NTP
National Toxicology Program

NTP Testing Program: Update on Nominations

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NTP Board of Scientific Counselors meeting
December 9-10, 2014

Outline

- Background
- Status of several recent nominations
- Some other issues we are working on

What Does the NTP Study?

- Individual or classes of chemical, biological, or physical substances with:
  - High public health concern based on the extent of human exposure and/or suspicion of toxicity
  - Substantial toxicological knowledge gaps
- Issue-based projects that:
  - Enhance the predictive ability of NTP toxicology studies
  - Address mechanisms of toxicity
  - Inform risk assessment approaches

Nominations to NTP for research and testing

- Many different sources
  - Anyone can nominate a substance or issue for study at any time
  - External and internal
- Selection for study primarily on the basis of:
  - Known or anticipated human exposure
  - Suspicion of toxicity based on chemical structure or existing data
  - Availability of adequate toxicological data
  - Extent of public concern
  - Utility of additional studies for public health decision-making

Responding to nominations

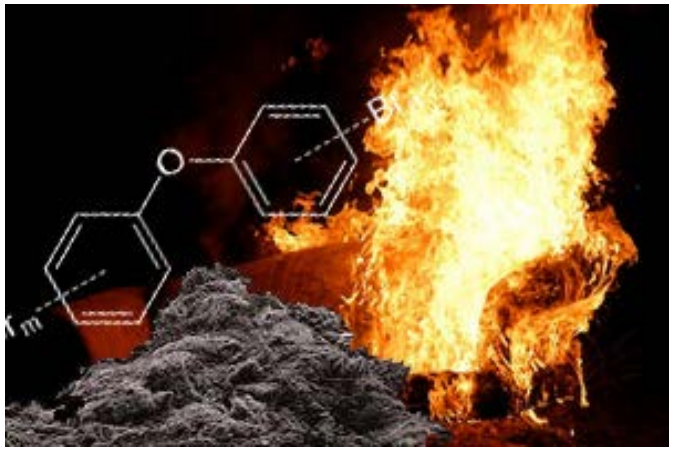
- Formal, structured review process
  - Internal and interagency reviews
  - NTP Board of Scientific Counselors review
  - Opportunities for public comment
- Formal process most useful for research projects of substantial scope and complexity
  - Preparation of NTP research concepts
- Other mechanisms for gathering input and communicating research plans
  - Appropriate where NTP has previously conducted studies or there is close alignment with current research efforts
- Fit with and integration into existing programs of work

Recent nominations

- Firemaster 550
- Decabromodiphenylethane
- Hydrochlorothiazide
- West Virginia chemical spill

NTP testing of flame retardants

- Many individual substances studied over the years
  - >30 test articles in one or more *in vivo* studies
  - Metal-based, halogenated, organophosphate
- Recent or pending 2 yr study reports
  - Tetrabromobisphenol A (TR-587)
  - Pentabromodiphenyl ether (DE-71)
- CPSC nomination, 2005
  - Chronic toxicity and carcinogenicity studies for antimony trioxide, tris(chloropropyl) phosphate (TCPP)
- Aromatic phosphate research program
  - Research concept presented to BSC December 2010



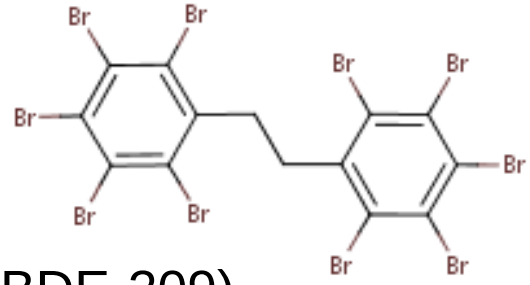
Firemaster 550

- Nomination
  - "…widespread exposures to U.S. residents in their homes and offices…preliminary findings [in Patisaul et al. 2013] warrant a larger-scale independent assessment of the toxicity of this mixture"
- Widely used flame retardant, alternative to PBDEs
- Mixture of brominated aromatic and aromatic phosphate components
- Detected in environment, biota, indoor dust
- Activity at nuclear hormone receptors (PPAR-γ, AHR) in in in vitro studies
- Very limited in vivo data for commercial mixture

Firemaster 550 cont.

- Incorporate into aromatic phosphate flame retardant research program
  - Class study of ~12 individual compounds
  - Includes two Firemaster 550 components (triphenyl phosphate and isopropylated triphenyl phosphate)
  - Short-term screening studies for all individual compounds in class
  - Pharmacokinetics and modified one-generation reproduction studies for representative compounds
- Brominated component (TBPH) included in fetal phthalate screen (Furr *et al*. Toxicol. Sci. 2014)
- Procure and characterize commercial mixture and brominated components

Decabromodiphenylethane



- Nomination based on
  - Increased demand
  - Use as alternative to decabromodiphenyl ether (BDE-209)
  - Structural similarity to Deca-BDE
- Widely detected in indoor and outdoor environments, biota, consumer products
- Subacute and subchronic toxicology studies in rats indicate liver is a target
- Included along with other brominated flame retardants as part of a short-term toxicogenomic evaluation

Hydrochlorothiazide

- Nomination
  - “At the recent IARC Working Group meeting [in June 2013], there was much discussion that additional studies need to be conducted to test the carcinogenic potential of hydrochlorothiazide in the presence of UV light”
- Widely prescribed diuretic to treat hypertension
- Known photosensitizer shown to induce DNA damage in presence of UVA
- Limited evidence in humans that it causes squamous-cell carcinoma of the skin and lip (IARC 2B)

Hydrochlorothiazide cont.

- 2-year dietary chronic toxicity and carcinogenicity (TR-379; 1989)
  - No evidence (male or female F344/N rats or female B6C3F_1 mice) or equivocal evidence (male B6C3F_1 mice) of carcinogenic activity
- Teratology, oral gavage, GD 6-15 (1985)
  - No dose-related fetal toxicity or significant increase in the incidence of malformations in rats or mice
- Current project led by NCTR
  - Utilize capabilities of NTP Center for Phototoxicology
  - Studies to address pharmacokinetics and potential photococarcinogenesis following oral exposure under consideration

Recent Nominations

West Virginia chemical spill

National Toxicology Program

- Coal processing chemicals spilled from a storage tank into the Elk River in January 2014
  - 4-methylcyclohexanemethanol (MCHM)
  - Other compounds including propylene glycol phenyl ethers
- Nominated by CDC/ATSDR July 2014
- NTP research plan (~12 month time frame)
  - Structure-activity relationship analysis
  - Alternative animal models
  - Short-term toxicogenomic studies
  - Guideline studies (prenatal developmental toxicity, irritation/sensitization, genotoxicity)

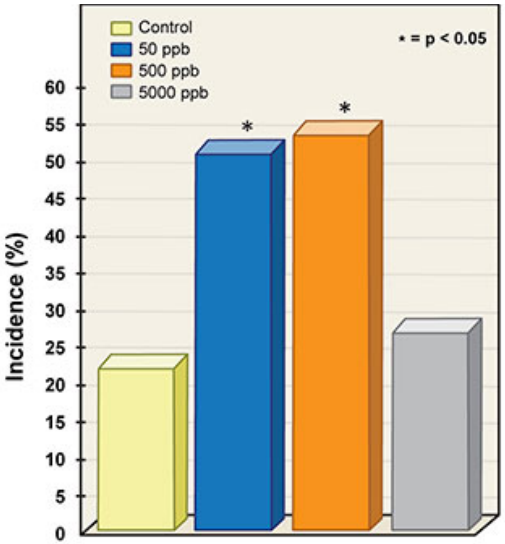
Photo by Raymond Thompson – West Virginia University researchers collect water samples at the confluence of the Elk and Kanawha Rivers.

New work on old problems

- Arsenic
- Polychlorinated biphenyls
- Microcystins

Arsenic

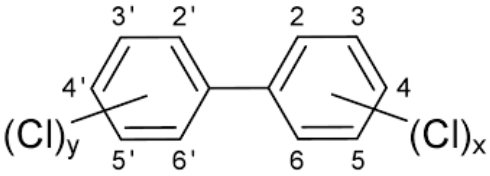
- Low dose carcinogenicity of inorganic arsenic in whole-life mouse study (Waalkes et al. 2014)
  - Male offspring mice developed significant increases in benign and malignant lung tumors at the two lower doses
- Complex dose-response
  - Qualitative and quantitative differences
  - Timing, duration, magnitude of exposure
- Critical questions
  - Windows of susceptibility
  - Dosimetry/PK across lifestage
  - Species comparison



Lung tumors occur in adult male mice after being exposed to low levels of arsenic throughout their life. The 50 parts per billion (ppb) concentration is within the range to which humans are exposed.

Waalkes MP, Qu W, Tokar EJ, Kissling G, Dixon D. 2014. Lung tumors in mice induced by “whole life” inorganic arsenic exposure at human relevant doses. Arch Toxicol; doi:10.1007/s00204-014-1305-8.

Polychlorinated biphenyls



- Large number (209) of individual congeners
  - Most work focused on the more potent congeners or commercial mixtures
- Current focus
  - Low molecular weight congeners
  - Inadvertent “mixtures”
  - Weak database relative to inhalation route of exposure
- Significant effort to define scope and strategy
  - Engage EPA, extramural investigators
- Challenges associated with identifying and procuring appropriate test articles

Microcystins

- Most common of the cyanobacterial toxins that contaminate recreational water and drinking water sources
- Robust literature on hepatotoxicity and mechanism
- No long-term studies
- Previously conducted toxicogenomic study following acute i.v. exposure
- Data gaps
  - Reproductive and developmental effects
  - Inhalation toxicity
  - Mixtures

- Investigating current availability and discussing potential needs with EPA

Questions or comments?