosensors confirmed earlier GLU-kinetics findings and accurately measured extracellular GLU release in a variety of media types. Overall, this study reveals a potential new mechanism for neurotoxicity, establishes a better understanding of GLU dynamics *in vitro*, and introduces innovative sensor technology.

PL 2018 Endoplasmic Reticulum (ER) Stress Inhibition Protects against Pyrethroid-Induced Disruption of Hippocampal Neurogenesis and Cognitive Deficits in Mice

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Cognitive impairment is increasing globally; currently more than 16 million people are living with cognitive impairment in the United States. However, age is the major risk factor, environmental exposure has been identified as a significant contributor for developing cognitive impairment. Deltamethrin is a broad-spectrum type II pyrethroid insecticide that has been increasingly used in agriculture and homes for pest control. Previously, we reported that repeated exposure to 3 mg/kg deltamethrin caused a marked reduction in hippocampal neurogenesis and impaired learning and memory in adult mice. Here, we sought to determine whether exposure to NOAEL of 1 mg/kg of deltamethrin elicits similar effects. We used the novel object recognition task, fear conditioning, and Morris water maze to determine the effects of deltamethrin on cognitive behavior. Our data revealed that repeated exposure to NOAEL of deltamethrin for 30 days caused significant deficits in novel object recognition and learning and memory in water maze and fear conditioning tasks. These behavioral deficits were accompanied by impairment of hippocampal neurogenesis as neural progenitor cell proliferation (BrdU+ cells and Ki67+ cells) and immature neurons (DCX+ cells) were significantly decreased in the DG of the hippocampus. Further, deltamethrin-treated mice exhibited remarkable ER stress as the protein levels of ATF-4, CHOP, and GRP-78 were significantly increased in the hippocampus. To determine whether ER stress is associated with impairment of the hippocampal neurogenesis and cognitive deficits, a group of mice were treated with intraperitoneal (i.p.) injections of 1 mg/kg salubrinal (eIF2α inhibitor) 30 min prior to deltamethrin administration. Our data showed that pre-treatment of mice with salubrinal prevented ER stress, restored neurogenesis, and improved cognitive deficits in deltamethrin-treated mice. We also used caspase-12 KO mice for further exploration of the role of ER stress in impairment of hippocampal neurogenesis and cognitive deficits. We found that caspase-12 KO mice showed significant protection against deltamethrin induced disruption of hippocampal neurogenesis and cognitive deficits when compared to WT mice. Together, these results demonstrate that repeated exposure to current NOAEL of deltamethrin leads to ER stress mediated inhibition of adult hippocampal neurogenesis which subsequently contribute to deficits in learning and memory in mice. *Supported by R01ES027481.*