Contents lists available at ScienceDirect

Neurotoxicology and Teratology

journal homepage: www.elsevier.com/locate/neutera

Introduction: The continuing importance of behavioral toxicology: In memory of Philip J. Bushnell, Ph.D.

This Special Issue on The Continuing Importance of Behavioral Toxicology is dedicated to our dear friend and colleague and former Editor-in-Chief of *Neurotoxicology and Teratology,* Dr. Philip J. Bushnell. Phil was a sincere and conscientious leader of our field and a valued, productive, and unfailing collaborator. In his personal life, he was a father, grandfather, and caring husband who often expressed his deep love for his wife, Sharon, and for their children and grandchildren. Phil had many friends with whom he shared his love of carpentry, music, hiking, and working on hiking trails. In all of his endeavors, he consistently worked to make this a better world in which to live. Having grown up in Hawaii probably influenced his love of the outdoors. Phil spent annual family vacations in a cottage his parents built on the Big Island. After inheriting it, he continued to improve it. He also volunteered in the National Park and frequently explored the island's mountains and trails.

At home, Phil built furniture and created many wood-turned household objects. He designed a thriving garden. He practiced saxophone or clarinet every day and was a member of the Triangle Jazz Orchestra and The Village Band. If not working outdoors on house repairs or garden projects, Phil could be found bicycling, volunteering on Triangle Nature Conservancy projects, or simply hiking local trails. He left a long legacy of many, varied activities that reflected his never-ending interest in discovering and learning something new.

Phil's scientific contributions were extensions of his rich personal, family, and community life. He had a kind and helpful approach that was also demanding of rigorous thought and experimental study. He began his behavioral toxicology research as a graduate student with Robert Bowman at the University of Wisconsin Primate Lab, where he conducted important early studies on behavioral impairments caused by developmental lead exposure. This included studies of persistent effects of lead on learning, memory, and social behavior. He opened the way for students who followed him at Wisconsin, including an editor (E. D. Levin) and an author (S. L. Schantz) in this Special Issue. In his long and productive career at the US-Environmental Protection Agency (US-EPA), Phil conducted ground-breaking work in the quantitative assessment of environmental and neural contributions to the behavioral toxicity of neurotoxicants, characterizing the behavioral toxicity of organic solvent exposure, and developing a rigorous and sensitive way to assess attentional function in rats.

It is appropriate that this Special Issue in memory of Phil be dedicated to behavioral toxicology. The use of behavioral approaches to understand the toxic effects of compounds on the nervous system has been an essential component of toxicological sciences for over 50 years and was central to the founding of the journal *Neurotoxicology and Teratology*. Moreover, as new compounds continue to be developed for industrial or consumer use and older ones accumulate in the environment, behavioral toxicology provides vital information for assessing the risks entailed by acute or chronic chemical exposures. This is because behavior, either as expressed in everyday activities or as signs of disease states, is the key medium through which the functional relevance of biochemically-induced neural changes can be understood. The aim of this Special Issue is to serve as a resource for current and future generations of behavioral toxicologists, as well as researchers in related fields, regulators, policy makers, clinicians, and the broader public.

Across the toxicological sciences and risk assessment communities, there is currently a strong push for development of more efficient, less expensive, and higher throughput assessments of chemical toxicology. Neurotoxicology is no exception, where the need for complementary testing approaches to developmental neurotoxicology has been particularly urgent. This has led to the rapid growth of molecular, computational, in vitro, and alternative species testing. Modeling the nervous system and neurodevelopment with simple systems, however, is difficult due to the complexity and integration of brain networks. Neurons and glia interact dynamically in systems serving as conduits for perception, emotion, cognition, and multiple physiological systems essential for well-being and life itself. Behavioral analysis provides not only an assessment of complex brain function, but also gives an important starting point for discovering the mechanisms of brain function and how these mechanisms are adversely affected by toxic exposures. Mechanisms of neurobehavioral function are bidirectional, both up and down levels of organization in the nervous system. Behavioral toxicology's top-down approach can have a useful confluence with bottom-up approaches of molecular- and cellular-based neurotoxicology.

This Special Issue contains a spectrum of studies of behavioral toxicology. Some of these address relationships between behavioral toxicity and brain mechanisms, including articles by Graham et al. (2021) about the functional effects of gestational GLP-1R activation, Garrick et al. (2021) concerning the specific brain areas involved in how paraoxonase deficiency changes motor behavior, Kendricks and Newland (2021) about the roles of dopamine in the attentional and memory impairments caused by methylmercury, and Honaker et al. (2022) concerning how the behavioral toxicity of developmental benzo[*a*]pyrene is altered by genetic differences in the Ahr and Cyp1a2 loci in a sex-selective manner.

Behavioral toxicity research can be also found across levels of analysis from experimental animal studies to human samples. Cruz and Bowen (2021) provide a comprehensive review of the field using inhalant neurobehavioral toxicology as an example in their article concerning solvent exposure. Vorhees and Williams (2021) discuss important methodological and interpretative issues in rodent

https://doi.org/10.1016/j.ntt.2022.107107

developmental behavioral toxicology. Complementary models also contribute to the behavioral toxicology field. Peppriell et al. (2021) explore behavioral toxicity in a drosophila model, while Boyda et al. (2021) use zebrafish to study the lifelong behavioral effects of early developmental toxicant exposure.

Neurotoxic chemicals affect behavior in the broader context of neurobehavioral and physiological function. Expression of behavioral toxicity is greatly influenced by interactions between toxicant exposure and behavioral stress. David Herr and colleagues (Beasley et al., 2022; McDaniel et al., 2022; Oshiro et al., 2022) have conducted extensive studies of the interactions of behavioral stress with neurobehavioral toxicology, in this case manganese. Kandel Gambarte and Wolansky (2022) investigated the role of the gut microbiome as an indicator of pesticide exposure.

Behavioral toxicology is also central to human epidemiological and clinical neurotoxicology research. Crossin (2021) investigated the relationship between inhalant abuse and suicide from a behavioral toxicology perspective, Merced-Nieves et al. (2022) studied sexually dimorphic associations between prenatal blood lead exposure and performance on a behavioral testing battery in children, and Sprowles et al. (2022) investigated the associations of PCB and PBDE exposure and executive function in adolescents.

In closing, we are grateful to Phil Bushnell for his work to further our field, and we wholeheartedly thank the contributors to this Special Issue for supporting the continuing importance of behavioral toxicology. We further hope that the readers of this issue will be inspired to carry on Phil's legacy by adding their own insights and discoveries to the field of behavioral toxicology.

References

Beasley, T.E., McDaniel, K.L., Oshiro, W.M., Moser, V.C., MacMillan, D.K., Herr, D.W., 2022. Impacts of a perinatal exposure to manganese coupled with maternal stress in rats: maternal somatic measures and the postnatal growth and development of rat offspring. Neurotoxicol. Teratol. 90, 107061.

Boyda, J., Hawkey, A.B., Holloway, Z.R., Trevisan, R., Di Giulio, R.T., Levin, E.D., 2021. The organophosphate insecticide diazinon and aging: neurobehavioral and mitochondrial effects in zebrafish exposed as embryos or during aging. Neurotoxicol. Teratol. 87, 107011.

Crossin, R., 2021. Exploring the link between adolescent inhalant misuse and suicidal behaviour: a behavioural toxicology perspective. Neurotoxicol. Teratol. 88, 107038.

Cruz, S.L., Bowen, S.E., 2021. The last two decades on preclinical and clinical research on inhalant effects. Neurotoxicol. Teratol. 87, 106999.

Garrick, J.M., Cole, T.B., Bammler, T.K., MacDonald, J.W., Marsillach, J., Furlong, C.E., Costa, L.G., 2021. Paraoxonase 2 deficiency in mice alters motor behavior and causes region-specific transcript changes in the brain. Neurotoxicol. Teratol. 87, 107010.

Graham, D.L., Madkour, H.S., Noble, B.L., Schatschneider, C., Stanwood, G.D., 2021. Long-term functional alterations following prenatal GLP-1R activation. Neurotoxicol. Teratol. 87, 106984.

Honaker, A., Kyntchev, A., Foster, E., Clough, K., Hawk, G., Asiedu, E., Berling, K., DeBurger, E., Feltner, M., Ferguson, V., Forrest, P.T., Jenkins, K., Massie, L., Mullaguru, J., Niang, M.D., Perry, C., Sene, Y., Towell, A., Curran, C.P., 2022. The behavioral effects of gestational and lactational benzo[a]pyrene exposure vary by sex and genotype in mice with differences at the Ahr and Cyp1a2 loci. Neurotoxicol. Teratol. 89, 107056.

Kandel Gambarte, P.C., Wolansky, M.J., 2022. The gut microbiota as a biomarker for realistic exposures to pesticides: a critical consideration. Neurotoxicol. Teratol. 91, 107074.

Kendricks, D.R., Newland, M.C., 2021. Selective dopaminergic effects on attention and memory in male mice exposed to methylmercury during adolescence. Neurotoxicol. Teratol. 87, 107016.

McDaniel, K.L., Beasley, T.E., Oshiro, W.M., Huffstickler, M., Moser, V.C., Herr, D.W., 2022. Impacts of a perinatal exposure to manganese coupled with maternal stress in rats: tests of untrained behaviors. Neurotoxicol. Teratol. 91, 107088.

Merced-Nieves, F.M., Chelonis, J., Pantic, I., Schnass, L., Téllez-Rojo, M.M., Braun, J.M., Paule, M.G., Wright, R.J., Wright, R.O., Curtin, P., 2022. Sexually dimorphic associations between prenatal blood lead exposure and performance on a behavioral testing battery in children. Neurotoxicol. Teratol. 90, 107075.

Oshiro, W.M., McDaniel, K.L., Beasley, T.E., Moser, V., Herr, D.W., 2022. Impacts of a perinatal exposure to manganese coupled with maternal stress in rats: learning, memory and attentional function in exposed offspring. Neurotoxicol. Teratol. 91, 107077.

Peppriell, A.E., Gunderson, J.T., Krout, I.N., Vorojeikina, D., Rand, M.D., 2021. Latent effects of early-life methylmercury exposure on motor function in Drosophila. Neurotoxicol. Teratol. 88, 107037.

Sprowles, J.L.N., Monaikul, S., Aguiar, A., Gardiner, J., Monaikul, N., Kostyniak, P., Schantz, S.L., 2022. Associations of concurrent PCB and PBDE serum concentrations with executive functioning in adolescents. Neurotoxicol. Teratol. 92, 107092.

Vorhees, C.V., Williams, M.T., 2021. Issues in the design, analysis, and application of rodent developmental neurotoxicology studies. Neurotoxicol. Teratol. 87, 107018.

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