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Environmental Neuroscience

Advancing the Understanding of How Chemical Exposures Impact Brain Health and Disease

PROCEEDINGS OF A WORKSHOP

Lisa Bain, Sheena M. Posey Norris, and Clare Stroud, *Rapporteurs*

Forum on Neuroscience and Nervous System Disorders

Board on Health Sciences Policy

Health and Medicine Division

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the content of the proceedings nor did they see the final draft before its release. The review of this proceedings was overseen by **MARK CULLEN,** Stanford University. He was responsible for making certain that an independent examination of this proceedings was carried out in accordance with standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the rapporteurs and the National Academies.

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1

Introduction and Background[1]

Humans are potentially exposed to more than 80,000 toxic chemicals in the environment,[2] yet their impacts on brain health and disease are not well understood (Hamblin, 2014). The sheer number of these chemicals has overwhelmed the ability to determine their individual toxicity, much less potential interactive effects. Early life exposures to chemicals can have permanent consequences for neurodevelopment and for neurodegeneration in later life (Bellinger, 2013). Toxic effects resulting from chemical exposure can interact with other risk factors such as prenatal stress, and persistence of some chemicals in the brain over time may result in cumulative toxicity. Because neurodevelopmental and neurodegenerative disorders—such as attention-deficit hyperactivity disorder and Parkinson's disease—cannot be fully explained by genetic risk factors alone, understanding the role of individual environmental chemical exposures is critical (Berkowitz, 2020; Ellis et al., 2011).

Workshop co-chair Deborah Cory-Slechta, professor of environmental medicine at the University of Rochester Medical Center, referred to environmental chemical exposures as "the ignored environmental risk factors for

[1] The planning committee's role was limited to planning the workshop, and the Proceedings of a Workshop was prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, and have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They should not be construed as reflecting any group consensus.

[2] For more information, see https://www.epa.gov/laws-regulations/summary-toxic-substances-control-act (accessed August 12, 2020).

neurodevelopmental disease and disorders." However, as recognition has grown about the substantial vulnerability of the nervous system to environmental effects, environmental neuroscience is emerging as an important topic in neuroscience, said Frances Jensen, professor and chair of neurology at the University of Pennsylvania Perelman School of Medicine. This has fueled a proliferation of clinical neuroscience research around the role of chemical pollutants and other kinds of environmental threats to the nervous system. The purpose of this workshop, hosted by the National Academies of Sciences, Engineering, and Medicine's Forum on Neuroscience and Nervous System Disorders on June 25, 2020, was to lay the foundation for future advances in environmental neuroscience, said Jensen (see Box 1-1).

Workshop co-chair Walter Koroshetz, director of the National Institute of Neurological Disorders and Stroke, added that the workshop was designed to explore new opportunities to bridge the gap between what is known about the genetic contribution to brain disorders and what is known, and not known, about the contribution of environmental influ-

BOX 1-1
Statement of Task

A planning committee of the National Academies of Sciences, Engineering, and Medicine will organize and conduct a 1-day public workshop that brings together experts and key stakeholders from academia, government, industry, and nonprofit organizations to explore the current knowledge landscape and future opportunities in neurotoxicology.

Invited presentations will be designed to:

- Provide an overview of what is known about neurotoxic exposures and how they lead to neurodevelopmental and neurodegenerative disorders;
- Explore how new technologies can be harnessed to identify previously unknown neurotoxic chemicals;
- Consider whether algorithms can be developed to better predict the effects of cumulative exposures and interactions across the life span on brain health; and
- Discuss research gaps and collaborative opportunities between neuroscientists and environmental health scientists.

The committee will develop the agenda for the workshop, select and invite speakers and discussants, and moderate the discussions. A proceedings of the presentations and discussions at the workshop will be prepared by a designated rapporteur in accordance with institutional guidelines.

ences, as well as to discuss what is known about how genetic and environmental factors interact. Noting that the problem spans variable types of environmental influences as well as multiple types of brain conditions, Koroshetz added that the workshop would focus on new technologies that allow previously unapproachable questions to be answered regarding chemicals and particular toxicants and their effects on neurodevelopmental and neurodegenerative conditions.

Held virtually in the shadow of the coronavirus disease 2019 (COVID-19) pandemic, the workshop also provided a unique and timely opportunity to discuss how pathogen-driven infections may interact with environmental toxicants. Moreover, behavioral changes in response to COVID-19 that have altered some environmental exposures, such as reducing air pollution in various cities, have provided new research opportunities, said Tracey Woodruff, the Alison S. Carlson Endowed Professor of Obstetrics, Gynecology, and Reproductive Sciences at the University of California, San Francisco. Cory-Slechta added that because both COVID-19 and toxic environmental exposures preferentially affect communities of color and low socioeconomic status, issues related to environmental justice must also be considered in discussions of environmental neuroscience.

WORKSHOP OBJECTIVES

A goal of the workshop, said Koroshetz, was to bring the fields of mechanistic and clinical neuroscience closer together with the fields of neurotoxicology and environmental health sciences. By building evidence from observational, population-based, and epidemiological studies and combining that evidence with neurobiological mechanistic studies, scientists from these two fields, working together, may find the central issue of causation. Thus, an aim of the workshop was to discuss a pathway to achieving that goal, said Koroshetz.

The discussions focused on four major themes: (1) What toxicants are of most concern? (2) What is the biology of toxicant interaction with the nervous system? (3) What is known about particular toxicants as drivers of abnormal development or neurodegeneration? and (4) What are the implications of this knowledge for policy and future research, including identifying gaps and opportunities to bridge those gaps? While the impact of neurotoxicants on neuropsychiatric and other neurological disorders is also a critical issue, it was not included in this 1-day workshop in the interest of time.

ORGANIZATION OF THE PROCEEDINGS

The organization of these proceedings reflects the fact that the topics discussed are intimately linked and cannot be discussed in isolation. Thus, Chapter 2 focuses on the neurotoxicants themselves; Chapter 3 considers what is known about how neurotoxicants impact neurological disorders; and Chapter 4 focuses through the lens of these disorders. Research gaps and opportunities are summarized in Chapter 5, and frameworks for moving forward as well as opportunities for multidisciplinary collaboration are discussed in Chapter 6.

2

Neurotoxicants and Their Risks to Human Health

HIGHLIGHTS

- Although humans are exposed to thousands of chemicals through the air, water, and soil and other commercial and industrial pathways, their impact on human health is not well understood and has received little attention (Cory-Slechta, McPartland).
- The combination of three environmental chemical exposures—lead, organophosphate pesticides, and methyl mercury—are responsible for greater IQ loss than medical conditions such as preterm birth, neurodevelopmental disorders, and socioeconomic and nutrition-related factors (Bellinger).
- No safe level of lead exposure in the blood of children has been identified (Cory-Slechta).
- Pesticides put into the environment intentionally target circuits in the nervous system found in insects that are also present in humans (Richardson).
- The National Health and Nutrition Examination Survey found elevated levels of organophosphate pesticides and neonicotinoid insecticide in urine samples of more than half to 96 percent of the U.S. population aged 3 to 59 (Ritz).

- The production of industrial chemicals increased dramatically between 2000 and 2016, and this may be linked to increased prevalence of autism and attention-deficit hyperactivity disorder (Bellinger, Woodruff).
- Flame-retardant chemicals such as polybrominated diphenyl ethers may disrupt normal thyroid hormone function, which plays an important role in brain development (Woodruff).
- Ultrafine particles in air pollution enable neurotoxicants to get into the brain and may trigger biological responses that cause neuropathology (Cory-Slechta, Petkus).
- Assessing the risk of neurotoxicant exposure should take into account that humans are exposed to multiple chemicals simultaneously, which may cause additive or synergistic effects in the brain (Cory-Slechta).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

More than 80,000 chemicals across multiple classes and types fall under the rubric of the Toxic Substances Control Act (TSCA),[1] said Deborah Cory-Slechta, yet chemical exposures receive little attention due to several incorrect assumptions: (1) chemical exposures are less important than genes from a mechanistic perspective; (2) exposures are very low with small effect sizes and thus of little concern; (3) the Environmental Protection Agency (EPA), which is responsible for fulfilling the requirements of TSCA, is protecting the public, so there is little to worry about; and (4) so many chemicals exist that it would be nearly impossible to know where to start.

According to Cory-Slechta, these are all mistaken assumptions. With regard to genetics, she pointed out that in the 1990s, prominent biologists predicted that mapping of the entire human genome would reveal the causes of common and debilitating diseases, including common psychiatric disorders. However, what genetics has shown instead is that these disorders are usually caused by either rare mutations; interactions of multiple genes; or interactions with epigenetic, environmental, and microbial factors that exert their effects as early as during fetal development and across the entire life span (Berkowitz, 2020). (Gene–environment interactions are discussed further in Chapters 3–5.) Many of these risk factors, including environmental factors, affect the brain, she added.

[1] For more information, go to https://www.epa.gov/laws-regulations/summary-toxic-substances-control-act (accessed August 12, 2020).

Moreover, said Cory-Slechta, humans are exposed to multiple chemicals through the air, from the soil through crops and meat, and from groundwater and surface water through drinking water and fish. EPA's Toxic Release Inventory (TRI) Program[2] records the release and management of certain toxic chemicals. It was established to provide a resource for researchers, policy makers, and the public. Maternal exposures may also result in exposure to the fetus during critical periods of development (Aylward et al., 2014) (see Figure 2-1). These include flame-retardant compounds, metals, pesticides, and herbicides.

Jennifer McPartland, senior scientist in the Health Program at the Environmental Defense Fund, added that for most chemicals in commerce, little information exists regarding potential hazards and extent of exposure, particularly as these factors relate to effects on the brain. Yet, she noted that new tools are available with the potential to fill these massive data gaps and complement some of the more traditional methods such as animal and epidemiological studies.

LEAD

The idea that exposures are too low to be of concern has also been repudiated, said Cory-Slechta. For example, people have been known since 2000 BC that lead—which she called "the poster child" of chemical exposures—has effects on the brain, yet not until 2012 did the Centers for Disease Control and Prevention decree that there is no safe level of lead exposure in the blood of children. Nonetheless, lead poisoning continues to kill children around the world, she said, noting that just in the past decade, several hundred children in Nigeria died from lead poisoning caused by metal smelting (Thurtle et al., 2014).

Adults are also susceptible to lead poisoning, said Cory-Slechta. Although the brain is the target organ for lead, it also accumulates in bone, where it will remain for decades, only to be released back into the bloodstream when the body requires extra calcium, such as during pregnancy and breast feeding. Once in the bloodstream, it can travel to the brain and other organs, and can also cross the placenta, exposing the fetus to toxic lead, she said.

Studies of lead poisoning have also repudiated the idea that effect sizes are too small to be of concern, said Cory-Slechta. A pooled analysis of eight research cohorts found an inverse relationship between blood lead level and IQ score and suggested there is "no evidence of a threshold for the adverse consequences of lead exposure" (Lanphear et al., 2005).

[2] For more information, see https://www.epa.gov/toxics-release-inventory-tri-program (accessed August 11, 2020).

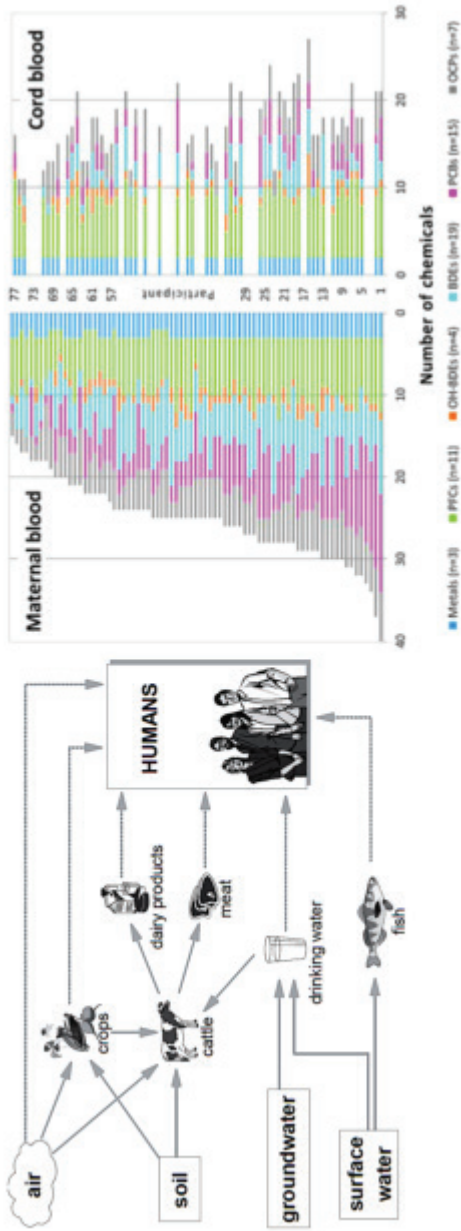

FIGURE 2-1 Human exposure to multiple environmental chemicals from the air, soil, groundwater, and surface water is reflected in high levels present in maternal and cord blood, including heavy metals, perfluorinated compounds (PFCs), brominated diphenyl ethers (BDEs), hydroxylated BDEs (OH-BDEs), polychlorinated biphenyls (PCBs), and organochlorine pesticides (OCPs). SOURCES: Presented by Deborah Cory-Slechta, June 25, 2020; European Commission, 2003 (left image); Morell-Frosch et al., 2016 (right image).

AGRICULTURAL CHEMICALS: HERBICIDES, PESTICIDES, INSECTICIDES, AND FUNGICIDES

Exposure to agricultural chemicals has also increased markedly in recent years, said Cory-Slechta. Data found on the U.S. Geological Survey (USGS) website illustrates the heavy use of three herbicides—atrazine, glyphosate (known as Roundup), and 2-4-D (see Figure 2-2). In animal models glyphosates have been linked to oxidative stress, neurotransmitter alterations, and depressive-like behaviors (Cattani et al., 2017).

Pesticides represent "a unique environmental factor," said Jason Richardson, professor of toxicology and associate dean for research in the Robert Stempel College of Public Health & Social Work at Florida International University. They are among the only chemicals intentionally put into the environment with the intention to kill by targeting circuits in the nervous system in insects that are also present in humans (Richardson et al., 2019). Moreover, they are particularly dangerous for children because many child- and toddler-specific behaviors such as playing close to the ground and putting hands to mouth may increase exposure, but also because children have immature physiological detoxification systems and are in a critical period of brain development (NRC, 1993), added Richardson.

The National Health and Nutrition Examination Survey (NHANES) has been documenting human exposure levels to pesticides and other environmental chemicals, said Beate Ritz, professor of epidemiology, environmental health sciences, and neurology at the University of California, Los Angeles. The NHANES 1999–2000 reported the presence of metabolites of organophosphate pesticides in more than half of the urine samples collected and chorpyrifos in more than 90 percent (Barr et al., 2004); the NHANES 2015–2016 reported that about half of the U.S. population aged 3 to 59 had urinary levels of neonicotinoid insecticides, which studies suggest may have neurodevelopmental toxicity (Kagawa and Nagao, 2018; Ospina et al., 2019).

INDUSTRIAL CHEMICALS AND FLAME-RETARDANT CHEMICALS

Statistics compiled by the Autism and Developmental Disabilities Monitoring Network[3] indicate that between 2000 and 2016, the prevalence of autism has tripled, according to Tracey Woodruff. The incidence of other neurodevelopmental disorders and attention-deficit hyperactivity disorder (ADHD) has also increased during this time, she said. Some of these

[3] For more information, see https://www.cdc.gov/ncbddd/autism/addm.html (accessed October 15, 2020).

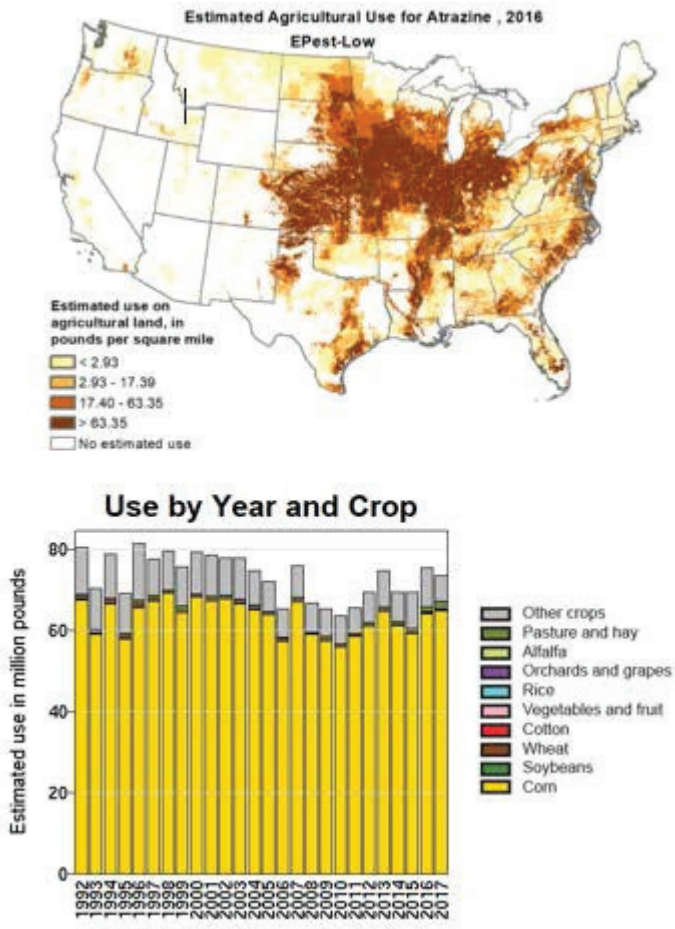

FIGURE 2-2 Human exposure to agricultural chemicals. Three common agricultural chemicals—atrazine, glyphosate, and 2-4-D—are widely used in the United States, with the use of glyphosate increasing dramatically to about 250 million pounds per year.
SOURCES: Presented by Deborah Cory-Slechta, June 25, 2020; USGS, 2020.

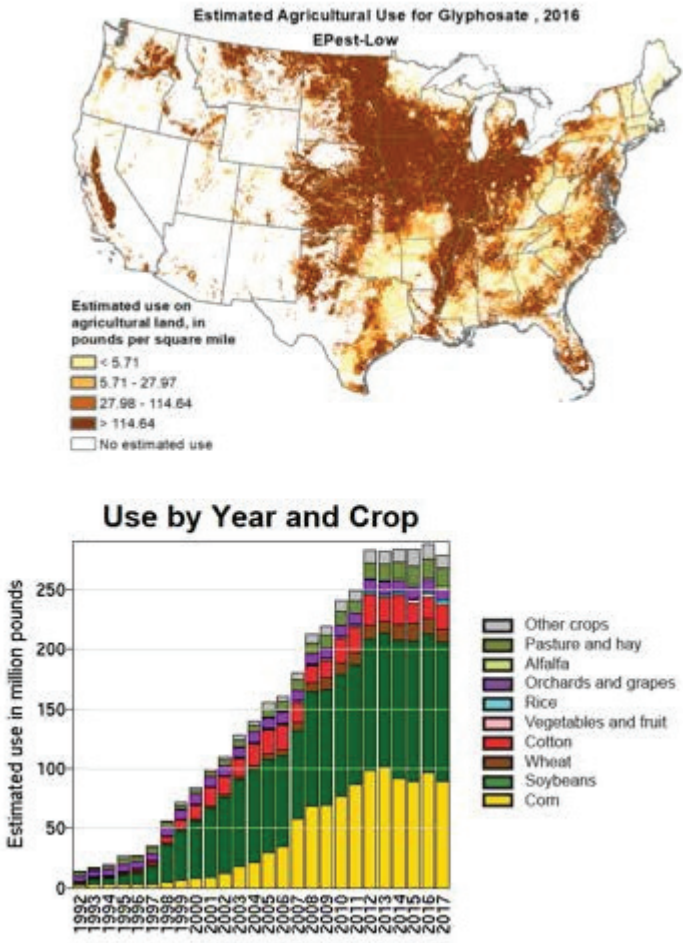

FIGURE 2-2 Continued

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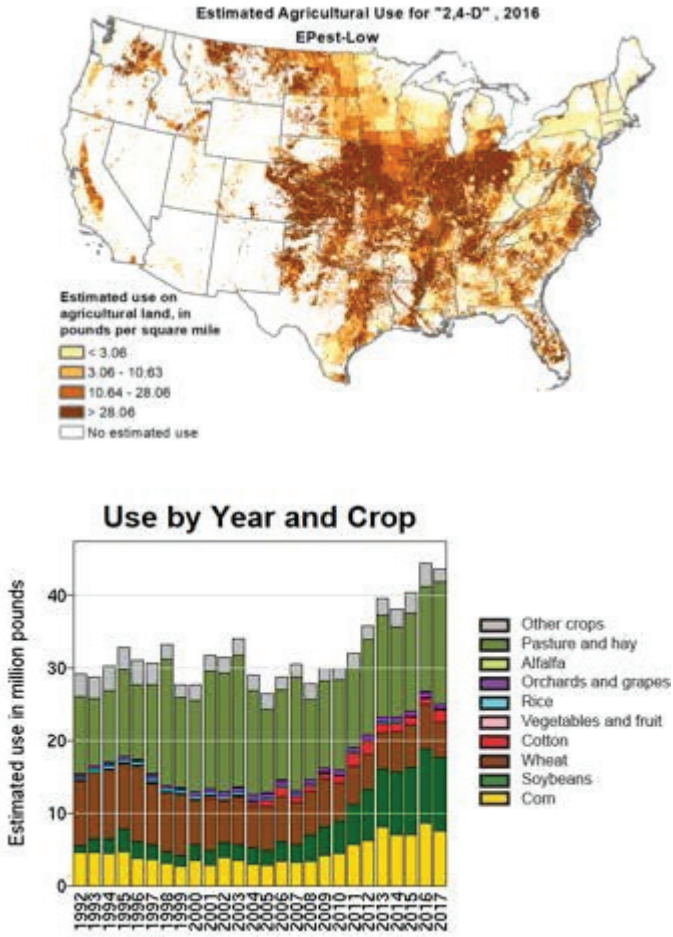

FIGURE 2-2 Continued

increases may be due to better diagnosis and awareness, but other factors are almost certainly contributing, particularly because genetics are unlikely to be changing substantially during this short time period, said Woodruff. What has changed, she said, is chemical production, which has increased more than 15-fold since the 1940s. Among the chemicals being produced at these high rates are industrial chemicals including perfluorinated chemicals such as Teflon, flame retardants used in consumer products such as mattresses and couches, plasticizers like phthalates, and chemicals used in food packaging, such as bisphenol A.

These chemicals are particularly problematic during critical periods of fetal brain development when they can affect different types of brain health effects that can result in effects on the brain that may not be apparent until childhood or later in life, said Woodruff. For example, David Bellinger, professor of neurology, psychology, and environmental health at Boston Children's Hospital, Harvard Medical School, and the Harvard T.H. Chan School of Public Health, and colleagues estimated the contribution of several risk factors to IQ loss in a population of 25.5 million children. They concluded that just three environmental chemical exposures—lead, organophosphate pesticides, and methyl mercury—are together responsible for greater IQ loss than medical conditions such as preterm birth, neurodevelopmental disorders such as autism and ADHD, and socioeconomic and nutrition-related factors such as iron deficiency and non-organic failure to thrive (Bellinger, 2012).

Woodruff and colleagues studied the risks posed by flame-retardant chemicals such as polybrominated diphenyl ethers (PBDEs). The chemical structure of PBDE chemicals bears a strong resemblance to the chemical structure of thyroid hormone, said Woodruff. This has raised concerns that PBDEs can disrupt the normal function of thyroid hormone, including the important role this hormone plays in brain development. Studies by Woodruff find that pregnant women across the United States are ubiquitously exposed to PBDEs during pregnancy and pregnant women in California have had the highest levels compared to pregnant women worldwide (Woodruff et al., 2011; Zota et al., 2011). In human embryonic stem cell model of neurogenesis, PBDEs affect cytotoxicity and the function of neural progenitor cells and cause global changes in the expression of genes involved in thyroid hormone signaling, central nervous system development, oxidative stress, and cell cycle targets (Chen et al., 2019). Moreover, said Woodruff, these effects occur at relatively low exposure levels. A systematic review of human studies has also shown there is sufficient evidence that PBDE exposure is linked to reduced IQ (Lam et al., 2017).

In the early 1970s, California began requiring the use of flame-retardant chemicals in polyurethane foam applications, but banned the use of PBDEs in 2003 as production of these chemicals began to be phased out nationally. Woodruff's research subsequently showed that the levels of PBDEs in pregnant women declined by 40 percent between 2008–2009 and 2011–2012 (Zota et al., 2013). Unfortunately, said Woodruff, PBDEs have been replaced with other flame-retardant chemicals, like organophosphate flame retardants, that may also be as toxic—resulting in regrettable substitutions.

AIR POLLUTION

In the past 10 years, air pollution has emerged as an important neurotoxicant, said Cory-Slechta. Air pollution consists of a complex mixture of particles and gases that come together to generate secondary pollutants. The particles, which occur in sizes ranging from ultrafine (< 100 nanometers in diameter) to fine (≤ 2.5 microns in diameter) to coarse (≤ 10 microns in diameter), adsorb many different contaminants such as trace elements, metals, and organic compounds, said Cory-Slechta. Ultrafine particles (UFPs) are the most reactive and are able to bypass the blood–brain barrier via uptake by the olfactory and trigeminal nerves into the brain. Dissolved, they can also cross the placenta to reach the fetal bloodstream, added Cory-Slechta. UFPs are so small that after birth they can get into the deepest areas of the lung directly into the blood, where they can bypass macrophages and travel via the vagal nerve directly to the brain stem. Yet, while EPA regulates fine and coarse particles, exposure to UFPs is not regulated.

Once air pollutants get into the body, they trigger biological responses such as increased oxidative stress and inflammation in the brain and periphery, which may contribute to the accumulation of neuropathology in the brain and the development of cerebrovascular disease, said Andrew Petkus, assistant professor of clinical neuropsychology at the University of Southern California.

ASSESSING THE RISK OF EXPOSURES

Regulatory agencies have developed risk assessment paradigms such as the four-step risk assessment process used by EPA, which characterizes the risk posed by a certain chemical by first identifying health problems caused by the particular pollutant and then assessing dose–response and extent of exposure over time, said Cory-Slechta (see Figure 2-3). Risk management decisions, however, consider not just the risk characterization, but economic and political considerations as well, she said. Furthermore, this paradigm considers just one chemical at a time, when in reality humans are exposed to multiple different chemicals simultaneously.

Consideration of concurrent and sequential exposures is necessary to establish a framework for interaction effects of exposures—both genetic and environmental, said Cory-Slechta. Moreover, these exposures occur in different social and economic contexts, she said. For example, exposure to air pollution is nearly always highest in communities of color and low socioeconomic status (Cushing et al., 2015; Johnson et al., 2016; Mullen et al., 2020). Lead exposure also occurs in the context of the stress of pov-

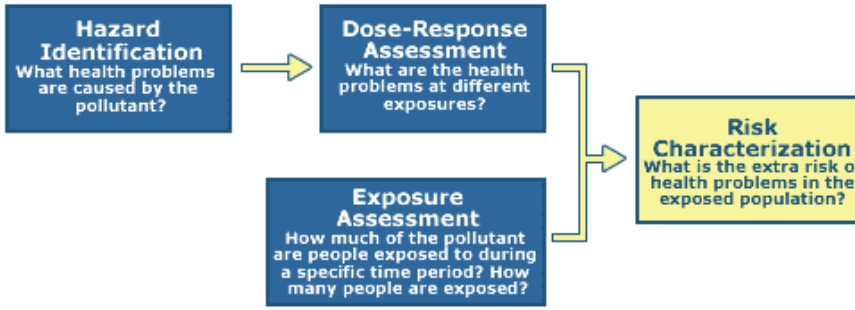

FIGURE 2-3 The Environmental Protection Agency (EPA) Risk Assessment Paradigm. The EPA risk assessment paradigm is used by EPA and other regulatory agencies to characterize the level of risk to a population posed by individual chemicals based on health problems associated with the chemical, the dose and timing of exposure, and the number of people exposed.
SOURCES: Presented by Deborah Cory-Slechta, June 25, 2020; EPA, 2020; NRC, 1983.

erty, where by comparison to higher socioeconomic status communities, residents may be exposed to violence, neighborhood crime, poor education, resource and economic deprivation, inadequate prenatal care, and other stressors, said Cory-Slechta. This is important, she said, because most of EPA's Toxic Release Inventory (TRI) facilities are located in areas with the highest percentage of non-white populations.

According to Cory-Slechta, these various stressors and risk factors may actually affect the same biological targets. For example, both lead exposure and prenatal stress are known to act on the hypothalamic-pituitary-adrenal axis and the mesocorticolimbic systems of the brain. Therefore, it is imperative when studying chemical exposures in animal models to provide realistic simulations of human environmental conditions, she said.

Cory-Slechta and colleagues have, nonetheless, learned a great deal about the combined effects of exposure to lead and prenatal stress by studying behavior and neurochemistry in animal models (Cory-Slechta et al., 2012; Virgolini et al., 2008). The interaction of lead and prenatal stress increased the rate of both behavioral and neurochemical effects in a way that would not have been seen if the two exposures were studied individually, said Cory-Slechta. It is likely, she said, that even when exposures affect the same system, they may do so through different mechanisms. The implication of that scenario is that homeostatic mechanisms that might have reregulated one component of a system may not be sufficient if multiple chemicals are acting on different components of the system.

3

The Exposome and Exploring the Multiple Factors That Contribute to Neurotoxicity

HIGHLIGHTS

- The exposome comprises all environmental exposures from conception onward and the corresponding biological responses that impact human health (Miller).
- High-resolution mass spectrometry can be used to measure the exposome in human biological samples, shedding light on environmental contributors of multiple conditions. The exposomic approach has shown promise as a tool for testing hypotheses in animal models (Miller).
- Metabolites from environmental toxicants in different ethnic groups may provide insight into why certain ethnic groups are at increased risk of neurological diseases such as Alzheimer's disease (Miller).
- Heritability studies show that in addition to genes, environmental factors are important contributors in the development of neurodevelopmental and neurodegenerative diseases; if a chemical exposure can be identified, there is the potential to minimize it or eliminate it during critical periods of brain development (Greenamyre, Zylka).
- The microbiome plays an important role in how the body deals with environmental toxicants (Woychik).

- Many environmental toxicants target the same molecular pathways linked to neurodevelopmental and neurodegenerative disorders (Greenamyre, Guilarte, Ritz, Zylka).
- Environmental conditions, including toxicant exposure and stress, may alter gene expression through epigenetic modifications to genes (Bartolomei).
- In animal models, the estrogen mimetic bisphenol A, which is used in the manufacture of many food and beverage containers, has been shown to disrupt the function of genes involved in fetal growth and the regulation of behavior, metabolism, and other processes; the metabolic phenotypes may be transmitted to subsequent generations (Bartolomei).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

Richard Woychik, director of the National Institute of Environmental Health Sciences and the National Toxicology Program, noted that while there have been and will continue to be many exciting developments in genetics and genomics, "people can get sick because of environmental exposures, and it's not just because of sequence variations in the genes they inherit from their parents that predispose them to disease."

He said there have also been many exciting developments in environmental health sciences over the past several decades. Moreover, he said, gene–environment interactions make it necessary to look at both genomic and environmental factors associated with neurotoxicity.

For example, it has become increasingly clear that low-level chronic exposures and windows of exposure are critically important for human health, including for neurological disorders; that there are interactions between biological pathogens and environmental exposures; and that the microbiome plays an important role in how the body deals with environmental toxicants, said Woychik.

THE EXPOSOME

Given the fact that disease phenotypes are the product of both genetic and environmental effects, Christopher Wild introduced the concept of the "exposome" in 2005 to capture the totality of environmental exposures that impact human health, in much the same way as the genome captures

the totality of genetic effects that contribute to disease (Wild, 2005). Rappaport and Smith advanced the idea in an article in *Science* (Rappaport and Smith, 2010), and the National Academies of Sciences, Engineering, and Medicine Standing Committee on the Use of Emerging Science for Environmental Health Decisions convened a public meeting on the topic (Brown, 2012). As the idea of the exposome began to take hold, Gary Miller, vice dean for research and strategy innovation and professor of environmental health sciences at the Columbia University Mailman School of Public Health, said he began thinking about it in the context of the research he was doing at Emory University. Over the next few years, he and colleague Dean Jones developed the concept further (Miller and Jones, 2014). Miller noted that the exposome is not restricted to chemical exposures, but also integrates ecosystems, lifestyle, and social factors (Vermeulen et al., 2020) (see Figure 3-1).

Miller and colleagues developed a platform to measure the exposome in biological samples using high-resolution mass spectrometry and different

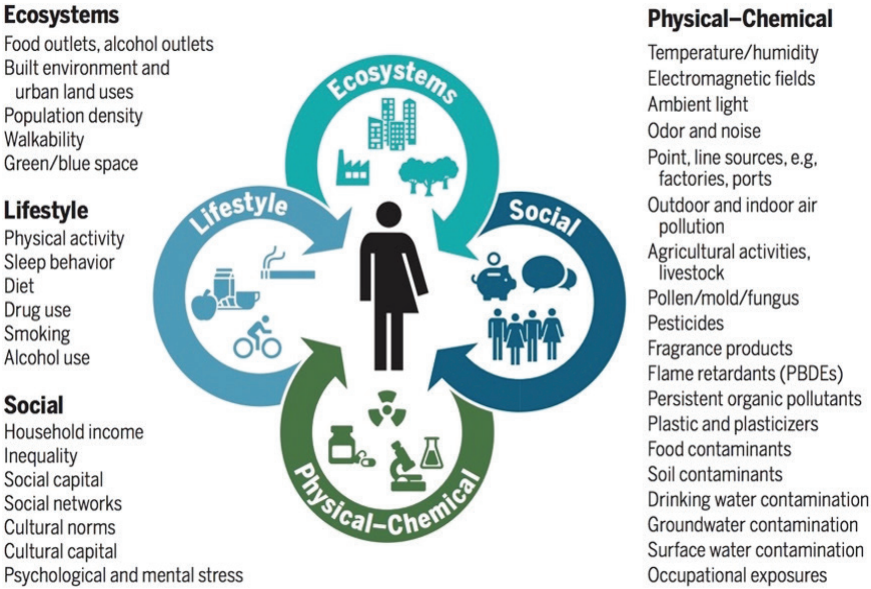

FIGURE 3-1 The exposome concept. The exposome integrates external and nongenetic factors such as what we eat and do, where we live and work, and our experiences with physical and chemical exposures.
NOTE: PBDE = polybrominated diphenyl ether.
SOURCES: Presented by Gary Miller, June 25, 2020; Vermeulen et al., 2020.

separation techniques to enable measurement of thousands of exogenous chemicals and endogenous metabolites (Jones, 2016). The idea was to standardize these systems and quantify thousands of compounds in an untargeted manner to learn more about both known and unknown environmental chemicals. For example, in a study of plasma from Alzheimer's disease (AD) patients and controls, three non-medication-related metabolites were identified that correlated reproducibly with AD biomarkers. One of them was an unknown halogenated compound that indicates an environmental origin and another (piperidine) a pepper derivative that indicates a dietary origin (Niedzwiecki et al., 2020).

In a collaboration with Richard Mayeux, chair of neurology at Columbia University, Miller is using the mass spectrometry approach to evaluate longitudinal blood samples from the multiethnic cohort enrolled in the Washington Heights-Inwood Columbia Aging Project (WHICAP) study. Interestingly, while genome-wide association studies (GWASs) have failed to pick up differences among ethnicities, high-resolution mass spectrometry identified ethnicity-related differences in metabolites. These differences help reveal why certain ethnic groups are at increased risk of AD (Vardarajan et al., 2020).

The exposomic approach has also shown promise as a tool for testing hypotheses in animal models, said Miller. For example, colleagues in his lab have exposed *C. elegans* to different mixtures and combinations of compounds and then looked at thousands of metabolomic features using mass spectrometry. Agreeing that more animal studies combining exposures and neurosciences are needed, Brenda Eskenazi, the Jennifer and Brian Maxwell Professor Emeritus of Maternal and Child Health and Epidemiology and director of the Center for Environmental Research and Children's Health at the University of California, Berkeley, noted that aligning animal and in vitro studies to human studies is also critical.

The beauty of high-resolution mass spectrometry approach for studying the exposome is that it works with multiple biological matrixes as well as in dust, water, and other environmental samples, said Miller. Thus, it provides the field with a tool that facilitates a systematic, comprehensive, and unbiased assessment of environmental contributors to multiple conditions, including neurodegenerative, neuropsychiatric, and neurodevelopmental disorders.

GENETIC FACTORS

Gene–environment interactions are implicated in many neurodevelopmental and neurodegenerative disorders, including autism, Parkinson's disease (PD), and AD. For example, over the past few years, hundreds of gene mutations have been linked to autism, said Mark Zylka, director of

the Neuroscience Center at the University of North Carolina at Chapel Hill (O'Roak et al., 2014; Pinto et al., 2014; Stessman et al., 2017). However, he said, heritability studies clearly show that environmental influence and environmental risks also play a role. The importance of this lies in the fact that unlike inherited mutations that cannot be avoided, if a chemical exposure can be identified, there is the potential to minimize it or eliminate it during critical periods of brain development and thus to eliminate environmentally induced forms of autism.

Moreover, he said many environmental toxicants target the same molecular pathways that are affected by de novo gene mutations linked to autism. Beate Ritz added that genetic variation in many different biological pathways may also influence susceptibility to exposure from pesticides and increase the risk of developing neurodegenerative diseases (see Figure 3-2).

Among the top pathways linked through genetics to autism that are also known to be affected by chemicals in the environment are the Wnt/β catenin pathway, genes associated with synaptic function, and genes associated with neuroinflammation. If a chemical targets one of those pathways, it may be able to increase the risk of autism, said Zylka. His lab and others are now using high-throughput screens and transcriptomic approaches to try to define chemicals that target these specific pathways, he said.

Multiple factors also contribute to the etiology of PD, said J. Timothy Greenamyre, Love Family Professor and vice-chair of neurology, chief of movement disorders, and director of the Pittsburgh Institute for Neurodegenerative Diseases at the University of Pittsburgh. At one end of the spectrum are monogenic causes. Despite the fact that about 20 genes have been implicated, monogenic causes together account for only about 10 percent of cases, said Greenamyre. At the other end of the spectrum are clearly defined environmental or toxicant exposures, including pesticides and industrial solvents that have been associated with PD. For most people with PD, Greenamyre believes the disease arises from their composite genetic makeup of resistance and susceptibility genes combined with a lifetime of environmental exposures.

Wnt/β Catenin Signaling Pathway

At least 19 percent of all genes linked to autism are in the Wnt signaling pathway, said Zylka (Bernier et al., 2014; Packer, 2018). One of the most commonly mutated genes in idiopathic autism is the chromodomain helicase DNA-binding protein 8 (CHD8). CHD8 regulates transcription by altering chromatin structure (Thompson et al., 2008) and has been associated with cortical overgrowth and enlarged brains, which is a common phenotype in many individuals with autism, said Zylka (Bernier et al., 2014). The antiepileptic drug valproate also activates Wnt signaling, and

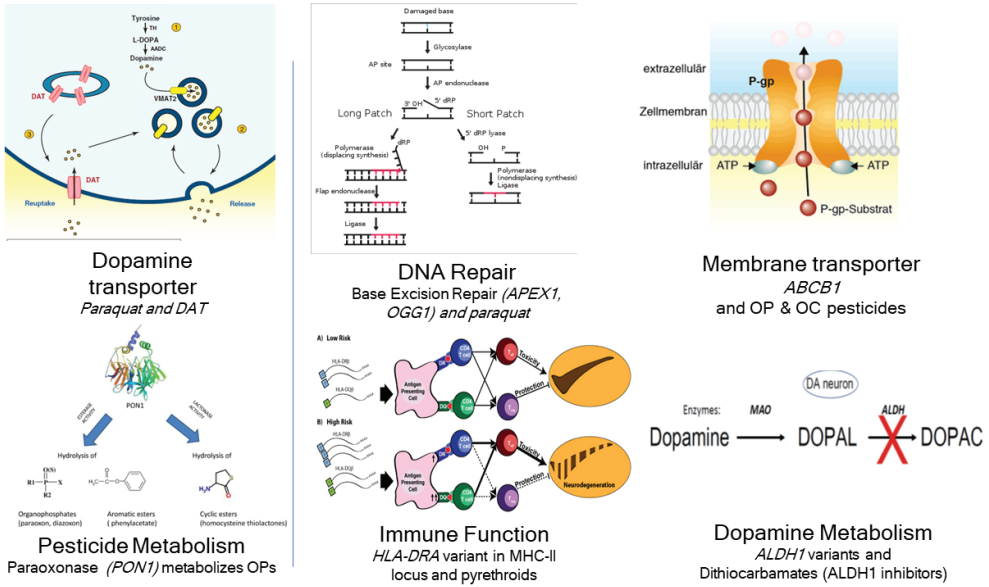

FIGURE 3-2 Genetic variation in many biological pathways influences susceptibility to exposure from pesticides and increases the risk of developing neurodegenerative diseases.
NOTES: Different pesticides have been linked to neurodegenerative disorders through multiple genetic mechanisms, including DNA repair, immune function, dopamine metabolism, and membrane transport; and by genetic variants in the dopamine transporter or enzymes that metabolize pesticides. ABCB1 = ATP binding cassette subfamily B member 1; ALDH1 = aldehyde dehydrogenase I; APEX1 = apurinic/apyrimidinic endodeoxyribonuclease 1; DAT = dopamine active transporter; HLA-DRA = major histocompatibility complex, class II, DR alpha; MHC-II = major histocompatibility complex II; OC = organochlorine; OGG1 = 8-oxoguanine glycosylase; OP = organophosphate.
SOURCE: Presented by Beate Ritz, June 25, 2020.

maternal use of the drug has been linked to an elevated risk of autism as well as increased brain growth (Christensen et al., 2013). Valproate thus represents an epidemiologically verified environmental risk, said Zylka. His lab is now using a collection of human neural progenitor cells, mouse cortical neurons, and other types of cells to examine how valproate and other chemicals affect signaling pathways in neural and other cells with common genetic variants associated with autism.

Synaptic Function

Autism-linked genes associated with synaptic function also are beginning to reveal clues about environmental risks, according to Zylka. Mutations in one of these genes, SCN2A, which is a voltage-gated sodium channel, have been shown to dampen or eliminate the function of the channel (Ben-Shalom et al., 2017; De Rubeis et al., 2014). Similarly, agricultural pesticides called pyrethroids, which have been linked epidemiologically to increased risk of both autism and attention-deficit hyperactivity disorder (ADHD), also inactivate this channel (Furlong et al., 2017; Shelton et al., 2014).

One of the leading mechanisms by which lead exposure impairs brain function is through its effects on synaptic function. According to Tomas Guilarte, dean of the Robert Stempel College of Public Health & Social Work at Florida International University, lead is a potent and selective non-competitive antagonist of N-methyl-d-aspartate (NMDA) receptors. Expression of NMDA receptors in the hippocampus is critical for learning and memory, said Guilarte. By inhibiting the NMDA receptor, lead exposure impairs synaptic plasticity and long-term potentiation, resulting in deficits in cognitive function (Nihei et al., 2000). In hippocampal neuron culture, this effect can be mitigated or reversed by exogenous addition of brain derived neurotrophic factor (BDNF) (Neal et al., 2010). A BDNF mimetic called 7,8-dihydroxyflavone, which is abundant in the human diet, has also been shown to reverse the effects of lead exposure on synaptic function (Zhang et al., 2018).

LRRK2

The most common autosomal dominant form of PD is caused by mutations in a gene called leucine-rich repeat kinase 2 (LRRK2) (Li et al., 2014). Many mutations in LRRK2 that result in increased activity of the kinase have been associated with PD; however, Greenamyre said other factors may also interact with LRRK2 and influence an individual's risk of developing PD. His laboratory has been exploring the role of LRRK2 in idiopathic

PD (iPD), the vast majority of cases in which the cause is unknown. Using an assay they developed, they demonstrated increased LRRK2 activity in postmortem brain tissue from patients with iPD (Di Maio et al., 2018); and reproduced this in an animal model of PD in which exposure to a common pesticide called rotenone replicates the key pathological and behavioral characteristics of PD (Betarbet et al., 2000). Greenamyre and colleagues hypothesize that rotenone produces reactive oxygen species, including superoxide, causing oxidative stress, which activates LRRK2 (Di Maio et al., 2018). In human PD and in the animal model, LRRK2 activity is also associated with endolysosomal deficits, which result in accumulation of disease-associated proteins such as α-synuclein (Rocha et al., 2020).

Greenamyre's lab went on to explore whether LRRK2 activation is a common feature of PD-associated environmental toxicants, such as trichloroethylene (TCE) (see Figure 3-3). TCE, rotenone, another pesticide called paraquat, and many other environmental toxicants are known to cause oxidative stress and mitochondrial dysfunction (Tanner et al., 2011). Investigators in Greenamyre's lab have shown that TCE exposure induces LRRK2 activity in dopaminergic neurons and that an inhibitor of LRRK2 attenuates neurodegeneration in the rotenone model of PD (De Miranda and Greenamyre, 2020). This suggests that LRRK2 inhibitors may be useful not only for individuals with LRRK2 mutations, but those with iPD as well.

EPIGENETICS

Epigenetics emerged in the early 2000s to help explain how environmental conditions can alter the expression of genes and how, for example, early life events can cause disorders with onset later in life, according to Marisa Bartolomei, Perelman Professor of Cell and Developmental Biology and co-director of the Penn Epigenetics Institute at the University of Pennsylvania. Bartolomei and colleagues have been investigating how bisphenol A (BPA)—an estrogen mimetic used in manufacturing many types of food and beverage containers—may reprogram the adult mouse brain through epigenetic modification of genes. During early development, genes are particularly vulnerable to environmental perturbations that lead to changes in the levels of DNA methylation, histone modifications, and other chemical alterations to genes, resulting in dysregulation of gene function, said Bartolomei. One group of genes that is protected from this genome-wide methylation is imprinted genes. These are genes expressed in a monoallelic parent-of-origin-specific manner (Bartolomei, 2009). They are essential for fetal growth and also are involved postnatally in regulating behavior, metabolism, and other processes, said Bartolomei (Kalish et al., 2014). Dys-

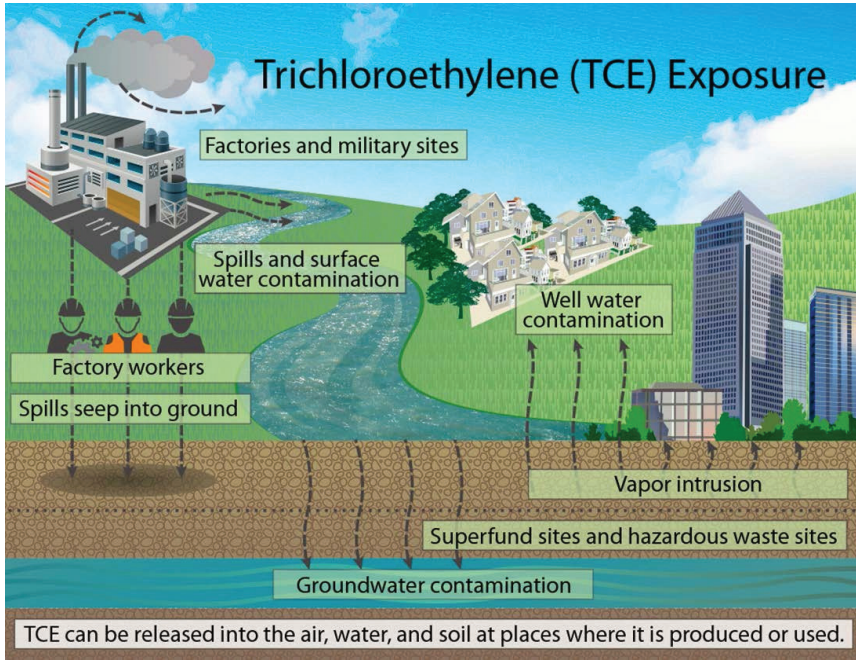

FIGURE 3-3 Trichloroethylene (TCE) exposure. The industrial solvent TCE, used in many industrial processes, is found in air, water, and soil near sites of production. Spills and surface contamination allow TCE to seep into groundwater, and through vapor intrusion it gets into drinking water. TCE has been shown to be a Parkinson's disease–associated environmental toxicant.
SOURCES: Presented by J. Timothy Greenamyre, June 25, 2020; HHS, 2016.

regulation of imprinted genes is associated with neurobehavioral disorders such as Prader Willi and Angelman syndromes, she said.

Human exposure to BPA is widespread and has been linked to behavioral abnormalities as well as cancer, metabolic disorders, and infertility (Susiarjo et al., 2013). In a 2005 study of urine samples collected in the Third National Health and Nutrition Examination Survey (NHANES III), BPA was detected in 95 percent of samples (Calafat et al., 2005). In 2007, Dolinoy and colleagues showed that exposure of pregnant mice to BPA resulted in a change in the color of their coats. These changes resulted from epigenetic changes—hypomethylation or loss of methylation—in a specific genetic locus, a retrotransposon called the intracisternal A particle (Dolinoy et al., 2007).

Bartolomei and colleagues were interested in learning how BPA affected imprinted genes. They exposed female mice to BPA at two physiologically relevant doses of BPA (lower and higher doses) both before mating (pre-oocyte development) and during pregnancy (earliest stage of embryonic development); then analyzed embryonic and placental tissue from pregnant mice euthanized at two time points. Genetic analyses of the tissue revealed that maternal BPA exposure during late stages of oocyte development and early embryonic development disrupted genomic imprinting in embryos and placentas of several genes associated with human imprinting disorders. Genome-wide methylation levels in the placenta, but not the embryo, was also reduced, said Bartolomei (Susiarjo et al., 2013).

They also assessed multigenerational behavioral and metabolic consequences of BPA exposure by allowing mice to be born, continuing to expose mothers to BPA through weaning, then weaning mice with no further BPA exposure and examining behavior and metabolism phenotypes in F1 (first generation) and F2 (second generation) mice. The F1 offspring of BPA-exposed mice exhibited male-specific, depressive-like behavior, as well as metabolic and skeletal phenotypes, said Bartolomei. She added that the metabolism phenotypes were multigenerational, but the behavioral phenotype was not transmitted to subsequent generations (Xin et al., 2018).

Cellular Mosaicism

Richard Woychik said there has been interest at the National Institutes of Health in looking at cellular mosaicism, where a person may have genetically different sets of cells in their bodies. This can be driven by activation of transposable elements through epigenetic activation or inactivation, he said, suggesting there might be an environmental trigger for this process. Zylka noted that mosaicism has been demonstrated in some people with idiopathic PD or AD and may be confined to the brain or another small region of the body. Mosaicism has also been seen in autism and epilepsy, he said.

CONCURRENT RISK FACTORS: STRESS AND POVERTY

Devon Payne-Sturges, associate professor at the Maryland Institute for Applied Environmental Health, added that the issue of cumulative exposures is particularly relevant in terms of environmental justice. In addition to multiple chemical exposures, the social context in which these exposures occur is important, she said, adding that environmental and social stressors have been shown to have similar biological targets and possible synergistic

effects. Indeed, said David Bellinger, disadvantaged children suffer disproportionately from neurotoxicants like lead. Not only are they more highly exposed to neurotoxicants, but the same magnitude of exposure has a greater adverse impact on them compared to more advantaged children, he said. For more on how social stressors may impact neurological disorders, see the section on autism and ADHD in Chapter 4. For more about research that is needed to better understand these interactions, see Chapter 5.

4

Chemical Toxicants as Drivers of Abnormal Neurodevelopment and Neurodegeneration

HIGHLIGHTS

- Early life exposure to neurotoxicants can impact brain development in later life, possibly by reducing an individual's ability to respond to neurological insults (Bellinger).
- Childhood lead exposure has cascading downstream effects on multiple behavioral domains and quality of life (Bellinger).
- Exposure to lead and polychlorinated biphenyls may increase a child's risk of developing attention-deficit hyperactivity disorder (Richardson).
- Studies in mouse models and humans indicate that the pyrethroid insecticide deltamethrin may be associated with increased hyperactivity and impulsivity (Richardson).
- Exposure to the pesticides paraquat and maneb is associated with an increased risk of Parkinson's disease (PD), which appears to be modified by function of the dopamine transporter (Ritz).
- There are variants of paraoxonase that differ in their ability to detoxify organophosphate pesticides that increase risk of developing PD (Ritz).
- Individuals exposed to traffic-related air pollution are at an increased risk of PD when they are carriers of a variant in the inflammatory gene interleukin-1β (Ritz).

- Exposure to air pollution and cigarette smoke may increase the risk of age-related brain volume loss and cognitive impairment (Finch).
- Multiple studies show that both heritability and environmental exposures—particularly chlorinated pesticides—are implicated as causes of amyotrophic lateral sclerosis (Feldman).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

Early life exposure to neurotoxicants can impact a child's developmental trajectory in multiple and sometimes unexpected domains, said David Bellinger. It can affect how well an individual is able to respond to neurological insults even later in life, possibly by reducing resilience or cognitive reserve, which may provide a link between neurodevelopment and neurodegeneration, he added. Bellinger noted, however, that effects at the individual level may be small and affected by many other factors, including the extent and time course of the exposure. Thus, in order to estimate the societal impact of neurotoxicant exposure, studies must look at the population rather than individual level, he said.

Bellinger also noted that the effects of neurotoxicants on brain development have been recapitulated in animal models. For example, a study in rats showed that animals that were exposed to lead recovered more poorly to an induced brain injury (Schneider, 2007).

NEURODEVELOPMENT, AUTISM, AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER

As discussed in Chapters 2 and 3, exposure to neurotoxicants such as lead and pesticides has been associated with increased rates of neurodevelopmental disorders such as autism and attention-deficit hyperactivity disorder (ADHD). With about 1 in 68 individuals affected by autism, according to Mark Zylka, this has become a major health problem. The linkages between environmental exposures and autism have already been discussed extensively; here we explore in more detail the association with ADHD.

In addition to effects of lead exposure on IQ, which was discussed in Chapter 2, lead exposure has also been reliably linked to other domains of neurodevelopment, such as attention, executive function, and impulse control, said Bellinger (Braun et al., 2006). Children with higher levels

of lead exposure in early life do less well in school, are more likely to be classified as learning or behaviorally exceptional, and less likely to be considered advanced or intellectually gifted (Miranda et al., 2007, 2010). Bellinger added that the impact of the same level of lead exposure on school achievement and behavior was considerably greater for children already at risk of having these problems due to low socioeconomic status and low parental education levels. As adults, children with higher blood lead levels achieve lower socioeconomic status (Reuben et al., 2017). Putting this all together, said Bellinger, suggests that childhood lead exposure has cascading downstream effects with real consequences on quality of life, including, for some children, greater criminal activity later in life (Boutwell et al., 2017; Coulton et al., 2020; Emer et al., 2020; Nkomo et al., 2017).

Bellinger acknowledged that the effect sizes are small at an individual level, but noted that on a population level, lead has a huge impact on cumulative IQ loss and thus is responsible for a substantial loss of societal intellectual resources (Bellinger, 2012).

Difficulties with attention and impulse control manifest in many children as a diagnosis of ADHD. Indeed, according to Jason Richardson, ADHD affects about 8 to 12 percent of children in the United States, with boys diagnosed about three to four times as often as girls. Like other neurodevelopmental and neurodegenerative disorders, ADHD has a strong genetic basis, but is also associated with multiple other factors, including environmental exposures, he said. In a recent meta-analysis of twin studies, the heritability of ADHD was estimated to be more than 70 percent (Faraone and Larsson, 2019), said Richardson, but factors such as low birthweight, perinatal hypoxia, and lead exposure are also associated with increased risk of ADHD. Environmental toxicants such as polychlorinated biphenyls (PCBs) may also be linked to ADHD, but have been less well studied, he added.

Richardson and colleagues used a gestational lactational exposure paradigm to study the behavioral and neurobiological effects of the pyrethroid insecticide deltamethrin in mice (Richardson et al., 2015). Using doses from 4- to 40-fold lower than the "no observable adverse effect level" established by the Environmental Protection Agency, pregnant mice were fed deltamethrin in peanut butter starting at gestation day 6 through weaning on postnatal day 22. At 6 weeks of age (equivalent to early adolescence in humans), a dose-related increase in locomotor activity was observed in males, which was attenuated by treatment with methylphenidate. Male mice also scored significantly higher on a task assessing impulsivity, said Richardson. The behavioral findings in mice were recapitulated in a separate human study, where pyrethroid pesticide exposure in children (assessed by measuring urinary levels of a pyrethroid metabolite) was shown to be

associated with ADHD, particularly in boys with hyperactive-impulsive symptoms (Wagner-Schuman et al., 2015).

In an effort to understand the mechanism underlying the effect of pyrethroids on locomotor activity, Richardson and colleagues showed significantly increased locomotor activity in male mice exposed to deltamethrin and given a dopamine-1 (D1) receptor agonist. This increase in activity was reduced to control levels by administration of a D1 receptor antagonist. Using receptor autoradiography, they also demonstrated increases in D1 receptors in the nucleus accumbens of these mice, a brain region associated with impulse control and substance abuse (Richardson et al., 2015). They also observed increases in D1 and dopamine transporter mRNA, which persisted through 1 year of age and suggested a possible epigenetic effect, said Richardson. His lab has proceeded to show in cell culture that knocking down DNA methyltransferase increases D1 receptor mRNA, which further supports an epigenetic mechanism.

NEURODEGENERATIVE DISORDERS: ALZHEIMER'S DISEASE, PARKINSON'S DISEASE, AND AMYOTROPHIC LATERAL SCLEROSIS

A complex combination of genetic and environmental factors is thought to contribute to the pathogenesis of neurodegenerative disorders such Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), although what initiates the process of neurodegeneration may be different from what drives it subsequently, said J. Timothy Greenamyre. Indeed, several of the mechanisms associated with neurotoxicant exposure that were discussed in Chapter 3, including effects on synaptic function and endolysosomal pathways, oxidative stress, epigenetic changes, and cellular mosaicism, have been linked to neurodegenerative disorders. Greenamyre and Jason Cannon have suggested that common mechanisms may underlie most neurodegenerative disorders (Cannon and Greenamyre, 2011).

Alzheimer's Disease

Accumulating data indicate that exposure to high levels of air pollution increase the risk for all-cause dementia, said Andrew Petkus (Peters et al., 2019). Indeed, according to Caleb Finch, ARCO Professor and William F. Kieschnick Chair in the Neurobiology of Aging at the University of Southern California, half of individual AD risk may be environmental (Gatz et al., 2006). Finch and Alexander Kulminski of the Duke Population Research Institute and Duke's Biodemography of Aging Research Unit, recently proposed an AD exposome as a framework for understanding

endogenous and exogenous environmental factors that may contribute to AD as well as gene–environment interactions (Finch and Kulminski, 2019).

Finch's research focuses on the role of air pollution and cigarette smoke as risk factors for accelerated aging and AD. He calls both of these "sterile gerogens"—sterile because they are toxicants rather than pathogens, and gerogens because they accelerate aspects of aging processes. Both air pollution and cigarettes shorten life span by about 5 to 10 years and accelerate disease of aging, said Finch. He noted that both contain fine and ultrafine particles that are deposited in the lungs as well as incompletely burned carbon particles, carcinogens, neurotoxicants, polyaromatic hydrocarbons, and the toxic metals iron and lead. In the Vietnam Era Twin Study of Aging, cigarette smoking was associated in a dose-dependent manner with brain volume loss (Prom-Wormley et al., 2015); and in the Women's Health Initiative Memory Study (WHIMS), exposure to particulate matter from air pollution was associated with accelerated loss of both gray and white matter as well as with a decline in episodic memory (Casanova et al., 2016; Younan et al., 2020).

Gene–environment interactions have been demonstrated as well, said Finch. In the Washington Heights-Inwood Columbia Aging Project (WHICAP) cohort, higher concentrations of air pollution were associated with more rapid cognitive decline, particularly in carriers of the APOE4 allele, which is the strongest genetic risk factor for AD (Kulick et al., 2020). Finch's lab is exploring in mouse models the mechanisms underlying this association. In APOE4-carrying mice, they have shown that oxidative stress from exposure to nano-sized, traffic-related air pollution particulate matter (nPM) results in accelerated production of the amyloid-β protein by reorganizing key enzymes involved in processing the amyloid precursor protein (Cacciottolo et al., 2020). They have also demonstrated that the effects of nPM on gene transcription differ depending on sex as well as APOE allele (Haghani et al., 2020).

Finch also noted "remarkable overlap" in the developmental impact of air pollution, cigarette smoke, and lead exposure (Finch and Morgan, 2020). Synergistic effects from exposure to cigarette smoke and air pollution also have been demonstrated for multiple morbidities, including cognitive aging, he said (Forman and Finch, 2018).

The oxidative stress and inflammation triggered by air pollution contribute to the accumulation of hallmark neuropathologies associated with AD, including amyloid β and tau tangles, brain atrophy, cognitive decline, and eventually dementia, said Petkus. A decline in episodic memory is typically the first cognitive sign of AD, he said (Petkus et al., 2020). Petkus added that air pollution induces variable effects on different aspects of episodic memory; for example, fine particulate matter (referred to as $PM_{2.5}$) appears to be more strongly associated with the encoding aspect of episodic

memory compared to retrieval and long-term recall aspects, suggesting that it may be impacting brain regions associated with learning new material versus long-term recall (Petkus et al., 2020). However, imaging studies using structural magnetic resonance imaging to assess brain atrophy have produced mixed findings, he said.

Parkinson's Disease

Pesticides have long been linked to onset of PD, although until recently it has been difficult to determine which specific pesticide exposures may be associated with PD, said Beate Ritz. For the past two decades, Ritz and Jeff Bronstein, director of the Movement Disorders Program at the University of California, Los Angeles, have collected biosamples and data on pesticide use in California in the Parkinson's Environment and Gene Study. By combining data on the timing and geo-location of pesticide application with lifelong address data, they have been able to determine long-term pesticide exposure across a large population. These modeled exposures have been validated against biomarkers of exposure (Paul et al., 2018b; Ritz and Costello, 2006). For example, they estimated levels of two pesticides—paraquat and maneb (see Figure 4-1). They also determined that when these two agents come together, there is an approximately 75 percent increase in risk of developing PD (Costello et al., 2009). The results of their study supported earlier work indicating that exposure to paraquat and maneb increase the risk of PD amongst those who carry risk alleles in the dopamine transporter by as much as five-fold, said Ritz (Kelada et al., 2006; Ritz et al., 2009).

Ritz described another way that gene–environment interactions contribute to the development of PD. Organophosphates (OPs) are another widely used class of pesticides that have been linked to an increased risk of PD. Ritz and colleagues have shown that this risk is affected by variants in the gene for paraoxonase (PON1), an enzyme that detoxifies OP pesticides. These gene variants determine how fast a person metabolizes OPs: those who are slow metabolizers have a much greater increased risk of developing PD, said Ritz (Lee et al., 2013). For example, people who frequently use OPs in their households and are slow metabolizers have about 2.5-fold increased risk of developing PD compared to people who are slow metabolizers, but do not use OPs frequently (Narayan et al., 2013). In other words, said Ritz, genetic susceptibility alone does not increase the risk of PD in the absence of exposure. She added that the combination of PON1 slow metabolizers and OP exposure also contributes to a decline in cognitive function over time, both in populations with ambient residential and occupational exposures from agricultural applications in a population of older Mexican Americans (Paul et al., 2017, 2018a).

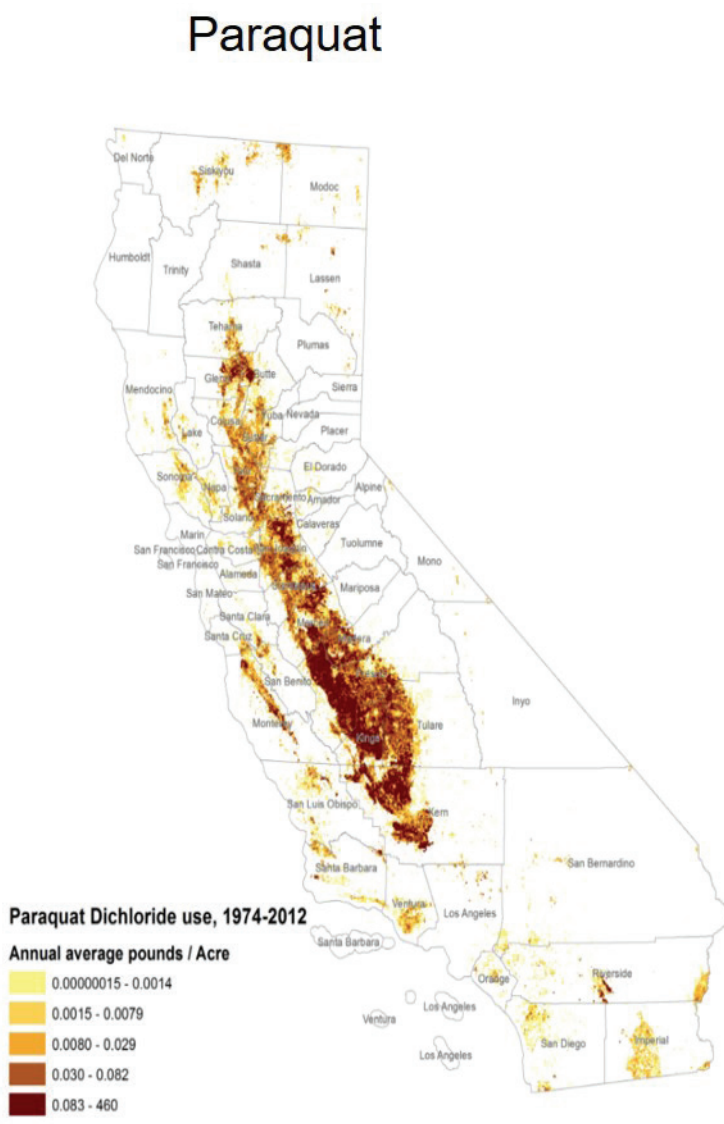

FIGURE 4-1 Paraquat and maneb are both widely used in the Central Valley of California.
SOURCES: Presented by Beate Ritz, June 25, 2020; California Department of Pesticide Regulation.

continued

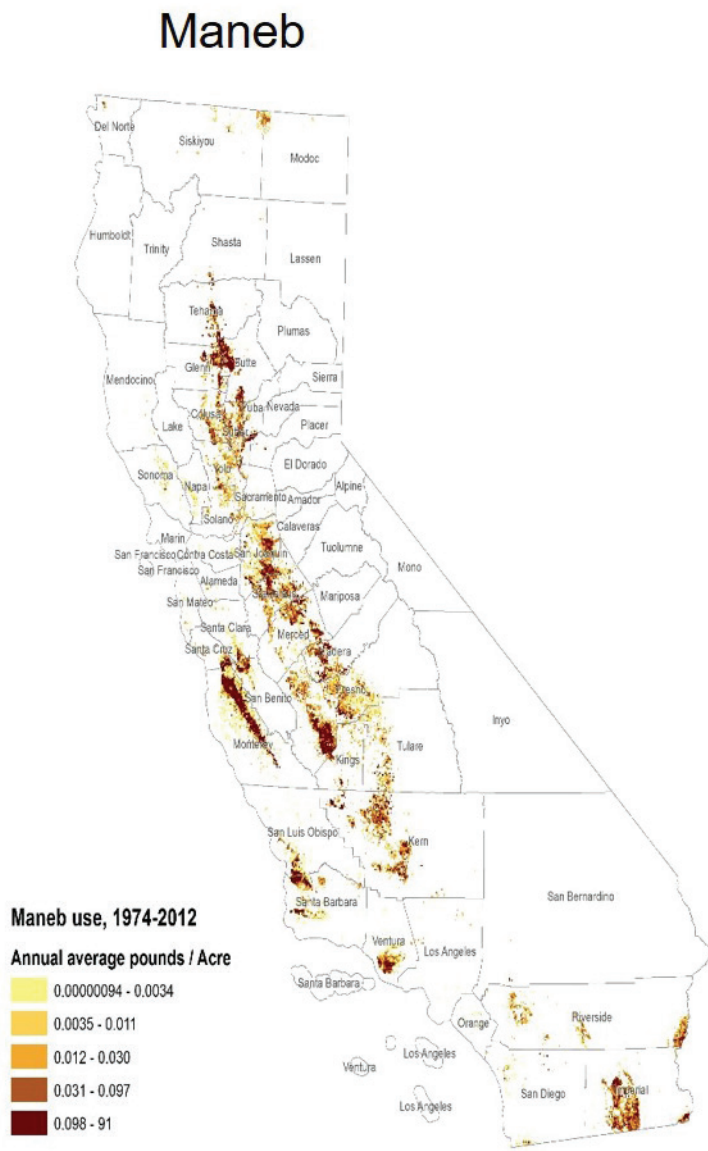

FIGURE 4-1 Continued

Ritz and colleagues have also been investigating the impact of air pollution on the development of PD. A study in Denmark combined sophisticated traffic-related exposure data over a 40-year period with incidence of PD and showed that people highly exposed to traffic had an increased risk of PD (Ritz et al., 2016). They also demonstrated a gene–environment interaction by showing that those exposed to traffic-related air pollution who also carried a polymorphism in the interleukin-1β gene, which is known to increase inflammatory responses in the brain, was associated with a three-fold increased risk of PD in those with high exposure to traffic (Lee et al., 2016).

Amyotrophic Lateral Sclerosis

ALS is a progressive, incurable degenerative disease of the motor neurons in the brain, brainstem, and spinal cord, which has a prevalence in North America of approximately 3.5 per 100,000. Eva Feldman, the Russell N. DeJong Professor of Neurology and director of the ALS Center of Excellence Pranger ALS Clinic at the University of Michigan, said that while heritability clearly plays a role, multiple studies show there is an environmental component as well. Scientists believe that in ALS, as in other neurodegenerative diseases, a clear genetic load or genetic predisposition combines with aging and cell damage and with environmental exposures to initiate a self-perpetuating decline to death, she said (Al-Chalabi and Hardiman, 2013).

Michigan is a hotspot with a high prevalence of ALS cases, said Feldman, which she suggested may result from the large number of uncleaned Superfund sites in the state (see Figure 4-2).

Against this backdrop, Feldman has been collaborating with Stephen Goutman, director of the Pranger ALS Clinic at Michigan Medicine, on a project designed to identify environmental and occupational toxic exposures, the sources of these exposures, and the effects of these exposures on the metabolome of 156 individuals with ALS compared to 128 controls. Using whole blood gas chromatography and mass spectrometry, they measured levels of three groups of chemicals: chlorinated pesticides, brominated flame retardants, and PCBs. In addition to being highly toxic, Feldman noted that these chemicals are also highly persistent in the environment, sometimes lasting for decades before dissipating. Their results, published in 2016, reported an association between persistent environmental pollutants and ALS. Chlorinated pesticides were associated with the greatest risk of developing ALS, said Feldman (Su et al., 2016).

Because they also saw that organic pollutants were highly correlated with each other in terms of case exposure, Goutman, Feldman, and colleagues collaborated with Stuart Batterman and Bhramar Mukherjee from the University of Michigan School of Public Health to assess exposures to

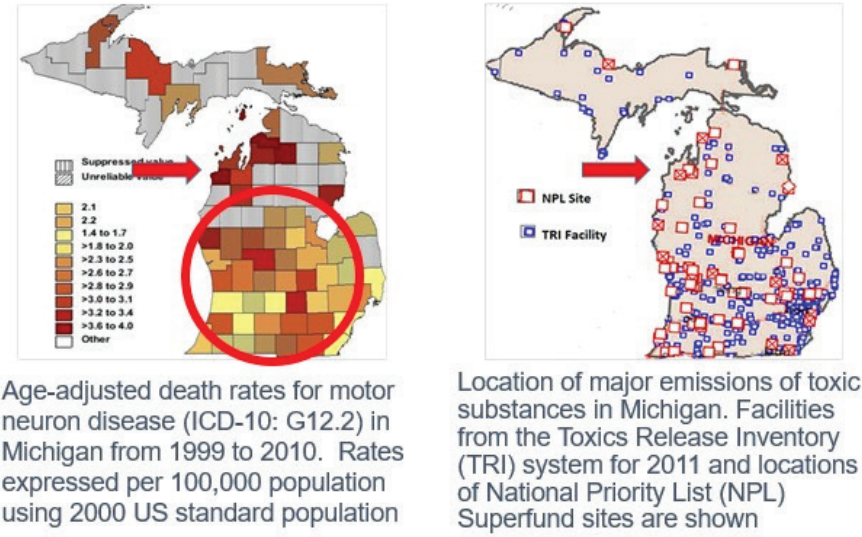

FIGURE 4-2 Identifying environmental risk factors for amyotrophic lateral sclerosis in Michigan. The map on the left depicts age-adjusted death rates for motor neuron disease, while the map on the right indicates locations of major emissions of toxic substances. Note the substantial overlap and the particularly high prevalence near the Leelanau Peninsula (red arrows), which has an extremely toxic uncleaned Superfund site.
SOURCE: Presented by Eva Feldman, June 25, 2020.

multiple pollutants. Using a mathematical model, they showed that the cumulative environmental risk score for mixtures of pollutants in ALS patients was more than seven times that of controls. They also showed that exposure to persistent organic pollutants influence survival. Individuals with the lowest environmental risk scores survived twice as long as those with the highest scores, said Feldman (Goutman et al., 2019).

Feldman and colleagues, led by Manish Aurora at Mount Sinai in New York City, have also explored how exposures during childhood and adolescence affect ALS risk. Using laser analysis of metals in teeth, this joint collaboration showed that 11 metal toxicants present in teeth—including zinc, chromium, and manganese, but not lead—were clearly associated with increased ALS risk (Curtin et al., 2020; Figueroa-Romero et al., 2020). Feldman added that metabolomics studies conducted by her lab have also demonstrated a significant difference in the metabolome of ALS patients associated with exposure to the chlorinated pesticide pentachlorobenzene. She noted that more environmental studies are needed to advance this research, especially in regard to recruiting and maintaining cohorts to later support more hypothesis-based studies.

5

Research Gaps and Opportunities

HIGHLIGHTS

- Unanswered questions regarding the effect of environmental exposures on humans include identifying subpopulations at risk, windows of exposure, transgenerational effects of exposure, mechanisms of toxicity, and gene–environment interactions (Cory-Slechta, Eskenazi, Hogberg, Richardson, Ritz).
- The coronavirus disease 2019 (COVID-19) pandemic has elevated the need to better understand how pathogen-driven infections interact with environmental toxicants (Finch).
- Tools for monitoring environmental exposures are inadequate, unavailable, or insufficiently used (Penning).
- An adverse outcome pathway approach could be useful in studying mechanisms of toxicity and linking those mechanisms through epidemiological studies to neurological disorders (Barone, Hogberg, Zylka).
- Data on biological processes in the context of adverse outcomes are essential to show their relevance to disease, morbidity, and mortality, and support decision making based on data; furthermore, this predictive toxicology approach can enable agencies such as the Environmental Protection Agency to bridge data gaps and make risk assessments in a chemically agnostic way (Barone).

- Genetic studies may help identify adverse outcome pathways (Greenamyre).
- Standardized methods for collecting data regarding potential toxicant exposures are needed (Richardson, Willis, Woodruff).
- New methods and tools including exposomic tools, machine-learning techniques applied to high-dimensional neuroimaging data, three-dimensional microphysiological systems derived from induced pluripotent stem cells, high-throughput sequencing-based screens, and tools to manipulate gene expression are being developed to advance the field of environmental neuroscience (Greenamyre, Hogberg, McParland, Petkus, Woychik, Zylka).
- New animal models more relevant to the human experience and novel ways of using existing animal models are needed to identify factors and exposures that drive disease progression, therapeutic targets, and biomarkers (Cory-Slechta, Greenamyre, Payne-Sturges).
- Population and real-world studies are essential to understand how exposures affect different subpopulations and to understand the interaction between genes and environment (Eskenazi, Feldman, Hill, Koroshetz, Ritz).
- Identifying factors that impact the susceptibility to potential adverse effects of environmental exposures may lead to the development of prevention strategies (Petkus, Ritz).
- Natural experiments that are providing intriguing clues about the effects of environmental exposures include the banning of pesticides and flame-retardant chemicals, reduced air pollution in China for the 2008 Olympics, and the reduction in air pollution from behavioral changes in reaction to COVID-19 (Cory-Slechta, Koroshetz, Lawler, McPartland, Woodruff).
- Combining geospatial methods with analysis of biosamples from existing cohort studies could provide valuable and low-cost opportunities to study environmental exposures (Eskenazi, Ritz).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

As described in earlier chapters, workshop participants discussed recent advances in knowledge related to the exposome and the spectrum of neurotoxicants to which humans are exposed; the mechanisms by which these exposures may impact the brain; and the broad array of neurodevelopmental and neurodegenerative disorders associated with neurotoxicant exposure. At the same time, individual workshop participants highlighted a number of research gaps.

Important unanswered questions regarding environmental exposures in human populations include identifying subpopulations at risk, their vulnerability at different points across the life span, and how genetic and environmental factors may be working together, said Jason Richardson. For example, in exploring the effects of air pollution in animal models, Deborah Cory-Slechta said her lab has begun to focus on specific developmental periods as opposed to lifetime or cross-developmental windows of exposures. She added that scientists are just beginning to investigate the transgenerational effects of lead exposure in mice. For example, she said, effects of lead exposure in the F-0 generation have been demonstrated even in the F-3 generation.

Brenda Eskenazi agreed on the importance of this issue, noting the need for more human studies as well. Different outcomes have been detected with different windows of exposure, she said, but more longitudinal studies are needed to assess exposures over the lifetime. Richardson said that answering these questions will require multidisciplinary research teams and the development of new technologies and methodologies to address polygenic and multiple environmental contributors as well as additional validated animal and cell-based models for various diseases.

Meanwhile, the coronavirus disease 2019 (COVID-19) pandemic has elevated the need to better understand how pathogen-driven infections interact with environmental toxicants, particularly as climate change and rising sea levels increase exposure to mosquito vectors in coastal areas, said Caleb Finch (Finch and Kulminski, 2020).

Other research gaps arise from deficits in availability and use of exposure monitoring tools, according to Trevor Penning, the Thelma Brown and Henry Charles Molinoff Professor of Pharmacology in the University of Pennsylvania Perelman School of Medicine. For example, he noted that disclosure to the Environmental Protection Agency's (EPA's) Toxic Release Inventory (TRI) Program is voluntary, unless a facility meets three specific criteria in which case they are required to report covered emissions.[1] Proprietary chemicals in the TRI may not be identified, and industry can claim exemptions from using the TRI to disclose their emissions. In addition, he

[1] For more information, see https://www.epa.gov/toxics-release-inventory-tri-program/basics-tri-reporting (accessed October 15, 2020).

said, there are EPA monitoring deserts in which no monitors are available to get air quality data.

With regard to mechanisms of toxicity, Helena Hogberg, deputy director of the Center for Alternatives to Animal Testing at the Johns Hopkins Bloomberg School of Public Health, said the knowledge gap is large. Little toxicology data exist for most chemicals on the market, and even less information is available regarding toxic effects on the nervous system. Gene–environmental interactions are also largely unexplored; more attention is needed to ensure the human relevance of mechanisms being modeled in labs, said Hogberg. Beate Ritz noted that she and colleagues from Harvard will soon begin a project to screen pesticides using induced pluripotent stem cells (iPSCs) from carriers of different genetic mutations linked to Parkinson's disease (PD) in order to better understand gene–environment interactions.

ADVERSE OUTCOME PATHWAYS

Considerable evidence shows that developmental exposures to chemicals may be linked to developmental adult neurological disorders and brain aging, said Hogberg. She advocated using an adverse outcome pathway approach, looking at mechanisms in animal and cellular models and then trying to link those mechanisms to adverse outcomes such as the development of PD.

Epidemiology will be needed to definitively link compounds identified through in vitro screening to adverse human outcomes, said Mark Zylka. Animal models and in vitro studies are both important for identifying classes of chemicals that target certain molecular pathways implicated in disease, he said, but to narrow down the hundreds of chemicals to those that represent exposure threats to humans will require working with scientists who can assess levels in the environment. Epidemiologists can then look at a smaller subset of chemicals linked to biological pathways to see if humans are indeed exposed and if that exposure increases the relative risk for certain disorders.

Stanley Barone, deputy director of the risk assessment division of the Office of Pollution Prevention and Toxics in the Office of Chemical Safety and Pollution Prevention at EPA, agreed that putting data on biological processes such as proliferation, migration, differentiation, apoptosis, myelination, and synaptic plasticity into the context of adverse outcomes is essential to show their relevance to disease, morbidity, and mortality and support decision making based on data. He said this predictive toxicology approach can enable agencies such as EPA to bridge data gaps and make risk assessments in a chemically agnostic way.

J. Timothy Greenamyre added that genetics may provide hints that can help identify adverse outcome pathways. For example, the many genes that have been identified as causing PD can be grouped by mechanism (e.g., endolysosomal/autophagy functioning, proteostasis, inflammation, etc.). Chemicals and other environmental factors present in environmentally relevant concentrations can then be screened to assess impact on those pathways, he added.

Future research is also needed to identify factors that impact the susceptibility to potential adverse effects of environmental exposures such as air pollution, said Petkus. For example, he said, a recent study in Sweden showed that the adverse effect of exposure to air pollution on the development of dementia was larger in people with comorbid cardiovascular disease (Grande et al., 2020). Lifestyle factors may also interact with air pollution to increase or reduce the risk of adverse outcomes, said Petkus. Future studies of exposure effects should also examine associations with the accumulation of biomarkers of Alzheimer's disease, including imaging biomarkers, he added.

STANDARDIZED DATA COLLECTION

National chemical, pesticide, and potential toxicant exposure data collected using standardized methods and driven by legislative efforts impermeable to change in leadership are essential, said Allison Willis, associate professor of neurology and epidemiology in the University of Pennsylvania Perelman School of Medicine. Richardson said some national data are available, including pesticide usage data from EPA. However, these data reflect primarily agricultural use, but not household use of pesticides, he said. Richardson also noted that the National Health and Nutrition Examination Survey (NHANES) has published a National Report on Environmental Exposures that includes urinary and blood metabolite data, and as described by Ritz in Chapter 2, these data can be used to assess population-exposure levels cross-sectionally for a limited number of agents while and GIS modeled data can be used for long-term exposure estimation, said Ritz. However, Tracey Woodruff noted that the NHANES data only cover about 300 chemicals out of the 2,000 to 4,000 chemicals that are highly used. Moreover, she said, regulatory policies and the proprietary nature of some of these data may limit access.

Woodruff added that while the Clean Air Act[2] requires the monitoring of certain air pollutants that are then required to be reported to a national database, and thus providing a central access point, there is no requirement

[2] For more information, see https://www.epa.gov/clean-air-act-overview (accessed September 8, 2020).

for central reporting of water pollution data. California has geographically resolved water contamination data that is available on a statewide level, along with air pollutants and pesticide use, she said. Eva Feldman said monitoring with uniform standards has not been implemented in other states such as Michigan, where there is a high prevalence of amyotrophic lateral sclerosis (ALS). For ALS at least, some of the clusters appear to be associated with the use of well water, which may not be tested for presence of pollutants, added Feldman.

NEW TOOLS ARE ADVANCING ENVIRONMENTAL NEUROSCIENCE

The environmental health science community is developing sophisticated tools to study the exposome and the totality of exposures over the course of a lifetime, said Richard Woychik. Meanwhile, neuroscientists bring to the table powerful imaging tools and other technologies and experimental approaches for studying neurodevelopment and function, and genome scientists bring new sequencing tools and genome analysis capabilities to better understand the complex traits involved in susceptibility to environmental exposure, he said.

Many new tools, or new uses of existing tools, were suggested to advance the field. For example, Jennifer McPartland advocated using a variety of methods, tools, and frameworks to define the universe of substances that affect the brain. That would require evaluating chemicals against known neurobiological targets, ensuring that knowledge about the etiology and pathology of neurological conditions is reflected in the chemical evaluation methods used to screen and characterize potential neurotoxicants, employing tools like exposomics to elucidate how different exposure patterns across populations relate to different neurological conditions, and considering these exposures in the context of other stressors. Other new technologies discussed included

- **Machine-learning approaches:** Andrew Petkus and others are using machine-learning approaches applied to high-dimensional neuroimaging data to examine associations between exposure and indexes of structural brain heath. Using imaging data from the Women's Health Initiative Memory Study (WHIMS), they generated a disease pattern similarity score (AD-PS) that represents an individual's neuroanatomical risk for AD (Casanova et al., 2018). Over a 5-year period, they showed that women exposed to higher amounts of $PM_{2.5}$ had higher annual increases in the AD-PS score, which corresponded to approximately a 24 percent increase in dementia risk (Younan et al., 2020). Higher AD-PS scores were

also associated with increased gray matter atrophy and declines in episodic memory. Petkus noted, however, that longitudinal studies are needed to validate this model.

- **Three-dimensional cellular models:** Hogberg described a new tool developed in her lab with funding from the National Center for Advancing Translational Sciences (NCATS)—a three-dimensional brain microphysiological system derived from iPSCs, composed of neurons, astrocytes, and oligodendrocytes (Pamies et al., 2017). Hogberg said microglia are not naturally present, but can be added to these "BrainSpheres" (Abreu et al., 2018). Her laboratory is using these BrainSpheres primarily for toxicology studies and is also partnering with neuroscientists to explore other uses. She noted that using iPSCs of different genetic backgrounds opens up multiple opportunities to explore gene–environmental interactions and link these findings with mechanistic studies.
- **High-throughput screens:** To help assess gene–environment interactions, Zylka advocated applying sophisticated new ways of conducting high-throughput sequencing-based screens.
- **Gene targeting:** Greenamyre added that manipulating gene expression with gene-targeting technologies such as antisense oligonucleotides, shRNAs, or viral vectors may also be helpful in teasing out regional vulnerabilities and the specificity of certain mechanisms. He noted that selective vulnerability is key to understanding neurodegenerative diseases.
- **New uses for existing models:** Greenamyre also suggested new ways of using existing animal models. For example, in the rotenone PD model, his lab has been studying the brain not only after parkinsonian symptoms develop, but also the quiescent period between exposure and subsequent development of symptoms to identify possible biomarkers of inevitable or preventable degeneration. He noted that initiating factors and factors that drive disease progression may be different; thus biomarkers and therapeutic targets may also differ across the continuum of the disease.
- **Animal models more relevant to humans:** Payne-Sturges added that animal models are needed that are more relevant to the human experience, particularly with regard to social stressor exposures. For example, she said restraint models are often used to mimic stress in animals, but may not be relevant to stress as it relates to living in poverty. Developing such models would require collaboration across disciplines, particularly with environmental health scientists interested in addressing issues around health disparities and cumulative risk, she said. Cory-Slechta said her lab has been working on a model of stress that reflects income inequality.

- **Neurotoxicant monitoring badges:** Walter Koroshetz, meanwhile, imagined tools that may be available in the future, such as a badge that measures organophosphate or pesticide exposures, akin to the badges that radiologists wear to alert them when their radiation exposure has exceeded a certain level. Building tools that capture exposure over time and that build a bridge to animal studies will require first the development of signatures of toxicant exposure in humans; an example is measurements in hair or the nasal mucosa, said Koroshetz.

POPULATION AND REAL-WORLD STUDIES

Population-based cohorts from broad geographic regions with phenotypic and omics data are needed to advance understanding of the relationship between environmental exposures and human diseases, said Eva Feldman. Carl Hill, vice president of scientific engagement at the Alzheimer's Association, suggested that these studies could also be used to explore what environmental factors are most important for which disproportionately affected populations, and why; for example, the role of cognitive reserve and resilience in resisting the effects of environmental toxicants. Eskenazi advocated for large investments in exposure sciences and environmental epidemiology similar to the investments that were made for genetics. Expanding exposure sciences so they can be applied on a large scale to large populations will be essential, she said.

Koroshetz suggested combining population studies that include genome-wide association study (GWAS) data with exposome data to better understand the interaction between genetics and environment. One of the challenges of this approach, Gary Miller noted, is developing statistical approaches appropriate for such complicated data. A concerted effort with advanced analytics would be needed to assess gene by environment in an unbiased way, he said. However, because both GWAS and exposure studies link directly to biological pathways, there may be an opportunity to "meet in the middle" to assess these connections, added Miller.

To better understand the real-world effects of environmental exposures, Koroshetz suggested analyzing what happens when a policy change affects use of a chemical. For example, as Woodruff described earlier, California banned the use of polybrominated diphenyl ethers (PBDEs) in 2003 and eventually banned all flame-retardant chemicals in the state. McPartland noted that because California is a large market, this ban had ripple effects across the country and, indeed, throughout the world. Cory-Slechta also noted that once lead was removed from paint and gasoline, studies showed that blood lead levels declined in every segment of the population in subsequent years. More recently, she said, studies have analyzed changes in

standardized student test scores since the removal of lead and shown positive outcomes (Reyes, 2012). However, Woodruff said investment has been limited in assessing how system-level changes such as this influence exposures and, moreover, it is difficult to link exposures to health effects because other risk factors can also contribute to those effects.

Cindy Lawler, acting chief of the Cellular, Organs, and Systems Pathobiology Branch in the Division of Extramural Research and Training at the National Institute of Environmental Health Sciences, said the institute is currently supporting a study to take advantage of a natural experiment in which China wanted to reduce air pollution in areas surrounding Beijing during the 2008 Olympics. The investigators identified women who were pregnant at the time in four urban districts for which data on the concentrations of various air pollutants were available. They showed that for babies whose eighth month of gestation occurred during the Olympics, decreased levels of air pollution were associated with higher birthweights (Rich et al., 2015). Other studies are examining whether this resulted in a decrease in conditions associated with low birthweight, including neurodevelopmental conditions such as autism, said Lawler.

Air quality changes have also been documented in large cities as a consequence of people sheltering in place during the COVID-19 pandemic. Woodruff said that the Environmental Influences on Child Health Outcomes (ECHO) study[3] has pivoted to some COVID-related research to understand what kind of environmental risk factors may be changing during the pandemic, including not only a reduction in air pollution, but also changes in diet that could result in changes in exposure to chemicals such as phthalates. While assessment of neurodevelopmental outcomes would have to come later, she suggested this could be an excellent opportunity to collect biospecimens.

Eskenazi suggested that combining emerging geospatial methods with biosamples from existing cohort studies such as the Adolescent Brain Cognitive Development (ABCD) study[4] could provide valuable and low-cost opportunities to examine environmental exposures. The estimation of exposures is now possible, she said, through satellite data and remote sensing methods. Comparing this information with data from cell phones and other body-worn sensors could enable estimation of real-time exposures in populations, she said. In addition, longitudinal and multigenerational studies that collect biosamples and exposure data during relevant periods are needed, particularly because new discoveries in epigenetics suggest multigenerational effects of environmental exposures, Eskenazi added. Residence-level monitoring of air quality and the use of wearable detectors

[3] For more information, see https://www.nih.gov/echo/about-echo (accessed July 23, 2020).
[4] For more information, see https://abcdstudy.org (accessed August 12, 2020).

that monitor toxicants and microbes could also provide real-world data to better understand the exposome, said Finch. Incorporating data on social determinants of health and multigenerational life history would also be valuable, he said.

Cory-Slechta noted that many years ago, the National Research Council Committee on the Health Risks of Phthalates developed an algorithm for assessing the effect of exposure on a specific disorder: Start with a known disease or disorder and identify those chemicals that are known to individually influence this disorder (NRC, 2008). Because they may have different mechanisms that converge downstream within the same physiological system, statistical methods can be used to quantify the risks of the different combined exposures. The economic costs of addressing risk from these chemicals could also be calculated for a cost–benefit analysis.

McPartland noted, however, that new regulatory frameworks and policies will be needed to account for exposures to mixtures of chemicals as well as those mixtures alongside other stressors. Indeed, said Eskenazi, measuring one chemical at a time does not reflect real-life human exposures. Yet, she noted that there are statistical challenges that will need to be addressed to enable multifactor analyses of toxic exposures. Ritz suggested implementing "pesticidovigilance," mirrored on the concept of "pharmacovigilance," to ensure that regulatory standards are aligned with public policy interests.

6

Potential Opportunities for Action and Multidisciplinary Collaborations

HIGHLIGHTS

- To strengthen the case made to stakeholders and policy makers on the urgency of environmental neuroscience research, new research frameworks are needed that enable accumulation of new data and repackaging of existing data (Bellinger, Cory-Slechta, Feldman, Willis).
- To demonstrate to regulators the relevance of biological science to exposure risk, cross-disciplinary dialogue is needed among clinicians, epidemiologists, basic researchers, and toxicologists (Barone).
- Evaluating the multiplicity of exposures and prioritizing those that represent the greatest threats to human health are essential (Breysse, Hogberg).
- More interdisciplinary work is needed to demonstrate the cumulative impact of environmental exposures and social stressors on neurodevelopmental and neurodegenerative disorders (Payne-Sturges).
- Addressing the problems associated with exposure to neurotoxicants will require an increased sense of urgency among public health and environmental health practitioners (Breysse).

- New approaches will be needed in academic institutions and government agencies to encourage and reward scientists to work collaboratively (Payne-Sturges, Woychik).
- Several opportunities for multidisciplinary collaboration are available from the National Institutes of Health and the National Institute of Environmental Health Sciences (Bartolomei, Richardson, Woodruff, Woychik).

NOTE: These points were made by the individual speakers identified above; they are not intended to reflect a consensus among workshop participants.

Throughout the workshop, several participants highlighted potential opportunities to address policy concerns in the field, foster multidisciplinary collaborations to advance research, and motivate action among stakeholders.

POLICY IMPLICATIONS FOR ENVIRONMENTAL NEUROSCIENCE

Improving human brain health by reducing exposures to environmental toxicants will require both an expanded research enterprise, as discussed in Chapter 5, as well as public policy changes that prioritize prevention of neurodevelopmental and neurodegenerative disorders, said David Bellinger. To accomplish this, new and existing data will need to be packaged and presented to stakeholders in a way that demonstrates the devastating impact of environmental exposures on brain development and function, and strengthens the case for increases in attention and resources. Experts from multiple fields must also advocate for these changes publicly with a unified voice, said Eva Feldman. Deborah Cory-Slechta added that these experts' voices must also be present on review committees and committees that are doing risk assessment at the Environmental Protection Agency (EPA).

The framework Bellinger proposed included

- Developing a broader and more integrated story about how early life exposure to neurotoxicants can impact a child's developmental trajectory in multiple and sometimes unexpected domains.
- Demonstrating how early life exposure to neurotoxicants can affect how effectively an individual is able to respond to neurological insults by reducing resilience and cognitive reserve; and thus, how

these exposures may be linked to neurodevelopmental and neurodegenerative disorders.
- Estimating the societal impact of neurotoxicant exposures by examining data at a population rather than an individual level; for example, by highlighting the association between lead exposure and criminal behavior in adolescence and young adulthood.

To make these messages resonate with policy makers, population health research—which focuses on the multiple factors that affect health outcomes in and across groups of people—may play an important role, said Allison Willis. She and her colleagues in the Division of Economic Research at the Leonard Davis Institute of Health Economics at the University of Pennsylvania have developed a public health framework for neurotoxicant exposure, disease risk, and public health outcomes. Most of the data presented at this workshop fit into this framework, she said, allowing policy holders to understand the data in their language and see the long-term and population health outcomes that are at risk from chemical exposures.

Carl Hill questioned what kind of framework would create momentum to move the field forward. He suggested bringing thought leaders from different fields together to develop a taxonomy that crosses these disciplines. Devon Payne-Sturges agreed, adding that more interdisciplinary work is needed to understand how the cumulative impact of environmental exposures and social stressors may help to explain the differences in prevalence of neurodevelopmental and neurodegenerative disorders by socioeconomic status, race, or ethnicity.

Convincing regulators of the relevance of biological science to exposure risk is an additional challenge, which will require cross-disciplinary dialogue among clinicians, epidemiologists, basic researchers, and toxicologists, added Stanley Barone. The screening and testing of chemicals is not a trivial pursuit, and cannot be done on all chemicals in the marketplace with current testing approaches, he said. Barone reinforced comments made by Helena Hogberg on the need to prioritize the worst chemicals to be tested first and to develop higher throughput approaches using molecular and cellular approaches.

Patrick Breysse, director of the National Center for Environmental Health/Agency for the Toxic Substances and Disease Registry (NCEH/ATSDR) within the Centers for Disease Control and Prevention, said one of the challenges is how to evaluate the multiplicity of exposures and incorporate that information into policies that are protective and that can be implemented at the state or health department level. NCEH/ATSDR works to translate scientific knowledge into protective measures that improve public health, according to Breysse. However, he noted that many public and environmental health practitioners fail to recognize the wide variety of

neurotoxicants in the environment and the wide range of biological effects. Thus, there is no sense of urgency to address these issues going forward, said Breysse.

New approaches are also needed within academic institutions and government agencies, including the National Institutes of Health (NIH), to encourage and reward scientists to get out of their silos and work collaboratively, said Richard Woychik. He advocated creating mechanisms that reward people for doing complementary and synergistic science across disciplines, including environmental science, neuroscience, biochemistry, and genetics, among others. Bringing the powerful tools from each of these scientific disciplines to bear on the questions raised in this workshop will also be essential, particularly in regard to the exposome, he said.

Payne-Sturges added that undergraduate and graduate programs in neuroscience also need to incorporate into their programs of study courses that raise awareness about the policy implications of neuroscience research and that emphasize the importance of interdisciplinary collaborations between neuroscientists and environmental health scientists, with a focus on research translation.

OPPORTUNITIES FOR MULTIDISCIPLINARY COLLABORATION

A broad approach that brings together expertise from multiple disciplines is needed to craft solutions to the problems imposed by environmental exposure to neurotoxicants, said Feldman. For example, she said multidisciplinary collaborations are needed to integrate what is known about persistent organic pollutants with longitudinal exposure data, and then coupling that with genome-wide association studies to determine polygenic risk scores. No one laboratory can do all of this, she said.

Andrew Petkus agreed that team science is essential to address the complex approaches used to estimate environmental exposures and understand their associations with multifactorial and heterogeneous disorders such as Alzheimer's disease (AD). His team, for example, includes neurologists and psychologists, as well as experts in exposure science with particular technical expertise in the complicated methodologies that enable linking EPA monitoring data with geographic covariates such as population density and urban versus agricultural land use.

Several collaborative programs have already been established by NIH and the National Institute of Environmental Health Sciences (NIEHS). For example, Jason Richardson mentioned that his work with the Collaborative Centers for Parkinson's Disease Environmental Research, funded by NIEHS, brought together cutting-edge neuroscience and environmental science, and set the standard for the types of collaborations that can occur.

Richardson said he has also received funding through NIEHS's Virtual Consortium for Translational/Transdisciplinary Environmental Research program. In one of these projects, he is collaborating with Brenda Plassman at Duke University to develop a comprehensive dataset, including cognitive measurements from her Agricultural Health Study of Memory, a panel of serum biomarkers associated with AD, and measurements of serum pesticides.

In 2015, NIH established the Environmental Influences on Child Health Outcomes (ECHO) Program,[1] a transinstitute research initiative to examine the effects of environmental influences on the health of children. ECHO compiled data from existing longitudinal cohorts comprising about 50,000 children across the United States. As part of this work, Tracey Woodruff and colleagues developed an approach for prioritizing chemicals to be studied for their contributions to child health including neurodevelopmental conditions in children as a pathway toward prevention. Criteria include (1) the presence of the chemical in consumer products; (2) biomonitoring of the chemical demonstrates levels greater than 10 percent in biospecimens or greater than 20 percent in environmental media such as air, house dust, food, or drinking water; and (3) potential for toxicity including neurotoxicity using data from EPA ToxCast, a high-throughput assay program that has screened thousands of compounds from many different endpoints including neurotoxicity. The panels selected chemicals that fall into five classes: organophosphorus and alternative flame retardants, alternative plasticizers, aromatic amines, environmental phenols, and pesticides, said Woodruff (Pellizzari et al., 2019). A pilot project has been launched to measure 100 of these novel chemicals prenatally, she said.

Meanwhile, NIEHS has funded the Toxicant Exposures and Responses by Genomic and Epigenomic Regulators of Transcription (TaRGET)-II Consortium[2] to explore exposure-induced epigenomic signatures and to determine whether target tissues can be used to assess the epigenetic consequences of various exposures (Wang et al., 2018), said Marisa Bartolomei. Consortium members will use the same exposure model that Bartolomei described in her studies of bisphenol A (see Chapter 3, in which pregnant mice are exposed to agents through food, water, or air; offspring continue to be exposed through weaning after which the exposure ends; and then tissues are sampled from progeny at various time points for epigenomic and transcriptomic analysis) (see Figure 6-1).

Among the questions to be addressed by the consortium are whether epigenetic perturbations in mice are relevant to human phenotypes and

[1] For more information, see https://www.nih.gov/research-training/environmental-influences-child-health-outcomes-echo-program (accessed September 8, 2020).

[2] For more information, see https://targetepigenomics.org (accessed September 8, 2020).

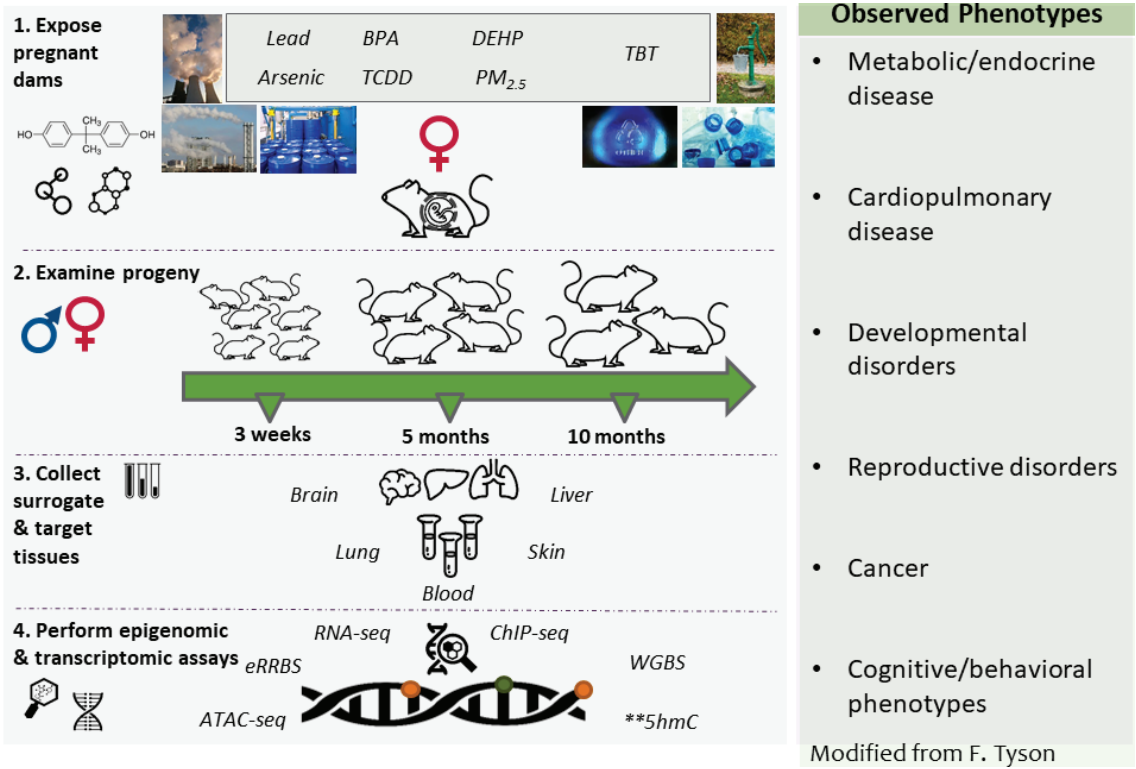

FIGURE 6-1 The TaRGET-II Consortium. TaRGET-II consortium members will use a common approach to identify epigenomic signatures in the DNA of people with a variety of diseases and phenotypes, including cognitive/behavioral phenotypes.
SOURCE: Presented by Marisa Bartolomei, June 25, 2020.

whether there is an exposure signature that can be assessed in certain surrogate tissues, said Bartolomei. She added that while the consortium is addressing only single exposures, more complex studies with multiple exposures will also need to be addressed in the future.

To increase understanding of gene–environment interactions, Richard Woychik from NIEHS advocated more intersection between environmental health scientists and neuroscientists, especially neuroscientists studying genetics. Beate Ritz noted that her research has only been possible because of funding for a multidisciplinary center for neurodegeneration at the University of California, Los Angeles. This enabled crosstalk among neuroscientists, animal experimenters, population scientists, and epidemiologists to determine which pesticides to select as well as which genes and pathways to interrogate.

MOTIVATING ACTION

Neurodegenerative disorders—that is, AD, Parkinson's disease, and amyotrophic lateral sclerosis—together account for more disability than cardiovascular disease, infectious disease, and cancer, said Ray Dorsey, neurologist at the University of Rochester. "And to a great extent, we've brought these diseases upon ourselves," he said, through the use of agricultural and industrial chemicals and air pollution.

Although more research is clearly needed, motivation to take action has been largely absent, said Dorsey. Economic considerations have kept chemicals such as paraquat and trichloroethylene on the market in the United States, although they have been banned by many other countries, despite strong linkages to Parkinson's disease and the availability of safer alternatives, he said.

Woychik said he believes there are high-profile geneticists who agree that environmental exposures have a significant impact on genes and genetic disorders and who are willing to work with environmental scientists to advance this research. The key, he said, is to bring together people with complementary points of view and different skillsets to discuss neurodevelopmental and neurodegenerative disorders from environmental, genetic, and neuroscience standpoints.

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B

Workshop Agenda

Environmental Neuroscience: Advancing the Understanding of How Chemical Exposures Impact Brain Health and Disease—A Virtual Workshop
June 25, 2020, via Zoom

Hosted by the National Academies of Sciences, Engineering, and Medicine's Forum on Neuroscience and Nervous System Disorders in Collaboration with the Board on Environmental Studies and Toxicology

Workshop Objectives: This public workshop will bring together experts and key stakeholders from academia, government, industry, and nonprofit organizations to explore the current knowledge landscape and future opportunities in neurotoxicology. Invited presentations and discussions will be designed to:

- Provide an overview of what is known about neurotoxic exposures and how they lead to neurodevelopmental and neurodegenerative disorders;
- Explore how new technologies can be harnessed to identify previously unknown neurotoxic chemicals;
- Consider whether algorithms can be developed to better predict the effects of cumulative exposures and interactions across the life span on brain health; and
- Discuss research gaps and collaborative opportunities between neuroscientists and environmental health scientists.

10:00–10:15 a.m. Welcome and opening remarks
Frances Jensen, University of Pennsylvania, *Neuroscience Forum Co-Chair*

Walter Koroshetz, National Institute of Neurological Disorders and Stroke, *Neuroscience Forum Member and Workshop Co-Chair*

10:15–10:40 a.m. Opening talk—Chemical exposures: The ignored environmental risk factor for neurodegenerative diseases and neurodevelopmental disorders
Deborah Cory-Slechta, University of Rochester, *Workshop Co-Chair*

Session I: What Are the Neurotoxicants?

Discussion questions:

- What neurotoxicants should we be concerned about?
- How can they be measured?
- How can we measure their effects on populations and on individuals?

10:40–10:45 a.m. Session overview
Deborah Cory-Slechta, University of Rochester, *Workshop Co-Chair and Session Moderator*

10:45–11:00 a.m. Exposure to neurotoxic chemicals and neurodevelopmental disease
Tracey Woodruff, University of California, San Francisco

11:00–11:15 a.m. Environmental contributors to neurodegeneration: Why not measure everything?
Gary Miller, Columbia University

11:15 a.m.–12:00 p.m. Panel discussion and Q&A

The two speakers above will be joined by panelists:
Jennifer McPartland, Environmental Defense Fund
Brenda Eskenazi, University of California, Berkeley

12:00–12:30 p.m. Break

Session II: Biology of Toxicant Interaction with the Nervous System

Discussion question:

- What is known about the biology of how "common" exposures to chemical and particulate toxicants might alter nervous system development or contribute to neurodegeneration?

12:30–12:35 p.m. Session overview
David Jett, National Institute of Neurological Disorder and Stroke, *Session moderator*

12:35–12:50 p.m. Exploiting genetics to identify environmental risks for autism
Mark Zylka, University of North Carolina at Chapel Hill

12:50–1:05 p.m. LRRK2 activation as a common mechanism of environmental toxicant-induced Parkinson's disease
J. Timothy Greenamyre, University of Pittsburgh

1:05–1:20 p.m. Environmental gerogens in the Alzheimer's disease exposome: Air pollution and cigarettes
Caleb Finch, University of Southern California

1:20–2:15 p.m. Panel discussion and Q&A

The three speakers above will be joined by panelists:
Helena Hogberg, Johns Hopkins University
Tomás Guilarte, Florida International University

2:15–2:30 p.m. Break

Session III: Chemical Toxicants as Drivers of Abnormal Neurodevelopment and Neurodegeneration

Discussion questions:

- What is the level of evidence for chemical toxicants as drivers of abnormal neurodevelopment and neurodegeneration?

- What research is needed to launch prevention efforts: either treatments or policy changes?

2:30–2:35 p.m.	Session overview **Walter Koroshetz,** National Institute of Neurological Disorders and Stroke, *Workshop Co-Chair and Session Co-Moderator* **Allison Willis,** University of Pennsylvania, *Session Co-Moderator*
2:35–2:50 p.m.	A developmental perspective on early-life exposures to neurotoxicants **David Bellinger,** Boston Children's Hospital
2:50–3:05 p.m.	In utero endocrine-disrupting chemical exposure may reprogram the adult mouse brain: A role for epigenetics **Marisa Bartolomei,** University of Pennsylvania
3:05–3:20 p.m.	Translational research on the role of developmental pesticide exposure and attention-deficit hyperactivity disorder **Jason Richardson,** Florida International University
3:20–3:35 p.m.	Using gene–environment interactions and omics approaches to understand neurodegenerative disease etiology **Beate Ritz,** University of California, Los Angeles
3:35–3:50 p.m.	Exposure to air pollution and risk of Alzheimer's disease **Andrew Petkus,** University of Southern California
3:50–4:05 p.m.	Identification and validation of amyotrophic lateral sclerosis environmental risk factors **Eva Feldman,** University of Michigan
4:05–4:30 p.m.	Panel discussion and Q&A *Panel composed of speakers above*
4:30–4:45 p.m.	Break

Session IV: Future Directions

Discussion questions:

- What are the critical research gaps, next steps, and promising areas for future action?
- What opportunities are there for collaboration among neuroscientists and environmental health scientists?

4:45–4:50 p.m.	Reflections from the workshop co-chairs **Deborah Cory-Slechta,** University of Rochester **Walter Koroshetz,** National Institute of Neurological Disorders and Stroke
4:50–5:15 p.m.	"Lightning round" remarks *(5 minutes each)* **Stanley Barone,** Environmental Protection Agency **Ray Dorsey,** University of Rochester Medical Center **Carl Hill,** Alzheimer's Association **Devon Payne-Sturges,** University of Maryland **Richard Woychik,** National Institute of Environmental Health Sciences
5:15 p.m.	Additional discussion with speakers, panelists, and audience members
5:30 p.m.	Adjourn workshop