NTP
National Toxicology Program

Peer Review of NTP Technical Report on Pentabromodiphenyl Ether Mixture (DE-71 Technical Grade) June 25, 2015

Chad Blystone, PhD, DABT
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
December 1-2, 2015

National Toxicology Program Technical Reports

- NTP conducts rodent toxicity and cancer studies on agents of public health concern to identify potential hazards for human health

- NTP technical reports describe the methods, results, and NTP conclusions as “levels of evidence” for carcinogenic activity under the specific conditions of the study

Levels of Evidence of Carcinogenic Activity

Clear evidence: Dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy

Some evidence: Chemical-related increased incidence of neoplasms in which the strength of the response is less than that required for clear evidence

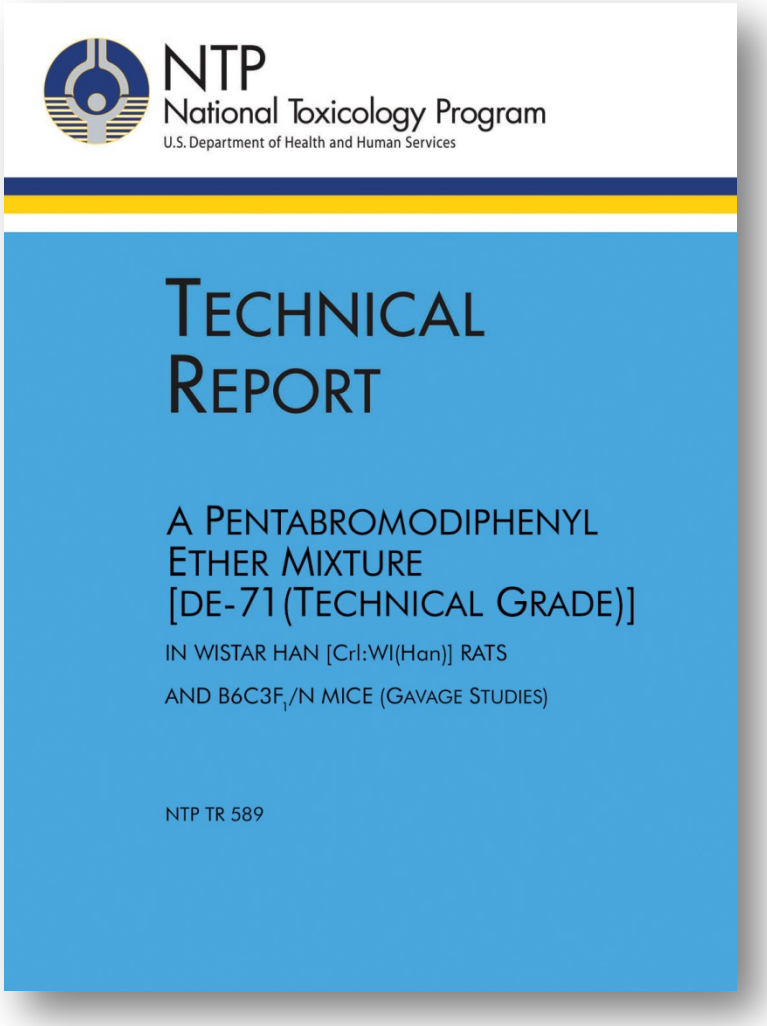
Equivocal evidence: Marginal increase of neoplasms that may be chemical related

No evidence: No chemical related increase in neoplasms

Inadequate study: Major limitations preclude interpretation

Draft Technical Report Peer Reviewed

- Pentabromodiphenyl Ether Mixture (DE-71 (Technical Grade))
  - Used as a flame retardant, often in furniture materials
  - Mixture contained:
    - BDE-99 (42%)
    - BDE-47 (36%)
    - BDE-100 (10%)
    - BDE-154 (4%)
    - BDE-153 (3%)



Charge to the Panel

- Review and evaluate the scientific and technical elements of the study and its presentation

- Determine whether the study's experimental design, conduct, and results support the NTP's conclusions regarding the carcinogenic activity and toxicity of the substance tested

Technical Report Peer Review Panel

- Kenneth M. Portier, PhD, American Cancer Society (Panel Chair)
- Russell Cattley, DVM, PhD, DACVP, Auburn University
- Michael W. Conner, DVM, Theravance, Inc
- Willem D. Faber, PhD, Willem Faber Toxicology Consulting, LLC
- Susan Felter, PhD, Procter & Gamble
- Gabriele Ludewig, PhD, University of Iowa
- Donald G. Stump, PhD, DABT, WIL Research

- Mary Beth Genter, PhD, University of Cincinnati (BSC Liaison)

Pentabromodiphenyl Ether Mixture DE-71 (TR-589)

Sex/Species	Level of Evidence	Neoplastic Lesions
Male Rats	Clear Evidence	Hepatocholangioma, hepatocellular adenoma, or hepatocellular carcinoma (combined)
Female Rats	Clear Evidence	Hepatocholangioma, hepatocellular adenoma, and hepatocellular carcinoma (combined)
Male Mice	Clear Evidence	Hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma
Female Mice	Clear Evidence	Hepatocellular adenoma and hepatocellular carcinoma

- The panel recommended accepting the conclusions (4 yes, 2 no, 0 abstentions) with following changes:
  - Recommended that the thyroid follicular cell adenomas alone (not adenomas or carcinomas combined) were related to exposure
  - NTP reviewed and agreed with the recommendation

Other Topics from the Review Meeting

- Inclusion of perinatal exposure in the two-year bioassay
  - Litter based statistics was used for analysis of tumor incidence
- Remote meeting: a first for Technical Report review
  - Logistics led by the NTP Office of Liaison, Policy, and Review

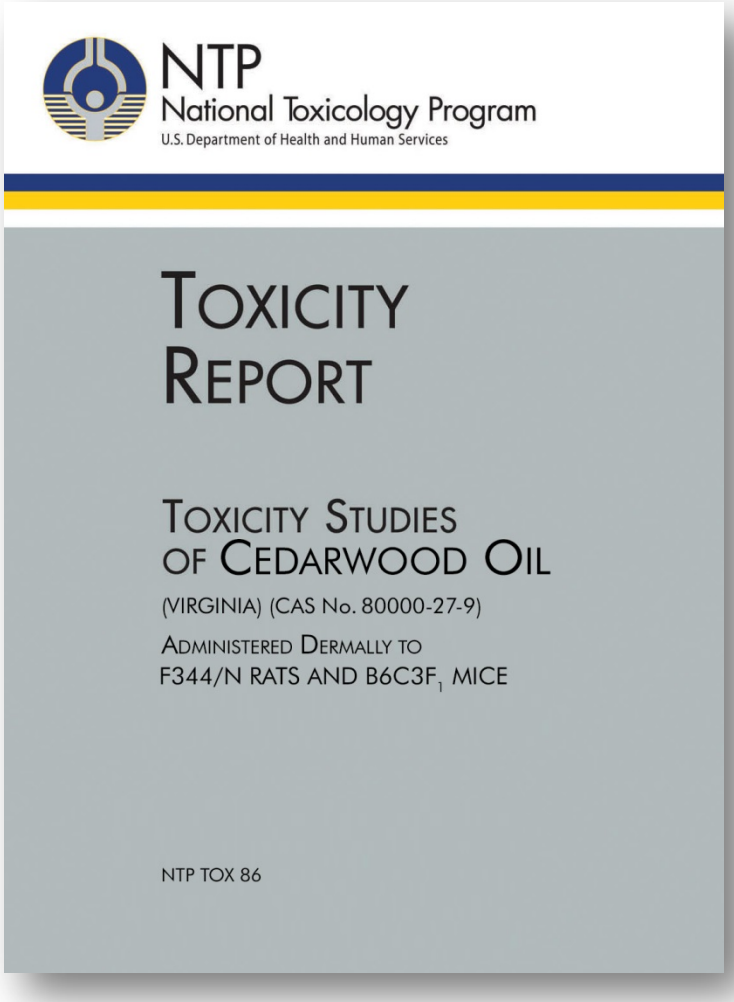
Upcoming Technical Reports

- Draft NTP Technical Reports will be posted soon for:
  - Antimony Trioxide (TR-590)
  - TRIM VX (TR-591)

- Review scheduled for February 16th, 2016

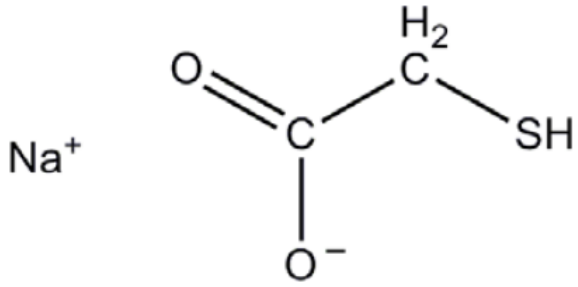
Other Reports

- NTP Toxicity Reports:
  - Typically present the findings for thirteen week studies
  - Draft reports are reviewed by mail
  - Final report posted to NTP website

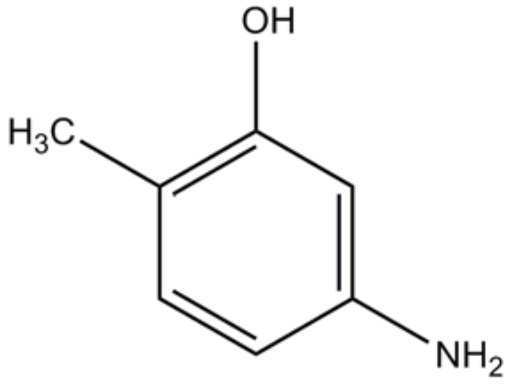


NTP Toxicity Reports

- Sodium Thioglycolate (TOX 80)
  - Used in cosmetic industry
  - Thirteen week studies characterized potential dermal toxicity
  - Skin lesions observed at site of application in rats and mice

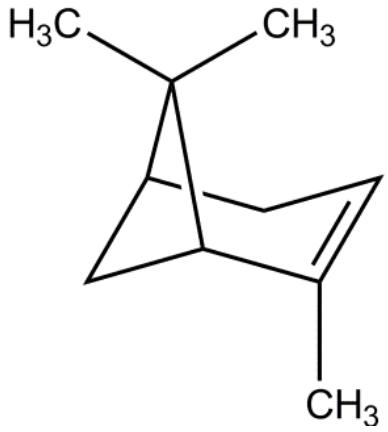


- 5-Amino-o-cresol (TOX 89)
  - Used in hair dye formulations
  - Thirteen week studies characterized potential dermal toxicity
  - No chemical related findings observed

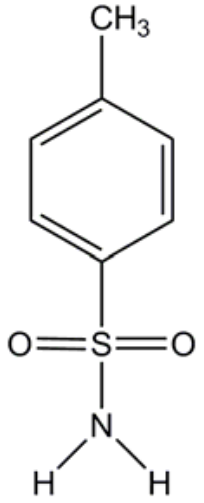


NTP Toxicity Reports

- α-Pinene (TOX 81)
  - Main component in turpentine and used for fragrance and flavoring ingredient
  - Thirteen week inhalation studies characterized potential toxicity
  - Kidney lesions observed in male rats and bladder lesions observed in mice



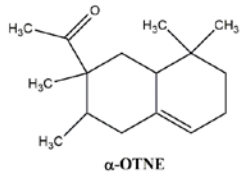
- p-Toluenesulfonamide (TOX 88)
  - Formed from chloramine-T, an antimicrobial agent used in aquaculture
  - Thirteen week feed studies characterized potential toxicity
  - Organ weight changes in rats and mice, no lesions observed

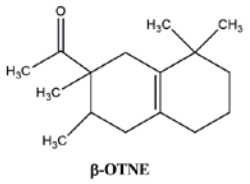


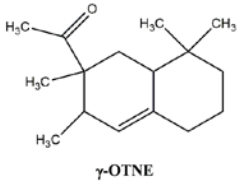
NTP Toxicity Reports

- Cedarwood Oil (TOX 86)
  - Used as a fragrance and as a pesticide
  - Thirteen week studies characterized potential dermal toxicity
  - Skin lesions observed at site of application in rats and mice, and kidney lesions in male rats and male mice

- Octahydro-tetramethyl-naphthalenylethanone (OTNE) (TOX 92)
  - Used as a fragrance in a variety of products
  - Thirteen week studies characterized potential dermal toxicity of isomer mixture
  - Skin lesions observed at site of application in rats and mice, and liver lesions in male mice







NTP DART Reports

- First reports of the NTP Developmental and Reproductive Toxicity Series to be reviewed next year
  - Draft Reports to be posted
  - Panel review of level of evidence conclusions

Questions

Toxicity Reports

- Draft NTP Toxicity Reports reviewed via letter review:
  - Sodium Thioglycolate (TOX 80)
  - Alpha-Pinene (TOX 81)
  - Cedarwood Oil (TOX 86)
  - p-Toluenesulfonamide (TOX 88)
  - 5-amino-o-cresol (TOX 89)
  - OTNE (TOX 92)

- First reports of the NTP Developmental and Reproductive Toxicity Series to be reviewed next year

Draft Report Review and Publication