Science of the Total Environment 593–594 (2017) 634–640

Contents lists available at ScienceDirect

Science of the Total Environment

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

Elucidating environmental dimensions of neurological disorders and disease: Understanding new tools from federal chemical testing programs

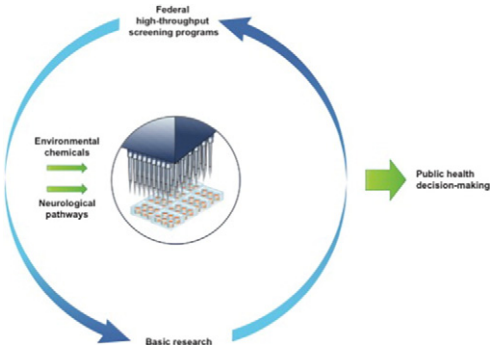
Jennifer McPartland[a,*], Heather Dantzker[b], Christopher Portier[a]

[a] Environmental Defense Fund, 1875 Connecticut Ave. NW, Ste. 600, Washington, DC 20009, USA
[b] Dantzker Consulting, LLC, 2613 N. Harrison St., Arlington, VA 22207, USA

HIGHLIGHTS

- ToxCast/Tox21 screening data can support hypothesis-driven research.
- Federal chemical screening is currently limited for identifying neurotoxicants.
- Broader scientific engagement can strengthen chemical testing programs.
- Use of ToxCast and Tox21 by the broader scientific community is encouraged.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 25 November 2016
Received in revised form 1 March 2017
Accepted 3 March 2017
Available online 29 March 2017

Editor: Jay Gan

ABSTRACT

Background: Federal agencies are making significant investments to advance predictive approaches to evaluate chemical hazards and risks. Environmental Defense Fund (EDF) believes that engagement with the broader scientific community is critical to building and maintaining a strong biological foundation for these approaches.
Objectives: On June 18–19, 2015, EDF organized a meeting to 1) foster a conversation between federal scientists advancing predictive approaches and environmental health researchers investigating environmental exposures and neurological outcomes, and 2) explore opportunities and challenges for the use of federal chemical high-throughput *in vitro* screening (HTS) data in hypothesis-driven research toward, ultimately, improved data for public health decision-making.
Discussion: The meeting achieved its objectives. Government scientists showcased their chemical testing programs and vision for how emerging data may be used to meet agency missions. Environmental health researchers shared their experiences using federal HTS data, offered recommendations for strengthening federal HTS platforms, and expressed great interest in continued engagement with evolving federal chemical testing initiatives.
Conclusions: The meeting provided an invaluable exchange between two scientific communities with a shared interest in protecting public health from harmful environmental exposures, but who have not sufficiently engaged with each other. Discussions identified opportunities and work ahead for the use of HTS data in hypothesis-driven research. Though the meeting focused on neurological outcomes, the purpose,

* Corresponding author at: 1875 Connecticut Ave. NW, Ste. 600, Washington, DC 20009, USA.
E-mail addresses: jmcpartland@edf.org (J. McPartland), heather@dantzker.com (H. Dantzker), cportier@edf.org (C. Portier).

http://dx.doi.org/10.1016/j.scitotenv.2017.03.024

objectives and experience of the meeting are broadly applicable. EDF strongly encourages more discourse and collaboration between federal and non-government scientists working to understand environmental influences on health outcomes.

1. Introduction

As part of a larger portfolio of federal research efforts to advance new approaches for the evaluation of chemical toxicity and risk, vast quantities of high-throughput *in vitro* screening (HTS) data continue to be generated by the U.S. Environmental Protection Agency's (EPA) ToxCast™ initiative (U.S. EPA, 2017a) and the Tox21 partnership led by the National Institute of Environmental Health Sciences (NIEHS)/National Toxicology Program (NTP) (Tice et al., 2013, U.S. EPA, 2017b). Though these and related federal chemical testing programs have made significant progress since their inception, more growth opportunities remain for these programs to reach their full potential of protecting public health and the environment.

Three goals must be achieved to realize the promise of predictive toxicology approaches in public health decision-making: 1) development of a scientific foundation supporting their use; 2) scientific acceptance of a new testing and analysis paradigm; and 3) health-protective policies that encourage their use (McPartland et al., 2015). Achieving these goals will require contributions from the broader scientific research community, particularly those on the forefront of understanding the etiology and pathology of environmentally-influenced disease (NRC, 2007).

Environmental Defense Fund (EDF), in cooperation with the U.S. EPA and NIEHS/NTP, brought federal ToxCast™ and Tox21 scientists together with environmental health researchers for a meeting entitled, *Elucidating Environmental Dimensions of Neurological Disorders and Disease: Understanding New Tools from Federal Chemical Testing Programs* (UC Davis Conference Center, June 18–19, 2015). The meeting's objectives included 1) fostering a conversation between government scientists and environmental health researchers on federal predictive chemical testing approaches and 2) exploring opportunities and challenges for the use of these data in hypothesis-driven research. Progress on these objectives will strengthen links between researchers and regulatory scientists, improve the use of predictive toxicology data in decision-making, and help protect public health.

Neurological outcomes affect millions of people worldwide: in the U.S. alone, approximately 60,000 people are diagnosed with Parkinson's disease each year (Parkinson's Disease Foundation, 2017); the percentage of children diagnosed with attention-deficit/hyperactivity disorder (ADHD) continues to rise from 7.8% in 2003 to 11.0% in 2011 (Visser et al., 2014); and in 2012, one in 68 children were estimated to have autism spectrum disorder (ASD), a 29% increase from 2008 (Christensen et al., 2016). Since genetic factors alone have been estimated to explain only 30 to 40% of all cases of neurodevelopmental disorders (Grandjean and Landrigan, 2006), understanding the role of the environment is critical if we are to better protect public health. Elucidating the impact of environmental exposures on neurological outcomes is particularly difficult owing to the underlying biological complexity of the nervous system. Approaches like HTS hold the potential to make progress toward identifying chemical exposures that interfere with normal brain development and function.

1.1. Overall meeting structure

The two-day meeting opened with presentations describing the ToxCast™ and Tox21 initiatives, including descriptions of their respective assay batteries, data, and accompanying user interfaces (U.S. EPA, 2016a, 2017c). The meeting then focused on how environmental health researchers are already integrating these data and tools for research on neurodevelopmental (*e.g.*, autism) and neurodegenerative (*e.g.*, Parkinson's) outcomes. Other presenters spoke to future possibilities for these data in basic and epidemiological research. Meeting participants were given the opportunity to engage with agency scientists on the various tools available to access and query federal HTS data. Throughout the meeting, participants exchanged ideas on key opportunities and challenges related to the use of HTS data in the field of environmental health.

2. Meeting outcomes

Meeting outcomes include discussions on 1) recent experiences using ToxCast™ and Tox21 data in hypothesis-driven research investigations; 2) potential applications of HTS data in future hypothesis-driven research; and 3) current barriers to the use of federal HTS data by the broader scientific community. We then discuss measures that agencies and environmental health researchers can both take to further the conversation.

2.1. ToxCast™ and Tox21 data in hypothesis-driven research: recent investigations

Compared to traditional toxicity testing approaches, HTS approaches are typically faster and provide greater insight into the mechanisms by which chemicals interfere with normal biology. These efficiencies provide researchers with tools and data to screen and identify chemical targets for additional investigation. HTS data can also be combined with other data types (*e.g.*, 'omics', *in silico* models, whole animal laboratory studies, and epidemiological data) to enrich investigations of environmental impacts on health.

2.1.1. Identifying novel targets for vitamin D receptor signaling

Dr. Seth Kullman (Department of Biological Sciences at North Carolina State University) is using data from Tox21 to examine linkages between environmental exposures, modulation of vitamin D receptor (VDR) signaling, and later life neurodevelopmental consequences. Dr. Kullman shared that vitamin D deficiency early in development can lead to neurobehavioral outcomes through, among other proposed mechanisms, interference with dopaminergic signaling (Cui et al., 2015). Using data from an 8500-compound library screened through a Tox21 human VDR assay, Kullman's team identified multiple putative VDR agonists and antagonists. Orthogonal *in vitro* testing (*e.g.*, human VDR transient transactivation assays and receptor-coregulator protein interactions assays) yielded generally concordant results. The strongest agonist and antagonist candidates were further examined for interaction with zebrafish VDR and demonstrated 100% concordance with the human VDR assays. Initial whole zebrafish studies of cadmium chloride, one of the identified VDR antagonists, revealed effects on larval locomotor activity. Dr. Kullman concluded that federal HTS data have been instrumental in identifying novel targets for his team's receptor of interest (VDR) that otherwise would have not likely been discovered.

2.1.2. Using HTS data to develop prediction models of chemical toxicity

Dr. Heather Patisaul (Department of Biological Sciences at North Carolina State University) investigates neuroendocrine disruption