Genetic and Environmental Toxicology Association of Northern California (GETA)

2023 Fall Hybrid Symposium

Thursday, October 19th, 1:30-5 PM (PT)

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_rcAcAKlSTKaFFf7_sW6dWw

Unraveling the Impact of Environmental Toxicants on Alzheimer's and Parkinson's Disease

Speakers:

- **Dr. Caleb Finch,** Professor in Leonard Davis School of Gerontology, University of Southern California. "*Air pollution and dementia in the social economic status (SES) gradient of aging.*"
- **Dr. Pamela Lein,** Department Chair and Professor in Molecular Biosciences, University of California, Davis. "*The effects of chronic exposure to ambient traffic-related air pollution on Alzheimer's disease phenotypes in wildtype and genetically-predisposed male and female rats.*"
- **Dr. Samuel Goldman,** Professor in School of Medicine, University of California, San Francisco. "*Searching for Gene-Environment Interaction in Parkinson's Disease."*

http://getanorcal.org/

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Program

12:30 - 1:30 pm	Registration, Reception, and Poster Session
1:30 - 1:40 pm	Welcome
1:40 - 2:25 pm	**Dr. Finch's talk and Q&A**
2:25 - 3:10 pm	**Dr. Lein's talk and Q&A**
3:10 – 3:15 pm	1st Lighting talk (Kevin Thai, UCR)
3:15 - 3:40 pm	Break and Poster Session
3:40 – 3:45 pm	2nd Lighting talk (Hector Delgadillo, UCD)
3:45 – 4:30 pm	**Dr. Goldman's talk and Q&A**
4:30 – 5:00 pm	Panel discussion [**Dr. Miller** will join with 3 speakers] and Wrap-up
5:10 – 6:30 pm	Happy Hour at La Cosecha (917 9th St, Sacramento, CA 95814)

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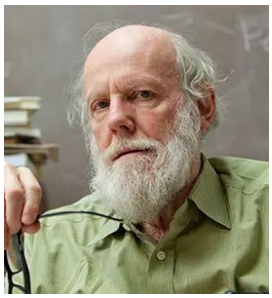
Keynote Speaker Abstracts

Air pollution and dementia in the social economic status (SES) gradient of aging

Dr. Caleb Finch,
Professor in Leonard Davis School of Gerontology,
University of Southern California.
cefinch@usc.edu



Biography

Caleb Finch, PhD, researches the basic mechanisms in human aging with a focus on inflammation. He has received most of the major awards in biomedical gerontology, including the Robert W. Kleemeier Award of the Gerontological Society of America in 1985, the Sandoz Premier Prize by the International Geriatric Association in 1995, and the Irving Wright Award of AFAR and the Research Award of AGE in 1999. He was the founder of the NIA-funded Alzheimer Disease Research Center in 1984. Finch became a University Distinguished Professor in 1989, an honor held by thirty other professors at USC who contribute to multiple fields. In 2018 Finch received an honorary doctorate from The French Academy. Dr. Finch has written six books and 600 articles.

Abstract

The modest heritability of human lifespan indicates the major importance of environmental and lifestyle in outcomes of aging. Across the US, college education is associated with a 10 year longer healthy lifespan and later onset of dementia than those with less than high school. In the Sacramento Area Latino Study on Aging (SALSA), the risk of dementia was proportionate to education level; moreover, high risk of dementia persisted for those with early exposure to social disadvantage who improved status as adult life[1]. Because household poverty is often associated with living near a roadway and adult smoking, we hypothesize that air pollution is a factor in these associations. In many populations, exposure to elevated air pollution increases risk of dementia; metabolism is also impacted with increased obesity[2].
As experimental models for air pollution exposure, adult mice were exposed to Los Angeles air pollution. Alzheimer-like changes included increased production of the amyloid peptide and loss of neuronal stem cells[3]. Moreover, gestational exposure to air pollution increased adult obesity and loss of neuronal stem cells[4]. These findings are consistent with the SALSA outcome that low SES increases dementia risk, even in those reaching higher SES as adults.

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[1] Zeki Al Hazzaouri A. et al. *Am J Epidemiol* 2011.
[2] Finch CE. *The Role of Global Air Pollution in Aging and Disease. Reading Smoke Signals, Academic Press, 2018.*
[3] Cacciottolo M et al. *Transl Psychiatry* 2017. Haghani A et al. *Elife* 2020.
[4] Haghani A et al. *Transl Psychiatry*, 2020.

The effects of chronic exposure to ambient traffic-related air pollution on Alzheimer's disease phenotypes in wildtype and genetically-predisposed male and female rats

Dr. Pamela Lein
Department Chair and Professor in Molecular Biosciences,
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Biography

Pamela (Pam) Lein earned a B.S. in Biology from Cornell University in Ithaca, NY, a M.S. in Environmental Health Sciences from East Tennessee State University in Johnson City, TN, and a Ph.D. in Pharmacology and Toxicology from the University of Buffalo in Buffalo, NY. She completed postdoctoral training in Molecular Immunology at the Roswell Park Cancer Institute in Buffalo, NY. Currently, Dr. Lein is Professor of Neurotoxicology and Chair of the Department of Molecular Biosciences in the University of California, Davis (UC Davis) School of Veterinary Medicine, and she holds a faculty appointment in the UC Davis MIND Institute. Her research focuses on the cellular and molecular mechanisms by which environmental stressors contribute to the pathogenesis of neurodevelopmental and neurodegenerative disorders. Dr. Lein has been continuously funded by the U.S. National Institutes of Health for over 30 years, and she has >275 peer-reviewed publications and book chapters. She is actively engaged in teaching and mentoring veterinary, graduate and undergraduate students in neuropharmacology and neurotoxicology. Her service activities include Director of the Career Development Program in the NIEHS-funded Environmental Health Sciences Center at UC Davis, Director and PI of the NIH-funded UC Davis CounterACT Center of Excellence, and Co-Editor-in-Chief of the journal *NeuroToxicology*.

Abstract

Epidemiological studies consistently link traffic-related air pollution (TRAP) to increased risk of Alzheimer's disease (AD). Preclinical data corroborating this association are largely from studies of male animals exposed acutely or subchronically to high levels of isolated fractions of TRAP. What remains unclear is whether chronic exposure to ambient TRAP modifies AD risk and the influence of sex on this interaction. To address these gaps, male and female TgF344-AD rats (Tg) that express human AD risk genes and wildtype (WT) littermates were housed in a vivarium adjacent to a heavily trafficked tunnel in Northern California and exposed for up to 14 months to filtered air (FA) or TRAP drawn from the tunnel and delivered to animals unchanged in real-time. Particulate matter (PM) concentrations in TRAP exposure chambers fluctuated with traffic flow but remained below 24-hour PM2.5 NAAQS limits. Ultrafine PM was a predominant component of TRAP, and nano-sized refractive particles were detected in the hippocampus of TRAP males and females by hyperspectral imaging. TRAP accelerated amyloid proteinopathy in Tg males and females, increased phosphorylated tau in WT males, promoted neuronal cell loss in both genotypes and sexes, and caused cognitive deficits in WT males. TRAP had no effect on

astrogliosis, but modulated microglial cell activation in Tg and WT males and females, although the temporal profile varied between sexes. The results of this realistic, chronic, and low-concentration exposure suggest that ambient TRAP promotes the progression of AD via complicated interactions with age, sex, and genotype. These findings suggest current PM2.5 regulations are insufficient to protect the aging brain. All animal studies were conducted humanely and in accordance with protocols approved by the University of California, Davis Institutional Animal Care and Use Committee. Supported by the NIEHS (grants R21 ES025570, P30 ES023513 and T32 ES007059) and NIA (grant P30AG010129).

Searching for Gene-Environment Interaction in Parkinson's Disease

Dr. Samuel Goldman,
Professor in School of Medicine,
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samuel.goldman@ucsf.edu

Biography

Sam Goldman is a Professor in the Division of Occupational, Environmental, and Climate Medicine and the Department of Neurology at UCSF, and an investigator at the San Francisco VA Health Care System. Prior to joining UCSF, Sam was a senior research scientist for many years at the Parkinson's Institute in Sunnyvale, CA. Sam studied neuroscience at the University of Michigan, attended medical school at the University of Texas Houston, and trained in Preventive Medicine and Environmental Health Science at UC Berkeley. He has published extensively on the epidemiology of Parkinson's disease and other neurodegenerative diseases, with a focus on environmental risk factors and their genetic interactions. In addition to his ongoing research and work with the OEM residency program, Sam has begun an intensive study of the foods, wines, and lifestyle of southern Spain.

Abstract

Parkinson's disease is the fastest growing neurological disease in the world. Although genetic forms have been identified, epidemiology increasingly implicates environmental risk factors as major determinants. I will briefly review the disease phenomenology and descriptive epidemiology before providing evidence to support the environmental hypothesis. After reviewing associations with pesticides and solvents, I will discuss the challenges of investigating gene-environment interactions and present several examples of synergistic interaction from our research group, with a focus on ongoing work and future directions.

Panelist

Gary W. Miller, Ph.D.

Vice Dean for Research Strategy and Innovation
Professor of Environmental Health Sciences
Mailman School of Public Health
Columbia University, New York, NY, USA
gary.miller@columbia.edu

Biography

Dr. Miller serves as Vice Dean for Research Strategy and Innovation and Professor of Environmental Health Sciences in the Mailman School of Public Health, and Professor of Molecular Pharmacology and Therapeutics in the Vagelos College of Physicians and Surgeons at Columbia University in New York. He completed his PhD in Pharmacology and Toxicology and postdoctoral training in Molecular Neuroscience. His laboratory studies the role of environmental factors in neurodegenerative diseases, including Parkinson's disease and Alzheimer's disease. Dr. Miller founded the first exposome center in the U.S. and wrote the first book on the topic. He has helped develop high-resolution mass spectrometry methods to provide an omic-scale analysis of the human exposome. He is a member of the National Institutes of Health All of Us Research Program Advisory Panel and the National Institute of Environmental Health Sciences Advisory Council. Dr. Miller is the founding editor of the new journal *Exposome*, published by Oxford University Press.

Poster Presentation Abstracts

Poster #1

Perfluorododecanoic Acid (PFDoA) and cancer progression in three breast cancer models

*Hector A. Delgadillo[1], Shenq-Shyang Huang[1], Aman Singla[1], Hidetoshi Mori[2], Michele A. La Merrill[1]

[1] Department of Environmental Toxicology, University of California, Davis, CA, [2] Pathology & Lab Medicine, University of California, Davis, CA

Per- and polyfluoroalkyl substances (PFAS) are a class of compounds commonly used as surfactants in food contact materials and household items due to their hydrophobicity. However, their physicochemical properties render them highly resistant to degradation in the environment and human body. Thus, these chemicals are environmentally ubiquitous and are estimated to be found in the serum of 98% of U.S. citizens. Additionally, evidence shows PFAS are linked to cancer progression and endocrine disruption, though the mechanisms remain unclear.

This research analyzes the effects of PFDoA ($C_{12}HF_{23}O_2$) on breast cancer viability, invasion, and migration *in vitro*. Using the aggressive human cell line Hs578T and mouse cell line UCD-PyMT, the effects of PFDoA are analyzed across environmentally relevant doses. Viable cell number is assessed through Trypan Blue Exclusion Assays; migration is assessed through Transwell Invasion Assays; and invasion is assessed through 2.5D and 3D Culture Assays using Matrigel. Results show an increasing dose-response trend in cell viability, increased migration at 100nM PFDoA, and increased spheroid invasion and protrusion quantity among all PFDoA doses tested. 2.5D results are currently being collected.

The results will help us better understand whether PFDoA, a CalEPA priority chemical, increases cancer progression as other PFAS have been shown to do and may help explain increasing cancer rate trends in younger people.

*****The author also presents a lighting talk.

Poster #2

Organochlorine Pesticide Exposure and Biomarkers of Inflammation and Cognition in Latina Women from the CHAMACOS Cohort

Weihong Guo[1], Robert Gunier[1], Marcella L Warner[1], Lucia Calderon[2], Katherine Kogut[1], Sruthi Vatsavai[1], Brenda Eskenazi[1], Julianna Deardorff[1], Jacqueline Torres[2], Nina Holland[1]

[1]University of California, Berkeley, CA, [2]University of California, San Francisco, CA

Introduction: Organochlorine (OC) pesticides have long half-lives, and may affect multiple biological systems and health outcomes. Interleukin 6 (IL-6) and C-Reactive Protein (CRP) are biomarkers of inflammation. Apolipoprotein E (Apo-E) is a biomarker of cognition and may predict the risk of developing dementia. We evaluated the relationship between OC pesticide exposures and these biomarkers in middle-aged Latina women living in agricultural Salinas Valley, CA and participating in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study.

Methods: The 451 women (39-65yr, >90% overweight/obese) were mostly first-generation immigrants from Mexico where DDT was used until 2000. OCs, including dichlorodiphenyldichloroethylene (DDE), dichlorodiphenyltrichloroethane (DDT), hexachlorobenzene (HCB), beta-hexachlorocyclohexane (β-HCH), and trans-nonachlor, were measured using high resolution gas chromatography mass spectrometry in blood collected from 2009-2010. The levels of IL-6 and Apo-E were measured by ELISA, and CRP was tested by hsCRP in blood collected in 2022-2023. We assessed the relationship between the OCs and biomarkers using linear regression models.

Results: CRP levels were associated with BMI, and exceeded the normal clinical range in the majority of women. IL-6, moderately correlated with CRP ($r=0.52$, $p<0.01$), was associated with age and BMI. IL-6 and CRP were associated with β-HCH ($p<0.018$, $p<0.028$) but not with other OCs. Apo-E levels were inversely associated with DDE ($p<0.018$), DDT ($p<0.074$), and β-HCH ($p<0.019$).

Conclusions: Among these middle-aged Latina women, OC pesticide levels were associated with biomarkers of inflammation and cognition >10 years later, suggesting that earlier life exposure may have long lasting negative health effects.

Poster #3

Evaluating health risks posed by pesticide residues on cannabis and hemp: California's novel approach

Anna A. Kalashnikova, Qiaoxiang Dong, Rachel Kubiak, Andrew L. Rubin, Svetlana Koshlukova, Shelley DuTeaux

Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA, USA.

Legalization of hemp in the US has prompted many states to approve hemp extracts (*e.g.*, cannabidiol) for use as ingredients in dietary supplements, food additives, and cosmetics. This raises questions regarding the regulation of pesticides in these products. Cannabis, for which cultivation, sale, and use remain prohibited at the federal level, already undergoes extensive pesticide testing in states where it is legally grown and sold. California's Department of Pesticide Regulation (DPR) established limits on allowable pesticide residues, referred to as "action levels," on cannabis products such as foods, drinks, tinctures, cured flowers intended for smoking, and cartridges intended for vaporization. To reduce public health risks, cannabis products cannot be sold in California if they contain pesticide residues that exceed these action levels. The main challenge to evaluating health risks from pesticide residues in cannabis products stems from a lack of residue and consumption data, both of which are critical to calculating exposure. An additional challenge is the potential for creation or release of toxic compounds when pesticides are heated or oxidized at high temperatures (pyrolysis) during smoking or vaping. To overcome both challenges, DPR developed a health-based approach to establishing pesticide action levels on cannabis in edible and inhalable products, to be used during cannabis product compliance testing. For edible products, action levels were set pesticides as residue threshold values calculated using a maximum consumption rate For inhalable products (flowers, vapes, etc.), DPR adopted threshold limit values established for tobacco along with new

methodology built-in for health protectiveness assessment. These methodologies incorporated consumption data for cannabis flowers generated by the ongoing California Cannabis Consumption Survey, as well as toxicity determinations for pyrolysis products.

DPR has developed a framework for assessing health risks from pesticide residues on cannabis products resulting in California being the first state to have health-based approaches and methodologies to establish action levels for pesticides on cannabis. Such approaches and methodology could be applied by regulatory agencies seeking to assess the health impact of pesticide residues on hemp products.

Poster #4

Contaminants in Biosynthetic Natural Gas

Leona Scanlan, Ken Kloc, Álvaro Alvarado

Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA, USA.

Biosynthetic natural gas (bioSNG) is methane that is produced from biomass such as almond husks or tree trimmings. The State of California is researching bioSNG's potential as a renewable source of methane that can be injected into natural gas pipelines throughout the state. The California Office of Environmental Health Hazard Assessment (OEHHA) is evaluating the human health risks associated with exposure to toxic trace contaminants that may be present in bioSNG and its combustion products.

We first conducted a systematic literature review to identify potential trace contaminants of concern (COC) in bioSNG and in precursor fuels. A total of 392 documents were identified as potentially relevant: only two reported measurements of contaminants in bioSNG. Thirty-four articles reported measurements of contaminants in bioSNG precursor gasses. We built a priority COC list that includes benzene, naphthalene, and nickel. Next, we are using Health Guidance Values (HGVs) to calculate concentrations of each COC in pipeline gas that would be protective of human health. For this, we assumed several realistic end-user exposure scenarios. Our evaluation will be periodically updated as more data on bioSNG trace contaminants becomes available.

This work product will be used by the California Public Utilities Commission and the California Air Resources Board to establish pipeline standards for bioSNG injected into natural gas pipelines in California.

Poster #5

The Effect of Wildfire Smoke Events and Wildfire PM2.5 on Children's Health: A Systematic Review

Amal Syed, Rupa Basu, Nancy Firchow

Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA, USA.

Importance: With global wildfires increasing, understanding the health issues caused by exposure to wildfire smoke and its associated pollutants, especially Fine Particulate Matter (PM2.5), is extremely important for healthcare providers and public health officials. Children and adolescents may be more exposed to wildfire smoke and more physiologically vulnerable to adverse health outcomes.

Objective: The objective of this literature review is to complete a comprehensive investigation of epidemiological studies examining a variety of health impacts of wildfires, wildfire smoke, and wildfire-specific particulate matter on children's health and wellness, globally. The aim is to identify research gaps and to inform decision-making to promote the well-being of children in wildfire-affected areas.

Evidence Review: Epidemiological studies that were published from January 1, 2006, to January 31, 2023, were eligible. The population of interest was individuals under the age of 18. Studies were included if they had wildfire event days, wildfire smoke exposure, or wildfire specific PM2.5 and PM10, as the main exposure and if they had an outcome related to children's health and well-being. There were no geographical limitations.

Findings: A total of 21 studies were included in this review. Seventeen out of the total 21 studies included the examination of respiratory outcomes in children and seven studies investigated non-respiratory outcomes. The 21 studies spanned multiple countries outside of the United States including Chile, Spain, and Australia. Of the 14 studies that examined adverse respiratory symptoms, 12 (86%) reported a significant increase in adverse respiratory symptoms due to the presence of/proximity to wildfires. Of the eight studies that looked at respiratory-related physician or emergency room visits or hospital/emergency room admissions, seven (86%) reported a significant increase in visits and admissions. Of the five studies that looked at medication usage due to symptoms caused by wildfire smoke exposure, two (40%) found significant positive associations. For non-respiratory outcomes, like physical activity, academic success, child mortality, immune response, and dermatological symptoms, all outcomes, except physical activity, had significant positive associations with wildfire smoke or events. The populations with the highest risk were asthmatic children, children residing in low-income countries, and children in families with a low socioeconomic status.

Conclusions and Relevance: This review suggests that wildfire smoke, wildfire event days, or exposure to wildfire-specific PM2.5 can have physiological (respiratory and non-respiratory) and behavioral effects on pediatric health and wellness, globally. Our findings show that while the present studies provide a solid baseline for the understanding of pediatric exposure and adverse respiratory outcomes, there is a need for further research on non-respiratory outcomes, like

mental health, academic success, and physical activity, that could negatively affect pediatric health and wellness.

Poster #6

Testing the multistage model and evolution-based predictions with global incidence data across 75 cancer sites

*Kevin Thai, Leonard Nunney

Department of Evolution, Ecology and Organismal Biology, University of California, Riverside, CA

The multistage model has long been used as the foundation for our understanding of cancer initiation. It describes cancer initiation as the result of an accumulation of somatic mutations in a single cell lineage. The model predicts a linear log-log regression between incidence and age, for a given cancer site, where the number of stages (*M*) can be estimated by one greater than the slope of the regression. By incorporating evolutionary principles into the multistage model, the Evolutionary Model of Carcinogenesis (EMMC) further predicts that the amount of evolved suppression (i.e. *M*) for a given site will depend on the intrinsic cancer risk of a given tissue, resulting in a steeper log-log slope for a high-risk tissue. The purpose of this work is to test the validity of these predictions using a large, detailed, and global age-incidence dataset of 75 human cancer types from 68 different countries, grouped into six continents. The linearity prediction of the multistage model was strongly supported: over 90% of sites were found to have linear regressions ($r \geq 0.9$) through adulthood with over half of these sites having near perfect linear fits explaining ≥98% variance ($r \geq 0.99$). We tested differences in intrinsic risk by comparing carcinomas, which generally originate in tissues with a high intrinsic risk given their relatively high division rates and large tissue sizes, against sarcomas and found carcinomas had a significantly higher *M*. The results validate the continued use of the multistage model for evaluating carcinogen risk for humans and the benefits of incorporating evolutionary principles to further refine expectations.

*The author also presents a lighting talk.

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.

Parking is available in numerous lots in Sacramento, and the Sacramento Valley Amtrak station is six blocks away. The map below shows parking and train options.