Butyl Benzyl Phthalate

Butyl benzyl phthalate is used as a plasticizer in cellulosic resins and polyvinyl chloride (PVC) products, such as soft plastic children's toys, shower curtains and vinyl flooring. Over time and use, butyl benzyl phthalate is expected to leach out of these products. Other uses of this phthalate include as a fixative in perfume, and as a dispersant, carrier, organic intermediate, and solvent. Biomonitoring studies demonstrate widespread human exposure to this chemical.

Butyl benzyl phthalate passed the animal data screen, underwent a preliminary toxicological evaluation, and is being brought to the Carcinogen Identification Committee for consultation. This is a compilation of the relevant studies identified during the preliminary toxicological evaluation.

Epidemiological data

No cancer epidemiology studies were identified.

Animal carcinogenicity data

- Long-term feeding studies
  - 103-week studies in male and female B6C3F_1 mice: NTP (1982)
    - *No treatment-related tumor findings in males or females*
  - 103-week studies in male and female F344/N rats: NTP (1982)
    - *Increase in mononuclear cell leukemia (by pairwise comparison and trend) in females*
    - *No treatment-related tumor findings in males, but the study was judged inadequate due to high mortality in treated animals.*
  - 105-week studies in male and female F344/N rats: NTP (1997a)
    - *Increase in pancreatic acinar cell adenoma, and adenoma and carcinoma (combined) (by pairwise comparison and trend) in males*
    - *Marginal increase in pancreatic acinar cell adenoma (significant compared to historical controls) and urinary bladder transitional epithelial papilloma (significant compared to historical controls) in females*
  - 24- or 30- or 32-month studies in male and female F344/N rats on restricted or *ad libitum* diets: NTP (1997b)
    - *Increase in urinary bladder carcinoma, and carcinoma and papilloma (combined) in females on restricted diet*
    - *Increase in pancreatic adenoma in males fed ad libitum (by pairwise comparison, for either ad libitum or weight-matched controls)*

        - *Increase in mononuclear cell leukemia in males and females fed ad libitum (pairwise comparison with weight-matched controls)*
        - *No treatment-related tumor findings in males on restricted diet*

- Short-term intraperitoneal injection study in mice
    - 24-week study in Strain A mice (injected 3 times/week for 8 weeks): Theiss *et al*. (1977), as reviewed by NTP (1982)
        - *No treatment-related increase in pulmonary tumors*

- Short-term co-carcinogenicity study in rats
    - 16-week study in female Sprague-Dawley rats (gavaged 7 times/week for one week, followed by a single dose of dimethylbenz[a]anthracene): Singletary *et al.* (1997), as described in IARC (1999, p. 118)
        - *No co-carcinogenic effects observed*

Other relevant data

- Genotoxicity
    - Review: NTP (1997a, pp. 7-8, 50); IARC (1999, pp. 123-124)
        - *Salmonella* reverse mutation assays (*negative)*
        - *Drosophila melanogaster* sex-linked recessive lethal mutation assays *(negative)*
        - Mouse lymphoma cell mutation assay *(negative)*
        - Sister chromatid exchange (SCE) in Chinese hamster ovary (CHO) cells *(negative)*
        - Chromosomal aberrations in CHO cells *(negative)*
        - SCE and chromosomal aberrations in mouse bone marrow cells *in vivo (positive)*

- Estrogenic activity
    - Induced delayed pubertal onset, and increased proliferative index and modified morphology and gene expression profile of female rat mammary gland following prenatal exposure: Moral *et al*. (2011)
    - Increased proliferative index in mammary terminal end buds and lobules, increased uterine weight/bodyweight ratio, decreased time to vaginal opening in female rats exposed on days 2-20 of life: Moral *et al*. (2007)
    - Induced neoplastic transformation of human breast epithelial cell line MCF-10F: Fernandez and Russo (2010)

    - Altered estrogen receptor (ER)-alpha mRNA expression, possibly through influencing aberrant DNA methylation in the promoter region of ER-alpha gene: Kang and Lee (2005)
    - Induced proliferation of human MCF-7 breast cancer cells: Harris *et al.* (1997); Okubo *et al*. (2003); Hashimoto *et al*. (2003); Kim *et al*. (2004)
    - Suppressed 17beta-estradiol induced proliferation of MCF-7 cells: Okubo *et al*. (2003)
    - Inhibited tamoxifen-induced apoptosis in MCF-7 human breast cancer cells: Kim *et al*. (2004)
    - Tested positive for estrogenicity in recombinant yeast screen: Harris *et al*. (1997)

- Other mechanistic considerations
    - Showed weak peroxisome proliferation inducing activity: Hurst and Waxman (2003)
    - Influenced actin distribution and cell proliferation in rat osteoblasts and increased levels of Cyclin D3 at G1 to S transition. Overexpressed Cyclin D3 could work as a proto-oncongene during tumor development: Agas *et al*. (2007)

Reviews

- IARC (1999)

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[1] Excerpts or the complete publication have been provided to members of the Carcinogen Identification Committee, in the order in which they are discussed in this document.

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