UNITED STATES ENVIRONMENTAL PROTECTION AGENCY FIFRA SAP

Reviewing Physiologically Based Pharmacokinetic (PBPK) Modeling to Address Pharmacokinetic Differences Between and Within Species (2017)

BIOGRAPHICAL SKETCHES

1. **Michael Bartels, Ph.D.**

Michael is a consultant in the areas of Toxicokinetics, Xenobiotic Metabolism and Biological Modeling of Systemic Exposures. He has led research teams in the conduct of both guideline and mechanistic toxicokinetic studies, as well as Environmental fate and effects evaluations of commercial products. He has also led the development, validation and implementation of a comprehensive toxicokinetic program to evaluate systemic exposure and metabolic fate in laboratory species, with extrapolation to humans, via *in vivo*, *in vitro* and *in silico* methodologies. Michael's current research interests are in the standardization of systemic exposure modeling methods for improved regulatory acceptance. Michael has numerous industry-wide activities in exposure assessment and/or biomonitoring (American Chemistry Council (ACC), Crop Life America), as well as biological modeling and metabolism (ACC, European Chemical Industry Council, US CDC-NCEH). Expert panel activities have included a workshop on the Derivation of Biomonitoring Equivalents, member of grant review panels for EPA, NSF, and NIH, and chair of a Continuing Education course on Toxicokinetics at the SOT meeting. He has been a presenter to numerous EPA Science Advisory Panel meetings. Recent presentations have been primarily in the area of Toxicokinetic Modeling: China Society of Toxicology (2015), US EPA HED (2015), NICEATM (2016), NICEATM/EPA (2016), and UK Toxicokinetics Discussion Group (2016). He has authored/coauthored over 110 publications and book chapters, primarily in the field of xenobiotic metabolism, toxicokinetic modeling and biomonitoring.

2. **Russell Carr, B.S., M.S., Ph.D.**

Russell Carr is an Associate Professor in the College of Veterinary Medicine at Mississippi State University. He received his B.S. in Biology and Chemistry from Delta State University and his M.S. in Zoology and Ph.D. in Animal Physiology from Mississippi State University. Dr. Carr has served on multiple US EPA Science Advisory Panels and as a reviewer for Developmental Neurotoxicology Methods for the National Toxicology Program. His research interests are in the area of developmental neurotoxicology with emphasis on agricultural pesticides. Using animal models, his current focus is investigating the effects of developmental insecticide exposure on long term effects on behavior and matching those effects with changes in gene expression and neurochemistry.

3. **Jeffrey Fisher, Ph.D.**

Dr. Jeffrey Fisher is a research toxicologist with the U.S. Food and Drug Administration, National Center for Toxicological Research. He was formerly a Professor in the Department of Environmental Health Science, College of Public Health at the University of Georgia (UGA). He joined the University of Georgia in 2000 and served as Department Head of the Department of Environmental Health Sciences from 2000 to 2006 and Director of the Interdisciplinary Toxicology Program at UGA from 2006-2010. He spent most of his career at the Toxicology Laboratory, Wright Patterson AFB, where he was Principal Investigator and Senior Scientist in the Toxics Hazards Division and Technical Advisor for the Operational Toxicology Branch. Dr. Fisher's research interests are in the development and application of biologically based mathematical models to ascertain health risks from environmental, food-borne and occupational chemical exposures and develop pediatric PBPK models for drugs. Dr. Fisher's modeling experience includes working with chlorinated and non-chlorinated solvents, fuels, pesticides, perchlorate and bisphenol A.

4. **Panos Georgopoulos, M.S., Ph.D.**

Dr. Panos Georgopoulos is a professor in the Department of Environmental and Occupational Health at Rutgers Biomedical and Health Sciences, School of Public Health, with a joint appointment in the Department of Pharmacology, Robert Wood Johnson Medical School. Since 1989, he has served on the faculty of Robert Wood Johnson Medical School and on the Graduate Faculties of Chemical & Biochemical Engineering, Biomedical Engineering, and of Environmental Sciences at Rutgers University. He is a member of the Environmental and Occupational Health Sciences Institute (EOHSI) of Rutgers, where he directs the Informatics and Computational Toxicology Core of the Center for Environmental Exposures and Disease (CEED) funded by the National Institute of Environmental Health Sciences (NIEHS).

Dr. Georgopoulos received his M.S. and Ph.D. Degrees in Chemical Engineering from the California Institute of Technology (Caltech) and his Dipl. Ing. Degree from the National Technical University of Athens. At EOHSI, he established and directs the Computational Chemodynamics Laboratory (CCL), a state-of-the-art facility for informatics and modeling of environmental and biological systems. Over the years he has directed or participated in many research projects funded by Federal, State and private agencies, including NIH, USEPA, USDOE, CDC/ATSDR, NIOSH, NJDEP, NJDOH, and ACC. Dr. Georgopoulos' research and teaching activities at Rutgers include development and implementation of innovative methods for high-content to high-throughput environmental risk analysis and informatics. Outcomes of this research include integrative computational models of toxicokinetic and toxicodynamic processes at the cellular, tissue and whole body levels. He has served as member of various national and international scientific and technical committees on environmental health issues, including currently the USEPA's Science Advisory Committee on Chemicals (SACC).

5. **Dale Hattis, Ph.D.**

Dr. Dale Hattis has been engaged in the development and application of methodology to assess the health, ecological and economic impacts of regulatory actions for the past 40 years. His work has focused on the development of methodology to incorporate human interindividual variability data and quantitative mechanistic information into risk assessments for both cancer and non-cancer endpoints. Specific studies have included pharmacokinetic modeling and risks from developmental effects of the organophosphate insecticide chlorpyrifos, dosimetric uncertainties in epidemiological information on dioxin cancer risks, age-related differences in pharmacokinetic processes and susceptibility for carcinogenesis, renal effects of cadmium, reproductive effects of ethoxyethanol, neurological and cardiovascular effects of methyl mercury, neurological effects of acrylamide, chronic lung function impairment from coal dust, four pharmacokinetic-based risk assessments for carcinogens (for perchloroethylene ethylene oxide, butadiene and diesel particulates), an analysis of uncertainties in pharmacokinetic modeling for perchloroethylene and an analysis of differences among species in processes related to carcinogenesis. He has been a member of the National Toxicology Program Board of Scientific Counselors, member of the Environmental Health Committee of the EPA Science Advisory Board, and as a member of the Food Quality Protection Act Science Review Board. He has been a councilor and is a Fellow of the Society for Risk Analysis.

6. **Wendy Heiger-Bernays, Ph.D.**

Wendy Heiger-Bernays, Ph.D. is an associate professor in the Department of Environmental Health at the Boston University School of Public Health where she applies her expertise in molecular toxicology to practical questions about the impact of a subset of industrial chemicals, consumer products and pharmaceuticals on people's health. She works with colleagues to assess toxicity of chemicals that are able to modify the metabolic pathways in juvenile and prenatal animal (fish and rodent) models, to characterize and screen chemicals with endocrine activity in water, characterize health risks posed by vapors in homes that originate beneath the ground, and to development of practical interventions to commonly measured chemical hazards in agricultural soils. Her research and teaching includes a focus on effective ways to translate findings from the laboratory to multiple audiences.

Dr. Heiger-Bernays teaches graduate courses in toxicology, risk assessment, water quality, and environmental health and is PI of the Research Translation Core (RTC) for the NIEHS-supported BU Superfund Program. Her work on the RTC is focused on technology and information transfer of the science to multiple audiences, including environmental regulatory and health agencies as well as with advocacy groups and community groups. Since leaving the laboratory, she has trained dozens of MS and MPH students and mentored doctoral students' in bench and regulatory toxicology. In 2015-2016, she was a AAAS Science and Technology Fellow hosted in the Office of Science Coordination and Policy at the US EPA, working in the Endocrine Disrupting Screening Program.

7. **Michael Honeycutt, Ph.D.**

Dr. Honeycutt is the director of the Toxicology Division of the Texas Commission on Environmental Quality (TCEQ). He has been employed by the TCEQ since 1996 and has managed the division of 14 toxicologists since 2003. His responsibilities include overseeing health effects reviews of air permit applications, overseeing the review of the results of ambient air monitoring projects, and overseeing the reviews of human health risk assessments for hazardous waste sites. Dr. Honeycutt spearheaded the updating of TCEQ's method for deriving chemical toxicity factors, which has been through two independent external scientific peer reviews and multiple rounds of public comment (http://www.tceq.texas.gov/toxicology/esl/guidelines/about.html). He has overseen the development of inhalation toxicity factors for over 100 chemicals using this process and has published numerous articles and book chapters on chemical risk assessment. Recent areas of research include risk analysis and characterization of emissions from natural gas operations and hydraulic fracturing, weight-of-evidence analyses in chemical risk assessment, and concentration-response considerations in ozone risk assessment. He has extensive experience and knowledge of the risk assessment and the regulation of both criteria and non-criteria air pollutants. Dr. Honeycutt serves as a technical resource in the areas of chemical toxicokinetics and toxicodynamics, and human health and environmental risk assessment, particularly as they relate to issues concerning air and water quality, drinking water contamination, and soil contamination. Dr. Honeycutt is an adjunct professor in two departments at Texas A&M University serves or has served on numerous external scientific committees, participated in and helped organize international scientific conferences, and has provided invited testimony at several Congressional hearings. He also serves as an expert witness in public and state legislative hearings, participates in public meetings, and has conducted hundreds of media interviews. He earned both a B.S. and Ph.D. in Toxicology from the University of Louisiana at Monroe.

8. **Eric Shu-Cheung Kwok, Ph.D., D.A.B.T.**

Dr. Eric S.C. Kwok is a Senior Toxicologist of the Exposure Assessment Section at the California Department of Pesticide Regulation, where he supervises a team of modelers and toxicologist to conduct pesticide exposure assessments on agricultural handlers, reentry workers, and bystanders. Dr. Kwok has over 17 years of experience in analyzing the Federal Insecticide, Fungicide, and Rodenticide Act guideline toxicology studies (e.g., developmental and neurotoxicity studies) and performing human exposure and health risk assessments of pesticides (e.g., organophosphate and pyrethroid insecticides) using different computational tools including stochastic human exposure assessment models and physiological based pharmacokinetic models. Dr. Kwok is a Diplomate of the American Board of Toxicology and a member of the Society of Toxicology. Dr. Kwok received his B.Sc. (Hons) degree in Zoology/Botany from the University of Hong Kong, M.Phil. degree in Biology (Environmental Microbiology) from the Chinese University of Hong Kong, and Ph.D. degree in Environmental Toxicology (Atmospheric Chemistry) from the University of California, Riverside. He also

received postgraduate trainings in pharmacokinetic modeling, quantitative structure activity relationship, and environmental mass spectrometry from the University of California, Riverside, CA, aqueous-phase chemistry and environmental analytical chemistry from the Brookhaven National Laboratory, Upton, NY, and biomedical accelerator mass spectrometry from the Lawrence Livermore National Laboratory, Livermore, CA. Dr. Kwok has published 27 scientific papers in peer reviewed scientific journals and authored multiple research reports on pesticide health risk assessments. He also received two Superior Accomplish Awards from the California Environmental Protection Agency in recognition of his exceptional contributions and services to State Government.

9. Stephen M. Lasley, Ph.D.

Dr. Stephen M. Lasley is a Professor of Pharmacology and Assistant Head of the Department of Cancer Biology and Pharmacology at the University of Illinois College of Medicine Peoria. His primary research interests include the neurotoxicology of lead and manganese and their effects on synaptic plasticity, and the cognitive impacts of stress and organophosphate exposure in mouse models of Gulf War Illness. Dr. Lasley is an Associate Editor of the journal NeuroToxicology, and serves on the editorial boards of two other journals. He has been Course Director for Medical Pharmacology for 10 years, and is also Chair of the Institutional Animal Care and Use Committee. His research program is currently funded by the Department of Defense Gulf War Illness Research Program.

10. Sidney Marlborough, Ph.D.

Dr. Sidney Marlborough is currently a Senior Environmental Toxicologist with Noble Energy, Inc. in Houston, Texas. He is responsible for corporate chemical stewardship program and is responsible for the risk evaluation of new products for oil and gas exploration and production. He received a BS in Environmental Management Systems, MS in Environmental Toxicology and Ph.D. in Environmental Science minoring in molecular genetics from Louisiana State University. He has 18 years of experience in environmental risk management, toxicology, risk assessment, litigation, and research. He has worked for state government, academia, private consulting and industry. He has developed numerous human health and ecological risk assessments for expert reports and remedial cleanup requirements. He has studied the toxicity of metals, chlorinated solvents, poly-aromatic hydrocarbons and pesticides in both human and ecological receptors. Dr. Marlborough has developed an uptake kinetic model simulating the phytoremediation of arsenic with various plant species. He has developed formulas for the extrapolation of toxicity of arsenate and arsenite as part of ecological risk assessment. He has conducted published research in the areas of marine toxicity to benthic invertebrates, arsenic speciation toxicity in ecological receptors, TNT exposure to benthic fish, phytoremediation of metals, and microsatellite instability in squamous cell carcinoma. Dr. Marlborough is currently a member of the Society of Toxicology, American Chemical Society and the Society of Petroleum Engineers.

11. Eva D. McLanahan, Ph.D.

Dr. Eva McLanahan is a U.S. Public Health Service officer (Commander) detailed to the Agency for Toxic Substances and Disease Registry's (ATSDR) Division of Community Health Investigations (DCHI) as an Environmental Health Scientist and Technical Project Officer (TPO). She is responsible for ensuring seven cooperative agreement states complete timely health assessments and community education and outreach activities related to hazardous waste sites to be protective of public health. In addition, she serves on ATSDR's Cancer Policy Workgroup. Prior to ATSDR, she served as a toxicologist for EPA's National Center for Environmental Assessment (NCEA) where she Co-Chaired EPA's Pharmacokinetics Workgroup (PKWG). The PKWG was responsible for evaluating and applying physiologically based pharmacokinetic (PBPK) models to risk assessment applications, especially within NCEA. At EPA, Dr. McLanahan led development of state-of-the-science reports on inhalation dosimetry, 1,4-dioxane toxicity, and application of PBPK models to support the perchlorate regulatory determination by the EPA's Office of Water. In addition, she Co-Chaired the Risk Assessment Training and Experience (RATE) workgroup responsible for developing and providing risk assessment training to staff within the EPA, stakeholders, and international audiences. She has expertise in PBPK and biologically based dose-response (BBDR) modeling, with special focus on thyroid active compounds. She currently serves as President of the Society of Toxicology's in the Biological Modeling Specialty Section. Dr. McLanahan is author/co-author of over 25 peer reviewed publications.

12. Moiz Mumtaz, Sc., M.S., Ph.D., FATS

Dr. Mumtaz's longtime research interests include the development of toxicity and risk assessment methods for environmental chemicals/pollutants. Service activities have included numerous expert panels for national and international government and NGOs. He is the principal representative of the Agency for Toxic Substances and Disease Registry (ATSDR/CDC) on the Department of Health and Human Services (DHHS) Interagency Coordinating committee on the validation of alternative methods (ICCVAM). He is a member of the Toxic Substances Control Act subcommittee of Society of Toxicology (SOT), SOT Government Liaison Group, and Oregon State University Superfund Center External Advisory Committee. He is a member of SOT and the past - president of its Mixtures Specialty Section. In 2013, he was elected a Fellow of the Academy of Toxicological Sciences (FATS) and won the SOT Lehman award for major contributions to risk assessment and the regulation of chemical agents. During the past three decades, Dr. Mumtaz has actively published his research findings in several peer-reviewed journals. His research interest covers a wide range of research areas pertinent to medicine and human health including dopamine metabolism/mental health, comparative toxicology, analysis of chemicals, use of computational tools. More recently, he has been the principal investigator of a multi-year effort for the development of ATSDR Computational Toolkit that consists of a series of human physiologically based pharmacokinetic (PBPK) models. The focus now is on the application of this toolkit in determination of internal doses, and use in human health risk assessment of environmental chemicals found at hazardous waste sites that impact public health.

13. Torka Poet, Ph.D.

Torka Poet is a Senior Associate at Summit Toxicology, a toxicology and risk assessment consulting firm. Torka received a B.A. in Molecular, Cellular, & Developmental Biology from the University of Colorado, an M.S. in Toxicology from the University of Arizona, and a PhD in Pharmacology and Toxicology from the University of Arizona. Torka specializes in human health risk assessment, in vitro to in vivo pharmacokinetic extrapolation, drug and chemical metabolism, and exposure assessment. To this end, she has been developing physiologically based pharmacokinetic (PBPK), and pharmacodynamic (PD) models for drugs and chemicals for over 15 years. Torka has published over 50 manuscripts on the topics of PBPK/PD modeling, in vivo and in vitro metabolism, dermal absorption, and exposure assessment. She has been a co-author on a top 10 abstract awarded by the Risk Assessment Specialty section of the Society of Toxicology. Torka has served on the editorial review board for Toxicological Sciences for the past 5 years, and has been a board member for the Biological Modeling Specialty section of the Society of Toxicology.

14. Brad Reisfeld, B.S., M.S., Ph.D.

Dr. Brad Reisfeld is an Associate Professor in the Department of Chemical and Biological Engineering and School of Biomedical Engineering at Colorado State University (CSU). His primary research interests are in quantitative and computational pharmacology and toxicology, computational systems biology, pharmacokinetics, and pharmacodynamics. He is a One Health Fellow at CSU and founded the Quantitative and Computational Pharmacology and Toxicology Research Group at this same institution. He is also Vice President elect of the Biological Modeling Specialty Section of the Society of Toxicology and Chair elect of the Systems Pharmacology focus group of the American Association of Pharmaceutical Sciences.

15. Jordan Ned Smith, B.S., Ph.D.

Jordan Ned Smith, PhD, is a scientist at the Pacific Northwest National Laboratory (PNNL), where he studies the implications of chemical exposures on human health. His research uses a combined experimental and computational approach to understand how absorption, distribution, metabolism, and excretion (ADME) processes affect target-tissue dosimetry and mediate toxicity. Dr. Smith has utilized this approach to understand pharmacokinetics and toxicity for a variety of compounds including pesticides, polycyclic aromatic hydrocarbons (PAHs), nanoparticles, organic esters, nicotine, and explosives. Dr. Smith has extensive experience developing, reviewing, and applying computational tools for exposure assessment, tissue dose, and toxicology.

16. Lisa M. Sweeney, Ph.D., D.A.B.T., CHMM

Lisa M. Sweeney, Ph.D., DABT, CHMM, is a Research Physical Scientist with the Naval Medical Research Unit—Dayton. She has a broad range of experience in the application of toxicology, chemistry, and engineering to problems in the health and environmental sciences. She has over 20 years of experience in risk assessment, pharmacokinetics, and biochemical engineering. She is an author of over 50 peer-reviewed publications, with over 20 publications as first author. Her experience has focused on the development and refinement of physiologically-based pharmacokinetic (PBPK) models and their application to risk assessment and experimental design. Other risk assessment experience includes preparing toxicological reviews and calculating human health risk for children and adults. She recently (2013-2017) served on the Society of Toxicology's Scientific Program Committee as a member and subject matter expert on topics pertaining to risk assessment, biological modeling, biomonitoring, regulation, and policy. She has previously served on U.S. EPA public peer review panels for a FIFRA Scientific Advisory Panel review, Integrated Risk Information System (IRIS) program reviews, and evaluated Provisional Peer Reviewed Toxicity Values (PPRTVs). She has also served as an external reviewer for Agency for Toxic Substances and Disease Registry manuscripts. She received her education at Case Western Reserve University (B.S.E) and Cornell University (Ph.D.) in chemical engineering and completed a postdoctoral fellowship in pharmacokinetic modeling at the Chemical Industry Institute of Toxicology. She is a Diplomat of the American Board of Toxicology and a Certified Hazardous Materials Manager.

17. David Ting, Ph.D., MPH

Dr. David Ting is chief of the Pesticide and Environmental Toxicology Branch of the Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. He has been with the department for more than 20 years. During that time, he developed health risk assessments on drinking water contaminants and pesticides as well as peer reviewed draft exposure and toxicity assessments prepared by the California Department of Pesticide Regulation. His research interests are in chemical-induced thyroid tumors, dose-response extrapolation, and the use of biomarkers in dosimetry.

18. Cynthia Van Landingham, M.S.

Cynthia Van Landingham is a Senior Science Advisor with Ramboll Environ with more than 30 years' experience in statistical analysis, dose-response modeling, biologically-based pharmacokinetic modeling, and Monte Carlo techniques. She has performed multiple projects using PBPK models to estimate internal dose metrics for use in dose-response modelling and to perform intra-species and route-to-route extrapolation. In addition, she has worked on the sensitivity, variability and uncertainty in PBPK models using statistical procedures to determine which of the model parameters has the most effect on the dose-metrics.

19. Raymond Yang, Ph.D.

Raymond S. H. Yang is Professor Emeritus of Toxicology and Cancer Biology, and the former leader of the Quantitative and Computational Toxicology Group, at the College of Veterinary Medicine and Biomedical Sciences, Colorado State University (CSU). Between October 2007 and July 2009, Dr. Yang had also been a Visiting Scientist at the National Center for Environmental Assessment, USEPA, Cincinnati, to work on TCDD and chemical mixture toxicology and risk assessment, among other projects. Dr. Yang's research interests focus on physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling, and other biologically-based computer modeling with a special emphasis on the toxicology and risk or safety assessment of chemical mixtures, poly-pharmacy, and multiple stressors including radiation. Dr. Yang has had extensive research and administrative experience in academia, chemical industry, and the federal government. During his tenure at CSU between 1990 and 2010, Dr. Yang had served in the capacity as a Department Head, a Center Director, and the Director for a NIEHS Quantitative Toxicology Training Program. Dr. Yang publishes extensively in biomedical journals and is the editor/co-editor of two books: (1) Toxicology of Chemical Mixtures: Cases Studies, Mechanisms, and Novel Approaches (1994); and (2) Physiologically Based Pharmacokinetics: Science and Applications (2005). Dr. Yang's experience in toxicology and risk assessment is broad and covers many sub-disciplines in these fields. Dr. Yang is a Fellow of Academy of Toxicological Sciences and served on many prestigious national and international committees and panels. In the last few years, Dr. Yang has served in an advisory capacity on various Panels/Committees for a variety of programs at the National Health Research Institutes in Taiwan, Republic of China. Presently, Dr. Yang is working part-time as an international consultant; part of this service includes Dr. Yang's continuing teaching of his "PBPK Modeling Workshop for Beginners" at CSU and elsewhere in the US, Europe, and Asia.