

Bisphenol A

Bisphenol A (BPA) is used primarily in the manufacture of epoxy resins and polycarbonate plastics. It can be found in interior coatings for cans and drums, reinforced pipe, adhesives, flooring, water main filters, baby bottles, artificial teeth, nail polish, and food packaging materials. Although insoluble in water, unreacted BPA can migrate from the resins used in food packaging to food surfaces. Therefore, the primary source of exposure to BPA for most people is through the diet. In 2004, the estimated production of BPA in the United States was approximately 2.3 billion pounds. Biomonitoring studies show that human exposure to BPA is widespread.

Bisphenol A 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 Fisher 344 rats: NTP (1982)
 - *Increases (marginal) in leukemia in females*
 - *Increase in leukemia (marginal), testicular interstitial cell tumors (by pairwise comparison and trend), and mammary gland fibroadenomas (by trend) in males*
 - 103 week studies in male and female B6C3F₁ mice: NTP (1982)
 - *No treatment-related tumor findings in females*
 - *Increase in pituitary chromophobe carcinoma (by trend), lymphoma (by pairwise comparison) in males*
- Prenatal exposure studies
 - Mammary tumor study in female Wistar-Furth rats; evaluation at age 110 days: Murray *et al.* (2007)
 - *Increase in mammary gland carcinoma in situ (by pairwise comparison) in female offspring*
 - Reproductive system tumor study in female CD-1 mice; evaluation at age 18 months: Newbold *et al.* (2009)
 - *Increase (non-significant) in reproductive system tumors*

- Postnatal exposure studies
 - Prostate tumor study - subcutaneous (s.c.) injection of newborn male Sprague-Dawley (SD) rats, evaluation at age 28 weeks: Ho *et al.* (2006)
 - *Increase in prostatic intraepithelial neoplasia (PIN) (by pairwise comparison)*
- Co-carcinogenicity studies

Mammary tumor studies

- Prenatal exposure of female Wistar rats plus *N*-nitroso-*N*-methylurea (NMU) exposure at age 50 days; evaluation at age 180 days: Durando *et al.* (2007)
 - *Increase in mammary ductal hyperplasia and carcinoma (by pairwise comparison)*
- Prenatal exposure of female FVB/N mice, plus two single gavage of dimethylbenzanthracene (DMBA) at age 5 and 6 weeks; evaluation at age 110 weeks: Weber and Keri (2011)
 - *Increase in squamous cell carcinoma of mammary gland (by pairwise comparison)*
- Neonatal and prepubertal exposure of female Charles River SD rats plus DMBA exposure at age 50 days; evaluation at age 12 months: Jenkins *et al.* (2009)
 - *Increase in mammary carcinoma (by pairwise comparison and trend)*
 - *Modulation of biomarkers potentially related to mammary carcinogenesis (steroid receptor coactivators (SRCs), Akt, phosphorylated Akt, progesterone receptor A and erbB3 proteins) (by pairwise comparison) .*
- Prenatal exposure of female Charles River SD rats, plus single gavage of DMBA on day 50 or 100; evaluation at age 12 months: Betancourt *et al.* (2010)
 - *Increase in mammary carcinomas (by pairwise comparison)*
 - *Modulation of biomarkers potentially related to mammary carcinogenesis (SRCs, PR-A, Bcl-2, estrogen receptor- α , epidermal growth factor receptor, phospho-insulin-like growth factor 1 receptor, and phospho-Raf) (by pairwise comparison)*

Uterine tumor studies

- Prenatal and neonatal exposure of female Crj:Donryu rats, plus single intra-uterine administration of *N*-ethyl-*N*'-nitro-*N*-

nitrosoguanidine (ENNG) at age week 11; evaluation at age 15 months: Yoshida *et al.* (2004)

- *No treatment-related uterine cancer findings*

Prostate tumor studies

- s.c. injection of newborn male SD rats, plus estradiol and testosterone at age 90 days; evaluation at age 28 weeks: Ho *et al.* (2006)
 - *Increase in prostatic intraepithelial neoplasia (PIN) (by pairwise comparison) and prostate adenomas*
- Prenatal and neonatal exposure of Fisher 344 rats, plus s.c. injections of 3,2'-dimethyl-4-aminobiphenyl (DMAB) on week 5; evaluation at age 60 weeks: Ichihara *et al.* (2003)
 - *No treatment-related prostate cancer findings*

- Xenograft studies

Mammary tumors

- Ovariectomized NCR/*nu/nu* (athymic)/ female mice with human breast MCF-7 cancer cell xenografts with BPA exposure by s.c. implant, for 9 weeks: Weber and Keri, (2011)
 - *BPA accelerated human estrogen-dependent breast cancer growth rate (by pairwise comparison)*

Prostate tumors

- NCR/*nu/nu* (athymic)/ male mice with human prostate LNCaP tumor cell xenografts with BPA exposure by s.c. implant, for 21 days: Wetherill *et al.* (2006)
 - *BPA accelerated human prostate tumor growth rate (by pairwise comparison)*

Other relevant data

- Genotoxicity

In vivo

- Meiotic aneuploidy in the female C57BL mouse
 - oral gavage exposure (*positive*): Hunt *et al.* (2003);
 - *in utero (positive)*: Susiarjo *et al.* (2007)
- Disruption of double-strand DNA repair in *Caenorhabditis elegans* (*positive*): Allard and Colaiácovo (2010)

- Chromosome abnormalities in *Caenorhabditis elegans* (positive): Allard and Colaiácovo (2010)
- DNA adducts in CD1 male rat liver (positive): Atkinson and Roy (1995b)

In vitro

- Salmonella reverse mutation assay,
 - by nitrosylated BPA (positive): Schrader *et al.* (2002);
 - by BPA (negative) Keri *et al.* (2007, pp. 245)
 - K-ras mutations (positive): Takahashi *et al.* (2001)
 - Mammalian gene (HPRT) mutation assay in V79 cells (negative): Keri *et al.* (2007, pp. 245)
 - Micronucleus formation
 - human breast cancer MCF-7 cells (positive): Kabil *et al.* (2008)
 - human lymphoblastoid MCL-5 cell line (positive): Parry *et al.* (2002)
 - Chinese hamster V79 cells (positive): Pfeiffer *et al.* (1997)
 - Aneuploidy in Syrian hamster embryo (SHE) cells (positive): Tsutsui *et al.* (1998)
 - Chromosomal abnormalities
 - Chinese Hamster ovary cell (CHO) chromosome aberrations (positive): Hilliard *et al.* (1998) and Galloway *et al.* (1998); (negative): Keri *et al.* (2007, pp. 245)
 - Aberrations of mitotic cell division in Chinese hamster cell line V79 line (positive): Parry *et al.* (2002)
 - Chromosome non-disjunction in human MCL-5 cell line (positive): Parry *et al.* (2002)
 - Sister chromatid exchange in CHO cells (negative): Keri *et al.* (2007, pp. 245)
 - DNA double strand breaks in human breast cancer MCF-7 cells (positive): Iso *et al.* (2006).
 - Unscheduled DNA synthesis in transformed human embryo fibroblast cells (positive): Takahashi *et al.* (2001)
 - DNA adducts in cultured SHE cells (positive): Atkinson and Roy (1995a), Tsutsui *et al.* (1998)
 - Cell transformation in SHE cells (positive): Tsutsui *et al.* (1998)
- Other mechanistic considerations
 - Cell Proliferation *in vivo*
 - Mammary tubular epithelial ductal cells in female SD rats (in utero exposure) (positive): Betancourt *et al.* (2010)

- Prostate basal cells in CD-1 male mice (in utero exposure) (*positive*): Timms *et al.* (2005)

- Epigenetic effects

- In vivo*

- Alteration in DNA methylation patterns of cell signaling genes in male SD rat prostate (neonatal low dose exposure): Ho *et al.* (2006) and Prins *et al.* (2008)
- DNA hypomethylation and change in phenotype (coat color) (in utero exposure) in agouti mice: Dolinoy *et al.* (2007)

- In vitro*

- Altered DNA methylation and gene expression in normal human breast epithelial cells (low-dose BPA exposure): Weng *et al.* (2010)
- Increase of DNA methylation human breast MCF-7 tumor cells: Weng *et al.* (2010)

- Estrogenic activity (selected recent papers)

- In vitro*

- Neoplastic transformation of human breast epithelial MCF-10F cells by estrogen receptor dependent pathway: Fernandez and Russo (2010)
- Promoted human testicular seminoma germ cell proliferation by G-protein coupled estrogen receptor dependent pathways (low dose exposure): Bouskine *et al.* (2009)
- Meta-analysis review on estrogenicity: *Positive* in most in vitro estrogenicity assays, including recombinant yeast screen, MCF-7 human breast cell proliferation and luciferase assays: Montañó *et al.* (2010)

- Neuroendocrine (hypothalamic-pituitary-gonadal axis) effects following neonatal exposure (s.c. injection in SD rats): Fernández *et al.* (2010)

- Decrease in gonadotropin-releasing hormone (GnRH) inter-pulse intervals in adult females
- Increase in testosterone and estradiol, but decrease in progesterone in adult females
- Polycystic ovarian syndrome. Human or animals with PCOS are at increased risk of developing endometrial cancer

- Effects on germ line cells
 - *In vivo*, disrupts early oogenesis in the female C57BL mouse: Susiarjo *et al.* (2007)
 - *In vitro*, human testicular seminoma germ cell proliferation: Bouskine *et al.* (2009)

Reviews

- Keri *et al.* (2007)

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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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