

Genotoxicity Annex A - references and abbreviations

In this guide

[In this guide](#)

1. [Genotoxicity - Background](#)
2. [Methods for assessing genotoxicity](#)
3. [Weight of evidence](#)
4. [Mode of action](#)
5. [Conclusion on hazard identification for genotoxicity effects of BPA](#)
6. [Uncertainty analysis for the genotoxicity assessment](#)
7. [Overall conclusions on genotoxicity](#)
8. [Genotox-references and abbreviations](#)
9. [Annex A evaluation of reliability of results of genotoxicity studies – general considerations](#)
10. [WoE approach](#)
11. [Evaluation of relevance of results of genotoxicity studies -general considerations](#)
12. [Uncertainty analysis for genotoxicity including results](#)
13. [Weight of evidence studies](#)
14. [Genotoxicity Annex A - references and abbreviations](#)

References

Abdel-Rahman HG, Abdelrazek HMA, Zeidan DW, Mohamed RM and Abdelazim AM, 2018. Lycopene: hepatoprotective and antioxidant effects toward bisphenol A-induced toxicity in female Wistar rats. *Oxidative Medicine and Cellular Longevity*, 2018.

Aghajanianpour-Mir SM, Zabihi E, Akhavan-Niaki H, Keyhani E, Bagherizadeh I, Biglari S and Behjati F, 2016. The genotoxic and cytotoxic effects of bisphenol-A (BPA) in

MCF-7 cell line and amniocytes. *International Journal of Molecular and Cellular Medicine*, 5(1), 19–29.

Amin DM, 2019. Role of copeptin as a novel biomarker of bisphenol A toxic effects on cardiac tissues: Biochemical, histological, immunohistological, and genotoxic study. *Environmental Science and Pollution Research International*, 26(35), 36037–36047.

Balabanič D, Filipič M, Krivograd Klemenčič A and Žegura B, 2021. Genotoxic activity of endocrine disrupting compounds commonly present in paper mill effluents. *Science of the Total Environment*, 794, 148489.

Chen ZY, Liu C, Lu YH, Yang LL, Li M, He MD, Chen CH, Zhang L, Yu ZP and Zhou Z, 2016. Cadmium exposure enhances bisphenol A-induced genotoxicity through 8-oxoguanine-DNA glycosylase-1 OGG1 inhibition in NIH3T3 fibroblast cells. *Cellular Physiology and Biochemistry*, 39(3), 961–974.

De Flora S, Micale RT, La Maestra S, Izzotti A, D'Agostini F, Camoirano A, Davoli SA, Troglio MG, Rizzi F, Davalli P and Bettuzzi S, 2011. Upregulation of clusterin in prostate and DNA damage in spermatozoa from bisphenol A-treated rats and formation of DNA adducts in cultured human prostatic cells. *Toxicological Sciences*, 122(1), 45–51.

Di Pietro P, D'Auria R, Viggiano A, Ciaglia E, Meccariello R, Russo RD, Puca AA, Vecchione C, Nori SL and Santoro A, 2020. Bisphenol A induces DNA damage in cells exerting immune surveillance functions at peripheral and central level. *Chemosphere*, 254, 126819.

Dobrzyńska MM and Radzikowska J, 2013. Genotoxicity and reproductive toxicity of bisphenol A and Xray/ bisphenol A combination in male mice. *Drug and Chemical Toxicology*, 36(1), 19–26.

Durovcova I, Spackova J, Puskar M, Galova E and Sevcovicova A, 2018. Bisphenol A as an environmental pollutant with dual genotoxic and DNA-protective effects. *Neuro Endocrinology Letters*, 39(4), 294– 298.

EFSA CEF Panel, 2015. (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2015. Scientific opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. *EFSA Journal* 2015;13(1):3978.

Elhamalawy OH, Eissa FI, El Makawy AI and El-Bamby MM, 2018. Bisphenol-A hepatotoxicity and the protective role of sesame oil in male mice. *Jordan Journal*

of Biological Sciences, 11(4), 461–467.

Fawzy EI, El Makawy AI, El-Bamby MM and Elhamalawy HO, 2018. Improved effect of pumpkin seed oil against the bisphenol-A adverse effects in male mice. *Toxicology Reports*, 5, 857–863.

Fic A, Žegura B, Sollner Dolenc M, Filipič M and Peterlin Mašič L, 2013. Mutagenicity and DNA damage of bisphenol A and its structural analogues in HepG2 cells. *Arhiv za Higijenu Rada i Toksikologiju*, 64(2), 189–200.

Gajowik A, Radzikowska J and Dobrzyńska MM, 2013. Genotoxic effects of bisphenol A on somatic cells of female mice, alone and in combination with X-rays. *Mutation Research. Genetic Toxicology and Environmental Mutagenesis*, 757(2), 120–124.

George VC and Rupasinghe HPV, 2018. DNA damaging and apoptotic potentials of bisphenol A and bisphenol S in human bronchial epithelial cells. *Environmental Toxicology and Pharmacology*, 60, 52–57.

Gonçalves GD, Semprebon SC, Biazi BI, Mantovani MS and Fernandes GSA, 2018. Bisphenol A reduces testosterone production in TM3 Leydig cells independently of its effects on cell death and mitochondrial membrane potential. *Reproductive Toxicology*, 76, 26–34.

Hu X, Biswas A, Sharma A, Sarkodie H, Tran I, Pal I and De S, 2021. Mutational signatures associated with exposure to carcinogenic microplastic compounds bisphenol A and styrene oxide. *NAR Cancer*, 3(1), zcab004. doi:10.1093/narcan/zcab004 [RefID 295-G].

Huang FM, Chang YC, Lee SS, Ho YC, Yang ML, Lin HW and Kuan YH, 2018. Bisphenol A exhibits cytotoxic or genotoxic potential via oxidative stress-associated mitochondrial apoptotic pathway in murine macrophages. *Food and Chemical Toxicology*, 215–224.

Iso T, Watanabe T, Iwamoto T, Shimamoto A and Furuichi Y, 2006. DNA damage caused by bisphenol A and oestradiol through estrogenic activity. *Biological and Pharmaceutical Bulletin*, 29(2), 206–210.

Johnson GE and Parry EM, 2008. Mechanistic investigations of low dose exposures to the genotoxic compounds bisphenol-A and rotenone. *Mutation Research*, 651(1–2), 56–63.

Kazmi STB, Majid M, Maryam S, Rahat A, Ahmed M, Khan MR and Haq IU, 2018. BPA induced hepatotoxicity in Sprague Dawley rats. *Biomedicine and Pharmacotherapy*, 102, 728–738.

Kose O, Rachidi W, Beal D, Erkekoglu P, Fayyad-Kazan H and Kocer Gumusel B, 2020. The effects of different bisphenol derivatives on oxidative stress, DNA damage and DNA repair in RWPE-1 cells: A comparative study. *Journal of Applied Toxicology*, 40(5), 643–654.

Lei BL, Xu J, Peng W, Wen Y, Zeng XY, Yu ZQ, Wang YP and Chen T, 2017. In vitro profiling of toxicity and endocrine disrupting effects of bisphenol analogues by employing MCF-7 cells and two-hybrid yeast bioassay. *Environmental Toxicology*, 32(1), 278–289.

Li XH, Yin PH and Zhao L, 2017. Effects of individual and combined toxicity of bisphenol A, dibutyl phthalate and cadmium on oxidative stress and genotoxicity in HepG 2 cells. *Food and Chemical Toxicology*, 105, 73–81.

Majid M, Ijaz F, Baig MW, Nasir B, Khan MR and Haq IU, 2019. Scientific validation of ethnomedicinal.

use of *Ipomoea batatas* L. Lam. as aphrodisiac and gonadoprotective agent against bisphenol A induced testicular toxicity in male Sprague Dawley rats. *BioMed Research International*, 2019, 8939854.

Masuda S, Terashima Y, Sano A, Kuruto R, Sugiyama Y, Shimoi K, Tanji K, Yoshioka H, Terao Y and Kinae N, 2005. Changes in the mutagenic and estrogenic activities of bisphenol A upon treatment with nitrite. *Mutation Research*, 585(1–2), 137–146.

Mohammed ET, Hashem KS, Ahmed AE, Aly MT, Aleya L and Abdel-Daim MM, 2020. Ginger extract ameliorates bisphenol A (BPA)-induced disruption in thyroid hormones synthesis and metabolism: Involvement of Nrf-2/HO-1 pathway. *Science of the Total Environment*, 703, 134664.

Mokra K, Kuźmińska-Surowaniec A, Woźniak K and Michałowicz J, 2017. Evaluation of DNA-damaging potential of bisphenol A and its selected analogs in human peripheral blood mononuclear cells (in vitro study). *Food and Chemical Toxicology*, 100, 62–69.

Mokra K, Woźniak K, Bukowska B, Sicińska P and Michałowicz J, 2018. Low-concentration exposure to BPA, BPF and BPAF induces oxidative DNA bases lesions in human peripheral blood mononuclear cells. *Chemosphere*, 201,

119-126.

Naik P and Vijayalaxmi KK, 2009. Cytogenetic evaluation for genotoxicity of bisphenol-A in bone marrow cells of Swiss albino mice. *Mutation Research*, 676(1-2), 106-112.

Özgür M, Gül Yılmaz ŞG, Uçar A and Yılmaz S, 2021. Cytotoxic effects of bisphenol A as an endocrine disruptor on human lymphocytes. *Iranian Journal of Toxicology*, 15(2), 115-120.

Pacchierotti F, Ranaldi R, Eichenlaub-Ritter U, Attia S and Adler ID, 2008. Evaluation of aneugenic effects of bisphenol A in somatic and germ cells of the mouse. *Mutation Research*, 651(1-2), 64-70.

Panpatil VV, Kumari D, Chatterjee A, Kumar S, Bhaskar V, Polasa K and Ghosh S, 2020. Protective effect of turmeric against bisphenol-A induced genotoxicity in rats. *Journal of Nutritional Science and Vitaminology*, 66(Supplement), S336-S342.

Porreca I, Ulloa Severino L, D'Angelo F, Cuomo D, Ceccarelli M, Altucci L, Amendola E, Nebbioso A, Mallardo M, De Felice M and Ambrosino C, 2016. "Stockpile" of slight transcriptomic changes determines the indirect genotoxicity of low-dose BPA in thyroid cells. *PLoS ONE*, 11(3), e0151618.

Ramos C, Ladeira C, Zeferino S, Dias A, Faria I, Cristovam E, Gomes M and Ribeiro E, 2019. Cytotoxic and genotoxic effects of environmental relevant concentrations of bisphenol A and interactions with doxorubicin. *Mutation Research. Genetic Toxicology and Environmental Mutagenesis*, 838, 28-36.

Ribeiro-Varandas E, Viegas W, Sofia Pereira HS and Delgado M, 2013. Bisphenol A at concentrations found in human serum induces aneugenic effects in endothelial cells. *Mutation Research*, 751(1), 27-33.

Sahu C, Charaya A, Singla S, Dwivedi DK and Jena G, 2020. Zinc deficient diet increases the toxicity of bisphenol A in rat testis. *Journal of Biochemical and Molecular Toxicology*, 34(10), e22549.

Santovito A, Cannarsa E, Schleicherova D and Cervella P, 2018. Clastogenic effects of bisphenol A on human cultured lymphocytes. *Human and Experimental Toxicology*, 37(1), 69-77.

Sharma AK, Boberg J and Dybdahl M, 2018. DNA damage in mouse organs and in human sperm cells by bisphenol A. *Toxicological and Environmental Chemistry*,

100(4), 465–478.

Sonavane M, Sykora P, Andrews JF, Sobol RW and Gassman NR, 2018. Camptothecin efficacy to poison top1 is altered by bisphenol A in mouse embryonic fibroblasts. *Chemical Research in Toxicology*, 31(6), 510–519.

Srivastava S and Gupta P, 2016. Genotoxic and infertility effects of bisphenol A on Wistar albino rats. *International Journal of Pharmaceutical Sciences Review and Research*, 41(1), 126–131.

Šutiaková I, Kovalkovičová N and Šutiak V, 2014. Micronucleus assay in bovine lymphocytes after exposure to bisphenol A in vitro. *In Vitro Cellular and Developmental Biology. Animal*, 50(6), 502– 506.

Tayama S, Nakagawa Y and Tayama K, 2008. Genotoxic effects of environmental estrogen-like compounds in CHO-K1 cells. *Mutation Research*, 649(1–2), 114–125.

Tiwari D and Vanage G, 2013. Mutagenic effect of bisphenol A on adult rat male germ cells and their fertility. *Reproductive Toxicology*, 40, 60–68.

Tiwari D, Kamble J, Chilgunde S, Patil P, Maru G, Kawle D, Bhartiya U, Joseph L and Vanage G, 2012. Clastogenic and mutagenic effects of bisphenol A: An endocrine disruptor. *Mutation Research*, 743(1–2), 83–90.

Ullah A, Pirzada M, Jahan S, Ullah H and Khan MJ, 2019. Bisphenol A analogues bisphenol B, bisphenol F, and bisphenol S induce oxidative stress, disrupt daily sperm production, and damage DNA in rat spermatozoa: A comparative in vitro and in vivo study. *Toxicology and Industrial Health*, 35(4), 294– 303.

Ulutaş OK, Yıldız N, Durmaz E, Ahbab MA, Barlas N and Çok İ, 2011. An in vivo assessment of the genotoxic potential of bisphenol A and 4-tert-octylphenol in rats. *Archives of Toxicology*, 85(8), 995– 1001.

Xin F, Jiang LP, Liu XF, Geng CY, Wang WB, Zhong LF, Yang G and Chen M, 2014. Bisphenol A induces oxidative stress-associated DNA damage in INS-1 cells. *Mutation Research. Genetic Toxicology and Environmental Mutagenesis*, 769, 29–33.

Xin LL, Lin Y, Wang AQ, Zhu W, Liang Y, Su XJ, Hong CJ, Wan JM, Wang YR and Tian HL, 2015. Cytogenetic evaluation for the genotoxicity of bisphenol-A in Chinese hamster ovary cells. *Environmental Toxicology and Pharmacology*, 40(2), 524–529.

Yu H, Chen Z, Hu K, Yang Z, Song M, Li Z and Liu Y, 2020. Potent clastogenicity of bisphenol compounds in mammalian cells – human CYP1A1 being a major activating enzyme. *Environmental Science and Technology*, 54(23), 15267–15276.

Yuan J, Kong Y, Ommati MM, Tang Z, Li H, Li L, Zhao C, Shi Z and Wang J, 2019. Bisphenol A-induced apoptosis, oxidative stress and DNA damage in cultured rhesus monkey embryo renal epithelial Marc- 145 cells. *Chemosphere*, 234, 682–689.

Zahra Z, Khan MR, Majid M, Maryam S and Sajid M, 2020. Gonadoprotective ability of *Vincetoxicum arnottianum* extract against bisphenol A-induced testicular toxicity and hormonal imbalance in male Sprague Dawley rats. *Andrologia*, 52(6), e13590.

Zemheri F and Uguz C, 2016. Determining mutagenic effect of nonylphenol and bisphenol A by using Ames/Salmonella/microsome test. *Journal of Applied Biological Sciences*, 10(3), 9–12.

Zhang S, Bao J, Gong X, Shi W and Zhong X, 2019. Hazards of bisphenol A—blocks RNA splicing leading to abnormal testicular development in offspring male mice. *Chemosphere*, 230, 432–439.

Zhang H, Wang Z, Meng L, Kuang H, Liu J, Lv X, Pang Q and Fan R, 2020. Maternal exposure to environmental bisphenol A impairs the neurons in hippocampus across generations. *Toxicology*, 432, 152393.

Zhou YX, Wang ZY, Xia MH, Zhuang SY, Gong XB, Pan JW, Li CH, Fan RF, Pang QH and Lu SY, 2017. Neurotoxicity of low bisphenol A (BPA) exposure for young male mice: implications for children exposed to environmental levels of BPA. *Environmental Pollution*, 229, 40–48.

Abbreviations

7-HF 7-hydroxyflavone

8-OHdG 8-hydroxy-2'-deoxyguanosine

ABT 1-Aminobenzotriazole

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AOPP	Advanced oxidation protein products
ATM	Ataxia-telangiectasia mutated
AU	Arbitrary units
BPA	Bisphenol A
BrdU	5-bromo-2-deoxyuridine
Bw	Body weight
CA	Chromosomal aberrations
CAT	Catalase
ChE	Cholinesterase
CHO cells	Chinese hamster ovary cells
CI	Cellular index
CYP450	Cytochrome P450 reductase
DCF	Dichlorofluorescein
DMSO	Dimethylsulphoxide

EM	Electron microscopy
ER	Oestrogen receptor
FACS	Fluorescence activated cell sorting
FISH	Fluorescence in situ hybridisation
Fpg	Formamide pyrimidine glycosylase
GGT	Gamma glutamyl transferase
GPx	Glutathione peroxidase
GR	Glutathione reductase
GSH	Reduced glutathione
Hb	Haemoglobin
HDL	High-density lipoprotein cholesterol
HPLC	High performance liquid chromatography
HUVEC	Human umbilical vascular endothelial cells
i.p.	Intraperitoneal
KET	Ketoconazole
LDH	Lactate dehydrogenase

LDL	Low density lipoprotein cholesterol
MDA	Malondialdehyde
MMC	Mitomycin
MMS	Methyl methane sulfonate
MPO	Myeloperoxidase
NAC	N-Acetyl-L-cysteine
NO	Nitric oxide
OTM	Olive tail moment
PBMC	Human peripheral blood mononuclear cells
PCE	Polychromatic erythrocytes
PCP	Pentachlorophenol
PHA	Phytohemagglutinin
POD	Peroxidase
RBC	Red blood cells
ROS	Reactive oxygen species
RT-PCR	Real time polymerase chain reaction

SCE	Sister chromatid exchange
SD	Sprague Dawley
SOD	Superoxide dismutase
TBARS	Thiobarbituric acid reactive substances
TC	Total cholesterol
TG	Test guideline
TP	Total protein
TUNEL	Terminal deoxynucleotidyl transferase dUTP nick end labelling
WBC	White blood cells
WGS	Whole genome sequencing