NTP
National Toxicology Program

NTP Study Nominations and Recommendations

Scott A. Masten, PhD, DABT

NTP Board of Scientific Counselors Meeting

June 13, 2006

NTP Study Nomination Review Process

Study Nominations

- Federal and State Agencies
- Public
- Labor Groups
- Academia
- International Organizations
- Industry
- Advocacy and Other Organizations

NTP Office of Chemical Nomination and Selection

Federal Interagency Review (ICCEC)

Public Comment

NTP Board of Scientific Counselors Review (Public Meeting)

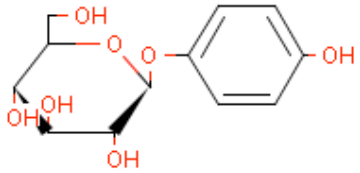
NTP Executive Committee Review and Selection

NTP designs and initiates studies based on resources, priorities and knowledge gaps

New Study Nominations

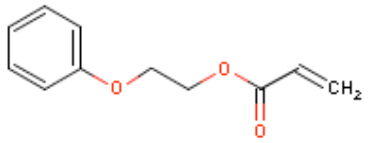
- 10 new nominations
  - Recommended for study (8)
  - Deferred until further information available (2)
- Primary use/exposure scenario
  - Consumer products (1)
  - Industrial chemicals (8)
  - Flame retardants (worker and consumer exposures)
- Review by the ICCEC January 2006
- Public comment period April-May 2006

Arbutin



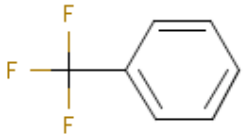
- Nominated by NIEHS
- Rationale: widespread consumer exposure through food, cosmetics, and dietary supplements; lack of adequate toxicological data; suspicion of toxicity based on chemical structure
- Natural product found in bearberry (Uva ursi)
- Metabolized to hydroquinone in humans
- Few toxicity data available*
- Recommended for: *in vitro* and *in vivo* metabolism and disposition studies; *in vitro* and *in vivo* genotoxicity studies
  - Focus on rodent and human differences in gastrointestinal metabolism and disposition, identifying an experimental animal model representative of humans, and biomarker development

Phenoxyethyl acrylate



- Nominated by NCI
- Rationale: high production volume, potential worker and consumer exposures; lack of adequate toxicity data
- Used to make polymers for various applications including coatings, inks, adhesives
- Very little toxicity data though acrylates in general are better studied
- Phenoxyethanol (a glycol ether) was a developmental and reproductive toxicant in NTP studies
- Recommended for: deferral pending further evaluation of information made available by the industry sponsor in the EHPV Program

Trifluoromethylbenzene



•Nominated by NCI

•Rationale: high production volume and potential for worker exposure; projected increase in use; lack of adequate toxicity data

•Used as an intermediate; new solvent cleaning applications

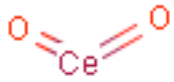
•CNS, GI tract, lung, kidney, and liver, postnatal development affected in short-term studies

•Structurally-related chemicals show a range of toxicities

– Benzotrichloride is a multi-site rodent carcinogen

•Recommended for: deferral pending review of 1) forthcoming TSCA production data, and 2) OECD Screening Information Data Set (SIDS) program output.

Ceric oxide (Microscale and nanoscale forms)



- Nominated by NIEHS
- Rationale: widespread and expanding industrial use and limited toxicity data, especially for nanoscale ceric oxide
- Used in microelectronics polishing, petroleum refining, fuel additives, cosmetics
- Lung effects in subchronic inhalation study
- No studies available of nanoscale form
- Recommended for: toxicological characterization including chemical disposition and toxicokinetics; comparative inhalation toxicity and dermal penetration studies of the microscale and nanoscale forms

Gypsum (calcium sulfate dihydrate)

•Nominated by Mount Sinai-Irving J. Selikoff Center for Occupational and Environmental Medicine and the Operative Plasterers' and Cement Masons' International Association

•Rationale: widespread human exposure and a lack of well-conducted epidemiology or toxicology studies relevant to assessing the potential for adverse long-term health effects

•Naturally occurring mineral primarily used to manufacture wallboard and plaster for homes, offices, and commercial buildings

•Human exposure during mining, manufacturing of building materials, building construction, demolition

•Fibrous or non-fibrous particulate; not durable or persistent in vivo*

•Non-specific lung effects observed; some weak evidence for potential carcinogenicity

•Recommended for: short-term pulmonary toxicity studies

- Comparative intratracheal and inhalation studies
- Considered to be of relatively low priority

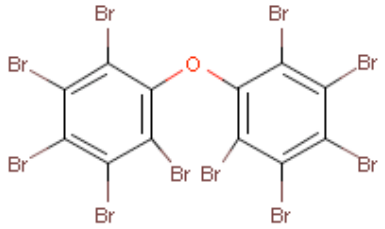
Flame retardants

- Nominated by CPSC
- CPSC flammability standards for mattresses/bedding and upholstered furniture final or in development
- Will lead to increased use and potential greater consumer exposures
- All are commercially used as flame retardants in many products
- Worker exposures and environmental exposures (product end-of-life disposal) also of concern
- CPSC staff and NRC conducted risk assessments of selected flame retardants
- Data needs identified for 11 flame retardants to better characterize potential risks
- NTP studies are one of several approaches for data development

Antimony trioxide

- Used as a synergist in combination with halogenated flame retardants such as decabromodiphenyl oxide
- Previously recommended for cardiac toxicity, chronic toxicity and carcinogenicity studies by the inhalation route of exposure
- No chronic oral studies available
- Liver, testes, hematological effects observed in subchronic oral studies
- Recommended for: oral chronic toxicity studies
  - Nanoscale form will be considered if found to be used in or released during flame retardant applications

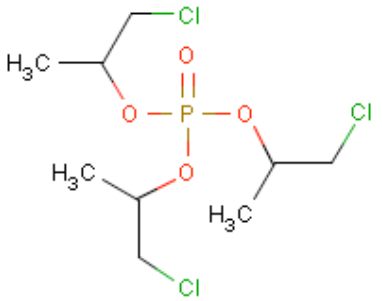
Decabromodiphenyl oxide



- Widely used in many applications including plastics, electronics, automobile interiors, furnishings, apparel
- Persistent in environment, may be dehalogenated to more bioavailable congeners
- Robust toxicology database but inadequate studies to address developmental exposures particularly regarding neurotoxicity
- International regulatory interest
- Recommended for: developmental neurotoxicity studies by the oral route of administration
  - Will only be conducted if an adequate private sector study is not identified

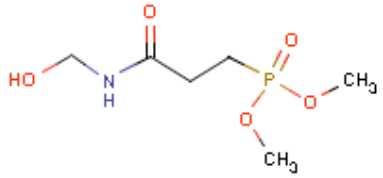
Tris(chloropropyl)phosphate, mixture of four isomers

Tris(1-chloro-2-propyl) phosphate
Tris(2-chloro-1-propyl) phosphate
Bis(1-chloro-2-propyl) 2-chloro-1-propyl phosphate
Bis(2-chloro-1-propyl) 1-chloro-2-propyl phosphate



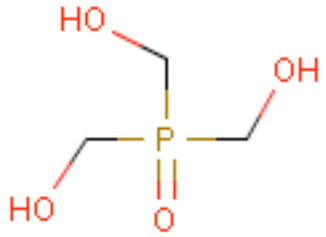
- Potential substitute for pentabromodiphenyl ether in flame-retarded flexible polyurethane foam (PUF)
- Limited toxicity data
- Other tris(dihalopropyl) phosphates are carcinogenic to rodents
- Recommended for: oral subchronic and chronic toxicity studies
  - Focus on the commercial mixture or one or more major isomers present in commercially used mixtures

Phosphonic acid, (3-((hydroxymethyl)amino)-3-oxopropyl)-, dimethyl ester



- Reactive flame retardant used with cellulosic fabrics, including children's sleepwear and upholstered furniture
- Covalently bound to fabric but may be released over time (also cleavage products, adducts)
- Very limited toxicity data
- Recommended for: oral subchronic and chronic toxicity studies; dermal absorption studies

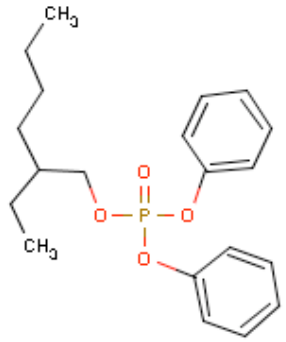
Tris(hydroxymethyl)phosphine oxide



- Parent compound (THPC) is a reactive flame retardant used with cellulosic and cellulosic blend fabrics, including children's apparel
- Polymer is bound to fabric; (consumer) exposure to THPC not expected
- THPO is a metabolite and extractable degradation product of THPC
- THPC: numerous non-neoplastic findings but no evidence of carcinogenicity in NTP 2-year gavage studies
- Recommended for: oral subchronic and chronic toxicity studies; dermal absorption studies

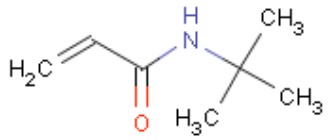
Aromatic phosphates

tert-Butylphenyl diphenyl phosphate
2-Ethylhexyl diphenyl phosphate
Isodecyl diphenyl phosphate
Phenol, isopropylated, phosphate (3:1)
Tricresyl phosphate
Triphenyl phosphate



- Used in flexible polyurethane foam (PUF) and upholstery cover fabrics, often as mixtures
- Extent of data availability mixed across this class
  - Neurotoxicity and reproductive toxicity demonstrated for some
  - TCP: no evidence of carcinogenicity in NTP studies
- Recommended for: oral subchronic and chronic toxicity studies; neurotoxicity and/or developmental neurotoxicity studies
  - One or more representative compounds
  - Coordinate with U.S. EPA as additional testing could be required of manufacturers

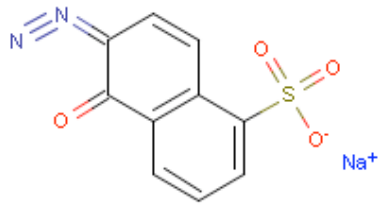
tert-Butylacrylamide



- Nominated by NCI
- Rationale: High production volume and potential for human exposure (particularly in the workplace), insufficient toxicological data, concern about the toxic/carcinogenic potential of acrylamides
- Monomer used in the production of many polymers including food packaging materials
- Neurotoxicity, testicular toxicity not observed in a few small studies
- Recommended for: metabolism and disposition, subchronic toxicity, and mammalian genotoxicity studies
  - As needed based on information made available by the industry sponsor in the EHPV Program.

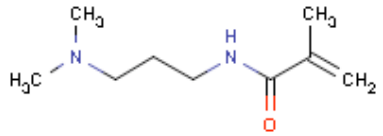
Diazonaphthoquinone derivatives

Sodium 1,2-naphthoquinone-2-diazide-5-sulfonate
2,3,4-Trihydroxybenzophenone tris(1,2-naphthoquinonediazide-5-sulfonate)
2,3,4-Trihydroxybenzophenone 1,2-naphthoquinonediazide-5-sulfonate



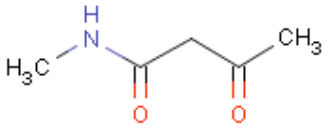
- Nominated by NIEHS
- Rationale: moderate production volume; lack of adequate toxicity data
- Exposure possible during manufacture and use, particularly photolithography processes in the (micro)electronics industry
- No toxicity data available*
- Recommended for: *in vitro* toxicity studies evaluating genotoxicity, immunotoxicity and phototoxicity; dermal penetration studies

3-Dimethylaminopropyl methacrylamide



- Nominated by NCI
- Rationale: high production volume, potential worker and consumer exposure, lack of adequate toxicity data, concern about possible nitrosation and the toxic/carcinogenic potential of acrylamides
- Used in synthesis of polymers for multiple applications e.g. coatings, paints, hair care products
- Liver, spleen, kidney, and testes effects in short-term studies
- Neurotoxicity and developmental toxicity observed for related chemicals
- Recommended for: metabolism and disposition, genotoxicity, and subchronic toxicity studies with low priority
  - As needed based on information made available by the industry sponsor in the EHPV Program
  - Further review of NTP study data for related chemicals before designing new studies

N-Methyl-3-oxobutanamide



- Nominated by NCI
- Rationale: high production volume, potential worker and environmental exposures, possible metabolism to a nitrosamide and release of formaldehyde; lack of adequate toxicity data
- Used as an intermediate; contaminant and metabolite of several pesticides (e.g. monocrotophos and dicrotophos)
- No exposure information and very limited toxicity data available
- Recommended for: *in vitro* and *in vivo* genotoxicity studies
  - Include structurally-related diketene compounds and selected N-phenyl derivatives used as pigments in cosmetics