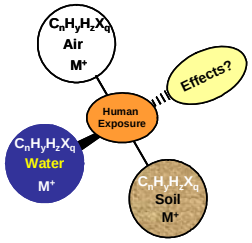


Superfund Research Program
University of California Davis

Dr. Bruce D. Hammock, Director

Research Update No. 4 **April 2011**

Introduction

This Research Update informs staff in State and Federal government involved in legislation and regulation of toxic substances in the environment about research results emanating from the UC Davis Superfund Program. The goal of these updates is to provide information about the National Institutes Environmental Health Sciences (NIEHS) funded Superfund Research Program (SRP)[1] that has been at UC Davis for the past 23 years. This national program was initiated to address human and environmental problems such as Love Canal, NY where improper disposal of chemical wastes occurred or Times Beach where oil containing chlorinated dioxins was sprayed as a dust suppressant. The mission of the SRP is stated below[2]

> "*Since its inception in 1987, the SRP has applied a multidisciplinary approach to basic research focused to provide a solid foundation which environmental managers and risk assessors can draw upon to make sound decisions related to Superfund and other hazardous waste sites. We believe that basic research plays a crucial role in addressing challenges posed by environmental contamination such as health risks, toxicity, exposure predictions, fate and transport, and the need for c*ost-effective treatments for hazardous *waste sites found throughout the United States"*

The Superfund Program at UC Davis[3] has provided basic research information to address these needs. We continue to develop innovative, novel technology to investigate human exposures, environmental fate and transport of toxic substances, as well as cost-effective methods for the treatment and remediation these chemicals. The success of our program is due to the breadth of the multidisciplinary approach to these complex scientific issues of chemical exposure that continue to pose hazards to human and environmental health.

This program exports its findings beyond academic journals and publications to other venues and audiences. As required by the NIEHS, we have concerted efforts to effectively partner with government, transfer technology to commercial ventures, or communicate with broader public audiences for the purpose of improving human and environmental health. Research Translation of scientific results is important for society to understand the goals of the SRP in the mitigation of toxic substances in the environment.

Results

This newsletter highlights two relevant areas of research from the program:

1) Dioxin cell-based assay to evaluate chemical structures to increase blood-cell transplant success
2) Understanding naphthalene toxicity in laboratory animals in relation to humans

[1] Name changed from Superfund Basic Research Program to Superfund Research Program in 2008
[2] www.niehs.nih.gov/research/supported/sbrp/about/index.cfm
[3] www-sf.ucdavis.edu/

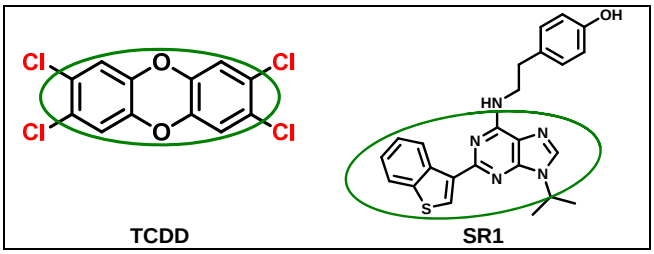
1) Dioxin cell-based assay to evaluate chemical structures to increase blood-cell transplant success

Background

In the first Research Update (May 2009), the novel cell-based method to detect chlorinated dioxins and furans (the CALUX bioassay) was highlighted. This method utilized liver cell lines that had been modified to respond to environmentally relevant concentrations of toxic chlorinated dioxins, furans and biphenyls extracted from a variety of matrices. The method was accepted by foreign regulatory agencies and eventually by the US EPA (Method 4435) as an alternative method to those that are more costly and currently in use. This detection system was used as a part of collaborative effort to discover other possible endogenous roles for the Ah Receptor (AhR). Researchers report that this receptor may have a major role in the regulation of the growth of stem cells that become blood and immune cells (Science 329, 1345-1348, 2010).

Impact

Much has been written over the past 40 years about the toxicity and environmental persistence of chlorinated dioxins that were contaminants in herbicides as well as combustion byproducts of natural and human manufactured products. While the role of the AhR in mediating the toxicity of these chemicals is clear, its role in normal endogenous biological and physiological processes is unclear. Insights into an endogenous role for the AhR would not only expand understanding of the developmental and biological processes to which the AhR appears to be involved, but will identify potential targets for the toxicity associated with exposure to chlorinated dioxins and related chemicals.



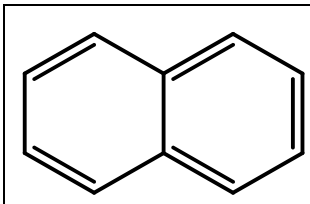
TCDD SR1

One role appears to be in the regulation of the growth and expansion of a class of stem cells that become blood and immune cells. Superfund investigator, Dr. Michael Denison, participated in the evaluation of a novel chemical structure (SR1), identified through screening of a chemical library that regulates the growth of hemopoietic stem cells through in an AhR-dependent manner. Using his cell based AhR (CALUX) bioassays he demonstrated that SR1 was a human-specific AhR inhibitor. The work in this study is significant as it demonstrated that inhibition of the AhR and AhR signaling pathway enhanced the growth and expansion of the hemopoietic stem cells, something that has been a major limitation in being able to effectively use these cells to their full clinical and research potential. The application of AhR cell-based high-throughput screening approaches will facilitate the evaluation of additional structures that may be even more effective. Sometimes research findings lead to advances and applications outside their intended use. This is certainly the case for this example and may lead to greater success for humans who need blood or immune cell transplants.

2) Understanding naphthalene toxicity in laboratory animals in relation to humans

Background

Naphthalene, the simplest polyaromatic hydrocarbon (PAH), is present in consumer products (e.g., moth balls), jet fuel, cigarette smoke, used as a chemical intermediate and occurs during combustion


Naphthalene


Mothballs

Its physical properties including a relatively high volatility, results in human exposure via inhalation. Recent NHANES studies (Fourth National Report on Human Exposure to Environmental Chemicals, 2009) demonstrated geometric mean levels of 1-naphthol in the urine of 2.5 µg/g creatinine. Conflicting toxicology outcomes result when rodent species (rats, mice) are exposed via inhalation, tumorigenic responses occur in different locations in the two species. Hence, solid evidence of carcinogenicity in humans when exposed to naphthalene is lacking and better understanding of the molecular toxicological interactions with laboratory animals could help in deciding which animal model is appropriate for human risk assessment.

Impact

Outside university collaborators with Professor Alan Buckpitt's laboratory evaluated the toxicological mechanistic consequences of naphthalene inhalation exposure: what, where, how many biochemical interactions occur and their relation to the formation of tumors. From these studies it is anticipated that a more refined human risk assessment can be derived. Interest in this research by the Agency of Toxic Substances and Disease Registry (ATSDR), US EPA and the military occurs because each has oversight over exposure to naphthalene, and in some cases regulatory authority. Industry participated in a meeting at UC Davis in 2009 that had representatives from the military, DOD, federal government (ATSDR) and outside industrial consultants to focus on the needs required to refine the risk assessment.

This newsletter continues to evolve to improve its intended purpose. Therefore, we value critique so that in the future it will improve and therefore better meet the needs of the recipients. Some areas on which we would like comment are content, effectiveness of communication and how it can build interactions and relationships with others outside the UC Davis Superfund Research Program. Please share this Research Update with your colleagues who may have an interest in the results of our research.

For more information about the UC Davis SRP, please contact: James R. Sanborn, Research Translation Coordinator, JRSanborn@ucdavis.edu or (530) 752-8465.