Conclusion on hazard identification for Reproductive and developmental toxicity of BPA

In this guide

264. The conclusions of the CEP panel are reproduced below:

- In the previous opinion on BPA assessment (EFSA CEF Panel, 2015), the CEF Panel concluded that the evidence is not sufficient to infer a causal link between BPA exposure and reproductive and developmental effects in humans but re-confirmed that BPA is a reproductive toxicant in experimental animal studies at high doses (above a Human Equivalent Dose (HED) of 3.6 mg/kg bw per day, corresponding to the No Observed Adverse Effect Level (NOAEL) HED for General toxicity). The CEF Panel assigned a likelihood level of ALAN to reproductive and developmental effects of BPA in animals at low doses (below HED 3.6 mg/kg bw per day).
- In adult animals exposed at doses lower than 3.6 mg/kg bw per day, reproductive effects were considered to be ALAN; the data suggested that low-dose BPA may have adverse effects on testis function, especially various measures of spermatogenesis, although these effects were modest, and in several multigeneration studies no effects were observed at dose levels from as low as 3 µg/kg bw per day up to at least 50 mg/kg bw per day. There was less evidence that BPA will significantly impair testis morphology or reproductive endocrinology, especially in the longer term.
- In animals exposed *in utero* at doses lower than 3.6 mg/kg bw per day, reported effects on reproductive function were contradictory and highly variable between studies. A likelihood level of Likely was assigned to BPA-induced proliferative changes in the mammary gland. The CEF Panel established a tolerable daily intake which was designated as temporary (t-TDI), pending the outcome of a long-term study in rats involving pre-natal as well as post-natal exposure to BPA then being undertaken by NTP/FDA.
- Based on the human data, none of the reproduction clusters was considered Likely. Female fertility and pre-eclampsia after adult exposure, pubertal development after exposure during pregnancy were considered ALAN. Male fertility after exposure during adulthood, prematurity, fetal and post-natal growth after exposure during pregnancy and pubertal development after exposure during childhood were considered Not Likely.
- In the animal studies, the likelihood of reproductive effects was assessed by WoE in three clusters (developmental toxicity, male reproductive toxicity, female reproductive toxicity), each subdivided according to exposure periods (developmental, developmental and adult, growth phase/young age, adult and indirect (germline) exposure).
- Based on the animal data, several endpoints in both female and male reproductive toxicity clusters were judged as Likely.
- In the female reproductive toxicity cluster, there were Likely effects on ovary weight and histology after developmental exposure, on implantation rate after growth phase/young age exposure and on follicle counts after adult

exposure. Therefore, these endpoints were taken forward for BMD analysis.

- In the male reproductive toxicity cluster, there were Likely effects on epididymis (exfoliated germ cells and inflammation) after developmental and adult exposure, on testis histology (increased seminiferous tubules with lumen and acrosomal vesicles) after growth phase/young age exposure and effects on sperm motility, morphology, viability and acrosome reaction after adult exposure. Therefore, these endpoints were taken forward for BMD analysis.
- In all three clusters studied in animal studies (developmental toxicity, male reproductive toxicity, female reproductive toxicity), several endpoints were rated ALAN.
- In the Developmental Toxicity cluster, mammary gland and bone development (both sexes) and body weight (described in Metabolic hazard identification section) after developmental exposure, and also for age at first oestrus and body weight effects after exposure during growth phase, were judged as ALAN.
- In the Female reproductive toxicity cluster, effects on uterus histology (increase in apoptosis and squamous metaplasia) after developmental and adult exposure, and on oestrus cyclicity after adult exposure, were judged as ALAN.
- In the Male reproductive toxicity cluster, effects on prostate (inflammation, reactive hyperplasia and apoptosis) and testis (polyarteritis, inflammation, reduced stage VIII seminiferous epithelial cells and increased germ cell degeneration) after developmental exposure were judged as ALAN.
- After the integration of the human and animal evidence, the overall likelihood of BPA effects was considered Likely for the clusters Female reproductive toxicity and Male reproductive toxicity, and ALAN for Developmental toxicity.
- Based mainly on the animal data and in reasonable agreement with the human data, a female reproduction hazard is identified in terms of likely effects on ovary weight and histology after developmental exposure, on implantation rate after growth phase/young age exposure and on follicle counts after adult exposure.
- Male reproductive toxicity effects identified from the animal data as Likely were epididymis (exfoliated germ cells and inflammation) after developmental and adult exposure, testis histology (increased seminiferous tubules with lumen and acrosomal vesicles) after growth phase/young age exposure and sperm (motility, morphology, viability and acrosome reaction) after adult exposure. This is broadly in agreement with the previous EFSA conclusion (EFSA CEF Panel, 2015) that doses of BPA below 3.6 mg/kg bw

per day may have modest adverse effects on testis function, especially on various measures of spermatogenesis.

- Mechanisms of action for the identified BPA reproductive toxicity endpoints have been non-systematically explored in the literature. They include oestrogen and AR interactions and associated downstream and cross-stream effects, including epigenetic changes. Other possible mechanisms, including notably BPA-induced generation of oxidative stress, have been less explored.