# Variability and Relevance of Current Laboratory Mammalian Toxicity Tests and Expectations for New Approach Methods (NAMs) for use in Human Health Risk Assessment

## Committee

## Weihsueh A. Chiu

**Chair**

Weihsueh A. Chiu (Chair) is a professor in the Department of Veterinary Integrative Biosciences at Texas A&M University. He also has a Research Fellow appointment at the Institute for Science, Technology, and Public Policy at the Bush School of Government and Public Service. Before joining the university in 2015, he worked at the U.S. Environmental Protection Agency (EPA) for more than 14 years, most recently as branch chief in the Office or Research and Development. His research in human health risk assessment includes toxicokinetics, physiologically-based pharmacokinetic modeling, dose-response assessment, characterizing uncertainty and variability, systematic review, and meta-analysis, with particular interest in Bayesian and probabilistic methods. He is author/co-author of over 100 peer-reviewed journal publications, many governmental and international agency reports, and several book chapters. Dr. Chiu has participated or chaired expert review panels for multiple government agencies (including membership on EPA's Science Advisory Board with a dual appointment on the Chemical Assessment Advisory Committee), international committees, and work groups. He has served on six National Academies of Sciences, Engineering and Medicine committees, including the Committee on Predictive-Toxicology Approaches for Military Assessments of Acute Exposures, the Standing Committee on Use of Emerging Science for Environmental Health Decisions, and the Committee to Review the IRIS Handbook. Dr. Chiu received an AB in Physics from Harvard University, a MA and PhD in Physics from Princeton University, and a Certificate in Science, Technology, and Environmental Policy from the Princeton School of Public and International Affairs.

## Kim Boekelheide

**Member**

Kim Boekelheide is Professor (Research) and Professor (Emeritus) in the Department of Pathology and Laboratory Medicine at the Brown University School of Medicine. He received his B.A. from Harvard University, and M.D. and Ph.D. from Duke University. Current research projects include the development of novel in vitro approaches to safety assessment and the discovery of sperm molecular biomarkers that reflect testicular injury. He was Director (2005-2016) of the Brown University Superfund Research Program and Director (2014-2017) of the Brown University Center to Advance Predictive Biology. His research has been continuously funded by the National Institute of Environmental Health Sciences since 1985 and he has received several awards including a Burroughs Wellcome Toxicology Scholar Award (1994-1999), and the Lifetime Achievement Award (2015) from the Reproductive and Developmental Toxicology Specialty Section of the Society of Toxicology. He served as member (2005-2007) of the NAS committee that produced the report “Toxicity Testing in the 21st Century: A Vision and a Strategy.” Since 2012, he has been a member, Chair, and Co-Chair of the NAS committee Emerging Science for Environmental Health Decision Making.

## Holly Davies

**Member**

Holly Davies is a Senior Toxicologist at the Washington State Department of Health with expertise in human health and ecological risk assessment, alternatives assessment, in vitro assay development, and chemical policy. Her work has focused on evaluating uses of toxic chemicals, including chemicals of emerging concern and persistent, bioaccumulative, and toxic chemicals (PBTs), and identifying actions needed to protect human health and the environment. Dr. Davies is a member of the Association for the Advancement of Alternatives Assessment and actively participates in the Children's Environmental Health Working Group within the Washington Chapter of the Collaborative on Health and the Environment. She has been a member of EPA’s Chemical Safety Advisory Committee (CSAC) and Science Advisory Committee on Chemicals (SACC) and served on EPA’s Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel on New Approach Methodologies. Her postdoctoral research is on mammalian reproduction and development, transcription factors, and genomics.

## Corie A. Ellison

**Member**

Corie A. Ellison received a Ph.D. degree in Pharmacology and Toxicology from the School of Medicine and Biomedical Sciences at The State University of New York at Buffalo. After graduation, he joined The Procter & Gamble Company as a Toxicologist in the Global Product Stewardship organization. Currently, Dr. Ellison is a Group Scientist in the Central Product Safety division where he leads several research projects as well as the human safety program for multiple technologies in P&G's global cosmetic businesses. He has expertise in pharmacokinetics, i.e., Absorption, Distribution, Metabolism and Excretion (ADME), and uses this knowledge to develop innovative approaches using physiologically-based pharmacokinetic (PBPK) models to predict systemic exposure and refine/advance the quantitative risk assessment for consumer products. Additionally, Dr. Ellison has authored multiple publications showing the utility of new approach methods in an animal free human safety assessment.

## Marie C. Fortin

**Member**

Marie C. Fortin is Associate Director of Toxicology at Jazz Pharmaceuticals. In this role, she designs nonclinical safety drug development programs to meet regulatory expectations and support adequate safety evaluation while optimizing consideration of the 3Rs. She develops in vitro and in vivo study protocols and oversees safety pharmacology and investigative and regulatory toxicology (non-GLP and GLP) studies. In addition, she contributes critical input on other aspects of drug development such as pharmacology and pharmacokinetics, evaluation of the risk-benefit ratio, and determination of first-in-human dose. As toxicology lead on multiple cross-functional teams, she authors the relevant sections or regulatory submissions and represents the toxicology function in regulatory interactions. In addition, Dr. Fortin is Adjunct Professor in the Department of Pharmacology and Toxicology at the Ernest Mario School of Pharmacy at Rutgers University where she mentors graduate students, teaches in the Joint Program in Toxicology, and co-directs the graduate risk assessment course. In her previous industry and consulting roles, she authored or oversaw the development of multiple human health risk assessments for pesticides, metals, pharmaceuticals, cosmetic ingredients, and chemicals for all routes of exposure (oral, inhalation, dermal, parenteral) and managed an in vitro safety testing laboratory focused on organotypic models. Dr. Fortin is a Board-certified and European-registered toxicologist who is particularly interested in the integration of new approaches to support the safety evaluation of pharmaceuticals and their translational application to the risk assessment of chemicals. She has received both her M.Sc. in Neurosciences (2004) and Ph.D. in Public Health - Toxicology (2009) from the Université de Montréal and completed a Postdoctoral Fellowship at the University of Medicine and Dentistry of New Jersey (now part of Rutgers University) (2011).

# Nancy E. Lane

**Member**

Nancy E. Lane (NAM) is an Endowed Professor of Medicine, Rheumatology, and Aging Research, Director for the Center for Musculoskeletal Health, Director of the K12 NIH Building Interdisciplinary Research Careers in Women's Health (BIRCWH), and Principal Investigator of the NIH funded Program on Sex Differences in Musculoskeletal Diseases Across the Lifespan at the University of California at Davis School of Medicine where she has served for the past 12 years. Dr. Lane is an internationally recognized scientist in the fields of both osteoporosis and osteoarthritis. As a translational scientist, she has significant experience in pre-clinical toxicity models for studies of human disease. She has supervised pre-clinical toxicology studies, including for FDA INDs, and has extensive experience in both validation and interpretation of the results. Her translational research team has been instrumental in defining the role of glucocorticoids in bone fragility including their effects on cell stress and vulnerable cell populations including osteocytes. As a faculty member at the University of California at San Francisco, she pioneered a seminal clinical trial to demonstrate that daily injections of the hormone PTH could reverse glucocorticoid induced osteoporosis, and performed research on the rate of recovery of immobilization induced bone loss. After transitioning to U.C. Davis, she a developed a novel compound to direct stem cells to the bone to grow new bone and treat osteoporosis. In addition she has uncovered novel genetic variations that predispose individuals to osteoarthritis and has studied novel treatments for osteoarthritis. Her research accomplishments have been recognized by the UC Davis School of Medicine Dean's Team Science Award (2012), the American College of Rheumatology for the Oscar Gluck Memorial Lecture for outstanding work in Osteoporosis (2011), the Remodeling in Bone “RIB Award” by the International Society of Bone and Mineral Research (2012), her election as a Master of the American College of Physicians (2012) and David Trentham Lectureship and Women in Medicine Lectureship at Harvard Medical School (2013).. She is also the recipient of the Bone and Joint Decade Outstanding Achievement Award for developing a mentoring program in grant writing (2009). Dr. Lane was President of the Board of the United States Bone and Joint Decade (2006-2008), co-led the International Bone and Joint Decade Conference in Washington DC (2010), was elected and served on the council of the American Society of Bone and Mineral Research (2010-2013), and the Orthopedic Research Society (2003-2005). Dr. Lane is on the editorial boards of Nature Reviews Rheumatology, Rheumatology (Associate Editor), Seminars in Arthritis and Rheumatism (Associate Editor), Co-editor Arthritis and Rheumatism (2005-2010), Journal of Rheumatology. Dr. Lane was elected to the National Academy of Medicine in 2013.

## Heather B. Patisaul

**Member**

Heather B. Patisaul is the Associate Dean for Research in the College of Sciences and a professor in the Department of Biological Sciences at North Carolina State University. She explores the mechanisms by which endocrine disrupting compounds (EDCs) alter neuroendocrine pathways in the brain related to sex specific physiology and behavior. She is specifically interested in phytoestrogens, flame retardants, and BPA (Bisphenol A). Dr. Patisaul is a NIEHS ONES Award recipient (2007) and has participated on several national and international expert panels and workshops related to health effects associated with soy, BPA, and other endocrine disruptors. She chaired the 2016 Gordon Research Conference on Environmental Endocrine Disruptors, and has co-edited several special issues on endocrine disruptors, brain and behavior. In addition, Dr. Patisaul served on four previous National Academies committees: the Committee reviewing EPA's ORD Staff Handbook for Developing IRIS Assessments (or IRIS Handbook), the Workshop Planning Committee on Understanding the Paradigm Change at the Interface of Emerging Sources of Environmental Health Data and Decision Making, Committee on Incorporating 21st Century Science in Risk-Based Evaluations, and Committee to Review EPA's Draft Paper, State of the Science on Nonmonotonic Dose Response (NMDR). She received a PhD in Population Biology, Ecology & Evolution from Emory University with a research focus on comparative neuroendocrinology.

## Elijah J. Petersen

**Member**

Elijah J. Petersen completed his PhD at the University of Michigan in Environmental Engineering in 2007. Then, he completed postdocs at the University of Joensuu (Finland) on a Fulbright scholarship and then the University of Michigan before joining NIST as a National Research Council postdoctoral fellow. He became a staff scientist at NIST in 2010 and works in the Cell Systems Science group in the Biosystems and Biomaterials division. His research currently focuses on the development of robust, reproducible in vitro test methods. He is an associate editor for Nanotoxicology and Nanoimpact and on the editorial board of Environmental Pollution, Nanomaterials, and Environmental Toxicology and Chemistry. He recently was honored with the 2020 Chemical Research in Toxicology Young Investigator Award and the Presidential Early Career Award for Scientists and Engineers (PECASE) in 2019. He is the chair of the ICCVAM nanomaterials workgroup and a co-chair of the validation workgroup.

# Kristi Pullen Fedinick

**Member**

Kristi Pullen Fedinick, Ph.D., is the Executive Director of the Center for Earth, Energy, and Democracy - a non-profit organization dedicated to ensuring that communities and policy makers have the tools and information they need to create just and sustainable energy and environmental policy. She also holds a part-time faculty appointment in the Department of Environmental and Occupational Health of the Milken Institute School of Public Health at The George Washington University.

Dr. Pullen Fedinick's multidisciplinary expertise spans from the molecular to the societal, including training and experience in biochemistry, molecular biology, computational biology, data science, toxicology, risk assessment, environmental policy, and the social determinants of health. Her research and work reside at the intersection of science and public policy and seeks to ensure that communities disproportionately burdened by environmental and social threats are centered in policy development. She leverages data science, geospatial, and environmental health tools to assess and communicate potential harms caused by environmental degradation, with particular focus on air quality, drinking water contamination, and climate change.

Dr. Pullen Fedinick is a member of the Chartered Science Advisory Board of the U.S. Environmental Protection Agency, with a dual appointment to the Chemical Assessment Advisory Committee. She has also served on multiple influential committees of the National Academies of Sciences, Engineering, and Medicine, including several consensus committees. Dr. Pullen Fedinick has authored numerous policy reports, peer-reviewed articles, and policy comments and is a regular member of ad hoc committees and panels for government and non-government entities.

Dr. Pullen Fedinick holds a bachelor's degree in biochemistry and molecular biology from the University of Maryland Baltimore County and a Ph.D. in molecular and cell biology with a focus on biochemistry, biophysics, and structural biology from the University of California, Berkeley. She was a Robert Wood Johnson Foundation Health and Society Scholar at the Harvard T. H. Chan School of Public Health.

## Martyn T. Smith

**Member**

Martyn T. Smith is Professor of Toxicology and Kaiser Professor of Cancer Epidemiology in the Division of Environmental Health Sciences in the School of Public Health at the University of California Berkeley. He received his Ph.D. in Biochemistry from St. Bartholomew's Hospital in London and did Post-Doctoral training in toxicology at the Karolinska Institute in Stockholm. Dr. Smith is a laboratory scientist with expertise in molecular epidemiology, toxicology and genomics, and his research is aimed at finding the causes of chronic diseases, including cancer and diabetes. He currently teaches Toxicology and Health Risk Assessment and mentors graduate students and postdoctoral scholars in the Molecular Toxicology, Epidemiology and Environmental Health Science programs. Dr. Smith is a Fellow of the American Association for the Advancement of Science. He received the 2010 Children's Environmental Health Network Award, became an Elected Fellow of the Collegium Ramazzini in 2012, and received the Alexander Hollaender Award from the Environmental Mutagenesis and Genomics Society in 2014. Since its inception in 1987, Smith has directed the Superfund Research Program (SRP) Center at the University of California, Berkeley (UC Berkeley). This program combines basic research, engineering, population studies, training, and community engagement to understand cumulative impacts from multiple environmental stressors. Smith is best known for his work on benzene toxicity, the exposome concept and the key characteristics framework, which helps risk assessors better identify, organize, and summarize the potential health risks of different chemicals.

## Robyn L. Tanguay

**Member**

Robyn L. Tanguay is currently a University Distinguished Professor at Oregon State University in the Department of Environmental and Molecular Toxicology. She started her Academic career at the University of Colorado in the School of Pharmacy in 1999. She is a Molecular Toxicologist that primarily uses the zebrafish model to answer toxicological, developmental, and behavioral questions relevant to human health. She received her BA in Biology from California State University-San Bernardino in 1988, her PhD in Biochemistry from the University of California-Riverside in 1995, and postdoctoral training in Developmental Toxicology from the University of Wisconsin-Madison 1995-1999. Over the past several years, she has pioneered the use of zebrafish as a systems toxicology model. She has authored approximately 300 manuscripts and book chapters across disciplines, many focused on advancing zebrafish for environmental health sciences research. She also serves on numerous academic, federal and commercial advisory boards and as an editor for several scientific journals. She previously served on the National Academy of Sciences Committee on Incorporating 21st Century Science into Risk-Based Evaluations (2015-2016).

## Christopher Vulpe

**Member**

Christopher Vulpe is a Professor at the University of Florida, Gainesville in the Center for Environmental and Human Toxicology. Dr. Vulpe received his M.D. (1996), PhD (1994) in Genetics from the University of California, San Francisco. Dr. Vulpe's group uses functional, genomic, and genetic approaches to provide insight into mechanisms of toxicity in diverse model systems including human models such as human cell culture, organoids, and rodents, as well as ecologically relevant organisms such as Daphnia magna. Most recently, his laboratory is utilizing genome wide and targeted CRISPR screens to understand the mechanisms of toxicity of environmental chemicals. Dr. Vulpe is an author or co-author on >150 papers in peer reviewed journals and books. He recently participated in the NAS Emerging Genome Editing Tools to Advance Environmental Health Research Workshop.

## Tracey J. Woodruff

**Member**

Tracey J. Woodruff is the Alison S. Carlson Endowed Professor in the Department of Obstetrics, Gynecology, and Reproductive Sciences at University of California, San Francisco and the Director of the Program on Reproductive Health and the Environment. She is a recognized expert on environmental chemical exposures and impacts on health and health equity, with a focus on pregnancy, infancy and childhood. She has expertise in environmental exposures and epidemiology, hazard and risk assessment, and in silico/in vitro approaches to evaluating environmental chemical influences on health. She was previously a senior scientist and policy advisor for the U.S. EPA's Office of Policy and is currently a member of the EPA's Board of Scientific Counselors Executive Committee.

## Joseph C. Wu

**Member**

Joseph C. Wu (NAM) is Director of Stanford Cardiovascular Institute and Simon H. Stertzer, MD, Professor of Medicine and Radiology at Stanford University. Dr. Wu received his MD from Yale University and PhD (Molecular & Medical Pharmacology) at UCLA. He is board certified in cardiology. His lab works on cardiovascular genomics and induced pluripotent stem cells (iPSCs). The main goals are to (i) understand basic disease mechanisms, (ii) accelerate drug discovery and screening, (iii) develop "clinical trial in a dish" concept, and (iv) implement precision medicine for patients. Dr. Wu has published >400 manuscripts with H-index of 108 on Google scholar. He is listed as top 1% of highly cited researchers by Web of Science (2018, 2019, 2020). He serves on the FDA Cellular, Tissue, and Gene Therapies Advisory Committee. Dr. Wu is an elected member of American Institute for Medical and Biological Engineering (AIMBE), American Association for the Advancement of Science (AAAS), American Association of Physicians (AAP), and National Academy of Medicine (NAM).