

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
Division of Extramural Research and Training
Cellular, Organs and Systems Pathobiology Branch

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Concept Clearance

DERT-NTP Collaborative Research Program

The overall goal of this Concept Clearance is to provide a basis for ongoing interactions between DERT and the NTP. The NTP funds research to assess the toxicity of environmental chemicals mainly via contract mechanisms. DERT supports investigator-initiated research mainly via a variety of grant mechanisms. While in the past there have been specific DERT funded RFAs developed to allow University researchers to use tissues from NTP studies, we now propose a more formal and long term plan that would allow DERT funded investigators to play a role in the design, interpretation and publication of NTP toxicity studies. Since, for the most part, the NTP toxicity studies are done via contracts they are somewhat limited in scope and endpoints. The involvement of DERT funded investigators will allow the NTP to incorporate technologies in use in the grantees laboratories that may better address disease focused endpoints. The interactions between DERT funded investigators and NTP funded studies will be open to discussion among DERT/NTP staff and will include a variety of mechanisms including joint RFAs using a variety of grant mechanisms, RFAs to develop consortium of investigators to work with NTP in the design and execution of toxicity studies, supplement programs and subcontract mechanisms. It is expected that these joint study designs will be a win-win-win for the NTP, the research scientists funded through DERT to work with the NTP and the American public who will receive a more comprehensive dataset on the toxicity of chemicals.

As an example of what can be accomplished under this new integrated DERT/NTP research program we propose an initial collaboration to assess the toxicity of bisphenol A.

Introduction:

Bisphenol A (BPA) is the monomer that is polymerized to make polycarbonate plastic. It is also used in epoxy resins that line many different kinds of metal cans and in heat sensitive receipts as well as a in a multitude of polycarbonate products. Human exposure results from release of the monomeric BPA which has been shown to have estrogenic properties. Detectable levels of BPA have been found in 93% of urine samples collected from people 6yrs and older. Infants have been shown to have almost 10x higher levels than adults. There are hundreds of articles describing the animal and human effects of BPA many of which have been funded by NIEHS as we have been a

major funder of research to understand the health effects of BPA. We currently fund over 30 grants, including twelve funded with ARRA funds covering in vitro, animal models and epidemiology studies. The specific goal of the ARRA funded BPA grants was to specifically address some of the data gaps and concerns of the FDA about the repeatability and applicability of investigator-initiated research to risk assessment.

In addition, the FDA, in conjunction with the National Toxicology Program (NTP), set up its own research program designed to fill data gaps, to be conducted at one of its research facilities, the National Center for Toxicological Research (NCTR), in Arkansas. Studies were designed to address gaps in pharmacokinetic modeling including rat and primate data that would create and validate a PBPK model that would predict internal exposures to free BPA in target tissues of fetuses and babies from food contact and medical devices exposures. Another aspect was to evaluate the toxicity of BPA in male and female SD rats exposed orally to BPA from gestation day 6-adulthood. This study was designed to include the typical reproductive endpoints as well as new endpoints noted in investigator-initiated studies including obesity/diabetes, cardiotoxicity, hepatotoxicity, immunotoxicity, thyroid toxicity, breast and prostate cancers, behavior, learning and memory and sexually dimorphic changes in brain structure and biochemistry. These studies were designed to be GLP compliant and to use standard toxicity testing protocols, including complete histopathological evaluation, with the addition of new endpoints, a large BPA dose range that includes putative human exposures, and measurement of internal dose.

During discussions between NTP and DERT staff it was determined that the upcoming chronic rat and mouse studies (and possibly others to be defined) provide a unique opportunity to leverage resources by developing a collaboration between NIEHS-funded extramural investigators studying BPA, and perhaps other chemicals in the future, and the NTP/FDA scientists to design and implement robust experimental protocols that would more fully utilize animals and tissues. The strengths of such a combined approach would be the well-accepted GLP-guideline study backbone of histopathology and dose-response combined with state of the art technologies and methodologies from university researchers to evaluate more completely toxicological outcomes. The expressed goal of this collaboration would be to provide information that is more useful to regulatory bodies for human risk assessment of BPA-containing products for the initial studies with a possibility of other designs and toxicant exposures in the future.

Research Goals and Scope:

The overall goal of this specific example of DERT-NTP collaboration is to develop a consortium of investigators to both aid in the design of the experimental protocol and also utilize animals and tissues from the NTP/FDA exposure studies. This will be accomplished by developing FOAs to solicit scientific expertise and endpoints for inclusion in the studies. The first FOAs would be focused on chronic rat and mouse studies to define BPA toxicity.

The FOAs will be set up as follows:

- The NTP/FDA will provide the GLP-compliant study design for the studies. The doses used and appropriate endpoints will be defined, in large part, by the results from the ongoing or previous NTP studies.

- Investigators will be asked to identify additional endpoints for the study and to include
 - o Rationale for addition of endpoint(s) to study design
 - o Data showing their background and expertise in the specific field
 - o Details of how their endpoint would be included in the study design
 - details of specific endpoint(s)
 - when endpoints would be measured
 - numbers of animals needed
 - details of methodology for obtaining endpoint
 - methodology for endpoints assessment
 - budget for study

Applications will be reviewed based on importance/rationale of including endpoints, ability to fill scientific data gaps, ability to be integrated into study design, and background expertise of investigator.

Based on the reviews, a consortium of investigators each with specific expertise (e.g. reproductive, immune, behavior, metabolic syndrome, cancer, cardiovascular, thyroid) will be funded and these investigators will work with NTP/FDA scientists to develop the final study design. The investigators will then assess their approved endpoints throughout the study and all the results will be integrated into the final NTP report.

An important aspect of the initial studies focusing on BPA toxicity will be whether the inclusion of specific endpoints related to the toxicities of BPA that have been reported in investigator-initiated studies will reveal effects that would not have been detected in a more standard guideline-compliant study. If so, these results will not only strengthen the database on dose-response for toxicological effects from BPA and other chemicals in the future, but could also establish new linkages between regulatory and investigative science to enhance the risk assessment process for endocrine-active substances.

Mechanism and Justification:

This first joint DERT/NTP initiative would use the U01 mechanism that would develop a consortium of investigators to collaborative with NTP/FDA scientists develop the protocol for rat chronic toxicity studies of BPA. This will be a 5 year initiative. Anticipated cost is \$ 3M per year for 5 years for the rat study with additional funds for a similar mouse study.

Other DERT/NTP research collaborations will be developed when the addition of DERT-funded investigators will provide added value/impact. They will use a variety of mechanisms: specific to each research project.