

Southeastern REGIONAL CHAPTER



of the
Society of Toxicology



2026 Southeastern Region of the Society of Toxicology Fall Meeting Program

Hosted by: University of Florida

October 23, 2026

Index

Welcome Message from the SESOT President	1
Agenda	2
Executive Committee	4
Venue/Meeting Map	5
Welcome Remarks and Keynote Speakers	6
Postdoctoral and Graduate Student Platform Speakers	9
Postdoctoral Platform.....	9
Graduate Student Platform	12
Poster Presentations by Number	17
Abstracts	21
Undergraduate Student Posters.....	21
Master's Student Posters	32
Doctoral Student Posters	35
Postdoctoral Posters.....	60
New Investigators.....	69

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Welcome Message from SESOT President, Zhoumeng Lin!

On behalf of the SESOT Executive Committee, I am delighted to welcome you to the 2026 Annual Meeting of the Southeastern Regional Chapter of the Society of Toxicology, held in partnership with the University of Florida's Center for Environmental and Human Toxicology (CEHT).

Hosting our regional toxicology community here at UF is an honor. We are thrilled to welcome researchers, educators, trainees, and professionals representing academia and industry across the Southeast, including Auburn University, Clemson University, Emory University, the University of Alabama at Birmingham, the University of Georgia, the University of Miami, the University of North Florida, the University of South Florida, and the University of Florida, alongside partners such as Amgen, Inc., UL Research Institutes, and Tiresias Consulting LLC. We also extend a warm welcome to colleagues joining us from neighboring chapters and institutions, including the University of Louisville and Southern Illinois University.

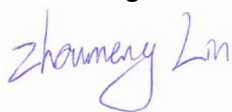
Our program reflects the depth and vitality of toxicology across our region. Anchored by welcome remarks from Dr. David Fuller and keynote presentations by Dr. Nancy Denslow and Dr. Marie Bourgeois, today's agenda highlights cutting-edge discoveries across all career levels. Above all, we celebrate our trainees. The platform and poster presentation competitions represent the heart of our gathering, providing emerging investigators with a supportive platform to share innovative findings and receive valuable professional feedback.

This joint meeting would not be possible without the generous commitment of our sponsors: the Chemical Insights Research Institute, the UF Center for Environmental and Human Toxicology, the UF College of Public Health and Health Professions Department of Environmental and Global Health, and the UF College of Veterinary Medicine Department of Physiological Sciences. Their support enables us to foster high-caliber scientific exchange and support the next generation of toxicologists. We also extend our heartfelt gratitude to the many dedicated volunteers who generously contribute their time and expertise to review abstracts and judge both the poster and platform presentations.

I encourage you to immerse yourself in the sessions, actively engage with colleagues old and new, and take full advantage of the collaborative spirit that defines SESOT. Thank you for being here and for your vital contributions to our society's continued success.

Welcome to Gainesville and the University of Florida!

Warm regards,



Zhoumeng Lin, BMed, PhD, DABT, ERT, CPH, ATS

President, Southeastern Regional Chapter of the Society of Toxicology

P.S. If you're looking for ways to get more involved with SESOT, consider volunteering to serve as an officer, we'd love to have you join us!

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SESOT Meeting Agenda

SESOT Annual Meeting, 2026, University of Florida, Gainesville, FL

Thursday, October 22, 2026

Welcome Reception	6:00 – 8:00 pm	Hilton University of Florida Conference Center Gainesville <u>Private Dining Room</u> 1714 SW 34 th ST, Gainesville, FL 32607
Optional post-reception student/postdoc activities	8:15 – 10:00 pm	First Magnitude Brewing Company 1220 SE Veitch St, Gainesville, FL 32601 (Please contact SESOT student representative Jess Okutsu (jokutsu@miami.edu) to sign up. Trainees can leave at 8:00 pm from Hilton and arrive at First Magnitude at 8:15 pm).

Friday, October 23, 2026

Optional field trip	6:30 – 8:30 am	Sweetwater Wetlands Park 325 SW Williston Rd, Gainesville, FL 32601 (Please see the flyer from SOT for details. Contact Field Trip coordinator Dr. Chris Vulpe (cvulpe@ufl.edu) to sign up. Pick up at 6:30 am at the Hilton hotel lobby and arrive at the park at 7:00 am).
Networking Breakfast & Registration	8:00 – 9:00 am	UF CGRC Building, Room 133 and Lobby 2033 Mowry Rd Rm 202, Gainesville, FL 32610
Welcome Remarks	9:00 – 9:05 am	CGRC Auditorium Room 101 Dr. David Fuller, University of Florida
Keynote Presentation	9:05 – 9:45 am	Dr. Nancy Denslow, University of Florida
Postdoc Platform Session	9:45 – 10:30 am	Jie Zhou, University of Florida Ho Young Lee, Emory University Sattibabu Merugu, University of Florida

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Morning Break	10:30 – 10:45 am	
Graduate Student Platform Session	10:45 – 11:45 am	Rosemaria Serradimigni, Clemson University Jeongmin Choi, University of Florida Kayleigh Linder, University of Florida Paige Powell, Clemson University
Lunch	11:45 – 12:45 pm	Room 133 and Lobby Note: The food and drinks are in Room 133. There are many tables in Room 133 and in the lobby.
Poster Session	12:45 – 2:45 pm	<u>Lobby</u> Odds from 12:45 – 1:45 pm, Evens from 1:45 – 2:45 pm Poster Session Networking Bingo: Pick up your bingo card at the registration desk. Once your card is complete or when the poster session wraps up, return it to the desk to claim a UF-branded prize! Gifts include stickers, fridge magnets, magnetic buttons, keychains, and pens (while supplies last).
Afternoon Break	2:45 – 3:00 pm	
Afternoon Keynote Presentation	3:00 – 3:45 pm	<u>Auditorium Room 101</u> Dr. Marie Bourgeois, University of South Florida
Awards and Closing Remarks	3:45 – 4:00 pm	<u>Auditorium Room 101</u> Dr. Zhoumeng Lin, University of Florida

Dietary Accommodations: If you indicated a dietary restriction on your registration form, special meals have been arranged for you:

- **Thursday Dinner Reception:** Please pick up a dietary restriction card at the check-in desk and present it to the hotel banquet staff, who will serve your designated meal directly to you.
- **Friday Breakfast & Lunch:** Individually packaged meal boxes labeled with your name will be available at the catering station.

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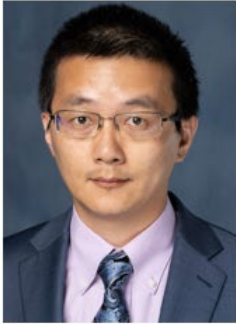


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SESOT Executive Committee 2026 – 2027



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2026 SESOT Meeting Map

2026 SESOT Venue

Meeting Location

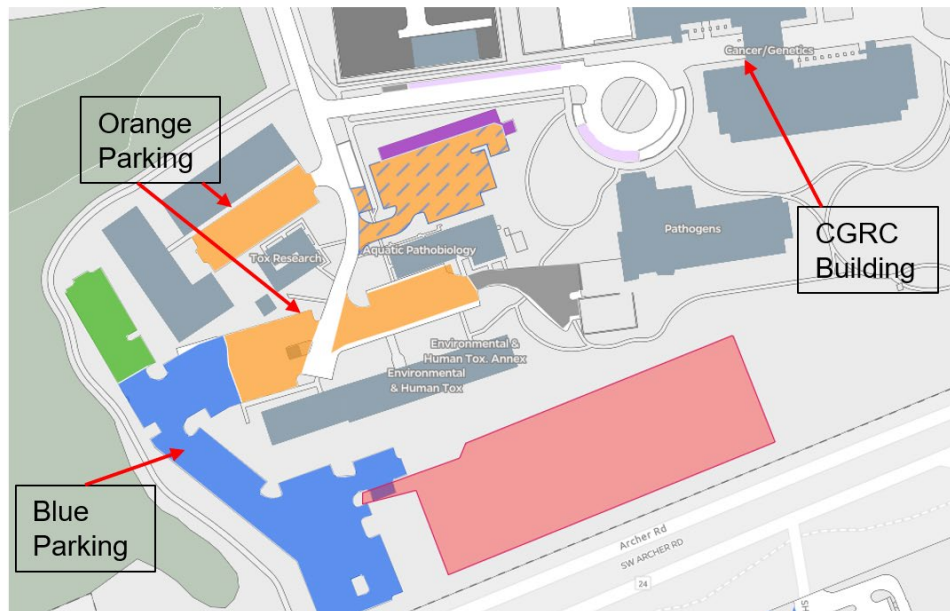
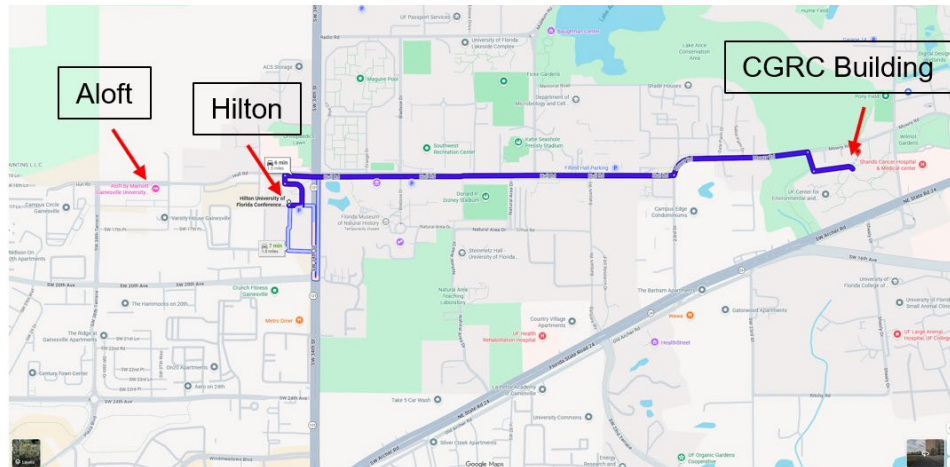
Cancer and Genetics Research Complex (CGRC)
University of Florida (UF)
2033 Mowry Road, Gainesville, FL 32610

Welcome Reception

Hilton UF Conference Center Gainesville
Private Dining Room
1714 SW 34th St, Gainesville, FL 32607

Note: At the CGRC Building, the check-in desk and poster session will be in the lobby. The presentation will take place in the Auditorium Room 101. Food is not allowed in Room 101. Breakfast and lunch will be in Room 133. There will be plenty of tables in the lobby where you can enjoy food.

Parking: There are many Blue or Orange or Guest parking spots near the CGRC building (see the map below). You can purchase a daily parking permit online through the Passport Parking app for \$8, plus a \$0.25 transaction fee for Main Campus following the instructions on this [website](#).



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Welcome Remarks and Keynote Speakers

Welcome Remarks



David Fuller, PhD

Associate Dean For Research
College of Public Health and Health Professions
University of Florida, Gainesville, FL 32610

Accomplished academic leader, scientist, educator, and administrator with 23 years of service at the University of Florida College of Public Health and Health Professions (PHHP), including roles as Associate Dean for Research, graduate program director, training grant director, center leader, educator, and mentor. Internationally recognized for research in spinal cord injury, respiratory neurobiology, neurorehabilitation, and neuromuscular disease, with 172 peer reviewed publications, over 11,700 citations, an h-index of 62, and more than 20 years of continuous NIH funding. Research contributions include establishing fundamental mechanisms of respiratory neuroplasticity, advancing translational science, gene therapy, and clinical trials for Pompe disease, and developing innovative therapeutic approaches in spinal cord injury spanning pharmacology, neurostimulation, oxygen therapy, and regenerative medicine. These efforts have helped move emerging therapeutics from laboratory discovery to human studies and clinical implementation.

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Keynote Speaker

Microcystin-Producing Cyanobacteria: Emerging Drivers of Pulmonary Toxicity



Nancy Denslow, PhD
Professor Emeritus
University of Florida

Nancy Denslow is a professor emeritus in the Department of Physiological Sciences and in the Center for Environmental and Human Toxicology at the University of Florida. She received her Ph.D. from the University of Florida in Biochemistry and Molecular Biology. Nancy has pioneered the use of molecular technologies for environmental toxicology especially focusing on high throughput in vitro assays, biomarker development and toxicogenomics approaches for evaluating contaminants of emerging concern. She has specialized in assessing the effects of legacy and current use pesticides and endocrine disruptors that are found at relatively high levels in the environment. Evaluating the effects of harmful algal bloom toxins is a relatively new area of research. Nancy has over 300 peer-reviewed publications. She has received several awards for her research including the Founders Award from the Society of Environmental Toxicology and Chemistry, the University of Florida Water Institute Distinguished Faculty Fellow and was made a Fellow of the International Society of Environmental Indicators. Nancy's research has received funding from EPA, NSF, USGS and NIH.

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Keynote Speaker

Integrating Avian Genomics, Environmental Toxicology, and Sentinel-2 Remote Sensing to Predict West Nile Virus Transmission Risk in Florida



Marie Bourgeois, PhD, MPH, COHC

Associate Professor

Global, Environmental, and Genomic Health Sciences

University of South Florida College of Public Health

SunshineERC, Director Health, Safety, and Environment

Center for Environmental/Occupational Risk Analysis and Management

Dr. Bourgeois conducts primary toxicology research and human health, environmental, and occupational exposure and risk assessments/analyses. She designs studies evaluating the adverse effects of industrial chemicals, environmental chemicals and licit/illicit drugs using in silico, in vivo and in vitro models. She has published and presented research on a variety of topics related to the effect of multiple factors on the urinary expression of biomarkers of inflammation, renal failure, oxidative stress, and cardiac dysfunction. Past research activities also include the effect of poly (ADP-ribose) polymerase (PARP) inhibition on chemical induced toxicity. Her current research focuses on elucidating mechanisms of chemical and drug-induced toxicity and studying populations with occupational or environmental exposures to contaminants of known or emerging concern.

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Postdoctoral Platform Session

Identification of Novel Urinary Protein and Exosome-based Biomarkers for Chronic Kidney Disease of Unknown Etiology (CKDu) in Sugarcane Farm Workers



Jie Zhou, Jaime Butler-Dawson, Kevin J. Kroll, Abdel A. Alli, Yang Yang, Lyndsay Krisher, Stephen Brindley, Lee S. Newman, Nancy D. Denslow, and Chris Vulpe

University of Florida, Gainesville, FL; University of Colorado, Aurora, CO; and University of Georgia, Athens, GA.

Background and Purpose: Chronic kidney disease of unknown etiology (CKDu) is a global health concern, and its underlying causes remain unclear. The disease disproportionately affects young, otherwise healthy agricultural workers, and there is a scarcity of biomarkers for early detection. We hypothesized that urinary proteins and exosomes could serve as novel biomarkers for early-stage detection.

Methods: We investigated 34 urine samples from sugarcane farm workers in a CKDu-endemic region of Guatemala. 21 kidney injury-associated proteins were quantified using a recently developed Luminex panel. Urinary exosomes were isolated by ultracentrifugation, characterized by NanoSight and TEM, and surface proteins were screened using a flow cytometry-based assay. The lipid composition was determined by mass spectrometry, and miRNAs were identified by next-generation sequencing.

Results: Several protein biomarkers, including MCP-1, clusterin, NGAL, and $\beta 2$ microglobulin, were significantly elevated in participants with CKDu. Our surface protein assay suggested that urinary exosomes were enriched for the universal markers CD63 and CD81, as well as a family of kidney-driven markers, including CD1c, CD3, and CD24. Importantly, renal damage-associated CD25 and CD45 were highly expressed in individuals with CKDu. We identified 21 potential lipid biomarkers that may distinguish agricultural workers with early-onset CKDu. Remarkably, 14 lipids showed intermediate expression levels in healthy individuals with acute post-work shift injury. Further, we identified 6 miRNAs significantly upregulated in the CKDu group, including miR-30a, miR-204, and miR-10a, which may play critical roles in early kidney disease diagnosis. miR-181a, a renal fibrosis and tubular injury marker, significantly decreased in the CKDu group after a work shift, suggesting its potential role in assessing acute renal damage.

Conclusion: Taken together, this study reveals that urinary protein and exosome-based biomarkers are promising for assessing kidney disease and acute renal damage. Our exploration may ultimately contribute to the early diagnosis of CKDu among farm workers.

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M2-like Macrophages Are More Sensitive to Carnitine Depletion Induced by Gut Microbiome-derived Metabolite Delta-Valerobetaine

Ho Young Lee, Choon-Myung Lee, Zack Jarrell, Jaclyn Weinberg, Dean Jones, Young-mi Go

Emory University School of Medicine, Atlanta, GA.

Background: Host-microbiome interaction has gained much attention for its far-reaching impacts on host physiology and health. Delta-Valerobetaine (VB) is a metabolite derived from gut microbiome that is found to be elevated in obesity and associated with hepatic steatosis. Previous studies revealed that VB impairs mitochondria-dependent fatty acid oxidation; we have recently shown that VB is detectable in various organ systems including the brain and showed that VB can utilize OCTN2 carnitine transporter, which may explain its ubiquitous nature. However, to our knowledge, the effects of VB on host immune system cells have not been reported. Macrophages, specifically, depend heavily on cellular metabolism and bioenergetics to function appropriately. Alternatively activated (M2) macrophages use carnitine-dependent fatty acid oxidation while classically activated (M1) macrophages rely on glycolytic pathway to provide all the necessary energy needed maintain its function. Therefore, we hypothesized that VB would deplete carnitine in human macrophages and that M2 macrophages would be more sensitive than M1 macrophages.

Methods: THP-1 monocytes were differentiated with PMA (50 ng/mL, 72 h), rested for 24h in PMA-free media, and polarized for 24h with LPS/IFN- γ (M1) or IL-4/IL-13 (M2). Unexposed M0, M1, and M2 cells were first profiled by untargeted, high-resolution mass spectrometry (HRMS) to define a reference profiling of macrophage polarization-associated metabolites. M1 and M2 cells were then exposed to VB (0–100 μ M) for 24h. Cells and conditioned medium were extracted in acetonitrile and analyzed by HILIC-positive and C18-negative electrospray ionization. Dose-response was evaluated by Spearman trend test with Benjamini-Hochberg correction (FDR = 0.05) across a 32-metabolite panel. In addition, human CCL18 was measured in M2 supernatants by ELISA.

Results: M1 and M2 polarization efforts produced distinct metabolic profiles. M1 macrophages displayed a drastic increase in itaconate (6.4-fold higher) and about 60% decrease in NAD⁺, whereas the ratio of acetylcarnitine to long-chain acylcarnitines was significantly higher in M2-like than in M1-like macrophages (~2.5-fold higher), indicating greater completion of β -oxidation at baseline. Clear breaks in TCA cycle intermediates were observed in M1-like macrophages. Exposure to VB resulted in a dose-dependent decrease in the carnitine pool of the M2 macrophages. Intracellular VB abundances were different among macrophage phenotypes with M2-like macrophages consistently displaying increased presence of VB across all doses. For M2-like macrophages exposed to 100 μ M VB, free carnitine and acetylcarnitine were reduced to 28–31% and 30–31% of control, respectively, and γ -butyrobetaine, butyryl-, C5, and oleoylcarnitine were also reduced, with significant loss at 10 μ M. In contrast, medium-chain acylcarnitines accumulated and were exported into the medium (~12-fold increase in hexanoylcarnitine). Itaconate, NAD⁺, polyamines, glutamine, glutamate, kynurenine, creatine, and taurine were not changed by VB, and glucose consumption and lactate output were unaltered, indicating no glycolytic compensation. Interestingly, secreted CCL18 showed significant decrease in M2-like macrophages exposed to 50 μ M and 100 μ M VB (66% vs that of the control group), potentially suggesting VB's impact on the efficiency of M2-like macrophage's function in immune regulation.

Conclusions: Our study indicates that macrophage polarization does produce distinct M0 vs M1 vs M2 metabolic profiles that can be confirmed via HRMS. We confirm that VB drastically decreases the intracellular levels of the carnitine pool in human macrophages and seems to target carnitine-dependent pathways. In addition, our HRMS metabolomic analysis show that M2-like macrophages, which display higher baseline carnitine-dependent flux, are approximately ten-fold more sensitive than M1 macrophages. Taking into consideration that this VB-induced carnitine depletion was accompanied by reduced CCL18 secretion, our efforts identify macrophages as a target of a microbiome-derived metabolite present in all individuals and nominate carnitine depletion as a mechanism linking gut microbial metabolism to innate immune function.

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A Dynamic Nano-QSAR Model to Predict Tumor-Targeting Delivery and Off-Target Biodistribution of Polymeric Nanoparticles



Sattibabu Merugu, Kun Mi, Qiran Chen, Chunla He, Nancy A. Monteiro-Riviere, Jim E. Riviere, Zhoumeng Lin

University of Florida, Gainesville, FL; Kansas State University, Manhattan, KS; North Carolina State University, Raleigh, NC

Research Background and Purpose: Nanoparticles (NPs) exhibit substantial variability in their physicochemical properties that may critically influence their biological interactions and toxicity. However, the dose-dependent and time dependent - resolved biodistribution of NPs remains one of the most fundamental and poorly understood challenges impeding rational nanomedicine design and clinical translation. The objective of this study was to integrate dose and time with material-specific factors to characterize across multi-tissue biodistribution in tumor-bearing mice.

Methods: Datasets from the Nano-Tumor Database on polymeric NPs in tumor-bearing mice following intravenous (IV) administration were analyzed using machine learning (ML) and chemoinformatic approaches; including quantitative structure-activity relationship (QSAR) models and data-driven grouping strategies. Physicochemical properties descriptors (such as hydrodynamic diameter, zeta potential), experimental design descriptors (tumor model, targeting strategy), and exposure conditions (dose, time) were systematically linked as percentage injected dose (%ID to six tissues (tumor, liver, spleen, lung, kidney, heart)). Dimensional-reduction techniques supported integrative analysis of model drivers and their mechanistic interpretation across endpoints.

Results: The Random Forest (RF) quantitative Multi-Tissue bioDistribution (qMTD) nano-QSAR model achieved high goodness-of-fit ($R^2 = 0.94$; RMSEC = 0.26), internal robust validation ($Q^2_{\text{LOO}} = 0.72$; RMSE_{LOO} = 0.53), and strong external predictivity ($Q^2_{\text{EXT}} = 0.82$; RMSE_P = 0.45); with tissue-wise predictivity ranging from $Q^2_{\text{EXT}} = 0.56 - 0.81$ across all six tissues. Zeta potential, hydrodynamic diameter, targeting strategy, time, dose, and tumor model were identified as key drivers across tissue outcomes. Passive, enhanced permeability and retention (EPR)-mediated targeting in a permissive allograft heterotopic tumor model emerged as the dominant strategy for maximizing tumor %ID, with an optimal design window defined by particle size (~100 – 200 nm), moderately negative surface charge (~-20 to -25 mV), low-to-moderate doses (0.5 – 4 mg/kg), and early-to-intermediate post-injection sampling (~10 h), collectively establishing actionable, evidence-based boundaries for polymeric NP design. Applicability domain analyses confirmed reliable predictions across the well-characterized formulation space, with uncertainty confined to high-dose, prolonged-exposure boundary conditions. The qMTD web-based interface is openly available, transforming formulation screening from an empirical, animal-intensive process into a computationally guided, predictive design workflow.

Conclusions: These results provide mechanistic evidence that polymeric-based NP biodistribution is closely linked to specific physicochemical, experimental design, and exposure descriptors. This approach supports the development of the next-generation dynamic QSAR models for polymeric NPs, advancing the rational design of nanomedicines towards clinical translation.

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Graduate Student Platform Session

Masters

Tetrabromobisphenol S (TBBPS)-induced developmental toxicity in zebrafish embryos: impacts on cytoskeletal proteins during gastrulation



Rosemaria Serradimigni, Heidi M. Sabatini, Christopher Chouinard, Subham Dasgupta

Clemson University, Clemson, SC

3,3',5,5'-Tetrabromobisphenol S (TBBPS) is an emerging brominated flame retardant that is widely detected in the environment, yet its toxic effects remain poorly understood. The objective of this study was to use zebrafish as a model and determine effects of TBBPS exposure on gastrulation stages of embryogenesis. We initiated TBBPS exposures (0 or 40 μ M) at 0.75 hours post fertilization (hpf), phenotyped hourly through cleavage, blastula, and gastrula stages, and showed that TBBPS-treated embryos exhibited delay in development beginning at $\sim$ 4 hpf, a stage corresponding to early gastrulation, with significant mortality during late-gastrulation. To examine the genetic basis of

TBBPS-induced effects, we conducted mRNA sequencing on exposures from 0.75–7 hpf, revealing downregulation of cytoskeletal organization and tight junction assembly. We then fluorescent-stained for multiple cytoskeletal and tight junction proteins (α -tubulin, β -tubulin, ZO-1, F-actin) following exposures to a wide range of TBBPS concentrations (0, 0.004, 0.04, 0.4, 4 and 40 μ M). F-actin expression was consistently upregulated across all exposed TBBPS concentrations. To determine whether activation of p38, a key regulator of F-actin polymerization, plays a role in TBBPS-induced F-actin disruption, we co-exposed embryos with TBBPS (0, 0.004, 4 or 40 μ M) and a known p38 inhibitor (5 μ M SB 203580) and assessed developmental phenotypes and F-actin levels. Treatment with p38 inhibitor significantly rescued TBBPS-induced effects, with co-exposure groups exhibiting cell stages and F-actin expression similar to controls. Collectively, these findings demonstrate that TBBPS exposures target gastrulation stages and define a novel mechanism in which TBBPS increases F-actin polymerization through p38/MAPK signaling pathways.

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*Doctoral***Developmental Exposure to Fire Retardants Sex-Dependently Prevents Pair Bond Formation and Alters Dopamine Signaling in Prairie Vole Striatum**

Kayleigh Linder, Kalynn Turner, Kemoi George, Colin Hafdahl, Gregory McCarty, David Dorris, Heather Patisaul, John Meitzen, and Leslie Sombers

University of Florida, Gainesville, FL; North Carolina State University, Raleigh, NC; National Institute of Environmental Health Sciences (NIEHS), Raleigh, NC

Neurodevelopmental disorders (NDDs) are widespread, particularly among adolescents, but the environmental factors that influence their onset and progression are not well characterized. Flame retardants, for example, have been linked to behavioral and cognitive issues in humans and a higher risk of NDDs, and are found in many everyday items such as furniture, baby clothes, and personal care products. These ubiquitous chemicals accumulate in the body and can be passed from mother to unborn child, leading to long-term effects. The prairie vole presents an ideal animal model to study the developmental effects of fire-retardant exposure compared to traditional models such as rats and mice because this species exhibits pro-social behaviors that mirror those of humans. Both male and female voles form strong monogamous pair bonds after mating, and exhibit signs of depression and grief when separated. It has been established that mesolimbic dopamine (DA) transmission is crucial for forming and maintaining these pair bonds, and that developmental exposure to the commercial flame-retardant mixture Firemaster® 550 (FM 550) sex-dependently prevents the formation of pair bonds in male but not in female prairie voles. Therefore, this study investigates how developmental exposure to FM 550 affects DA signaling in the prairie vole striatum. Quantitative, real-time measurements of DA release and reuptake kinetics were made using fast-scan cyclic voltammetry in live striatal tissue slices from pair-bonded and non-paired voles that have been developmentally exposed to either FM 550 or a vehicle control. Preliminary experiments reveal that FM 550-naïve female voles displayed higher DA release and slower DA clearance as compared to naïve males, and that these differences were exacerbated upon application of the DA reuptake inhibitor nomifensine. These initial results demonstrate inherent sex differences present in striatal DA signaling dynamics in prairie voles. The studies provide a foundation for elucidating how developmental fire-retardant exposure disrupts dopaminergic signaling, which will help to clarify DA's role in normal and abnormal socio-emotional behaviors. Ultimately, this study will provide mechanistic insight important for the development of improved therapeutic treatment strategies for neurodevelopmental disorders, especially those resulting from chronic exposure to environmental contaminants.

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Integrating Physiology and Contaminant Monitoring to Develop Shark-Specific PBTK Models for Mercury and PFAS



Paige C. Powell, Romina Dotson, Gregory Aniolek, Bryan S. Frazier, Ashley Galloway, Kylie D. Rock

Clemson University, Clemson, SC; South Carolina Department of Natural Resources, Columbia, SC

Sharks are apex predators essential for maintaining marine ecosystem balance, yet their long lifespans, high trophic status, and slow reproduction make them particularly susceptible to toxicological stressors. Mercury (Hg) and per- and polyfluoroalkyl substances (PFAS) are two globally distributed contaminants that bioaccumulate in marine food webs and have been shown to disrupt neurological, hepatic, and reproductive processes in vertebrates.

However, the internal distribution and physiological processing of these contaminants remain poorly characterized due to ethical and logistical limits on lethal sampling. We hypothesize that contaminant concentrations in non-lethal tissues, specifically blood and muscle, can reliably predict burdens in internal organs that are critical for shark health and reproduction (e.g., liver, brain, gonads). By integrating empirical contaminant data, trophic ecology, and shark-specific physiological parameters, we can address this critical gap by mechanistically describing contaminant transport and accumulation across tissues using physiologically based toxicokinetic (PBTK) modeling.

During summer 2025 and 2026, blood and muscle samples were collected non-lethally from finetooth (*Carcharhinus isodon*) and blacktip (*Carcharhinus limbatus*) sharks in Bulls Bay and St. Helena Sound, South Carolina, in collaboration with the South Carolina Department of Natural Resources (SCDNR). Opportunistic organ samples (liver, brain, gonads, spleen, stomach) from incidental mortalities were collected to aid model calibration. Hg concentrations were quantified by thermal decomposition–amalgamation atomic absorption spectrophotometry (EPA Method 7473), and PFAS congeners are being analyzed via high-performance liquid chromatography tandem mass spectrometry. Preliminary finetooth data has shown a strong correlation between Hg concentration in muscle and kidneys, brain, and gonads ($R^2 = 0.96, 0.97, 0.99$, respectively) and blacktip data has shown a strong correlation between Hg concentrations in muscle and liver and muscle and kidneys ($R^2 = 0.94, 0.83$, respectively). This data suggests that muscle may serve as a good proxy for estimating Hg concentrations in these organs.

Ongoing work is quantifying circulatory dynamics through Doppler-based measurements of cardiac output and regional blood flow, which, together with tissue:blood partition coefficients, organ volumes, metabolic rates, and clearance parameters will be integrated into Bayesian calibrated PBTK models developed in R and Berkeley Madonna. The developing model will allow prediction of organ-specific Hg and PFAS burdens from blood and muscle samples, enhancing conservation and chemical risk management for species where lethal sampling is not possible. In partnership with SCDNR and NOAA, this work will advance evidence-based risk assessment, support proactive conservation strategies, and strengthen ecosystem-based management of apex predators in coastal environments.

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Development of a physiologically based pharmacokinetic model for ivermectin in cattle



Jeongmin Choi, Zhicheng Zhang, Melissa A. Mercer, Lisa A. Tell, Jennifer L. Davis, Fiona P. Maunsell, Ronald E. Baynes, Jim E. Riviere, Zhoumeng Lin

University of Florida, Gainesville, FL; University of California, Davis, CA; Virginia Tech, Blacksburg, VA; North Carolina State University, Raleigh, NC; Kansas State University, Olathe, KS

Background and Purpose: Ivermectin is a widely used broad-spectrum antiparasitic drug in food-producing animals. However, its high lipophilicity can lead to accumulation in edible tissues, raising food safety concerns. Emergency situations, including New World screwworm outbreaks, may require extra-label drug use (ELDU) in cattle, highlighting the need for science-based prediction of tissue residue depletion and safe withdrawal intervals (WDIs). Although physiologically based pharmacokinetic (PBPK) models have been developed for ivermectin in humans and companion animals, no PBPK model has been developed for ivermectin in food-producing animals. This study developed and

evaluated a PBPK model to predict ivermectin plasma and tissue concentrations in cattle following subcutaneous (SC) and oral (PO) administration. The model was subsequently extended to a population PBPK framework to estimate WDIs under different regulatory residue standards. Finally, the population PBPK model was implemented as an interactive, open-source PBPK web interface to facilitate practical application across a range of ELDU scenarios, providing a supportive tool for veterinarians, regulators, and other stakeholders.

Methods: A seven-compartment PBPK model, including plasma, liver, kidney, muscle, fat, lung, and the rest of the body, was developed using the R package “mrgsolve.” Pharmacokinetic data used for model development were compiled from the Food Animal Residue Avoidance Databank (FARAD) Comparative Pharmacokinetic Database and FDA Freedom of Information records. Model calibration and parameter optimization used intravenous (IV) administration datasets to optimize fecal, biliary, and urinary elimination parameters, oral administration datasets to optimize oral absorption parameters, and SC administration datasets to optimize SC absorption and tissue partition coefficients. Model performance was evaluated using the coefficient of determination (R^2) to assess how well model predictions agreed with observed concentrations, while prediction accuracy was assessed using the average absolute fold error (AAFE) and the percentages of predictions within 2- and 3-fold of observed concentrations. The validated model was subsequently extended to a population PBPK framework using Monte Carlo simulations to account for parameter variability and uncertainty. Each simulation generated 1,000 virtual animals, with parameter distributions defined based on reported literature values or specified ranges. WDIs were estimated by comparing the 95th and 99th percentiles of predicted tissue concentrations with Codex Maximum Residue Limits (MRLs) and FDA tolerance limits, respectively. The population PBPK model was implemented as an interactive web-based interface using R Shiny.

Results: The PBPK model adequately described ivermectin tissue concentrations in cattle, with R^2 of 0.81 and 0.79 and AAFE of 1.71 and 1.67 for the calibration and evaluation datasets, respectively. Overall, 72.7% of model predictions were within 2-fold of observed concentrations, and 92.3% were within 3-fold of observed concentrations. At the labeled dose of 0.2 mg/kg SC or PO, the predicted WDI based on the historical U.S. Food and Drug Administration (FDA) liver tolerance (0.1 ppm) was 34 days following SC administration and 24 days following PO administration, closely matching the FDA approved withdrawal periods of 35 days for SC and 24 days for PO administration, respectively. When Codex MRLs (0.8 ppm for liver and 0.03 ppm for muscle) were applied, the corresponding predicted WDIs were 9 days for SC administration and 4 days for PO administration. At the extra-label dose of 0.3 mg/kg, the predicted WDIs based on the historical FDA liver

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tolerance increased to 40 days for SC administration and 29 days for PO administration, while application of Codex MRLs resulted in predicted WDIs of 15 and 6 days, respectively. Finally, the population model was successfully implemented in an interactive PBPK (iPBPK) web dashboard, enabling users to evaluate ivermectin tissue depletion and WDIs across different dosing scenarios and regulatory standards without having to write complex model code.

Conclusion: This study introduces a novel, robust, and science-based PBPK model for predicting ivermectin tissue depletion and estimating WDIs in cattle. The model and iPBPK platform can support the appropriate use of ivermectin in emergency ELDU scenarios in the field. Furthermore, the platform provides a foundation for its use as a next-generation tool for food safety assessment, while reducing reliance on additional animal studies.

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Poster Presentations by Number:

Sorted by degree and alphabetically by first name with the exception of the postdocs' posters

Poster #	Author	Affiliation	Title	Page #
Undergraduate				
1	Gianna Thomas	University of Florida	Knowledge-Based Embeddings for Organ-Specific Toxicity Prediction Across a Diverse Chemical Library	21
2	Jacqueline Gutierrez	University of Florida	An Integrative Toxicological Assessment of the Herbicide Tebuthiuron: Elucidating Biochemical and Behavioral Responses in Developing Zebrafish	23
3	Jivitesh Bir	University of Florida	Behavioral and neurotoxicity assessment of perfluorohexanoic acid (PFHxA) on developing zebrafish (Danio rerio)	24
4	Kathryn Greenberg	University of Florida	Assessing the effect of repeated heat exposure on the development of Chronic Kidney Disease of Unknown Etiology (CKDu) in a rat model	25
5	Leeyu Addisu	University of Florida	Glyphosate induces mitochondrial dysfunction and cell death in glomerular mesangial cells	26
6	Mya McKinney	University of Alabama	Investigating Cadmium Exposure: The suppression of Efferocytosis in Macrophages.	27
7	Romina Dotson	Clemson University	From Microbes to Megafauna: Investigating PFAS Fate and Transfer Across Estuarine Food Webs	28
8	Sreyan Rahman	University of Florida	A Physiologically Based Pharmacokinetic Model for Tyrosine Kinase Inhibitor Vimseltinib in Adults	29
9	William Riedel	University of Florida	Investigating the Potential for Oxidative Stress in Larval Zebrafish Following Perfluorohexanoic Acid (PFHxA) Exposure.	30
10	Savannah Grace Idle	Clemson University	Concentration-Dependent Toxicity of Environmental Chemicals in Retinal Pigment Epithelial Cells	31
Master's				
11	Greg Aniolek	Clemson University	You Are What You Eat: Examining Trophic Role in Comparative Microplastic Uptake and Toxicology Among Shark Species	32
12	Joshua Tolson	University of Georgia	Chronic post-natal fentanyl exposure alters molecular signaling, white matter development, and neural network connectivity in a translational piglet model	33
13	Katherine Nguyen	University of North Florida	Overcoming Sotorasib Resistance Through Combination Treatments with Exportin 1 Inhibitors	34
Doctoral				

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14	Ali Rehman	University of Georgia	<i>CeMbio Gut Microbiota Influences the Neuroprotective Effects of Tea Catechins in a Transgenic C. elegans Parkinson's Disease Model</i>	35
15	Alyssa Meyers	University of Florida	<i>Impact of Developmental Exposure to Environmentally Relevant Levels of PFAS and PFAS Mixtures on Multi-tissue Transcriptomic Profiles in Adult Zebrafish</i>	36
16	Andrew Huang	University of Georgia	<i>Enhanced fluid absorption as a newly recognized mechanism for vaginal dryness</i>	37
17	Ansley Elkins	Clemson University	<i>Investigating the direct effects of phthalates on the cervicovaginal epithelium</i>	38
18	Carlos Eduardo Carlos Lopes	Auburn University	<i>Behavioral effects of polystyrene microplastic exposure in zebrafish (Danio rerio) larvae</i>	39
19	Emma VanderMeulen	University of Florida	<i>Occurrence and cumulative burden of pharmaceutical and personal care products in the Lake Huron-Lake Erie Corridor: a two-year surface water surveillance study</i>	40
20	Kalynn Turner	University of Florida	<i>This Data's on Fire: Real-Time Co-detection of Serotonin and Histamine Reveals Potential Mechanisms Underlying Social and Inflammatory Disorders Resulting from Prenatal Flame-Retardant Exposure</i>	41
21	Kanchaka Senarath Pathirajage	Clemson University	<i>Aryl hydrocarbon receptor (AHR) signaling mediates Tetrabromobisphenol A (TBBPA) induced cartilage developmental toxicity in zebrafish</i>	42
22	Kaylinn Escobar	University of Florida	<i>Shared Lives, Shared Hazards: Exposure to PFAS, Arboviruses, and Psychosocial Stress in Dog-Owner Dyads Across Housing Status</i>	44
23	Kristofer Meier	University of Georgia	<i>Dysregulation of preimplantation uterine fluid movement as a mechanism of RU486 as a contraceptive</i>	45
24	Lifan Yang	University of Georgia	<i>Behavioral and organismal adverse effects of individual and multiple mycotoxin exposures in Caenorhabditis elegans</i>	46
25	Lishuang Wang	University of Florida	<i>Association of Nanoparticle Physicochemical Properties with Systemic Clearance and Half-Life</i>	47
26	Manoj Gundeti	University of Florida	<i>Comparative Safety Assessment of Traditional and Commercial Kratom Products Using a Novel Integrated PK-PD Approach</i>	48
27	Naga Venkata Sai Ayyappa Kota	University of Alabama at	<i>Carbon Black Exposure induces Macrophage Dysfunction and alters CHI3L1, ATF2 and MFGE8 expressions associated with Pulmonary Fibrosis.</i>	49

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		<i>Birmingham</i>		
28	<i>Pei-Yu Wu</i>	<i>University of Florida</i>	<i>Development of a Physiologically Based Pharmacokinetic Model for Tiletectinib in Dogs and Humans</i>	50
29	<i>Roselyn Davour</i>	<i>University of Florida</i>	<i>PFAS Contamination in Food and Drinking Water: A Multi-Level Policy Analysis and Review of Regulatory Instruments, Thresholds, and Equity Considerations.</i>	51
30	<i>Sheridan Wilkinson</i>	<i>University of Florida</i>	<i>Unveiling the impacts of polyester microfibers on the gut-brain axis in a marine species, the pinfish (Lagodon rhomboides)</i>	52
31	<i>Syed Ferdous</i>	<i>Clemson University</i>	<i>Leveraging Zebrafish as a Model to Screen Environmentally Relevant PFAS Mixtures Emulated from 11 South Carolina Military Sites</i>	53
32	<i>Trevor Kalinowski</i>	<i>University of Georgia</i>	<i>Delayed effects of Gulf War Illness: sex-specific neurochemical alterations across brain regions reflects accelerated aging within two pre-clinical mouse models</i>	54
33	<i>Xinyue Chen</i>	<i>University of Florida</i>	<i>A Coupled Mechanistic and Machine Learning Physiologically Based Pharmacokinetic Framework for Predicting Nanoparticle Drug Release Kinetics in Tumors</i>	56
34	<i>Zhicheng Zhang</i>	<i>University of Florida</i>	<i>Redevelopment of a physiologically based pharmacokinetic model for meloxicam in laying hens</i>	57
35	<i>Arnob Sarker</i>	<i>Clemson University</i>	<i>Developmental toxicity of Perfluorononanoic acid (PFNA): impacts on eye and brain</i>	59
Postdoctoral				
36	<i>Kun Mi</i>	<i>University of Florida</i>	<i>Physiologically Based Pharmacokinetic (PBPK) Modeling to Predict Tissue Distribution and Withdrawal Intervals of Doramectin in Cattle</i>	60
37	<i>Haiyan Lu</i>	<i>University of Louisville</i>	<i>Development of a Very Low-Serum Medium for Human Lung Fibroblast–Epithelial Co-Culture and Evaluation of Cr(VI) Responses</i>	62
38	<i>Chi-Yun Chen</i>	<i>University of Florida</i>	<i>An Integrated Physiologically Based Pharmacokinetic Model Incorporating DNA and Cardiolipin Binding Mechanisms to Characterize the Biodistribution of Nanoparticle-Encapsulated Doxorubicin</i>	63
39	<i>Idoia Meaza Isusi</i>	<i>University of Louisville</i>	<i>A Whale of a Problem: First Evidence of Micro/Nanoplastics Presence in Blubber of Humpback Whales from Gulf of Maine and Co-Occurrence with Nonessential Metals</i>	64
40	<i>Abhishek Gour</i>	<i>University of Florida</i>	<i>Evaluation of Opioid-Associated Neonatal Toxicity Following Prenatal Exposure to Mitragynine</i>	65

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41	<i>Evelyn Lopez Gonzalez</i>	<i>University of Florida</i>	<i>Toxicological Characterization of Perfluoro-3-methoxypropanoic Acid (PFMOPrA) in Early Developmental Stages of Zebrafish (Danio rerio).</i>	66
42	<i>Dhruthi Reddy Mutyala</i>	<i>University of Alabama</i>	<i>PAD4 Deficiency Attenuates Arsenic Trioxide–Induced Lung Injury and Interstitial Neutrophil Accumulation.</i>	67
43	<i>Fatma Ceren Kirgiz</i>	<i>University of Florida</i>	<i>Effect of N-EtFOSAA Exposure on Developmental and Cardiac Toxicity in Zebrafish (Danio rerio) Embryos</i>	68
New Investigator				
44	<i>Alex Yoon</i>	<i>University of Florida</i>	<i>The Association Between Per- and Polyfluoroalkyl Substances and Prostate Cancer Risk in the Southeastern United States</i>	69
45	<i>Jones B Graceli</i>	<i>SIUC</i>	<i>Subacute exposure to a mixture of tributyltin, cadmium, and mercury impairs the hypothalamic–pituitary–gonadal axis at different levels by disruption in estrogen receptor alpha/ Akt signaling and changes pregnancy outcomes in female rats</i>	70
46	<i>Isil Gazioglu</i>	<i>University of Florida</i>	<i>Optimization of HPLC–MS Conditions for Reliable Quantification of Zeta-Cypermethrin Isomers in Toxicological Residue Analysis</i>	71
47	<i>Tatilla Luz da Silva Frota Gomes</i>	<i>University of Florida</i>	<i>Optimized Extraction of Glyphosate from Rat Vertebral Bone</i>	72

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Undergraduate Poster Abstracts

Knowledge-Based Embeddings for Organ-Specific Toxicity Prediction Across a Diverse Chemical Library

Gianna Thomas, Kun Mi, Zhoumeng Lin

University of Florida, Gainesville, FL

Background and purpose: Quantitative structural activity relationships (QSAR) is a computational method of predicting toxicology using the structure of molecules and determining the toxicity across various endpoints. These structure-based representations, however, have recognized limitations that hinder it from being fully accurate when testing chemicals. Some weaknesses include being insensitive to small structural changes that produce large shifts in toxicity, and do not capture mechanistic, pharmacological, or exposure context that lies outside two-dimensional structure. Decades of toxicological findings remain distributed across the public literature domain and public chemical databases. By integrating the concept of computational toxicology prediction and the use of the vast array of pharmaceutical research, we may be able to more accurately derive information about chemicals and determine toxicity among other information, giving a more well-rounded view. This method called Quantitative Knowledge Activity Relationships (QKAR) has shown promising results with a FDA-Approved drug data set. However, it is up to question whether this same method can be used to predict other chemicals like environmental chemicals and see their effect across various endpoints.

Methods: Using Python, a library of 1,743 chemicals was each identified by Chemical Abstract Service (CAS) number with chemicals spanning from pharmaceuticals, agrochemicals, and industrial compounds. Each chemical had to be matched to the correct toxicity label; we aligned all records by CAS number. This identity-based matching removed compounds that could not be reliably paired and yielded a final analysis set of 1,269 chemicals. The key goal was to represent each chemical by the information derived from text. Three descriptions were made. DrugName (the compound name alone), Simpletox (a short 100–200-word summary about the toxicology), and Pharmtox (A more cohesive summary with guided prompts intended to be used for more clinical applications). With each endpoint in mind, these summaries were made specifically for the unique features of the endpoints and also split into groups based on the type of chemical (e.g. industrial compound). Each description was then converted into numbers a computer model can work with, using an LLM-based embedding tool creating a list of 3072 numbers that capture the meaning of that text the LLM compiled. Chemicals described in similar ways end up with similar lists of numbers. These number lists became the input the models learned from, in place of the molecular structure used in traditional approaches. Using them, we trained models to cardiotoxicity and developmental toxicity. To test the model performance repeated stratified five-fold cross-validation was used. The chemicals were divided into five groups, each keeping the same proportion of toxic and non-toxic compounds as the full set. The models trained on four groups and were tested on the fifth, rotating until every group had served as the test set once. We repeated this whole procedure 20 times with different random groupings, giving 100 separate train-and-test rounds.

Results: Across both endpoints, logistic regression (LR) outperformed the decision tree (DT). LR reached a Matthews correlation coefficient (MCC) of about 0.60 and an ROC-AUC near 0.88, while the decision tree trailed at an MCC of roughly 0.45–0.53 and an ROC-AUC of 0.76–0.81. Because MCC ranges from –1 (perfectly wrong) through 0 (no better than chance) to +1 (perfect), an MCC near 0.60 indicates a clear, consistent predictive signal from the text-based embeddings. Within the stronger LR model, adding more knowledge made essentially no significant difference. For cardiotoxicity, MCC was 0.599 using the compound name alone (DrugName), 0.617 using the short summary (SimpleTox), and 0.607 using the full pharmacological and toxicological summary (PharmTox). For developmental toxicity, the three were even closer: 0.600, 0.599, and 0.601, respectively. Every difference between descriptions (at most 0.018) was

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smaller than the run-to-run variation in the scores. This means the descriptions cannot really be distinguished from one another. The same pattern held for every other measure — ROC-AUC varied by no more than 0.007 within an endpoint. In short, the detailed PharmTox summary predicted organ toxicity no better than the compound's name alone.

Conclusion: These findings show that large language models (LLM) knowledge embeddings show promise in predicting organ toxicity across various endpoints, but adding detailed pharmacological prompts doesn't seem to have much difference compared to the chemical name alone. Rather than being a limitation, this raises questions as to where the information is really taken from. The chemical name can say a lot about a molecule, which may already be enough for the LLM to gather the information from. This may mean that a simpler approach may be enough for the models to perform well and predict toxicology. The next step is to examine whether richer descriptions help specifically with less-studied chemicals. Finally, we will compare these embeddings directly with traditional structure-based QSAR methods, and test whether combining the two is better than either alone. Utilizing the digital space as a tool to aid our research on chemicals is the next step in pharmaceutical research and can have many worthwhile applications in the future.

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An Integrative Toxicological Assessment of the Herbicide Tebuthiuron: Elucidating Biochemical and Behavioral Responses in Developing Zebrafish

Jacqueline Cristina Gutierrez, Giovane Ferreira, Amany Sultan, Fatma Ceren Kirgiz, Evelyn C. López González, Christopher J. Martyniuk

University of Florida, Gainesville, FL; University of São Paulo, São Carlos, Brazil; Animal Health Research Institute, Agriculture Research Centre, Giza, Egypt; Hatay Mustafa Kemal University, Hatay, Türkiye; Universidad Nacional del Litoral-Consejo Nacional de Investigaciones Científica y Técnicas (CONICET-UNL), Santa Fe, Argentina

Pesticides represent a significant threat to aquatic ecosystems due to their persistence and widespread use in agricultural areas, altering environments and exerting adverse effects on non-target organisms. Tebuthiuron is a phenylurea herbicide extensively used as an agrochemical to control pests and weeds in various crops, which often leads to contamination of aquatic environments. Despite its high water solubility and relatively long half-life in soil, studies on Tebuthiuron toxicity in fishes at environmental concentrations are limited. This study aimed to unravel the toxicity mechanisms of Tebuthiuron using the zebrafish model. Zebrafish embryos were exposed to Tebuthiuron (one concentration of either 0.1, 10, 1000 and 5000 µg/L) for 5 days and assessed for hatchability, heart rate, locomotor activity, oxygen reactive species, apoptosis and gene expression. There was no change in frequency of hatch, heart rate, or apoptosis. However, behavioral changes were noted, with hyperactivity in zebrafish larvae during the first light (at 10 µg/L), second light (at 10 and 1000 µg/L) and third dark (10 µg/L) periods of the Visual Motor Response assay. Biochemically, a significant depletion of basal ROS levels was observed at 1000 µg/L. At the molecular level, downregulation of oxidative stress-related genes (*cat*, *sod1*, and *sod2*) in larval fish was noted with exposure to 10 and 5000 µg/L Tebuthiuron, suggesting a depletion of antioxidant enzymes. In addition, some neurotoxicity-related genes were downregulated, such as acetylcholinesterase (*ache*), while some genes were upregulated, like microtubule-associated protein tau b (*maptb*) and synapsin 2 alpha (*syn2a*), with 5000 µg/L Tebuthiuron exposure. In conclusion, Tebuthiuron induces sublethal toxicity characterized by irregular, concentration-specific disruptions to photomotor behavior, basal ROS levels, and transcriptional markers of oxidative stress and synaptic function, even in the absence of acute morphological defects. Future research should prioritize functional assays targeting mitochondrial bioenergetics and antioxidant enzyme activities, alongside evaluations of later developmental stages, to fully elucidate the long-term ecological risks of phenylurea herbicides to non-target aquatic species.

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Behavioral and neurotoxicity assessment of perfluorohexanoic acid (PFHxA) on developing zebrafish (*Danio rerio*)

Jivitesh S Bir, William F Riedel, Victoria Lopez-Scarim, Aubree G Robinson, Tristan Lescuyer, Benjamin A Schreibman, Rishi V Patel, Amany Sultan, Evelyn C Lopez Gonzalez, Christopher J Martyniuk

University of Florida, Gainesville, FL

Perfluorohexanoic acid (PFHxA) is a short carbon chain Per- and Polyfluoroalkyl substance (PFAS) that is commonly used as a replacement to perfluorooctanoic acid (PFOA). While the long-chain PFAS have been studied extensively, toxicity data for the short chain PFAS on aquatic species remains limited. In this study, zebrafish embryos were exposed to seven different concentrations of PFHxA (log2 scale) - 7.815, 15.625, 31.25, 62.5, 125, 250 and 500 µg/L - along with two control groups- a solvent control (0.1% dimethyl sulfoxide, DMSO) and an embryo rearing media (ERM) control. Exposures were conducted for 5 days, after which, the survival rate, locomotor activity (light-dark motor response test), and expression of neurotoxicity biomarkers were measured. There was no difference in survival rate among experimental groups, suggesting low acute toxicity of PFHxA. However, there were significant changes in behavior in all 3 dark periods as well as light period 2. Hyperactivity was observed during dark period 1 (at 125 µg/L) and light period 2 (at 15.625 and 500 µg/L). However, hypoactivity in larval fish was observed during dark period 1 (at 250 µg/L) and dark period 2 (at 15.625 and 250 µg/L). Thus, there were complex, dose-dependent effects of PFHxA in larval fish for locomotor activity. In terms of transcripts, myelin basic protein (mbp) and NK2 homeobox 2a (nkx2.2a) were downregulated in fish following exposure to PFHxA (100 µg/L for mbp and 31.25 µg/L for nkx2.2a). In zebrafish, nkx2.2a is responsible for the specification and division of oligodendrocyte cells, while mbp is a key gene in the development of the myelin sheath. This suggests that PFHxA may affect the development of the myelin sheath on neurons, leading to slower and less efficient travel of the electrical impulses in the neurons. Overall, the findings of this study show that PFHxA may affect neuronal function based upon disruptions in locomotor activity and altered levels of transcripts related to neurotransmission.

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Assessing the effect of repeated heat exposure on the development of Chronic Kidney Disease of Unknown Etiology (CKDu) in a rat model

Kathryn Greenberg, Phoebe Su, Daniel Verdugo, Shaolin Xiang, Valentina Stevenson, Yang Yang, Nancy Denslow, Jie Zhou, Chris Vulpe

University of Florida, Gainesville, FL; University of Georgia, Athens, GA

Background and Purpose: Chronic kidney disease of unknown etiology (CKDu) is an urgent health issue with increased mortality among farmworkers across the globe. Geographic data suggested a cluster of reported CKDu in agricultural communities from regions with hot and humid climates, like Central America and South Asia. Multiple factors, including heat exposure, have been reported to contribute to the development of CKDu, but the underlying cause(s) of the disease remain unclear. Here, we established a controlled exposure system in male Sprague-Dawley (SD) rats to model the effects of heat stress exposure on the development of kidney disease.

Methods: Young adult male SD rats were repeatedly dosed with water or glyphosate (200 mg/kg) then with or without heat exposure (4 hours a day, 5 days a week at 35 °C with 50±10% humidity) for up to 8 weeks. Animals' core body temperature (CBT) and activity levels were continuously monitored using implanted probes. Concentrations of glyphosate and aminomethylphosphonic acid (AMPA) in the kidney, liver, and plasma were quantified using liquid chromatography–mass spectrometry (LC-MS). To further assess the effect of repeated chronic heat exposure on the kidney, we assessed kidney histopathology changes using customized AI and deep learning algorithms developed in the HALO AI platform (Indica Labs). We carried out a holistic assessment of rat kidney histopathologic changes, which we term Whole Slide Imaging (WSI) analysis, by combining quantitative structural analysis with functional staining-based objective quantification.

Results: During the 4-hour heat session, the animals lost ~3% of their body weight, despite significantly higher water intake as compared to the non-heat control. After 6 weeks, we found the body weight of non-heat control and glyphosate-only animals increased by 13.46% and 1.26% respectively, while water+heat and glyphosate+heat animals decreased by 1.1% and 1.48% respectively. LC-MS data revealed that after 4 weeks of heat exposure, kidney glyphosate concentration was lower in glyphosate+heat animals in comparison to glyphosate-only animals ($p=0.037$). A similar trend in liver AMPA concentration was noted between the two groups, although not quite significantly different. During the heat sessions, animals' CBT were increased by approximately 1°C and the activity levels across all groups were decreased. We validated that the heat-exposed animals had an increased expression of Calb1 mRNA in the kidney and increased expression of haptoglobin (Hp) protein in the liver, an acute-phase protein previously associated with thermal acclimation. Furthermore, the whole slide histology analysis indicated glomerular and tubular injuries, as well as evidence of renal interstitial fibrosis in the heat-exposed animals. Specifically, we noted glomerular shrinkage and increased intratubular proteinuria, accompanied by significant intraglomerular accumulation of IBA-1 indicative macrophages and PAS+/Trichrome+ deposits in the kidney.

Conclusions: Our present study reveals that heat stress was associated with impaired animal growth and histopathological changes in the kidney. These findings may have relevance to the development of chronic kidney disease of unknown etiology in heat-stressed individuals.

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Glyphosate induces mitochondrial dysfunction and cell death in glomerular mesangial cells

Leeyu Addisu, Ling Yu, Niharika Bala, and Abdel Alli

University of Florida, Gainesville FL

Glyphosate is one of the most widely used pesticides worldwide and its exposure has been associated with cellular toxicity and kidney injury. Previous studies have shown that glyphosate reduces cell viability and promotes apoptosis in renal proximal tubule cells; however, its effect on human glomerular mesangial cells has not been investigated. Mesangial cells provide structural support to the glomerular tuft, secrete extracellular matrix components, and act in concert with endothelial cells and podocytes of the glomeruli to form a functional filtration unit. This study investigated the effects of glyphosate exposure on cellular stress responses, mitochondrial function, and oxidative stress in primary cultures of human mesangial cells. Human mesangial cells were treated with vehicle or glyphosate at concentrations of 1 mg/L for up to 24 hours. Mitochondrial respiration and ATP production were assessed using a Seahorse XFe Mito Stress Test to evaluate mitochondrial function. Immunofluorescence microscopy studies were performed using mesangial cells to assess changes in NOX4 protein expression following glyphosate exposure. Patch clamp electrophysiology was performed to assess changes in large-conductance calcium-activated potassium (BK) channel activity in response to glyphosate treatment. Glyphosate exposure impaired mitochondrial function, resulting in decreased mitochondrial respiration and ATP production. Immunofluorescence analysis demonstrated significantly increased NOX4 levels following treatment with 1 mg/L and 10 mg/L glyphosate compared with vehicle-treated cells ($p < 0.001$), indicating an increase in NOX4-associated oxidative stress. In addition, glyphosate treatment significantly decreased BK channel activity (NPo) ($p < 0.001$) and the number of channels in a patch ($p < 0.001$) in human mesangial cells. Since BK channels are known to regulate membrane potential and NOX4 has been proposed to induce inflammation and apoptosis, glyphosate exposure could potentially have a negative effect on the diverse functions of mesangial cells.

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Investigating Cadmium Exposure: The suppression of Efferocytosis in Macrophages

Mya McKinney, Nilda C. Sanchez, Dhruthi Mutyala, Sai Kota, Naga Venkata Sai Ayyappa, Ranu Surolia

University of Alabama at Birmingham, AL

Background: Cadmium is a heavy metal toxicant that can enter the body through inhalation and contribute to lung injury, inflammation, and chronic pulmonary disease. Maintenance of pulmonary homeostasis depends in part on efferocytosis, macrophage-mediated recognition, engulfment, and removal of apoptotic cells. The solution to maintaining pulmonary homeostasis is a process called efferocytosis. Efferocytosis allows macrophages to recognize, engulf, and remove apoptotic cells. It is often referred to as the body's cellular cleanup system. Peptidyl arginine deiminase 4 (PAD4) is an inflammatory enzyme implicated in immune-cell activation and neutrophil extracellular trap formation; however, its contribution to macrophage efferocytosis during cadmium exposure remains unclear.

Methods: To show the suppression of efferocytosis in macrophages, bronchoalveolar lavage (BAL)-derived macrophages were evaluated from wild-type (WT), PAD4-deficient (PAD4), and PAD4-deficient cadmium-exposed (PAD4 + Cd) groups. Cells were stained with Giemsa stain to enhance cellular morphology and examined by light microscopy. Efferocytosis was quantified by counting macrophages containing engulfed apoptotic cells relative to non-engulfing cells.

Results: Macrophage efferocytosis differed among the experimental groups. WT macrophages exhibited 443 engulfed cells, whereas PAD4 macrophages exhibited 216 engulfed cells, and PAD4 + Cd macrophages exhibited 131 engulfed cells. Thus, cadmium exposure in the PAD4-deficient group was associated with the lowest number of engulfed cells. Microscopic analysis also identified phagocytic activity, cellular aggregation, cell death, and cell-in-cell structures consistent with apoptotic-cell engulfment. These findings suggest that cadmium-induced cellular stress and inflammation impair alveolar macrophage function.

Conclusion: Cadmium exposure was associated with reduced macrophage efferocytosis, particularly in PAD4-deficient mice. Impaired clearance of apoptotic cells may prolong pulmonary inflammation and contribute to cadmium-associated lung injury. Further studies are needed to define the mechanistic role of PAD4 and NF-kB signaling in regulating macrophage efferocytosis during cadmium exposure.

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From Microbes to Megafauna: Investigating PFAS Fate and Transfer Across Estuarine Food Webs

Romina Dotson, Paige Powell, Melissa Walker, Gregory Aniolek, Zachary Padgett, Bryan Frazier, Jessica Donaldson, Joseph Bisesi, John Bowden, Bentley Boyd, Matt Heselton, Barbara Campbell, Dinuka Patabandige, Scott Hamilton-Brehm, Norm Shea, Ethan Friend, Andrew Tweel, Kylie Rock

Clemson University, Clemson, SC; South Carolina Department of Natural Resources, Columbia, SC; University of Florida, Gainesville, FL; Southern Illinois University, Carbondale, IL

Estuaries are a crucial biome that provide critical ecological services such as nursing juvenile organisms and filtration and cycling of nutrients. These biomes are increasingly impacted by per- and polyfluoroalkyl substances (PFAS), which are persistent and harmful contaminants that can influence microbial processes and bioaccumulate through the food web to apex predators. Understanding PFAS fate in these ecosystems requires investigation across trophic levels, from microbial communities that regulate biogeochemical cycling to sharks that integrate contaminant exposure over time. Microbes are key regulators of estuarine nutrient cycling and contaminant transformation, yet their interactions with PFAS remains poorly understood. We hypothesize that some estuarine microbial taxa can tolerate or potentially transform PFAS, resulting in shifts in community composition, microbial activity, and carbon cycling. To test this, sediment-derived microbial communities from developed and less-developed South Carolina estuaries were exposed to PFOS in culture experiments. After 30 days of PFOS-exposure, the cultures exhibited greater microbial abundance than the controls, while NMR analyses indicated declining PFOS concentrations over time. These findings suggest that PFOS may influence microbial growth and activity, and warrant further investigation into potential transformation pathways. To evaluate how PFAS moves through higher trophic levels, we are also investigating PFAS and mercury bioaccumulation in finetooth (*Carcharhinus isodon*) and sandbar (*Carcharhinus plumbeus*) sharks from South Carolina estuaries. Sharks are essential apex predators that help maintain ecosystem balance, but are particularly vulnerable to contaminants due to their long lifespans, high trophic status, and slow reproduction. PFAS and mercury are contaminants of interest due to their ability to bioaccumulate in the food web, causing neurological, hepatic, and reproductive issues in vertebrates. The distribution and physiological processing of these contaminants remain poorly understood as well, with many ethical barriers. We hypothesize that contaminant concentrations can reliably be predicted in non-lethal tissues such as blood and muscle. Shark blood and muscle samples were collected from estuaries in South Carolina, along with organ samples from incidental mortalities. Mercury concentrations were quantified using thermal decomposition-amalgamation atomic absorption spectrophotometry, and PFAS concentrations were analyzed via HPLC-MS/MS. Preliminary data in finetooth shark species have shown a strong correlation between mercury concentration in muscle and kidneys, muscle and brain, and muscle and gonads ($R^2 = 0.96, 0.97, \text{ and } .99$, respectively), while blacktip data have shown a strong correlation between mercury concentrations in muscle and liver, and muscle and kidneys ($R^2 = 0.94 \text{ and } 0.83$, respectively). This data suggests that muscle samples may be able to serve as a proxy for calculating mercury concentrations in internal organs. Together, these studies provide a food-web perspective on PFAS dynamics in estuarine ecosystems, linking contaminant processing by microbial communities to bioaccumulation in apex predators.

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A Physiologically Based Pharmacokinetic Model for Tyrosine Kinase Inhibitor Vimseltinib in Adults

Sreyan Rahman, Lishuang Wang, Zhoumeng Lin

University of Florida, Gainesville, FL

Background and Purpose: Tenosynovial giant cell tumor (TGCT) is a rare, locally aggressive tumor with dysregulation in the colony-stimulating factor 1 (CSF1) pathway [1]. CSF1 overproduction activates colony-stimulating factor 1 receptor (CSF1R), facilitating expansion and recruitment of CSF1R-expressing macrophages into tumor tissue [1]. Vimseltinib (ROMVIMZA®) is an orally administered, selective switch-control inhibitor of CSF1R developed by Deciphera Pharmaceuticals. In February 2025, vimseltinib received FDA approval for adults with symptomatic TGCT for whom surgical resection may cause worsening functional limitations or severe morbidity [2]. This study aimed to use GastroPlus® to develop a physiologically based pharmacokinetic (PBPK) model to simulate plasma concentration-time profiles across doses under fed, fasted, and elevated gastric pH conditions and evaluate factors affecting vimseltinib exposure.

Methods: A vimseltinib PBPK model was developed using the ACAT model in GastroPlus® v9.9. PK data came from the EMA report, U.S. prescribing information, and 2025 Deciphera food-effect and drug-interaction posters. Plotted data were digitized from the source figures [1–4]. Model parameters were derived from published sources, databases, regulatory data, or predicted using ADMET Predictor v11.2 and GastroPlus®. Calibration data were obtained from fasted and fed 30-mg profiles in 18 healthy adults aged 20–56 years [3]. Independent 30-mg fasted, 30-mg with rabeprazole, and 6–50-mg data were used for evaluation [1,2,4]. PKPlus noncompartmental analysis estimated apparent oral clearance as $CL/F = \text{dose}/AUC_{0-\infty}$. Monte Carlo simulations covered all nine profiles. Goodness-of-fit was determined by plotting observed and simulated PK parameters and concentration-time data with identity and fold limits. R^2 , simulated-to-observed C_{max} and AUC_{0-t} ratios, and twofold agreement determined model performance. Observed AUC_{0-t} was calculated: 480 h for the calibration, independent 30-mg fasted, and rabeprazole DDI datasets, and 24 h for the remaining evaluation datasets [1,3,4]. Parameter sensitivity analysis (PSA) evaluated effects on C_{max} and AUC_{0-t} in the 30-mg fasted model.

Results: The PBPK model demonstrated good predictive performance, with R^2 values of 0.922 and 0.801 for the pooled calibration and evaluation datasets, respectively, and an overall pooled R^2 of 0.816. Simulated-to-observed ratios ranged from 0.98 to 1.34 for C_{max} and 0.92 to 1.41 for AUC_{0-t} ; both endpoints for all nine profiles were within twofold of observed values. Monte Carlo simulations generally encompassed the observed concentration–time profiles. PSA identified logD- and solubility-pH-related inputs, plasma binding, clearance/perfusion, blood-to-plasma ratio, intestinal radius, and permeability as the principal determinants of C_{max} and/or AUC_{0-t} over the tested ranges.

Conclusions: In pooled analyses of nine profiles, the PBPK model demonstrated reasonable agreement with observed plasma concentration–time and exposure data for vimseltinib across the studied oral doses, fasted, fed, and elevated gastric pH states in healthy adults. Its performance across the evaluation datasets supports its use as a mechanistic framework to investigate factors affecting vimseltinib exposure.

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Investigating the Potential for Oxidative Stress in Larval Zebrafish Following Perfluorohexanoic Acid (PFHxA) Exposure

William F Riedel, Jivitesh S Bir, Victoria Lopez-Scarim, Aubree G Robinson, Tristan Lescuyer, Benjamin A Schreibman, Rishi V Patel, Amany Sultan, Evelyn C Lopez Gonzalez, Christopher J Martyniuk.

University of Florida, Gainesville, FL

Perfluorohexanoic acid (PFHxA) is a per- and polyfluoroalkyl substance (PFAS). These chemicals are often referred to as “forever chemicals” because they are resistant to degradation and persist in the environment. PFAS chemicals are also toxic to aquatic organisms, inducing immune dysfunction, neurotoxicity, and oxidative stress. Despite this, PFHxA is often used in food packaging, firefighting foams, non-stick coatings, emulsifiers, dispersants, and textiles. It has been detected in trace amounts in bodies of water, especially in industrial areas. Zebrafish (*Danio rerio*) are often used to assess chemical toxicity and developmental defects due to their small size, rapid development, embryo transparency, and genetic similarity to humans. Although many PFAS chemicals have been studied, research on the impact of PFHxA is still limited. To address this knowledge gap, the objective of this study was to determine whether PFHxA induces oxidative stress in developing zebrafish. To determine this, we measured ROS (Reactive Oxygen Species) levels in whole larval fish, as an indicator of oxidative stress. We also compared the expression of genes related to oxidative stress in zebrafish exposed to either our control groups (a solvent control of 0.1% dimethyl sulfoxide -DMSO and embryo rearing media control -ERM) or one concentration of PFHxA (7.815, 15.625, 31.25, 62.5, 125, 250, and 500 µg/L) after 5 days of exposure. We found that PFHxA has no effect on ROS levels in zebrafish. We also tested transcripts related to stress, such as catalase (cat), heme oxygenase 1 (ho-1), kelch-like ECH-associated protein 1a (keap-1), nfe2 like bZIP transcription factor 2a (nrf2), superoxide dismutase 1, soluble (sod1) and superoxide dismutase 2, mitochondrial (sod2). There was no significant change measured with any genes tested. Thus, we conclude that PFHxA did not induce oxidative stress in larval fish. Further studies are needed to determine if longer exposures lead to oxidative stress or damage. This study improves our understanding of the mechanisms underlying PFAS-induced toxicity in fish.

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Concentration-Dependent Toxicity of Environmental Chemicals in Retinal Pigment Epithelial Cells

Savannah Idle, Rose Serradimigni, Subham Dasgupta

Clemson University, Clemson, SC

Background and Purpose: The eye is a sensitive target for many environmental chemicals since it is a superficial organ exposed to ambient air pollutants. Within the eye, retinal pigment epithelium (RPE) is important for providing nutritional, metabolic and barrier support to the retina, specifically the photoreceptors. This experiment leveraged retinal pigmented epithelium (RPE-1) cell line to examine the toxic effects of a battery of environmental chemicals (flame retardants, phthalates, PAHs and PFASs) on the RPE. Based on our initial screening at limited concentrations, we selected two representative chemicals, the organophosphate flame retardant isopropylated phenyl phosphate (IPP) and oxygenated polycyclic aromatic hydrocarbon (oxy-PAH) 7-benzanthracene-7-dione (7-Benz) for further studies. IPP is an organophosphate flame retardant widely used in consumer products and construction materials and has been detected in both environmental matrices and human biological samples. Previous studies have associated IPP exposure with developmental toxicity and neurotoxic effects; however, its potential impact on ocular cell types remains poorly characterized. 7-Benz is formed through the oxidation of benz[a]anthracene, a PAH generated during incomplete combustion processes. Prior research has demonstrated that 7-Benz possesses genotoxic and mutagenic properties, indicating its potential to induce cellular damage following exposure. These documented toxicological effects, together with the limited understanding of their impacts on retinal pigment epithelial cells, motivated further investigation of IPP and 7-Benz in RPE-1 cells.

Methods: We used MTS assay-a cell viability assay-and alamarBlue-a metabolic assay-to assess concentration-dependent toxicity. RPE-1 cells were seeded in 96-well plates for 24 h, exposed to increasing concentrations of each chemical for 24 hrs, and cell viability and metabolic activity were measured relative to untreated controls. Statistical significance was estimated using a 1-way ANOVA, followed by Dunnett's test ($p < 0.05$).

Results: In the MTS assay, IPP produced no significant change in viability at lower concentrations of 12.5 μM and below, but cell viability was reduced to approximately 83% at 25 μM , 76% at 50 μM , and 68% at 100 μM . A stronger response was observed with 7-Benz, with viability decreasing to approximately 88% at 6.25 μM , 90% at 12.5 μM , 86% at 25 μM , 48% at 50 μM , and 34% at 100 μM . The alamarBlue assay also showed increased effects at higher concentrations of both chemicals. IPP reduced Alamar Blue signal to approximately 75% at 12.5 μM , 49% at 25 μM , 49% at 50 μM , and 33% at 100 μM . 7-Benz similarly produced a concentration-dependent decrease, with signal decreasing to approximately 80% at 12.5 μM , 52% at 25 μM , 45% at 50 μM , and 27% at 100 μM . Overall, both assays showed that IPP and 7-Benz reduce RPE-1 cell viability and metabolic activity most strongly at higher concentrations, although the magnitude of the response differed between MTS and alamarBlue.

Conclusion: The data suggest that both chemicals can result in concentration-dependent cytotoxicity in RPE-1 cells and demonstrate the value of using complementary assays to characterize chemical toxicity. Together, these findings suggest that environmental chemicals such as IPP and 7-Benz may impair the viability and metabolic function of retinal pigment epithelial cells, demonstrating the potential for environmental exposure to negatively impact retinal health and normal eye function.

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Master's Poster Abstracts

You Are What You Eat: Examining Trophic Role in Comparative Microplastic Uptake and Toxicology Among Shark Species

Gregory D. Aniolek, Paige C. Powell, Jane Zheltov, Stefanie L. Whitmire, Peter V.D. Hurk, Kylie D. Rock

Clemson University

Introduction: Synthetic micropolymers (MPs; <5 mm) are an emerging class of anthropogenic environmental pollutants that are now considered a global ecotoxicological concern due to their persistence, ubiquity, and potential for biological interaction. MPs are introduced into marine systems through urban runoff, wastewater effluent, and degradation of larger plastic debris, where they absorb hydrophobic contaminants and concentrate in sediments and biota. Mounting evidence from laboratory models, including zebrafish, bivalves, and marine worms, demonstrate that MPs can induce oxidative stress, inflammation, reproductive impairment, as well as altered behavior through physical obstruction, reactive oxygen species (ROS) generation, and endocrine disruption. However, many studies that have historically produced these data use particles and concentrations that are uncharacteristic of the particles found in the environment. One aspect that is missed in these studies are secondary contaminant toxicity, which is a high concern as plastics and rubbers have the capability of acting as a vector in transporting contaminants such as polycyclic aromatic hydrocarbons (PAHs), plasticizers, PFAS, and chemicals that can bio transform into dangerous oxidizers like 6PPD-q. Data on the biological effects of environmentally relevant MP concentrations in large marine vertebrates also remains sparse, particularly in long-lived and highly exposed predators such as sharks. Coastal South Carolina estuaries, including Charleston Harbor and Winyah Bay, represent MP hotspots, receiving high inputs from urban, industrial, and riverine sources. MPs have been documented in local sediments, plankton, fishes, and even bottlenose dolphins, but shark exposure remains uncharacterized. Because sharks occupy high trophic positions, exhibit species-specific feeding strategies (pelagic, demersal, omnivorous), and possess a conserved vertebrate immune and oxidative stress system, they represent ideal sentinels for evaluating MP/secondary contaminant bioaccumulation and associated physiological effects.

Aims: To examine the trends regarding MP uptake and stress, we will be 1) characterize and quantify tissue and trophic guild specific MP profiles, 2) quantifying secondary contaminant concentration within the liver, and 3) correlate polymer load to known markers of toxicological stress, including detoxification enzyme activity, lipid peroxidation, DNA mutations and inflammatory biomarkers. We hypothesize that demersal feeders will exhibit higher MP burdens than pelagic species due to greater benthic contact and ingestion of sediment-associated prey, and that MP load will positively correlate with secondary contaminant concentrations and toxicological stress.

Methods: Sharks will be sourced from incidental mortality on routine population survey studies with South Carolina DNR. Plastic will be extracted from the intestines and livers of our shark species via a chemical digestion with 10% KOH and sieved onto a 20-micron mesh. Extracted plastic will be analyzed via laser direct infrared (LDIR) microscopy at the Baruch Institute in Georgetown. PAHs will be quantified via HPLC at NOAA Holling Marine Lab in Charleston, and inflammatory response/oxidative stress biomarkers will be analyzed via kits. All contaminant concentrations and biomarkers will be analyzed both against each other via generalized linear models, as well as against trophic guild using a one-way ANOVA to give an indication of how diet and polymer concentration may lead certain shark species to increase toxicity.

Results: Preliminary LDIR analysis confirmed the presence of MPs in our target species with crumb rubber as the most abundant MP detected.

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Chronic post-natal fentanyl exposure alters molecular signaling, white matter development, and neural network connectivity in a translational piglet model

Joshua B. Tolson, Paisli S. Ivey, Morgan H. LaBalle, Sayed Islam, Briana Clary, Soon Lee, Sydney Sneed, Hea Jin Park, Jarrod A. Call, Qun Zhao, Franklin D. West

University of Georgia, Athens, GA

Fentanyl is an opioid often used for analgesia and sedation in pediatric clinical care, especially in Neonatal Intensive Care Units (NICUs). Despite widespread use, pharmacokinetic, safety, and dosing data are still being refined, resulting in growing concern about the effects of prolonged fentanyl exposure during critical developmental stages. In this study, we seek to study the effects of early post-weaning fentanyl exposure on the developing brain in a highly relevant translational porcine model that shares important neurodevelopmental, anatomical, and physiological characteristics with the human brain. We investigated how prolonged fentanyl exposure during early post-weaning development contributes to changes in brain structure, connectivity, and function in piglets. Ten castrated male Yorkshire-cross piglets were assigned to one of two groups: fentanyl exposure group (FE, n=5) or control group (control, n=5). Fentanyl-exposed piglets received a continuous transdermal dose of 5 µg/kg/h for 30 days. At day 30 post-FE, three-dimensional T1-weighted magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), and resting-state functional MRI (rsfMRI) were performed. Following euthanasia, hippocampal tissue was collected for bulk RNA sequencing. DTI analysis demonstrated decreased fractional anisotropy (FA) and increased radial diffusivity (RD) in the left optic radiation. Increased mean and axial diffusivity (MD and AD) were also shown in the right anterior thalamic radiation. ICA correlation analysis of fMRI demonstrated decreased BOLD signaling in the FE piglets within the visual and primary somatosensory networks and other key brain regions, including the hippocampus. Whole-brain graph-theoretic analysis demonstrated decreased functional connectivity in FE piglets. These findings indicate reduced connectivity and functional activity within networks supporting sensory processing and hippocampal function after prolonged fentanyl exposure as compared to naïve controls. Principal component analysis of gene expression within the hippocampus demonstrated a complete separation of treatment groups along PC1, which explained 21.6% of total transcriptomic variance. Using the Differential Gene Expression (DGE) list, Gene Set Enrichment Analysis (GSEA) was performed. Of 14,131 genes, 1,104 genes were differentially expressed and 46 Gene Ontology Biological Process pathways were significantly enriched. Altered pathways were predominantly negatively enriched, indicating that genes associated with neurodevelopment like neurite outgrowth, neuronal ensheathment, and myelination were predominantly expressed at lower levels in FE piglets compared with controls. Together, these findings indicate that chronic post-weaning fentanyl exposure is associated with coordinated alterations across molecular, structural, and functional levels of the brain, consistent with disruptions of neurodevelopmental processes.

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Overcoming Sotorasib Resistance Through Combination Treatments with Exportin 1 Inhibitors

Katherine Nguyen, Weimin Gao

University of North Florida, Jacksonville, FL

Research Background and Purpose: Non-small cell lung cancer (NSCLC) is the most common form of lung cancer, affecting both men and women worldwide. Oncogenic mutations in KRAS occur frequently in NSCLC, and advances in targeted therapy for KRAS G12C led to the development of sotorasib, the first FDA-approved KRAS G12C inhibitor. However, resistance to sotorasib is considered inevitable based on the current literature. In addition, exportin 1 (XPO1), also known as chromosome region maintenance 1 (CRM1), is a well-characterized nuclear export protein. Studies have shown that XPO1 plays an important role in lung cancer development and may serve as a potential adjuvant therapeutic target by modulating multiple cancer-associated pathways, including KRAS signaling. Leptomycin B (LMB) is a well-characterized XPO1 inhibitor. Therefore, the objective of this study was to investigate the potential combinative therapeutic effects of targeting KRAS with sotorasib and XPO1 with either LMB or genetic knockdown to overcome sotorasib resistance.

Methods: We used NCI-H358 cells, which are sensitive to sotorasib due to their dependence on KRAS G12C signaling; A549 cells, which exhibit intrinsic resistance to sotorasib; and our previously established A549XPO1- cells, which have XPO1 knockdown. MTT assays were conducted to evaluate cytotoxicity following treatment with the indicated drugs, sotorasib (0-5 μ M for NCI-H358; 0-50 μ M for A549 and A549XPO1-) and/or LMB (0.5 nM) for 24, 48, and 72 hours (h). Molecular mechanisms were evaluated using quantitative real-time polymerase chain reaction (qRT-PCR) and Western blotting to measure the mRNA and protein expression levels of survivin, an inhibitor of apoptosis protein that promotes cell survival, and p21, a cyclin-dependent kinase inhibitor that promotes cell cycle arrest, respectively.

Results: The MTT assays demonstrated that the IC₅₀ values of sotorasib after 48 and 72 h treatments in NCI-H358 cells (0.02-0.16 μ M) were substantially lower than those in A549 cells (40-50 μ M), indicating that NCI-H358 cells are more sensitive to sotorasib, consistent with previous reports. However, sotorasib resistance in A549 cells was partially reversed by combination treatment with sotorasib and LMB (0.5 nM), which resulted in lower IC₅₀ values than treatment with sotorasib alone. The combinative effects of sotorasib and XPO1 inhibition were further confirmed in A549XPO1- cells. Based on the cytotoxicity results, qRT-PCR and Western blot analyses were performed using A549 cells treated for 24 and 48 h with the following groups: (1) control, (2) 0.5 nM LMB, (3) 10 μ M sotorasib, (4) 10 μ M sotorasib + 0.5 nM LMB, (5) 25 μ M sotorasib, and (6) 25 μ M sotorasib + 0.5 nM LMB. Combination treatment with sotorasib and LMB produced opposing effects on gene expression, significantly decreasing survivin and increasing p21 compared with sotorasib alone and the control groups. Western blotting further confirmed the qRT-PCR findings at the protein level.

Conclusions: Overall, these results suggest that XPO1 inhibition can overcome sotorasib resistance in A549 cells, at least in part, by suppressing cell survival and promoting cell cycle arrest. These findings support XPO1 inhibition as a potential novel adjuvant strategy to enhance the efficacy of sotorasib in NSCLC. Future studies using sotorasib-acquired resistant cell lines and animal models will further validate these findings and determine the therapeutic potential of XPO1 inhibition for overcoming sotorasib resistance.

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PhD Poster Abstracts

CeMbio Gut Microbiota Influences the Neuroprotective Effects of Tea Catechins in a Transgenic *C. elegans* Parkinson's Disease Model

A. Rehman, J. Wang, and L. Tang

University of Georgia, Athens, GA

The gut microbiota has a direct influence on the metabolism and neuroprotective potential of dietary polyphenols such as tea catechins (TCs). The study conducted has investigated how defined gut microbial communities (CeMbio consortium) exerts a modulating TC-mediated neuroprotection in the *Caenorhabditis elegans* Parkinson's disease (PD) model UA44, which expresses human α -synuclein in dopaminergic neurons. Twelve bacterial strains from the CeMbio community were tested individually and as a pooled mixture against the standard laboratory diet *E. coli* OP50. L4-stage UA44 worms were exposed to 0-200 $\mu\text{g/mL}$ TCs for seven days at 25 °C. Dopaminergic neuron integrity was assessed by fluorescence microscopy using a neuronal damage scoring scale (0-3), where 0 = all six head neurons intact and 3 = all six neurons degenerated ($n = 30 \text{ worms} \times 3 \text{ replicates}$). Dopamine-linked behaviors—area-restricted search (ARS) and basal slowing response (BSR)—were quantified under food and no-food conditions using video-based analysis. TC treatment significantly reduced neuronal degeneration in a dose- and strain-dependent manner (two-way ANOVA, $p < 0.001$).

- In OP50-fed worms, the mean degeneration score decreased from 2.4 ± 0.3 (control) to 1.6 ± 0.2 at 200 $\mu\text{g/mL}$ TC (33 % improvement).
- CeMbio-mix-fed worms showed greater protection, with scores of 1.1 ± 0.2 at 100 $\mu\text{g/mL}$ and 0.8 ± 0.1 at 200 $\mu\text{g/mL}$, corresponding to ~65 % less degeneration than OP50-fed worms ($p < 0.001$).
- Among individual strains, *Lelliottia amnigena* (JUB 66) and *Stenotrophomonas maltophilia* (JUB 19) exhibited the lowest damage scores (0.9 ± 0.2 and 1.0 ± 0.2 , respectively), whereas *Pseudomonas lurida* (MYb11) remained highly susceptible (2.3 ± 0.3).
- Behavioral assays mirrored the neuronal trends: CeMbio-fed worms displayed a higher basal slowing index (0.68 ± 0.04) compared with 0.42 ± 0.05 in OP50-fed controls ($p < 0.01$) and recovered ARS turning frequency to 14.6 ± 1.2 turns/min versus 9.5 ± 1.5 turns/min ($p < 0.05$).

CeMbio-associated microbes significantly potentiate the neuroprotective effects of TCs by reducing dopaminergic neuronal degeneration and improving dopamine-regulated behaviors. The protection is strain-specific, with *Lelliottia amnigena* and *Stenotrophomonas maltophilia* providing the most pronounced benefit. These results suggest that microbial enzymatic conversion of catechins into bioactive metabolites (e.g., phenolic acids, valerolactones) underlies the observed reduction in α -synuclein-associated neurotoxicity in the *C. elegans* PD model.

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Impact of Developmental Exposure to Environmentally Relevant Levels of PFAS and PFAS Mixtures on Multi-tissue Transcriptomic Profiles in Adult Zebrafish

A. Meyers, Danielle Meyer, Alex Haimbaugh, Mackenzie L. Connell, Brianna Vo, Ashley Guarino, Emma Cavaneau, Grace Winny, Chia-Chen Wu, Camille Akemann, and Tracie R. Baker

University of Florida, Gainesville, FL; Wayne State University, Detroit, MI

Background and Purpose: Concern over the potential effects of per- and polyfluoroalkyl substances (PFAS) commonly present in the environment (including drinking water) have risen since the early 2000s. Although certain PFAS, including perfluorosulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) are no longer used in manufacturing in the United States, they are ubiquitous in the environment due to their strong carbon fluorine bonds rendering them effectively indestructible. PFOA and PFOS have been reported to induce immunotoxicity, endocrine toxicity, and developmental toxicity. Epidemiological studies have associated PFAS with multiple adverse health outcomes, including altered immune function, liver disease, lipid metabolism dysregulation, kidney disease, miscarriages, and cancer.

Methods: In this study, we sought to determine the effect of environmentally-relevant levels to PFOA (70ng/L), PFOS (240 ng/L), and a mixture of each (35 ng/L of PFOA + 120 ng/L of PFOS) on larval zebrafish from 0-5 days post-fertilization (dpf) that were then raised to adulthood (~18 months). RNA-Seq (3' mRNA-seq) transcriptomic analyses was then used to analyze extracted RNA from liver, and kidney tissue of male and female control and exposed fish (n=2-4/treatment; 4-8/respective control). Libraries were quantified using a Qubit 2.0 fluorometer and run on an Agilent TapeStation 2200 for quality control. The samples were sequenced on an Illumina HiSeq 2500 and analyzed using a combination of the Lexogen Bluebee Genomics Platform and Lexogen in-house data analysis. Reads were aligned to *D. rerio* (Build GRCz11). Differentially expressed genes (DEGs) were determined via DESeq2 and defined by absolute log2 fold change value $\geq |1|$; $p < 0.05$. DEGs were compared for overlap using UpsetR and were uploaded into Ingenuity Pathway Analysis (IPA).

Results: Previously, we reported that developmental PFAS exposure altered lipid transcriptomics and light/dark swim distance in larval fish (5 dpf) and impacted fecundity in PFOA-exposed fish raised to adulthood (4-6 months). Comparisons between larval and adult-onset differential gene expression, revealed significantly higher effect later in life. The number of DEGs were low (ranging from 1-106) in larval fish, whereas adult fish exposed during development were found to have anywhere from 2-7090 DEGs. IPA analysis of DEGs revealed significant enrichment of several disease pathways, including fatty metabolism disruption (z-score = -4.08 Mixture male liver), organismal survival (z-score = 30.52 PFOS male liver), liver carcinoma (z-score = 2.38, 2.71 PFOS male liver, PFOS female liver), and death of infant organism (z-score= 15.535 PFOS male liver) in PFAS exposed fish. Outcomes were found to be highly elevated in the mixture exposure. Several upstream regulators including beta-estradiol (z-score = -9.949 PFOS male liver), HNF4A (logratio = -7.736 PFOS female liver), FOXA2 (logratio= -7.701 PFOS female liver) and PPARa (logratio = -3.418 Mixture male liver) were identified to be altered regulators of observed diseases.

Conclusion: Early life PFAS exposure at environmentally relevant levels has multisystemic effects months after the initial exposure. Ongoing studies are supporting the associated links of PFOA and PFOS in human populations with animal toxicology studies including zebrafish. Several theorized molecular mechanisms of PFAS were observed to be dysregulated, potentially leading to the diseases observed. Animal studies such as this are important for confirming findings of epidemiologic and cell line toxicology studies. This research is important to determining the effect of PFAS on public health and the relative safe level of PFAS in drinking water.

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Enhanced fluid absorption as a newly recognized mechanism for vaginal dryness

Andrew Huang, Jonathan Matthew Hancock, Taylor Elijah Martin, and Xiaoqin Ye

University of Georgia, Athens, GA

Vaginal dryness affects 46% of postmenopausal women and 15% of premenopausal women and is a common side effect of combined hormonal contraceptive pills. Despite its broad impact, mechanisms regulating vaginal moistness remain poorly understood. Since estrogen play an essential role to keep moisture in the female reproductive tract (FRT), the general view is that reduced estrogen levels (e.g., in postmenopausal women) cause decreased vaginal moisture production. Estrogen mainly acts through estrogen receptor α (ER α /Esr1) in the FRT and epiER α ^{-/-} (Esr1f^{-/-}Wnt7aCre^{+/+}, ER α deficiency in FRT epithelium) mice have reduced uterine fluid. Our mRNA-seq data (GSE311705) implicate disrupted two-way traffic, with a general trend of reduced fluid secretion and increased fluid absorption in epiER α ^{-/-} uterus. This trend may also present in epiER α ^{-/-} vagina. Upon injection of Alexa Fluor 488 hydrazide (AH) into FRT lumen, we can trace AH absorption into FRT epithelium as a proxy for bulk fluid absorption (seen as smeared cellular fluorescence) during estrous cycle. In the estrus stage, there is no fluid absorption in the Esr1f^{-/-} control vagina due to the cornified layer as a barrier, while in the epiER α ^{-/-} vagina, the vaginal epithelium is exposed due to a disrupted cornified layer and both bulk fluid absorption and endocytosis (seen as fluorescent vesicles) could be detected. In the diestrus stage, there is mainly endocytosis in Esr1f^{-/-} vaginal epithelium but bulk absorption in epiER α ^{-/-} vaginal epithelium. These observations indicate enhanced fluid absorption as a newly recognized mechanism for vaginal dryness caused by impaired estrogen signaling. We continue investigating mechanisms in regulating vaginal moistness.

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Investigating the direct effects of phthalates on the cervicovaginal epithelium

Ansley Elkins, Sophie Childs, Paige Powell, Sasha Suggs, Hannah Zierden, and Kylie Rock

Clemson University, Clemson, SC; University of Maryland, College Park, MD

Background and Purpose: Phthalates are endocrine disrupting chemicals (EDCs) widely used as plasticizers, solvents or stabilizers in personal care and feminine hygiene products. Recent epidemiological evidence has associated exposure to phthalates found in feminine hygiene products, such as tampons, with higher incidence of bacterial vaginosis (BV) and vaginal inflammation. However, the molecular mechanisms connecting direct, intravaginal phthalate exposure to epithelial dysfunction and microbial imbalance remain poorly understood. This study aims to investigate the direct effects of phthalate exposure on vaginal and cervical epithelial cells, with a focus on epithelial barrier integrity, inflammatory signaling, and cellular stress responses. We hypothesize that phthalates disrupt the vaginal microenvironment by activating inflammatory and stress-response pathways in vaginal and cervical epithelial cells, leading to weakened barrier integrity and altered cytokine signaling.

Methods: Human vaginal (VK2/E6E7), ectocervical (Ect1/E6E7), and endocervical (End1/E6E7) epithelial cell lines were cultured per ATCC guidelines and exposed to diethylhexyl (DEHP), dibutyl (DBP), diethyl (DEP), dimethyl (DMP), and diisobutyl (DiBP) phthalates, alone or as a mixture, at 0.001-1.0 µg/mL for 24 hours. Cell viability was confirmed via CCK-8 assay, and quantitative RT-PCR was used to quantify gene expression of proinflammatory and barrier-associated targets (IL-6, IL-8, TNF-α, TGF-β1, occludin, and claudins 1-4). Additional transcriptional targets included structural (KRT8) and hormonally responsive genes (ESR1).

Results: Phthalate exposure did not significantly alter epithelial viability but induced marked, cell-type-specific transcriptional responses. Endocervical epithelial cells (End1) displayed significant upregulation of IL-6 and TNF-α, coupled with suppression of TGF-β1 and tight junction transcripts (occludin, claudin-1), suggesting barrier weakening and proinflammatory activation. Vaginal epithelial cell lines (VK2) displayed reduced TGF-β1 and IL8 expression but displayed a significant increase in the cytoskeletal gene KRT8. As expected, all cell lines exhibited reduced ESR1 expression, consistent with impaired hormone responsiveness. These findings indicate that phthalates can directly alter epithelial structural integrity and hormone and immune responsiveness, providing evidence for a potential mechanism by which phthalate exposure may contribute to vaginal inflammation and increase susceptibility to infection. Ongoing studies include quantifying cytokine production, evaluating transepithelial resistance, using immunohistochemistry to visualize tight junction proteins, and testing the impact of the full phthalate mixture.

Conclusions: This work establishes an in vitro framework for understanding the mechanisms linking phthalate exposure to vaginal inflammation and dysbiosis. Our findings demonstrate that environmentally relevant phthalate exposures have the potential to disrupt both vaginal and cervical epithelium function. Collectively, these findings suggest that phthalate induced inflammation and reduced barrier gene expression which may weaken epithelial defenses, and potentially increase susceptibility to infection. This work has far reaching implications for reducing EDC exposures in women's health products and mitigating reproductive health disparities.

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Behavioral effects of polystyrene microplastic exposure in zebrafish (*Danio rerio*) larvae

Carlos Lopes, Abner Nunes, Seth Vogt, Priscila Falagan-Lotsch, Katharine Horzmann

Auburn University, Auburn, AL

Microplastics (MPs) are microscopic plastic particles that commonly originate from the breakdown of plastics. Their ability to cross biological barriers, bioaccumulate, and transport harmful agents poses a risk to exposed organisms. However, effects of MPs during developmental stages remain poorly understood. To test the hypothesis that developmental MP exposure alters neurodevelopment, we aim to evaluate the effects of two different MPs on zebrafish larval behavior. At twenty-four hours post fertilization (hpf), embryos were mechanically dechorionated and exposed to 0, 0.1, 1, or 10 µg/ml of MP solutions derived from disposable red plastic drinking cups (solo cups) or plastic forks. Larval behavior was monitored in response to light and tapping stimuli at 120 hpf with a Noldus DanioVision observation chamber. For the visual motor response (VMR) test, larvae were exposed to a series of 10-minute periods that alternate between dark and light for a total of 50 min. Data for movement endpoints such as distance moved, velocity, time spent moving, turn-angle, angular velocity, mean meander, and turning direction were collected and analyzed with EthoVision software. For the tapping response test, a solenoid at the base of the observation chamber was used for mechanical stimulation. Each trial consisted of 10 min of acclimation, followed by a single tap (level 8 [most intense]), to elicit startle responses in darkness. For startle responses, the same movement endpoints were analyzed over a period of 3 s after the tap. MP exposure induced source- and concentration-dependent behavioral effects in zebrafish larvae. In the VMR assays, significant hyperactivity was observed for both fork- and cup-derived MPs, with increased distance moved, velocity, and/or time spent moving across concentrations. Changes in the path shape (turn angle, angular velocity and mean meander) and rotation (clockwise and anticlockwise turning) were significantly associated with intermediate to higher concentrations, regardless of the microplastic source. Similar increased larval locomotor behavior was observed for the tapping response assay solely in groups treated with cup-derived microplastics. We found no statistically significant differences in behavior after the tapping stimulus for fork-derived MPs. These findings indicate that MP origin influences toxicity profiles, with distinct assay-based behavioral phenotypes emerging from different particle sources.

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Occurrence and cumulative burden of pharmaceutical and personal care products in the Lake Huron-Lake Erie Corridor: a two-year surface water surveillance study

Emma A. VanderMeulen, Bridget B. Baker, Tracie R. Baker

University of Florida, Gainesville, FL

Background and Purpose: Pharmaceuticals and personal care products (PPCPs) are contaminants of emerging concern detected in surface waters globally, entering aquatic systems through wastewater effluent, agricultural runoff, and improper disposal. The Lake Huron to Lake Erie Corridor (HEC) is in the southeastern region of the state of Michigan, US, connecting two of the Great Lakes and bordering Canada. It serves as a major recreational fishing hub along with serving as a drinking water source for over 4 million people in both the US and Canada. The combined ecological risk from PPCP mixtures in this region remains poorly characterized. Previous literature has established varying levels of risk to humans and aquatic organisms attributed to PPCPs in the environment with mechanisms including endocrine disruption and antibiotic resistance. Using a One Health framework, this study assessed frequency, cumulative concentrations, and ecological risk in HEC surface water with a total 49 detected PPCPs.

Methods: 49 PPCPs were quantified across 16 sites in the HEC sampled in May 2025 and 2026. Detection frequency (DF), descriptive statistics of detected analytes, and cumulative concentrations per site for each year were calculated in R, with non-detects reported as zero. Ecological risk was assessed using risk quotients using apical and nonapical perceived no effect concentrations (PNEC) from literature review. Mixture risk was calculated as a sum of individual analyte risk quotients (RQ) under the conservative concentration addition assumption.

Results: Out of 140 PPCPs tested for, 49 were detected from 2025-2026 with three analytes reaching a DF $\geq 50\%$ (cotinine, 97%; metformin, 86%; atenolol, 62%). Cumulative concentrations across sites ranged from 14.8 to 3,150 ng/L per sample with a median of 107 ng/L. The Huron River upriver site and river mouth had maximum cumulative values of PPCP concentrations. X-ray contrast and antidiabetic drugs were the most prevalent with 80% of total detections. Tributary mouths exceeded cumulative concentrations compared to upstream sites at 4 of 7 paired sites. 4 PPCPs were detected at drinking water intakes including metformin. Apical fish RQs remained below 1 at all sites. Nonapical RQs exceeded 1 in 5 of 29 samples, primarily due to diltiazem in the Clinton River.

Conclusion: Our findings show the ubiquitous nature of PPCPs in the HEC, albeit at concentrations lower than the risk of thresholds for humans and fish. There is some evidence of the potential for sublethal effects in fish, and the persistent nature of these contaminants warrants further investigation. Detection of PPCPs at drinking water intakes also highlights a need to better understand how PPCPs could potentially impact human health while also considering the exposure risk to communities during recreation activities in surface waters.

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This Data's on Fire: Real-Time Co-detection of Serotonin and Histamine Reveals Potential Mechanisms Underlying Social and Inflammatory Disorders Resulting from Prenatal Flame-Retardant Exposure

Kalynn M. Turner, Gregory S. McCarty, Chathuri De Alwis, Natalia Duque-Wilckens, Leslie A. Sombers

University of Florida, Gainesville, FL; North Carolina State University, Raleigh, NC

The central and peripheral nervous systems are heavily innervated with several classes of neurotransmitters that work in concert to drive physiological function. The monoamines, which include histamine and serotonin, represent one such class of neurochemicals that work together to modulate a range of physiological functions, including inflammatory processes. As such, dysregulation in these systems has been implicated in a range of disorders such as major depressive disorder, inflammation-related disorders, along with other sociability disorders. Due to this functional overlap of serotonin and histamine, the ability to co-detect these two species at the same space and time promises to inform mechanisms that underlie central and peripheral nervous system functionality – allowing for a better understanding of when these systems are disrupted by pharmacologics or environmental contaminants. Herein, an electrochemical voltammetric technique was explored for the co-detection of serotonin and histamine at the same space and time. First, this optimized detection strategy was shown to have significantly increased sensitivity to histamine, compared to previously used waveforms, and exhibited well-resolved peaks for serotonin and histamine, allowing for the differentiation of these analytes from acidic pH shifts that commonly occur *in vivo*. Next, this technique was employed to co-detect serotonin and histamine in both peripheral and central biological systems, to demonstrate its usability to study serotonin and histamine in both systems. To demonstrate the usability of this technology in the peripheral nervous system, mouse mast cells were isolated from the peritoneal space of mice that had been prenatally exposed to polybrominated diphenyl ethers (PBDEs), which are synthetic flame retardants that have been historically used in furniture, electronics, and other consumer products. Though they were phased out in the early 2000s, these PDBEs bioaccumulate into the environment and have been shown to contribute to inflammatory disorders and impaired sociability. The persistence of PBDEs in the environment and their recycling into new consumer products have led to continued contamination and widespread human exposure, which raises concerns about their effect on neurodevelopmental processes in infants. Mast cells harvested from mice that had been prenatally exposed to PDBEs were shown to have impaired ability for repeated degranulation, rather than their ability to mount an initial immunological response. These results indicate that persistent impairment of mast-cell derived neurotransmitter release is a potential mechanism underlying the effect of prenatal PDBE exposure on physiological and behavioral dysfunction. Lastly, this technique was employed for the co-detection of serotonin and histamine in rat brain slices containing the dorsal raphe nucleus. For decades, serotonin dysregulation has been impacted in major depressive disorder and, more recently, the cytokine hypothesis of depression has been under investigation as histamine has been shown to converge on the serotonin system. Utilization of this co-detection strategy allows for the simultaneous detection of serotonin and histamine from live brain tissue. Selective pharmacological manipulations of these signals can be carried out to validate the presence of the analytes of interest. The incorporation of this waveform allows for the direct, real-time, simultaneous detection of serotonin and histamine, thus providing a tool to study the interaction of these crucial neurochemical systems, how they work together in modulating physiological function, and how they are impacted by a range of pharmacological agents and environmental toxins.

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Aryl hydrocarbon receptor (AHR) signaling mediates Tetrabromobisphenol A (TBBPA) induced cartilage developmental toxicity in zebrafish

Kanchaka Senarath Pathirajage, Sunil Sharma, Tyler Johnson, Arnob Sarker, Subham Dasgupta

Clemson University, Clemson, SC

Research Background: Tetrabromobisphenol A (TBBPA) is extensively used in commercial products such as synthetic textiles, plastic paints, and electronic devices to reduce flammability, but can be potentially toxic from indoor exposures. Our prior work using zebrafish as a model shows that at environmentally low-level exposures, TBBPA disrupts development of head cartilage- crucial for vital body functions such as feeding and respiration. Using mRNA-seq and whole-mount immunohistochemistry (IHC), we also show that TBBPA significantly induces aryl hydrocarbon receptor (AHR) signaling pathway and increase of CYP1A protein, a canonical biomarker of AHR activation respectively. Within this study, we hypothesize that TBBPA-induced developmental cartilage toxicity is driven by AHR activation.

Purpose: Leveraging zebrafish embryos, we study the mechanistic role of AHR signaling in driving TBBPA-induced head cartilage developmental disruptions.

Methods: At 6 hours post fertilization (hpf), embryos were exposed to TBBPA (0 or 5 μ M), followed by phenotyping, tissue uptake quantification by LC-MS and mRNA sequencing at 24 hpf (N=3, each replicate has 10 embryos). Based on the hypothesis, we utilized a reverse genetic approach to study the role of AHR in TBBPA induced cartilage developmental disruption. Embryos were microinjected with an AHR translation-blocking morpholino to knock down AHR protein and exposed to 0 or 0.5 μ M TBBPA from 6 to 120 hpf. Following this, Alcian Blue assay was conducted to measure head cartilage development at 120 hpf. In addition, whole-mount IHC was performed in AHR morphants to assess CYP1A protein levels, together with stem cell markers such as SOX2 (modulator of neural crest cells (NCC)), cadherins, and precursor proteins associated with cartilage development trajectory such as SOX10 (marker for NCC). To investigate the interaction between AHR and TBBPA, in silico molecular docking analysis was performed between AHR and TBBPA, along with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)- a known AHR agonist. For co-exposure experiments a 2-way ANOVA, followed by Sidak's test, was used to determine the statistically significant differences ($p < 0.05$).

Results: Our LC-MS data showed that tissue uptake at 5 μ M is 62 ± 41 ng/g that aligns with environmentally detected levels in serum and cord plasma. Analysis of mRNA revealed significant enrichment of xenobiotic metabolism by cytochrome P450 pathways, along with disruption of biological processes involved in early cell-fate specification and NCC migration which are vital for cartilage development. Specifically, we saw a strong upregulation of AHR signaling genes, including *cyp1a* ($\log_2$ fold change = +6.16), *cyp1c1*(+3.74) and *ahr2* (+0.70). In addition, significant changes were observed in genes associated with cartilage development (*mmp9*, +3.09; *sox12*, -0.86). TBBPA exposures showed a concentration-dependent increase in CYP1A protein and molecular docking studies revealed comparable binding between TBBPA and TCDD (a known AHR ligand) to ligand binding domain of AHR protein. AHR knockdown revealed that a partial rescue of TBBPA-induced increase of CYP1A protein expression. In addition, AHR knockdown partially rescued the expression of key stem cell and cell-adhesion markers, including SOX2, SOX10, and cadherins, suggesting that aberrant AHR activation disrupts the proteins and molecular programs required for normal craniofacial cartilage development trajectory. Finally, Alcian Blue staining showed that AHR morphants significantly rescued TBBPA-induced cartilage developmental parameters.

Conclusion: This study demonstrates that TBBPA disrupts cartilage development through AHR dependent signaling and provides a foundation for an adverse outcome pathway (AOP) linking molecular initiating events

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such as AHR activation to tissue-level dysfunction such as cartilage developmental defects. Given the evolutionary conservation of AHR signaling and key pathways regulating the craniofacial development across vertebrates, these findings raise important concerns about the potential developmental health risks of TBBPA exposure in humans, particularly during sensitive windows of embryonic development. Future studies will study the role of AHR in cartilage developmental disruption in long term TBBPA exposures.

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Shared Lives, Shared Hazards: Exposure to PFAS, Arboviruses, and Psychosocial Stress in Dog-Owner Dyads Across Housing Status

Kaylinn Escoboar, Caroline J Waddell, Roselyn Delase Davour, Emma A. VanderMeulen, Sarah Wingfield, Tracie R. Baker*, Jennifer Applebaum* *Co-senior authors

University of Florida, Gainesville, FL; St. Francis Veterinary Care, Gainesville, FL

Introduction: Environmental toxicants (i.e., PFAS), infectious agents (i.e., arboviruses), and psychosocial conditions (i.e., psychosocial stress), together referred to as “multiple stressors,” co-occur in communities across the United States (U.S.) yet are typically studied in isolation. There are limited scalable methods to capture multiple stressors at the individual level across housing environments. Most U.S. households own pets, and dogs have been proposed as sentinels of these individual stressors. Using a One Health approach, we investigated whether dog-owner dyads share environmental conditions and behaviors indicative of potential exposure to multiple stressors in both housed and unhoused populations.

Methods: We conducted a cross-sectional pilot survey of 30 adults and their pet dogs (18 housed, 12 unhoused) recruited at community veterinary events in Florida. Structured surveys captured PFAS-related exposures (proximity to contamination sources, occupation, diet, tap water consumption, consumer product use), arbovirus-related risk (outdoor time, repellent use, sleeping location), shared-environment factors (co-sleeping, shared water), and perceived stress. We used chi-square and t-tests to compare exposures by housing status.

Results: Dog-owner dyads had a high frequency of co-sleeping and shared drinking water sources (90%), regardless of housing status. Unhoused participants reported higher frequency of environmental conditions indicative of potential exposure, including more often spending >4 hours outside daily (58% vs. 11%; $p=0.006$), living near historical PFAS point sources like airports, industrial sites, agriculture, and military bases (83% vs. 28%; $p=0.003$), and higher perceived stress (M score=24 vs. 17; $p=0.023$). Despite greater time spent outdoors, most unhoused participants (58%) rarely or never used mosquito repellent.

Implications: Human-dog dyads inhabit shared environments carrying co-occurring, unequally distributed exposures that single-stressor studies may fail to capture. Our findings support pet dogs as plausible sentinels of cumulative environmental mixture exposure and offer an equity-centered pathway to include hard-to-reach communities in environmental health surveillance. Future work should measure these hazards in human-dog dyads to validate pet dogs as individual-level sentinels.

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Dysregulation of preimplantation uterine fluid movement as a mechanism of RU486 as a contraceptive

Kristofer Ashton Meier, Taylor Elijah Martin, Honglu Diao, Shuo Xiao, and Xiaoqin Ye

University of Georgia, Athens, GA

Progesterone (P4) signaling via the progesterone receptor (PR) is essential for implantation and early pregnancy in all mammals studied. RU486/Mifepristone is a mixed PR antagonist/agonist that has been used as an abortifacient and an emergency contraceptive. One RU486 pill contains 200 mg (4~2 mg/kg with body weight of 50~100 kg) and up to 800 mg RU486 was used in clinical studies. Our dose-response and time-course studies in mice revealed blockage of embryo implantation (initiating ~day 4.0 post-coitum (D4.0)) by a single dose of 200 µg RU486 (8 mg/kg) given on D2@9h ~ D3@18h, accompanied by excessive uterine fluid retention. Although uterine fluid has not been systemically studied in infertile women, uterine fluid retention at the time of embryo transfer correlates with failed embryo implantation in patients undergoing in vitro fertilization with embryo transfer (IVF-ET). In addition, fluid retention is a “side effect” of hormonal contraceptives. A causal effect was observed in mice that preimplantation intraluminal injection of non-toxic fluid (0.9% saline) impaired embryo implantation. These studies show the adverse effect of uterine fluid retention on embryo implantation. Since uterine fluid moves through the uterine epithelium and RU486 has the strongest binding affinity with PR to exert its effects, we employ *epiPR*^{-/-} (*Pgr*^{fl/-} *Wnt7a*^{Cre/+}) mouse model with PR deficiency in the uterine epithelium. *Pgr*^{fl/-} control and *epiPR*^{-/-} mice were treated with oil (vehicle) or 200 µg RU486 at both D1@11h and D2@11h. At D3@11h they were intraluminally injected with Alexa Fluor 488 hydrazide (AH) for 5 minutes to trace uterine fluid absorption before dissection. RU486 treatment induced uterine fluid retention. Limited data indicate that uterine fluid absorption (revealed by AH injection) in the uterine luminal epithelium (LE) does not show statistical difference between oil and RU486-treated groups. Since uterine fluid volume is the net result of fluid absorption and secretion, and Cl⁻ is the dominant anion in the uterine fluid and secretion of Cl⁻ will increase fluid secretion following the osmotic gradient, we employ immunohistochemistry to detect cystic fibrosis transmembrane conductance regulator (CFTR) and calcium-activated chloride channel accessory 1 (CLCA1), which play roles in Cl⁻ secretion. RU486 treatment increases CFTR and CLCA1 expression in the apical membrane of uterine epithelial cells, implicating possible enhanced fluid secretion that contributes to uterine fluid accumulation. Realtime PCR of RU486-treated samples shows upward trends in the expression of *Trpv6* (a theoretically mechanosensory ion channel), which may indicate enhanced intrauterine hydrostatic pressure, as well as *Cftr* and *Clca1*, further evidencing the hypothesis of enhanced Cl⁻ secretion. Preliminary data suggests the antagonistic effects of RU486 on PR are recapitulated in *epiPR*^{-/-} mice.

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Behavioral and organismal adverse effects of individual and multiple mycotoxin exposures in *Caenorhabditis elegans*

Lifan Yang, Jiasheng Wang

University of Georgia, Athens, GA

Mycotoxins are secondary metabolites of toxigenic fungi that commonly occur in cereal grains and groundnuts during their production and storage. Previous studies have focused primarily on individual mycotoxins and their adverse effects on numerous toxic endpoints, including genotoxicity, carcinogenicity, immunotoxicity, and reproductive toxicity; however, less attention has been given to the effects of their exposure on locomotor and neurobehavioral outcomes. In this study, we evaluated four major foodborne mycotoxins, aflatoxin B1 (AFB1), fumonisin B1 (FB1), deoxynivalenol (DON), and zearalenone (ZEA) commonly found in U.S. staple foods and feeds for their impact on locomotor and neurobehavioral activities using a model organism, *Caenorhabditis elegans* (*C. elegans*). Age-synchronized wild-type N2 worms were exposed to individual mycotoxins and their defined mixture formulations for 72 h. Six behavioral endpoints were evaluated, in which center point speed (CPS), track length (TL), and cumulative reversal time (CRT) represent locomotor behavior, and number of pirouettes (NP), turn count (TC), and absolute peristaltic speed (APS) represent neurobehavioral function. Complementary organismal endpoints including growth and reproduction outcomes were also accessed. Exposure to individual mycotoxins produced distinct concentration and endpoint specific profiles. FB1 at 200 μ M reduced TL and APS to 15.6% and 15.1% of control rates, respectively, whereas the same concentration reduced brood size to 8.2% of the control rate ($p < 0.001$). Exposure to various mycotoxin mixtures altered locomotor and neurobehavioral outcomes. At the medium exposure level, AFB1 + FB1 (12.5 μ M AFB1 and 125 μ M FB1) reduced TL, NP, and TC to 16.1%, 32.8%, and 28.0% of controls, respectively ($p < 0.05$), whereas FB1 + DON + ZEA (93.75 μ M FB1, 125 μ M DON, and 31.25 μ M ZEA) reduced TL and APS to 21.8% and 18.3% of controls, respectively ($p < 0.01$). Brood size was the most consistently responsive organismal endpoint, and DON + ZEA (125 μ M DON and 31.25 μ M ZEA) produced significantly greater reproductive suppression than predicted by Bliss independence ($p < 0.01$). Exposure to AFB1 with other three mycotoxin mixtures further reduced growth, reproduction, and APS. Principal component analysis captured 75.0% of behavioral variation in the first two components, reflecting shared endpoint variation and a CRT/NP-versus-APS/TL contrast, and distinguished formulation-specific profiles and concentration-related trajectories. These findings demonstrated that locomotor and neurobehavioral outcomes can serve as sensitive functional measures for characterizing the adverse effects of exposure to individual mycotoxins and their mixtures.

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Association of Nanoparticle Physicochemical Properties with Systemic Clearance and Half-Life

Lishuang Wang, Xinyue Chen, Zhoumeng Lin

University of Florida, Gainesville, FL

Background: Nanoparticles (NPs) have been applied clinically as novel drug delivery platforms to improve treatment benefits. The pharmacokinetic (PK) parameters of systemic clearance (CL_{sys}) and terminal half-life (t_{1/2}) of nanoparticles characterize their biodistribution and tissue exposure, thereby affecting therapeutic outcomes. However, how NP physicochemical properties should be optimally designed to achieve desirable CL_{sys} and t_{1/2} remains unclear. To investigate these relationships, this study used the Nano-Tumor Database, a curated literature database developed by Cheng et al. and subsequently expanded by Chen et al. through a systematic literature review to include experimental time-dependent tumor, blood/plasma, major-organ biodistribution, and NP physicochemical data from tumor-bearing mouse studies (Chen et al. 2023; Cheng et al. 2020). This study aimed to collect and standardize data from the Nano-Tumor Database, derive CL_{sys} and t_{1/2} from blood/plasma concentration–time data, develop predictive models linking NP physicochemical properties to these PK parameters, and identify property profiles associated with desirable systemic PK to guide rational NP design.

Methods: After data cleaning and standardization in Google Colab, 333 of 535 datasets from the Nano-Tumor Database were included for further non-compartmental analysis (NCA), while 202 datasets were excluded due to a lack of reported plasma concentration–time profile, or administered doses could not be normalized. NCA was performed in Phoenix WinNonlin™ using plasma/serum %ID/g as the concentration, the reported administered dose of the NP as the input, and linear trapezoidal integration with linear interpolation. Systemic clearance was calculated from dose and AUC, and terminal half-life from the terminal elimination slope (λ_z). As an initial exploratory analysis, associations of NP physicochemical properties with systemic clearance and terminal half-life were assessed using Spearman's rank correlation for continuous variables (e.g., particle size, zeta potential, and PDI) and rank eta-squared (η^2) for categorical variables (particle type, shape, etc.).

Results: In the collected datasets, for NPs material, organic NPs accounted for 73.4%, polymeric materials 44.6%, passive targeting 66.6%, negatively charged particles 68.2%, and spherical particles 87.9%. Both CL and terminal half-life showed substantial inter-dataset variability. Most individual physicochemical properties showed relatively weak associations with PK parameters. Hydrodynamic size was positively correlated with CL ($\rho = 0.20$) and negatively correlated with terminal half-life ($\rho = -0.12$), while zeta potential was negatively correlated with CL ($\rho = -0.18$). TEM-measured particle size showed a weak positive correlation with CL ($\rho = 0.17$). Among categorical factors, material subtype showed the strongest association with both terminal half-life (rank $\eta^2 = 0.138$) and CL (rank $\eta^2 = 0.100$), whereas particle type, targeting strategy, surface charge, and shape showed smaller associations.

Conclusions: The observed variability in CL and terminal half-life, together with the generally modest effects of individual physicochemical properties, suggests that NP systemic disposition is determined by combinations of formulation characteristics rather than by a single property. Future work will develop and validate machine learning models to predict systemic clearance and terminal half-life from NP properties and identify property combinations that may guide the design of NPs with desired PK profiles.

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Comparative Safety Assessment of Traditional and Commercial Kratom Products Using a Novel Integrated PK-PD Approach

Manoj Gundeti, Siva Rama Raju Kanumuri, Sarvesh K. Verma, Sushobhan Mukhopadhyay, Christopher R. McCurdy, Abhisheak Sharma

University of Florida, Gainesville, FL

Background and Purpose: Kratom (*Mitragyna speciosa*) is increasingly used for self-management of pain, mood symptoms, and opioid withdrawal, yet the rapid expansion of commercial kratom products has outpaced systematic evaluation of their pharmacology and safety. Variability in alkaloid composition and product potency, together with the absence of standardized dosing, complicates interpretation of exposure-related risk. Conventional studies further provide limited information on the relationship between systemic alkaloid exposure and physiological response. To address this gap, we applied an integrated preclinical approach that combined automated blood sampling with continuous telemetry to compare a conventional leaf based, lyophilized kratom tea (LKT) and a commercially available organic extract-based product, MIT45, within the same experimental framework.

Methods: Female Sprague Dawley rats (n = 4, per group) received single oral doses of LKT (20 mg/kg, mitragynine equivalent) or MIT45 (40 mg/kg, mitragynine equivalent). The BASi Culex automated blood sampling system enabled serial plasma collection over 48 h, while implanted DSI telemetry continuously monitored electroencephalographic activity, heart rate, systolic and diastolic blood pressure, locomotor activity, and body temperature. Plasma concentrations of mitragynine and its major metabolites, including 7-hydroxymitragynine, 9-hydroxycorynantheidine, and mitragynine acid, together with other kratom alkaloids such as speciociliatine, corynantheidine, mitraciliatine, and isopaynantheine, were determined by a validated LC-MS/MS method.

Results: The products showed distinct physiological response patterns. LKT produced more sustained decreases in heart rate, systolic blood pressure, and mean blood pressure, whereas MIT45 produced greater increases in electroencephalographic (EEG) delta activity. EEG beta activity varied over time without a consistent sustained direction, and body temperature remained relatively stable, with only small transient deviations from baseline.

Conclusions: Overall, at the administered doses, LKT showed a greater cardiovascular response, whereas MIT45 showed a more pronounced neurophysiological response characterized by increased EEG delta activity, while thermoregulation remained largely unchanged.

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Carbon Black Exposure induces Macrophage Dysfunction and alters CHI3L1, ATF2 and MFGE8 expressions associated with Pulmonary Fibrosis

Naga Venkata Sai Ayyappa Kota, Dhruthi Reddy Mutyala, Mya Mckiney, Jaroslaw Zmijewski, Surolia Ranu

University of Alabama at Birmingham, AL

Background: Carbon black (nCB) exposure is associated with persistent pulmonary inflammation and fibrotic responses. Macrophages help resolve inflammation by engulfing apoptotic cells, a process called efferocytosis. Whether nCB disrupts this function, and how proteins associated with inflammation and apoptotic-cell clearance respond to exposure, remain unclear.

Methods: RAW 264.7 murine macrophages were exposed to nCB either acutely for 24 hours or episodically, with two 5 µg/mL treatments over seven days. Whole-cell lysates were collected for Western blot analysis of CHI3L1/YKL-40, ATF2, and MFGE8. Macrophage efferocytosis was assessed after acute exposure. In parallel, C57BL/6J mice were exposed to nCB for one or eight weeks. Lung tissue was collected for Western blot and densitometric analyses, and lung collagen content was assessed by hydroxyproline assay. Lung-function testing using FlexiVent was performed in the eight-week exposure group.

Results: Compared with controls, nCB exposure increased CHI3L1 expression, decreased ATF2 and MFGE8 expression, and reduced macrophage efferocytosis. In vivo, lung function was reduced in the eight-week nCB-exposed group, and the hydroxyproline assay (HPA) showed increased lung collagen content, consistent with increased collagen deposition. Together, these findings associate nCB exposure with impaired apoptotic-cell clearance, mitochondrial dysfunction, and a fibrotic lung response.

Conclusions: nCB exposure was associated with increased CHI3L1 expression, reduced ATF2 and MFGE8 expression, impaired macrophage efferocytosis, mitochondrial dysfunction, and increased lung collagen content. These findings suggest that defective apoptotic-cell clearance may contribute to persistent pulmonary inflammation and fibrotic responses. Future studies should determine how macrophage phenotypes differ between acute and episodic or prolonged nCB exposure, and whether the CHI3L1–ATF2–MFGE8 pathway causally contributes to those changes.

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Development of a Physiologically Based Pharmacokinetic Model for Taletrectinib in Dogs and Humans

Pei-Yu Wu, Lishuang Wang, Zhoumeng Lin

University of Florida, Gainesville, FL

Taletrectinib is a next-generation ROS1 and NTRK inhibitor that has demonstrated clinical activity in patients with ROS1-positive non-small cell lung cancer. This study aimed to develop and validate physiologically based pharmacokinetic (PBPK) models of taletrectinib in dogs and humans to support translational and clinical pharmacology applications. PBPK models were developed in GastroPlus® using a middle-out approach. The dog model was first developed using intravenous pharmacokinetic data to characterize systemic disposition and was subsequently calibrated for oral absorption using oral pharmacokinetic data. The human model was developed using a single 400-mg dose under fasted conditions and validated and evaluated against a 400-mg fed dataset and independent steady-state datasets following once-daily administration of 400, 600, and 800 mg. Simulated concentration-time profiles were consistent with the observed data across species and dosing conditions. All available simulated-to-observed ratios for area under the curve (AUC) and maximum plasma concentration (C_{max}) were within the 0.5- to 2-fold range. Regression analyses further demonstrated agreement between simulated and observed concentrations, with R² values of 0.882 and 0.947 for the dog intravenous and oral datasets, respectively, and values ranging from 0.829 to 0.963 across the human datasets. These results indicate that the developed PBPK models adequately characterized the pharmacokinetics of taletrectinib across the evaluated preclinical and clinical datasets. To our knowledge, this is the first reported PBPK model of taletrectinib and provides a basis for future model-informed evaluation and optimization of taletrectinib in clinical pharmacology applications..

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PFAS Contamination in Food and Drinking Water: A Multi-Level Policy Analysis and Review of Regulatory Instruments, Thresholds, and Equity Considerations

Roselyn Delase Davour, Jonathan Muniz, Logan Hibshman, Victoria Fernandez, Divya Puthanveetil, Raegan Weems, Gabriel Costa, Candela Jimenez Lopez, Jose F. Colon-Burgos

University of Florida, Gainesville, FL

Background: Per- and polyfluoroalkyl substances (PFAS) are persistent environmental contaminants linked to several adverse health outcomes. Food and drinking water are the leading sources of human exposure, and PFAS have been widely detected in food supply/packaging and drinking water in the United States. This scoping review examined federal, state, and local policy instruments addressing PFAS contamination in food and water in the United States. Additionally, we conducted a multi-level policy analysis to map geographic and jurisdictional disparities in protection.

Methods: We hand-searched Google Scholar and federal, state, and local agency websites, then systematically searched five databases (PubMed, Scopus, Embase, PAIS, and the Congressional Research Service) between February and June 2026. Queries combined terms for PFAS, policy, food, and water. We included policy instruments and articles addressing PFAS regulation of drinking water or food. Screening was conducted in Covidence and analysis in R (v4.5.1).

Results: We identified a total of 105 policy instruments (2002-present) and 19 peer-reviewed articles. Most instruments (84%) were enacted after 2020, reflecting decades of delayed regulatory action. State-level instruments were predominant (67%) followed by 17% federal (17%) and local (16%). California and Massachusetts accounted for 31% of state/local action. Fourteen states, mostly in the U.S. South, had no policy instruments, potentially leaving residents with limited protection from oral PFAS exposure despite increased detection in local drinking water and food. No federal PFAS standards exist for private wells or bottled water, and no enforceable federal instruments address agricultural supply, as food-related PFAS policies only addressed packaging/monitoring.

Conclusions: Findings underscore the need for comprehensive federal policies and community-engaged policy advocacy to ensure equitable protection from oral PFAS exposure. Future directions for policymaking include standards to regulate private drinking water wells and contamination in the agricultural supply..

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Unveiling the impacts of polyester microfibers on the gut-brain axis in a marine species, the pinfish (*Lagodon rhomboides*)

Sheridan M. Wilkinsons, Gil Nadler, Sarafina Mowea, Tiange Changa, Iske Larkinb, Christopher Vulpea, Christopher J. Martyniuka

University of Florida, Gainesville, FL

Plastic, particularly microplastic, pollution is an emerging threat to marine ecosystems, with surveys of aquatic marine debris consistently identifying microfibers as the most ubiquitous microplastic shape both in the environment and ingested by wild marine organisms. Despite the prevalence of microfibers, ecotoxicological research remains heavily biased toward smooth, spherical polystyrene or polyethylene microbeads, leaving a distinct knowledge gap regarding the physiological impacts of more environmentally relevant irregular, weathered fibers. Furthermore, while independent studies show that microplastics can cause gut dysbiosis, neural toxicity, and immune suppression separately, a comprehensive mechanistic framework linking these multi-system pathologies remains largely undefined. This research addresses these critical gaps by investigating the impacts of environmentally relevant polyester microfiber consumption on the gut-brain-microbiota axis in the pinfish (*Lagodon rhomboides*). The central hypothesis is that dietary microfiber exposure drives significant gut dysbiosis, compromising intestinal epithelial barrier integrity—producing "leaky gut"—and precipitating systemic neuroinflammation. An in vivo 45-day dietary exposure using juvenile pinfish will determine the foundational pathway mechanisms under controlled environmentally relevant (10 particles/day) and high (100 particles/day) dosages of angular polyester microfibers. Methodologically, this research integrates high-resolution multi-omics and advanced analytical chemistry. Changes in cross-kingdom gut microbial diversity (bacteria, fungi, viruses, and archaea) will be resolved via 16S rRNA sequencing and shotgun metagenomics. Neuroendocrine transmitter concentrations and brain lipidomic remodeling will be mapped using targeted UHPLC-MRM-MS/MS and high-resolution Orbitrap mass spectrometry, respectively. This research will address two critical knowledge gaps by testing our hypotheses with environmentally relevant microfibers at environmentally relevant concentrations, a facet that is lacking in current microplastic toxicity research, and moving beyond basic ingestion metrics to instead evaluate the systemic physiological consequences of, not only microplastic consumption, but environmentally relevant consumption.

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Leveraging Zebrafish as a Model to Screen Environmentally Relevant PFAS Mixtures Emulated from 11 South Carolina Military Sites

Syed Rubaiyat Ferdous, Md. Sameul Islam, Subham Dasgupta

Clemson University, Clemson, SC

Background & Purpose: Per- and polyfluoroalkyl substances (PFAS) are persistent environmental contaminants that commonly occur as complex mixtures rather than as individual compounds. However, much of PFAS toxicology has focused on single compounds, which may not adequately represent real-world exposures. PFAS-containing firefighting foams (AFFF) have contributed to high PFAS contamination at several military sites in South Carolina. The state also contains multiple locations with distinct PFAS contamination profiles, providing an opportunity to evaluate the toxicity of environmentally representative PFAS mixtures. This study aimed to evaluate the developmental toxicity of site-emulated PFAS mixtures in zebrafish using complementary molecular and behavioral endpoints.

Methods: Eleven South Carolina military sites were selected using PFAS occurrence data reported in the Environmental Working Group (EWG) PFAS contamination map. Site-specific PFAS mixtures were formulated in our lab according to the reported concentrations and composition of detected PFAS in groundwater at each location. The reported environmental concentrations were designated as 1x, with additional exposures conducted at 10x and 100x concentrations, representing uncertainly factors for risk assessment. Zebrafish embryos were exposed to site-emulated PFAS mixtures from 24 to 48 hpf or 120 hpf (hours post-fertilization). Following exposure, toxicity was assessed using multiple endpoints, including reactive oxygen species (ROS) using H2DCFDA stain, apoptosis using Acridine orange stain, DNA damage using γH2AX immunohistochemistry, lipid accumulation using Nile Red staining, metabolic activity using Alamar Blue reduction, and behavior using larval photomotor response (LPR).

Results: Across the 11 site-emulated PFAS mixtures, significant molecular and behavioral responses were observed, with the magnitude and pattern of effects varying among mixtures and exposure concentrations. At 1x concentrations, akin to site levels, 4 of 11 mixtures altered ROS, 5 of 11 altered apoptosis, 4 of 11 altered γH2AX levels, and one mixture altered LPR. At their strongest, different sites induced up to 74% increase in ROS, 100% increase in apoptosis, 96% increase in DNA damage relative to vehicle controls. PFAS mixture exposure also increased Alamar Blue reduction and perturbed lipid accumulation, with the most pronounced effects observed at 10x concentrations. Amongst the sites, Parris Island MCRD site appeared to exhibit the greatest overall toxicity, with approximately 35% and 45% increases in ROS and DNA damage, respectively, a 50% decrease in apoptosis, a 58% reduction in neutral lipid accumulation, and a 188% increase in membrane lipid levels. Interestingly, there was no congruence between PFAS concentrations and toxicity, with low concentration sites (such as Beaufort MCAS) often eliciting higher toxicity.

Conclusion: Our findings show that PFAS mixtures representing South Carolina contamination profiles can induce significant metabolic, redox and genotoxic effects at 1x environmentally reported concentrations, highlighting the biological relevance of real-world PFAS mixtures. Since ROS and DNA damage can be associated with cancer-related processes and metabolic disruptions are associated with obesogenic and metabolic syndromes, this screening approach can help prioritize PFAS mixtures for further human-health risk evaluation in South Carolina.

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Delayed effects of Gulf War Illness: sex-specific neurochemical alterations across brain regions reflects accelerated aging within two pre-clinical mouse models

Trevor Kalinowski, Brice Hudson, Fabian Tejedor-Rojas, Jessica Carpenter, John Wagner, Donald Harn, Thomas Norberg, Nikolay Filipov

University of Georgia, Athens, GA; Uppsala University, Uppsala, Sweden

Background and Purpose: During the 1990-1991 Persian Gulf War, United States soldiers were exposed to toxicants such as: pyridostigmine bromide (PB), permethrin (PM) N,N-Diethyl-meta-toluamide (DEET), and sarin. After, 25-30% of the deployed soldiers, including female ones developed Gulf War Illness (GWI), a chronic, multi-symptom illness, with symptoms including memory, mood, and cognitive deficits potentially linked to neurochemical dysregulation. GWI varies in symptom severity, is associated with types of exposures and higher proportions of GWI diagnosis is reported female veterans. Mechanistically, findings are limited, with sex differences in cognitive and mood deficits being unexplored at a neurochemical level in long-term preclinical GWI models. To address this and account for female veterans with GWI, sex-specific neurotransmitter homeostasis was investigated using high-performance liquid chromatography electrochemical detection (HPLC-ECD) and western blot of synaptic proteins in two preclinical GWI models.

Methods: Adult male and female C57BL/6J mice were exposed to Gulf War chemicals; The first model (PB/PM) exposed mice to 0.7mg/kg PB and 200mg/kg PM or vehicle DMSO for 10 days, via daily intraperitoneal injections. The second model (PB/DEET/CORT/DFP) exposed mice to daily subcutaneous injections of 2 and 30 mg/kg of PB and DEET respectively, for 14 days. On days 8-14, mice were also administered corticosterone (CORT) via drinking water (200 mg/L in 1.5% EtOH/H₂O) *ad libitum*. On day 15 mice underwent a single injection of 3.75 mg/kg of the sarin surrogate: diisopropyl-fluorophosphate (DFP). After 9 months mice were euthanized. Brain region-specific samples were collected in six regions: prefrontal cortex (PFC), striatum (STR), dorsal hippocampus (DHIP), ventral hippocampus (VHIP), lateral septum (LS) and brainstem (BS). Brain monoamines and amino acid neurotransmitters and their metabolites were analyzed with HPLC-ECD. Dopamine (DA) and synaptic function-related proteins were analyzed via western blot probing for tyrosine hydroxylase (TH), synaptophysin (SYP), and PSD-95 in the PFC, STR, and VHIP.

Results: Global effects, model-specific, and/or sex-specific neurochemical effects of GWI were observed. GWI modulation of DA and or its metabolites was evident in both sexes and models in VHIP. DHIP gamma-aminobutyric acid (GABA) was decreased in males, while PFC serotonin (5-HT) and glutamate (GLU) increased independent of GWI model. PB/DEET/CORT/DFP -specific noradrenergic and serotonergic dysregulation was observed. Specifically, decreased 5-hydroxyindoleacetic acid (5-HIAA) and increased norepinephrine (NE) in the BS. PB/PM model specifically, decreased 5-HT and or 5-HIAA in the VHIP and STR. PB/DEET/CORT/DFP-specific DHIP DA dysregulation was sexually dimorphic increasing and decreasing in females and males, respectively. Synaptic protein dysregulation was region-specific within GWI model, where PB/PM decreased PFC SYP and PSD-95 overall, and PB/DEET/CORT/DFP decreased both synaptic proteins in the VHIP of male mice. Dopamine synthesis rate-limiting enzyme TH was decreased notably in the STR of male mice of the PB/DEET/CORT/DFP model.

Conclusions: Long-term after GWI-related exposures neurochemical dysregulation in a sex- and exposure-specific manner across multiple brain regions was observed. Notably, elevated GLU in the PFC underscores male-biased excitotoxicity. The hippocampal decline in GABA post PB/PM exposure and shifts in 5-HT turnover are likely associated with the hippocampal atrophy and mild cognitive impairment reported in previous studies. PB/DEET/CORT/DFP-mediated dopaminergic depletion in the STR and VHIP, combined with BS 5-HT deficits and NE hyperactivity underscore the more severe pathology of associated with GWI-related chronic stress and/or nerve gas exposures in both sexes. Additionally, the cortical neurochemical

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deficits, i.e., elevated 5-HT in the PB/DEET/CORT/DFP mice are male-biased, suggesting that male veterans under such exposure scenarios are affected more broadly, at least neurologically. Collectively, the combination of region-specific neurotransmitter and protein dysregulation with respect to model and sex, mechanistically ties with symptoms of memory deficits, mood disorders, and early cognitive decline reported veterans with GWI. Targeting restoration of neurotransmitter dysfunction might be a viable therapeutic option.

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A Coupled Mechanistic and Machine Learning Physiologically Based Pharmacokinetic Framework for Predicting Nanoparticle Drug Release Kinetics in Tumors

Xinyue Chen, Qiran Chen, Zhoumeng Lin

University of Florida, Gainesville, FL

Background and Purpose: Nanoparticle (NP) drug delivery systems show highly variable tumor exposure across formulations. Characterizing this variability currently requires extensive animal testing. A physiologically based pharmacokinetic (PBPK) framework coupled with machine learning (ML) could instead predict tumor drug exposure directly from formulation properties. We extended a validated NP-tumor disposition PBPK model by adding a mechanistic drug-release layer. We then paired it with artificial intelligence (AI)-quantitative structure-activity relationship (QSAR) models to predict the new release parameters from formulation descriptors.

Methods: We curated a database of 211 NP-drug formulations. It comprises 936 paired biodistribution measurements reporting both NP and drug tumor percent injected dose (%ID) over time. Six NP disposition parameters were carried over as fixed inputs from a previously validated foundational PBPK model. A hierarchical empirical-Bayes procedure then fit three new drug-release parameters against observed tumor drug %ID. These parameters were loaded-drug fraction (f_{load}), release rate (k), and tumor clearance rate (k_{out}), fit using a coupled ordinary-differential-equation PBPK model. Fitted parameters were used to train multiple machine-learning regression algorithms. Models were compared with and without additional carrier-polymer repeat-unit descriptors and evaluated by stratified group k-fold cross-validation.

Results: Results reflect a preliminary analysis of 105 of the 211 curated formulations. Within this set, adding carrier-polymer repeat-unit descriptors improved predictive performance in a target-specific way. For tumor clearance rate, descriptors consistently improved performance across all algorithms tested. Random forest performed best, reaching an R-squared of 0.80 in a high- and moderate-confidence subset ($n=24$) and 0.50 in the full subset ($n=58$). For loaded-drug fraction, random forest reached a modest R-squared of 0.38 across the full 105-profile subset. For release rate, descriptors provided essentially no improvement over the no-descriptor baseline. This result indicates that currently included formulation descriptors carry little predictive information for release rate specifically.

Conclusions: A three-parameter drug-release layer, built on a validated NP disposition backbone, captures meaningful cross-formulation variance in tumor clearance rate. This improvement depended on carrier-polymer repeat-unit descriptors, which currently cover only a subset of formulations. Release rate prediction remained limited regardless of algorithm choice or descriptor set. This suggests that the descriptors tested here do not yet explain this parameter. Extending carrier-polymer descriptor coverage to the remaining PEGylated and copolymer formulations might help close this gap.

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Redevelopment of a physiologically based pharmacokinetic model for meloxicam in laying hens

Zhicheng Zhang, Melissa A Mercer, Lisa A Tell, Jennifer L. Davis, Zhoumeng Lin

University of Florida, Gainesville, FL; University of California, Davis, CA; Virginia Tech, Blacksburg, VA

Background and Purpose: Meloxicam, a nonsteroidal anti-inflammatory drug, is used extra-label in backyard and commercial laying hens. The Animal Medicinal Drug Use Clarification Act permits such use only when a scientifically supported withdrawal interval (WDI) is observed for edible tissues and eggs, but no tolerance has been established for meloxicam in poultry. Physiologically based pharmacokinetic (PBPK) modeling is the tool of choice for deriving these intervals, but a previously published laying-hen meloxicam PBPK model-predicted WDIs were substantially longer than those observed in the underlying residue depletion studies using the traditional tolerance limit method. The purpose of this work was to rebuild the PBPK model from the primary residue data, evaluate, and determine why the earlier predictions diverged.

Methods: A residue dataset was assembled from five controlled studies in laying hens comprising a single intravenous dose and repeated oral regimens of 1 mg/kg every 24 hours for 8 days and every 12 hours for 10 days. A flow-limited PBPK model was constructed with explicit ovary and oviduct compartments and an egg-formation module describing sigmoidal yolk growth and a timed albumen deposition window. Parameters were selected by normalized sensitivity coefficient screening and estimated by a staged least-squares procedure on log10 residuals, fitting systemic parameters to plasma, tissue partition coefficients one matrix at a time, and egg transfer constants last. Studies were split by regimen: the intravenous study and the every-24-hour studies were used for calibration, and the every-12-hour studies, the regimen for which the long published intervals were reported, were held out entirely for evaluation. Reproducibility was confirmed from two independent starting vectors.

Results: Calibration R^2 was 0.82 and evaluation R^2 was 0.82 on the log10 scale; four calibration observations irreconcilable with plasma measured in the same birds were excluded from the objective under a pre-specified rule and reported separately. Estimated plasma clearance (0.038 L/h/kg) and steady-state volume of distribution (0.19 L/kg) agreed with non-compartmental values from the intravenous study (0.042 L/h/kg and 0.18 L/kg). Predicted WDIs to the limit of quantitation after 1 mg/kg orally every 12 hours for 10 days were 1.3 days for liver and kidney, 1.0 days for breast muscle, 0.5 days for fat, and 4.7 days for whole egg, with yolk (6.0 days) rather than albumen (1.2 days) limiting. These intervals are consistent with the last quantifiable samples in those studies, 1.5 days for liver and kidney, and 4.5 days for whole egg, although yolk residues persisted to 9.5 days, indicating that the egg interval is the least certain. The difference between the previous PBPK model and the current one stems from two issues in the earlier calibration. First, without intravenous data, the model could not distinguish between bioavailability and clearance; underestimating one forced an underestimation of the other, artificially inflating all intervals. Second, the unweighted least-squares method allowed a few barely detectable observations to disproportionately skew the tissue partition coefficients. To resolve the first issue, we fixed bioavailability at 100% (unity), a decision supported by an intravenous-to-oral AUC ratio of 1.18 (95% CI: 0.99 to 1.36).

Conclusion: A laying-hen meloxicam PBPK model calibrated against an intravenous arm and evaluated on a held-out regimen reproduces the observed tissue and egg depletion and supports substantially shorter withdrawal intervals than previously reported, with egg yolk as the limiting matrix. More broadly, a residue PBPK model can appear well fitted and still be markedly biased for withdrawal-interval estimation when the calibration design cannot identify bioavailability and when values near the limit of quantitation drive parameter estimates. To ensure robust regulatory residue models, we recommend three key safeguards: holding out an entire dosing regimen, benchmarking against a no-kinetics null model to demonstrate that the mechanistic complexity genuinely improves prediction, and pre-specifying the treatment of censored data. Overall, this

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study improves our understanding of the pharmacokinetics, tissue distribution, and egg residue depletion of meloxicam in laying hens. This model provides a scientifically-informed tool to derive extra-label WDIs for meloxicam in laying hens.

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Developmental toxicity of Perfluorononanoic acid (PFNA): impacts on eye and brain

Arnob Sarker, Sunil Sharma, Syed Rubaiyat Ferdous, Md. Sameul Islam, Heidi Sabatini, Christopher Chouinard, Subham Dasgupta

Clemson University, Clemson, SC

Background and Purpose: Perfluoronanoic acid (PFNA) is a synthetic long chain homologue of per and polyfluoroalkyl substances (PFAS) which is frequently detected in environment as an emerging contaminant with potential threats to living organisms. It has broad applications in industrial and consumer products including adhesives, water and paint repellent surfaces, non-sticky coatings and lubricants. PFNA is very stable and persistent in the environment due to high energy carbon-fluorine bonds and anti-degradation (photo and microbial) properties. Studies show that PFNA caused immune, cardiac, endocrine, reproductive and developmental toxicity. This study investigates the developmental toxicity of PFNA using behavioral assay especially focus on organ specific toxicity via transcriptomic analysis.

Methods: Tropical 5D zebrafish embryos were exposed to different concentrations of PFNA (0, 0.031, 0.31, 3.12, 6.25 and 12.5 mM) from 2-hour post fertilization (hpf) to 120 hpf under dark conditions in temperature-controlled incubator at 28 °C. Larval photomotor response (LPR) was conducted to assess change in behavioral patterns. LC-MS was conducted on embryos to assess tissue burden of PFNA. For organic specific toxicity, embryos were exposed to 0 and 12.5 mM of PFNA for 120 hpf. Brain and eyes were dissected and extracted RNA was sent to Novogene for sequencing. WGCNA was performed on RNA-seq data from the brain and eye to identify gene modules associated with PFNA exposure. GO and KEGG enrichment analyses were then performed to characterize the biological functions and pathways associated with these PFNA-responsive modules. Following this, a Nile Red assay was conducted on the embryos to assess lipid perturbation. For statistical analysis, Kruskal-Wallis test followed by Dunn's test was opted for behavior data using GraphPad Prism While R software was used for differential expression analysis.

Results: PFNA exposure led to significant behavioral alterations in zebrafish larvae at 6.25 and 12.5 mM characterized by hyperactivity in the LPR assay. This hyperactivity indicates neurotoxic and visual impairments which enabled us to focus on transcriptomic analysis of brain and eye. LC-MS data showed significant PFNA uptake, with an average of ~478 nM across 3 pooled samples. RNA sequencing showed 287 differentially expressed genes (DEGs) in brain while that of 683 in eye. Module-trait relationship analysis identified two important modules in the brain and one in the eye. In the brain, genes in the most significant module were associated with circadian gene expression, circadian rhythm, and several signaling pathways, including adipocytokine, Wnt, and cadherin signaling. Similarly, the most significant eye module was also enriched for circadian rhythm, showing a similar response to the brain module. In addition, adipocytokine signaling pathway was among the most enriched pathways, along with fatty acid biosynthesis and metabolism. Consistent with this, Nile Red assay showed increased lipid deposition in the eye.

Conclusion: This study demonstrates that PFNA exposure disrupts neurodevelopmental processes in zebrafish embryos by impairing circadian rhythm, and metabolism. The findings underscore the neurotoxic potential of PFNA and its ability to interfere with both behavioral and molecular pathways. Collectively, this research highlights the need for environmental and regulatory evaluations of PFNA and other PFAS, focusing on their long-term impacts on neurodevelopment, lipid metabolism and circadian rhythm and potential health risks in contaminated ecosystems and populations.

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Postdoctoral Poster Abstracts

Physiologically Based Pharmacokinetic (PBPK) Modeling to Predict Tissue Distribution and Withdrawal Intervals of Doramectin in Cattle

Kun Mi, Zhicheng Zhang, Jeongmin Choi, Xue Wu, Melissa Mercer, Lisa A. Tell, Jennifer L. Davis, Fiona P. Maunsell, Ronald E. Baynes, Jim E. Riviere, Zhoumeng Lin

University of Florida, Gainesville, FL; University of California, Davis, CA; Virginia Tech, Blacksburg, VA; North Carolina State University, Raleigh, NC; Kansas State University, Olathe, KS

Background and purpose: Doramectin (DOR) is an FDA-approved parasiticide for the control of endo- and ectoparasites in cattle, including nematode and arthropod parasites, and has recently received Emergency Use Authorization for the prevention and treatment of New World screwworm infestations in the United States. The need for extralabel use of veterinary drugs (e.g., shorter dose intervals or higher doses) to treat parasitic infections is common; however, to ensure food safety, such use is permitted by the Animal Medicinal Drug Use Clarification Act (AMDUCA) only when a scientifically based extended withdrawal interval has been established. Physiologically based pharmacokinetic (PBPK) modeling is a valuable and flexible tool for predicting drug residues in edible tissues and determining withdrawal intervals (WDIs). This study aimed to develop a PBPK model for DOR in cattle to determine the WDIs, providing a tool for estimating extended WDIs and informing food safety assessment.

Methods: Pharmacokinetic data of DOR in cattle after intravenous (IV), intramuscular (IM), subcutaneous (SC), and topical (TOP) administration were collected from the Food Animal Residue Avoidance Databank (FARAD) for PBPK model calibration and evaluation. The PBPK model was composed of major edible tissues, including liver, kidney, muscle, fat, and the rest of body, which were connected by the blood circulatory system. IM and SC administrations were described by a two-compartment injection model consisting of a fast absorption fraction and a slow-release depot. A three-compartment mechanistic model describing DOR transport through the stratum corneum, viable epidermis, and dermis was used to characterize drug absorption following TOP administration. The distribution of DOR from plasma to tissues was perfusion-limited, which was controlled by the tissue-to-plasma partition coefficient. DOR was primarily eliminated through bile, with a smaller fraction excreted in urine, following first-order kinetics. Model performance was evaluated by comparing with observed and model-predicted data, determination coefficient (R^2), mean absolute percentage error (MAPE), and the percentage of predicted data within 2-fold/3-fold error of observed data. Global sensitivity analysis, using the “extended-FAST” method, was performed to assess the influence of PBPK parameters on model predictions [240-h area under concentration-time curves (AUC_{240h})] across tissues. Integrating the PBPK model with Monte Carlo simulations, the population PBPK model was developed to simulate the drug concentration-time curves in edible tissues of 1000 virtual animals. WDIs were determined as the times when drug concentrations in the tissues fell below the tolerance for the 99th percentile of the simulated population.

Results: The PBPK model accurately captured the observed kinetics of DOR in plasma and edible tissues (liver, muscle, kidney, and fat) after different administration routes, with R^2 of 0.87 and 0.86 for calibration and evaluation sets, respectively. Overall, 85.5% and 95.3% of the predictions fell within 2-fold and 3-fold errors, respectively, and the MAPE values for plasma, liver, kidney, fat, and muscle were 46.1%, 32.3%, 48.6%, 31.1%, and 45.8%, respectively. For the sensitivity analysis results, the dissolution rate constant of DOR from the depot after IM (K_{dissim}) and SC (K_{dissc}), and bile elimination rate constant (K_{bileC}) were the highly sensitive parameters impacting the predicted AUC_{240h} in all tissues under IM and SC administration, while logarithmic partition coefficient of DOR between the stratum corneum and water ($\log P_{sw}$) and Mass transfer factor (MTf) were the important parameters for TOP administration. Across the administration routes, tissue-

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to-plasma partition coefficient in the liver (PL), kidney (PK), and muscle (PM) were highly sensitive parameters in corresponding tissues, whereas fractional fat volume (VFC) was an important parameter for fat. The estimated WDIs by the population PBPK model for IM administration of 0.2 mg/kg, SC administration of 0.2 mg/kg, and TOP administration of 0.5 mg/kg were 35, 35, and 45 days, respectively, which were consistent with the FDA approved WDIs, highlighting the reliability of the developed DOR PBPK model.

Conclusion: The developed PBPK models serve as a useful and flexible tool for predicting tissue residues and estimating WDIs of DOR in cattle after different administration routes, thereby supporting food safety assessment. A user-friendly web interface will be developed in future work to facilitate the PBPK model application, building bridges between theoretical modeling and practical applications. This PBPK model framework provides a basis for extrapolating to other macrocyclic lactone endectocides and to other food animal species.

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Development of a Very Low-Serum Medium for Human Lung Fibroblast–Epithelial Co-Culture and Evaluation of Cr(VI) Responses

Haiyan Lu, James T. F. Wise, Sandra S. Diven, Yutian Qian, Idoia Meaza, Tayler J. Croom-Perez, John Pierce Wise, Sr

University of Louisville, Louisville, KY; University of Hawai'i at Mānoa, Honolulu, HI

Lung cancer remains the leading cause of cancer-related death in the United States. Hexavalent chromium [Cr(VI)] is a well-established human lung carcinogen of major public health concern, yet the mechanisms underlying Cr(VI)-induced lung carcinogenesis remain incompletely understood. Pathological studies of chromate-exposed workers show that chromium preferentially accumulates and persists at bronchial bifurcations, sites associated with Cr-related lung lesions and tumors. Microscopic analyses further demonstrate that retained chromium is localized predominantly in the bronchial stroma rather than the epithelium, despite the epithelial origin of Cr-associated lung tumors. These findings suggest that fibroblast-to-epithelial cell signaling may contribute to Cr(VI)-induced carcinogenesis, but the effects of Cr(VI) on this intercellular communication remain poorly characterized. Investigation of this mechanism requires a co-culture model that supports both fibroblasts and epithelial cells. However, human lung fibroblasts are traditionally maintained in medium containing 15% serum, a condition that can induce unwanted differentiation of epithelial cells. Further, lung fibroblasts are commonly cultured in DMEM/F12 medium while lung epithelial are more optimally grown in LHC-8 medium. Therefore, the aim of this study was to develop culture conditions capable of supporting both cell types that also recapitulates the genotoxic response to Cr(VI). Human lung bronchial fibroblasts (WTHBF-6) were continuously cultured either in DMEM/F12 supplemented with 15% cosmic calf serum (standard fibroblast medium) or in LHC-8 supplemented with sodium pyruvate and 1.25% cosmic calf serum (co-culture medium). Human lung epithelial cells (BEP2D) were cultured in either LHC-8 (standard epithelial medium) or in co-culture medium. Growth curves were used to compare cell proliferation between culture conditions. Both cell lines exhibited similar growth curves in standard versus co-culture media indicating the co-culture media was well tolerated by both cell lines. To assess whether the cytotoxic, genotoxic and DNA repair response to Cr(VI) was recapitulated, cells were exposed to Cr(VI) for 24 or 120 h and colony formation, DNA double-strand breaks (gamma-H2A.X foci) and homologous recombination repair (RAD51 foci) were evaluated. The data show Cr(VI) remained cytotoxic and genotoxic in co-culture media to each cell line in a similar manner compared to monocultures in their respective standard medium, though there were some differences in magnitude of response that may indicate a shift in Cr uptake. These findings demonstrate that very low-serum LHC-8 supports the growth of both WTHBF-6 fibroblasts and BEP2D epithelial cells and is therefore suitable for establishing a fibroblast–epithelial co-culture model. This work was supported by the National Institute of Environmental Health Sciences [R35ES032876 and R01ES016893 to JPW].

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An Integrated Physiologically Based Pharmacokinetic Model Incorporating DNA and Cardiolipin Binding Mechanisms to Characterize the Biodistribution of Nanoparticle-Encapsulated Doxorubicin

Chi-Yun Chen, Zhoumeng Lin

University of Florida, Gainesville, FL

Background and Purpose: Nanoparticle-based drug delivery systems have transformed cancer therapeutics by improving pharmacokinetics, enhancing tumor targeting, and reducing systemic toxicity. Liposomal doxorubicin (Doxil®) is a landmark example, yet quantitative understanding of how intact drug loaded nanoparticles and their released payload distribute throughout the body in tumor bearing hosts remains incomplete. To address this gap, we developed an integrated physiologically based pharmacokinetic (PBPK) model that concurrently characterizes the biodistribution of encapsulated and released doxorubicin from liposomal nanoparticles in tumor-bearing mice.

Methods: The joint PBPK model consists of submodels for encapsulated and released doxorubicin, respectively, sharing an identical physiological structure comprising major organs (lungs, liver, spleen, kidneys, heart, muscle), tumor tissues, blood, and a rest-of-body compartment. Both submodels incorporate plasma albumin binding and biliary, fecal, and urinary excretion. All tissue compartments are permeability-limited rather than governed by traditional partition coefficients, allowing permeability coefficients to capture DNA and cardiolipin binding in the extravascular space. The encapsulated submodel additionally includes reticuloendothelial system (RES) subcompartments in the liver, lungs, spleen, and kidneys to represent nanoparticle uptake and clearance. The two submodels are mechanistically linked: doxorubicin, internalized by RES cells or tumor-associated macrophages, is released into the corresponding free-drug compartments. Model calibration used paired native and released doxorubicin PK data from matched studies, with independent datasets reserved for evaluation. Model optimization followed a sequential strategy, first establishing native doxorubicin disposition and non-linear binding parameters in mice before parameterizing liposomal delivery.

Results: The calibrated model closely reproduced in vivo PK data over 72 hours. Following parameter optimization, the model demonstrated high accuracy across blood, plasma, and solid organs, achieving a geometric mean fold error of 1.46, an RMSE of 1.5, with 82.14% of predictions within 2-fold. Iterative calibration and sensitivity analyses confirmed that membrane permeability coefficients and organ-specific cardiolipin binding capacities are critical determinants governing early tissue uptake and terminal elimination phases.

Conclusions: This mechanistic PBPK framework explicitly captures non-linear intracellular binding and payload release kinetics that traditional empirical partition models omit. By accurately coupling vascular permeability with saturable DNA and cardiolipin binding, the model provides an extensible platform for distinguishing encapsulated from free drug kinetics and guiding rational nanomedicine design. We anticipate that refining macrophage uptake parameters will improve the model's ability to distinguish encapsulated from released drug across organs and tumor tissue, ultimately supporting formulation optimization and rational nanomedicine design.

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A Whale of a Problem: First Evidence of Micro/Nanoplastics Presence in Blubber of Humpback Whales from Gulf of Maine and Co-Occurrence with Nonessential Metals

Idoia Meaza, Jamie Lynn Wise, Rachel M. Wise, Robert M. Taylor, Eve Rowland, Marcus A. Garcia, Laurissa Barela, Matthew J. Campen, Edward Lyman, Iain Kerr, John Pierce Wise, Sr.

University of Louisville, Louisville, KY; University of New Mexico, Albuquerque, NM; NOAA Hawaiian Islands Humpback Whale National Marine Sanctuary, Kihei, HI; Ocean Alliance, Gloucester, MA

Micro/nanoplastics are ubiquitous pollutants of global concern. These plastic particles originate either from the degradation of larger plastic debris or are manufactured for specific products, like exfoliants. Micro/nanoplastics are particularly prominent in the marine environment, where they can be suspended in the water column, deposited in the sediments or can be resuspended into air through oceanic winds. Great whales are sentinel species for ocean health because they are long-lived species, occupy high trophic chain levels and share major routes of exposure with humans, including inhalation and ingestion, the two most prominent routes for these pollutants. There are limited studies on micro/nanoplastic pollution on great whales and the majority only investigate levels in gastrointestinal tract, fecal samples or tissues postmortem. Thus, the translocation to internal tissues in living animals remains poorly understood. Another major data gap in the field is the co-exposure between different types of micro/nanoplastics and other pollutants, such as metals. Metals in particular are interesting for the field of micro/nanoplastics as they are used as additives in plastic production and micro/nanoplastics are also known to adsorb metals, acting potential as vectors of these chemicals. Our study collected skin biopsies from free ranging humpback whales (*Megaptera novaeangliae*) from the Gulf of Maine from 2021 to 2023. In total, 12 humpback whales were sampled, including 9 females (3 calves, 6 adults) and 3 males (1 calf, 2 adults). Of these individuals, four were mother-calf pairs. From the skin biopsy, the skin was divided into two sections, one for DNA extraction to determine the sex of the individuals and the other half was digested for metal analyses using inductively coupled plasma mass spectrometry (ICP-MS). The blubber was dissected and digested to measure micro/nanoplastics using pyrolysis gas chromatography-mass spectrometry (py-GC/MS). Twelve polymers were found in whale samples, with polyethylene being the most abundant polymer, followed by polypropylene and polyvinyl chloride. These three polymers are some of the most abundant polymers found in the oceans. Lower levels of styrene butadiene rubber, nylon 6, acrylonitrile butadiene styrene, polycarbonate, polyurethane and polystyrene were also found. Among the four mother-calf pairs, three calves had higher levels of polymers than their mothers, which might suggest a potential exposure of the calves from the mothers. Metal analysis also revealed presence of nonessential metals in skin samples, with aluminum, chromium and nickel being particularly high. Correlation analyses were performed to better understand whether specific polymers cooccur with other polymers or essential and nonessential metals. Correlation analyses showed almost all polymers significantly correlated with the levels of other polymers, and in some cases correlations with nonessential metals and essential metals were also found. This study is the first to show the presence of plastic particles in blubber tissues of free-ranging humpback whales and show particularly high levels of polymers in calves compared to adults. In addition, we show for the first time positive polymer-polymer and polymer-metal correlations in whale tissues. These results indicate that plastics are translocating from exposure sites to distal tissues in free-ranging adults and calves, and highlight the importance of investigating metals as co-occurring contaminants with micro/nanoplastics. This work was supported in part by grant R35ES032876 (JPWSr) from the National Institute of Environmental Health Sciences (NIEHS) and also by grant P20GM130422 from the National Institute of General Medical Sciences (NIGMS).

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Evaluation of Opioid-Associated Neonatal Toxicity Following Prenatal Exposure to Mitragynine

Abhishek Gour, Sarvesh Kumar Verma, Michelle A Kuntz, Kofi Frimpong-Manson, Sushobhan Mukhopadhyay, Christopher R. McCurdy, Jenny Wilkerson, Abhishek Sharma

University of Florida, Gainesville, FL; Rutgers New Jersey Medical School, Newark, NJ

Purpose: *Mitragyna speciosa* Korth., commonly known as kratom, is widely used by women of reproductive age for pain management, mood enhancement, and relief of opioid withdrawal symptoms. As some users may become pregnant while consuming kratom, and opioid-dependent women may perceive kratom as a safer alternative to prescribed or illicit opioids, its use during pregnancy is a growing concern. Multiple cases of neonatal abstinence syndrome (NAS) have been reported following maternal kratom use during pregnancy. Kratom contains more than 40 alkaloids, with mitragynine is one of its major constituents. Therefore, this study aimed to evaluate opioid-associated neonatal toxicity following prenatal exposure to mitragynine and characterize its maternal-fetal disposition during pregnancy.

Methods: To evaluate opioid-associated neonatal toxicity, dams were exposed to mitragynine (20 mg/kg, oral, BID), oxycodone (10 mg/kg, oral), morphine (5-32 mg/kg, oral, BID), or oxycodone before pregnancy followed by a switch to mitragynine during gestation. We utilized postnatal naltrexone treatment to precipitate potential opioid-mediated withdrawal and assessed NAS-related behaviors. Withdrawal-related behaviors were compared among pups born to dams exposed to different treatment regimens during pregnancy. Maternal and pup plasma were characterized to identify the major metabolite(s) of mitragynine and oxycodone. To better understand fetal exposure to mitragynine, feto-maternal pharmacokinetic study was also conducted on gestational day 14 in Sprague Dawley rats to characterize its maternal and fetal disposition during pregnancy.

Results: Prenatal exposure to mitragynine was associated with opioid-related neonatal toxicity. Upon naltrexone challenge, pups exposed prenatally to morphine, oxycodone or mitragynine exhibited significant increases in withdrawal-related behaviors, including headshaking, paw-treading, body-stretching, and rolling. These behavioral responses were more pronounced in pups born to dams that received oxycodone before pregnancy and were subsequently switched to mitragynine during gestation. Prenatal maternal exposure resulted in significant dysregulation of cytokine expression (IL-1 β , CCL11, and IL-17A/CTLA-8) in the brains of rat pups, indicating neuroimmune alterations. Metabolite profiling revealed that 9-hydroxycorynantheidine was the major metabolite found in both dams and pups following mitragynine exposure. Noroxymorphone was the major metabolite found in dams and pups exposed to oxycodone.

Conclusion: Prenatal exposure to mitragynine resulted in opioid-associated neonatal toxicity comparable to that observed following morphine and oxycodone exposure. These findings warrant caution regarding the use of mitragynine-containing kratom products during pregnancy and highlight the need for further investigation of their developmental and neonatal toxicological effects.

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Toxicological Characterization of Perfluoro-3-methoxypropanoic Acid (PFMOPrA) in Early Developmental Stages of Zebrafish (*Danio rerio*)

Evelyn C. Lopez Gonzalez, Amany Sultan, Fatma C. Kirgiz, Christopher J. Martyniuk

University of Florida, Gainesville, FL; Universidad Nacional del Litoral (UNL) – Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Santa Fe, Argentina; Animal Health Research Institute, Agriculture Research Center (ARC), Giza, Egypt. Hatay Mustafa Kemal University, Hatay, Türkiye

Perfluoro-3-methoxypropanoic acid (PFMOPrA) is a short-chain perfluoroalkyl ether carboxylic acid (PFECA) used as an alternative to legacy PFAS. PFMOPrA has been detected in surface waters, sediments, and biota near fluorochemical manufacturing sites, highlighting its environmental mobility and persistence. However, toxicological information on this emerging PFAS remains scarce, and knowledge regarding its developmental and behavioral toxicity, and molecular effects in aquatic vertebrates remains limited. Therefore, the present study evaluated the effects of early-life exposure to PFMOPrA in zebrafish (*Danio rerio*). Embryos (6–8 h post-fertilization, hpf) were exposed for 5 days to nominal concentrations ranging from 0.1 to 1000 µg/L in a 10-fold dilution series. Biological endpoints including survival, hatchability, heart rate, locomotor activity, reactive oxygen species (ROS) production, and the expression of genes associated with cellular stress and neurotoxicity, were assessed to characterize the potential adverse effects of PFMOPrA exposure. PFMOPrA exposure reduced larval survival, with the greatest effects observed at 0.1, 1, and 100 µg/L. In addition, developmental deformities were observed at the highest concentrations. Heart rate was significantly altered at 100 µg/L, showing a marked increase at this concentration. Behavioral assessments revealed increased locomotor activity during the Visual Motor Response assay, including the first dark phase at 100 µg/L, the first light phase at 0.1 µg/L, and the third dark phase at 1 µg/L. At the molecular level, PFMOPrA induced the upregulation of the following genes associated with neurodevelopment and cellular stress responses. Expression of *elavl3* was significantly increased at 100 µg/L, *gap43* and *nestin* at 10 and 100 µg/L, *ho-1* at 1000 µg/L, and *hsp70* at 10, 100, and 1000 µg/L. No significant changes in ROS production were detected. Collectively, these findings demonstrate that early-life exposure to PFMOPrA induces developmental, behavioral, and transcriptional alterations in zebrafish larvae, highlighting the potential biological activity of this emerging PFAS.

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PAD4 Deficiency Attenuates Arsenic Trioxide–Induced Lung Injury and Interstitial Neutrophil Accumulation

Dhruthi Mutyala, Nilda Sanchez, Sai Kota, Mya Mickenney, Jaroslaw Zmijewski, and Ranu Surolia

University of Alabama at Birmingham, AL

Background: Arsenic trioxide (ATO) exposure can cause acute lung injury (ALI), but the contribution of neutrophil extracellular traps (NETs) to this response remains incompletely defined. Peptidyl arginine deiminase 4 (PAD4) promotes histone citrullination during NET formation. We examined whether PAD4 contributes to ATO-induced lung injury and whether its effects differ between alveolar and interstitial neutrophil compartments.

Methods: Acute inhalation of ATO (20 mg/kg) resulted in 40% mortality in WT mice, whereas PAD4^{-/-} mice demonstrated 100% survival at 24 hours. Neutrophil responses were further evaluated at 10 mg/kg, a sub lethal dose at which all animals survived during the observation period. Outcomes included lung histopathology, protein leak, pulmonary neutrophil and NET-associated staining, and flow-cytometric analysis of alveolar and interstitial neutrophil populations.

Results: PAD4 deficiency reduced mortality following high-dose ATO exposure. At the sublethal dose, PAD4-deficient mice showed less histologic lung injury, neutrophilic inflammation, and protein leak than wild-type mice. ATO increased pulmonary neutrophil elastase and citrullinated histone H3 staining, consistent with neutrophil recruitment and NET formation. Flow-cytometric analysis showed difference in the measured alveolar neutrophil populations between genotypes. In contrast, the interstitial neutrophil population was lower in PAD4-deficient mice (4.6%) than in wild-type mice (11.0%). In the interstitium, CD49d⁺CXCR4⁺ frequencies were comparable across groups; however, viable neutrophils expressed citrullinated histone H3 (Cit-H3) in both WT and PAD4^{-/-} mice. These findings suggest that PAD4-dependent lytic NETosis drives mortality in ATO-induced ALI, while PAD4-independent histone citrullination pathways may contribute to non-lytic neutrophil activation.

Conclusions: PAD4 deficiency attenuates ATO-induced lung injury and is associated with reduced interstitial neutrophil accumulation. Cit-H3 persists in viable PAD4-deficient neutrophils; future studies will determine its source and distinguish it from lytic NET formation.

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Effect of N-EtFOSAA Exposure on Developmental and Cardiac Toxicity in Zebrafish (*Danio rerio*) Embryos

Fatma Ceren Kirgiz, Amany Sultan, Evelyn C. Lopez Gonzalez, Christopher J. Martyniuk

University of Florida, Gainesville, FL; Hatay Mustafa Kemal University, Hatay, Turkiye; Animal Health Research Institute, Agriculture Research Centre, Giza, Egypt; Universidad Nacional del Litoral-Consejo Nacional de Investigaciones Científica y Técnicas (CONICET-UNL), Santa Fe, Argentina

N-Ethyl perfluorooctane sulfonamidoacetic acid (N-EtFOSAA) is a perfluoroalkyl and polyfluoroalkyl substance (PFAS) and a precursor of perfluorooctane sulfonate (PFOS) that has been detected in consumer products, environmental matrices, human blood, wastewater, biosolids, and biosolids-amended soils. Given the environmental persistence and bioaccumulation potential of long-chain PFAS, concerns have been raised regarding their potential effects on aquatic organisms. Therefore, this study aimed to evaluate the developmental and physiological effects of N-EtFOSAA exposure in zebrafish (*Danio rerio*) embryos and larvae. Zebrafish embryos were exposed to N-EtFOSAA at concentrations of 0.1, 1, 10, 100, and 1000 µg/L for 5 days. Survival, developmental abnormalities, heart rate, locomotor activity, and reactive oxygen species (ROS) levels were evaluated. ROS levels were normalized to total protein content determined using the BCA protein assay. No statistically significant differences in BCA-normalized ROS levels were observed between any N-EtFOSAA exposure group and the DMSO control. N-EtFOSAA exposure significantly affected locomotor activity during the Dark 1, Dark 2, and Dark 3 phases, with particularly pronounced effects at 1000 µg/L. During the light phases, no significant differences were generally observed between N-EtFOSAA exposure groups and the DMSO control; however, a significant difference was detected during Light 2 at 1 µg/L (adjusted $p = 0.0211$). In addition, Dunnett's multiple comparisons test, using the DMSO control as the reference group, revealed an increase in heart rate in the 10 µg/L N-EtFOSAA exposure group. Overall, these findings suggest that N-EtFOSAA exposure can alter cardiac function and locomotor behavior during zebrafish development, with responses varying according to exposure concentration and behavioral phase, while no significant changes in BCA-normalized ROS levels were detected under the conditions tested. This study contributes to the understanding of N-EtFOSAA-associated developmental and physiological effects in aquatic organisms.

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New Investigator Poster Abstracts

The Association Between Per- and Polyfluoroalkyl Substances and Prostate Cancer Risk in the Southeastern United States

Alex H Yoon, Jae Jeong Yang, Sung Min Han, Christiaan Leeuwenburgh, Zhoumeng Lin, Mi-Jeong Yoo, Jie Wu, Xiao-Ou Shu, Wei Zheng, Qiuyin Cai

University of Florida, Gainesville, FL; Clarkson University, Potsdam, NY; Vanderbilt University Medical Center, Nashville, TN

Background and Purpose: Prostate cancer is the second common malignancy among U.S. men, and both PFAS exposure and prostate cancer burden vary across racial and socioeconomic groups. Perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) are classified by IARC as carcinogenic (Group 1) and possibly carcinogenic (Group 2B), respectively, yet epidemiologic evidence for prostate cancer remains limited and inconsistent. We evaluated whether pre-diagnostic PFAS levels are associated with subsequent prostate cancer risk among Southern U.S. residents with low socioeconomic status.

Methods: We conducted a nested case-control study of prostate cancer cases (n=280) and controls (n=543), including 195 Black men and 85 White men. The 543 matched controls comprised 379 Black men and 164 White men from the Southern Community Cohort Study. Pre-diagnostic plasma PFAS were quantified using a global semiquantitative metabolomics platform, and PFOA and PFOS were log-transformed and categorized into tertiles. Conditional logistic regression estimated odds ratios (OR) and 95% confidence intervals (CI), adjusting for covariates.

Results: The mean age at study enrollment was 56.5 years for cases and 56.2 years for controls (p=0.62). The mean age at cancer diagnosis was 61.1 years, with a median interval of 5.0 years between enrollment and prostate cancer diagnosis. In the stratified analysis by race, White men in the highest tertile of PFOA concentrations showed approximately a threefold increased risk of prostate cancer compared to those in the lowest tertile (OR=3.26, 95% CI: 1.35-7.89; p-trend=0.009), which remained significant even after mutual adjustment for PFOS concentrations (OR=3.02, 95% CI: 1.10-8.30; p-trend=0.033). Among White men, the highest tertile of PFOS was associated with increased odds of prostate cancer (OR=2.14, 95% CI: 0.93-4.89; p-trend=0.046), but this association was attenuated after mutual adjustment for PFOA concentrations (OR=1.60, 95% CI: 0.64-3.96; p-trend=0.21). Meanwhile, neither PFOA nor PFOS was associated with prostate cancer risk among Black men. Among men with obesity (BMI ≥ 30 kg/m²), the highest tertile of PFOA exhibited an almost threefold increased odds (OR=2.88, 95% CI: 1.43-5.80; p-trend=0.003), while the association was attenuated upon mutual adjustment for PFOS (OR=2.09, 95% CI: 0.99-4.42; p-trend=0.049). Similarly, the highest tertile of PFOS was associated with a 2.43-fold increase in risk of prostate cancer (OR=2.43, 95% CI: 1.27-4.65; p-trend=0.009). No associations were observed among non-obese men (BMI <30 kg/m²). However, the interaction tests by obesity status were not statistically significant (p-interaction=0.20 for PFOA and 0.36 for PFOS). In race-stratified analyses among men with obesity, obese White men in the highest tertiles of PFOA and PFOS had about 4.3-fold elevated odds of developing prostate cancer after mutual adjustment for other PFAS (OR=4.36, 95% CI: 0.82-23.1; p-trend=0.11 for PFOA; and OR=4.30, 95% CI: 1.26-14.7; p-trend=0.011 for PFOS), whereas obese Black men revealed nonsignificant positive associations.

Conclusions: Higher pre-diagnostic PFOA was associated with increased prostate cancer risk among White American men, and PFOS was associated with elevated risk among men with obesity, with statistically significant interactions by BMI. These findings suggest that PFAS may synergize with adverse metabolic status to promote prostate tumor progression, supporting obesity-related susceptibility as a plausible mechanism and a novel hypothesis that warrants further investigation.

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Optimization of HPLC–MS Conditions for Reliable Quantification of Zeta-Cypermethrin Isomers in Toxicological Residue Analysis

Isil Gazioglu

University of Florida, Gainesville, FL

Zeta-cypermethrin is a synthetic pyrethroid insecticide composed of several stereoisomeric forms. Under certain high-performance liquid chromatography conditions, these isomers may appear as partially resolved peaks, split peaks, or a primary peak accompanied by shoulders. Such chromatographic profiles can complicate peak integration, reduce consistency between injections, and introduce uncertainty into quantitative residue analysis. This study aimed to optimize HPLC–MS conditions that would allow zeta-cypermethrin and its associated isomeric forms to be detected as a single, well-defined peak suitable for reliable quantitative analysis.

Method development focused on stationary-phase selectivity, mobile-phase composition, gradient profile, flow rate, column temperature, and mass spectrometric detection parameters. Initial experiments were performed using an Ascentis Biphenyl column (50 × 2.1 mm, 2 µm) at a flow rate of 300 µL/min. Despite adjustments to the gradient and flow conditions, the resulting chromatograms showed broad and partially separated isomeric responses. A Kinetex Biphenyl column was subsequently evaluated at a flow rate of 350 µL/min. Although the overall peak shape improved, multiple chromatographic components remained visible, indicating that the biphenyl stationary phases did not produce the desired single quantitative response.

The method was then transferred to a Zorbax Eclipse XDB Phenyl column (2.1 × 50 mm, 5 µm). This stationary phase produced a dominant zeta-cypermethrin peak at approximately 7.72 min, representing a substantial improvement compared with the biphenyl columns. However, residual peak splitting and shoulder formation were still present. Further optimization therefore focused on column temperature, flow rate, mobile-phase gradient, and MS response. Increasing the temperature improved peak coalescence and reduced the visible shoulders. The final temperature was set at 40 °C to balance chromatographic performance and column protection. The flow rate was increased from 300 to 350 µL/min, and the gradient was refined to improve peak shape and elution behavior. The mass spectrometer was operated in positive-ion mode with an ionization voltage of 4800 V to enhance signal response.

The final optimized conditions consisted of a Zorbax Eclipse XDB Phenyl column, a flow rate of 350 µL/min, a column temperature of 40 °C, and a positive-ion voltage of 4800 V. Under these conditions, a 12.5 ng/mL zeta-cypermethrin standard produced a single, well-defined peak at approximately 7.06 min. No clearly visible secondary isomer peak was observed, and shoulder formation was substantially reduced compared with the chromatograms obtained during earlier method-development experiments. The optimized response was achieved at a lower concentration than some preliminary experiments, demonstrating that adequate detection was maintained while producing a cleaner chromatographic profile.

The results indicate that stationary-phase selectivity was the primary factor controlling the chromatographic behavior of zeta-cypermethrin isomers. Further optimization of flow rate, temperature, gradient conditions, and ionization voltage converted the complex isomeric profile into a single quantifiable peak, supporting more consistent and reliable HPLC–MS residue analysis.

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Subacute exposure to a mixture of tributyltin, cadmium, and mercury impairs the hypothalamic–pituitary–gonadal axis at different levels by disruption in estrogen receptor alpha/ Akt signaling and changes pregnancy outcomes in female rats

F.C.F. Dos Santos, M. D. De Oliveira, C. F. Januário, J.B. Graceli

Federal University of Espírito Santo, Brazil; Zambeze University, Mozambique; Southern Illinois University, Carbondale, IL

Environmental contaminants are a public health concern because exposure commonly occurs to mixtures rather than individual chemicals. Tributyltin (TBT), cadmium (Cd), and mercury (Hg) are reproductive toxicants that can exert adverse effects even at low TBT doses and at exposure levels relevant to occupational Hg and Cd exposure; however, the effects of their combined exposure on female reproductive function remain poorly understood. Here, we tested whether subacute exposure to a TBT+Cd+Hg mixture (MIX) disrupts the hypothalamic–pituitary–gonadal (HPG) axis and pregnancy outcomes in female rats. Adult female rats (12 weeks old, $\pm$ 230g, $n=5-10$) were exposed to a MIX, such as TBT (100 ng/kg/day, by gavage), Cd (100 mg/L, by drinking water) and Hg (1st dose: 4.6 mg/kg, subsequent doses: 0.07 mg/kg/day by intramuscular injection) for 15 days. All protocols were approved by CEUA-UFES (04/2023). The rats were euthanized in metestrus–diestrus phase. Hormones levels were evaluated using ELISA kits. To analyze the estrous cycle, vaginal smears were collected daily at 9:00 a.m. Ovarian sections were stained with hematoxylin and eosin (H&E) and assessed for general histological parameters. The protein expressions were evaluated by immunoblotting and immunohistochemistry analysis. The data were shown as mean $\pm$ SEM, followed Student's t-test. MIX rats spend more time in proestrus and less time in estrus phase. Increased and borderline increased serum FSH and estrogen levels were observed in MIX rats compared to controls, respectively. Reduced Akt protein expression in MIX rats was observed in the hypothalamus and pituitary compared to controls. Pituitary ER α and FSH β protein expression were reduced in MIX rats compared to controls. MIX exposure reduced corpora lutea (CL) number and increased preantral follicles number. CL ovarian ER α protein expression of MIX rats was reduced compared to controls. Ovarian stroma PR and CL FAS (apoptosis marker) protein expressions increased in MIX rats compared to controls. After ovariectomy (OVX), MIX-OVX rats reduced serum FSH levels compared to control-OVX rats. After estrogen replacement (OVX+E2), we observed a similar level of FSH in control-intact and control-OVX+E2 rats. In MIX rats, we observed an increase in FSH levels in MIX-OVX+E2 rats compared to intact-MIX rats. Despite the similar reduction in OVX uterus weight in control- and MIX-OVX, we do not observe differences between intact and OVX+E2 in control and MIX groups. Furthermore, uterine irregularities were observed in MIX rats. Compared to controls, an increase in uterine area, presence of hyperplastic glands and inflammatory cells inside of glands were observed in the MIX rats. A reduction in the number, height and mucus score of uterine glands was observed in MIX rats compared to controls. These alterations have been linked with pregnancy outcomes, such as increased gestational length in MIX dams. Additionally, prenatal MIX exposure reduced body weight and increased serum glucose levels in the offspring, which may contribute to an unhealthy developmental environment. These data suggest that exposure to a MIX lead to abnormal function of HPG axis at different levels in female rats, by disrupting estrogen receptor alpha/Akt signaling, contributing to irregular ovary and uterus function and, abnormalities in the prenatal exposure to offspring.

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Optimized Extraction of Glyphosate from Rat Vertebral Bone

Tatilla L. S. Frota Gomes, J. Ignacio Aguirre, Cindy Cruz-Camacho, Kevin K. Kroll, Sara E. Bisesi, Nancy D. Denslow

University of Florida, Gainesville, FL

Background & Purpose: Glyphosate (GLY) is a highly polar aminophosphonate whose extraction from mineralized tissues may be influenced by interactions with the bone matrix. To develop a bone-specific workflow, we evaluated overnight extraction followed by ELISA detection of GLY in ground rat vertebral bone, providing a rapid, scalable screening tool.

Methods: Male Sprague–Dawley rats (n=24) received vehicle, GLY at 1.0 mg/kg/day, or GLY at 100 mg/kg/day in drinking water for 14 days. Vertebrae were cryogenically ground; 0.1 g aliquots were extracted overnight at 4 °C in 1 mL and 1 % formic acid. Extracts were vortexed, sonicated, centrifuged, filtered through 3-kDa centrifugal filters, diluted 1:200, derivatized, and quantified with the ABRAXIS® Glyphosate ELISA kit. GLY levels were normalized to the starting bone mass (ng/g). The optimized ELISA workflow was benchmarked against independently generated LC–MS/MS data from identical samples processed with the same overnight extraction.

Results: A two-way repeated measures ANOVA revealed significant effects of analytical method ($F(1,12)=25.37$, $P=0.0003$), treatment group ($F(2,12)=580.1$, $P<0.0001$), and method by treatment interaction ($F(2,12)=25.88$, $P<0.0001$). Bonferroni adjusted comparisons showed both methods detected markedly higher GLY in the High Dose group than in Vehicle and Low Dose groups (adjusted $P<0.0001$). In Vehicle and Low Dose samples, ELISA and LC–MS/MS estimates did not differ (adjusted $P>0.9999$). In the High Dose group, LC–MS/MS quantified $18\,780 \pm 1\,050$ ng/g, whereas ELISA reported $10\,182 \pm 980$ ng/g (adjusted $P<0.0001$).

Conclusions: These findings demonstrate that overnight 1% formic-acid extraction followed by ELISA accurately captures exposure-dependent increases in vertebral GLY, producing concentration estimates within the same order of magnitude as LC–MS/MS. The discrepancy at the highest exposure level suggests an opportunity for further refinement. This workflow provides a practical, matrix-adapted approach for rapid comparative screening and prioritization of bone samples in experimental studies; LC–MS/MS remains the gold standard for definitive quantitative confirmation.

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