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Bisphenol A: BfR proposes health based guidance value, current exposure data are needed for a full risk assessment

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Bisphenol A (BPA) is a chemical compound used as a raw material in the production of polycarbonate plastics and epoxy resins. It is present in numerous consumer products such as smartphones, drinking bottles, plastic tableware, paints, adhesives and food can coatings. Exposure to this compound is mainly through diet, but air, dust or water are also possible sources of BPA uptake. BPA is of low acute toxicity. However, in long-term animal studies, BPA has been linked with certain toxicological effects. The health risk assessment of BPA has been ongoing subject of scientific and public debate worldwide for years.

In April 2023, the European Food Safety Authority (EFSA) published a re-evaluation of BPA (https://www.efsa.europa.eu/en/efsajournal/pub/6857). Therein, the provisional tolerable daily intake (TDI) derived by EFSA in 2015 (4 micrograms per kilogram of body weight per day) was reduced by a factor of 20,000 to yield 0.2 nanograms per kilogram of body weight per day. The TDI describes the amount of a particular compound that can be ingested daily over the lifetime without posing any health risk. Although the total intake of BPA in the population has been declining for years, this level already exceeds the new TDI value for people of all ages by several orders of magnitude. EFSA lowered the TDI primarily based on observations in studies in mice. According to these data, the offspring of dams that had ingested BPA during and after pregnancy showed an increased proportion of a certain type of T helper cell (i.e., Th17 cells).

The BfR does not support the new TDI derived by EFSA due to several scientific and methodologic divergencies. For example, there is currently no evidence that the observed relative increases in the levels of Th17 cells trigger any adverse effects on the mice studied, and the relevance of the results to human health is questionable. The Regulation (EC) 178/2002 sets out provisions relating to diverging scientific opinions. On EFSA's website, both BfR's position statement in the public consultation on EFSA's opinion (https://open.efsa.europa.eu/consultations/a0c1v00000JA9rGAAT) and the report on diverging views are published (https://www.efsa.europa.eu/sites/default/files/2023-04/bfr-efsa-art-30.pdf). In addition to the BfR, the European Medicines Agency (EMA) has also presented its different views on the methodology of the EFSA re-evaluation.

Based on a detailed analysis of the scientific data on toxicological effects from gastrointestinal (oral, via the mouth) exposure to BPA, the BfR has derived a TDI value of 0.2 micrograms (which corresponds to 200 nanograms) per kilogram of body weight per day. This value is 20 times lower than EFSA's previous provisional TDI, derived in 2015. The BfR used a conservative approach, also considering several uncertainties in a quantitative, statistics-based way. The evaluation focused on the critical endpoints identified in the EFSA 2023 opinion (immune effects, reproductive toxicity, increased serum uric acid levels). However, due to the conservativeness and based on evaluations from other authorities, the BfR-derived TDI is also protective with respect to other toxicological endpoints (e.g., general toxicity, carcinogenicity, effects on brain and behaviour). The BfR suggests the use of this TDI value of 0.2 micrograms per kilogram of body weight per day as a basis for risk assessment.

Since current exposure estimates for the German or European population are not available, a reliable and comprehensive risk assessment of BPA cannot be performed at this time. Based on data mainly from the years 2008 – 2012, EFSA estimated in 2015 the exposure via food for the European population to be 0.1 – 0.4 (adults) and 0.1 – 0.9 micrograms per kilogram body weight per day (infants and children). However, urine data from human biomonitoring suggest that this exposure estimate may be too high. In addition, exposure is expected to have continued to decline in recent years, in part due to regulatory measures. In order to assess whether or not BPA poses a health risk to consumers, the BfR recommends to collect and evaluate additional and more current exposure data.

For both institutions, EFSA and the BfR, it is important to emphasise that discussions about methodology and interpretation of results are part of the normal scientific process. They contribute to the further development of risk assessment methods and thus, in the long term, to a better appreciation of possible health risks.

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1 Subject of the assessment

The industrial chemical BPA (also named 2,2-bis(4-hydroxyphenyl)propane or 4,4'-isopropylidenediphenol), CAS No 80-05-7, EC No 201-245-8, is predominantly used as a starting material for the manufacture of polycarbonate plastics and synthetic epoxy resins. Polycarbonate is used in building and vehicle construction, in consumer products such as DVDs and smartphones, as well as in food packaging and bottles. BPA is also used in the production of internal coatings for beverage and food cans. Until a ban in the EU was put in place in early 2020, BPA was also used in thermal papers.

In July 2016, BPA was classified by the European Chemicals Agency (ECHA) as toxic to reproduction Cat. 1B according to the European Regulation for Classification, Labelling and Packaging (CLP; Regulation (EU) No 1272/2008). Based on this classification, BPA was identified in January 2017 as a Substance of Very High Concern (SVHC) according to Article 57c of the REACH Regulation (Regulation (EU) 1907/2006). In June 2017, BPA was again identified as an SVHC due to its properties as an endocrine disruptor (substances that can cause damage by acting similar to hormones) for human health according to REACH Art. 57f. In 2018, it was identified as SVHC for being an endocrine disruptor for the environment. For example, in 2011, BPA was banned in baby bottles.

In 2015, EFSA derived a provisional TDI of 4 µg/kg bw/d based on toxic effects on the kidneys of mice in a two-generation reproductive toxicity study, taking into account remaining uncertainties for mammary gland, reproductive, neurobehavioural, immune and metabolic system effects by an additional uncertainty factor (EFSA, 2015). Recently, EFSA has lowered the TDI by a factor of 20,000 to 0.2 ng/kg bw/d. The new TDI was based on a study in mice showing a statistically significant increase of the relative proportion of T helper 17 (Th17) cells (Luo, 2016). Here, BfR provides a re-evaluation of the critical endpoints identified by EFSA (2023) to provide an independently-derived TDI.

2 Results

2.1 Literature search and study evaluation

In the first step, a comprehensive and systematic literature screening yielded more than 500 studies on reproductive toxicity and more than 100 studies on immunological effects of BPA. Of these, roughly 100 studies on reproductive toxicity and 26 studies on immunological effects were assessed as relevant for hazard characterisation. Their reliability was evaluated based on pre-defined parameters (e.g. statistical power, reporting, blinding or possible background exposure) and the studies were grouped into three categories (Tiers) reflecting the respective weight of evidence.

Only three epidemiological studies and one rodent study were identified covering the metabolic endpoint of increased serum uric acid. Due to methodological weaknesses or biological implausibilities in the study results, all of them were rated as Tier 3 and thus not considered for TDI derivation.

Since the BfR criticised the factor used for the extrapolation from critical doses in rodent studies (especially for mice) to human equivalent doses in the draft version of EFSA (2023), the available literature on the toxicokinetics of BPA in rodents and humans was also reviewed. In total, 13 studies were identified yielding relevant information, and three studies each for mice and rats as well as two studies in humans were evaluated as suitable to derive a factor to establish human equivalent doses from animal studies.

2.2 Toxicological effects related to oral BPA exposure

2.2.1 Toxicokinetics and derivation of human equivalent dose factors

In order to extrapolate doses from animal studies to humans, toxicokinetic data for BPA in animals and humans (where available) were used to derive a range of human equivalent dose factors (HEDF), calculated from free BPA blood concentrations in animals and humans.

The HEDFs were calculated to be in a range of 0.11 – 1.58 (median: 0.56) for rats and 0.19 – 1.56 (median: 0.56) for mice. The 5th and 95th percentile as well as the median of the range were submitted to the probabilistic uncertainty assessment for the derivation of the TDI.

Toxicokinetic studies were not available for rabbits, hence the standard allometric scaling according to REACH guidance was applied.

2.2.2 Immunotoxicity

As by EFSA (2023), several studies in mice were identified that upon BPA exposure reported immunological effects. Results included an increased proportion of Th17 cells in spleen, increased serum interleukin (IL) 17 levels or increased specific immunoglobulin E (IgE) and eosinophils infiltration in broncheoalveolar lavage fluid (BALF) in airway allergy models. However, upon evaluation, the data were found to be differing between studies regarding effect size and effect dose, lacked standardization (i.e. comparability) and suffered from shortcomings in experimental design and reporting. Tier 1 studies were not identified for the critical endpoints identified by EFSA (2023).

In addition, in the opinion of the BfR, the measured effects only represent intermediate endpoints, for which a causal link to apical effects in a dose range relevant for human exposure – especially for effects on the unchallenged immune system – is unclear. So far, an established adverse outcome pathway does not exist. Regarding a link to adverse apical effects, the adverse outcome (most prominently inflammation) expected to be linked to the measured intermediate endpoints in EFSA (2023) (e.g. increased Th17 cell activity) has not been observed in several (sub)chronic or multigenerational studies up to very high BPA doses. Only in challenged immune systems like murine asthma models, apical effects were observed, including increased inflammatory scores of lung sections and reduced lung functions upon methacholine challenge.

The transferability of these results to humans is unclear. The disease models are far from representing the human situation. No other species than mice has been tested for these effects, and BPA-induced IL-17 related effects were not observed in an *in vitro* study using human cells. In addition, although often similar, some important differences between murine and human immune systems have been identified, e.g. different maturation and regulation processes. Furthermore, the methods for measuring an increase in the percentage of Th17 cells that include their extraction, stimulation, sorting and/or counting have not been standardized or validated. For all of the intermediate endpoints stated above, a positive control allowing a quality assessment of the measurements as well as information on the uncertainty inherent to the assays do not exist.

Consequently, the intermediate biomarker “relative Th17 cell increase” and the other identified immunological effects are currently not sufficiently justified as a predictor of adverse health outcome in animals or humans and should therefore not be used to derive a HBGV. Still, in

order to address the endpoints identified by EFSA, the effects were modelled as a part of this opinion. As a result, benchmark responses of 100% (doubling of effect size) based on the biological variations for IL-17 serum levels as well as eosinophils or neutrophils infiltration into BALF are covered by the TDI proposed by the BfR.

Hence, the BfR concluded that adverse immunological effects in humans – if they occur at all – are unlikely to result from BPA exposure in the range of the TDI of 0.2 µg/kg bw/d. The BfR emphasises that further research and standardisation in the field of immunological effects of chemicals are needed.

2.2.3 Reproductive toxicity

After weighing the evidence in the studies resulting from the literature search, the BfR concluded that effects on the male reproductive system (e.g. sperm count, sperm motility, testis histology) were observed in studies in mice, rats and rabbits. As also noted by EFSA (2023), there was a high variability in incidence and effect dose in the database: In some studies, effects were seen from approximately 100 µg/kg bw/d upwards, whereas other comparable studies did not report effects up to 450 000 µg/kg bw/d. However, in a conservative approach, BfR identified effects on the male reproductive system as the most sensitive endpoint and based its TDI derivation on the effect dose for reduced sperm count observed in two studies using Wistar rats.

Effects on the female reproductive system (e.g. ovar and uterus) were also reported, but at much higher doses, considered irrelevant for current human exposure.

2.2.4 Increased serum uric acid

The available studies on increased serum uric acid linked to BPA exposure were evaluated as not suitable for quantitative hazard assessment due to methodological weaknesses or biological implausibilities in the study results. However, uncertainty remains with respect to this endpoint, and more data should be generated.

2.3 Derivation of a tolerable daily intake (TDI) and implications for risk communication and management

BfR based its TDI derivation on two studies showing reduced sperm count after subchronic BPA exposure of adult Wistar rats (Liu et al., 2013a; Srivastava and Gupta, 2018). Dose-response analysis was performed by means of Benchmark Dose Modelling, resulting in a $BMDL_{10}$ of 26 µg/kg bw/d and a NOAEL of 50 µg/kg bw/d, respectively. These results were subjected to a probabilistic uncertainty assessment according to the approach proposed by WHO IPCS (2018). Therein, the distribution of possible HEDFs resulting from the evaluation of literature on toxicokinetics was combined with typical distributions for other uncertainties (e.g. interhuman variability, study duration). For this, two different approaches regarding conservativeness of possible uncertainty contributions were compared.

When using the more conservative approach as suggested by WHO IPCS (2018), the process resulted in a confidence interval for the TDI of 0.14 to 39 µg/kg bw/d (Liu et al., 2013a) and 0.20 to 78 µg/kg bw/d, (Srivastava and Gupta, 2018), respectively. In following a conservative approach, the BfR decided to select the mean of the lower limit of the confidence intervals as

TDI. Hence, the TDI value is calculated to 0.2 µg/kg bw/d, which is also protective for any other relevant effect discussed in the present assessment.

It should be emphasised again that a detailed evaluation of available literature by the BfR was limited to the areas reproductive toxicity, immunologic effects, increased serum uric acid and toxicokinetics. However, based on evaluations from other authorities (ECHA, 2014; EFSA, 2015; EFSA, 2023), the BfR derived TDI of 0.2 µg/kg bw/d is considered protective with respect to other toxicological endpoints (general toxicity, carcinogenicity, effects on brain and behaviour) as well.

Furthermore, although the changes in immunological intermediate endpoints as described in EFSA (2023) were rated as not adverse and, in part, of limited relevance for humans, and irrespective of the shortcomings in many of the immunological studies (e.g. with respect to the actual BPA dose applied), the BfR-derived TDI of 0.2 µg/kg bw/d would still be protective for a 100% increase in the respective intermediate endpoints. As stated above, in the opinion of the BfR adverse immunological effects in humans – if at all – are unlikely to result from BPA exposure in the range of the TDI of 0.2 µg/kg bw/d.

Actual exposure estimation for the German or European population is not available. Hence, a comprehensive risk assessment could not be performed. In 2015, EFSA evaluated (based on data mainly from 2008-2012) exposure via food of the European population to be in the range of 0.1-0.4 µg/kg bw/d (adults) and 0.1-0.9 µg/kg bw/d (infants and children), respectively (EFSA, 2015). However, urine data from human biomonitoring suggested that this exposure estimation might have been too high (EFSA, 2015). In addition, mainly due to regulatory measures already in place (e.g. in thermal papers), BPA exposure is expected to have further decreased in recent years (compare e.g. Boon et al. (2017)). A risk assessment based on the TDI of 0.2 µg/kg bw/d can be performed once current exposure data become available.

3 Rationale

3.1 Hazard identification and characterisation

3.1.1 Methodology

The EFSA report of 2015 was supported by BfR at that time and used as starting point for the current hazard assessment. A literature search was conducted covering data since ca. 2013 until present (exact time points are given in the individual sections for the different health outcome categories (HOCs)) to identify new toxicological and toxicokinetic information potentially challenging the provisional t-TDI of 4 µg/kg bw/d from EFSA (2015). For this, BfR focused on those endpoints, which – according to EFSA (2023) – were the most sensitive ones, possibly leading to a very low HBGV:

- Immunotoxicity (IL-17 related immunity, allergic lung inflammation, specific IgE levels)
- Reproductive toxicity related to sexual function and fertility (sperm count and motility; testis histology; ovarian histology; uterus histology)
- Metabolic effects (increased uric acid serum concentration)
- Toxicokinetics (as these are needed for the derivation of a TDI and the BfR disagrees with the respective study evaluation in EFSA (2023))

For other endpoint categories (e.g. general toxicity, genotoxicity, carcinogenicity), where EFSA (2015), EFSA (2023) and ECHA (2014) consistently reported the absence of adverse effects in the dose range of interest (≤ 4 µg/kg bw/d for humans), additional literature search was not performed.

Endpoint-specific sets of search terms were selected and used for a targeted literature search in the Pubmed, Web of Science, Embase, Scopus, and Wiley Online Library databases. In addition, citations of relevant articles were screened without limitation by the publication date in addition to relevant previous regulatory assessments. It should be noted, that the body of literature considered for the present evaluation may not be fully exhaustive.

From the totality of literature collected, only studies fulfilling the criteria given below were assessed in detail.

(1) original research
(2) oral application route
(3) mammalian species
(4) for quantitative assessment “wild-type” (e.g. no knockout) strains and “intact” animals (e.g. no castrated males etc.)
(5) additional criteria for reproductive toxicity studies
    a. at least three dose groups + control
    b. *in vivo* study

In order to decide on their scientific weight and reliability, the obtained studies were rated into Tiers according to the requirements given in Table 1:

***Table 1**: Criteria for the classification into different Tiers reflecting the respective weight of evidence.*

Animal studies					
	Sample size (n)*	Doses	Exposure characterisation	Study design, documentation	test model
Tier 1 (highly relevant)	≥ 10	3 or more doses + control	High confidence; well-defined, background exposure reduced to minimum, phytoestrogen-free food; BPA purity/source known	Randomisation; blinding; validated measurement method; documentation complete; calculated values retraceable; adjustment for litter effects;	*in vivo*
Tier 2 (limited relevance)	≥ 5	≥ 2 doses + control	Phytoestrogen-containing food in all dose groups; background exposure uncertain (e.g. housing materials or feed or water), but assessed as not relevant for study outcome	One or more of the above insufficient, but not hindering a quantitative assessment	*in vivo*
Tier 3 (only in some cases with some relevance)	< 5	Only 1 dose + control	background exposure unclear (e.g. by housing materials and food and water) and assessed as relevant for study outcome	One or more of the above not sufficient, with high impact hindering a quantitative assessment	*in vivo* or *in vitro*

*for studies with developmental exposure, n was the number of the dams, irrespective of the given number for investigated pups

In general, GLP-compliant studies conducted according to internationally accepted testing guidelines (e.g. OECD) were considered the most reliable and relevant. Sample size ≥ 5 was accepted for quantitative assessment, however, a sample size < 10 led to downgrading to Tier 2. It should be noted, that 5 animals per dose group represent a comparatively low statistical power. E.g. for a subchronic study according to OECD Testguideline 408, 20 animals per dose group (10 males, 10 females) are required. For low incidence long-term effects like cancer, the according OECD Testguideline 453 states, that 100 animals per dose group (50 males, 50 females) shall be used. However, with these high requirements with respect to animal number, most studies would have been excluded from the quantitative hazard assessment in this

opinion, although they might contribute valuable evidence to the overall Weight of Evidence (WoE). However, the outcome from individual studies might be associated with high uncertainty.

It should be noted, that BPA background exposure was seen in several studies, even though careful measures were taken to avoid background exposure (Bauer et al., 2012; Camacho et al., 2019; Churchwell et al., 2014; Delclos et al., 2014; Heindel et al., 2015; Nygaard et al., 2015; Petzold et al., 2014). BPA contamination in uncontrolled standard chow or drinking water but also housing in polycarbonate or polysulfone cages (Howdeshell et al., 2003) can be a source of BPA background exposure. It can be expected that background exposure is even higher in studies, which did not take careful measures for avoidance. However, the influence of this background exposure is important especially in studies with very low nominal doses (i.e. below 10 µg/kg bw/d), but becoming irrelevant at high doses in the mg/kg bw/d range.

The received literature was evaluated by at least two experts per endpoint category. BPA-induced effects within the endpoint categories given above were evaluated with respect to adversity and relevance for humans and with consideration of exposure period. Data for dose-response evaluation were either directly taken from tables or extracted from figures using WebPlotDigitizer (https://apps.automeris.io/wpd/). Data from Tier 3 studies were considered only for qualitative (but not quantitative) information. In addition, to include also older relevant studies for endpoints with effect levels relevant for human exposure, studies assessed in EFSA (2015) were re-evaluated and included in the WoE.

Dose-response evaluation was done by means of benchmark dose (BMD) modelling according to the EFSA guidance on the use of the benchmark dose approach in risk assessment (EFSA, 2022). The benchmark dose and the respective lower and upper confidence limits (BMDL/BMDU) were calculated with Bayesian Model Averaging using the “Bayesian BMD” tool provided by EFSA via the R4EU platform (https://r4eu.efsa.europa.eu) with the default settings (except critical effect size CES/BMR, which was set to a previously defined value). In parallel, they were calculated with standard model averaging using EFSA's “bmd” tool (PROAST web software version 70.0; also via the R4EU platform). Where a BMD could not be calculated (due to missing dose-response), the NOAEL or, if that was not available either, the LOAEL from the respective study was used as the Point of Departure (PoD) for risk assessment.

Species-specific and data-based human equivalent dose (HED) factors (HEDFs) were calculated from the area under the curve (AUC) of blood concentrations of free BPA in animal studies compared to human studies (see next section for details).

For a given species, the 5^{th} and 95^{th} percentiles as well as the median of the range of possible HEDFs were taken as the uncertainty range regarding toxicokinetic interspecies variability, which was then used to create a probability distribution as input for the combined uncertainty analysis/TDI derivation step (for details, cf. section 3.1.8). Similarly, uncertainty distributions were established for all other steps of hazard characterisation (LOAEL-to-NOAEL, exposure duration, interspecies toxicodynamic, and human interindividual extrapolation), where applicable, and a TDI was calculated for each individual study, combining the PoD with these uncertainty distributions as explained in WHO IPCS (2018) (cf. section 3.1.8). In order to get a health-based guidance value, which is protective for all adverse effects assessed in this report, the lowest TDI determined from all relevant individual studies was selected as final TDI and used for hazard characterisation.

3.1.2 Toxicokinetics and Human equivalent dose factors

In order to extrapolate derived BMDLs from animal studies to humans, it was decided – in accordance with EFSA (2015); EFSA (2023) – to use toxicokinetic data for BPA in animals and humans (where available) to derive species-specific human equivalent dose factors (HEDFs). The HEDF is calculated as the ratio of the area under the curve (AUC) of blood concentration-time profiles of free BPA in animals and humans at the same external (oral) dose:

$$HEDF_{species} = \frac{AUC_{species}}{AUC_{humans}}$$

Thus, the HEDF represents a value to be multiplied with the external dose from an animal study to obtain the respective external human exposure resulting in a comparable internal dose (i.e. concentration of free BPA in blood) as in the animals.

For this purpose, toxicokinetic studies using oral application of BPA in humans and in animals (rats, mice, rabbits) were considered for this assessment. The respective AUCs as reported in the literature were linearly dose-adjusted to an external dose of 100 µg/kg bw. This is justified as there is a linear relationship between external oral exposure and serum concentration of free BPA in blood over a wide dose range, reflecting linear kinetics (compare e.g. EFSA (2008); EFSA (2010); Poet and Hays (2018); Taylor et al. (2011)). It is noted that it has been speculated (EFSA, 2015; EFSA, 2023) that toxicokinetics of BPA might be dose dependent, e.g. due to saturation of conjugating enzymes in the intestine at high doses (Hanioka et al., 2022). Accordingly, the dose-adjusted AUC of unconjugated BPA in serum would be higher at higher doses in comparison to lower doses. However, Taylor et al. (2011) and others (see citations above) have clearly shown a high linearity of the concentrations of unconjugated BPA in serum of mice measured 24 h after oral administration over a wide dose range (2 – 100,000 µg/kg bw). Also, the linearly dose-adjusted serum concentration-time profiles after oral administration of 400 and 100,000 µg/kg bw, respectively, match perfectly – except for the latest time point of 24 h (lower dose), where analytical problems may have occurred (Taylor et al., 2011). The presence of linear kinetics seems plausible with respect to the moderately hydrophobic properties (octanol-water partition coefficient of ~3.3) and the low solubility of BPA in water. BPA administered in fat (e.g., corn oil) or rodent chow, as in many studies considered in this opinion, will according to its physicochemical properties only slowly be partitioned into the aqueous phase of the intestinal lumen and cells. Hence, saturation of the enzymes in the intestinal cells as seen in *in vitro* experiments (Hanioka et al., 2022) seems unlikely *in vivo* even for comparably high doses.

It is of note that there are limitations in the HED approach as described here, mainly due to the fact that only single (bolus) dosing of BPA was considered. A study by Pollock and deCatanzaro (2014) provided relevant information on the impact of repeated dosing on toxicokinetics of BPA. In that study, 50 µg/kg bw ^{14}C-BPA was administered orally (in 0.2 g peanut butter as food supplement) to adult female mice as single dose, over 7 daily doses, or over 28 daily doses. Serum concentration of total BPA was measured 24 h post-dose. Single dosing resulted in a serum concentration of 14 ng/L (0.58 nmol/L), which translates into 1.2 nmol/L for a dose of 100 µg/kg bw. This dose-adjusted serum concentration at 24 h post-dose fits well with that reported in Sieli et al. (2011) (cf. Fig. 4G of Part II in EFSA (2015)). Repeated dosing resulted in 4 - 5-fold higher serum levels of total BPA which can be expected to apply as well to unconjugated BPA, given the running-in-parallel of the terminal slopes of the log-

scaled plasma-concentration-time profiles of total and unconjugated BPA (cf. Fig. 4 in EFSA (2015)). The repeated-dosing effect on serum BPA levels suggests longer apparent elimination half-lives in mice being very likely caused by enterohepatic recycling (EHR).

It has been known for a very long time that EHR of BPA occurs in rodents to a much higher extent than in humans due to the species differences in molecular mass threshold for biliary elimination in rats and humans. Due to the EHR, the blood concentrations and elimination half times in rodents are higherwhen compared to humans. For more details, compare e.g. EFSA (2007); EFSA (2008). A more recent study comparing different species confirmed results from earlier studies (Collet et al., 2015).

3.1.2.1 Rats

Three studies were identified reporting toxicokinetic data on adult rats, suitable for derivation of an oral HEDF for adult rats (Doerge et al., 2010; Domoradzki et al., 2003; Pottenger et al., 2000). The AUC for unconjugated BPA in these studies, adjusted to an external dose of 100 µg/kg bw, ranged from 0.1 ng*h/mL to 5 ng*h/mL (see Table 2). It has to be noted that the values for free BPA from Domoradzki et al. (2003) were calculated as difference between total BPA (calculated from total ^{14}C amount) and BPA glucuronate, thereby ignoring other possible metabolites such as BPA sulfate. In contrast, the values for free BPA as reported by Doerge et al. (2010) and Pottenger et al. (2000) were explicitly measured. However, the ratio of free BPA to total BPA was in the same range in all studies.

***Table 2**: Overview of studies on BPA toxicokinetics suitable for the derivation of an oral HEDF for adult rats.*

Study	species	dose (µg/kg bw)	AUC* Free BPA	AUC* Total BPA	Free BPA/Total BPA
Doerge (2010)	rat adult	100	0.594	155.2	0.0038
Pottenger (2000)	rat female	100	4.400	94.9	0.0464
Pottenger (2000)	rat female	10	4.200	95.4	0.0440
Pottenger (2000)	rat male	100	0.100	66.5	0.0015
Domoradzki (2003)	rat non pregnant	10,000	3.000	61.0	0.0492
Domoradzki (2003)	rat pregnant GD6-10	10,000	1.000	124.0	0.0081
Domoradzki (2003)	rat pregnant GD14-18	10,000	3.000	71.0	0.0423
Domoradzki (2003)	rat pregnant GD17-21	10,000	5.000	102.000	0.0490

*in ng*h/mL adjusted to an external dose of 100 µg/kg bw/d
Administration in all cases as gavage bolus

In many toxicological studies considered in this opinion, BPA exposure takes place via the dams during gestation and lactation (developmental exposure of fetuses and

newborns/juveniles) or during adolescence. Due to incomplete development of the metabolism, the corresponding concentrations of free BPA in the blood of newborn or juvenile rodents are much higher than in adult rodents – and also higher than in newborn humans, given the same dose (Doerge et al., 2010; EFSA, 2007; EFSA, 2008; EFSA, 2015). Hence, it could be argued that the internal blood concentration of free BPA in rodents at this specific time of exposure is underestimated in comparison to humans when applying the HEDF derived from adult animals and humans – thus leading to a too low HEDF. However, in order to be conservative, the BfR decided to apply the lower (i.e., more conservative) HEDF derived from studies with adult animals also for studies addressing developmental (and adult) BPA exposure.

3.1.2.2 Mice

Three studies were identified providing toxicokinetic data for adult mice, suitable for derivation of an oral HEDF (Doerge et al., 2011; Sieli et al., 2011; Taylor et al., 2011). However, in Doerge et al. (2011), levels of free BPA above the detection limit were only obtained for the first three time points and only in one or two of the twelve mice investigated per time point. Therefore, the AUC of free BPA was very low. It can be concluded that the data of this study do not capture EHR. Accordingly, the AUC for free BPA and thus the HEDF was very low compared to those obtained from other studies (Sieli et al., 2011; Taylor et al., 2011). In addition, the ratio of total BPA to free BPA in serum differs significantly from the other studies. Moreover, in all other studies, including those using intravenous application (Collet et al., 2015; Doerge et al., 2012; Sieli et al., 2011; Taylor et al., 2011), the concentration-time profile of free BPA in serum was reflected by a similarily shaped (but vertically displaced) concentration-time course of total BPA. This was not the case in Doerge et al. (2011), because the study could not capture the terminal phase when the effect of EHR becomes visible. Accordingly, BfR concludes that the data reported in Doerge et al. (2011) is not suitable for derivation of a plausible HEDF.

In Taylor et al. (2011), the last data point (at 24 h post dose) for the concentration of free BPA in blood after oral administration of 400 µg/kg bw is very likely too high, probably due to an analytical problem, which lead to deconjugation of glucuronated BPA during sample workup. Consequently, the resulting AUC is very likely too high. However, the dose-adjusted concentration-time profile for the 100,000 µg/kg bw group is, apart from the last data point, almost identical to that of the 400 µg/kg bw group. Hence, the BfR decided to replace the last data point of the 400 µg/kg bw group with the dose-adjusted last data point from the 100,000 µg/kg bw group, resulting in a corrected AUC for the lower dose group (see Table 3). The resulting AUC for free BPA (excluding the uncorrected values from Taylor et al. (2011)) are in a range from 1.005 – 2.960 ng*h/ml.

***Table 3**: Overview of studies on BPA toxicokinetics suitable for the derivation of an oral HEDF for adult mice.*

Study	species	dose (µg/kg bw)	AUC[1] Free BPA	AUC[1] Total BPA	Free BPA/Total BPA	comment
Sieli (2011)	Adult mouse	20,000	1.005	109.8965	0.0091	
Sieli (2011)	Adult mouse	13,000[2]	1.137	88.825	0.0128	

Taylor (2011)	Adult mouse	400	4.180	Not given	-	AUC0-24h[3]
Taylor (2011)	Adult mouse	400	9.680	Not given	-	AUC0-inf[3]
Taylor (2011)	Adult mouse	400	2.960	-	-	AUC0-inf corrected[4]
Taylor (2011)	Adult mouse	100,000	2.936	367.887	0.0080	

[1] in ng*h/mL adjusted to an external dose of 100 µg/kg bw
[2] Application in the diet, in all other cases as oral bolus
[3] analytical problem at data point for 24 h, value too high
[4] Calculated with 24 h dose-adjusted value for 100,000 µg/kg bw dose (figure 6 in Taylor et al. 2011)

3.1.2.3 Rabbits

For rabbits, data on toxicokinetics, suitable for derivation of an oral HEDF were not available. Hence, allometric body weight scaling was applied by calculating the allometric scaling factor as (human bw/animal bw)$^{0.25}$, with a default human bw of 70 kg, in line with the REACH guidance on Information requirements and chemical safety assessment, section R.8 (ECHA, 2012) and then used as the median AF accounting for interspecies toxicokinetic variability.

3.1.2.4 Humans

Two studies were identified reporting toxicokinetic data on adult humans, suitable for derivation of an oral HEDF for adult humans (Teeguarden et al., 2015; Thayer et al., 2015). In Teeguarden et al. (2015), 10 men were provided a tomato soup containing 30 µg/kg bw of d6-BPA, one hour after they had been provided with breakfast. In Thayer et al. (2015), 14 volunteers – six men and eight women - were provided a cookie containing 100 µg/kg bw of d6-BPA after they had fasted starting at midnight; after the cookie was eaten, the subjects were provided a glass of water to drink. The mean AUCs for free BPA – adjusted to 100 µg/kg bw – were 5.3 ng*h/mL (Thayer et al., 2015) and 1.9 ng*h/mL in (Teeguarden et al., 2015), respectively. It was discussed, whether the higher value after ingestion of a cookie might be due to the longer time that the cookie (which contained the BPA in much higher concentration than the soup) remained in the mouth compared to tomato soup. It is plausible, that a longer duration results in higher uptake of BPA via the mucosa of the mouth and thus to higher free BPA concentrations in blood. However, interindividual differences with respect to study population (population size, sex, age, body-mass-index etc.) as well as different fasting status (1 h after breakfast vs. several hours fasted) should be taken into consideration, too.

***Table 4**: Overview of studies on BPA toxicokinetics suitable for the derivation of an oral HEDF for adult humans.*

Study	species	dose (µg/kg bw)	AUC* Free BPA	AUC* Total BPA	Free BPA/Total BPA	comment
Thayer (2015)	Adult human	100	5.3	973.2	0.0054	oral bolus (cookie+ glass

						of water) after fasting
Teeguarden (2015)	Adult human	30	1.9	804.3	0.0024	tomato soup 1 h after breakfast

* in ng*h/mL adjusted to an external dose of 100 µg/kg bw

3.1.2.5 Calculation of Human equivalent dose factors (HEDF)

In Table 5, the HEDFs for mice and rats are shown, calculated as ratio of the AUC at 100 µg/kg bw in the respective species and the AUC in humans at 100 µg/kg bw as described above. All studies in the respective species were set into relation with both toxicokinetic studies in humans, resulting in a range of possible HEDFs. The corresponding median, 5th and 95th percentile for this range are also given in the table below. In doing so, uncertainty related to this step in the hazard characterisation becomes apparent.

For rats, in order not to give too much weight to the studies of Pottenger et al. (2000) and Domoradzki et al. (2003) in comparison to the study of Doerge et al. (2010), the different results from the first two studies were averaged for each study.

***Table 5**: HEDF for mice and rats calculated as ratio of the AUC at 100 µg/kg bw in the respective species and the AUC in humans at 100 µg/kg bw.*

Species	Animal study	Human study	HEDF
Mouse	Sieli (2011) (oral bolus 20 mg/kg bw)	Thayer (2015) (cookie + water, 100 µg/kg bw)	0.19
	Sieli (2011) (feed 13 mg/kg bw)		0.22
	Taylor (2011) (oral bolus 0.4 mg/kg bw; data adjusted)		0.56
	Taylor (2011) (oral bolus 100 mg/kg bw)		0.56
	Sieli (2011) (oral bolus 20 mg/kg bw)	Teeguarden (2015) (tomato soup, 30 µg/kg bw)	0.53
	Sieli (2011) (feed 13 mg/kg bw)		0.60
	Taylor (2011) (oral bolus 0.4 mg/kg bw; data adjusted)		1.56
	Taylor (2011) (oral bolus 100 mg/kg bw)		1.54
	Median		**0.56**
	95th percentile		**1.55**
	5th percentile		**0.20**
Rat	Doerge (2010) (gavage 0.1 mg/kg bw)	Thayer (2015) (cookie + water, 100 µg/kg bw)	0.11
	Pottenger (2000) (gavage 0.1 or 0.01 mg/kg bw; mean of all data)		0.55
	Domoradzki (2003) (gavage 10 mg/kg bw; mean of all data)		0.57

	Doerge (2010) (gavage 0.1 mg/kg bw)	Teeguarden (2015) (tomato soup, 30 µg/kg bw)	0.31
	Pottenger (2000) (gavage 0.1 or 0.01 mg/kg bw; mean of all data)		1.52
	Domoradzki (2003) (gavage 10 mg/kg bw; mean of all data)		1.58
	Median		**0.56**
	95th percentile		**1.56**
	5th percentile		**0.16**

A recent review article (Poet and Hays, 2018) concluded that a HEDF of 0.9 would be scientifically sound for both, rats and mice. As shown in the table above, this value is well within the range of possible HEDF for mice and rats and seems plausible also with respect to the effect of repeated-dose administration as discussed earlier. However, the BfR decided not to use a single HEDF value but the calculated range for derivation of a TDI within the uncertainty assessment.

3.1.3 Immunotoxicity

3.1.3.1 Methodology

A systematic literature research was performed using key words and several life science bibliographic data bases covering a time frame from 2014 -01-01 to 2022-09-29 (Figure 1). In total, 127 entries were received from which studies that lacked the following criteria were excluded:

- Reviews and studies without original data
- Studies with other than oral exposure routes
- Studies not addressing the adverse immunotoxicity endpoints identified by EFSA, 2023

Thus, this evaluation focused on the four adverse immunotoxicity endpoints identified by EFSA, 2023 (EFSA, 2023):

- Cellular immunity: increased Th17 cell percentages in spleen (likely)
- Allergic lung inflammation: increased specific IgE levels (very likely)
- Allergic lung inflammation: increased BALF eosinophil infiltration (likely)
- Inflammation: neutrophil-mediated epididymis (likely)

The systematic literature search yielded 14 studies. Article selection was further extended by a non-systematic approach adding additional studies listed by EFSA opinions (EFSA, 2007; EFSA, 2015; EFSA, 2023) (8 studies) or from other sources, e.g. citations (4 studies, Figure 1). As in EFSA, 2023 (EFSA, 2023), non-test guideline and non-GLP studies were included. In total, 26 studies from 18 different laboratories were assessed. All studies were performed in mice except Ogo et al., 2018 (Ogo et al., 2018), which used rats for the endpoint neutrophil infiltration into the epididymis. From the 26 studies analyzed, 12 were part of the EFSA, 2023 (EFSA, 2023) evaluation.

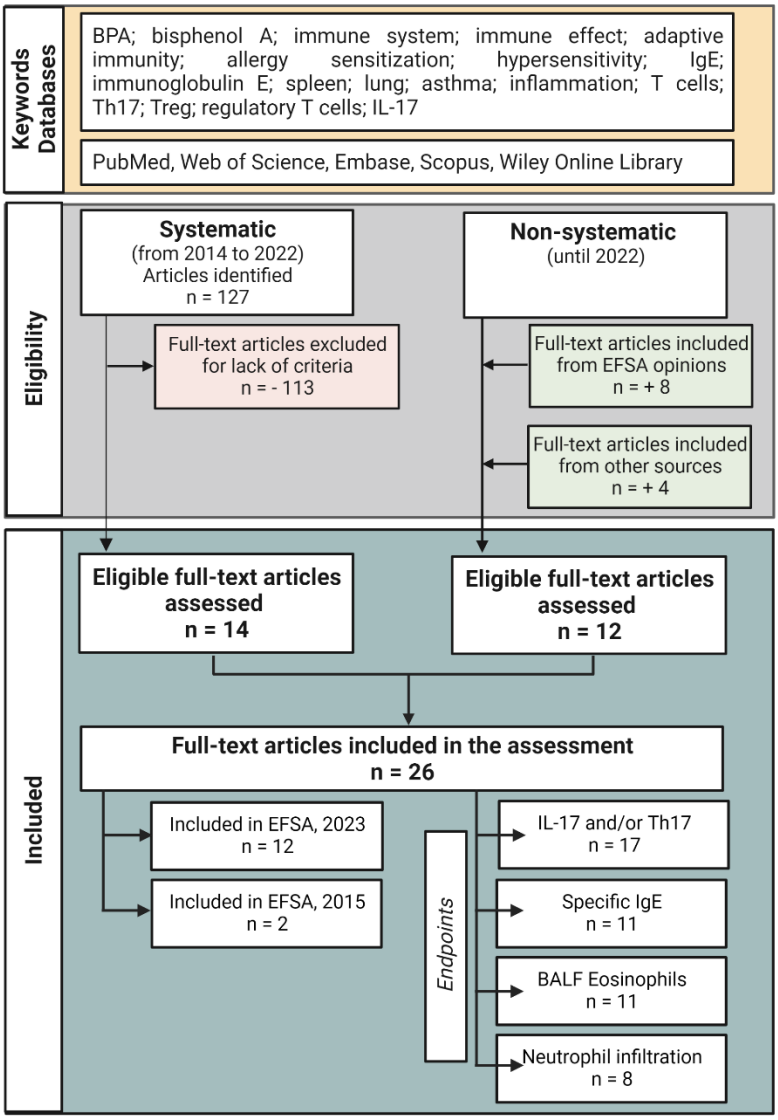

Figure 1: *Study selection for BPA immunotoxicity hazard evaluation. Flowchart overview showing the number of studies obtained by a systematic literature research using the indicated databases. The resulting study selection was complemented by a non-systematic search.*

Tier 1 studies were not identified, but seven Tier 2 studies were available. The remaining studies were assigned Tier 3. The main reasons for a tier downgrading were an insufficient sample size, a limited number of dose groups and unclear information on background exposure in case of very low dose exposures. From the 12 studies that were identical to EFSA, 2023 (EFSA, 2023), an identical BfR tier was assigned to half of them (6/12). One study was assigned a higher tier (Nygaard et al., 2015) and five were assigned a lower Tier (Luo et al., 2016; Malaisé et al., 2017; O'Brien et al., 2014; Ogo et al., 2018; Tajiki-Nishino et al., 2018).

Nygaard et al., 2025 (Nygaard et al., 2015) had been assigned Tier 3 by EFSA, 2023 (EFSA, 2023) because information on the source and purity of BPA was missing. However, the authors

carefully addressed BPA background contamination and upon contact confirmed that BPA from TCI with a purity of ≥99% was used, which is why Tier 2 was assigned in this assessment.

Four immunotoxicity studies rated Tier 1 by EFSA, 2023 (EFSA, 2023) were assigned Tier 3 by BfR. Luo et al., 2016 (Luo et al., 2016) lacked information on background BPA contamination from the polycarbonate cages and used standard feed in combination with a very low exposure dose group of 0.475 µg/kg bw/d. Similarly, BPA background contamination was not sufficiently addressed by Ogo et al., 2018 (Ogo et al., 2018). The study did not provide information on water bottles and used standard feed while reporting rather strong effects on IL-6 secretion at a dose of 20 µ/kg bw/d. Tajiki-Nishino et al., 2018 (Tajiki-Nishino et al., 2018) did not provide information on feed or housing material and, in addition, a gating strategy or markers used for BALF eosinophil identification are missing. O'Brien et al., 2014 (O'Brien et al., 2014) was assigned BfR Tier 3 due to the low sample size (n = 4 dams per group). Malaise et al., 2017 (Malaisé et al., 2017) was assigned Tier 2 by EFSA, 2023 (EFSA, 2023) but Tier 3 by BfR because only a single BPA dose was tested.

These differences in tier assignment were not decisive for the differences in TDIs derivation by BfR and EFSA (EFSA, 2023) since the same immunotoxic effects were identified (although with slight differences whether an effect was likely or very likely). The higher BfR TDI is due to methodological differences including BMD modeling, HED factor derivation and BMR setting. For the reasons discussed below, BfR decided not to use an immunotoxicity-related endpoint for TDI derivation. Still, it was checked whether immunotoxicity would be covered by the BfR TDI using a higher BMR than EFSA (100% instead of 20-40%), as discussed below.

3.1.3.2 IL-17-related immunity

Seventeen articles from 11 research groups that describe murine in vivo studies for the effects of BPA on IL-17-related immunity were evaluated . Most studies used IL-17A-specific detection. A few kits were able to detect both IL-17A and IL-17F and it was not specified, which cytokine was detected, but it can be reasonably assumed it was IL-17A (Bauer et al., 2012; Bodin et al., 2014; Luo et al., 2016; Nygaard et al., 2015; Wang et al., 2020a).

Serum IL-17 levels

Assessment of the effect

BPA effects on serum IL-17 levels have been investigated by two laboratories in Shenyang (Dong et al., 2020; Gao et al., 2020a) (both Tier 2, C57BL/6 strain) and Anhui (Luo et al., 2016; Wang et al., 2020a) (both Tier 3, ICR strain). One study is part of the EFSA, 2023 evaluation (Luo et al., 2016). The studies used developmental exposure from GD0 or GD6 until PND21. In addition, Gao et al., 2020 (Gao et al., 2020a) tested continuous exposure until PND50. Analysis time points were between PND21 and PND50.

All four studies report a dose-dependent increase in the IL-17 serum level in both sexes upon BPA exposure. Significant results started at BPA exposures of ~50 µg/kg bw/d (Dong et al., 2020; Gao et al., 2020a; Wang et al., 2020a) and ~5 µg/kg bw/d (Luo et al., 2016). Thus, the effect seems reproducible although reversible, given the lower magnitude at the later analysis time point (Luo et al., 2016). Reversibility is further supported by Wang et al., 2020 (Wang et al., 2020a) showing that exposure of dams to vitamin D (4 µg/kg bw/d) rescued the BPA-induced IL-17 serum increase at ~50 µg/kg bw/d. In addition, effects were similar independent from a continuous BPA exposure until adulthood (PND50) indicating some adaptability for the effect (Gao et al., 2020a).

Overall, the effect of BPA on IL-17 serum levels during developmental or developmental to adult phase exposure in mice were assigned a likelihood level of LIKELY.

Besides IL-17, other serum cytokines were investigated but mostly by one laboratory, so results were not independently reproduced. TGFβ and IFNγ were downregulated (Dong et al., 2020; Gao et al., 2020a) (unchanged in (Luo et al., 2016; Wang et al., 2020a)), while TNFa, IL-21, IL-6 and IL-23 were upregulated (Luo et al., 2016; Wang et al., 2020a).

Link to adverse (apical) endpoints

Disease or immune-induction models were not studied, so the increases in IL-17 serum levels could not be linked to an adverse outcome.

Effect sizes and reasoning for BMD modeling

Serum IL-17 levels can be rather easily quantified by commercial kits and results are less dependent on experimental conditions compared to the assessment of IL-17-producing cells or IL-17 tissue levels. Background levels of serum IL-17 were ~10 pg/ml for three of the four studies while for Wang et al., 2020 (Wang et al., 2020a) they were ~20 pg/ml. Therefore, a BMR of 100% was set and the results of BPA-influenced IL-17 serum levels in mice were used for dose-response analysis.

Effect levels in the ~50 µg/kg bw/d exposure groups ranged from plus 5-12 pg/ml IL-17 in addition to the background levels. For the higher dose groups of ~500 µg/kg bw/d (Dong et al., 2020; Gao et al., 2020a) up to 15 pg/ml IL-17 increase were observed.

Data on the link between the intermediate endpoint IL-17 serum levels in mice and an adverse apical outcome in humans is very limited, as discussed below in the section providing some background information on Il-17-related immunity. It was outside the scope of this opinion to determine, whether a BMR of 100% is predictive for adverse effects humans. A dedicated investigation would be required, also for the other intermediate immunotoxicity endpoints including spleen Th17 cell percentages, IL-17 secretion by splenocytes, specific serum IgE levels and BALF eosinophil infiltration. So far, standardization, positive controls and validations are lacking for these intermediate immunotoxicity endpoints. Data obtained by a cursory review indicate that human serum IL-17 levels are lower and multiply by much more than a 100% in disease with huge variation e.g., in systemic sclerosis (healthy 0.6±2 pg/ml, n=21, disease 4.68±16 pg/ml, n=12) (Robak et al., 2019).

Spleen Th17 cell percentages (determined by flow cytometry)

Assessment of the effect

Similar to serum cytokine levels, the investigation of spleen cells indicates systemic immune effects. Three laboratories (7 studies) assessed BPA effects on splenic Th17 cell percentages via visualization of intracellular IL-17 production by spectral flow cytometry (or FACS, both terms are used interchangeably). Three of the studies are part of the EFSA, 2023 evaluation (Luo et al., 2016; Malaisé et al., 2017; Malaisé et al., 2018). Besides the four studies that investigated IL-17 serum levels (two Tier 2 and two Tier 3 studies), three Malaisé et al. studies from Toulouse addressed this endpoint (Malaise et al., 2020a; Malaisé et al., 2017; Malaisé et al., 2018) (all Tier 3). All studies used developmental exposure regimes where BPA dosing stops at PND21 at weaning and offspring was analyzed at ~PND50. Exceptions included Gao et al., 2020 who also included exposure into adulthood until PND50 and Malaise et al., 2017 which analyzed on PND45 and PND170 (Gao et al., 2020a; Malaisé et al., 2017).

Spleen cells were stimulated for 4-6 h with PMA-Ionomycin in the presence of Golgi-inhibitors to detect intracellular IL-17 production. Only relative increases in Th17 percentages were reported, Th17 cells were not quantified. The Shenyang and Anhui laboratory studies used CD4+IL-17+ as markers for Th17 cell identification, the Malaisé et al. studies from Toulouse CD3+ RORγT+IL-17+ staining.

All seven studies showed significant increases in the percentage of Th17 cells in the spleens upon BPA exposure to ~50 µg/kg bw/d for both sexes. Luo et al., 2016 (Luo et al., 2016) was the only study showing this effect at lower doses with a significant results starting at ~5 µg/kg bw/d. Dose-dependent increases were found up to 520 µg/kg bw/d (Dong et al., 2020; Gao et al., 2020a). Again, the effect seemed reversible as shown by the longitudinal analysis or by blockage with Vitamin D (Luo et al., 2016; Malaisé et al., 2017; Wang et al., 2020a).

Overall, an increase in the percentage of spleen Th17 cells due to BPA exposure during developmental or developmental to adult phase exposure in mice (C57BL/6, ICR, C3H/HeN strains) is considered VERY LIKELY.

Increased tissue levels of RAR-related orphan receptor gamma (RORγT) protein (Dong et al., 2020; Gao et al., 2020a) or mRNA (Luo et al., 2016; Wang et al., 2020a) also argue for an absolute increase in IL-17-producing cells in the spleen. This, however, could include other cell populations like IL-17 producing CD8+ T cells, NKT cells, γδ T cells or ILCs.

The increase in Th17 cell percentages was generally accompanied by a decrease in the percentage of Tregs, which were identified in all studies as CD4+CD25+Foxp3+ (Dong et al., 2020; Gao et al., 2020a; Malaise et al., 2020a; Malaisé et al., 2018) (no change for (Malaisé et al., 2017)). These data were supported by a decrease in Foxp3 protein levels (Dong et al., 2020; Gao et al., 2020a).

The three Malaisé studies also analyzed small intestine lamina propria (siLP) cells under the same experimental conditions. Results showed an increase in the two later studies (Malaise et al., 2020a; Malaisé et al., 2018) and a (small) decrease in the older study (Malaisé et al., 2017).

Misme-Aucouturier et al, 2022 (Misme-Aucouturier et al., 2022) reported a dose-dependent increase in Th17 cell percentages in mesenteric lymph nodes (MLN) upon growth and adult phase BPA exposure to 0.4, 4 and 40 µg/kg bw/d. Here, the authors used CD3+CD4+ RORγT+ expression to identify Th17 cells, not an intracellular IL-17 stain. Thus, a much larger proportion of cells was stained (roughly ~5 % vs. ~1% in the control groups). Again, Treg cell percentages were decreased.

Link to adverse (apical) endpoints

All studies investigating functional (IL-17 producing) Th17 cell percentages did not use a disease or immune-induction model. Still, some hints for adverse apical endpoints may be considered from the Malaisé et al. studies. Malaisé et al., 2017 (Malaisé et al., 2017) observed that 50 µg/kg bw/d BPA developmental exposure provoked metabolic disorders in male offspring C3H/HeN with increased body weight (not reproduced by (Malaisé et al., 2020a)), perigonadal white adipose tissue weight and M1 macrophage infiltration and increased blood glucose levels accompanied by decreased insulin tolerance on the long term (PND170). Fecal IgA and lysozyme levels (antimicrobial functions) were reduced. Results on impaired gut barrier functions and increased colonic permeability accompanied by decreases in lysozyme expression, gut and fecal IgA levels and antimicrobial fecal function were described. Anti-commensal *E. coli* IgG levels were increased (both studies), which may be a consequence of the gut barrier leakage. However, anti-food IgG remained unchanged, arguing against increase

food antigen exposure or/or for tolerance induction (Malaisé et al., 2020a; Malaisé et al., 2018). Similarly, anti-E-coli IgG were increased in an IL-10-/- knockout strain (Malaisé et al., 2020b), but colitis was not exacerbated.

Misme-Aucouturier et al.,2018 (Misme-Aucouturier et al., 2022) sensitized mice to wheat gliadin in a food allergy model but observed only very small changes, for instance in body temperature (down) or plasma MCP-1 levels (up) in the presence of BPA up to 40 µg/kg bw/day.

In conclusion, BPA effects on the gut barrier were identified reproducibly in several studies that used gavage as BPA exposure route (i.e. a daily bolus BPA application).

Effect sizes and reasoning for BMD modeling

The isolation and stimulation of splenocytes with PMA-Ionomycin and subsequent intracellular IL-17 stain is moderately dependent on the experimental conditions. In controls, ~0.1 – 2% Th17 cells were observed among the studies. Effect sizes upon BPA exposure ranged from plus 0.1 – 2.0 percent on top of the control sample. Due to this variability in background and effect size the results were not forwarded for dose-response analysis.

Tissues like the siLP have a much higher proportion of Th17 cells, ~7-17% and BPA-induced effect sizes were also larger (-2,4 up to 6%; (Malaise et al., 2020b; Malaisé et al., 2017; Malaisé et al., 2018). Thus, each tissue needs to be considered separately while isolation conditions are difficult to standardize, especially for non-lymphoid organs (Steinert et al., 2015). In humans, usually only blood Th17 cell percentages are accessible and also show large variation in health and disease (e.g. healthy: usually <1%; COPD: 0.9-23%, mean 9.8%; CD3+CD4+IL-17+ cells, n=37 (Aparicio-Soto et al., 2020; Vargas-Rojas et al., 2011)). EFSA, 2023 (EFSA, 2023) cited a paper for rheumatoid arthritis (0.91%, n=12) and ankylosing spondylitis (0.94%, n=20) where smaller percentage changes occurred in patients vs. healthy donors (0.5%, n=16; p = 0.005 for both comparisons) (Shen et al., 2009). In summary, experimental and inter donor variabilities in health and disease complicate the setting a BMR for the endpoint increased spleen and other tissue Th17 cell percentages.

Spleen cell IL-17 secretion (determined by cytokine detection in culture supernatants)

Assessment of the effect

BPA-related effects on IL-17 production may be investigated in supernatants from stimulated spleen cells. Depending on the simulation conditions used, this read-out can detect IL-17 secretion by various cells including Th17 cells, CD8+ T cells, $\gamma\delta$ T cells or ILCs. The readout further lacks single cell resolution since individual cells produce very different quantities of effector cytokines (Helmstetter et al., 2015). Studies mainly used polyclonal stimulation via CD3/CD28 cross-linking for 72 h (Malaisé et al., 2020a; Malaisé et al., 2020b; Malaisé et al., 2017; Malaisé et al., 2018) or Concanavalin A (ConA) stimulation for 48 h (Cetkovic-Cvrlje et al., 2017). One study used LPS for 48 h, which activates B cells and monocytes, thus only indirectly stimulated IL-17 secretion from e.g., Th17 cells (Bodin et al., 2014). Antigen-specific stimulation was achieved using MOG peptide (72 h) (Krementsov et al., 2013), Lupin extract (5 d) (Nygaard et al., 2015), OVA protein or *E.coli* lysate (72 h) (Malaisé et al., 2020b).

In total, 8 studies were analyzed for this endpoint (two tier 2 and six tier 3 studies) and only two were not part of the EFSA, 2023 evaluation (Malaise et al., 2020a; Malaise et al., 2020b).

The three Malaisé studies investigating developmental BPA exposure reproduced the effect seen by FACS on Th17 cell percentages showing increases in IL-17 protein levels upon 3 d in

vitro stimulation (Malaise et al., 2020a; Malaisé et al., 2017; Malaisé et al., 2018). A trend or statistically significant increased INFγ expression was also observed.

Bodin et al., 2014 (Bodin et al., 2014) used the diabetic prone NOD/ShiLtJ strain. After developmental exposure, the authors observed a significantly increased IL-17 production for the top BPA dose of 4500 µg/kg bw/d, which was accompanied by a much higher increase in IL-10 levels, upon stimulation of splenocytes with LPS at PND77. Effects were not observed at lower doses (45, 450 µg/kg bw/d) or on Th, Treg or NKT cells from lymph node or spleen cells. Similar as in other studies, effects at lower doses may have reverted at this rather late analysis time point.

Krementsov et al., 2013 (Krementsov et al., 2013) also analyzed developmental BPA exposure combined with a late analysis point (PND86). Two different mouse strains and experimental autoimmune encephalomyelitis (EA) induction protocols, a model for human multiple sclerosis (MS) were used. EAE-specific peptide (MOG_{35-55} for C57BL/6 and $PLP_{135-151}$ for SJL cells) stimulation of spleen and lymph node cells (combined analysis) did not show a change in IL-17 (or IFNg) production for male and female cells, respectively.

Nygaard et al., 2015 (Nygaard et al., 2015) applied continuous BPA exposure from GD0 until PND64 (developmental, growth and adult phase exposure) with up to 22000 µg/kg bw/d. Combined with lupin extract allergy induction (food allergy model) a trend for an increased IL-17 secretion after a 5-day specific stimulation of spleen cells, combined with a much higher significant increase in IL-13 levels was observed. The IL-17 result were not significant and not observed at lower BPA doses (230 and 2300 µg/kg bw/d). In a second airway allergy model using only developmental exposure and analysis on PND30, a change in IL-17 production was not observed in ConA (48 h) stimulated splenocytes.

IL-17 production by stimulated splenocytes was unchanged or reduced in studies investigating adult exposure (Cetkovic-Cvrlje et al., 2017; Malaisé et al., 2020b). Malaisé et al., 2020 (Malaisé et al., 2020b) exposed mice from PND56-98 (0.5, 5 and 50 µg/kg bw/d). Spleen cells did not show dose-dependent effects for increasing BPA doses for both polyclonal (CD3/CD28)or OVA-specific Il-17 release by splenocytes in OVA tolerized or OVA immunized mice. IL-10-/- knockout cells responded with slightly increased *E. coli*-specific Il-17 secretion upon BPA exposure of 5 µg/kg bw/d, indicating that the effect is not completely abolished.

Cetkovic-Cvrlje et al., 2017 (Cetkovic-Cvrlje et al., 2017) exposed C57BL/6 mice to 160 and 1600 µg BPA/kg bw/d (PND28-112) in streptozotocin (STZ)-based diabetes induction. ConA-stimulated spleen cells did not show increased IL-17 release at both exposure doses and at two analysis time points (PND74, PND113). Similarly, changes were not observed for IL-2, -4, -6, -10, TNFa or IFNg cytokine levels.

Since studies using adult only exposure had been missing for the endpoints IL-17 in serum and increased spleen Th17 cell percentages, these results are the first that hint towards a more susceptible developmental exposure time for BPA-induced IL-17-related immune effects with lesser or absent effects upon adult exposure.

In conclusion, as the increase in the percentage of spleen Th17 cells, an effect of BPA on IL-17 cytokine production by stimulated spleen cells is considered as LIKELY. Effects seem to be less profound upon adult exposure and reversible.

Link to adverse (apical) endpoints

In addition to the studies already discussed above (endpoint spleen Th17 cell percentages) (Malaisé et al., 2020a; Malaisé et al., 2020b; Malaisé et al., 2017; Malaisé et al., 2018), adverse apical endpoints from BPA exposure may be discussed for the other studies (Bodin et al., 2014; Cetkovic-Cvrlje et al., 2017; Krementsov et al., 2013; Nygaard et al., 2015).

Bodin et al., 2014 (Bodin et al., 2014) showed a trend for an increase in diabetes incidence using diabetic prone NOD/ShiLtJ, accompanied by increased insulitis (pancreas H&E staining score, 4500 µg/kg bw/d). Macrophage infiltration was reduced and Tregs were increased.

A trend for a dose-dependently increased diabetes induction was also observed by Cetkovic-Cvrlje et al., 2017 up to 1600 µg/kg bw/d of BPA exposure (Cetkovic-Cvrlje et al., 2017) (both studies without statistical significance for diabetes incidence).

Krementsov et al., 2013 (Krementsov et al., 2013) did not observe changes in the incidence, progression and severity of the two EAE models upon BPA exposure to 900 µg/kg bw/d of dams.

Nygaard et al., 2015 (Nygaard et al., 2015) showed that in the food allergy models, BPA did not alter the clinical anaphylaxis score or temperature change up to 22000 µg/kg bw/d. MMCP-1 levels, indicative of mast cell activation, were reduced, arguing against proinflammatory BPA effects in this model.

Overall, evidence for a worsening of inflammatory disease even at very high doses remains inconsistent among these studies.

Effect sizes and reasoning for BMD modeling

Experimental conditions are extremely variable for this endpoint. Cell isolation and handling, culture conditions and polyclonal (CD3/CD28, LPS, ConA) versus antigen-specific (OVA, lupin extract, peptides or *E.coli* lysates) stimulatory regimes as well as incubation times (1-5 days) differ. All these factors can effect cell survival, proliferation and cytokine producing capabilities, as represented by the wide range of IL-17 levels from 3 to >1100 pg/ml in stimulated spleen cells from control samples across studies (Malaisé et al., 2020b; Nygaard et al., 2015). Thus, a suitable BMR could not be established for this effect and the results were not put forward to dose-response analysis.

Tissue IL-17 levels

Assessment of the effect

BPA effects on tissue IL-17 levels were investigated by five studies and comprised different tissues (liver, heart and pancreas; one Tier 2, four Tier 3 studies). Read-outs comprised IL-17 mRNA (relative levels compared to a control gene) (Malaisé et al., 2017) and protein levels (pg per 1 mg of total protein for tissues and pg/mL for BALF).

Bauer et al., 2012 (Bauer et al., 2012) did not observe changes in BALF IL-17 levels in a mucosal sensitization model up to the highest BPA dose in both sexes (500 µg/kg bw/d, developmental exposure and analysis on ~PND63-91; results only mentioned in the text, not shown).

O'Brien et al, 2014 (O'Brien et al., 2014) observed significantly decreased Il-17 BALF levels with dose-dependent effects in an asthma model in which dams were developmentally exposed to BPA doses of 0.0075, 7.5 and 7500 µg/kg bw/d and analyzed on PND95.

Two other studies used developmental BPA exposure, but without asthma model.

Bansal et al., 2017 (Bansal et al., 2017) observed a trend for increased IL-17 and IL-6 levels in pancreatic lysates of male F1 offspring upon exposure to 10000 µg/kg bw/d BPA (until PND21, analysis PND112-117). Results were significant in F2 offsprings but here also the controls had only half the background cytokine levels.

Malaisé et al., 2017 (Malaisé et al., 2017) found a significant but reversible increase of IL-17 in liver tissue (i.e. decreased to baseline at the later time point, PND170 vs. PND45). White adipose tissue (WAT) IL-17 was increased at both time points.

Only one study investigated adult BPA exposure. Bruno et al., 2019 (Bruno et al., 2019) used 5 µg/kg bw/d and virus-induced myocarditis to observe increased IL-17 levels in heart tissue supernatant measured by ELISA.

Overall, data on a possible increase of IL-17 in tissues upon BPA exposure remain very limited. As for the other IL-17-related endpoints, effects seem reversible and depending on the initial BPA dose and the time since analysis, effects may wane. We thus consider a BPA-mediated increase on IL-17 in tissues as ALAN.

Link to adverse (apical) endpoints

Bauer et al, 2012 (Bauer et al., 2012) did not observe enhanced eosinophil, neutrophil or lymphocyte infiltration in BALF or lung tissue. In female (not male) mice, enhanced lung inflammation was determined by H&E stain of lung tissue sections at 50 and 500 µg/kg bw/d. Additional studies performed at lower doses (up to 5 µg/kg bw/d) did not show any effect. In the other sensitization model using i.p. OVA injection, lung eosinophilia was dampened and increased airway resistance was not observed up to 500 µg/kg bw/d.

O'Brien et al., 2014 (O'Brien et al., 2014) observed unchanged or diminished BALF leukocyte cell counts, BALF cytokines and pulmonary histopathology inflammatory scores up to the highest dose (of 7500 kµg/kg bw/d).

Bansal et al., 2017 (Bansal et al., 2017) did not observe consistent effects on insulin release (not dose-dependent, different in male vs. female). Pancreas histology showed significant CD3 and macrophage infiltration mainly in F1 offsprings for the higher BPA dose of 10000 µg/kg bw/d.

Malaisé et al., 2017 has already been discussed above under "spleen Th17 cell percentages" (Malaisé et al., 2017).

Adult BPA exposure to 0.5, 5 and 50 µg/kg bw/d in adult mice during viral-induced pericarditis increased immune cell infiltration in a dose-dependent manner, accompanied by CD4+ T cell infiltration (Bruno et al., 2019).

Effect sizes and reasoning for BMD modeling

The analysis of IL-17 levels in tissues has not been standardized. Values determined via mRNA and protein levels cannot be compared. Another possible read-out, the numbers of IL-17+ cells/mm^2 was not addressed in the evaluated studies. For protein IL-17 levels, observed

data were in the range of several orders of magnitude between experiments for control samples and different tissues. Thus, a BMR could not be established and results were not forwarded to dose-response analysis.

In vitro studies and mode of action for BPA

Malaisé et al. 2020 (Malaisé et al., 2020) investigated in vitro effects of BPA . The authors detected BPA-increased IL-17 secretion in murine splenocytes (CD3/CD28 for 4 d) after incubation for the last three days with 0.05 - 5 nM BPA. The result was reproduced for naïve CD4+ T cells in a priming assay and with siLP cells. The latter cells also responded to the aryl hydrocarbon receptor (AhR) agonist 6-formylindolo[3,2-b]carbazole (FICZ) while BPA-induced IL-17 secretion was blocked in the presence of an AhR antagonist. BPA-mediated IL-17 secretion was smaller or absent at higher BPA concentrations (500 nM, 50 µM), which may be due to toxic effects (interference with T cell function before actual cell toxicity can be observed) in this several day long cultures.

Interestingly, under the same experimental conditions (except CD3/CD28 beads instead of coated cross-linked antibodies were used), human PBMC did not respond to BPA exposure. This result is the only known addressing a possible transfer of murine BPA-induced IL-17-related effects to human cells and argues against a transferability of results. In this study, only relative signal increases are shown, absolute effect sizes remain unknown (Malaise et al., 2020a).

An influence on IL-17 immunity by BPA in vitro was also shown by Gao et al., 2020 (Gao et al., 2020a). After a 24 h incubation with PHA, murine PBMC were exposed to 80 and 160 µM BPA for 30 min und increased protein levels of RORγT and decreased levels of foxp3 were detected. Effects could be blocked with rapamycin, indicating an mTOR-dependent pathway.

Loffredo et al., 2020 (Loffredo and Berdnikovs, 2020) observed reduced growth of an epithelial cell line upon exposure to 10-100 nM BPA. He et al., 2016 (He et al., 2016) showed BPA-induced IL-1b, IL-6 and CCL3 mRNA expression in a murine macrophage-like cell line upon 2.2-22 µM BPA exposure for 12 h.

BPA-related impaired dendritic cell (DC) maturation (reduced upregulation of MHC II, CD80 or CCR7 upon 27 h LPS/poly(I:C) stimulation) was shown ex vivo using siLP and spleen-derived cells in mice developmentally BPA-exposed to 50 µg/kg bw/d (Malaisé et al., 2018). Petzold et al. 2014 (Petzold et al., 2014) generated BALB/cByJ bone marrow-derived DC (BMDC) and human monocyte-derived DC (MoDC) in the presence of 0.1-10 µM BPA and observed reduced IL-12 production in both species which indicates impaired DC function.

On a molecular level, the mode of action for BPA remains unknown. The effector molecules could be BPA or a metabolite. BPA binding to estrogen, glucocorticoid and androgen receptors (ER, GR and AR) has been shown but other proteins may be targeted, too (Li et al., 2015). Regarding Il-17-related immune effects, AhR and mTOR antagonists blocked the effect, suggesting an involvement of the respective receptor-mediated pathways (Gao et al., 2020a; Gao et al., 2022; Malaise et al., 2020a).

Background information on IL-17-related immunity

The pleiotropic cytokine IL-17A is the major member of the IL-17 family. It initiates the expression of antimicrobial peptides and pro-inflammatory cytokines and chemokines, e.g., IL-6, G-CSF or GM-CSF. IL-17 functions via the heterodimeric membrane receptor complex IL-

17RA/IL-17RC expressed on macrophages, endothelial cells, fibroblasts, epithelial cells and keratinocytes, among others. Due to structural and functional similarity, Il-17A and IL-17F are often considered together. Here, the focus is on IL-17A, for which IL-17 is used as abbreviation (as has been done in the evaluated murine studies) (Li et al., 2018c; Zwicky et al., 2020).

About 17 years ago, Th17 cells have been discovered as distinct T cell lineage and main producers of IL-17 (Harrington et al., 2005). Since then, Th17 cells have been at the epicenter of immunological research. Other IL-17 producers comprise CD8+ T cells, γδ T cells, invariant natural killer T (iNKT) cells and innate lymphoid cells (ILC) including natural killer (NK) cells and type 3 ILC. In mice, a commitment to the Th17 cell lineage in naïve T cells can be induced by TGFβ and IL-6 via STAT3 and the master transcription factor RORγT. IL-23, among other factors, seems essential for the development of a pathogenic Th17 cell phenotype (Schnell et al., 2023). A recent genetic study challenged the murine IL-23/Th17 paradigm for humans showing Il-23 as dispensable for Th17-mediated immunity but essential for IFNγ production in innate-like adaptive immune cells (Philippot et al., 2023). This finding challenges the assumption that successful therapeutics targeting the anti-IL23 pathway and IL-23R polymorphisms linked to disease are associated with Th17 cell-mediated inflammation in humans.

Th17 cells populate barrier organs in great numbers where they exert essential protection from infection and maintain tissue homeostasis and barrier integrity as well as inflammation. The developmental trajectories of homeostatic vs. pathogenic Th17 cells, their phenotypic plasticity, underlying regulatory networks, metabolic requirements, microbial interactions and relationships with other Th cell lineages as well as the overall role of IL-17 are still being explored. In the absence of gain of function mutations, genetic proof for the involvement of IL-17 in the pathogenesis of human autoimmmunity or allergy remains missing (Li et al., 2018c; Sallusto, 2016; Stockinger and Omenetti, 2017).

Increased IL-17 serum and tissue levels as well as percentages and absolute number of different Il-17 producing cell subsets that include Th17 cells have been reported in various mouse models and human diseases. Dysregulated cytokine networks present as hallmarks of inflammatory allergic and autoimmune diseases like asthma or multiple sclerosis (MS). However, a correlation with clinical symptoms does not mean causation and many clinical anti-IL-17 trials have fallen far short of expectations (Zwicky et al., 2020).

So far, human plaque psoriasis, psoriasis arthritis and ankylosing spondylitis have shown successful therapeutic blockade of the IL-17 pathway in patient subpopulations (Zwicky et al., 2020). These results had been predicted from animal models, but it was shown that in mice IL-17 from local ILC and γδ T cells (not Th17 cells) is decisive for disease (Pantelyushin et al., 2012). Generally, mouse models potentially inflate IL-17-related pathology due to the presence of additional IL-17-producing cell populations (Zwicky et al., 2020). The simultaneous presence of lesional and non-lesional skin in psoriasis patients while serum IL-17A are system-wide elevated illustrates the importance of the local tissue microenvironment (Fotiadou et al., 2015; Kolbinger et al., 2017; Teunissen et al., 1998). Difficult to target, tissue-resident IL-17-producing autoantigen-specific memory CD4+ and CD8+ T cells (Trm) likely constitute the fundamental drivers of human psoriasis. However, only two autoantigens have been identified to date (Arakawa et al., 2021; Clark, 2015; Lande et al., 2014).

In MS, one anti-IL-17 trial was inefficient, another promising even though associated with higher infection rates (Schnell et al., 2023). In murine EAE models, GM-CSF and T-bet positive T cells seem to represent a pathogenic (ex-) Th17 subtype linked to disease induction. As possible environmental triggers of pathogenic Th17, a high-salt diet (Kleinewietfeld et al., 2013;

Wu et al., 2013) or long-chain fatty acids (Haghikia et al., 2015) have been published. However, the high-salt diet theory has been disputed and contrary findings were published (Na et al., 2021). Environmental ligands of the AhR, expressed by Th17 cells and Treg subpopulations, may have protective effects (Gagliani et al., 2015). Similarly, Vitamin D with its manifold effects in the immune system and body may be beneficial (Chang et al., 2010). Overall, the role of T cell-derived IL-17 and T cells in the intestine is not completely understood in EAE as well as the extent to which results may be transferred to humans (Schnell et al., 2023).

In rheumatoid arthritis, phase II clinical trials targeting IL-17 and IL-17AR have been modestly effective. A central pathogenic role for IL-17 seems to only occur in a small subgroup of patients (Zwicky et al., 2020). In inflammatory bowel disease (IBD), Il-17 blockade worsened symptoms, illustrating the essential role for IL-17 in barrier integrity. In patients with asthma, clinical phase II anti-IL17RA trials lacked effects, similar to those in COPD (Li et al., 2018c; Zwicky et al., 2020). Therefore, the role of IL-17 in the pathophysiological pathway of asthma is not conclusively defined (Hofmann et al., 2021).

Current caveats of Th17 research include the unclear origins of IL-17A in cytokine measurements and difficulties to fate-map Th17 cells in vivo (Stockinger and Omenetti, 2017). Further research on the main drivers of pathogenic Th17 cell development beyond the role of IL-23 is needed.

3.1.3.3 Specific IgE levels

Assessment of the effect

Eleven murine in vivo studies with results on specific IgE were evaluated . Four of them are part of the EFSA, 2023 evaluation (Nygaard et al., 2015; O'Brien et al., 2014; Petzold et al., 2014; Tajiki-Nishino et al., 2018), one study was part of the EFSA, 2015 evaluation (Bauer et al., 2012) and six have not been evaluated by EFSA (He et al., 2016; Loffredo and Berdnikovs, 2020; Midoro-Horiuti et al., 2010; Misme-Aucouturier et al., 2022; Wang et al., 2020b; Yanagisawa et al., 2019).

Specific IgE form upon allergy induction. Studies used mainly OVA immunization in combination with asthma models, while two studies also assessed IgE in the context of food allergy (Misme-Aucouturier et al., 2022; Nygaard et al., 2015) and one study, as a control to airway allergy, contact hypersensitivity (Tajiki-Nishino et al., 2018). Some studies investigated different allergy models, e.g. for asthma and food allergy (Nygaard et al., 2015).

Four studies did not use adjuvant (suboptimal sensitization) but repeated allergen exposures in order to better detect BPA-induced pro-inflammatory effect, three via airway (i.t. or i.n.) sensitization (He et al., 2016; Loffredo and Berdnikovs, 2020; Yanagisawa et al., 2019), one via i.p sensitization before airway challenge (Nygaard et al., 2015). The majority of studies, used i.p. sensitization with varying OVA doses and alum as adjuvant (Midoro-Horiuti et al., 2010; O'Brien et al., 2014; Petzold et al., 2014; Wang et al., 2020b). For oral sensitization, wheat gliadins and alum (Misme-Aucouturier et al., 2022) or lupin extract and cholera toxin (Nygaard et al., 2015) were combined. Bauer et al., 2012 used i.t. OVA with LPS as adjuvant (Bauer et al., 2012). Tajiki-Nishinio et al., 2018 performed dermal sensitization with the chemical sensitizer toluene-2, 4-diisocyanate (TDI) with acetone as irritant in combination with dermal or airway elicitation for the contact hypersensitivity or asthma model, respectively.

The age of the mice at the time point of sensitization was not always exactly specified (Bauer et al., 2012; Loffredo and Berdnikovs, 2020). Some studies started sensitization in very young mice, e.g. on PND4 (Midoro-Horiuti et al., 2010; Nygaard et al., 2015) which, in case of Nygaard, 2015, may lead to tolerance induction (absence of adjuvant). The other studies

sensitized adult mice between PND 21 – 84. The numbers, spacing and doses of antigen exposures for sensitization and elicitation varied and optionally included prior tolerance induction or a separate boost regime. Further, mouse strains and BPA exposure regimes (doses and times e.g. developmental or adult phase exposure, exposure during or outside of sensitization and/or elicitation) varied, challenging the integration of study results.

In the absence of allergen exposure, total IgE levels are very low which is why total IgE levels upon specific allergen sensitization may serve as substitute for specific IgE levels as reported in the lupin food allergy model (Nygaard et al., 2015) and dermal sensitization model (Tajiki-Nishino et al., 2018).

Bauer et al., 2012 (Bauer et al., 2012) assessed circulating levels of anti-OVA IgE in a mucosal sensitization model and did not identify changes up to the highest dose tested (500 µg/kg bw/d, developmental exposure, allergy induction at PND63 or later). Regarding apical adverse effects, one result observed was an enhanced lung inflammation for offspring female mice at 50 and 500 µg/kg bw/d determined by H&E stain of lung tissue sections, which, however, was not confirmed by enhanced eosinophil, neutrophil or lymphocyte infiltration among BAL fluid or lung. Additional studies at lower doses (up to 5 µg/kg bw/d) did not show any effect. In a i.p. sensitization model, no increased airway resistance was observed up to 500 µg/kg bw/d and circulating anti-OVA IgE significantly decreased at all doses (up to 500 µg/kg bw/d). In summary, BPA-related effects in allergic lung inflammation may start at 50 µg/kg bw/d according to this study but indications for functional consequences are missing.

Nygaard et al., 2015 (Nygaard et al., 2015) detected a non-significant trend of increased anti-OVA IgE in a model of OVA-induced airway allergy inflammation. Dams were exposed to 43700 µg/kg bw/d BPA, which resulted in a modest effect in augmenting airway allergy in offspring. No change in IgE levels were observed in the food allergy models.

Midoro-Horiuti et al., 2010 (Midoro-Horiuti et al., 2010) sought to determine whether exposure of dams to a BPA dose of 800 µg/kg bw/day alters allergic pulmonary inflammation in offspring. The authors observed increased lung hyperreactivity and increased anti-OVA IgE antibody levels in sera. No changes were observed in anti-OVA IgG levels.

O'Brien et al., 2014 (O'Brien et al., 2014) observed no or diminished lung inflammation in female and male offspring, respectively. Animals were developmentally exposed via their dams to 0.0075, 7.5 and 7500 µg/kg bw/d BPA and immunized late at PND84. Anti-OVA IgE antibodies in sera significantly increased upon BPA exposure following a dose-dependent tendency.

Wang et al., 2020 and Yanagisawa et al., 2019 (Wang et al., 2020b; Yanagisawa et al., 2019) determined the effects of BPA exposure on the development of allergic asthma in adult mice. Wang et al., 2020 (Wang et al., 2020b) applied an OVA-induced model of lung inflammation in adult female mice. BPA at 25, 50 and 100 µg/kg bw/d augmented pathological changes and decreased lung function. The authors reported a significant increase in serum levels of anti-OVA IgE, which followed a dose-dependent response. Yanagisawa et al., 2019 (Yanagisawa et al., 2019) utilized OVA-induced allergic asthma model in adult male mice exposed to 0.09, 0.9 or 9 µg/kg bw/d BPA. The authors observed enhanced pulmonary inflammation and increased levels of serum anti-OVA IgE and anti-OVA IgG1 at all doses compared to vehicle group. Only the two higher doses induced significant increase of specific Ig levels compared to the OVA treated group.

He et al., 2016 (He et al., 2016) investigated the effects of BPA on allergic lung inflammation in adult male mice at a dose of 20000 µg/kg bw/d. Authors observed increased goblet cell proliferation accompanied cell infiltration in the airways, but only a trend for increased serum

level of anti-OVA IgE. Level of serum anti-OVA IgG1 increased significantly in OVA sensitized mice exposed to BPA.

Loffredo et al., 2016 (Loffredo and Berdnikovs, 2020) observed BPA-induced sensitization to OVA in a tolerogenic model in absence of adjuvant administration. Serum levels of anti-OVA IgE increased and reached significance upon exposure of adult mice to a BPA dose of 5000 µg/kg bw/d.

Petzold et al., 2014 (Petzold et al., 2014) sought to investigate the effect of BPA exposure at different time points on the development of asthma disease induced in adulthood. Offsprings or adult mice were exposed using four different exposure regimes to 0.45 µg/kg bw/d BPA. Changes in anti-OVA IgE were not observed upon developmental exposure. In the regime of lifelong exposure (starting from birth) airway hyperreactivity and anti-OVA IgE levels in sera increased. Limited exposure during the sensitization period reduced allergic asthma and sera level of anti-IgE antibodies.

Overall, an increase in allergen-specific IgE levels was mainly detected if developmental exposure to higher BPA doses occurred or if BPA exposure was present during adulthood when there was a time overlap or proximity to the immune challenge. In the latter case, an increase in allergen-specific IgE production and the development of lung inflammation was more robustly and reproducibly, even at lower doses. BPA-induced increase on allergen-specific IgE levels is therefore considered as VERY LIKELY.

Link to adverse (apical) endpoints

Several studies observed an increased lung inflammatory phenotype as determined by immunohistochemistry or reduced lung function, e.g. methacholine challenge, concomitant with increased allergen-specific IgE serum levels (He et al., 2016; Midoro-Horiuti et al., 2010; Petzold et al., 2014; Wang et al., 2020b; Yanagisawa et al., 2019). These studies applied a regime of adult exposure to BPA which ended up to 48 h before the parameter measurements.

No increase in allergic lung inflammation was seen for the O'Brien et al., 2014 study (O'Brien et al., 2014), which had a comparably much longer lag phase between developmental exposure and allergy induction. This was similar to Bauer et al., 2014 (Bauer et al., 2012), which also found no change in lung function for the peritoneal sensitization model arguing for the reversibility of BPA-induced immune effects once exposure stops also in combination with immune challenge.

Effect sizes and reasoning for BMD modeling

Serum total and allergen-specific IgE levels can be easily quantified by commercial kits. Some studies, however, only report relative values (raw absorbance values or relative increases compared to the buffer), which are not suitable for dose-response analysis (Bauer et al., 2012; Misme-Aucouturier et al., 2022). From the studies that quantified IgE (ng/mL), the sensitization protocol critically determines the resulting allergen-specific IgE levels, leading to large variations in background IgE amount. Thus, the calculation with a simple percentage increase in a BMR response should not be used. Further, the link between the intermediate endpoint allergen-specific IgE serum levels in mice and an adverse apical outcome in both species remains poorly understood, as discussed below. As a consequence, a BMR could not be defined, the assessment of a suitable range was outside the scope of this opinion. A dose-

response analysis was not performed. For all the intermediate immunotoxicity endpoints (IL-17-related, specific IgE levels, BALF eosinophils, neutrophil infiltration), dedicated investigations are required to determine quantitative changes that would translate into adverse apical outcome, as discussed above in the section on IL-17-related immunity.

Background information on specific IgE levels

Since the discovery of IgE in the 1960s, the diagnosis and management of allergic disease has been greatly impacted by this parameter. IgE is central to the immediate allergic response. Antibody isotype class switching to IgE occurs in the draining lymph nodes of bronchial tissue and the nasal and intestinal mucosae. Upon antigen/allergen uptake, DC present the processed antigen to cognate naïve T cells that, in the presence of IL-4 and IL-13, acquire a Th2 phenotype. As Th2 cells engage with cognate B cells (which also have antigen-presenting capacity) in the germinal centers of the lymph nodes, B cells undergo class-switch recombination. Allergen specific IgE amplify signals by engaging FcεRI receptors on mast cells and basophils or CD23 (FcεRII) receptors on B cells.

Careful consideration is required to evaluate, whether total and/or allergen-specific IgE levels are clinically relevant. In humans, total serum IgE levels are largely age dependent, low in cord serum (<4.8 ng/mL), then increasing up to 15 years followed by a decline from the 2nd through the 8th decade of life. In the presence of a high enough total IgE antibody amount (i.e. >20 kU/L, > 48 ng/ml), a negative allergen-specific IgE response can exclude a risk of allergic sensitization and allergy towards the tested allergen. A positive allergen-specific IgE response represents a state of allergic sensitization and a risk for allergic disease. However, in the absence of a history of allergic symptoms, it is clinically irrelevant (EACCI Molecular Allergology User's Guide 2.0, 2022). Factors such as allergen-specific IgE antibody concentration, antibody affinities and the ratio of allergen-specific to total IgE determine the strength of the effector molecule release and ultimately the clinical symptoms. Thus, it remains difficult to establish a correlation beyond sensitization between allergen-specific IgE antibody levels in serum and allergic clinical symptoms, which is why provocation studies remain the standard to determine individual elicitation thresholds (Shamji et al., 2021).

Maternal immunoglobulins are also transferred to the offspring during gestation and lactation. Maternal specific IgG may protect from allergic sensitization through a pathway that includes Tregs (Lupinek et al., 2019; Mosconi et al., 2010). These factors are not taken into account in the murine experimental studies. Furthermore, the available data on BPA-related effects on allergen-specific IgE responses were obtained in only one species, mice, applying a model allergen (OVA) to achieve an artificial allergic asthma-like disease. Mice do not naturally/spontaneously develop allergies or allergic asthma (Eckl-Dorna and Niederberger, 2013; Zosky and Sly, 2007). Therefore, protocols with high doses of allergens are used for sensitization and challenge of mice and the phenotype underlying the allergic/asthmatic outcome may vary greatly in different mouse strains (Shinagawa and Kojima, 2003). None of the studies applied a clinical relevant allergen and the doses used do not correspond to the allergen doses sensitized individuals are exposed to and which boost an allergen-specific IgE response in these patients. The Th2 type asthmatic response developed in mouse model, characterized by high allergen-specific IgE levels and cytokines such IL-4, IL-5 and IL-13, may be primed by the use of the adjuvant (often alum), lack chronicity and repeated antigen challenges lead to allergen tolerance and, ultimately, to immune suppression(Zosky and Sly, 2007).

3.1.3.1 BALF eosinophil infiltration

Assessment of the effect

Eleven articles that describe murine in vivo studies with results on BALF eosinophil infiltration were evaluated . Four studies are part of the EFSA, 2023 evaluation (Nygaard et al., 2015; O'Brien et al., 2014; Petzold et al., 2014; Tajiki-Nishino et al., 2018), two studies were part of the EFSA, 2015 evaluation (Bauer et al., 2012; Nakajima et al., 2012), five had not been considered by EFSA opinions yet.

Bauer et al., 2012 (Bauer et al., 2012) assessed eosinophil cell counts in offspring BALF upon mucosal sensitization and did not identify changes up to the highest dose tested for dam exposure (500 µg/kg bw/d). Regarding apical adverse effects, one result observed by Bauer, 2012 was an enhanced lung inflammation for female mice at 50 and 500 µg/kg bw/d determined by H&E stain of lung tissue sections, which, however, was not confirmed by enhanced eosinophil, neutrophil or lymphocyte infiltration among BALF or lung. Additional studies at lower doses (up to 5 µg/kg bw/d) did not show any effect. In an i.p. sensitization model, increased airway resistance was not observed up to 500 µg/kg bw/d and BALF eosinophils did not accumulate at any dose (up to 500 µg/kg bw/d). In summary, BPA-related effects in allergic lung inflammation may start at 50 µg/kg bw/d according to this study but indications for functional consequences are missing.

Nygaard et al, 2015 (Nygaard et al., 2015) detected a significant increase in BALF eosinophil counts in a model of OVA-induced airway allergy in offspring of BPA exposed animals. Dams were exposed to a BPA dose of 43700 µg/kg bw/d.

Midoro-Horiuti et al., 2010 (Midoro-Horiuti et al., 2010) sought to determine whether BPA exposure of dams altered allergic pulmonary inflammation in offspring. The authors observed increased lung hyperreactivity and increased BALF eosinophil counts upon exposure to a dose of 800 µg/kg bw/d.

Nakajima et al., 2012 (Nakajima et al., 2012) reported that BPA exposure of dams to a dose of 800 µg/kg bw/d enhanced asthma propensity in pups. Eosinophil counts in BALF increased significantly only upon pre-natal or pre-natal and breast-feeding BPA exposure. This study was part of the EFSA, 2015 assessment and counted as hint that a developing immune system is more sensitive for BPA-induced effects.

O'Brien et al., 2014 (O'Brien et al., 2014) reported absent or diminished lung inflammation in female and male offspring, respectively, of dams exposed to BPA doses of 0.0075, 7.5 and 7500 µg/kg bw/d. BALF eosinophil counts in offspring did not change or decreased upon BPA exposure of dams.

Tajiki-Nishino et al., 2018 (Tajiki-Nishino et al., 2018) investigated the exacerbation of allergic dermal and airway inflammation in TDI-induced models upon adult exposure to BPA at the doses of 60 and 200 µg/kg bw/d. Dermal inflammation (ear swelling) diminished significantly upon BPA exposure, lung inflammation augmented. Influx of eosinophils in BALF increased in a dose-dependent manner.

Wang et al, 2020 and Yanagisawa et al, 2019 (Wang et al., 2020b; Yanagisawa et al., 2019) sought to determine the effects of BPA exposure on the development of allergic asthma in adult mice. Wang et al. applied an OVA-induced model of lung inflammation in adult female mice. Exposure to BPA 25, 50 and 100 µg/kg bw/d augmented pathological changes and decreased lung function. The authors reported a significant increase in serum BALF eosinophil counts, which followed a dose-dependent response. Yanagisawa et al. utilized OVA-induced

allergic asthma model in male mice exposed to 0.09, 0.9 or 9 µg/kg bw/d BPA. The authors observed enhanced pulmonary inflammation and increased counts of eosinophils in BALF at all doses. Both studies reported an increase of Th2 cytokine production by BALF and by mesenteric lymph node cells, respectively.

He et al., 2016 (He et al., 2016)h investigated the effects of BPA on allergic lung inflammation in adult male mice exposed to a BPA dose of 20000 µg/kg bw/d. Authors observed increased eosinophil counts in BALF and goblet cell proliferation in the airway tissue.

Loffredo et al., 2016 (Loffredo and Berdnikovs, 2020) observed that BPA exposure enabled OVA sensitization in absence of adjuvants administration in an otherwise tolerogenic model. Counts of BALF eosinophils significantly increased in adult female mice exposed to a dose of 5000 µg/kg bw/d of BPA.

Petzold et al., 2014 (Petzold et al., 2014) sought to investigate the effects of BPA exposure at different time points on the development of asthma disease. Dams or female and male adult mice were exposed during the developmental or the adult phases, respectively, to 0.45 µg/kg bw/d BPA. Developmental exposure to BPA did not change asthma phenotype and counts of eosinophils in BALF in offspring. Only in the regime of lifelong exposure (starting from birth) airway hyperreactivity and BALF eosinophil counts increased. Limited BPA exposure to the sensitization period reduced allergic asthma and BALF eosinophil counts.

Overall, the effect of BPA-enhanced BALF eosinophil infiltration is considered very likely.

Link to adverse (apical) endpoints

The same studies as for specific IgE levels also investigated BALF eosinophil infiltration and observed an increased lung inflammatory phenotype as determined by immunohistochemistry or reduced lung function, e.g. upon metacholin challenge (He et al., 2016; Midoro-Horiuti et al., 2010; Petzold et al., 2014; Wang et al., 2020b; Yanagisawa et al., 2019). These studies applied a regime of adult exposure to BPA which ended up to 48 h before the parameter measurements. In addition, Nakajima et al., 2012 also observed reduced lung function (Nakajima et al., 2012).

Effect sizes and reasoning for BMD modeling

The cell composition of BALF, including eosinophil counts, was mainly determined by cytology, i.e. BALF cells were stained and counted on slides. One study used FACS analysis but with unclear gating strategy (no dose-response analysis possible) (Tajiki-Nishino et al., 2018).

Similar to the reasoning for specific IgE, the number of eosinophils infiltrating BALF varies with the sensitization and elicitation protocol used. Thus, percent changes for a BMR have to be set with caution if total values for background differ. We here set a BMR of 100 % to analyze the dose-response relationship for this endpoint, which should not be considered a final value for effect size consideration (as written above, detailed investigation required). Regarding suitable studies, only three met the specified criteria (e.g. a sufficient sample size and at least two doses) for this endpoint (Bauer et al., 2012; Nygaard et al., 2015; Wang et al., 2020b).

Background information on BALF eosinophil infiltration

Asthma is a complex, chronic and heterogeneous disease associated with genetic factors and influenced by lifestyle as well as environmental cues. Asthma affects more than 350 million people worldwide and 30 million in Europe. In industrialized countries, asthma prevalence has greatly increased over the past 60 years. Exposure to environmental pollutants may have probably played a role. Genetic factors that predispose to asthma are well established, such as parental allergy and susceptible gene loci identified by genome-wide association studies.

Allergic eosinophilic asthma is the most common and most characterized endotype (phenotype) of asthma (Agache and Akdis, 2019; Lötvall et al., 2011; Tan et al., 2019). Repeated exposure to the allergen induce a type IV/b hypersensitivity reaction with infiltration of Th2 cells and eosinophils. Eosinophils migration/trafficking to the airways is mediated by type 2 cytokines (e.g. IL-4, IL-5, IL-13). Once reaching the lung, eosinophils participate in allergic inflammation and airway injury, repair and remodeling, through the release of granule proteins. Eosinophil activation occurs in the late stage of the allergic reaction and plays a central role in the pathogenesis of asthma (Akdis et al., 2020). Airway accumulation of eosinophils may be associated with persistent airflow obstruction (Dunican et al., 2018).

Global Initiative for Asthma (GINA) guidelines recommend the use of blood eosinophil (EOS) counts to identify patients who are most at risk of asthma exacerbations. Elevation of eosinophils in peripheral blood (>150 cells/µL) and sputum (>2%) suggests a type 2 inflammation phenotype and marks an increased risk for asthma exacerbations, although the underlying mechanism has not been fully established (Wenzel, 2012). Studies of mild to severe asthma suggest that around 50% of asthma cases may be associated with high numbers of eosinophils (Wenzel et al., 1999; Woodruff et al., 2009). Despite 75% of individuals have positive allergen skin tests, clinical allergic reactions are absent or small. Th2 response involved in allergic asthma may differ from the early-onset allergic phenotype (Wenzel, 2012).

3.1.3.2 Neutrophil infiltration into the epididymis and BALF in allergic diseases

Regarding the epididymis, Ogo et al., 2018 (Ogo et al., 2018) (Tier 3) showed increased neutrophil but not macrophage infiltration in Wistar rats exposed to BPA during the growth phase (PND36-66) at a BPA dose of 200 µg/kg bw/d. The lower dose at 20 µg/kg bw/d did not show an effect. Neutrophil numbers were determined by myeloperoxidase (MPO) activity, macrophage numbers by N-acetyl-b-D-glucosaminidase (NAG) activity. Tissue IL-6, determined by immunohistochemistry, increased rather strongly at the lower dose of 20 µg/kg bw/d and did not show dose-dependent effects.

BALF neutrophil infiltration was further analyzed in studies using OVA-induced asthma models that have been discussed above. O'Brien et al., 2014 (O'Brien et al., 2014) did not observe enhanced neutrophil infiltration, similar to Bauer et al., 2012 (Bauer et al., 2012) and Petzold et al., 2014 (Petzold et al., 2014). In the Yanagisawa et al., 2019 study, neutrophil infiltration showed no consistent or dose-dependent effect.

Two studies analyzed only a single BPA dose and observed neutrophil significant BPA-induced increased neutrophil infiltration (He et al., 2016; Loffredo and Berdnikovs, 2020). Wang et al., 2020 observed a dose dependent increase in neutrophil infiltration (Wang et al., 2020b).

Several long-term studies (not evaluated in detail here) that included very high exposure doses in mice and rats did not report consistent changes in general immune inflammatory endpoints

in the unchallenged immune system (Delclos et al., 2014; Li et al., 2018a; Li et al., 2018b; Tyl et al., 2008b).

Given the inconsistent evidence, an overall likelihood level of LIKELY for the endpoints neutrophil infiltration into the epididymis and into BALF in allergic disease models has been assigned.

Link to adverse (apical) endpoints

Immune cell infiltration into target tissue may be already considered an adverse apical endpoint. However, functional defects shown by reduced lung function, e.g. upon metacholine challenge would support conclusions on adversity.

Ogo et al., 2018 did not report further functional endpoints (Ogo et al., 2018). O'Brien et al., 2014 reported a decreased severity grade for lung inflammation for H&E-stained tissue section (O'Brien et al., 2014). Wang et al., 2020 reported an increased lung inflammatory score for stained tissue sections and decreased lung function upon methacholine challenge (Wang et al., 2020b). Results for the lower dose exposures performed by Yanagisawa et al., 2019 showed similar trends but mostly without statistical significance (Yanagisawa et al., 2019).

Effect sizes and reasoning for BMD modeling

BPA effects on epididymis neutrophil infiltration from Ogo et al., (Ogo et al., 2018) were submitted to dose-response analysis since modeling has also been performed by EFSA (EFSA, 2023) to evaluate whether the effect would be covered by the BfR-derived TDI. Regarding allergic lung inflammation, neutrophil infiltration can be considered in a similar manner as eosinophil infiltration. Results of the Wang et al., 2020 study and Bauer et al., 2012 fulfilled criteria for dose-response analysis and were forwarded for dose-response analysis (Bauer et al., 2012; Wang et al., 2020b).

Conclusion on BPA immunotoxicity

The lack of standardized guidelines for immunotoxicity endpoints still manifests in relative few, low tier studies, also with regard to the critical endpoints identified by EFSA (EFSA, 2023). Although intermediate endpoints like percentage of Th17 cells were commonly addressed across several studies, results on associated adverse apical outcomes were less standardized and individual results may also suffer from publication bias (DeVito and Goldacre, 2019). Nevertheless, the overall WoE showed consistent immunotoxic effects of BPA in male and female mice (male rats for Ogo, et al., 2018) for the same endpoints that were identified by EFSA (EFSA, 2023).

- Increased IL-17 serum levels (likely)
- Increased Th17 cell percentages in spleen (very likely)
- Increased IL-17 production by stimulated spleen cells (likely)
- Increased tissue IL-17 levels (ALAN)
- Increased specific IgE in allergic lung inflammation (very likely)
- Increased BALF eosinophils in allergic lung inflammation (very likely)
- Increased neutrophil-mediated epididymis and BALF neutrophil infiltration in allergic lung inflammation (likely)

Effects are considered reversible and adaptive with smaller effects upon adult exposure. Sensitization and elicitation in the presence of BPA increased inflammatory responses. In the unchallenged situation very large BPA doses can be tolerated without changes in generally assessed immune parameters (Delclos et al., 2014; Li et al., 2018a; Li et al., 2018b; Tyl et al., 2008b).

For the critical immunotoxicity endpoints, only one species has been tested (mice, except one study in rats for epididymis neutrophil infiltration). Thus, the transfer of results to other species remains to be determined, especially in light of one in vitro study using human cells in parallel to murine cells that confirmed IL-17-related effects in murine but not for human cells. In addition, the transferability of the investigated animal models to humans remains unclear and, again, no second species was assessed for the effects occurring under immune challenge. For the human situation, EFSA (2023) assessed the qualitiy of available epidemiological studies as too low to base a (quantitative) risk assessment on them. The BfR did not reevaluate these studies, and it is emphasised that high quality studies (i.e. with repeated 24h urine samples and properly controlled for confounders like socio-economic status) would be required to further substantiate human risk assessment.

Whenever suitable, the dose-response relationships for the individual endpoints were evaluated to investigate whether effects would be covered by the BfR-derived TDI. Since standard do not exist exists, some reasoning for a calculation with BMR of 100% for IL-17 serum levels, BALF eosinophils in allergic lung inflammation and neutrophil infiltration is provided but further investigations are needed. In total, three (Dong et al., 2020; Gao et al., 2020a; Luo et al., 2016), two (Nygaard et al., 2015; Wang et al., 2020b) and two (Ogo et al., 2018; Wang et al., 2020b) studies were forwarded for dose-response analysis for the respective endpoints.

3.1.4 Reproductive Toxicity

3.1.4.1 Methodology

In their opinion of 2015, EFSA concluded that BPA causes toxic effects to reproduction in experimental animal studies at high doses (above a HED of 3.6 mg/kg bw/d). EFSA also recognised that there was a high “variability in the incidence and magnitude of adverse effects, if any, between the studies assessed” in particular when investigating effects at lower doses. Hence, the likelihood for reproductive effects after pre- and postnatal exposure below a HED of 3.6 mg/kg bw/d was rated as ALAN by EFSA. Since 2013, numerous studies reporting on effects of BPA exposure on reproductive toxicity have emerged. However, the variability of results and dose-response relationships is still considerable.

In the present evaluation, focused was given on parameters related to fertility and sexual function in males (sperm count and motility; testis histopathology) and females (ovarian histopathology; uterus hyperplasia).

The initial literature search covered the period from 2013-01-01 to 2022-10-25 and revealed a total of 1905 studies. After selecting studies that addressed the effects of BPA on reproductive parameters related to fertility and sexual function, only studies that met the following criteria were considered:

- original data
- mammalian *in vivo* studies
- oral exposure

This approach yielded 529 studies. Of these, only English-language studies using intact animals exposed to at least three oral doses of BPA plus control group were considered. This yielded 101 studies which were further categorised into the three Tiers as described above and used for dose-response analysis if appropriate (only Tier 1 and 2). In addition, the results from key studies used by EFSA (2015) were included in the dose-response analysis if data on the endpoints considered were available.

Of all reproductive toxicity studies obtained by this literature search, 19 were rated as Tier 1, 23 as Tier 2 and the remaining 59 studies as Tier 3.

The evaluation focused on endpoints identified by EFSA as likely in the reproductive toxicity cluster such as sperm motility, ovary and uterus histology, and testis and epididymis histology. Nonetheless, the following organs/tissues/parameters were evaluated: testes, epididymis, prostate, sperm parameters, time to balano-preputial separation, ano-genital distance, ovary, uterus, vagina, oestrous cycle, time to vaginal opening, implantations. In case effects were judged as likely/relevant, these were considered for TDI determination (e.g. (epididymal) sperm count).

3.1.4.2 Male reproduction

Sperm count

For sperm counts after BPA exposure in adult animals, three studies were assigned to Tier 2 and 10 to Tier 3, but none to Tier 1. One Tier 2 study was conducted in rabbits (Karabulut and Gulay, 2020), while the other two studies used rats (Liu et al., 2013a; Srivastava and Gupta, 2018). In all three studies, decreased sperm counts measured in ejaculate or epididymis were reported, respectively. The rabbits were exposed for 9 weeks, the rats in the Liu study for 60 days and the rats in the Srivastava study for 90 days. Effects on sperm counts were significant at 10 mg/kg bw/d (Karabulut and Gulay, 2018), 0.2 mg/kg bw/d (Liu et al., 2013) and 0.5 mg/kg bw/d (Srivatava und Gupta, 2018), respectively. One mouse study with adult BPA exposure (Alabi et al., 2021) was initially rated Tier 2 following our criteria, however data on sperm counts were presented without SD or SEM. Thus, this study was downgraded to Tier 3 for this endpoint. In addition, most Tier 3 studies using doses in the mg/kg/d range in adult animals showed statistically significant decreases in sperm counts. Although those were not taken forward to the dose-response analysis, the Tier 3 study results support an effect of adult BPA exposure on sperm count.

One study exposing juvenile rats for four weeks (weighing 140-160 g at the beginning of the experiment) also was rated as Tier 2 (Wang et al., 2014a). In this study, sperm concentration was affected at doses of 100 and 200 mg/kg bw/d.

In two Tier 1 studies (Camacho et al., 2019; Delclos et al., 2014), rats were exposed prenatally until adulthood (GD6 – PND 365 or GD6 - PND 90, respectively) and were included into the dose-response analysis. In these studies, an effect of BPA treatment on sperm count was not observed.

Sperm were counted in six Tier 2 studies with pre- or perinatal exposure in rats and mice (Camacho et al., 2019; Hass et al., 2016; Quan et al., 2017; Rahman et al., 2017; Rahman et al., 2021; Ullah et al., 2019b). Both studies by Hass and Quan did not show dose-response relationship (only the lowest dose or the two lowest doses revealed a significant effect, respectively). In both studies by Rahman, the data shown refer to three replicate experiments with three animals per replicate for sperm counts, so these studies were not used for the dose-

response analysis due to the unclear statistics. In the study by Ullah with exposure from GD 1 until PND 1, an effect on caudal sperm count was not shown. Likewise, in the STOP-dose arm of the CLARITY study (Camacho et al., 2019), with an BPA exposure from GD 6 until PND 21, statistically significant effects on sperm counts were not identified.

From the studies published before 2013 and considered in the EFSA 2015 opinion, a two-generation mouse study and a three-generation rat study were rated Tier 2 (Tyl et al., 2008b; Tyl et al., 2002). Effects of BPA exposure on sperm counts were observed at the highest dose tested in the F1 generation in the mouse study (450 mg/kg bw/d) or the F0 generation in the rat study (600 mg/kg bw/d).

In summary, effects on sperm count were reported in several Tier 2 and Tier 3 studies with exposure in adult animals of different species, however effective doses varied by several orders of magnitude. In contrast, Tier 1 studies with exposure from gestation to adulthood even high doses did not show statistically significant effects on sperm counts and studies with perinatal exposure only showed either non-monotonic or no responses at all. In its current opinion, EFSA (EFSA, 2023) concluded that effects on sperm counts were not likely in any exposure scenario. Despite the partially discrepant results, BfR considers effects of adult BPA exposure on sperm counts to be too relevant to be discarded from TDI determination.

Sperm motility

Three Tier 2 studies were identified that measured effects on sperm motility following BPA exposure in adulthood or puberty, one in rabbits (Karabulut and Gulay, 2020) and two in rats (Ullah et al., 2019a; Wang et al., 2014a). The rabbit study reported decreased proportions of motile sperms at the lowest dose of 10 mg/kg bw/d (Karabulut and Gulay, 2020) and the pubertal mouse study at 200 mg/kg bw/d (Wang et al., 2014a), respectively. In the adult mouse study, only a marginal decrease in motile sperm number was observed at the highest dose (50 mg/kg bw/d) (Ullah et al., 2019a). The Tier 1 rated studies (Delclos et al., 2014) and the continuous arm of the CLARITY study (Camacho et al., 2019) with prenatal and adult exposure (GD6 – PND 365 or GD6 - PND 90) to a broad dose range up to 300 and 25 mg/kg bw/d, respectively did not report any effects on sperm motility. For dose-response analysis modelling data from the three Tier 2 studies mentioned above as well as the Tier 1 studies by Delclos et al. and Camacho et al. were used.

The key study on sperm motility identified by EFSA 2023 (Wang et al., 2016) was rated as Tier 3 under our selection protocol due to unclear background exposure from both cages and water bottles as well as undefined feed. In that study, statistically significant effects on sperm motility were observed at all doses tested (10 - 250 µg/kg bw/d) after 8 weeks of exposure of adult mice.

Two studies with prenatal or perinatal exposure of rats were used for dose-response analysis (Camacho et al., 2019; Ullah et al., 2019b). In the stop arm of the CLARITY study, rats were exposed from GD 6 - PND 21, in the Ullah study from GD1 - PND1. A third study with exposure from GD 14 - GD 21 showed a decrease of motile sperm density that was not dose dependent and only significant at the two lowest doses (Quan et al., 2017). Again, in the two studies by Rahman for this endpoint data were based on three animals only and not used for quantitative assessment (Rahman et al., 2017; Rahman et al., 2021). Neither the Camacho study (CLARITY) nor the Ullah study found significant changes. This was also true for the Tier 2 rated Tyl studies (Tyl et al., 2008b; Tyl et al., 2002) which were evaluated in the EFSA 2015 opinion.

In summary, BfR judges BPA effects on sperm motility as unlikely at doses below 1 mg/kg bw/d range. Nevertheless the studies discussed above were taken forward to dose-response analysis and TDI derivation.

Testis histology

In total, 15 studies classified as Tier 1 or 2 investigated some aspect of testis histology. In this evaluation, only studies with quantitative determinations were considered for quantitative hazard assessment. Immunohistological studies investigating the expression of specific proteins were also not included in TDI determination.

In the Clarity study (Camacho et al., 2019), rat testes were evaluated histopathologically after perinatal exposure (GD 6 – PND 21). The only significant effect on testis histology (polyarteritis) was observed in animals of the second highest dose group (2500 µg/kg/d) of the stop dose arm. In a two-generation reproductive toxicity study in mice, BPA exposure up to 600 mg/kg bw/d caused minimal hypoplasia of seminiferous tubules (Tyl et al., 2008a). In the three-generation rat study of the same authors, alterations in incidences of seminiferous tubule atrophy or degeneration were not observed (Tyl et al., 2002). In the CLARITY-associated study by (Dere et al., 2018), effects on the number of apoptotic cells identified by TUNEL staining were not reported up to doses of 25 mg/kg bw/d. In contrast, three other studies showed an increase of TUNEL stained cells in testis sections: two with prenatal exposure (Karmakar et al., 2020; Quan et al., 2017) and one with pubertal exposure (Wang et al., 2014a). Effects were observed at doses of 50 mg/kg bw/d, 1 mg/kg bw/d and 100 mg/kg bw/d, respectively. However, in the study by Karmakar et al. (2020) some limitations were identified related to documentation. In particular, more F1 animals were evaluated than dams were treated, and information was lacking whether data were represented with SD or SEM. Therefore, this study was downgraded to Tier 3.

Three developmental toxicity studies from the same university reported a decrease in stage VIII tubules, suggesting an inhibition of the spermatogenesis process (Karmakar et al., 2020; Rahman et al., 2017; Rahman et al., 2021) and two developmental studies (Karmakar et al., 2020; Rahman et al., 2021) reported an increase of abnormal seminiferous tubules in mice. For reasons described above, the Karmarakar study was excluded from further analysis. Likewise, for the Rahman studies, it is not unequivocally clear, if the statistics refer to the litter as statistical unit. A decrease of stage VIII tubules was also reported in one study with adult rats from another lab, but only one BPA dose (200 µg/kg bw/d) was tested for this parameter (Liu et al., 2013a).

The NTP study (Delclos et al., 2014) reported incidences of giant cells in seminiferous tubules and degeneration of germinal epithelium. The degeneration of the germinal epithelium was not altered at any of the BPA doses tested and an increase of giant cells in the seminiferous epithelium was only significant at the lowest dose. Thus, a treatment-related effect of BPA on these endpoints was considered not likely for this study. Two studies by Ullah et al., (Ullah et al., 2019b; Ullah et al., 2018a) reported data on testis histology. In the prenatal study (Ullah et al., 2019b) percentage of the area of seminiferous tubules and interstitial space, percentage of the area of lumen and epithelium, seminiferous epithelial height and seminiferous tubules diameter were slightly altered. Except for the percentage of interstitial space area the changes had an effect size of below 5%. Together with the marginally altered sperm parameters (see above) relevance of this alteration of this parameter remains uncertain. In addition, the assignment of the pups to the litters is not sufficiently described, which adds further uncertainty. Thus, testis histology parameters from this study were not taken forward to TDI derivation. In the adult study (Ullah et al., 2018a) only epithelial height was significantly altered at the highest

dose tested (50 mg/kg bw/d), while no change was observed for the percentage of the area of seminiferous tubules and interstitial space and the seminiferous tubule diameter.

Another study with adult exposure but with higher doses (Sencar et al., 2021) reported changes in the height of the seminiferous epithelium and the diameter of seminiferous tubules in addition on the Johnson's score. It should be noted, with exception of the CLARITY studies (Camacho et al., 2019; Dere et al., 2018) information on blinding of histology samples were lacking.

The EFSA-assessed study on seminiferous tubule diameter (Gurmeet et al., 2014) was rated as Tier 3 according to our methodology due to unknown background exposure and lack of information on feed. However, in this study, effects only occurred at the highest dose of 100 mg/kg bw/d.

Further parameters

In addition to the parameters described above, organ weight of testis as well as sperm morphology data and sperm viability were evaluated qualitatively. The majority of all studies (three Tier 1 studies, 11 Tier 2 studies and both studies by Tyl) that looked at testicular weight did not showed an effect after BPA exposure.

In the Delclos/NTP study, incidence of small testes was increased at doses of 0.26 and 300 mg/kg bw/d, but not at the doses in between. In the CLARITY associated study (Dere et al., 2018) a decreased testis weight was only observed at the additional high dose (250 mg/kg bw/d). In a study on prenatally exposed mice (GD1 until birth, Ma et al., 2017) a decrease of absolute and relative testis weight was observed at all doses (50 – 2500 mg/kg bw/d). In contrast, a study with prenatally exposed rats (GD 14 – GD 21) reported an increase of testis weight only at the mid dose of 10 mg/kg bw/d (Quan et al., 2017). One study using adult rats reported a dose-dependent decrease of testis weight at 0.5 and 1 mg/kg bw/d (Srivastava and Gupta, 2018). In the three-generation rat study by Tyl et al., 2002, relative testis weight increased in all generations at the highest dose of 500 mg/kg bw/d, while absolute testis weight decreased at 50 and 500 mg/kg bw/d. In the two-generation study in mice by Tyl et al., 2008, testis weight decreased at the highest dose of 600 mg/kg bw/d.

In agreement with the 2023 EFSA opinion, testis weight was not considered to be a likely endpoint for BPA exposure, at least not at low doses.

For sperm morphology data, no significant effect was observed in rats in the study by Delclos. Also in the CLARITY study, abnormal sperm counts in rats were not influenced by BPA exposure in either study arm. The number of sperm abnormalities was increased in one study when adult mice were exposed (Alabi et al., 2021). The mice were exposed for only 5 days, and the analysis of sperm from the epididymis took place 35 days later, when spermatogenesis was complete. In one study with pubertal exposure in rats initially ranked in Tier 2, the data reporting was not clear (Wang et al., 2014a) and therefore excluded from further assessment. One Tier 2 study with exposure from GD14 - GD21 reported an increase of sperm malformation at doses in the range of mg/kg bw/d range without dose dependence (Quan et al., 2017). In the multi-generation studies in mice and rats (Tyl et al., 2008a; Tyl et al., 2002), percentage of abnormal sperm was unaffected by BPA exposure. In summary, it was concluded that effects on sperm morphology are not likely to be caused by BPA exposure.

For sperm viability, no effects were observed in rats in the Tier 1 study by Delclos and in the Tier 2 study by Ullah(Ullah et al., 2019b)). EFSA concluded that effects of BPA on sperm viability are likely based on the study by Wang (Wang et al., 2016) which we assessed as Tier 3. In contrast, we consider this endpoint not to be affected by BPA exposure.

3.1.4.3 Female reproduction

Ovarian histology

For effects on ovarian histology in rats and mice (including ovarian follicle count), three Tier 1 studies (Camacho et al., 2019; Delclos et al., 2014; Patel et al., 2017), one Tier 2 study (Wang et al., 2014b), and nine Tier 3 studies were identified (Berger et al., 2016; Cao et al., 2018; Hu et al., 2018; Lin et al., 2021; Mahalingam et al., 2017; Osman et al., 2021; Rashid et al., 2018; Shi et al., 2019; Wei et al., 2020). The key study on ovarian histology used by EFSA for BMD modelling (Hu et al., 2018) was rated as Tier 3 based on our criteria due to unclear background exposure (via cages and water bottles as well as due to undefined feed), and in particular due to lack of blinding with high risk of bias for the measured outcome (follicle counts). The parameters finally considered by BfR were:

- Follicle counts (ratio primary/total follicles) after developmental (prenatal and postnatal until weaning) as well as developmental + adult (prenatal and postnatal in pups until adulthood) exposure in rats (Patel et al., 2017), and after prenatal exposure in mice (Wang et al., 2014b).
- Incidence of ovarian lesions (e.g. follicular cysts, depletion of corpora lutea, depletion of antral follicles, interstitial cell hyperplasia) after developmental (prenatal and postnatal until weaning) as well as developmental + adult (prenatal and postnatal in pups until adulthood) in rats and mice (Tyl et al., 2008a).

Uterus histology

For effects on uterus histology in rats and mice, four Tier 1 studies (Camacho et al., 2019; Delclos et al., 2014; Kendziorski and Belcher, 2015a; Kendziorski and Belcher, 2015b), and one Tier 3 study (Yuan et al., 2018) were identified. The study by Kendziorski and Belcher (2015b) was rated as Tier 1 only in the case CD-1 mice were used, as the number of animals in the case of C57B1/6N mice was less than five (therefore Tier 3). In our opinion, for CD-1 mice, both after adult (Kendziorski and Belcher, 2015b) as well as after developmental + adult exposure (Kendziorski and Belcher, 2015a), treatment-related changes in the incidence of uterus cysts were not observed. Similarly in the studies by Tyl and co-workers considered previously by EFSA (EFSA, 2015), no effects on the uterus histopathology were reported (Tyl et al., 2008a; Tyl et al., 2002). Therefore, the parameters finally used for dose-response analysis were:

- Incidence of uterine lesions (cystic endometrial hyperplasia, squamous endometrial metaplasia, uterus apoptosis) after developmental (prenatal and postnatal until weaning) (Camacho et al., 2019) as well as developmental + adult (prenatal and postnatal in pups until adulthood) exposure in rats (Camacho et al., 2019; Delclos et al., 2014).

Oestrous cycle

For effects on oestrous cycle in rats and mice, four Tier 1 studies (Camacho et al., 2019; Delclos et al., 2014; Hass et al., 2016; Tucker et al., 2018), two Tier 2 (Leung et al., 2017; Wang et al., 2014b), and one Tier 3 study (Cao et al., 2018) were identified. Some studies reported the mean of time spent in a particular cycle phase (Cao et al., 2018; Tucker et al.,

2018) or the percentage of time spent in different phases (Wang et al., 2014b), whereas others recorded the frequency of animals with abnormal cycles (Camacho et al., 2019; Delclos et al., 2014; Hass et al., 2016). Leung et al. (2017) mentioned that there were no effects of BPA on oestrous cyclicity in offspring after developmental exposure but data were not shown. Data on time or percentage of time spent in a particular phase of the cycle are not directly comparable to the frequency of animals with abnormal cycles. Therefore, and as the Tier 1 and 2 studies by Tucker et al. (2018), Wang et al. (2014b) and the studies considered by (EFSA, 2015) (Tyl et al., 2008a; Tyl et al., 2002) did not, in our opinion, show treatment-related effects on oestrous cycle, the following parameter was used for dose-response analysis:

- Incidence of animals rats with abnormal cycles after developmental (prenatal and postnatal until weaning) (Camacho et al., 2019; Hass et al., 2016) as well as developmental + adult exposure (prenatal and postnatal in pups until adulthood) (Camacho et al., 2019; Delclos et al., 2014).

Vaginal histology

For histopathological findings in the vagina in rats, two Tier 1 studies were identified (Camacho et al., 2019; Delclos et al., 2014). Since the studies by Tyl and co-workers on rats and mice (Tyl et al., 2008a; Tyl et al., 2002) reported no effects on the vagina, the following parameter was considered for dose-response analysis:

- Vaginal epithelium hyperplasia after developmental (prenatal and postnatal until weaning) as well as developmental + adult exposure (prenatal and postnatal in pups until adulthood) (Camacho et al., 2019; Delclos et al., 2014).

Mammary gland

For effects on the (female) mammary gland in rats and mice, five Tier 1 studies (Camacho et al., 2019; Delclos et al., 2014; Mandrup et al., 2016; Montévil et al., 2020; Tucker et al., 2018) and one Tier 2 study (Leung et al., 2017) were identified. In addition, the results of a 2-generation reproductive study in mice (Tyl et al., 2008a) used by EFSA in its previous opinion (EFSA, 2015) were considered.
Of these studies the BfR only considered the effects observed in Delclos et al. (2014) as treatment-related. Therefore, the following parameter was considered for dose-response analysis:

- Incidence of mammary gland duct hyperplasia after developmental (prenatal and postnatal until weaning) as well as developmental + adult (prenatal and postnatal in pups until adulthood) exposure (Delclos et al., 2014).

3.1.5 Metabolic effects

In its recent opinion EFSA (2023) identified 8 health outcome categories (HOC) based on animal studies and 5 HOC based on human studies. For the human data, none of the metabolic clusters (obesity, cardiometabolic effects, thyroid effects, type 2 diabetes mellitus (T2DM) and gestational diabetes mellitus) showed effects that were considered “Very Likely” or “Likely”. Only the positive association between BPA exposure and obesity and T2DM was judged “As Likely As Not” (ALAN). In the animal studies, the clusters were obesity, fat deposition in the liver, glucose regulation, blood lipids, uric acid, type 1 diabetes mellitus (T1DM), other metabolic hormones and thyroid hormones. None of these clusters were considered “Very Likely”. However, the association between uric acid (UA) and BPA exposure was categorized

as “Likely”, if exposure occurs during adulthood. The following clusters were classified ALAN: obesity, fat deposition in the liver, glucose regulation, blood lipids and T1DM.

Unlike in other mammals, UA is the final metabolic product of purine metabolism in primates and secreted predominantly via the urine. It is synthesised by xanthine oxidase from xanthine, an intermediate product of purine metabolism. In non-primate mammals, UA is further metabolized into allantoin. As a consequence, UA serum levels are higher in humans than in other mammalien species, including rodents (Kratzer et al., 2014)

In male SD rats, serum concentrations between 0.5-1.6 mg/dL (Kurtz and Travlos, 2018) have been reported. In contrast, due to the metabolic differences, the UA concentration in human serum is in the range between 3.5-7 mg/dl in men and 2.5-5.9 mg/dL in women. Within the nephron uric acid is actively secreted into the distal tubule and actively reabsorbed in the proximal tubule (Kurtz and Travlos, 2018). This reabsorption is affected by many factors like drugs and food (composition). Ma and co-workers (Ma et al., 2018) showed that BPA induced a concentration dependent increase of UA in serum of one rat strain and two mouse strains. The authors provided evidence that BPA activates xanthine oxidase, which converts hypoxanthine and xanthine into UA. However, the animal data showed extraordinary high UA concentrations already in the control group (appr. 18 mg/dL in CD1 mice, 7.5 mg/dL in C57BL/6 mice and 5 mg/dL in SD rats). The reason for the highly elevated concentrations is not clear. Since the UA measurements in serum are not described in the “materials and methods” section, the applied methods might be not be appropriate and false elevated concentrations might be reported (Watanabe et al., 2014). Overall, the reliability of the test system and the generated data is low. In addition, dose-response analysis indicated a high uncertainty in the data (EFSA, 2023). The NOAEL was 5 µg/kg bw/d in both mice strains, but not determinable in rats, because only one dose (500 µg/kg bw/d) was applied.

Furthermore, the authors (Ma et al., 2018) showed a weak, statistically positive association between the serum UA concentration and serum BPA concentration in 240 human subjects. However, information on the enrollment process and on known confounders of metabolic disease, such as the socioeconomic status of the subjects or their household was not provided. Information on potential drug uptake and composition of recently eaten food, which have an influence on the UA concentration (Sanchez-Lozada et al., 2020), was missing. Moreover, serum BPA was measured only once. Due to the rapid metabolism of BPA, the serum concentration can vary over one order of magnitude within 24 h (Fleck et al., 2018). Single concentration measurements of BPA do not necessarily reflect the daily average exposure.

The same group also investigated the association between BPA and UA in a 6-year prospective study with 482 participants (Hu et al., 2019). Again, based on single BPA determinations in serum the authors concluded, that subjects with high BPA concentration exhibited a 2-fold higher risk in the development of hyperuricemia within the subsequent 6 years. Several potential confounding parameters such as diet, alcohol consumption or diseases were considered and the analysis was corrected for these factors. The correlation between BPA and the annual change in serum UA was very weak but significant ($r = 0.18$). The authors stated that ‘The number of subjects who developed hyperuricemia were 12, 24, and 26 in the low, median, and high tertile, respectively.’ However, the exact time points of sampling and the number of serum analyses were not given. It might be the case that the results are based on 2 measurements at the beginning and the end of the study, only.

In a third epidemiological study (Lee et al., 2022) the association between spot-urine BPA concentration and serum UA was studied among school-aged children (n=489, mean age 6y). No association was observed. Again, a major limitation in this study was the single determination of both parameters, which vary over a broad range within one day, due to the

rapid metabolism. Referring to Ma et al. (2018) the proposed direct activation of xanthine oxidase by BPA should occur independent of the age of the studied population.

Based on the criteria (3.1.1), the listed studies were categorized as Tier 3. The effect of BPA on human xanthine oxidase has not been shown experimentally. The epidemiological studies had limitations in the sampling conditions, test system suitability and consideration of confounding factors. Recent studies from a third party that would support the correlation are not available. In particular, an acute study showing a correlation between BPA exposure and UA increase in humans is missing. Therefore, the BfR judges the effect as ALAN. However, it is noted, that uncertainty remains with respect to this effect.

3.1.6 Other toxicity

As discussed above, the BfR focused its literature search on the endpoints seen as most relevant for TDI derivation, i.e. reproduction toxicity, immunologic effects, increased serum uric acid and toxicokinetics. However, additional endpoints were also discussed in the literature and in risk assessment reports of competent authorities.

3.1.6.1 Genotoxicity and carcinogenicity

The BfR agrees with the conclusion in EFSA (2023), “that it is Unlikely to Very Unlikely that BPA presents a genotoxic hazard, the causes of which include a direct mechanism”, and that “the results of rodent studies did not demonstrate a tumorigenic activity of BPA”.

3.1.6.2 General toxicity

The BfR agrees with the conclusion in EFSA (2015) and EFSA (2023), that adverse effects on several organs, especially kidney and liver, are seen in rodent studies, but at much higher doses compared to the effects the new TDI derivation is based on.

3.1.6.3 Neurodevelopmental toxicity

Effects on brain and behaviour were seen in various studies and evaluated as relevant both by EFSA (2023) and ECHA (2014). However, evaluation of adversity and relevance for humans especially of behavioural effects like anxiety or emotionality is uncertain. In addition, the results significantly varied in incidence and effect dose and very often were not suitable for dose-response analysis due to high uncertainty in the data.

ECHA (2014) derived a “derived no effect level” (DNEL, comparable to a TDI, but not limited to food) for effects on brain and behaviour, based on a NOAEL of 50 µg/kg bw/d from a developmental study in mice (Xu et al., 2010). Based on this, the TDI newly derived by the BfR would also be protective for effects on brain and behaviour.

3.1.7 Dose-response Analysis

3.1.7.1 Selection of studies

The selection of relevant studies for the respective endpoints has been described above. Only studies rated Tier 1 or Tier 2 were included.

3.1.7.2 Procedure for derivation of the Points of Departure (PoDs) for hazard assessment

For each endpoint the Critical Effect Size (CES, acc. to EFSA terminology) or Benchmark Response (BMR, terminology used in this assessment) for adversity was defined upfront, i.e. 10 % for all but the immunological effect types (for which it was set to 100 %), cf. the respective endpoint-specific sections.

As the default, Benchmark Dose (BMD) analysis was carried out to determine the PoDs for deriving the TDI value. In line with the recommendations in EFSA (2022), the BMD, BMDL and BMDU were calculated with Bayesian Model Averaging (BMA) using the "Bayesian BMD" tool from EFSA's R4EU platform (https://r4eu.efsa.europa.eu) with the default settings (except CES/BMR, which was set to the predefined value). In parallel, they were calculated with the "standard" model averaging (SMA) using EFSA's "bmd" tool (based on the "PROASTweb" software version 70.0; also via the R4EU platform).

If either or both of the two approaches failed to produce a single model-averaged BMDL/BMD/BMDU triplet or BMDL/BMDU values, respectively, but gave two or more individual model results, the mean BMD, lowest BMDL and highest BMDU from these models were used for the further calculations.

Each BMDL derived in this way was checked against the recommendation in EFSA (2022) according to which:

"Alternatives to the BMDL as a reference point, as described below, are recommended when:

- *none of the candidate models fit the data sufficiently well (see Section 2.5.3)*
- *BMD/BMDL > 20, or*
- *the BMD is 10 times lower than the lowest non-zero dose or*
- *BMDU/BMDL > 50."* [1]

If, for a given study and endpoint, after this procedure still BMDLs/BMDs/BMDUs from both the standard and the Bayesian modelling approach were available and acceptable, the result after BMA was chosen, as this approach reflects current EFSA recommendations.

If an acceptable BMDL/BMD/BMDU triplet (or a BMDL/BMDU-pair, resp.) was not available, this was generally resolved by using the NOAEL or (if unavailable) LOAEL from the respective study as PoD for TDI derivation.

The BMDL values are presented in the following subsections, but only for those endpoints where at least one study showed a dose response. Their use for TDI derivation is described in section 3.1.8.

[1] It is noted that only the Bayesian BMD tool produces a BMD value, therefore the second and third rule could only be applied to the outputs from this tool.

The immunological endpoints and studies identified by EFSA (2023) were evaluated as not suitable for TDI derivation by the BfR with respect to adversity, human relevance, weight of evidence and/or study quality. However, the respective studies were still submitted to BMD modelling in order to evaluate, to which extent the TDI derived by the BfR would also be protective for these immunological effects – despite the aforementioned reservations.

3.1.7.3 Results: possible PoDs for hazard assessment

BMDLs and BMDUs (where available) and NOAELs/LOAELs (where applicable) were derived for all Tier 1 and Tier 2 studies considered relevant for the assessment. Tier 3 studies were considered too unreliable to be used as the basis for quantitative hazard assessment. Table 6 Table 6 and Table 7 provide an overview of all possible PoDs derived in this way. Those PoDs taken forward to quantitative hazard assessment are given in bold print.

Reproductive toxicity

***Table 6**: Overview of the NOAELs, LOAELs and BMD/BMDL/BMDU values derived from all Tier 1 and Tier 2 studies, which were decided to be submitted to dose-response analysis (see respective section above). All numbers represent doses in µg/kg bw/d, rounded to integers (Only for representation in this table, all decimal figures were maintained for further calculations), unless such rounding would have resulted in an increase or reduction > 10 % (in which case rounding was to the next significant figure). MA = Model Averaging, na = not available/applicable.*

Study	Tier	Species	Endpoint	Dose range		NOAEL	LOAEL	Standard MA		Bayesian MA		
				Lowest	Highest			BMDL	BMDU	BMDL	BMD	BMDU
Sperm counts (BMR = 10 %)												
(Camacho et al., 2019)	1	rat	caudal count, SD, 1-yr interim	2.5	25000	**25000**	na	na	na	na	na	na
	1	rat	caudal count, CD, 1-yr interim	2.5	25000	**25000**	na	na	na	na	na	na
(Delclos et al., 2014)	1	rat	caudal count (no outliers)	2.5	300000	840	2700	18000	684000	**764**	1907	4248
	1	rat	testicular count (no outliers)	2.5	300000	**300000**	na	na	na	na	na	na
	1	rat	testicular count (HRSH)	2.5	250000	**250000**	na	na	na	na	na	na
(Ullah et al., 2019b)	2	rat	sperm count, caput/corpus epididymis	0.6	6	**6**	na	na	na	na	na	na
	2	rat	caudal count	0.6	6	**6**	na	na	na	na	na	na
(Wang et al., 2014a)	2	rat	caudal count	50000	200000	50000	100000	**7310**	131000	na	na	na
(Hass et al., 2016)	2	rat	caudal count	25	50000	**50000**	na	na	na	na	na	na
(Liu et al., 2013a)	2	rat	caudal count	2	200	20	200	2	130	**26**	96	298
(Quan et al., 2017)	2	rat	sperm density	1000	100000	**100000**	na	na	na	na	na	na
(Srivastava and Gupta, 2018)	2	rat	caudal count	50	1000	**50**	500	0.7	173	na	na	na
(Tyl et al., 2002)	2	rat	epididymal count, F0	0.9	450000	**450000**	na	na	na	4829	124440	3E06

Study	Tier	Species	Endpoint	Dose range		NOAEL	LOAEL	Standard MA		Bayesian MA		
				Lowest	Highest			BMDL	BMDU	BMDL	BMD	BMDU
	2	rat	epididymal count, F1	1	500000	45000	450000	17500	437000	**136602**	326447	573429
	2	rat	epididymal count, F2	1	500000	**450000**	na	na	na	na	na	na
	2	rat	epididymal count, F3	1	500000	**450000**	na	na	na	na	na	na
(Tyl et al., 2008b)	2	mouse	caudal count, F0	3	600000	600000	na	144000	616000	**362761**	505285	657065
	2	mouse	caudal count, F1	3	600000	**600000**	na	na	na	na	na	na
	2	mouse	caudal count, F1 retained	3	600000	600000	na	4490	2E06	**354442**	609314	1E06
(Karabulut and Gulay, 2020)	2	rabbit	conc. in ejaculate	10000	100000	na	10000	0.01	8980	**1364**	4376	13844
Sperm motility (BMR = 10 %)												
(Camacho et al., 2019)	1	rat	percent motility, SD, 1-yr interim	2.5	25000	**25000**	na	na	na	na	na	na
	1	rat	percent motility, CD, 1-yr interim	2.5	25000	**25000**	na	na	na	na	na	na
(Delclos et al., 2014)	1	rat	percent motility	2.5	300000	300000	na	**319000**	581000	na	na	na
(Ullah et al., 2019a)	2	rat	percent motility	5000	50000	**25000**	50000	na	na	na	na	na
(Wang et al., 2014a)	2	rat	percent motility	50000	200000	**100000**	200000	137000	6E06	na	na	na
(Quan et al., 2017)	2	rat	percent motility	1000	100000	**100000**	na	na	na	na	na	na
(Tyl et al., 2002)	2	rat	percent motility, F0	0.9	450000	**450000**	na	na	na	na	na	na
	2	rat	percent motility, F1	0.9	450000	**450000**	na	na	na	na	na	na
	2	rat	percent motility, F2	0.9	450000	**450000**	na	na	na	na	na	na

Study	Tier	Species	Endpoint	Dose range		NOAEL	LOAEL	Standard MA		Bayesian MA		
				Lowest	Highest			BMDL	BMDU	BMDL	BMD	BMDU
	2	rat	percent motility. F3	0.9	450000	**450000**	na	na	na	na	na	na
(Tyl et al., 2008b)	2	mouse	percent motility. F0	3	600000	**600000**	na	na	na	na	na	na
	2	mouse	percent motility. F1	3	600000	**600000**	na	na	na	na	na	na
	2	mouse	percent motility. F1 retained	3	600000	**600000**	na	na	na	na	na	na
(Karabulut and Gulay, 2020)	2	rabbit	percent motility	10000	100000	na	10000	4	4750	**1496**	2520	6105
Sperm morphology (BMR = 10 %)												
(Camacho et al., 2019)	1	rat	abnormal sperm. SD. 1-yr interim	2.5	25000	**25000**	na	na	na	na	na	na
	1	rat	abnormal sperm. CD. 1-yr interim	2.5	25000	**25000**	na	na	na	na	na	na
(Delclos et al., 2014)	1	rat	abnormal sperm (no outliers)	2.5	300000	**300000**	na	0.16	31200	na	na	na
(Quan et al., 2017)	2	rat	abnormal sperm	1000	100000	10000	100000	**3210**	49300	2843	15461	258159
(Tyl et al., 2002)	2	rat	abnormal sperm. F0	0.9	450000	**450000**	na	na	na	na	na	na
	2	rat	abnormal sperm. F1	0.9	450000	**450000**	na	na	na	na	na	na
	2	rat	abnormal sperm. F2	0.9	450000	**450000**	na	na	na	na	na	na
	2	rat	abnormal sperm. F3	0.9	450000	**450000**	na	na	na	na	na	na
(Tyl et al., 2008b)	2	mouse	abnormal sperm. F0	3	600000	**600000**	na	na	na	na	na	na
	2	mouse	abnormal sperm. F1	3	600000	**600000**	na	na	na	na	na	na
	2	mouse	abnormal sperm. F1 retained	3	600000	**600000**	na	na	na	na	na	na
(Alabi et al., 2021)	2	mouse	abnormal sperm	500	5000	500	1000	**293**	394	na	na	na

Study	Tier	Species	Endpoint	Dose range		NOAEL	LOAEL	Standard MA		Bayesian MA		
				Lowest	Highest			BMDL	BMDU	BMDL	BMD	BMDU
Testis histology (BMR = 10%)												
(Camacho et al., 2019)	1	rat	polyarteritis. SD. terminal	2.5	25000	**25000**	na	na	na	na	na	na
	1	rat	polyarteritis. CD. terminal	2.5	25000	**25000**	na	na	na	na	na	na
(Delclos et al., 2014)	1	rat	giant cells in seminiferous tubules	2.5	300000	**300000**	na	na	na	na	na	na
	1	rat	germinal epithelium. degeneration	2.5	300000	**300000**	na	na	na	na	na	na
(Dere et al., 2018)	1	rat	apoptotic cells	2.5	250000	**250000**	na	na	na	na	na	na
(Quan et al., 2017)	2	rat	apoptotic cells	1000	100000	na	**1000**	1E-06	0.03	na	na	na
(Wang et al., 2014a)	2	rat	apoptosis	50000	200000	50000	100000	287	36400	**3538**	21423	65919
(Sencar et al., 2021)	2	rat	epithelial height	50000	200000	na	**50000**	na	na	na	na	na
	2	rat	diameter of seminiferous tubules	50000	200000	na	**50000**	na	na	na	na	na
(Ullah et al., 2018a)	2	rat	epithelial height	5000	50000	5000	25000	12700	43000	**22638**	33250	49111
(Rahman et al., 2017)	2	mouse	stage VIII seminiferous epithelial cells	50	50000	50	5000	0.003	863	**458**	1928	7148
	2	mouse	abnormal seminiferous tubules. F1	50	50000	50	5000	98	2460	**839**	2467	7121
	2	mouse	abnormal seminiferous tubules. F2	50	50000	**5000**	50000	15	4190	86	1135	5479

Study	Tier	Species	Endpoint	Dose range		NOAEL	LOAEL	Standard MA		Bayesian MA		
				Lowest	Highest			BMDL	BMDU	BMDL	BMD	BMDU
	2	mouse	stage VIII seminiferous epithelial cells F1	50	50000	**50**	5000	3	1170	27	57	150
	2	mouse	stage VIII seminiferous epithelial cells F2	50	50000	**50**	5000	0.1	2000	17	49	129
Ovary / follicles (BMR = 10%)												
(Camacho et al., 2019)	1	rat	cystic follicles CD 1-yr int	2.5	25000	25000	na	0.00034	514000	**6315**	18745	41249
	1	rat	interstitial cell hypertrophy CD 1-yr int	2.5	25000	250	2500	0.015	25600	**6418**	17929	37352
	1	rat	corpora lutea depletion CD 1-yr int	2.5	25000	250	2500	0.00028	29900	**6949**	18936	38672
	1	rat	cystic follicles SD 1-yr int	2.5	25000	**250**	2500	3	2720	45	659	8230
	1	rat	interstitial cell hypertrophy SD 1-yr int	2.5	25000	25000	na	0.7	4E06	**9579**	23857	56475
	1	rat	copora lutea depletion SD 1-yr int	2.5	25000	2500	25000	2	647000	**8816**	20010	35563
(Delclos et al., 2014)	1	rat	ovary, cystic follicles	2.5	300000	100000	300000	3390	166000	**95460**	174313	297245
	1	rat	corpora lutea depletion	2.5	300000	100000	300000	**94200**	233000	na	na	na
	1	rat	antral follicles, depletion	2.5	300000	100000	300000	38200	248000	**59796**	131787	295506
(Tyl et al., 2002)	2	rat	Ovary cyst follicle F0	0.9	500000	**500000**	na	na	na	na	na	na
	2	rat	Ovary cyst follicle F1	0.9	500000	**500000**	na	na	na	na	na	na
(Tyl et al., 2008b)	2	mouse	Ovary histology F0	3	600000	**600000**	na	na	na	na	na	na
	2	mouse	Ovary histology F1	3	600000	**600000**	na	na	na	na	na	na
(Wang et al., 2014a)	2	mouse	ovarian follicle counts	0.5	50	**50**	na	na	na	na	na	na

Study	Tier	Species	Endpoint	Dose range		NOAEL	LOAEL	Standard MA		Bayesian MA		
				Lowest	Highest			BMDL	BMDU	BMDL	BMD	BMDU
Estrous cycle (BMR = 10%)												
(Delclos et al., 2014)	1	rat	anoestrus	2.5	300000	100000	300000	87600	239000	**79054**	166038	320080
	1	rat	abnormal cycle	2.5	300000	100000	300000	12800	204000	**53092**	136472	289824
(Hass et al., 2016)	2	rat	abnormal cycle	25	50000	**50000**	na	3E-06	1E06	na	na	na
Uterus histology (BMR = 10%)												
(Camacho et al., 2019)	1	rat	uterus cystic hyperplasia, SD, interim	2.5	25000	2500	25000	88	31800	**8019**	17549	30509
	1	rat	uterus cystic hyperplasia, SD, terminal	2.5	25000	2500	25000	0	350000	**7237**	24930	80837
	1	rat	uterus cystic hyperplasia, CD, interim	2.5	25000	**25000**	na	0.2	1.4E06	na	na	na
	1	rat	uterus cystic hyperplasia, CD, terminal	2.5	25000	25000	na	0.5	7E06	**7189**	23565	76864
	1	rat	uterus squamous metaplasia, SD, interim	2.5	25000	**25000**	na	1920	1.3E06	na	na	na
	1	rat	uterus squamous metaplasia, SD, terminal	2.5	25000	**25000**	na	25400	3.6E06	0	5370	∞
	1	rat	uterus squamous metaplasia, CD, interim	2.5	25000	25000	na	0.002	1.5E06	**10100**	22961	46479
	1	rat	uterus squamous metaplasia, CD, terminal	2.5	25000	25000	na	na	na	**15908**	27717	53844
	1	rat	uterus apoptosis, SD, interim	2.5	25000	25000	na	100	241000	**9171**	19257	32127
	1	rat	uterus apoptosis, CD, interim	2.5	25000	**25000**	na	0.08	17900	24	8963	90124

Study	Tier	Species	Endpoint	Dose range		NOAEL	LOAEL	Standard MA		Bayesian MA		
				Lowest	Highest			BMDL	BMDU	BMDL	BMD	BMDU
(Leung et al., 2020)	1	rat	uterus apoptosis TUNEL subchronic	2.5	25000	**2500**	25000	9E-06	11500	1	54	369
	1	rat	uterus apoptosis TUNEL chronic	2.5	25000	**2500**	25000	na	na	40	8932	1.7E06
(Delclos et al., 2014)	1	rat	uterus hyperplasia	2.5	300000	**300000**	na	2170	262000	na	na	na
	1	rat	uterus metaplasia	2.5	300000	**100000**	300000	0.03	3E08	na	na	na
Vaginal epithelium (BMR = 10%)												
(Camacho et al., 2019)	1	rat	vaginal epithelium hyperplasia SD, interim	2.5	25000	2500	25000	50	431000	**8883**	19371	33229
	1	rat	vaginal epithelium hyperplasia CD, interim	2.5	25000	250	2500	0.8	21200	**625**	14578	40264
(Delclos et al., 2014)	1	rat	vagina, mucocyte hyperplasia	2.5	300000	**300000**	300000	na	na	na	na	na
(Tyl et al., 2002)	2	rat	vagina, mucocyte hyperplasia F0	0.9	500000	**500000**	na	na	na	na	na	na
	2	rat	vagina, mucocyte hyperplasia F1	0.9	500000	**500000**	na	na	na	na	na	na
(Tyl et al., 2008b)	2	mouse	vagina, mucocyte hyperplasia F0	3	600000	**600000**	na	na	na	na	na	na
Mammary gland (BMR = 10%)												
(Delclos et al., 2014)	1	rat	Mammary gland duct hyperplasia, PND21 female	2.5	300000	**840**	2700	0.02	4490	1	126	87269
	1	rat	Mammary gland duct hyperplasia, PND90 female	2.5	300000	100000	300000	0.006	66600	**9719**	53248	296668

Study	Tier	Species	Endpoint	Dose range		NOAEL	LOAEL	Standard MA		Bayesian MA		
				Lowest	Highest			BMDL	BMDU	BMDL	BMD	BMDU
	1	rat	Mammary gland duct hyperplasia, PND21 male	2.5	300000	**840**	2700	10000	760000	na	na	na
	1	rat	Mammary gland duct hyperplasia, PND90 male	2.5	300000	**300000**	na	284000	6E090	na	na	na
(Mandrup et al., 2016)	1	rat	Mammary gland intraductal hyperplasia, PND400 female	25	50000	**50000**	na	na	na	na	na	na
	1	rat	Mammary gland intraductal hyperplasia, PND100 male	25	50000	250	25000	0.000014	26400	**6586**	27025	84523
(Camacho et al., 2019)	1	rat	mammary gland hyperplasia SD, interim	2.5	25000	**25000**	na	na	na	na	na	na
	1	rat	mammary gland hyperplasia CD, interim	2.5	25000	**25000**	na	na	na	na	na	na
(Leung et al., 2017)	2	rat	Mammary gland hyperplasia	2.5	2500	**2500**	na	na	na	na	na	na
(Tyl et al., 2008b)	2	mouse	Mammary gland hyperplasia F1	3	600000	**600000**	na	na	na	na	na	na
(Tucker et al., 2018)	1	mouse	Terminal-end bud count	500	50000	**50000**	na	na	na	na	na	na

Immunological effects

***Table 7**: Overview of the NOAELs, LOAELs and BMD/BMDL/BMDU values derived from all Tier 1 and Tier 2 studies, which were decided to be submitted to dose-response analysis (see respective section above). All numbers represent doses in µg/kg bw/d, rounded to integers (Only for representation in this table, all decimal figures were maintained for further calculations), unless such rounding would have resulted in an increase or reduction > 10 % (in which case rounding was to the next significant figure). MA = Model Averaging, na = not available/applicable.*

Study	Tier	Species	Endpoint	Dose range		NOAEL	LOAEL	Standard MA		Bayesian MA		
				Lowest	Highest			BMDL	BMDU	BMDL	BMD	BMDU
Immunology (BMR = 100 %)												
(Bauer et al., 2012)	2	mouse	eosinophils in BALF	50	500	**500**	na	na	na	na	na	na
	2	mouse	neutrophils in BALF	50	500	**500**	na	na	na	na	na	na
(Dong et al., 2020)	2	mouse	serum IL-17	0.2	2	na	30	18	191	**12**	29	97
(Gao et al., 2020a)	2	mouse	serum IL-17	52	517	na	51.71	29	459	**35**	56	99
	2	mouse	serum IL-17	52	517	na	51.71	138	1590	**88**	360	574
(Luo et al., 2016)	2	mouse	serum IL-17. PND21 males	0.5	48	0.5	5	21	121	**46**	90	183
	2	mouse	serum IL-17. PND21 females	0.5	485	0.5	5	30	502	**17**	37	78
	2	mouse	serum IL-17. PND21 males + females	0.5	48	0.5	5	35	175	**33**	62	121
	2	mouse	serum IL-17. PND42 males	0.5	48	0.5	5	61	180000	**28**	122	1546
	2	mouse	serum IL-17. PND42 females	0.5	48	0.5	5	98	226000	**14**	233	11062
	2	mouse	serum IL-17. PND42 males + females	0.5	48	0.5	5	76	111000	**58**	778	10464
(Nygaard et al., 2015)	2	mouse	eosinophils in BALF males	1410	13700	1410	13700	**296**	**14100**	na	na	na
	2	mouse	eosinophils in BALF females	1410	13700	**1410**	13700	15.8	2.5E06	na	na	na
	2	mouse	eosinophils in BALF males + females	1410	13700	**1410**	13700	na	na	na	na	na

Study	Tier	Species	Endpoint	Dose range		NOAEL	LOAEL	Standard MA		Bayesian MA		
				Lowest	Highest			BMDL	BMDU	BMDL	BMD	BMDU
(Wang et al., 2020b)	2	mouse	Neutrophils in BALF	25	100	25	50	na	na	**17**	31	56
	2	mouse	eosinophils in BALF	25	100	25	50	17	42	**55**	68	83
(Ogo et al., 2018)	2	rat	neutrophils in epididymis caput	20	200	20	200	40	146	**58**	115	234

3.1.8 Combined uncertainty assessment and TDI derivation

3.1.8.1 Introduction

Quantitative hazard characterisation (HC) is associated with numerous uncertainties. To avoid insufficient protection of the human population on the one hand, and risk management decisions based on overly conservative or unrealistic assumptions leading to undesirable economical or societal side-effects on the other, these uncertainties need to be made transparent.

Important issues in this respect are discussed briefly in the subsequent sections to explain the methodological choices made for the uncertainty assessment in this report. For a more in-depth conceptual treatment, the reader is referred to Chiu and Slob (2015) and WHO IPCS (2018).

3.1.8.2 Quantitative uncertainty analysis

Deterministic hazard characterisation

Traditional “deterministic” HC starts with the determination of a Point of Departure (PoD), usually a No Observed Adverse Effect Level (NOAEL), Lowest Observed Adverse Effect Level (LOAEL), or a Benchmark Dose (BMD), which is then divided by one or more assessment factors (AF) taking account of the uncertainty and variability in the underlying data and methodology, to obtain a Health-Based Guidance Value (HBGV), i.e. the Tolerable Daily Intake (TDI) in the case of the present assessment for BPA.

Where the PoD is a BMD, usually its lower confidence limit (BMDL) is used. In addition, although individual values may be subject to discussion with respect to their degree of conservatism, the AF are conceptually designed to individually represent reasonable worst-case assumptions (or, as put in WHO IPCS (2018), to “cover most cases”) for the respective aspect of HC, such as the extrapolation from the median animal to the median human (interspecies extrapolation), from the median human to sensitive humans, or from subchronic to chronic exposure. As a result, deterministic HBGVs derived in this way are often believed to “err on the safe side”.

Nevertheless, this deterministic approach may be subject to criticism based *inter alia* on the following arguments:

- Usually, neither the uncertainty, nor the conservatism of the HBGV estimate are made transparent.
- The extent to which the population is put at risk (both in terms of the effect magnitude M and the population incidence I) when exceeding the TDI is not made transparent. On the contrary, the single point estimate provided suggests that any exceedance would result in an unacceptable risk, which is not necessarily the case.

Multiple worst-case assumptions are usually combined, resulting in an overall unrealistic “worst-worst-case” estimate: *“Another drawback is that multiplying individual conservative values results in an overall factor that is even more conservative, the more so when the number of aspects in the specific hazard characterization is larger. This implies that the outcome from a particular hazard characterization might be more conservative than would be considered desirable or necessary”* (WHO IPCS, 2018).

(Approximate) Probabilistic Analysis (APROBA)

Chiu and Slob (2015) have laid out a unified probabilistic framework for the dose-response assessment of human health effects. This concept together with a practical approach ("Approximate Probabilistic Analysis", or APROBA) for its application has been described in detail in WHO IPCS (2018). It is important to highlight that it is fully compatible with the traditional deterministic approach, and should be seen as its extension and complementation.

In brief, in the first step of the WHO IPCS concept, the uncertainty in each HC aspect is not represented by a worst-case point estimate (an AF or a lower-bound PoD), but by a range or probability distribution instead. At the same time, two important practical simplifications are introduced, i.e.

- the respective probability distributions are assumed to follow a lognormal distribution and
- if the exact distribution is not available, it can be estimated from the median (P50) and 95th percentile (P95), provided they are known or can be obtained by other means, e.g. based on expert judgment.

In the second step, these individual HC aspect probability distributions can then be combined into an overall probability distribution for the HBGV, i.e. TDI in the present report, to be estimated.

The charm of this concept lies in the fact that TDI derivation and uncertainty analysis are not separated as in a traditional analysis; rather the TDI is determined as the result of the uncertainty analysis in an integrated way. In addition, the combination of individual uncertainties in a statistically sound way instead of piling up worst-case assumptions on top of each other provides for an in summary more realistic overall uncertainty estimate.

As another important aspect of the WHO IPCS concept the user is forced to explicitly specify the protection goal in terms of effect magnitude M (as defined by the critical effect size or Benchmark response (BMR) and population incidence I (cf. Chiu and Slob (2015) for details).

Along with the WHO IPCS concept, also a simple spreadsheet tool called "APROBA" has been provided (see WHO IPCS (2018) for details), which was used in the present assessment[2]. The APROBA tool provides various outputs for a quantitative characterisation of the overall uncertainty in the HBGV estimate:

- The "deterministic" Reference Dose (RfD, e.g. a TDI) is given as the PoD point estimate divided by the Overall Assessment Factor (OAF, the product of all individual AF).
- A "non-probabilistic" output; its Lower Confidence Limit (LCL) corresponds to the "worst-worst-case" scenario, i.e. the combination of worst-case assumptions for all HC aspects. The Upper Confidence Limit (UCL) represents the "best-best-case" scenario, i.e. the combination of all best-case assumptions. The resulting range ("Fold Range of

[2] Here, the original version 1.00 was used, which focused on hazard characterisation. An updated version including improved features for exposure and risk characterisation called APROBAplus is available from the website of the Dutch authority RIVM (https://www.rivm.nl/en/aproba-plus, last accessed 2023-03-09).

Uncertainty") typically spans many orders of magnitude, but encompasses 100% of the quantifiable uncertainties.

- The actual APROBA output: here, the two-sided confidence interval for the probabilistic RfD/TDI (obtained by the (approximate) probabilistic combination of the probability distributions for all HC aspects) is given. The lower bound of this interval can then be used as the "probabilistic" TDI. If a two-sided 90% confidence interval is used (this is typically the case in BMD calculations and was also used as default in WHO IPCS (2018)), this probabilistic TDI represents the P05 of its probability distribution, i.e. it represents the TDI estimate with 95% confidence that the "true" TDI is not lower than this value.

One obvious question about the APROBA concept relates to how realistic probability distributions for the individual HC aspects can be obtained. There are in fact several options:

- The respective substance-specific distribution may be known based on experimental data (e.g. for the toxicokinetic aspects of inter- or intraspecies extrapolation).
- Reliable substance-specific estimates for P50 and P95 may be available.
- Commonly used default AF can be transformed into ranges, for which P50 and P95 values can be specified. For instance, the default factor of 10 for human interindividual variability commonly used by EFSA or under REACH[3] can be interpreted as an extrapolation factor from the median human (therefore P50 = 1) to sensitive humans, as represented by a high percentile of the population. Unfortunately, the exact protection level, i.e. the exact percentile of the population protected by an intraspecies factor of 10 is not known. However, current risk assessments assume that it provides a high level of protection which is sufficient in the sense that e.g. a TDI derived by using this factor, on average over a great number of chemicals, sufficiently protects the human population including sensitive subpopulations such as children and the elderly.

  In the present assessment, this notion is translated into the assumption that "sufficient" means that the default intraspecies factor protects 99 % of the population, with 95 % confidence or, in other words, that it achieves a population incidence goal I = 1 %. If human intraspecies variability is then given as a probability distribution, the default factor of 10 can then be equated to the P95 of that distribution (P05 is then obtained by P50/P95, i.e. in this case P05 = P50/P95 = 1/10 = 0.1). In the same way, other "sufficiently protective" default factors can be equated to the P95 of the respective probability distributions.
- Default probability distributions may also be obtained from the assessment of large historical datasets comparing e.g. clearance data across species for a large number of chemicals. WHO IPCS (2018) includes a number of such default distributions, which are also implemented in the APROBA tool (however, alternative user inputs are always possible). Of note, such default distributions also depend on the population incidence goal I, cf. WHO IPCS (2018), Table 4.5.

In this assessment, each dose-response data set was assessed by two approaches in parallel:

[3] Regulation (EC) 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of chemicals

- "BfR" approach: substance-specific data were given precedence over default assumptions where available and sufficiently reliable, but if not, EFSA default values (as per EFSA (2012)) or, if those were not available either, REACH default values were used for the AF. In contrast to EFSA (2012), however, allometric scaling was applied in line with ECHA ECHA (2012), using REACH default body weights as specified in ECHA (2017)[4], unless reliable study-specific data were available to suggest otherwise. For details. cf. next section.

  Overall, the BfR approach is considered to best reflect the common assumptions used in chemical risk assessments, ensuring compatibility with previous risk assessments of BPA and other chemicals.
- "WHO" approach: the WHO IPCS default distributions for the AF are often more conservative than the default AF typically used in EFSA assessments or under REACH. The latter are more established in risk assessment and therefore their use in an assessment will safeguard the consistency of that particular assessment with general risk assessment practice, as explained under the BfR approach. On the other hand, EFSA/REACH default AF often represent pragmatic approaches and their exact numerical basis is not always clear. For instance, the statement that the AF for intraspecies extrapolation protects 99 % of the population with 95 % confidence, and therefore the assumption that it represents the P95 (cf. above), is associated with uncertainty.

The WHO IPCS defaults represent data-based evaluations over a large number of chemicals, which allow for a more precise characterisation of the respective AF (distributions). On the other hand, they have been derived for substances and effects which may or may not be similar enough to the one(s) under assessment. Therefore, to examine the impact of using the more conservative WHO defaults on the overall TDI, the APROBA for all relevant dose-response data was performed using the WHO AF default distributions in parallel to the BfR approach. This can be seen as an additional component of the uncertainty analysis, because in this way aspects of the standard risk assessment assumptions implemented by the BfR approach are highlighted (and can then be discussed), for which the assessment might not be conservative enough.

Application of APROBA to the relevant dose-response data available for BPA

General procedure

An APROBA was carried out on all dose-response datasets of sufficient quality from studies showing a treatment-related adverse effect, unless considered irrelevant for humans. The study selection process is presented in the respective endpoint-specific sections. For quantitative risk assessment, only Tier 1 and Tier 2 studies were considered for which a reliable PoD could be determined (cf. section 3.1.7.3 for details).

With respect to the protection goal magnitude of effect (M), the BMR as defined in the previous sections was used. With respect to the protection goal incidence (I), a value of 1 % was used[5]

[4] Of note, both EFSA and REACH use a default body weight of 70 kg for the adult general population.
[5] As explained above, for the BfR approach this means that the EFSA/ECHA default AF of 10 was interpreted as representing P95 with a population incidence of 1 %. The possible lack of conservatism in making this assumption was then examined by comparison with the output from the WHO approach.

in all cases, i.e. at least 99 % of the population should be protected from an effect of magnitude M or higher.

PoDs

The derivation of the PoDs for quantitative risk assessment is described in section 3.1.7.2 of this document.

AF for using NOAELs or LOAELs instead of the BMD

In the unified framework established by Chiu and Slob (2015), a NOAEL is conceptualised as an estimate of the BMDL. Therefore, if a NOAEL was used instead of a BMDL, the respective default distribution from WHO IPCS (2018) (P50 = 0.33, P95 = 4.7) for NOAEL-to-BMD extrapolation was applied in addition to the other AFs/AF distributions (both approaches). If a LOAEL was used as PoD, an additional AF of 6 (in between the range of 3 – 10 recommended by ECHA (2012)) for LOAEL-to-NOAEL extrapolation was applied, which was converted into a distribution by setting P50 = 1 and P95 = 6 (and thus, P05 = 1/6; both approaches).

AF for exposure duration

BfR approach: Since the TDI refers to chronic exposure, an additional AF of 2 (or, as a distribution: P50 = 1, P95 = 2, P05 = 0.5) was applied for subchronic-to-chronic extrapolation as recommended by both, EFSA (2012) and ECHA (2012). For subacute-to-subchronic extrapolation, an AF of 6 (P50 = 1, P95 = 6, P05 = 1/6) was used in line with the recommendation in ECHA (2012). For studies with developmental/perinatal exposure, no additional extrapolation factor was applied, since the relevant human exposure duration was considered fully covered.

WHO approach: The respective WHO IPCS default distribution was applied (subchronic-to-chronic: P50 = 2, P95 = 8, P05 = 0.5; subacute-to-chronic: P50 = 5, P95 = 40, P05 = 5/8).

AF for interspecies extrapolation (toxicokinetic part)

By default, the species-specific default weights provided in ECHA (2012), i.e. 0.022 kg for mice, 0.5 kg for rats, 2 kg for rabbits and 70 kg for the adult general population, were used. As an exception to this rule, study-specific body weight data were used in one study in rabbits (Karabulut and Gulay, 2020), where the authors reported a significant deviation from the default (i.e. upon the start of the study, the rabbits weighed between 2.7 and 3.7 kg and therefore an average body weight of 3.2 kg was used for the calculations).

Both approaches: for mice and rats, based on several studies, substance-specific Human Equivalent Dose Factors (HEDF) for BPA were determined, resulting in a distribution of HEDFs, ranging from 0.20 (P05) to 1.55 (P95) for mice and from 0.16 (P05) to 1.56 (P95) for rats (cf. section 3.1.2). Converted into AF (AF = 1/HEDF), the corresponding P05 – P95 AF ranges are 0.64 – 5 for mice and 0.64 – 6.14 for rats[6]. The upper bound of these ranges was used to calculate the deterministic TDI (e.g., for rats, instead of applying the default REACH

[6] Rounded values, values used in the calculations were not rounded.

and EFSA default AF of 10 for interspecies extrapolation, an AF of 6.14 x 2.5 (cf. next subsection) = 15.4 was used).

For rabbits, study-specific data for BPA were not available, therefore, this part of the interspecies AF was determined by allometric scaling, i.e. the allometric scaling factor (ASF) was calculated as $(70 \text{ kg/bw animal})^{0.25}$ in line with ECHA (2012). The resulting ASF was used as the P50 of the lognormal distribution. The uncertainty in the ASF was then captured by using the formula provided in WHO IPCS (2018), i.e.

$$P95/P50 = (bw_{human}/bw_{animal})^{1.64 \times 0.024} = (bw_{human}/bw_{animal})^{0.03936}.$$

AF for interspecies extrapolation (residual toxicokinetic/toxicodynamic part)

BfR approach: in line with WHO IPCS (2018), the basic assumption is that the P50 for the corresponding distribution is 1, while the default factor of 2.5 recommended by both, EFSA (2012) and ECHA (2012) represents the P95 (or, as a distribution: P50 = 1, P95 = 2.5 and P05 = 0.4).

WHO approach: a slightly higher P95 of 3 was used (P50 = 1, P95 = 3, P05 = 1/3), based on the default distribution given in WHO IPCS (2018).

AF for human intraspecies/interindividual extrapolation

BfR approach: the default AF of 10 recommended by both, EFSA (2012) and ECHA (2012), was applied (P50 = 1, P95 = 10, P05 = 0.1). This reflects the above assumption that the default AF covers the P95 of the interindividual variability distribution for a population incidence goal of I = 1 %.

WHO approach: as the WHO approach was meant to serve as a probe for the conservatism of the BfR approach, the WHO IPCS default values corresponding to a population incidence goal of I = 1 % were used (P50 = 9.69, P95 = 41.88, P05 = 2.24).

AF used when calculating the deterministic TDI

In order to closely follow current regulatory practice, the deterministic TDI (i.e. PoD divided by AF), was calculated based on the parameters chosen for the BfR approach.

3.1.8.3 Determination of the overall TDI

The overall TDI will be determined as the lowest TDI of the TDIs calculated, in the way described above, based on the PoDs from all studies included in the quantitative risk assessment (cf. section 3.1.7.3). An overview of all TDIs derived from individual studies is given in Table 8 and Table 9 at the end of this section. Note that studies for which the PoD was the NOAEL obtained as the highest dose tested were excluded from further assessment, since for these studies it is unclear at which dose, if any, the BMR would have been reached or, in fact, whether an effect might have been observed at any higher dose.

Of the remaining studies with a PoD which was either a BMDL, a LOAEL or a NOAEL that was not the highest dose tested, two studies investigating the effect of BPA on sperm counts in Wistar rats following subchronic exposure were considered most relevant for TDI setting.

The TDIs calculated for the study by Liu et al. (2013a) were 2 – 954 µg/kg bw/d (BfR approach, P95 and P05 of the probabilistic TDI) and 0.14 – 39 µg/kg bw/d (WHO approach). The TDIs calculated based on the study by Srivastava and Gupta (2018) were 3 – 1873 µg/kg bw/d (BfR) and 0.2 – 78 µg/kg bw/d (WHO). Averaging the TDIs for the two studies results in a TDI of 0.2 µg/kg bw/d based on the WHO approach LCLs and a TDI of 2.5 µg/kg bw/d based on the BfR approach LCLs.

Overall, a TDI of 0.2 µg/kg bw/d is derived based on the more conservative WHO approach, which offers an additional safety margin of 10 to the lowest TDI of 2.5 µg/kg bw/d derived based on the BfR approach, which more closely reflects the assumptions (and, hence, the degree of conservatism) applied in current risk assessment practice.

It is noted that this TDI is considered protective also for all effects reported in any of the other studies taken forward to dose-response analysis.

Reproductive toxicity

***Table 8**: Results of the deterministic and approximate probabilistic quantitative TDI derivation and uncertainty analyses. Studies are only listed of their PoD was either a BMDL, a LOAEL or a NOAEL that was not the highest dose tested. Overall Assessment Factors (OAF) are dimensionless, all other values are in µg/kg bw/d. PoDs > 1 OAFs and TDIs are rounded to integers and all other numbers are rounded to the first significant figure, unless the rounding error would exceed 10 %, in which case they were rounded to the second significant figure[7]. Values used for the hazard assessment are printed bold.*

Study	Tier	Species	Strain	Endpoint	Deterministic							Probabilistic BfR		Probabilistic WHO	
					PoD	Type	LOAEL-to-NOAEL AF	Duration AF	Interspecies TK AF	OAF[8]	TDI	TDI LCL	TDI UCL	TDI LCL	TDI UCL
Sperm count															
(Delclos et al., 2014)	1	rat	SD	caudal count (no outliers)	764	BMDL	1	2	6.14	307	**2**	**48**	17176	**3**	698
(Wang et al., 2014a)	2	rat	SD	caudal count	7310	BMDL	1	6	6.14	921	**8**	**442**	552109	**12**	8937
(Liu et al., 2013a)	2	rat	Wistar	caudal count	26	BMDL	1	2	6.14	307	**0.09**	**2**	954	**0.14**	39
(Srivastava and Gupta, 2018)	2	rat	Wistar	caudal count	50	NOAEL	1	2	6.14	307	**0.16**	**3**	1873	**0.2**	78
(Tyl et al., 2002)	2	rat	SD	epididymal count, F1	136602	BMDL	1	2	6.14	307	**445**	**7762**	2.6E06	**511**	104039
(Tyl et al., 2008b)	2	mouse	CD-1 (Swiss)	caudal count, F0	362761	BMDL	1	2	5.00	250	**1452**	**16789**	4.4E06	**1117**	176603
	2	mouse	CD-1 (Swiss)	caudal count, F1 retained	354442	BMDL	1	2	5.00	250	**1419**	**20121**	6E06	**1334**	228107
(Karabulut and Gulay, 2020)	2	rabbit	NZW	conc. in ejaculate	1364	BMDL	1	2	2.44	122	**11**	**119**	33871	**8**	1362

[7] Cf. EFSA (2012): „Derived values, such as health-based guidance values, should be rounded to a single significant figure if the impact of rounding is less than 10%, and to two significant figures if the impact of rounding to one significant figure exceeds that percentage. Rounding should happen as late as possible in the assessment process."

[8] Overall Assessment Factor; product of the LOAEL-to-NOAEL (if applicable), duration extrapolation (if applicable) and interspecies toxicokinetics AF shown in this Table, a default factor of 2.5 for residual interspecies differences in toxicokinetics and – dynamics, and a default factor of 10 for human interindividual variability.

Study	Tier	Species	Strain	Endpoint	Deterministic							Probabilistic BfR		Probabilistic WHO	
					PoD	Type	LOAEL-to-NOAEL AF	Duration AF	Interspecies TK AF	OAF[8]	TDI	TDI LCL	TDI UCL	TDI LCL	TDI UCL
Sperm motility															
(Delclos et al., 2014)	1	rat	SD	percent motility	319000	BMDL	1	2	6.14	307	**1039**	**12858**	3.7E06	**852**	147566
(Ullah et al., 2019a)	2	rat	SD	percent motility	43355	BMDL	1	6	6.14	921	**47**	**2893**	4.3E06	**37**	15943
(Karabulut and Gulay, 2020)	2	rabbit	NZW	percent motility	1496	BMDL	1	2	2.44	122	**12**	**97**	20189	**7**	799
Sperm morphology															
(Alabi et al., 2021)	2	mouse	Swiss albino	abnormal sperm	293	BMDL	1	6	5.00	749	**0.4**	**8**	4779	**0.2**	75
(Quan et al., 2017)	2	rat	SD	abnormal sperm	3210	BMDL	1	1	6.14	154	**21**	**279**	144492	**51**	8382

Study	Tier	Species	Strain	Endpoint	Deterministic							Probabilistic BfR		Probabilistic WHO	
					PoD	Type	LOAEL-to-NOAEL AF	Duration AF	Interspecies TK AF	OAF[8]	TDI	TDI LCL	TDI UCL	TDI LCL	TDI UCL
Testis histology															
(Quan et al., 2017)	2	rat	SD	abnormal sperm	1000	LOAEL	6	1	6.14	921	**1.1**	**56**	91985	**6**	2410
(Wang et al., 2014a)	2	rat	SD	apoptosis	3538	BMDL	1	6	6.14	921	**4**	**216**	274627	**6**	4448
(Rahman et al., 2017)	2	mouse	CD-1	stage VIII seminiferous epithelial cells	458	BMDL	1	1	5.00	125	**4**	**50**	20519	**8,5**	1278
(Rahman et al., 2021)	2	mouse	CD-1	abnormal seminiferous tubules, F1	839	BMDL	1	1	5.00	125	**7**	**76**	24428	**13**	1481
	2	mouse	CD-1	abnormal seminiferous tubules, F2	5000	NOAEL	1	1	5.00	125	**40**	**550**	286050	**92**	18209
	2	mouse	CD-1	stage VIII seminiferous epithelial cells F1	50	NOAEL	1	1	5.00	125	**0.4**	**5.5**	2861	**0.9**	35
	2	mouse	CD-1	stage VIII seminiferous epithelial cells F2	50	NOAEL	1	1	5.00	125	**0.4**	**5.5**	2861	**0.9**	35
(Sencar et al., 2021)	2	rat	Wistar	epithelial height	50000	LOAEL	6	6	6.14	5529	**9**	**1346**	4255771	**54**	45391
	2	rat	Wistar	diameter of seminiferous tubules	50000	LOAEL	6	6	6.14	5529	**9**	**1346**	4255771	**54**	45391
(Ullah et al., 2018a)	2	rat	SD	epithelial height	22638	BMDL	1	6	6.14	921	**25**	**1338**	1903184	**17**	7099

Study	Tier	Species	Strain	Endpoint	Deterministic							Probabilistic BfR		Probabilistic WHO	
					PoD	Type	LOAEL-to-NOAEL AF	Duration AF	Interspecies TK AF	OAF[8]	TDI	TDI LCL	TDI UCL	TDI LCL	TDI UCL
Ovary / follicles															
(Camacho et al., 2019)	1	rat	SD	cystic follicles CD 1-yr int	6315	BMDL	1	1	6.14	154	**41**	**457**	145249	**80**	8794
	1	rat	SD	interstitial cell hypertrophy CD 1-yr int	6418	BMDL	1	1	6.14	154	**42**	**446**	136815	**79**	8249
	1	rat	SD	corpora lutea depletion CD 1-yr int	6949	BMDL	1	1	6.14	154	**45**	**475**	143872	**84**	8660
	1	rat	SD	cystic follicles SD 1-yr int	250	NOAEL	1	1	6.14	154	**2**	**24**	13434	**4**	861
	1	rat	SD	interstitial cell hypertrophy SD 1-yr int	9579	BMDL	1	1	6.14	154	**62**	**669**	205930	**118**	12421
	1	rat	SD	corpora lutea depletion SD 1-yr int	8816	BMDL	1	1	6.14	154	**57**	**537**	148688	**96**	8857
(Delclos et al., 2014)	1	rat	SD	ovary, cystic follicles	95460	BMDL	1	2	6.14	307	**311**	**4829**	1.5E06	**319**	60382
	1	rat	SD	corpora lutea depletion	94200	BMDL	1	2	6.14	307	**307**	**4336**	1.3E06	**287**	51924
	1	rat	SD	antral follicles, depletion	59796	BMDL	1	2	6.14	307	**195**	**3609**	1.2E06	**237**	50572
Estrous cycle															
(Delclos et al., 2014)	1	rat	SD	anoestrus	79054	BMDL	1	2	6.14	307	**257**	**4431**	1.5E06	**292**	58847
	1	rat	SD	abnormal cycle	53092	BMDL	1	2	6.14	307	**173**	**3321**	1.2E06	**218**	47917

Study	Tier	Species	Strain	Endpoint	Deterministic							Probabilistic BfR		Probabilistic WHO	
					PoD	Type	LOAEL-to-NOAEL AF	Duration AF	Interspecies TK AF	OAF[8]	TDI	TDI LCL	TDI UCL	TDI LCL	TDI UCL
Uterus histology															
(Camacho et al., 2019)	1	rat	SD	uterus cystic hyperplasia, SD, interim	8019	BMDL	1	1	6.14	154	**52**	**478**	130416	**52**	2600
	1	rat	SD	uterus cystic hyperplasia, SD, terminal	7237	BMDL	1	1	6.14	154	**47**	**620**	240118	**63**	5124
	1	rat	SD	uterus cystic hyperplasia, CD, terminal	7189	BMDL	1	1	6.14	154	**47**	**608**	231332	**105**	14282
	1	rat	SD	uterus squamous metaplasia, CD, interim	10100	BMDL	1	1	6.14	154	**66**	**646**	185073	**115**	11070
	1	rat	SD	uterus squamous metaplasia, CD, terminal	15908	BMDL	1	1	6.14	154	**104**	**906**	240785	**163**	14271
	1	rat	SD	uterus apoptosis, SD, interim	9171	BMDL	1	1	6.14	154	**60**	**529**	141761	**95**	8410
(Leung et al., 2020)	1	rat	SD	uterus apoptosis TUNEL subchronic	2500	NOAEL	1	2	6.14	307	**8**	**60**	16905	**4.0**	679
	1	rat	SD	uterus apoptosis TUNEL chronic	2500	NOAEL	1	1	6.14	154	**16**	**65**	15504	**12**	905
(Delclos et al., 2014)	1	rat	SD	uterus metaplasia	100000	NOAEL	1	2	6.14	307	**326**	**2877**	796204	**317**	87705

Study	Tier	Species	Strain	Endpoint	Deterministic							Probabilistic BfR		Probabilistic WHO	
					PoD	Type	LOAEL-to-NOAEL AF	Duration AF	Interspecies TK AF	OAF[8]	TDI	TDI LCL	TDI UCL	TDI LCL	TDI UCL
Vaginal epithelium															
(Camacho et al., 2019)	1	rat	SD	vaginal epithelium hyperplasia SD, interim	8883	BMDL	1	1	6.14	154	**58**	**526**	142963	**94**	8497
	1	rat	SD	vaginal epithelium hyperplasia CD, interim	625	BMDL	1	1	6.14	154	**4.1**	**82**	78071	**13**	5220
Mammary gland															
(Delclos et al., 2014)	1	rat	SD	Mammary gland duct hyperplasia, PND21 F	840	NOAEL	1	1	6.14	154	**5**	**75**	48654	**13.4**	2892
	1	rat	SD	Mammary gland duct hyperplasia, PND90 F	9719	BMDL	1	2	6.14	307	**32**	**1009**	727125	**64.4**	30368
	1	rat	SD	Mammary gland duct hyperplasia, PND21 M	840	NOAEL	1	1	6.14	154	**5**	**75**	48654	**13.4**	2892
(Mandrup et al., 2016)	1	rat	SD	Mammary gland intraductal hyperplasia, PND100 M	6586	BMDL	1	1	6.14	154	**43**	**543**	260839	**101**	14998

Immunological effects

***Table 9**: Results of the deterministic and approximate probabilistic quantitative TDI derivation and uncertainty analyses. Studies are only listed of their PoD was either a BMDL, a LOAEL or a NOAEL that was not the highest dose tested. Overall Assessment Factors (OAF) are dimensionless, all other values are in µg/kg bw/d. PoDs > 1 and Overall AFs are rounded to integers and all other numbers are rounded to the first significant figure, unless the rounding error would exceed 10 %, in which case they were rounded to the second significant figure[7]. Values used for the hazard assessment are printed bold.*

Study	Tier	Species	Strain	Endpoint	Deterministic							Probabilistic BfR		Probabilistic WHO	
					PoD	Type	LOAEL-to-NOAEL AF	Duration AF	Interspecies TK AF	OAF[8]	TDI	TDI LCL	TDI UCL	TDI LCL	TDI UCL
Immunology															
(Dong et al., 2020)	2	mouse	C57BL/6	serum IL-17	12	BMDL	1	1	5.00	125	**0.1**	**1.1**	337	**0.2**	20
(Gao et al., 2020a)	2	mouse	C57BL/6	serum IL-17	35	BMDL	1	1	5.00	125	**0.3**	**2**	501	**0.4**	16
	2	mouse	C57BL/6	serum IL-17	88	BMDL	1	2	5.00	250	**0.35**	**7**	2328	**0.4**	94
(Luo et al., 2016)	2	mouse	ICR	serum IL-17, PND21 males	46	BMDL	1	1	5.00	125	**0.4**	**3**	822	**0.6**	48
	2	mouse	ICR	serum IL-17, PND21 females	17	BMDL	1	1	5.00	125	**0.14**	**1.3**	331	**0.23**	20
	2	mouse	ICR	serum IL-17, PND21 males + females	33	BMDL	1	1	5.00	125	**0.27**	**2.2**	556	**0.4**	33
	2	mouse	ICR	serum IL-17, PND42 males	28	BMDL	1	1	5.00	125	**0.22**	**4**	3297	**0.7**	218
	2	mouse	ICR	serum IL-17, PND42 females	14	BMDL	1	1	5.00	125	**0.11**	**3**	15785	**0.4**	1162
	2	mouse	ICR	serum IL-17, PND42 males + females	58	BMDL	1	1	5.00	125	**0.5**	**10**	18137	**1.6**	1262

Study	Tier	Species	Strain	Endpoint	Deterministic							Probabilistic BfR		Probabilistic WHO	
					PoD	Type	LOAEL-to-NOAEL AF	Duration AF	Interspecies TK AF	OAF[8]	TDI	TDI LCL	TDI UCL	TDI LCL	TDI UCL
(Nygaard et al., 2015)	2	mouse	C3H/HeJ	eosinophils in BALF males	296	NOAEL	1	1	5.00	125	**2.4**	**42**	31016	**7**	2035
	2	mouse	C3H/HeJ	eosinophils in BALF females	1410	NOAEL	1	1	5,00	125	**11**	**86**	64754	**14**	4254
	2	mouse	C3H/HeJ	eosinophils in BALF males + females	1410	NOAEL	1	1	5,00	125	**11**	**86**	64754	**14**	4254
(Wang et al., 2020b)	2	mouse	C57BL/6	eosinophils in BALF	17	BMDL	1	2	5.00	250	**0.07**	**1.1**	268	**0.2**	16
	2	mouse	C57BL/6	neutrophils in BALF	55	BMDL	1	2	5.00	250	**0.22**	**2.6**	554	**0.5**	32
(Ogo et al., 2018)	2	rat	Wistar	neutrophils in epididymis caput	58	BMDL	1	6	5.00	749	**0.08**	**2**	1654	**0.1**	71

3.1.8.4 Relevant unquantifiable uncertainties

It is noted that a number of further studies on the endpoint sperm counts is available in Sprague-Dawley (SD) rats and New Zealand White rabbits. In SD rats, the next lowest TDI for this endpoint was found for the study by Delclos et al. (2014), i.e. 3 – 698 µg/kg bw/d (WHO approach) and 48 – 17176 µg/kg bw/d (BfR approach), i.e. 15 – 24 times higher. It is unknown whether Wistar rats are more sensitive than SD rats for this endpoint, however it can be highlighted that the available studies in Wistar rats already represent the far lower end of the TDI range for this effect in rats. Notably, Delclos et al. (2014) were rated as Tier 1 in this report, while the two key studies used to derive the overall TDI were only rated Tier 2, i.e. their results have to be considered as associated with higher uncertainty.

BPA is likely one of the best-investigated chemical substances in the world and the authors of this report have performed a thorough literature research in addition to the comprehensive search performed by EFSA for their recently revised Opinion on BPA. The possibility that an existing TDI-relevant study has been completely missed out in this process is considered negligible. For various, scientifically well-founded reasons, a substantial number of potentially relevant studies has been rated as Tier 3 and has therefore not been included in the quantitative risk assessment. However, since this rating implies that the experimental design contains certain flaws which prevent a robust quantitative (and sometimes even qualitative) assessment of the reported effects, it is pointless to speculate whether these effects would also have been observed if the study design had been flawless.

3.1.9 Conclusion on hazard assessment

BfR based its TDI derivation on two studies showing reduced sperm count after subchronic BPA exposure of adult Wistar rats (Liu et al., 2013a; Srivastava and Gupta, 2018). Dose-response analysis was performed by means of Benchmark Dose Modelling, resulting in a $BMDL_{10}$ of 26 µg/kg bw/d and a NOAEL of 50 µg/kg bw/d, respectively. These results were submitted to a probabilistic uncertainty assessment according to the approach proposed by (WHO IPCS, 2018). Therein, the distribution of possible HEDFs resulting from the evaluation of literature on toxicokinetics was combined with typical distributions for other uncertainties (e.g. interhuman variability, study duration), aiming to protect at least 99% of the population. In course of this, two different approaches (BfR and WHO approach, respectively) regarding conservativeness of assumptions for possible uncertainties were compared.

The process resulted in 90% confidence intervals for the TDI derived from the study by Liu et al. (2013a) of 2 – 954 µg/kg bw/d (BfR approach, P95 and P05 of the probabilistic TDI) and 0.14 – 39 µg/kg bw/d (WHO approach). The 90% confidence intervals for the TDI calculated based on the study by Srivastava and Gupta (2018) were 3 – 1873 µg/kg bw/d (BfR) and 0.2 – 78 µg/kg bw/d (WHO).

The BfR decided in a very conservative approach to select the mean of the two P05 resulting from the WHO approach as TDI. Hence, the TDI value was calculated to 0.2 µg/kg bw/d, protecting 99% of the population with 95% confidence. The TDI is also protective for any other relevant effect discussed in the present assessment. To underline this, in Figure 2 below, the confidence intervals of the TDI values derived via the WHO approach are shown for all studies submitted to dose-response analysis (including studies, where the NOAEL was identified as the highest dose). Therein, in the only study with a confidence interval reaching significantly

below the TDI (Ullah et al., 2019b), an effect was not present even in the highest dose. Hence, this study is not relevant for derivation of the TDI.

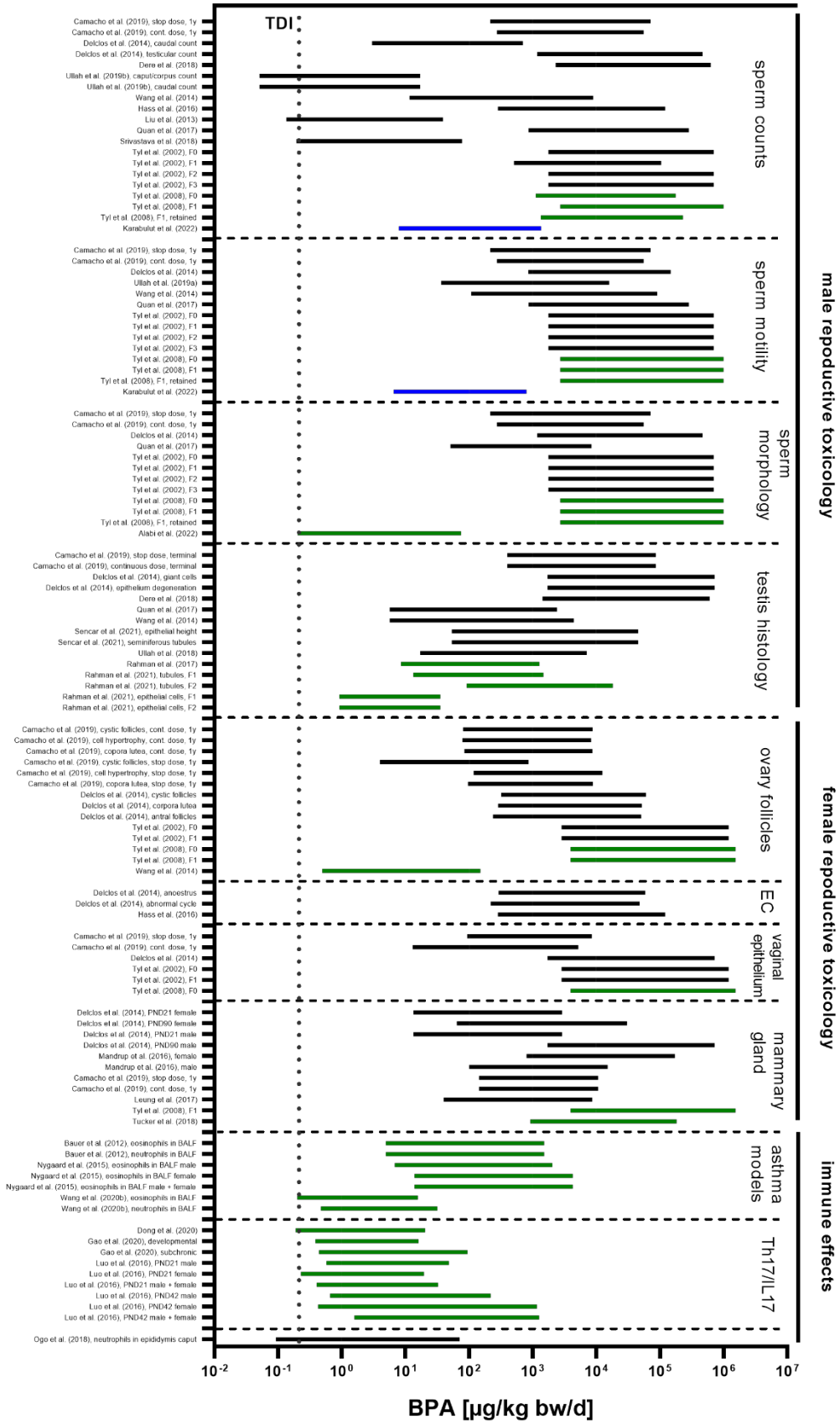

Figure 2: 90% Confidence intervals of the TDI values derived from the studies submitted to dose-response analysis using the WHO approach in comparison to the TDI of 0.2 µg/kg bw/d. Note logarithmic scale. Black = rat, green = mouse, blue = rabbit

It should be emphasised again that a detailed evaluation of available literature in this assessment was limited to the areas of reproductive toxicity, immunologic effects, increased serum uric acid and toxicokinetics. However, based on evaluations from other authorities (ECHA, 2014; EFSA, 2015; EFSA, 2023), the TDI of 0.2 µg/kg bw/d as derived by the BfR is also protective with respect to other toxicological endpoints (general toxicity, carcinogenicity, effects on brain and behaviour).

Furthermore, although the changes in immunological intermediate endpoints as described in EFSA (2023) were evaluated as not adverse and, in part, of limited relevance for humans, and irrespective of the shortcomings in many of the immunological studies (e.g. with respect to the actual BPA dose applied), the TDI of 0.2 µg/kg bw/d as derived by the BfR would still be protective for a 100% increase in the respective intermediate endpoints. As stated above, in the opinion of the BfR adverse immunological effects in humans – if at all – are unlikely to result from BPA exposure in the range of the TDI of 0.2 µg/kg bw/d.

3.2 Exposure Assessment

An actual exposure assessment for the German or European population is not available. In 2015, EFSA evaluated (based on data mainly from 2008-2012) the exposure via food for the European population to be in the range of 0.1-0.4 µg/kg bw/d (adults) and 0.1-0.9 µg/kg bw/d (infants and children), respectively (EFSA, 2015). However, urine data from human biomonitoring suggested that this exposure estimation might have been too high (EFSA, 2015). In addition, mainly due to regulatory measures already in place, human BPA exposure is expected to have further decreased in recent years (compare e.g. Boon et al. (2017)).

3.3 Risk characterisation

Current exposure estimation for the German or European population is not available. Hence, a comprehensive risk assessment could not be performed. A risk assessment based on the TDI of 0.2 µg/kg bw/d can be performed once current exposure data become available.

4 Abbreviations

AF	Assessment factor
AhR	Aryl hydrocarbon receptor
ALAN	As likely as not
AR	Androgen receptor
AUC	Area under the curve
BfR	German Federal Institute for Risk Assessment
BALF	Bronchoalveolar lavage fluid
BMA	Bayesian Model Averaging

BMD	Benchmark dose
BMDL	Benchmark dose lower confidence limit
BMDU	Benchmark dose upper confidence limit
BMR	Benchmark response
BPA	Bisphenol A
bw	Body weight
CES	Critical effect size
CD	Cluster of differentiation
CLARITY	Consortium Linking Academic and Regulatory Insights on BPA Toxicity
CLP	Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures
ConA	Concanavalin A
d	Day
DC	Dendritic cell
dL	Deciliter
DNEL	Derived no effect level
EAE	Experimental autoimmune encephalomyelitis
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EHR	Enterohepatic recycling
EKE	Expert Knowledge Elicitation
ELISA	Enzyme-linked immunosorbent assay
EOS	Eosinophils
ER	Estrogen receptor
EU	European Union
FACS	Fluorescence activated cell sorting
GD	Gestational day
GLP	Good laboratory praxis
GR	Glucocorticoid receptor
h	Hour
HBGV	Health-based guidance value
HC	Hazard characterisation
H&E	Hematoxylin & Eosin

HED	Human equivalent dose
HEDF	Human equivalent dose factor
HOC	Health outcome category
IFNγ	Interferon gamma
Ig	Immunoglobulin
IL	Interleukin
ILC	Innate lymphoid cell
i.n.	Intranasal
i.p.	Intraperitoneal
IPCS	International Programme on Chemical Safety
i.t.	Intratracheal
kg	Kilogram
LCL	Lower confidence limit
LOAEL	Lowest observed effect level
LPS	Lipopolysaccharide
MA	Model averaging
MCP-1	Mast cell protease-1
mg	Milligram
MHC	Major histocompatibility complex
mL	Milliliter
MLN	Mesenteric lymph nodes
mRNA	Messenger ribonucleic acid
MS	Multiple sclerosis
µg	Microgram
na	Not available/applicable
ng	Nanogram
NKT cell	Natural killer T cell
NOAEL	No observed effect level
NTP	National Toxicology Program
OAF	Overall assessment factor
OVA	Ovalbumin
PND	Postnatal day
PoD	Point of Departure

REACH	Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals
RORγT	RAR-related orphan receptor gamma
RfD	Reference dose
SD	Standard deviation
SD rat	Sprague Dawley rat
SEM	Standard Error of the Mean
siLP	Small intestine lampina propria
SMA	“Standard” model averaging
SVHC	Substance of very high concern
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TDI	Tolerable daily intake
TGFβ	Transforming growth factor beta
Th17 cells	T helper 17 cells
TNFα	Tumor necrosis factor alpha
t-TDI	Temporary tolerable daily intake
Treg cell	Regulatory T cell
TUNEL	TdT-mediated dUTP-biotin nick end labeling
UA	Uric acid
UCL	Upper confidence limit
UF	Uncertainty factor
WAT	White adipose tissue
WHO	World health organization
WoE	Weight of Evidence

Weitere Informationen auf der BfR-Website zum Thema Bisphenol A

A-Z Index Bisphenol A
https://www.bfr.bund.de/en/a-z_index/bisphenol_a-129760.html

BfR “Opinions” App

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6 Appendix A: Study selection and evaluation for reproduction toxicity

Authors	Year	Title	Journal	Tier
Alabi, O. A., Ologbonjaye, K. I., Sorungbe, A. A., Shokunbi, O. S., Omotunwase, O. I., Lawanson, G. and Ayodele, O. G.	2021	Bisphenol A-induced Alterations in Diferent Stages of Spermatogenesis and Systemic Toxicity in Albino Mice (Mus musculus)	Journal of Health and Pollution	2
Arambula, S. E., Fuchs, J., Cao, J. and Patisaul, H. B. CLARITY	2017	Effects of perinatal bisphenol A exposure on the volume of sexually-dimorphic nuclei of juvenile rats: A CLARITY-BPA consortium study	NeuroToxicology	1
Barberio, L., Paulesu, L., Canesi, L., Grasselli, E. and Mandalà, M.	2021	Bisphenol a Interferes with Uterine Artery Features and Impairs Rat Feto-Placental Growth	International journal of molecular sciences	3
Berger, A., Ziv-Gal, A., Cudiamat, J., Wang, W., Zhou, C. and Flaws, J. A.	2016	The effects of in utero bisphenol A exposure on the ovaries in multiple generations of mice	Reproductive Toxicology	3

Authors	Year	Title	Journal	Tier
Cao, Y., Qu, X., Ming, Z., Yao, Y. and Zhang, Y.	2018	The correlation between exposure to BPA and the decrease of the ovarian reserve	Int J Clin Exp Pathol	3
Cao, T., Cao, Y., Wang, H., Wang, P., Wang, X., Niu, H. and Shao, C.	2020	The Effect of Exposure to Bisphenol A on Spermatozoon and the Expression of Tight Junction Protein Occludin in Male Mice	Dose-Response	3
Christiansen, S., Axelstad, M., Boberg, J., Vinggaard, A. M., Pedersen, G. A. and Hass, U.	2014	Low-dose effects of Bisphenol a on early sexual development in male and female rats	Reproduction	2
DeCatanzaro, D., Berger, R. G., Guzzo, A. C., Thorpe, J. B. and Khan, A.	2013	Perturbation of male sexual behavior in mice (Mus musculus) within a discrete range of perinatal bisphenol-A doses in the context of a high- or low-phytoestrogen diet	Food and Chemical Toxicology	2
Delclos, K. B., Camacho, L., Lewis, S. M., Vanlandingham, M. M., Latendresse, J. R., Olson, G. R., Davis, K. J., Patton, R. E., Da costa, G. G., Woodling, K. A., Bryant, M. S., Chidambaram, M., Trbojevich, R., Juliar, B. E., Felton, R. P. and Thorn, B. T.	2014	Toxicity evaluation of bisphenol a administered by gavage to sprague dawley rats from gestation day 6 through postnatal day 90	Toxicological Sciences	1
Dere, E., Anderson, L. M., Huse, S. M., Spade, D. J., McDonnell-Clark, E., Madnick, S. J., Hall, S. J., Camacho, L., Lewis, S. M., Vanlandingham, M. M. and Boekelheide, K. CLARITY	2018	Effects of continuous bisphenol A exposure from early gestation on 90 day old rat testes function and sperm molecular profiles: A CLARITY-BPA consortium study	Toxicology and Applied Pharmacology	1
Dobrzyńska, M. M. and Radzikowska, J.	2013	Genotoxicity and reproductive toxicity of bisphenol A and X-ray/bisphenol A combination in male mice	Drug and Chemical Toxicology	3
Dobrzyńska, M. M., Jankowska-Steifer, E. A., Tyrkiel, E. J., Gajowik, A.,	2014	Comparison of the effects of bisphenol a alone and in a combination with X-irradiation on sperm count and quality in male adult and pubescent mice	Environmental Toxicology	3

Authors	Year	Title	Journal	Tier
Radzikowska, J. and Pachocki, K. A.				
Dobrzyńska	2015	Male-mediated F1 effects in mice exposed to bisphenol A, either alone or in combination with X-irradiation	Mutat Res Genet Toxicol Environ Mutagen	3
Dobrzyńska, M. M., Gajowik, A., Jankowska-Steifer, E. A., Radzikowska, J. and Tyrkiel, E. J.	2018	Reproductive and developmental F1 toxicity following exposure of pubescent F0 male mice to bisphenol A alone and in a combination with X-rays irradiation	Toxicology	3
Dobrzyńska, M. M., Gajowik, A. and Radzikowska, J.	2022	The impact of preconceptional exposure of F0 male mice to bisphenol A alone or in combination with X-rays on the intrauterine development of F2 progeny	Mutation Research - Genetic Toxicology and Environmental Mutagenesis	3
Eckstrum, K. S., Edwards, W., Banerjee, A., Wang, W., Flaws, J. A., Katzenellenbogen, J. A., Kim, S. H. and Raetzman, L. T.	2018	Effects of exposure to the endocrine-Disrupting chemical bisphenol a during critical windows of murine pituitary development	Endocrinology	3
Fang, Z., Liu, X., Yang, X., Song, X. and Chen, X.	2015	Effects of Wnt/βcatenin signaling on bisphenol A exposure in male mouse reproductive cells	Molecular Medicine Reports	3
Gao, T., Yin, Z., Wang, M., Fang, Z., Zhong, X., Li, J., Hu, Y., Wu, D., Jiang, K. and Xu, X.	2020	The effects of pubertal exposure to bisphenol-A on social behavior in male mice	Chemosphere	2
Hass, U., Christiansen, S., Boberg, J., Rasmussen, M. G., Mandrup, K. and Axelstad, M.	2016	Low-dose effect of developmental bisphenol A exposure on sperm count and behaviour in rats	Andrology	2
Hu, Y., Yuan, D. Z., Wu, Y., Yu, L. L., Xu, L. Z., Yue, L. M., Liu, L., Xu, W. M., Qiao, X. Y., Zeng, R. J., Yang, Z. L., Yin, W. Y., Ma, Y. X. and Nie, Y.	2018	Bisphenol A Initiates Excessive Premature Activation of Primordial Follicles in Mouse Ovaries via the PTEN Signaling Pathway	Reproductive Sciences	3
Huang, D. Y., Zheng, C. C., Pan, Q., Wu, S. S., Su, X., Li, L., Wu, J. H. and Sun, Z. Y.	2018	Oral exposure of low-dose bisphenol A promotes proliferation of dorsolateral prostate and induces epithelial-mesenchymal transition in aged rats	Scientific Reports	2

Authors	Year	Title	Journal	Tier
Jiang, X., Yin, L., Zhang, N., Han, F., Liu, W. B., Zhang, X., Chen, H. Q., Cao, J. and Liu, J. Y.	2018	Bisphenol A induced male germ cell apoptosis via IFNβ-XAF1-XIAP pathway in adult mice	Toxicology and Applied Pharmacology	3
Kalb, A. C., Kalb, A. L., Cardoso, T. F., Fernandes, C. G., Corcini, C. D., Junior, A. S. V. and Martínez, P. E.	2016	Maternal Transfer of Bisphenol A during Nursing Causes Sperm Impairment in Male Offspring	Archives of Environmental Contamination and Toxicology	3
Karabulut, H. and Gulay, M. S.	2020	Influence of bisphenol A on spermatological parameters of New Zealand White Rabbits	Medycyna Weterynaryjna	2
Karmakar, P. C., Ahn, J. S., Kim, Y. H., Jung, S. E., Kim, B. J., Lee, H. S. and Ryu, B. Y.	2020	Gestational exposure to bisphenol a affects testicular morphology, germ cell associations, and functions of spermatogonial stem cells in male offspring	International Journal of Molecular Sciences	2
Karnam, S. S., Ghosh, R. C., Mondal, S. and Mondal, M.	2015	Evaluation of subacute bisphenol - A toxicity on male reproductive system	Veterinary World	3
Kazemi, S., Bahramifar, N., Moghadamnia, A. A. and Jorsarae, S. G.	2016	Detection of Bisphenol A and Nonylphenol in Rat's Blood Serum, Tissue and Impact on Reproductive System	Electron Physician	3
Kazemi, S., Feizi, F., Aghapour, F., Joorsaraee, G. A. and Moghadamnia, A. A.	2016	Histopathology and histomorphometric investigation of bisphenol a and nonylphenol on the male rat reproductive system	North American Journal of Medical Sciences	3
Kendziorski, J. A. and Belcher, S. M.	2015	Effects of whole life exposure to Bisphenol A or 17α-ethinyl estradiol in uterus of nulligravida CD1 mice	Data in Brief	1
Kendziorski, J. A. and Belcher, S. M.	2015	Strain-specific induction of endometrial periglandular fibrosis in mice exposed during adulthood to the endocrine disrupting chemical bisphenol A	Reproductive Toxicology	1
Leung, Y. K., Biesiada, J., Govindarajah, V., Ying, J., Kendler, A., Medvedovic, M. and Ho, S. M. CLARITY	2020	Low-dose bisphenol a in a rat model of endometrial cancer: A clarity-bpa study	Environmental Health Perspectives	1
Leung, Y. K., Govindarajah, V., Cheong, A., Veevers, J., Song, D., Gear, R.,	2017	Gestational high-fat diet and bisphenol A exposure heightens mammary cancer risk	Endocrine-related cancer	2

Authors	Year	Title	Journal	Tier
Zhu, X., Ying, J., Kendler, A., Medvedovic, M., Belcher, S. and Ho, S. M.				
Li, J., Mao, R., Zhou, Q., Ding, L., Tao, J., Ran, M. M., Gao, E. S., Yuan, W., Wang, J. T. and Hou, L. F.	2016	Exposure to bisphenol A (BPA) in Wistar rats reduces sperm quality with disruption of ERK signal pathway	Toxicology Mechanisms and Methods	3
Li, L., Wang, M. Y., Jiang, H. B., Guo, C. R., Zhu, X. D., Yao, X. Q., Zeng, W. W., Zhao, Y. and Chi, L. K.	2022	Bisphenol A induces testicular oxidative stress in mice leading to ferroptosis		3
Lin, M., Hua, R., Ma, J., Zhou, Y., Li, P., Xu, X., Yu, Z. and Quan, S.	2021	Bisphenol A promotes autophagy in ovarian granulosa cells by inducing AMPK/mTOR/ULK1 signalling pathway	Environment International	3
Lite, C., Ahmed, S. S. S. J., Santosh, W. and Seetharaman, B.	2019	Prenatal exposure to bisphenol-A altered miRNA-224 and protein expression of aromatase in ovarian granulosa cells concomitant with elevated serum estradiol levels in F1 adult offspring	Journal of Biochemical and Molecular Toxicology	3
Liu, C., Duan, W., Li, R., Xu, S., Zhang, L., Chen, C., He, M., Lu, Y., Wu, H., Pi, H., Luo, X., Zhang, Y., Zhong, M., Yu, Z. and Zhou, Z.	2013	Exposure to bisphenol A disrupts meiotic progression during spermatogenesis in adult rats through estrogen-like activity	Cell Death and Disease	2
Liu, R., Cai, D., Li, X., Liu, B., Chen, J., Jiang, X., Li, H., Li, Z., Teerds, K., Sun, J., Bai, W. and Jin, Y.	2022	Effects of Bisphenol A on reproductive toxicity and gut microbiota dysbiosis in male rats	Ecotoxicology and Environmental Safety	3
Liu, X., Wang, Z. and Liu, F.	2021	Chronic exposure of BPA impairs male germ cell proliferation and induces lower sperm quality in male mice	Chemosphere	3
Liu, X. L., Chen, X. Y., Wang, Z. C., Shen, T. and Zhao, H.	2013	Effects of exposure to bisphenol A during pregnancy and lactation on the testicular morphology and caspase-3 protein expression of ICR pups	Biomedical Reports	3
Lv, Y., Li, L., Fang, Y., Chen, P., Wu, S., Chen, X., Ni, C., Zhu,	2019	In utero exposure to bisphenol A disrupts fetal testis development in rats	Environmental Pollution	3

Authors	Year	Title	Journal	Tier
Q., Huang, T., Lian, Q. and Ge, R. S.				
Ma, S., Shi, W., Wang, X., Song, P. and Zhong, X.	2017	Bisphenol A Exposure during Pregnancy Alters the Mortality and Levels of Reproductive Hormones and Genes in Offspring Mice	BioMed Research International	2
Mahalingam, S., Ther, L., Gao, L., Wang, W., Ziv-Gal, A. and Flaws, J. A.	2017	The effects of in utero bisphenol A exposure on ovarian follicle numbers and steroidogenesis in the F1 and F2 generations of mice	Reproductive Toxicology	3
Mandrup, K., Boberg, J., Isling, L. K., Christiansen, S. and Hass, U.	2016	Low-dose effects of bisphenol A on mammary gland development in rats	Andrology	1
Molangiri, A., Varma, S., M, S., Kambham, S., Duttaroy, A. K. and Basak, S.	2022	Prenatal exposure to bisphenol S and bisphenol A differentially affects male reproductive system in the adult offspring	Food and Chemical Toxicology	3
Montévil, M., Acevedo, N., Schaeberle, C. M., Bharadwaj, M., Fenton, S. E. and Soto, A. M. CLARITY	2020	A combined morphometric and statistical approach to assess nonmonotonicity in the developing mammary gland of rats in the clarity-BPA study	Environmental Health Perspectives	1
Osman, M. A., Mahmoud, G. I., Elgammal, M. H. and Hasan, R. S.	2021	Bisphenol a hormonal disrupture and preventive effect of rose water and clove oil	Biointerface Research in Applied Chemistry	3
Pan, X., Wang, X., Sun, Y., Dou, Z. and Li, Z.	2015	Inhibitory effects of preimplantation exposure to bisphenol-A on blastocyst development and implantation	International Journal of Clinical and Experimental Medicine	3
Pan, X., Wang, X., Wang, Z., Wang, X., Dou, Z. and Li, Z.	2015	Bisphenol a influences blastocyst implantation via regulating integrin β3 and trophinin expression levels	International Journal of Clinical and Experimental Medicine	3
Patel, S., Brehm, E., Gao, L., Rattan, S., Ziv-Gal, A. and Flaws, J. A. CLARITY	2017	Bisphenol a exposure, ovarian follicle numbers, and female sex steroid hormone levels: Results from a CLARITY-BPA study	Endocrinology	1
Prins, G. S., Hu, W. Y., Xie, L., Shi, G. B., Hu, D. P., Birch, L. and Bosland, M. C. CLARITY	2018	Evaluation of bisphenol a (BPA) exposures on prostate stem cell homeostasis and prostate cancer risk in the NCTR-Sprague-Dawley rat: An NIEHS/FDA CLARITY-BPA Consortium Study	Environmental Health Perspectives	1

Authors	Year	Title	Journal	Tier
Qiu, L. L., Wang, X., Zhang, X. H., Zhang, Z., Gu, J., Liu, L., Wang, Y., Wang, X. and Wang, S. L.	2013	Decreased androgen receptor expression may contribute to spermatogenesis failure in rats exposed to low concentration of bisphenol A	Toxicol Lett	3
Quan, C., Wang, C., Duan, P., Huang, W. and Yang, K.	2017	Prenatal bisphenol a exposure leads to reproductive hazards on male offspring via the Akt/mTOR and mitochondrial apoptosis pathways	Environmental Toxicology	2
Radko, L. Minta, M. Jasik, A. Stypuła-Trębas, S. Żmudzki, J.	2015	Usefulness of immature golden hamster (Mesocricetus auratus) as a model for uterotrophic assay	Journal of Veterinary Research	1
Rahman, M. S., Kwon, W. S., Karmakar, P. C., Yoon, S. J., Ryu, B. Y. and Pang, M. G.	2017	Gestational exposure to bisphenol A affects the function and proteome profile of F1 spermatozoa in adult mice	Environmental Health Perspectives	2
Rahman, M. S., Kwon, W. S., Ryu, D. Y., Khatun, A., Karmakar, P. C., Ryu, B. Y. and Pang, M. G.	2018	Functional and Proteomic Alterations of F1 Capacitated Spermatozoa of Adult Mice Following Gestational Exposure to Bisphenol A	Journal of Proteome Research	3
Rahman, M. S., Pang, W. K., Ryu, D. Y., Park, Y. J., Ryu, B. Y. and Pang, M. G.	2021	Multigenerational impacts of gestational bisphenol A exposure on the sperm function and fertility of male mice	Journal of Hazardous Materials	2
Rashid, H., Sharma, S., Beigh, S., Ahmad, F. and Raisuddin, S.	2018	Bisphenol A-induced endocrine toxicity and male reprotoxicopathy are modulated by the dietary iron deficiency	Endocrine, Metabolic and Immune Disorders - Drug Targets	3
Ruiz-Pino, F., Miceli, D., Franssen, D., Vazquez, M. J., Farinetti, A., Castellano, J. M., Panzica, G. and Tena-Sempere, M.	2019	Environmentally relevant perinatal exposures to bisphenol a disrupt postnatal Kiss1/NKB neuronal maturation and puberty onset in female mice	Environmental Health Perspectives	2
Samova, S., Doctor, H. and Verma, R.	2018	PROTECTIVE EFFECT OF QUERCETIN ON BISPHENOL A - INDUCED ENZYMATIC CHANGES IN TESTIS OF MICE	International Journal of Pharmaceutical Sciences and Research	3
Samova, S., Patel, C. N., Doctor, H., Pandya, H. A. and Verma, R. J.	2018	The effect of bisphenol A on testicular steroidogenesis and its amelioration by quercetin: An: in vivo and in silico approach	Toxicology Research	3

Authors	Year	Title	Journal	Tier
Sencar, L., coskun, G., Şaker, D., Sapmaz, T., Tuli, A., Özgür, H. and Polat, S.	2021	Bisphenol A decreases expression of Insulin-like factor 3 and induces histopathological changes in the Testes of Rats	Toxicology and Industrial Health	2
Sharma, A. K., Boberg, J. and Dybdahl, M.	2018	DNA damage in mouse organs and in human sperm cells by bisphenol A	Toxicological and Environmental Chemistry	3
Shi, M., Sekulovski, N., MacLean, J. A., II and Hayashi, K.	2018	Prenatal exposure to bisphenol A analogues on male reproductive functions in mice	Toxicological Sciences	3
Shi, M., Sekulovski, N., MacLean, J. A., Whorton, A. and Hayashi, K.	2019	Prenatal Exposure to Bisphenol A Analogues on Female Reproductive Functions in Mice	Toxicological Sciences	3
Srivastava, S. and Dhagga, N.	2019	Dose exposure of Bisphenol- A on female Wistar rats fertility	Hormone Molecular Biology and Clinical Investigation	3
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	2
Srivastava, S. and Gupta, P.	2018	Alteration in apoptotic rate of testicular cells and sperms following administration of Bisphenol A (BPA) in Wistar albino rats	Environmental Science and Pollution Research	2
Tarapore, P., Hennessy, M., Song, D., Ying, J., Ouyang, B., Govindarajah, V., Leung, Y. K. and Ho, S. M.	2016	Data on spermatogenesis in rat males gestationally exposed to bisphenol A and high fat diets	Data in Brief	3
Tarapore et al.	2017	High butter-fat diet and bisphenol A additively impair male rat spermatogenesis		3
Thilagavathi, S., Pugalendhi, P., Rajakumar, T. and Vasudevan, K.	2018	Monotonic Dose Effect of Bisphenol-A, an Estrogenic Endocrine Disruptor, on Estrogen Synthesis in Female Sprague-Dawley Rats	Indian Journal of Clinical Biochemistry	3
Tucker 2018	2018	Evaluation of Prenatal Exposure to Bisphenol Analogues on Development and Long-Term Health of the Mammary Gland in Female Mice	Environ Health Perspect	1

Authors	Year	Title	Journal	Tier
Tian, J., Ding, Y., She, R., Ma, L., Du, F., Xia, K. and Chen, L.	2017	Histologic study of testis injury after bisphenol A exposure in mice: Direct evidence for impairment of the genital system by endocrine disruptors	Toxicology and Industrial Health	3
Uchtmann	2020	Fetal bisphenol A and ethinylestradiol exposure alters male rat urogenital tract morphology at birth: Confirmation of prior low-dose findings in CLARITY-BPA	Reproductive Toxicity	1
Ullah, A., Pirzada, M., Jahan, S., Ullah, H. and Khan, M. J.	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	2
Ullah, A., Pirzada, M., Jahan, S., Ullah, H., Razak, S., Rauf, N., Khan, M. J. and Mahboob, S. Z.	2019	Prenatal BPA and its analogs BPB, BPF, and BPS exposure and reproductive axis function in the male offspring of Sprague Dawley rats	Human and Experimental Toxicology	2
Ullah, A., Pirzada, M., Jahan, S., Ullah, H., Shaheen, G., Rehman, H., Siddiqui, M. F. and Butt, M. A.	2018	Bisphenol A and its analogs bisphenol B, bisphenol F, and bisphenol S: Comparative in vitro and in vivo studies on the sperms and testicular tissues of rats	Chemosphere	2
Vijaykumar, T., Singh, D., Vanage, G. R., Dhumal, R. V. and Dighe, V. D.	2017	Bisphenol a-induced ultrastructural changes in the testes of common marmoset	Indian Journal of Medical Research	3
Vilela, J., Hartmann, A., Silva, E. F., Cardoso, T., Corcini, C. D., Varela-Junior, A. S., Martinez, P. E. and Colares, E. P.	2014	Sperm impairments in adult vesper mice (Calomys laucha) caused by in utero exposure to bisphenol A	Andrologia	3
Wang, H. F., Liu, M., Li, N., Luo, T., Zheng, L. P. and Zeng, X. H.	2016	Bisphenol a impairs mature sperm functions by a CatSper-relevant mechanism	Toxicological Sciences	3
Wang, P., Luo, C., Li, Q., Chen, S. and Hu, Y.	2014	Mitochondrion-mediated apoptosis is involved in reproductive damage caused by BPA in male rats	Environmental Toxicology and Pharmacology	2
Wang, W., Hafner, K. S. and Flaws, J. A.	2014	In utero bisphenol A exposure disrupts germ cell nest breakdown and reduces fertility with age in the mouse	Toxicology and Applied Pharmacology	2

Authors	Year	Title	Journal	Tier
Wang, Y., Wu, Y. and Zhang, S.	2022	Impact of bisphenol-A on the spliceosome and meiosis of sperm in the testis of adolescent mice	BMC Veterinary Research	3
Wei, Y., Han, C., Geng, Y., Cui, Y., Bao, Y., Shi, W. and Zhong, X.	2019	Maternal exposure to bisphenol A during pregnancy interferes testis development of F1 male mice	Environmental Science and Pollution Research	3
Wei, Y., Han, C., Li, S., Cui, Y., Bao, Y. and Shi, W.	2020	Maternal exposure to bisphenol A during pregnancy interferes ovaries development of F1 female mice	Theriogenology	3
Witchey, S. K., Fuchs, J. and Patisaul, H. B.	2019	Perinatal bisphenol A (BPA) exposure alters brain oxytocin receptor (OTR) expression in a sex- and region- specific manner: A CLARITY-BPA consortium follow-up study	NeuroToxicology	1
Wong, R. L. Y., Wang, Q., Treviño, L. S., Bosland, M. C., Chen, J., Medvedovic, M., Prins, G. S., Kannan, K., Ho, S. M. and Walker, C. L.	2015	Identification of Secretaglobin Scgb2a1 as a target for developmental reprogramming by BPA in the rat prostate	Epigenetics	3
Wu, J., Huang, D., Su, X., Yan, H. and Sun, Z.	2016	Oral administration of low-dose bisphenol A promotes proliferation of ventral prostate and upregulates prostaglandin D2 synthase expression in adult rats	Toxicology and Industrial Health	2
Wu, S., Huang, D., Su, X., Yan, H., Ma, A., Li, L., Wu, J. and Sun, Z.	2020	The prostaglandin synthases, COX-2 and L-PGDS, mediate prostate hyperplasia induced by low-dose bisphenol A	Scientific Reports	2
Wu, S., Huang, D., Su, X., Yan, H., Wu, J. and Sun, Z.	2019	Oral exposure to low-dose bisphenol A induces hyperplasia of dorsolateral prostate and upregulates EGFR expression in adult Sprague-Dawley rats	Toxicology and Industrial Health	2
Xu 2015	2015	Sex-specific effects of long-term exposure to bisphenol-A on anxiety- and depression-like behaviors in adult mice	Chemosphere	3
Ye, Y., Tang, Y., Xiong, Y., Feng, L. and Li, X.	2019	Bisphenol A exposure alters placentation and causes preeclampsia-like features in pregnant mice involved in reprogramming of DNA methylation of WNT2	FASEB Journal	2
Yin, L., Dai, Y., Cui, Z., Jiang, X., Liu, W.,	2017	The regulation of cellular apoptosis by the ROS-triggered PERK/EIF2α/chop pathway plays a	Toxicology and Applied Pharmacology	3

Authors	Year	Title	Journal	Tier
Han, F., Lin, A., Cao, J. and Liu, J.		vital role in bisphenol A-induced male reproductive toxicity		
Yuan, M., Hu, M., Lou, Y., Wang, Q., Mao, L., Zhan, Q. and Jin, F.	2018	Environmentally relevant levels of bisphenol A affect uterine decidualization and embryo implantation through the estrogen receptor/serum and glucocorticoid-regulated kinase 1/epithelial sodium ion channel α-subunit pathway in a mouse model	Fertility and Sterility	3
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	3
Ziv-Gal, A., Wang, W., Zhou, C. and Flaws, J. A.	2015	The effects of in utero bisphenol A exposure on reproductive capacity in several generations of mice	Toxicology and Applied Pharmacology	3
Zou, H., Wang, S., Liu, Y., Mo, J., Yang, L., Zhao, Y., Yi, P., Niu, Y., Huang, Y. and Lu, Y.	2020	The effect of hormonal levels and oxidative stress on bisphenol A and soy isoflavone reproductive toxicity in murine offspring	Molecular Medicine Reports	3

Tier 1 studies: (Arambula et al., 2017; Camacho et al., 2019; Delclos et al., 2014; Dere et al., 2018; Kendziorski and Belcher, 2015a; Kendziorski and Belcher, 2015b; Leung et al., 2020; Mandrup et al., 2016; Montévil et al., 2020; Patel et al., 2017; Radko et al., 2015; Tucker et al., 2018; Uchtmann et al., 2020; Witchey et al., 2019)

Tier 2 Studies: (Alabi et al., 2021; Christiansen et al., 2014; DeCatanzaro et al., 2013; Gao et al., 2020b; Hass et al., 2016; Huang et al., 2018; Karabulut and Gulay, 2020; Karmakar et al., 2020; Leung et al., 2017; Liu et al., 2013a; Ma et al., 2017; Quan et al., 2017; Rahman et al., 2017; Rahman et al., 2021; Ruiz-Pino et al., 2019; Sencar et al., 2021; Srivastava and Gupta, 2016; Srivastava and Gupta, 2018; Ullah et al., 2019a; Ullah et al., 2019b; Ullah et al., 2018a; Wang et al., 2014a; Wang et al., 2014b; Wu et al., 2016; Wu et al., 2020; Wu et al., 2019; Ye et al., 2019)

Tier 3 studies: (Barberio et al., 2021; Berger et al., 2016; Cao et al., 2020; Cao et al., 2018; Dobrzyńska et al., 2018; Dobrzyńska et al., 2022; Dobrzyńska et al., 2015; Dobrzyńska et al., 2014; Dobrzyńska and Radzikowska, 2013; Eckstrum et al., 2018; Fang et al., 2015; Gurmeet et al., 2014; Hu et al., 2018; Jiang et al., 2018; Kalb et al., 2016; Karnam et al., 2015; Kazemi et al., 2016a; Kazemi et al., 2016b; Li et al., 2016; Li et al., 2022; Lin et al., 2021; Lite et al., 2019; Liu et al., 2022; Liu et al., 2013b; Lv et al., 2019; Mahalingam et al., 2017; Molangiri et al., 2022; Osman et al., 2021; Pan et al., 2015a; Pan et al., 2015b; Qiu et al., 2013; Rahman et al., 2018; Rashid et al., 2018; Samova et al., 2018a; Samova et al., 2018b; Samova et al., 2018c; Sharma et al., 2018; Shi et al., 2018; Shi et al., 2019; Srivastava and Dhagga, 2019; Tarapore et al., 2016; Tarapore et al., 2017; Thilagavathi et al., 2018; Tian et al., 2017; Ullah et al., 2018b; Vijaykumar et al., 2017; Vilela et al., 2014; Wang et al., 2016; Wang et al., 2022; Wei et al., 2019; Wei et al., 2020; Wong et al., 2015;

Xu et al., 2015; Yin et al., 2017; Yuan et al., 2018; Zhang et al., 2019; Ziv-Gal et al., 2015; Zou et al., 2020)

7 Appendix B: Study selection and evaluation for metabolic effects (uric acid)

Author	Year	Title	Journal	Tier
Lee Y.J., Lim Y.H., Shin C.H., Kim B.N., Kim J.I., Hong Y.C., Cho Y.M., and Lee Y.A.	2022	Relationship between bisphenol A, bisphenol S, and bisphenol F and serum uric acid concentrations among school-aged children	PLoS ONE	3
Hu J., Peng C., Li J., Gao R., Zhang A., Ma L., Zhang L., Yang Y., Cheng Q., Wang Y., Luo T., Wang Z., Qing H., Yang S., and Li Q.	2019	Serum Bisphenol A is an independent risk factor of hyperuricemia: A 6-year prospective study	Seminars in Arthritis and Rheumatism	3
Ma L., Hu J., Li J., Yang Y., Zhang L., Zou L., Gao R., Peng C., Wang Y., Luo T., Xiang X., Qing H., Xiao X., Wu C., Wang Z., He J.C., Li Q., and Yang S.	2018	Bisphenol A promotes hyperuricemia via activating xanthine oxidase	The FASEB Journal	3

8 Appendix C: Study selection and evaluation for immunotoxicity

Author	Year	Title	Journal	Tier
Bansal, A., Rashid, C., Xin, F., Li, C., Polyak, E., Duemler, A., van der Meer, T., Stefaniak, M., Wajid, S., Doliba, N., Bartolomei, M. S., Simmons, R. A.	2017	Sex- and Dose-Specific Effects of Maternal Bisphenol A Exposure on Pancreatic Islets of First- and Second-Generation Adult Mice Offspring	Environmenatl Health Perspective	3
Bauer, S. M., Roy, A., Emo, J., Chapman, T. J., Georas, S. N., Lawrence, B. P.	2012	The effects of maternal exposure to bisphenol A on allergic lung inflammation into adulthood	Toxicological Sciences	2
Bodin, J., Bølling, A. K., Becher, R., Kuper, F., Løvik, M., Nygaard, U. C.	2014	Transmaternal bisphenol A exposure accelerates diabetes type 1 development in NOD mice	Toxicological Sciences	3
Bruno, K. A., Mathews, J. E., Yang, A. L., Frisancho, J. A., Scott, A. J., Greyner, H. D., Molina, F. A., Greenaway, M. S., Cooper, G. M., Bucek, A., Morales-Lara, A. C., Hill, A. R., Mease, A. A., Di Florio, D. N., Sousou, J. M., Coronado, A. C., Stafford, A. R., Fairweather, D.	2019	BPA Alters Estrogen Receptor Expression in the Heart After Viral Infection Activating Cardiac Mast Cells and T Cells Leading to Perimyocarditis and Fibrosis	Frontiers in Endocrinology	3
Cetkovic-Cvrlje, M., Thinamany, S., Bruner, K. A.	2017	Bisphenol A (BPA) aggravates multiple low-dose streptozotocin-induced Type 1 diabetes in C57BL/6 mice	Journal of Immunotoxicology	2
Dong, Y. D., Gao, L., Wu, F. J., Lin, R., Meng, Y., Jia, L. H., Wang, X. F	2020	Abnormal differentiation of regulatory T cells and Th17 cells induced by perinatal bisphenol A exposure in female offspring mice	Molecular and Cellular Toxicology	2
Gao, L., Dong, Y., Lin, R., Meng, Y., Wu, F., Jia, L.	2020	The imbalance of Treg/Th17 cells induced by perinatal bisphenol A exposure is associated with activation of the PI3K/Akt/mTOR signaling pathway in male offspring mice	Food and Chemical Toxicology	2

Author	Year	Title	Journal	Tier
He, M., Ichinose, T., Yoshida, S., Takano, H., Nishikawa, M., Shibamoto, T., Sun, G.	2016	Exposure to bisphenol A enhanced lung eosinophilia in adult male mice	Allergy, Asthma and Clinical Immunology	3
Krementsov, D. N., Katchy, A., Case, L. K., Carr, F. E., Davis, B., Williams, C., Teuscher, C.	2013	Studies in experimental autoimmune encephalomyelitis do not support developmental bisphenol a exposure as an environmental factor in increasing multiple sclerosis risk	Toxicological Sciences	3
Loffredo, L. F., Berdnikovs, M. E. C. S.	2020	Endocrine disruptor bisphenol a (BPA) triggers systemic para-inflammation and is sufficient to induce airway allergic sensitization in mice	Nutrients	3
Luo, S., Li, Y., Li, Y., Zhu, Q., Jiang, J., Wu, C., Shen, T.	2016	Gestational and lactational exposure to low-dose bisphenol A increases Th17 cells in mice offspring	Environmental Toxicology and Pharmacology	3
Malaisé, Y., Menard, S., Cartier, C., Gaultier, E., Lasserre, F., Lencina, C., Harkat, C., Geoffre, N., Lakhal, L., Castan, I., Olier, M., Houdeau, E., Guzylack-Piriou, L.	2017	Gut dysbiosis and impairment of immune system homeostasis in perinatally-exposed mice to Bisphenol A precede obese phenotype development	Scientific Reports	3
Malaisé, Y., Ménard, S., Cartier, C., Lencina, C., Sommer, C., Gaultier, E., Houdeau, E., Guzylack-Piriou, L.	2018	Consequences of bisphenol a perinatal exposure on immune responses and gut barrier function in mice	Arch Toxicol	3
Malaisé, Y., Le Mentec, H., Sparfel, L., Guzylack-Piriou, L.	2020	Differential influences of the BPA, BPS and BPF on in vitro IL-17 secretion by mouse and human T cells	Toxicology in Vitro	3
Midoro-Horiuti, T., Tiwari, R., Watson, C. S., Goldblum, R. M.	2010	Maternal bisphenol a exposure promotes the development of experimental asthma in mouse pups	Environmental Health Perspective	3
Misme-Aucouturier, B., De Carvalho, M., Delage, E., Dijoux, E., Klein, M., Brosseau, C., Bodinier, M., Guzylack-Piriou, L., Bouchaud, G.	2022	Oral exposure to bisphenol A exacerbates allergic inflammation in a mouse model of food allergy	Toxicology	3
Nakajima, Y., Goldblum, R. M., Midoro-Horiuti, T.	2012	Fetal exposure to bisphenol A as a risk factor for the development of childhood asthma: an animal model study	Environmental Health	3

Author	Year	Title	Journal	Tier
Nygaard, U. C., Vinje, N. E., Samuelsen, M., Andreassen, M., Groeng, E. C., Bølling, A. K., Becher, R., Lovik, M., Bodin, J.	2015	Early life exposure to bisphenol A investigated in mouse models of airway allergy, food allergy and oral tolerance	Food and Chemical Toxicology	2
O'Brien, E., Bergin, I. L., Dolinoy, D. C., Zaslona, Z., Little, R. J. A., Tao, Y., Peters-Golden, M., Mancuso, P.	2014	Perinatal bisphenol A exposure beginning before gestation enhances allergen sensitization, but not pulmonary inflammation, in adult mice	Journal of Developmental Origins of Health and Disease	3
Ogo, F. M., de Lion Siervo, G. E. M., Staurengo-Ferrari, L., de Oliveira Mendes, L., Luchetta, N. R., Vieira, H. R., Fattori, V., Verri, W. A. Jr., Scarano, W. R., Fernandes, G. S. A	2018	Bisphenol A Exposure Impairs Epididymal Development during the Peripubertal Period of Rats: Inflammatory Profile and Tissue Changes	Basic Clin Pharmacol Toxicol	3
Petzold, S., Averbeck, M., Simon, J. C., Lehmann, I., Polte, T.,	2014	Lifetime-dependent effects of bisphenol a on asthma development in an experimental mouse model	PLoS ONE	3
Tajiki-Nishino, R., Makino, E., Watanabe, Y., Tajima, H., Ishimota, M., Fukuyama, T.	2018	Oral Administration of Bisphenol A Directly Exacerbates Allergic Airway Inflammation but Not Allergic Skin Inflammation in Mice	Toxicological Sciences	3
Wang, G., Li, Y., Li, Y., Zhang, J., Zhou, C., Wu, C., Zhu, Q., Shen, T.	2020a	Maternal vitamin D supplementation inhibits bisphenol A-induced proliferation of Th17 cells in adult offspring	Food and Chemical Toxicology	
Wang, S., Yang, Y., Luo, D., Wu, D., Liu, H., Li, M., Sun, Q., Jia, L.	2020	Lung inflammation induced by exposure to Bisphenol-A is associated with mTOR-mediated autophagy in adolescent mice		2
Yanagisawa, R., Koike, E., Win-Shwe, T. T., Takano, H.	2019	Oral exposure to low dose bisphenol A aggravates allergic airway inflammation in mice	Toxicology Reports	2

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