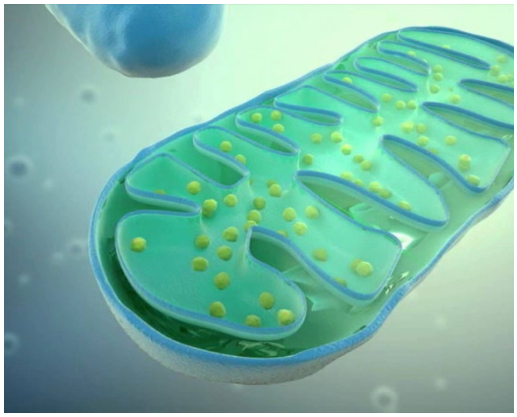
Genetic and Environmental Toxicology Association of Northern California (GETA)

2024 Fall Hybrid Symposium

Tuesday, November 5th, 1:00 - 5 PM (PST)

In person: California EPA Building, Sierra Hearing Room, 2nd Floor
1001 I Street, Sacramento, CA 95814
Online: Zoom meeting, registration link:
https://us02web.zoom.us/webinar/register/WN_gDf0wB_7SEmMZbEvmB3GHw#/registration

Cell danger response – environmental health, mitochondria, and chronic illness



Speakers:

- **Dr. Linlin Zhao,** Associate Professor of Chemistry and Environmental Toxicology at the University of California, Riverside. "*Decoding Nucleic Acid Signals of Environmental Chemical Exposures.*"
- **Dr. Kelli Malott,** SafeBridge Consultants, Inc; UC Irvine. "*Toxicant Effects on Mitochondria in Oocytes; A growing understanding of the intersection between metabolism and genetics.*"
- **Dr. Gino Cortopassi,** Professor of Environmental Toxicology, Pharmacology and Toxicology Graduate Group, University of California, Davis "*Quaternary Ammonium Compounds (QACs) found in sprayed disinfectants."*

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Cell danger response – environmental health, mitochondria, and chronic illness

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1001 I Street, Sacramento, CA 95814

Program

12:00 - 1:00 pm	Registration, Reception, and Poster Session
1:00 - 1:10 pm	Welcome
1:10 - 2:00 pm	**Dr. Linlin Zhao's talk and Q&A**
2:00 - 2:50 pm	**Dr. Kelli Malott's talk and Q&A**
2:50 – 3:10 pm	Break and Poster Session
3:10 - 3:20 pm	Student Lighting talk (Nathifa Nasim, UCD)
3:20 – 4:10 pm	**Dr. Gino Cortopassi's talk and Q&A**
4:10 – 4:30 pm	Panel discussion and Wrap-up
4:30 – 5:00 pm	Social hour and Poster Session

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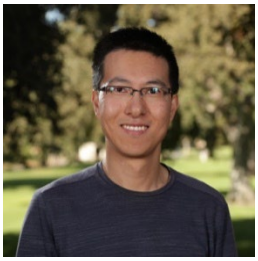
Invited Speakers Abstracts

1. **Decoding Nucleic Acid Signals of Environmental Chemical Exposures**



Dr. Linlin Zhao,
Associate Professor of Chemistry and Environmental Toxicology at the University of California, Riverside.
linlin.zhao@ucr.edu

Biography

Linlin Zhao, Ph.D., is an Associate Professor of Chemistry and Environmental Toxicology at the University of California, Riverside, where he also serves as the Director of the Environmental Toxicology Graduate Program. He earned his B.S. in Chemistry from Jilin University and his Ph.D. in Bioanalytical Chemistry from the University of Connecticut. Dr. Zhao completed his postdoctoral fellowship at Vanderbilt University School of Medicine, where he investigated the mechanisms of chemical carcinogenesis and DNA polymerase enzymology. His laboratory specializes in chemical biology and the enzymology of DNA damage and repair, with a particular focus on mitochondrial processes. Notably, his research team discovered a new role for TFAM in mitochondrial DNA turnover and repair. Additionally, his lab develops advanced DNA sequencing technologies to study various DNA modifications. Dr. Zhao's work has been published in prestigious journals, including Proceedings of the National Academy of Sciences USA, Nucleic Acids Research, Journal of the American Chemical Society, and Angewandte Chemie. He is the principal investigator on multiple NIH-funded projects and has served as a reviewer for multiple funding agencies and scientific journals.

Abstract

In higher eukaryotic cells, mitochondria are essential subcellular organelles for energy production, cell signaling, and the biosynthesis of biomolecules. The mitochondrial DNA (mtDNA) genome is indispensable for mitochondrial function and maintained by multiple mechanisms, including mtDNA redundancy, base excision repair, and mtDNA turnover, along with mitochondrial dynamics and mitophagy. Damaged mtDNA can be extruded from the mitochondria in various forms, and depending on their characteristics, these extruded mtDNA molecules play a crucial role in innate immunity and inflammation. Consequently, mtDNA has emerged as a genotoxic stress sensor in cells. My laboratory employs a multi-faceted approach to decipher the signaling cues embedded in mtDNA molecules. We seek to clarify the mechanisms of damaged mtDNA degradation, identify major products formed, and determine the enzymes and proteins involved in these processes. In addition, we design and synthesize chemicals specifically targeting mtDNA to manipulate its turnover and isolate fragmented mtDNA. Through these efforts, we anticipate gaining a deeper understanding of the biological cues related to chemical exposure and cellular stress and developing reliable markers to monitor these processes.

2. **Toxicant Effects on Mitochondria in Oocytes; A growing understanding of the intersection between metabolism and genetics**

Dr. Kelli Malott
SafeBridge Consultants, Inc
University of California, Irvine.
khfmalott@gmail.com

Biography

Dr. Kelli Malott is a toxicologist with SafeBridge Consultants. In her current role she is the subject matter expert on reproductive and developmental toxicology and sensitive subpopulations. She earned her doctorate in Environmental Health Sciences from University of California, Irvine where she studied gestational air pollution exposure, premature ovarian failure, and oocyte developmental competence. Prior to that, Kelli was a post-baccalaureate intramural research fellow at the National Institute on Aging in the National Institutes of Health and earned her Bachelor of Science degree in Cellular and Molecular Biology from the University of Michigan.

Abstract

Oocyte mitochondria are unique organelles that establish a founder population in primordial germ cells (PGCs). As the oocyte matures in the postnatal mammalian ovary during folliculogenesis it increases exponentially in volume, and the oocyte mitochondria population proliferates to about 100 000 mitochondria per healthy, mature murine oocyte. The health of the mature oocyte and subsequent embryo is highly dependent on the oocyte mitochondria. Mitochondria are especially sensitive to toxic insults, as they are a major source of reactive oxygen species (ROS), they contain their own DNA (mtDNA) that is unprotected by histone proteins, they contain the electron transport chain that uses electron donors, including oxygen, to generate ATP, and they are important sensors for overall cellular stress. In this talk we review the effects that toxic insults including chemotherapeutics, toxic metals, plasticizers, pesticides, polycyclic aromatic hydrocarbons (PAHs), and ionizing radiation can have on oocyte mitochondria, with a special focus on PAHs and metabolism.

3. Decoding Nucleic Acid Signals of Environmental Chemical Exposures

Dr. Gino Cortopassi,
Professor of Molecular Biosciences
Pharmacology and Toxicology Graduate Group
Environmental Toxicology at the University of California, Davis.
gcortopassi@ucdavis.edu

Abstract

Quaternary Ammonium Compounds (QACs) have been in use since the 1940's as potent biocides and disinfectants and cleaning supplies. The two most-used QACs in the USA are Benzalkonium Chloride (BAC) and Didecyl-dimethylammonium Chloride (DDAC). QACs effusiveness in killing a variety of microbes led to their increased use as aerosolized sprays, foams, and wipes, and aerosolized QACs are widespread, Clorox alone sells 23 branded products containing BAC as a pump spray.

QACs have always been presumed to be safe, for three main reasons: 1) QACs mechanism of action was thought to be soaplike; 2) orally-dosed QACs do not penetrate the body to a significant extent; and 3) the LD50s of orally dosed QACs to rodents were relatively high, 240-500mg/kg. Our finding in 2017 that QACs are dose-dependent mitochondrial toxins began to challenge the notion that QACs were 'safe as soap'. Also, two studies of human populations measured QACs at 2-40nM in blood of 80% of participants from Virginia Tech (Hrubec 2021), and 2-24nM in majority of breast milk samples tested from lactating mothers (Salamova, 2022). So if QACs aren't a natural compound, and pass through the GI tract unabsorbed, how do they get into the blood and breastmilk of human subjects?

The above findings motivated us to test the toxicity of aerosol- and lung-delivered QACs. Mice were dosed at ascending dosages of BAC and DDAC QACs by OroPharyngeal Aspiration (OPA). We found OPA-dosed QACs are 100-fold more toxic (LD50 ~2mg/kg) than orally dosed QACs (~>240mg/kg). We discovered a sexual dimorphism in response to QACs, significantly more males die than females exposed to OPA-dosed BAC and DDAC. Conversely, females are significantly protected from OPA-dosed BAC and DDAC death. Females had increased neutrophilic infiltration to the lungs, which we hypothesize may underlie their protection.

Our data suggest a new hypothesis for how QACs come to be at 1-40nM in 80% of blood of human subjects—they may enter the body as aerosols through the lung. If this is correct route of exposure and administration, the finding that lung concentrates some QACs 10-fold vs blood, and that lung exposure raises QAC's toxicity by 100-fold seems impactful. These new findings might support alternative rational and informed regulation of aerosolized QACs whose potent anti-microbial disinfectant action could have unintended side effects and consequences.

Poster Presentation Abstracts

Poster #1

Comparing effects of gaseous vs. particulate components of traffic-related air pollution on Alzheimer's disease-relevant phenotypes in a genetically susceptible rat model

Mei-Yun Cheng[1], Nathifa Nasim[1], Heui Hye Park[1], Anthony Valenzuela[1], Keith Bein[2], Laura S. Van Winkle[3], Pamela J. Lein[1]

[1]Molecular Biosciences, University of California, Davis, School of Veterinary Medicine, Davis, CA, USA
[2]Air Quality Research Center, University of California, Davis, CA, USA
[3]Anatomy, Physiology and Cell Biology, University of California, Davis, School of Veterinary Medicine, Davis, CA, USA

Alzheimer's disease (AD) predominates as the most common cause of dementia in the United States. It is now consensus that individual risk for most forms of AD is determined by complex gene X environment interaction. Recent epidemiologic studies link exposure to traffic-related air pollution (TRAP) to increased occurrence of AD and AD-related dementia. While preclinical studies support a causal relationship between TRAP and increased AD risk, many of these latter studies used concentrated ambient particles or diesel exhaust that do not recapitulate the levels or complexity of current, real-world TRAP exposures. Further, there remains significant uncertainty about how TRAP promotes the onset and/or progression of AD. We hypothesize that TRAP triggers inflammation in the lung that subsequently promotes neuroinflammation in the brain to promote AD-relevant outcomes.

To test this hypothesis, and to gain insight on whether gaseous versus particulate matter (PM) contribute to the effects of TRAP on the brain, we leveraged an exposure facility that draws TRAP directly from a heavily trafficked tunnel in Northern California and delivers this polluted air in real-time to animals housed in the facility. Control animals are housed in the same facility but exposed to filtered air (FA). Male and female TgF344-AD rats that express human AD risk genes were transported to the tunnel facility at 1 month of age and then randomly assigned to one of six exposure groups: (1) FA; (2) gaseous emissions from light-duty vehicles (LDV) and heavy-duty vehicles (HDV); (3) particulate matter (PM) from LDV; (4) PM from LDV+HDV); (5) PM+Gas from HDV+LDV; and (6) PM+Gas from LDV. Tissues were collected from subsets of animals within each exposure group at 4, 9, 12 and 15 months of age. As an initial assessment of AD pathology, the ratio of amyloid-beta (Aβ) 40 to 42 in the soluble and insoluble fractions of cortical brain tissue was quantified using ELISA; to evaluate peripheral inflammation, plasma was sent to Eve Technologies (Calgary, Canada) for multiplex analysis of TGF-β1.

Across all exposure groups and in both sexes, the ratio of Aβ 42:40 in the detergent-insoluble fraction was higher at 9 months, decreased at 12 months, and slightly increased at 15 months. When analyzed as the geometric mean ratio (GMR) of the Aβ 42:40 ratio in a TRAP exposure group relative to the value in sex- and age-matched FA controls, the Aβ 42:40 in the PM+Gas(HDV+LDV) was significantly increased in the 15-month old females. In contrast to the detergent-insoluble fraction, the Aβ 42:40 ratio in the detergent-soluble fraction trended towards elevated Aβ 42:40 at 12 months of age with a subsequent decrease at 15 months of age. Analysis of the GMR indicated that the Aβ 42:40 ratio in the detergent-soluble fraction was significantly higher in 9 month-old females in the PM+Gas(HDV+LDV) and the PM+Gas(LDV)

exposure groups relative to sex- and age-matched FA controls. Plasma levels of TGF-β1 trended towards an increase from 4 months to 9 months, and then a noticeable reduction at 12 and 15 months of age.

These data suggest complex effects of TRAP exposure on Aβ 42:40 ratios that vary according to time (age and/or duration of exposure), sex- and specific TRAP fractions. Combined exposure to PM and gas, e.g., PM+Gas(HDV+LDV) and PM+Gas(LDV), were more likely to exacerbate AD pathology than either gas or PM alone. A notable decline in plasma TGF-β1 levels at later timepoints suggest that TRAP effects on peripheral inflammation are time-dependent and transient. Supported by NIA (grant # RF1AG074709).

Poster #2

Quaternary Ammonium Compounds are acutely toxic when delivered directly to lung

Adcock L, Montgomery CB, Barkhordari S, Datta S, Van Winkle LS, Cortopassi G

Dept. of Molecular Biosciences, University of California, Davis, 95616

Quaternary Ammonium Compounds (QACs) have been in use since the 1940's as potent biocides and disinfectants and cleaning supplies. The two most-used QACs in the USA are Benzalkonium Chloride (BAC) and Didecyl-dimethylammonium Chloride (DDAC). QACs effectiveness in killing a variety of microbes led to their increased use as aerosolized sprays, foams, and wipes, and aerosolized QACs are widespread, Clorox alone sells 23 branded products containing BAC as a pump spray.

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Poster #3

The association between fine particulate matter and mitochondrial dysfunction in children

Laura Diaz et al.

University of California, Berkley, School of Public Health

Exposure to fine particulate matter ($PM_{2.5}$) is associated with a proinflammatory state that may lead to adverse health outcomes among children. The impact of this proinflammatory state on mitochondrial function may underlie the relationship between $PM_{2.5}$ exposure and adverse health effects. We aimed to examine the association between $PM_{2.5}$ and mitochondrial DNA copy number (mtDNAcn), a measure of mitochondrial function, in a pediatric population. We performed a cross-sectional analysis of 308 children enrolled in the Pediatric ACEs Screening and Resiliency Study (PEARLS) at Benioff Children's Hospital Oakland, a Federally Qualified Health Center enrolled between 2017-2019. Modeled monthly $PM_{2.5}$ estimates were averaged for the 12 months prior to biospecimen collection. Absolute mtDNAcn was measured in participant buccal swabs. Multivariate linear regression was used to measure the association between $PM_{2.5}$ and mtDNAcn, adjusting for child's age, gender, and caregiver education. The children in our study were predominantly non-Hispanic Black (50.0%), male (53.2 %), and had a mean age of 6 years (SD=3.3). Most caregivers completed high school or greater (87.4%). The median annual average $PM_{2.5}$ concentration was 11.63 μg/m3 (IQR: 2.2); and the median mtDNAcn was 6.69 (IQR: 0.49). We found that a one unit increase in $PM_{2.5}$ was associated with a 0.062 [95% CI = 0.039, 0.085] higher mtDNAcn when adjusting for child's age, gender and caregiver education. Our results suggest that chronic $PM_{2.5}$ exposure is associated with greater mtDNAcn in children, suggesting further exploration of mitochondrial dysfunction as a mechanism for pollution effects on child health.

Poster #4

Perinatal Exposure to Smoke from the 2018 Camp Fire is Associated with Sex-Dependent Weight Changes

Guess, A.[1], Shrestha D.[1], Tran, GVV.[1], Siegel, NA.[1], Miller, LA.[1,2*]

[1] California National Primate Research Center, University of California, Davis

[2] Department of Anatomy, Physiology, and Cell Biology, School of Veterinary Medicine,

University of California Davis, Davis, CA 95616, USA

The 2018 Camp Fire was among the most destructive wildfires in the history of California, with peak fine particulate matter ($PM_{2.5}$) from its smoke reaching "very unhealthy" and "hazardous" air quality conditions throughout northern California. It has been previously reported in a cohort of outdoor-housed rhesus macaque monkeys at the California National Primate Research Center that prenatal exposure to smoke from the 2018 Camp Fire event was associated with an increased risk of pregnancy loss and adverse behavioral effects in offspring at infancy. Based upon these earlier findings, we hypothesized that early life exposure to wildfire smoke is associated with persistent developmental changes. To test this hypothesis, we surveyed animals exposed to smoke from the 2018 Camp Fire in utero or infancy, using weight as a developmental proxy. Age-matched outdoor-housed rhesus macaque monkeys born in 2019 served as controls. Between the dates of November 8, 2018, and November 25, 2018, cumulative daily $PM_{2.5}$ exposure of both early life exposure cohorts peaked at 4,434 μg/m3. Weight data from n=806

monkeys were sampled from archival medical records, and the timeframe was standardized for the control. We observed an increased slope in female exposed cohorts compared to the 2019 control, indicating an association of increased weight in association with the 2018 Camp Fire. However, a decreased weight slope in male exposed cohorts was found compared to the 2019 control was observed, which correlates reduced weight with the 2018 Camp Fire. Our collective findings suggest a sex-dependent response in the physiological development of monkeys that were exposed perinatally to smoke $PM_{2.5}$ from the 2018 Camp Fire.

Poster #5 (LIGHTNING TALK)

Effects of Different Components of Traffic-Related Air Pollution on Alzheimer's Phenotypes in a Transgenic Rat Model of Alzheimer's Disease

Nathifa Nasim[1]*, Heui Hye Park[1], Mei-Yun Cheng[1], Anthony E. Valenzuela[1], Keith J. Bein[2], Anthony Wexler[2], Pamela J. Lein[1]

[1] Molecular Biosciences, School of Veterinary Medicine, University of California, Davis, CA, USA
[2] Air Quality Research Center, University of California, Davis, CA, USA

One of the environmental risk factors associated with Alzheimer's disease (AD) is near roadway exposure to traffic-related air pollution (TRAP). TRAP is a heterogeneous mixture of particulate matter (PM), volatile organic compounds, and gases. Both epidemiological and experimental studies have demonstrated a causal link between chronic exposure to ambient TRAP and the development of AD-relevant neurological outcomes. However, how specific components of TRAP affect AD, and which components are the primary drivers of neurodegenerative effects remain unclear. To address this, we utilized a transgenic AD rat model subjected to chronic ambient TRAP exposure. Six exposure groups were used to differentiate the effects of PM and gases, individually or in combination, as well as exposure to emissions from diesel and non-diesel vehicles. Amyloid plaques, neurofibrillary tangles, and neuronal counts in AD-affected brain regions were analyzed via immunohistochemistry at 4, 9, 12, and 15 months of age. Our findings revealed that the impact of TRAP on amyloid deposition in the brain varied based on the type of exposure, sex, brain region, and duration of exposure. Compared to sex- and age-matched filtered air controls, increased amyloid deposition was observed in 9-month-old females and 15-month-old animals exposed to both gases and PM, or PM alone. TRAP exposed animals also demonstrated increased rate of amyloid aggregation, in the entorhinal cortex. Notably, these changes were detected using immunohistochemistry targeting early amyloid aggregations, but were not observed with stains identifying later-stage fibrils, suggesting that TRAP may play a role in the early stages of AD. This was supported by the absence of neuronal loss relative to controls. Overall, our observations suggest that PM is a critical component of TRAP's effect on AD, and that its effects are modulated by both sex and age. These observations support further research into other aspects of AD pathology in these exposure groups to delineate the route of exposure for PM and mechanism of TRAP-mediated AD effects. Identifying PM as a critical component of TRAP driven effects on AD is also important for informing future regulatory policy to reduce risk for those living, working or attending schools near roadways.

*This author will present a lightning talk.

Poster #6

Acute Wood Smoke Exposure Elevates Markers of Neuroinflammation in Mouse Hippocampus

Angela Tang-Tan[1], Alexandra Demetriou[1], Kristina Shkirkova[1], Selena Chen[1], Caleb Franklin[1], Sindhu Daggupati[1], Christine Bent[1], Lifu Zhao[1], Max A. Thorwald[2], Jose Godoy Lugo[2], Ariel Sauri[2], Constantinos Sioutas[3], Christian Pike[2], David Scieszka[4], Matthew Campen[4], Caleb E. Finch[2], William J. Mack[1]

[1] Keck School of Medicine, Department of Neurosurgery, University of Southern California
[2] Leonard Davis School of Gerontology, University of Southern California
[3] Viterbi School of Engineering, University of Southern California
[4] Department of Pharmaceutical Sciences, College of Pharmacy, University of New Mexico

Exposure to wildfire particulate matter may induce neurotoxicity that contributes to brain aging processes and potentially increasing the risk of neurodegenerative diseases. Previous studies from our group have investigated the neurotoxicity of other inhaled toxins including nanoparticulate matter (nPM) and diesel exhaust particulate (DEP). Wood smoke inhalation is increasingly relevant as broad swathes of the United States are impacted by seasonal wildfires; however, few studies have examined the specific effects neurotoxicity of acute wood smoke exposure in an animal model. This study investigated the relationship between acute wood smoke exposure and markers of microglial activation, oxidative damage, white matter integrity, and complement activation in young male and female wildtype mice.

Two-month-old male and female C57BL/6J mice were exposed to inhaled wood smoke for a single four-hour session at an average exposure concentration of 500 µg/m³. Mice were humanely euthanized and frozen brain hemispheres sectioned at 15 µm. Levels of ionized calcium-binding adapter molecule 1 (IBA1), 4-hydroxynonenal (4-HNE), 8-Oxo-2'-deoxyguanosine (8-OHDG), C5 complement protein, C5a, and degraded myelin basic protein (dMBP) were assayed via immunofluorescence. Regions assayed included the corpus callosum as well as the CA1 and dentate gyrus regions of the hippocampus.

In mice exposed to wood smoke, the CA1 Radiatum region of the hippocampus demonstrated increased C5 (+95%, $p<0.001$). No additional significant findings were noted from markers IBA1, 4-HNE, 8-OHDG, C5a, or dMBP in the corpus callosum or hippocampus.
4-hour wood smoke exposure activated complement as signified by elevation of C5 in the hippocampal CA1 region, which plays a role in input integration and memory retrieval. The absence of significant increases in other markers of oxidative stress, microglial activation, and myelin damage contrasts with major increases in oxidative stress and microglial activation that we showed in mice after an acute 5-hour DEP exposure. Notably, 5-hour DEP exposure did not result in C5 elevation. Together, these findings better characterize the brain's response to different environmental toxins.

These findings were previously presented at the 2024 Bridging the Gap Summer Student Research Symposium at the Keck School of Medicine of USC.

Acknowledgements: These studies were supported by National Institute of Aging grants to CE Finch (P01 AG055367) and M Campen (R01ES026673)

Poster #7

Urinary Biomarkers of Air Pollution Exposure in Schoolchildren from California

Guo W.[1], Castorina R.[1], Hurley S.[2], Sultana D.[3], Bradman A.[4], Holland N.[1]

[1]University of California, Berkeley
[2]California Department of Public Health
[3]Office of Environmental Health Hazard Assessment, [4]University of California, Merced

Air pollution is a growing concern worldwide including California, due to increased wildfires and extreme heat waves caused by climate change. Exposure to air pollution is associated with adverse health effects such as asthma, lung cancer, and cardiovascular diseases. Children are among the most vulnerable populations. This study aimed to evaluate the biomarkers of oxidative stress and inflammation in relation to biomarkers of air pollution in children. Children (4-14yr) were recruited from an AB 617 school in Stockton, CA, under the Stockton Air Pollution Exposure Project. Repeated samples (n = 67) were collected over a two-week period in December 2021. Urinary biomarkers of oxidative stress (8-Isop and 8-OHdG) and inflammation (PGE2 and CC16) were measured using ELISA. Urinary metabolites of VOCs including acrolein, acrylonitrile, benzene, 1,3-butadiene, crotonaldehyde and propylene oxide and PAHs including fluorene, naphthalene, phenanthrene and pyrene were measured using LC-MS/MS. Specific gravity adjustment and Random effects model were used for statistical analysis. Biomarkers of oxidative stress and inflammation varied by age, gender, and BMI being higher in older children, boys, and children with higher BMI, and were correlated with each other. 8-Isop was significantly associated with 5 metabolites of VOCs and PAHs, 8-OHdG with two metabolites while CC16 and PGE showed positive association with 3 metabolites, but not the same ones. Use a panel of four biomarkers captured potential early effects of air pollution more comprehensively in children. Urinary biomarkers of oxidative stress and inflammation are useful tools for biomonitoring of air pollution.

Poster #8

Understanding PFAS Toxicity Through Transthyretin Binding

Nuno M. S. Almeida[1], Anatoly Soshilov[1,*]

California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, 1001 I St, Sacramento, CA, 95814, USA

Per- and polyfluoroalkyl (PFAS) substances are man-made chemicals that have major implications in human and animal health. One of the proposed mechanisms of PFAS thyroid toxicity is through displacement of 3,3′,5-triiodothyronine (T3) and thyroxine (T4) from the serum transport protein transthyretin (TTR). In this investigation, computational approaches were utilized to understand how PFAS bind to TTR including docking, molecular dynamics (MD), and quantitative structure activity relationship (QSAR) models. The human docking model worked best for PFAS with

carboxylic acidic groups up to eight carbons (R^2=0.7). Two developed QSAR models offered reliable and accurate approaches to predicting activity against TTR for a large range of PFAS. MD simulations demonstrated overall similar affinities for PFAS-TTR binding in human and rat models despite distinct interactions with key amino residues. All developed models predict TTR binding for alternative PFAS of environmental relevance, GenX, and ADONA that lack experimental data.

Building Logistics

The CalEPA building (1001 "I" Street, Sacramento, CA 95814) entrance is at 10th and I streets. For more information, go to: https://calepa.ca.gov/headquarters-sacramento/location/

Check-in and obtain a badge from security in the main lobby of the building. The Sierra Hearing Room is on the second floor and is accessible via stairs or elevator.

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