Toxicology 313 (2013) 94–102

Contents lists available at ScienceDirect

Toxicology

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

Mixtures research at NIEHS: An evolving program

Cynthia V. Rider[a], Danielle J. Carlin[b], Micheal J. DeVito[a], Claudia L. Thompson[b], Nigel J. Walker[a,*]

[a] Division of the National Toxicology Program (DNTP), National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH), 111 Alexander Drive, Research Triangle Park, NC, USA
[b] Division of Extramural Research and Training (DERT), National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH), 111 Alexander Drive, Research Triangle Park, NC, USA

ARTICLE INFO

Article history:
Received 3 May 2012
Received in revised form 3 October 2012
Accepted 6 October 2012
Available online 9 November 2012

Keywords:
Combined exposures
Cumulative
Multi-pollutant
Co-exposure
Stressors

ABSTRACT

The National Institute of Environmental Health Sciences (NIEHS) has a rich history in evaluating the toxicity of mixtures. The types of mixtures assessed by the Division of the National Toxicology Program (DNTP) and the extramural community (through the Division of Extramural Research and Training, DERT) have included a broad range of chemicals and toxicants, with each study having a unique set of questions and design considerations. Some examples of the types of mixtures studied include: groundwater contaminants, pesticides/fertilizers, dioxin-like chemicals (assessing the toxic equivalency approach), drug combinations, air pollution, metals, polycyclic aromatic hydrocarbons, technical mixtures (e.g., pentachlorophenol, flame retardants), and mixed entities (e.g., herbals, asbestos). These endeavors have provided excellent data on the toxicity of specific mixtures and have been informative to the human health risk assessment process in general (e.g., providing data on low dose exposures to environmental chemicals). However, the mixtures research effort at NIEHS, to date, has been driven by test article nominations to the DNTP or by investigator-initiated research through DERT. Recently, the NIEHS has embarked upon an effort to coordinate mixtures research across both intramural and extramural divisions in order to maximize mixtures research results. A path forward for NIEHS mixtures research will be based on feedback from a Request for Information (RFI) designed to gather up-to-date views on the knowledge gaps and roadblocks to evaluating mixtures and performing cumulative risk assessment, and a workshop organized to bring together mixtures experts from risk assessment, exposure science, biology, epidemiology, and statistics. The future of mixtures research at NIEHS will include projects from nominations to DNTP, studies by extramural investigators, and collaborations across government agencies that address high-priority questions in the field of mixtures research.

Published by Elsevier Ireland Ltd.

1. Introduction

The National Institute of Environmental Health Sciences (NIEHS), located in Research Triangle Park (RTP), North Carolina, is one of the 27 Institutes and Centers of the National Institutes of Health (NIH). The NIEHS is comprised of three divisions: the Division of Intramural Research (DIR), the Division of Extramural Research and Training (DERT) and the Division of the National Toxicology Program (DNTP). The mission of the NIEHS is to reduce the burden of human illness and disability, by understanding how the environment influences the development and progression of human disease.

Recently, the NIEHS developed its 2012–2017 Strategic Plan (http://www.niehs.nih.gov/about/strategicplan/) to prioritize research activities. Although the topic of mixture is relevant to many of the Strategic Plan goals, Goal 4 of the plan entitled "Combined Exposures" specifically focuses on elucidating human health effects associated with chemical and nonchemical stressors. This goal is in recognition that humans are exposed to multiple chemicals including man-made and natural chemicals, throughout their lifetimes. Therefore, it is necessary to consider the action of diverse exposures including chemical (man-made and natural) and nonchemical stressors that can vary widely in populations, in order to gain a better understanding of the effects of the environment on human health. It follows that mixtures have been and will continue to be the focus of research projects in both the extramural and intramural NIEHS community.

1.1. History of mixtures testing at DNTP

The National Toxicology Program (NTP) is an interagency, government research program that was established in 1978 as a

* Corresponding author at: National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH), 111 Alexander Drive, PO Box 12233, MD K2-02, Research Triangle Park, NC 27709, USA. Tel.: +1 919 541 4893; fax: +1 301 451 5596.
E-mail addresses: ridercv@niehs.nih.gov (C.V. Rider), carlindj@niehs.nih.gov (D.J. Carlin), devitom@niehs.nih.gov (M.J. DeVito), thomps14@niehs.nih.gov (C.L. Thompson), walker3@niehs.nih.gov (N.J. Walker).

0300-483X/$ – see front matter Published by Elsevier Ireland Ltd.
http://dx.doi.org/10.1016/j.tox.2012.10.017

Table 1
Past NIEHS mixtures grant portfolio.

Project number	Title	PI	Organization	Years
R01ES009681*	cDNA Microarray to Detect Cellular Responses to Mixtures	Buckpitt, Alan	University of California-Davis	1999–2002
P42 ES010344	Genetic/Epigenetic Susceptibility to Superfund Chemicals	Costa, Max	New York University School of Medicine	2000–2005
R03ES014725	The Effect of a Mixture of Pesticides on the Rat Cardiac Proteome	Crow, John	Mississippi State University	2006–2009
R03ES016433	Environmental Exposure to Metal Mixtures and Kidney Disease	Fox, Mary	Johns Hopkins University	2007–2010
R01ES009673*	Asbestos and NO_2 in Environmental Lung Disease	Heintz, Nicholas	University of Vermont & State Agric College	1998–2002
R01ES009642*	Immunotoxicity of Dermal Permethrin and cis-Urocanic Acid	Holladay, Steven	Virginia Polytechnic Inst and State University	1998–2001
R03ES012929	Metabolic Effects of Chemical Interactions in Toxicity	Jones, Dean	Emory University	2004–2007
R01ES009683*	Biologically Based Cancer Risk Assessment for Mixtures	Luebeck, Georg	Fred Hutchinson Cancer Research Center	1998–2003
K99ES016806	Additive Effects of Mixtures of Endocrine-active Compounds to Medaka	Rider, Cynthia	Duke University	2009–2010
R01ES009690*	Strategy to Identify Nonadditive Response to Chemical Mixtures	Vogel, John	University of California-LLNL	1998–2000
R01ES009676*	Modulation of Benzene Metabolism by Exposure to Environment	Weisel, Clifford	UMDNJ-Robert Wood Johnson Medical School	1998–2002
R01ES015447	Mechanisms of Resistance of Aquatic Vertebrate Populations to Mixtures	Wirgin, Isaac	New York University School of Medicine	2006–2010
R01ES009655*	Developing a Predictive Strategy for Chemical Mixtures	Yang, Raymond	Colorado State University-Fort Collins	1998–2004

cooperative effort to coordinate toxicology testing programs within the federal government. The goals of the NTP are to strengthen the science base in toxicology, develop and validate improved testing methods, and provide information about potentially toxic chemicals to health regulatory and research agencies, scientific and medical communities, and the public. The NTP is headquartered within the DNTP of NIEHS, and encompasses NTP mission-relevant activities at NIEHS, along with the National Center for Toxicological Research (NCTR) of the Food and Drug Administration (FDA) and the National Institute for Safety and Health (NIOSH) of the Centers for Disease Control and Prevention (CDC). Together, the NIEHS and NTP are key contributors to supporting and conducting research to assess the human health effects of agents in our environment.

Assessing the potential hazard posed by mixtures has been a key area of interest for the NTP for many years. The earliest work by NTP on mixtures was in the early 1980s–1990s, spearheaded by Dr. Raymond Yang, and focused on understanding the effects of well-defined "complex mixtures" of compounds that are frequently found as groundwater contaminants near hazardous waste sites (NTP, 1993a). Those studies focused on a complex mixture of organic compounds and metals, the dose levels of which were environmentally relevant based on a USEPA survey. A second set of companion studies focused on a pesticide/fertilizer mixture (NTP, 1993b) that was representative of groundwater contaminants in California and Iowa.

These studies in some way set a tone for the coming decades of NTP mixtures research in that they highlighted some of the governing principles that are considered when approaching such problems, namely: "environmental" relevance of the mixture; simplification of complex exposure scenarios through the attainment of good exposure data to develop tractable study design; and use of defined mixtures to explore interactions within mixtures and mixed exposure scenarios. In addition, these projects provided important empirical datasets, which informed the mixtures risk assessment process. Subsequent NTP projects addressing mixtures were built on this foundation.

In addition to these projects, NTP has been engaged in a series of component-based mixture projects, including: assessing dose additive interactions within mixtures of dioxins and PCBs that bind the aryl hydrocarbon receptor (AhR) and are included in the dioxin toxic equivalency factor (TEF) scheme; effects of phthalate mixtures on reproductive tract development in collaboration with Dr. Earl Gray (US EPA/NHEERL); polybrominated diphenyl ether (PBDE) technical mixtures; and chemical studies to support risk assessment of mixtures of water disinfection byproducts.

Some of the projects that came later addressed a variety of mixtures and mixed exposures including: combinations of AIDS therapeutics (AZT, Lamivudine (3TC), Nevirapine and Nelfinavir mesylate) to assess the impact of combination therapy on the hazard posed by AZT; whole mixtures testing of botanical extracts used in dietary supplements including aloe vera extracts, ginseng, kava kava, ginkgo biloba extract, and green tea extract; technical mixtures used as flame retardants; and mixed exposures to fumes created during welding.

Building on this history of mixtures work, recent events have brought into focus the need for a comprehensive strategy on assessing mixtures and mixed exposures. Recent environmental disasters such as the Deepwater Horizon oil spill in the Gulf of Mexico and increased efforts by regulatory agencies to handle risk assessments of chemicals that may act through similar mechanisms of action highlight a desire to provide the public with a more comprehensive assessment of the hazards posed by real-life exposures.

1.2. History of mixtures research by NIEHS extramural scientists

The NIEHS and DERT have a long history of funding research in the area of mixtures (Table 1). The first NIEHS dedicated mixtures grants were funded in 1998 as a response to the Request for Applications (RFA: ES-98-002) titled "Chemical Mixtures in Environmental Health". This RFA, developed in collaboration with the U.S. Environmental Protections Agency (US EPA), encouraged innovative experimental approaches and computational, statistical or predictive strategies that focused on the mechanistic basis for chemical interactions, related health effects, and the development of biologically relevant risk assessment models for human exposure to chemical mixtures. Research resulting from the RFA