Bisphenol A

Health-based recommendation on occupational exposure limits

To: the State Secretary of Social Affairs en Employment
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Health Council of the Netherlands

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samenvatting

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid (SZW) heeft de Gezondheidsraad de gezondheidskundige advieswaarde voor beroepsmatige blootstelling aan bisfenol A geactualiseerd.

Dit advies is tot stand gekomen in de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS). Op www.gezondheidsraad.nl staat informatie over de taken van deze vaste commissie van de Gezondheidsraad. De samenstelling van de commissie is te vinden achterin dit advies.

Bisfenol A: schadelijk voor ogen, huid, luchtwegen en vruchtbaarheid

Bisfenol A (in de volksmond beter bekend als BPA) is een weekmaker. Het wordt onder meer gebruikt in plastic flessen. Bisfenol A is geclassificeerd als schadelijk voor de vruchtbaarheid (gevarencategorie 1B). Daarnaast kan blootstelling aan bisfenol A leiden tot schade aan de ogen, allergische huidreacties en irritatie van de luchtwegen. Er bestaan binnen de EU beperkingen voor het gebruik van bisfenol A. Zo is het sinds 2011 verboden in flesjes voor babyvoeding en het gebruik in thermisch papier (voor kassabonnen) is sinds 2016 aan banden gelegd. Voor het gebruik in materialen die in contact komen met voedsel gelden maxima voor de hoeveelheid bisfenol A die eruit vrij mag komen.

Gezondheidskundige advieswaarde

Voor schadelijke stoffen waaraan mensen tijdens hun werk kunnen worden blootgesteld, gaat de commissie na of er uit wetenschappelijk onderzoek een concentratie is vast te stellen waarbij geen gezondheidseffecten te verwachten zijn. Deze gezondheidskundige advieswaarde is de basis waarop de minister een grenswaarde voor beroepsmatige blootstelling kan vaststellen.

In 1996 heeft de Gezondheidsraad voor beroepsmatige blootstelling een advieswaarde afgeleid van 10 milligram (mg) inhaleerbaar bisfenol A per kubieke meter (m^3) lucht, en een advieswaarde van 5 mg per m^3 voor respirabel bisfenol A. Momenteel geldt een grenswaarde van 2 mg inhaleerbaar bisfenol A per m^3 lucht. Die grenswaarde is gebaseerd op een advies van de *Europese Scientific Committee on Occupational Exposure Limits* (SCOEL) uit 2013.

Sinds 2013 zijn er tal van wetenschappelijke onderzoeken verschenen over mogelijke gezondheidseffecten van bisfenol A. Voor het beoordelen van onderzoeken tot 2015 is de commissie uitgegaan van een rapport van de *European Food Safety Authority* (EFSA). Voor de onderzoeken vanaf 2015 heeft de commissie zelf gezocht naar publicaties.

Wel of geen monotone dosis-ffectrelatie?

Bij het afleiden van een gezondheidskundige advieswaarde wordt uitgegaan van het principe dat een effect groter wordt bij een hogere dosis (een monotone dosis-effect relatie). Sommige onderzoekers veronderstellen dat voor bisfenol A effecten kunnen optreden volgens een niet-monotone dosis-effectrelatie. De commissie is van oordeel dat daar onvoldoende bewijs voor is en hanteert daarom haar gebruikelijke werkwijze.

Voorkeur voor onderzoeken naar inademing

Voor het afleiden van een advieswaarde in de lucht gebruikt de commissie bij voorkeur onderzoeken waarin blootstelling via de lucht plaatsvond. Er zijn in de laatste jaren slechts enkele studies uitgevoerd met blootstelling aan bisfenol A via de lucht en daarin werden geen duidelijke nadelige effecten gevonden. Daarom gebruikt de commissie het onderzoek van Nitschke en anderen uit 1988, waarin ratten aan bisfenol A zijn blootgesteld via de luchtwegen en waardoor ontstekingen in de neusholte ontstonden. Dit onderzoek heeft ze ook in haar eerdere advies gebruikt en ook het advies van de SCOEL uit 2013 is er op gebaseerd.

Op basis van het onderzoek van Nitschke komt de commissie uit op een advieswaarde van 3,3 mg/m^3. Deze waarde is lager dan de eerdere waarde van de commissie en wijkt af van het advies van de SCOEL. Deze verschillen zijn terug te voeren op verschillen in werkwijze. Zo heeft de commissie in het verleden geen onzekerheidsfactor toegepast voor de vertaling van diergegevens naar de mens en rondt de SCOEL de afgeleide waarden af tot zogenoemde voorkeurswaarden.

Voor effecten op voortplanting ook onderzoeken naar inname meegenomen

In het onderzoek van Nitschke is niet gekeken naar mogelijke effecten van bisfenol A op de voortplanting. Er zijn veel onderzoeken waarin proefdieren (met name ratten en muizen) oraal bisfenol A krijgen toegediend, waarbij wel mogelijke effecten op de voortplanting zijn bestudeerd. Veel van deze onderzoeken zijn van onvoldoende kwaliteit en voldoen niet aan de internationale richtlijnen voor toxiciteitsonderzoek. De commissie heeft de resultaten van het meest geschikte onderzoek, waarin overigens geen effecten op de voortplanting werden gevonden, omgerekend tot een advieswaarde in de lucht. Die waarde is vergelijkbaar met de waarde die is afgeleid van het onderzoek van Nitschke naar bisfenol A blootstelling via de luchtwegen.

Blootstelling via de huid

De commissie concludeert op basis van de huidige stand van de wetenschap dat een huidnotatie voor bisfenol A niet nodig is. Huidcontact draagt namelijk niet substantieel bij

aan de totale inwendige blootstelling bij een concentratie ter hoogte van de advieswaarde.

Advies aan de staatssecretaris

Voor de beroepsmatige blootstelling aan bisfenol komt de commissie tot een gezondheidskundige advieswaarde van 3,3 mg bisfenol A per m^3 lucht. Deze waarde geldt voor de inhaleerbare fractie (dat deel van de in de lucht aanwezige stof dat kan worden ingeademd via mond en/of neus) en als een gemiddelde concentratie over een achturige werkdag.

executive summary

At the request of the Ministry of Social Affairs and Employment, the Health Council of the Netherlands has derived a health-based advisory value for bisphenol A. This advisory report has been composed by the Dutch Expert Committee on Occupational Safety (DECOS). More information on the tasks of this permanent committee of the Health Council of the Netherlands can be found at www.gezondheidsraad.nl. The members of the Committee are listed on the last page of this report.

Bisphenol A: Hazardous to eyes, skin, airways and reproduction

Bisphenol A (BPA) is a plasticizer. It is used in a wide range of consumer products such as plastic bottles. Bisphenol A is classified as reproduction toxicant (Category 1B; for fertility). Exposure to bisphenol A can also lead to damage to the eyes, allergic skin reactions and irritations of the airways. Bisphenol A has been restricted in several products in the EU. For instance, bisphenol A is restricted in thermal paper since 2016 and banned from infant feeding bottles since 2011. Also, bisphenol A can be used in materials that are in contact with food, but there is a maximum amount that is allowed to leach out of the material.

Health-based advisory value

For hazardous substances to which people can be occupationally exposed, the Committee determines whether a concentration can be derived at which no adverse health effects are expected. These health-based advisory values are the basis at which the State Secretary can set an occupational exposure limit.

In 1996, the Health Council has derived an advisory value for occupational exposure of 10 milligram (mg) inhalable bisphenol A per cubic metre (m^3), and an advisory value of 5 mg/m^3 for respirable bisphenol A. Currently, an occupational exposure limit of 2 mg inhalable bisphenol A per m^3 air is applied. This occupational exposure limit is based on a recommendation of the *European Scientific Committee on Occupational Exposure Limits* (SCOEL) from 2013.

Since 2013, many studies have been published on the toxicity of bisphenol A. For the evaluation of studies until 2015, the Committee has adopted the conclusions of the 2015 opinion of the *European Food Safety Authority* (EFSA). Publications from 2015 and onwards were evaluated by the Committee itself.

Monotonic or non-monotonic dose-response relationship?

When deriving health-based advisory values, the principle is applied that an effect increases with an increasing dose (a monotonic dose-response relationship). Some investigators assume that for bisphenol A, effects can develop according to a non-monotonic exposure-

response relationship. The Committee is of the opinion that there is insufficient evidence of such a relationship and therefore applies its usual approach.

Preference for inhalation studies

For derivation of health-based advisory values in air, the Committee preferentially uses studies with exposures by inhalation. In recent years, only few inhalation studies with bisphenol A were published and in none of them, clear adverse effects have been observed. The Committee therefore uses the rat inhalation study by Nitschke et al. (1988), in which animals developed inflammation in the epithelium of the anterior portion of the nasal cavity. This study was used by the Committee for its previous report and it also forms the basis of the SCOEL recommendation from 2013. From the Nitschke et al. (1988) study the Committee has derived a health-based advisory value of 3.3 mg/m^3. This value is lower than the Committee's previous value, and differs from the recommendation of the SCOEL. These differences can be explained by differences in methodology. Namely, for its previous advisory value the Committee did not apply an uncertainty factor for extrapolation from animals to humans and the SCOEL applied the so-called preferred value approach.

For effects on reproduction oral studies taken into account

In the study by Nitschke et al. (1988), possible effects of bisphenol A on reproduction were not addressed. Many animal studies are available (mostly with rats and mice) investigating possible effects on reproduction after oral exposure to bisphenol A. Many of these studies are of insufficient quality and do not meet international testing guidelines. The Committee has translated the results of the most relevant oral study with bisphenol A, in which no specific effects on reproduction were observed, to derive a value in air. This value is comparable with the advisory value that is based on the inhalation study by Nitschke et al. (1988).

Skin exposure

The Committee concludes that the data available do not indicate that a skin notation for bisphenol A is warranted. Dermal absorption does not substantially contribute to the internal exposure to bisphenol A, at the level of the advisory value.

Advice to the State Secretary

For occupational exposure to bisphenol A, the Committee derives a health-based advisory value of 3.3 mg bisphenol A per m^3 air. The value relates to the inhalable fraction (the fraction of the substance in air that can be inhaled through mouth and/or nose) and represents a mean concentration during an 8-h working day.

01 scope

1.1 Background and objective

At request of the Minister of Social Affairs and Employment, the Dutch Expert Committee on Occupational Safety (DECOS), a committee of the Health Council of the Netherlands, performs scientific evaluations on the toxicity of chemical substances that are used in the workplace. The purpose of these evaluations is to recommend a health-based occupational exposure limit for concentrations in the air, provided the database allows derivation of such a value. In the Netherlands, these recommendations serve as a basis in setting public occupational exposure limits by the Minister.

In this advisory report, an evaluation is made for bisphenol A.

1.2 Committee and procedure

This document contains the assessment of the DECOS, hereafter called the Committee. The members of the Committee and consulted experts are listed at the end of the report.

In July 2017, the Committee released a draft report for public review. The Committee has taken the comments received into account, and released a second draft version in October 2018. No comments were received on the second draft report. The comments on the first draft report and the response of the Committee can be found on the website of the Health Council.

1.3 Data

An extensive dataset on bisphenol A toxicity is available. Also several risk assessments and opinions have been published, including those prepared by the EU (2003, 2008), the European Food Safety Authority (EFSA) (2015), the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) (2015; 2017), the Risk Assessment Committee (RAC) of the European Chemicals Agency (ECHA) (2015), the Scientific Committee on Occupational Exposure Limits (SCOEL) (2004, 2013) and the Dutch National Institute for Public Health and the Environment (RIVM) (2014, 2016).[1-12] Most relevant in the context of deriving a health-based recommended exposure limit (HBROEL) are the quantitative assessments on health risks and exposure to bisphenol A, which are related to either the workplace (evaluations of the DECOS, the SCOEL, and the RAC)[3,10,13] or consumers (the EFSA)[5,6]. The recent evaluations by the RIVM are also of interest, as the RIVM concluded that recently published literature suggests that exposure limits derived previously should be reconsidered (most notably the t-TDI derived by EFSA for consumers and exposure via food and the recommended occupational exposure limit (OEL) derived by the SCOEL for workers and exposure through air).[8,7]

In particular, the Committee notes the thorough evaluation of the literature on bisphenol A by the EFSA.[6] The Committee used this evaluation as starting point for the hazard assessment, although it recognizes that the EFSA evaluation focusses on oral exposure while inhalation is the most

relevant route for the workplace.The literature reviewed by the EFSA was used as such and not re-evaluated by the Committee. An additional literature search was done until May 2018 using key words “bisphenol A” and “tox*” to identify literature published since the publication of the EFSA opinion. Relevant publications were selected based on the abstracts.

02
uses, existing guidelines and standards

2.1 Uses

Bisphenol A (BPA, 4,4'-Isopropylidenediphenol, CAS-number 80-05-7) is manufactured from phenol and acetone by an acid or alkaline catalysed condensation reaction. Bisphenol A is used as a monomer in the manufacture of polycarbonates, which is its main use, and epoxy resins and as an additive in plastics. It is subsequently present in a wide range of consumer products such as plastic bottles and receipts. Due to its hazardous properties, bisphenol A has already been restricted in several products in the EU. For instance, bisphenol A is restricted in thermal paper since 2016 and banned from infant feeding bottles since 2011. Also, there is a maximum amount of bisphenol A that is allowed to leach out of the materials that are in contact with food.[a] Other uses include for example flame retardants, unsaturated polyester resins and polyacrylate, polyetherimide and polysulphone resins.[4-6,9]

2.2 Current exposure limits for the working population

Current occupational exposure limits of several countries are presented in Table 2.1.

Table 2.1. Occupational exposure limits applied word-wide. (source: Social Economic Council[#]; Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (IFA)[##])

Country (organization)	Concentration (mg/m^3)	TWA	Type of OEL
The Netherlands	2	8h	Inhalable fraction
Germany (AGS)	5	8h	Inhalable fraction
France	10	8h	
UK	10	8h	
EU	2	8h	Inhalable fraction
USA			
NIOSH	None		
OSHA	None		

[#] https://www.ser.nl/nl/thema/arbeidsomstandigheden/Grenswaarden-gevaarlijke-stoffen/Grenswaarden (accessed March 3, 2019).

[##] Gestis Limit Values: http://limitvalue.ifa.dguv.de (accessed March 9, 2019).

2.3 Classification

According to the harmonised classification and labelling (ATP09) approved by the EU, bisphenol A may damage fertility (Repr. 1B; H360F), causes serious eye damage (Eye Dam.; H318), may cause an allergic skin reaction (Skin sens.1; H317) and may cause respiratory irritation (STOT SE 3; H335).

[a] https://chemicalsinourlife.echa.europa.eu/bisphenol-a (accessed December, 2018)

03
selection of previous evaluations and recent literature

3.1 The Netherlands Health Council (1996)

In a previous evaluation in 1996, the Committee concluded that there were insufficient human data available to derive a health-based recommended occupational exposure level (HBROEL).[13] Therefore, it derived a HBROEL for Bisphenol A based on animal data.

The Committee based its derivation on a study by Nitschke et al. (1988)[a]. In this study, groups of 30 rats per sex were exposed by inhalation to 0, 10, 50 or 150 mg/m^3 bisphenol A for 6 hours/day, for 5 days/week for 13 weeks.[14] Animals were necropsied either on the day following the last exposure, or allowed to recover for 4 or 12 weeks. Terminal body weights of male rats exposed to 10, 50 or 150 mg/m^3 were not different from controls. Body weights of female rats in the highest dose group were decreased (approximately 11%). The following effects on organ weight were noted: decreased absolute liver weight in males at 10 or 150 mg/m^3; decreased absolute liver and kidney weights in females exposed to 150 mg/m^3; increased relative brain weights in females exposed to 50 or 150 mg/m^3; and increased relative lung weights in females exposed to 150 mg/m^3.

These changes were not accompanied by microscopic changes. Enlarged ceca were found the day after exposure but were not apparent after 12 weeks recovery. Examination of the respiratory tract revealed very slight to slight epithelial hyperplasia and chronic inflammation of the submucosa in the nasal cavity of rats exposed to 50 or 150 mg/m^3. These effects were fully reversible within 12 weeks after cessation of exposure.

The Committee used a NOAEL of 10 mg/m^3 as a starting point. To extrapolate from rat to humans, a safety factor was not considered necessary because of the absence of systemic effects and the fact that the margin of safety between the NOAEL and the LOAEL for local effects is a factor 5. The Committee proposed a HBROEL of 5 mg/m^3 for respirable bisphenol A, and of 10 mg/m^3 for the compound in inhalable form, to be averaged over an eight-hour workday (8-h TWA).

3.2 The Scientific Committee on Occupational Exposure Limits (SCOEL) (2013)

In 2013, the SCOEL published an update of its earlier criteria document (2004) and amended its original recommendation.[9,10] The SCOEL evaluated the existing toxicological literature on bisphenol A up to May 2012, covering the data published since the publication of previous evaluation.

To establish a recommended OEL, the SCOEL focused on the available data relating to inhalation exposure. The SCOEL identified respiratory tract irritation as the most critical effect of bisphenol A upon inhalation and therefore used the same study as the Committee for derivation of an OEL, i.e. that of Nitschke et al. (1988).[14] Also the SCOEL derived a NOAEL of 10 mg/m^3, with mild olfactory epithelium inflammation as the critical

[a] The Committee referred to a ‘study from 1988,reported by Webb (1990)’. This appears to be the study by Nitschke et al. (1988), which was also used by the SCOEL.

adverse effects at 50 and 150 mg/m^3.[14] No evidence of systemic toxicity was noted in this study according to the SCOEL.

This NOAEL was taken as the starting point for deriving a recommended OEL, and divided by an assessment factor of 3 to cover the uncertainties related to the inter-species extrapolation. Using the preferred value approach, 3 mg/m^3 was rounded to a recommended value of 2 mg/m^3 (as inhalable dust). The SCOEL also noted that concern has been raised for systemic toxicity after long-term exposure. This was related to the effects on kidney weight and liver seen in rodents, for which a BMDL10 of 3.5 mg/kg bw and a NOAEL of > 5 mg/kg bw was derived, respectively. According to the SCOEL, these doses are equivalent to an inhalation exposure level of 34 and 49 mg/m^3, respectively. Because the observed liver and kidney effects were very mild even at the highest dose levels, the recommended value was considered sufficiently conservative by the SCOEL (covering also the extrapolation to long-term exposure, and possible remaining inter- and intra-species differences in toxicokinetics and toxicodynamics).

3.3 The European Food Safety Authority (EFSA) (2015)

In 2015, the EFSA updated its opinion on the human health hazards of bisphenol A exposure, based on an extensive assessment of the available literature.[4-6] In this hazard evaluation, the EFSA also reconsidered its tolerable daily intake[a] (TDI) derived previously. For the selection of a starting point, the EFSA determined in a weight of evidence approach the likelihood that a particular effect was associated with exposure to bisphenol A. Regarding general toxicity, bisphenol A was considered to affect kidney and liver weight based on observations in parental animals and in the following generations of rats (Tyl et al., 2002)[15] and mice (Tyl et al., 2008)[16] examined in multi-generation studies. In addition, the EFSA indicated that bisphenol A might induce several other adverse health effects at exposure levels below the NOAEL for general toxicity, involving effects on the mammary gland, as well as on reproduction, metabolism, neuro-behaviour and the immune system. However, due to methodological shortcomings in the evaluated studies, these effects were not considered 'likely' by the EFSA and therefore not used as starting point for deriving a health-based guidance value.

The EFSA used general toxicity observed in a reproduction toxicity study by Tyl et al. (2008)[16] as starting point to derive a TDI. In this 2-generation study in mice, animals (28 per sex per group) received bisphenol A in the diet at concentrations of 0, 0.018, 0.18, 1.8, 30, 300, or 3500 ppm (equivalent to 0, 0.003, 0.03, 0.3, 5, 50, or 600 mg bisphenol A/kg bw/day. The only systemic effects in the F0-generation were observed in males: centrilobular hepatocyte hypertrophy at ≥ 300 ppm (50 mg/kg bw/day), and reduced body weight, increased kidney and liver weights, centrilobular hepatocyte hypertrophy, and renal nephropathy at ≥ 3500 ppm (600 mg/kg bw/day). There were no effects on fertility reported. Only at the highest exposure dose, developmental effects were observed.

[a] An estimate of the amount of a substance in food or drinking water which is not added deliberately (e.g. contaminants) and which can be consumed over a lifetime without presenting an appreciable risk to health.

These involved reduced F1/F2-generation weanling body weight, reduced weanling spleen and testes weights (with seminiferous tubule hypoplasia), slightly delayed preputial separation (PPS), and increased the incidence of undescended testes (only in weanlings, which did not result in adverse effects on adult reproductive structures or functions), and increased gestational length by 0.3 days in F1/F2-generations. The EFSA concluded that alteration in kidney weight was the most critical effect because other effects were only observed at higher doses. However, the EFSA noted that there were remaining uncertainties about possible toxic effects below the dose at which effects on the kidney are observed. The EFSA included these effects in an overall uncertainty evaluation to derive a temporary tolerable daily intake (t-TDI) as described hereafter.[6]

The EFSA performed benchmark dose analyses on the multi-generation reproductive toxicity study in mice (Tyl et al., 2008)[16] and subsequently used a BMDL10[a] of 8.96 mg/kg bw/day, for alteration in kidney weight in mice, as a starting point for derivation of a TDI.[6]

The $BMDL_{10}$ based on mouse data was translated into a human dose level (the human equivalent dose (HED)), by considering the ratio between internal exposure (area under the curve; AUC) derived from toxicokinetic studies in mice and the internal exposure predicted using physiologically-based pharmacokinetic (PBPK) modeling in humans. Using AUCs of 0.244 (mice) and 3.6 nmol × h × L^{-1} (human reference value), the $BMDL_{10}$ of 8.96 mg/kg bw/day in mice was translated to an HED of 609 µg/kg bw/day. Due to the remaining uncertainties about possible toxic effects below this $BMDL_{10}$ and its corresponding HED, the EFSA applied an extra safety factor of 6 in addition to a factor of 25 (consisting of a factor of 2.5 for interspecies differences, and a factor of 10 for intraspecies differences), resulting in a total uncertainty factor of 150. Applying this uncertainty factor subsequently resulted in a t-TDI of 4 µg/kg bw/day.

3.4 The Risk Assessment Committee (RAC) (2015)

In 2015, the RAC of the European Chemicals Agency (ECHA) published an opinion on an Annex XV dossier proposing restrictions on bisphenol A.[3] This restriction proposal concerns the health risks identified for pregnant workers and consumers (in particular for their unborn children) exposed to bisphenol A contained in thermal paper they may handle.

The RAC took a number of evaluations into account (EU, 2003, 2008); SCOEL, 2014; SCENIHR, 2015, with an emphasis on the most recent evaluation of EFSA 2015.[1,2,4-6,9-11]

Taking into account the overall data set, the RAC agreed with the HED approach applied by the EFSA for the risk assessment of bisphenol A. The RAC considered that for kidney effects, the HED of approximately 600 µg/kg bw per day would result in a DNEL of 24 µg/kg bw/day using default assessment factors (600 divided by 2.5 (remaining factor for interspecies differences) and divided by 10 (factor for intraspecies differences).

The RAC, however, also agreed with the EFSA that kidney effects are not the most critical effects of bisphenol A , noting that studies on other endpoints do not provide a sufficiently robust starting point. The EFSA

argued that other adverse effects could occur starting from a HED of 100 µg/kg bw/day (approximately 6-fold lower than the HED for kidney effects). Applying an additional factor of 6 to a DNEL of 24 µg/kg bw/day results in a DNEL 4 µg/kg bw/day, which is equal to the t-TDI derived by the EFSA. The RAC therefore supported the t-TDI derived by the EFSA for the use as an oral-DNEL for the general population. The corresponding oral DNEL for workers was therefore set at 8 µg/kg bw/day (due to a 2-fold lower uncertainty factor for intraspecies differences).

3.5 The National Institute for Public Health and the Environment (RIVM) (2014, 2016)

In 2016, the RIVM published a recommendation on bisphenol A for human and environmental risk management.[7] In this report, the RIVM provided an overview of human health issues and assessments published up to March 2014.[1-11] In addition, the RIVM identified a number of scientific publications on the developmental effects of bisphenol A exposure on the immune system that were not taken into account by the EFSA and the RAC. For an evaluation of these studies, the Committee refers to a workshop report on developmental immunotoxicity studies with bisphenol A in the context of the opinion by the EFSA.[17]

The RIVM concluded that for pre- or perinatal exposure to bisphenol A, a LOAEL of 5 µg/kg bw/day can be derived for effects on the immune system, possibly resulting in increased risk of food intolerance, inflammation and sensitivity to infections in the offspring in rats. The RIVM furthermore concluded that these effects could also be possible at 0.5 µg/kg bw/day, but noted that the studies supporting these conclusions have limitations and that a more detailed weight of evidence analysis of the underlying data is needed to determine whether effects at this lower dose level should be considered adverse.

The RIVM stated that the recent insights into the immunotoxicity warrant reconsideration of both the t-TDI derived by the EFSA and the DNELs derived by the RAC. The available information on occupational exposure and the exposure limit applied led the RIVM to conclude that there is a health risk for workers from inhalation of bisphenol A during the manufacture of bisphenol A, and possibly during the manufacture of epoxy resins. However, the RIVM did not address the derivation of a health-based advisory value for occupational exposure by inhalation.

3.6 Recent literature

Literature published after finalisation of the EFSA report is summarised in Annex B.

Inhalation exposure

Data on adverse effects after inhalation exposure to bisphenol A are very limited. The only recent inhalation study is a study on the effects on the oestrous cycle, spatial learning, and memory in rats exposed by inhalation to 0, 10, 30, and 90 mg/m^3 for 6 hr/day, 5 days/week for 8 weeks (equivalent to 1.4, 4.3 and 12.9 mg/kg bw).[18] The particle size mostly

ranged from 2.10 to 7.0 µm, accounting for 75% of the total distribution. Mortality, clinical signs, body weight, haematology, serum chemistry, oestrous cycle parameters, performance in the Morris water maze test[a], and organ weights, as well as gross and microscopic histopathological findings, were studied. At the highest exposure concentration, slight but statistically significant decreases were observed for total serum cholesterol and adrenal gland weight. However, these effects were not considered adverse and there were no effects reported on the other endpoints in any of the male or female rats exposed to bisphenol A.
The Committee derives a 90-d NOAEL of 90 mg bisphenol A/m^3 from this study.

Oral exposure

A large number of additional studies on bisphenol A toxicity in rats and mice after oral administration has been published.[19-73] Most of these studies do not follow international guidelines. A summary table of the recent publications (from 2014 until May 2018) on effects of bisphenol A at dose levels below the starting point of EFSA's assessment (9 mg/kg bw/day) is provided in Annex B. To determine whether one or more of these studies might provide an alternative starting point for deriving a HBROEL, the Committee assessed them by applying three criteria:

- More than one dose level has been tested
- The studied effect parameter is considered as a relevant adverse health effect
- A statistically significant dose-response relationship has been established.

The Committee is of the opinion that none of the recently published studies fulfils all criteria. Many studies have only applied a single dose of bisphenol A. In addition, for most of them it is not clear whether the studied effect should be considered as an adverse health effect. The reported studies often analysed changes in very specific and unconventional parameters, for which it is not clear whether they should be considered as, or to lead to, adverse health effects. These effects include, for example, changes in gene expression, protein levels, receptor expression, DNA methylation and signalling pathways, and may equally well reflect reversible physiological adaptations preventing adverse outcomes.

Several well-conducted studies have been published on relevant endpoints and include multiple doses. However, in these studies no adverse effects have been observed, or only at relatively high doses. Delclos et al. (2014) performed a FDA/GLP-compliant subchronic study with rats exposed from gestation until start of labor, and the pups subsequently from birth to day 90.[62] Clear adverse effects were only observed at doses of 100 and 300 mg/kg bw/d. Another well-conducted study is the core study of the CLARITY-bisphenol A program[a]. The results

[a] Consortium Linking Academic and Regulatory Insights on BPA Toxicity: a research program developed by NIEHS, NTP, and the U.S. Food and Drug Administration (FDA). This program consists of two parts: a core study according to federal regulatory and statutory guidelines for toxicity testing and grantee studies conducted by university researchers but testing a broader range of health endpoints.

of this extensive FDA-guideline perinatal and chronic extended dose-range finding study of bisphenol A in rats are currently only available in a draft report.[72] In this study, rats were administered bisphenol A by oral gavage (0-25 mg/kg) from gestation day 6 continuously, directly to pups from postnatal day 1 until termination at one or two years. In addition to a continuous study, a stop-dose group was included with animals dosed until post-natal day 21. In this study, no treatment-related effects were observed. The other studies within the CLARITY project did not follow international guidelines but used animals raised in the same conditions and exposed to the same doses of bisphenol A as the core study. Most of these studies do not report any effects[57,67-69,73] or do not report on effect parameters that are considered to be related to adverse health effects[19,59,63] (see Annex B).

Overall, the Committee concludes that the recent literature does not provide an alternative for the starting point used previously by the EFSA, the RAC or the Committee. The Committee notes that several studies have been published that suggest that bisphenol A causes developmental effects at exposure levels far below the EFSA starting point. However, all of these studies have limitations as noted by both the EFSA and the Committee above. Importantly, in addition to limitations in design and reporting, these studies describe findings that are not consistent with results obtained in other studies. In view of the extensive dataset on bisphenol A, the Committee considers the likelihood of incidental findings high. The Committee is therefore of the opinion that these studies are not suitable for risk assessment and no conclusions can currently be drawn based on the findings reported in these studies.

04 hazard assessment

4.1 Evaluation of (non-)monotonic dose response relationships

The Committee notes that it has been suggested that bisphenol A-induced effects can develop according to a non-monotonic dose-response relationship (NMDR). NMDRs have been defined as non-linear relationships between dose and effect where the slope of the dose-response curve changes sign somewhere within the range of doses examined (a 'u-shaped' dose-response curve). For bisphenol A, NMDRs have been reported for various endpoints in in vitro, in vivo, and human studies (reviewed in Vandenberg 2014).[51] The existence of such NMDRs would conflict with the methodology used by the Committee to establish HBROELs, which is based on monotonic dose-response relationships. Therefore, the Committee will first consider the potential role of NMDRs in bisphenol A toxicity.

After the publication of the EFSA evaluation[6], EFSA initiated a project in which the evidence for the NMDR hypothesis was evaluated by critically reviewing the scientific peer-reviewed literature from 2002 onwards for bisphenol A and other substances for which NMDRs have been reported.[74] Although the focus in this project differed from the Committee's focus (i.e. exposure via food by oral consumption versus exposure via inhalation), the Committee considers this review of the NMDR hypothesis for bisphenol A of relevance since it addresses systemic effects and it is likely that such effects could also occur after exposure by inhalation.

The authors noted that a formal method for (dis)proving NMDRs does not exist. They applied a tiered approach, in which first literature was identified that indicated NMDR for a substance relevant within the area of food (other than essential nutrients, pharmaceuticals, hormones, radioactive substances, nanomaterial or abstracts of botanicals) based on abstract and title. Thereafter, the relevant studies were first selected by applying criteria relating to the indication of possible NMDRs, number of dose groups applied, substance composition, and reliability (see for details the publication by Beausoleil et al. (2016)[74]).

The dose-responses described in the remaining studies were analysed using six 'checkpoints' consisting of the following questions:

1. Can the apparent NMDR be explained by random fluctuations around a horizontal dose-response (=no effect at all)?
2. Can the apparent NMDR be explained by random fluctuations around a monotonic dose response?
3. Can the apparent NMDR be explained by one single potential outlying dose group?
4. Is the effect size in one of the directions of the NMDR smaller than 5%?
5. Is the steepness of the dose-response curve outside the range of biologically plausible/realistic dose-response shapes?
6. Does the apparent NMDR consist of more (or less) than two directions?

The checkpoints were applied to weigh the evidence of a potential NMDR, without ranking them in a particular order. The total number of fulfilled checkpoints (i.e. when the answer to the question was 'no') was used to

rank the datasets; datasets with more fulfilled checkpoints were considered to contain more evidence for NMDR than datasets with fewer fulfilled checkpoints.

The Committee has retrieved and examined the detailed results of the review by Beausoleil et al. (2016)[74] on bisphenol A. When focussing on in vivo studies, only 4 studies (Angle et al. (2013)[75]; Kendig et al. (2012)[76]; Tyl et al. (2002)[15] and Zsarnovszky et al. (2005)[77]) fulfilled the requirements set for the initial relevance and reliability assessment. These four studies contained 34 datasets, which were evaluated according to the 6 checkpoints outlined above. None of the datasets fulfilled all 6 or 5 checkpoints, 6 datasets fulfilled 4 checkpoints, 5 datasets fulfilled 3 checkpoints, 4 datasets fulfilled 2 checkpoints, 16 datasets fulfilled 1 checkpoint, and 3 datasets fulfilled none of the checkpoints (see Table 4.1).

Importantly, only 3 datasets meet checkpoint 3, which means that for most datasets a possible NMDR can be explained by one single potential outlying dose group. Also, the endpoints for which 3-4 checkpoints are fulfilled show no consistency between studies (i.e. involve different types of effect and different tissues) and for most effects analysed, it is unclear whether it should be considered an adverse health effect.

The Committee concludes that there is currently insufficient evidence to support the existence of a NMDR for bisphenol A. Based on the weight of evidence available, the Committee considers a NMDR for bisphenol A not likely and therefore, does not take it into account in the hazard assessment.

4.2 Hazard identification

In the evaluations published before on bisphenol A,[1,3,6,7,9] data from animal experiments are summarised that indicate that bisphenol A can cause a diversity of toxic effects, including acute toxicity, irritation, sensitisation, repeated dose toxicity (including inflammation and hyperplasia of the airways after inhalation exposure, and effects on liver and kidneys), and developmental toxicity. Also with respect to specific developmental toxicity, a diversity of effects are reported in recent studies, including effects on the prostate, mammary gland, brain and behaviour, and recently, on the immune system.

4.2.1 Assessment of relevant studies

In previous evaluations by the EU, the SCOEL and the EFSA, the quantitative hazard assessment is based on animal data as it is concluded that the available human data are not suitable. The Committee adopts this conclusion and will focus therefore on animal data. Although inhalation studies are most relevant for the occupational situation, the Committee

Table 4.1. Results of the analysis of Beausoleil et al. (2016) on the in vivo studies on bisphenol A that met the reliability criteria. Red: answer to the checkpoint = yes (checkpoint is not met); green: answer to checkpoint = no (checkpoint is met)

First author	Animal species	Strain *(EFSA: id_strain)*	Duration of administration of test substance (if developmental include age). *(EFSA: exp_duration and id_duration_unit)*	Outcome/effect/ endpoint measured (that indicates NMDR) *(EFSA: effect_desc)*	Number of dose levels tested (excl. negative control)	Checkpoint 1 fulfilled	Checkpoint 2 fulfilled	Checkpoint 3 fulfilled	Checkpoint 4 fulfilled	Checkpoin t 5 fulfilled	Checkpoint 6 fulfilled	Total number of checkpoints fulfilled
Angle	Mouse	CD-1	GD 9-18	Body weight at day of birth	5							0
Angle	Mouse	CD-1	GD 9-18	Body weight week 3	5							1
Angle	Mouse	CD-1	GD 9-18	Body weight week 13	5							1
Angle	Mouse	CD-1	GD 9-18	Body weight week 19	5							1
Angle	Mouse	CD-1	GD 9-18	Body weight average weeks 7-19	5							1
Angle	Mouse	CD-1	GD 9-18	Energy intake week 3-4	5							1
Angle	Mouse	CD-1	GD 9-18	Energy intake week 4-5	5							1
Angle	Mouse	CD-1	GD 9-18	Energy intake week 15-19	5							1
Angle	Mouse	CD-1	GD 9-18	Gonadal fat pad weight	5							1
Angle	Mouse	CD-1	GD 9-18	Renal fat pad weight	5							2
Angle	Mouse	CD-1	GD 9-18	Total abdominal fat	5							1
Angle	Mouse	CD-1	GD 9-18	Cell number in gonadal fat pad	5							4
Angle	Mouse	CD-1	GD 9-18	Gonadal adipocyte volume	5							3
Angle	Mouse	CD-1	GD 9-18	Cell number in renal fat pad	5							4
Angle	Mouse	CD-1	GD 9-18	Renal adipocyte volume	5							3
Angle	Mouse	CD-1	GD 9-18	Liver weight	5							2
Angle	Mouse	CD-1	GD 9-18	Glucose tolerance AUC	5							2
Angle	Mouse	CD-1	GD 9-18	Insulin tolerance AUC	5							1
Angle	Mouse	CD-1	GD 9-18	Serum Leptin	5							3
Angle	Mouse	CD-1	GD 9-18	Serum Adiponectin	5							4
Kendig	Mouse	CD-1	from arrival until necropsy, including pre-mating, mating, pregnancy, …P and F1 generation until necropsy	Sperm count	5							4
Kendig	Mouse	CD-1	from arrival until necropsy, including pre-mating, mating, pregnancy, …P and F1 generation until necropsy	Sperm motility	5							4
Kendig	Mouse	CD-1	on PND14 for female F1 and PND21 for male F1	Male AGD at PND 14	5							0
Kendig	Mouse	CD-1	on PND14 for female F1 and PND21 for male F1	Male AGD at PND 21	5							1
Tyl	Rat	Sprague-Dawley	3-generations (F0-F3)	Liver weight	6							1
Tyl	Rat	Sprague-Dawley	3-generations (F0-F3)	Relative liver weight	6							1
Tyl	Rat	Sprague-Dawley	3-generations (F0-F3)	Relative liver weight	6							1
Tyl	Rat	Sprague-Dawley	3-generations (F0-F3)	Relative liver weight	6							2
Tyl	Rat	Sprague-Dawley	3-generations (F0-F3)	Paired testes weight	6							1
Tyl	Rat	Sprague-Dawley	3-generations (F0-F3)	Paired testes weight	6							1
Tyl	Rat	Sprague-Dawley	3-generations (F0-F3)	Anogenital distance in F2 females	6							0
Tyl	Rat	Sprague-Dawley	3-generations (F0-F3)	Absolute liver weight	6							4
Tyl	Rat	Sprague-Dawley	3-generations (F0-F3)	Relative liver weight	6							3
Zsarnovszky	Rat	Sprague-Dawley	n.a.	pERK-IR cell number in the cerebellar cortex at P10.	7							3

also considers systemic effects observed in oral studies relevant when these are also expected to occur after inhalation exposure.
For the previously proposed occupational exposure limits or tolerable intake level, one of two studies has been used as starting point. The DECOS, the SCOEL and the EU have used the repeated dose inhalation study in rats by Nitschke et al. (1988)[14], whereas the EFSA has used the oral multi-generation studies in mice by Tyl et al. (2002, 2008)[15,16] The Committee considers all these guideline-compliant studies suitable for risk assessment. Tyl et al. (2002, 2008)[15,16], however, applied the oral route which is considered less suitable to derive an advisory value for concentrations in air.
As outlined in section 3.6 (Recent literature), the Committee concludes that the recent low dose studies on bisphenol A do not provide an alternative starting point to derive an HBROEL.

4.3 Quantitative hazard assessment

In line with the earlier reports of the DECOS, the SCOEL and the EU, the Committee prefers data on inhalation exposure as starting point for deriving a HBROEL, since inhalation exposure is most relevant for occupational settings. Only two inhalation studies are available: the 13-week repeated dose inhalation study of Nitschke et al. (1988)[14] and the recently published 8-week repeated dose inhalation study by Chung et al. (2017)[18] Since Chung et al. (2017).[18] did not report any adverse effects up to 90 mg/m^3, the Committee considers the study of Nitschke et al. (1988)[14], from which a NOAEL of 10 mg/m^3 was established, the critical study for quantitative hazard assessment. This NOAEL is based on the absence of inflammation of the upper respiratory tract epithelium and olfactory epithelium, and relates to the inhalable fraction. This study was previously used by the Committee to derive an HBROEL of 10 mg/m^3.[13] According to its current guideline, the Committee applies an uncertainty factor of 3 for intraspecies extrapolation, which results in a HBROEL of:

10 mg/m^3 / 3 = 3.3 mg/m^3 (inhalable fraction)

This approach of deriving an advisory value is similar to the approach applied by the SCOEL[a].

The Committee notes that the inhalation studies do not address potential effects on the offspring. Three oral repeated dose toxicity studies that are suitable for risk assessment have included potential developmental effects. In the recent perinatal and chronic toxicity study in rats by the NTP, no treatment-related findings were reported up to the highest dose tested (25 mg/kg bw/d). Also, in the multi-generation studies of Tyl et al. (2002, 2008) in rats and mice no developmental effects were noted. The most critical effect observed consisted of alterations in kidney weight in mice, as has been outlined by EFSA.[6] Based on a corresponding BMDL[10]

[a] Because the SCOEL applies the preferred value approach, it recommends a limit value of 2 mg/m^3.

of 8.96 mg/kg bw/day, an HBROEL can be derived taking into account default uncertainty and conversion factors:

8.96 mg / (3 x 3 x 2[a]) = 500 μg/kg bw/d

500 x 70/10[b] = 3.5 mg/m³

This value, based on oral toxicity studies that take effects on the offspring into account, is comparable with the HBROEL based on a repeated dose inhalation toxicity study. Thus, it is assumed that the HBROEL proposed also covers these endpoints. The Committee notes that a derivation based on oral studies results in a substantially higher value than the t-TDI derived by the EFSA. This difference is explained by the fact that the Committee does not take into account potential toxicokinetic differences between species, and applies a less conservative approach for its uncertainty factors.

The Committee is aware of the fact that in some studies, neurodevelopmental effects after oral administration have been reported at doses in the range of 0.5 µg bisphenol A/kg bw. However, as outlined above, the Committee considers these studies not suitable for deriving an health-based advisory value.

[a] 3 for intraspecies differences, 3 for interspecies species, 2 for subchronic to chronic extrapolation
[b] 70 kg for assumed body weight, 10 m³ for assumed inhalation volume in workers

4.4 Skin notation

The Committee applies the ECETOC strategy to decide on assigning a skin notation.[78] In this strategy, a skin notation is warranted when absorption through 2000 cm² exposed skin in 1 h is estimated to exceed 10% of the systemic dose after inhalation during a day exposure at a level of the HBROEL (if HBROEL is based on a systemic toxicity endpoint). This is the case when the Critical Absorption Value (CAV; the rate of absorption above which dermal exposure is considered an important contributor to the total exposure) exceeds:

(10 [m³] x OEL [mg/m³] x f x 0.1)/2,000 [cm²]

in which 10 m³ is the human inhalation volume per 8h working day, f is the absorption factor for inhalation (here assumed to be 1), 0.1 denotes the 10% criterion, 2,000 cm² is the surface area of the hands and forearms, and OEL is in this case the HBROEL. Thus the CAV will be:

*(10 [m³] x 3.3 [mg/m³] x 1 x 0.1)/2,000 [cm²] = 1.65 µg/cm²*h*

The RAC[3] notes a publication by Marquet et al. (2011)[79], reporting the measured cutaneous absorption flow of bisphenol A, varying between 0.026 µg.cm^{-2}.h^{-1} (minimum) and 0.331 µg.cm^{-2}.h^{-1} (maximum). Because the estimated CAV is higher than this reported cutaneous absorption flow range, the Committee considers a skin notation not necessary.

4.5 Groups with increased risk

Bisphenol A is classified as a substance toxic for reproduction (Cat 1B). Furthermore, some recent animal data suggest that developmental effects can occur at relatively low exposure levels. Although the Committee considers these studies not suitable for risk assessment, it is of the opinion that pregnant women and their offspring represent groups at increased risk.

4.6 Conclusions and recommendation

For bisphenol A, the Committee recommends an occupational exposure limit of 3.3 mg/m^3 (inhalable fraction), as a mean concentration during an 8-h working day. In addition, the Committee concludes that a skin notation is not indicated.

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annex

A recent literature

Reference	Analysed species and sex	Study design	Tested doses	Critical effect(s) observed	Studied generation	Lowest effect level	Comments/Main limitations for risk assessment
Arambula et al. (2016)[19]	Rat, male and female	Part of CLARITY. Pregnant female rats were exposed by gavage GD6 until birth. At PND1 the hippocampal and hypothalamic transcriptome was analysed.	0, 2.5, 25, 250, 2,500, and 25,000 µg/kg bw	Sex-specific transcriptional changes in mainly hypothalamus; ER expression.	F1	2.5 µg/kg bw/d (in females; males no statistical significant Effects observed)	Not clear whether effects should be considered adverse; no dose-response relationship observed.
Arambula et al. (2017)[63]	Rat, males and females	Part of CLARITY. Animals were dosed by oral gavage continuously and were euthanized on postnatal day (PND) 1. Subsequently, amygdalae were microdissected and gene expression was assessed.	0, 2.5, 25, 250, 2,500 and 25,000 µg/kg bw/d	Changes in gene expression pathways in the amygdale (estrogen, oxytocin, and vasopressin signalling pathways).	F1	No significant/treatment related effects were observed	Not clear whether effects should be considered adverse; no functional parameters assessed; limited dose-response relationships observed.
Berger et al. (2016)[21]	Mouse, female	Mice were exposed by gavage, daily from GD11-birth. Ovaries were collected at PND 4 and 21 from the F1–F3 generations and subjected to histological evaluation (trans-generational effects on germ cell breakdown; only in F2 en F3), anti-oxidant gene expression, and distribution of follicle types.	0, 0.5, 20, and 50 µg/kg bw	No transgenerational effects on germ cell nest breakdown and gene expression on PND 4, but it caused transgenerational changes in expression in multiple genes on PND 21.	F1, F2, F3	0.5 µg/kg bw/d	Not clear whether effects should be considered adverse; critical effect size unclear; no apparent dose-response in changes in follicle type.
Borman et al. (2017)[22]	Mouse, female	Mice were subcutaneously exposed at GD1-4, uterine histo-morphology and immunohistochemistry was performed at GD6.	0, 3 and 4 mg/kg bw	Reduction in proportion positive for Cad-11. No statistically significant effects on development implantation sites.	F0	3 mg/kg bw/d (effect on implantation sites not stat. sig)	Not clear whether effects should be considered adverse; effect shown only at one dose; exposure route not relevant.
Brouard et al. (2016)[23]	Rat, male	Animals were exposed from day 15 30 post-partum. At day 30, testis was weighed, histologically analysed at day 30. Also DNA fragmentation was determined and RNA was extracted.	0 and 50 µg/kg bw	Increased testis weight; increase testicular markers (proteins and gene expression); decrease in gene expression of blood-testis-barrier.	No study on developmental effects.	50 µg/kg bw/d	Promoting effects on spermatogenesis not in line with most other publications; adversity of endpoints unclear; only one dose tested.

Reference	Analysed species and sex	Study design	Tested doses	Critical effect(s) observed	Studied generation	Lowest effect level	Comments/Main limitations for risk assessment
Castro et al. (2018)[71]	Rat, male, juvenile	BPA was administered BPA subcutaneously from gestational day 12 to parturition, pups received the same dose from PND1-21. Thereafter, levels of 5α-R isozymes and aromatas in prostate and plasma testosterone and di-hydrotestosterone were measured in offspring.	2.4 and 10 µg/kg bw	Significantly decreased mRNA and protein levels of 5α-R2 in prostate tissue. Also decreased levels of testosterone and di-hydrotestosterone, and increased levels estradiol in plasma were measured.	F1	2.4 µg/kg	Only 2 doses tested; not clear whether effects should be considered adverse; sub-cutaneous exposure route.
Chen et al. (2016)[24]	Rat, adult, male	Animals were exposed to 50 µg/kg bw/d in diet for 35 weeks. Thereafter testes and epididymis were dissected and weighed, testes and epididymis coefficients were calculated and one testis from each animal was used for protein determination and the other testis was used HE staining and TUNEL experiments.	0 and 50 µg/kg bw	Decreased protein/lysine acetylation levels and decreased histone acetylation in testes; increased protein expression of deacetylase Sirt1 and reduced binding of Sirt1, together with increased binding of oestrogen receptor β (ERβ) to caveolin-1 (Cav-1).	No study on developmental effects.	50 µg/kg bw/d	not clear whether effects should be considered adverse; only one dose tested.
Chianese et al. (2018)[70]	Rat, male	Dams received the treatment all over lactation and at weaning; each newborn received the same treatment of the mother via drinking water. Possible effects of BPA on the first round of spermatogenesis (apoptosis, oxidative stress, metabolism and energy homeostasis), the male newborns were sacrificed at 17 PND, 45 PND, or 60 PND.	0.1 mg/L in drinking water (equivalent to 130 µg/kg bw)	Reduced the body weight gain in male offspring at 45 postnatal days and the first round of spermatogenesis, with impairment of blood testis barrier, reactive oxygen species production, DNA damage and decreased expression of $SIRT1^2$.	F1	130 µg/kg bw	Only one dose tested; no guideline followed.

Reference	Analysed species and sex	Study design	Tested doses	Critical effect(s) observed	Studied generation	Lowest effect level	Comments/Main limitations for risk assessment
Chung et al. (2017)[18]	Rats, males and females	Rats were exposed 6 hr/day, 5 days/week for 8 weeks via whole-body inhalation. Mortality, clinical signs, body weight, haematology, serum chemistry, oestrous cycle parameters, performance in the Morris water maze test, and organ weights, as well as gross and histopathological findings, were assessed.	0, 10, 30, and 90 mg/m^3	No adverse effects observed.		No (signi icant) treatment-related effects were observed.	Results water maze test not reported.
Delclos et al. (2014)[62]	Rat, males and females	Rat dams were dosed daily from gestation day 6 until the start of labor, and their pups were directly dosed from PND1 through PND90. Analyses including gestation and litter endpoints, pup preweaning survival, growth, clinical chemistry (serum hormones), organ weights and histopathology, sperm parameters.	2.5, 8, 25, 80, 260, 840, 2,700, 100,000, 300,000 µg/kg bw/d	Clear adverse effects including depressed gestational and postnatal body weight gain, effects on the ovary (increased cystic follicles, depleted corpora lutea, and antral follicles), and serum hormones (increased serum estradiol and prolactin and decreased progesterone).	F1	100,000 µg/kg bw	Conducted in compliance with FDA GLP regulations.
Dere et al. (2018)[69]	Rat, male	Part of CLARITY. Animals were gavaged from gestational day (GD) 6 until parturition, and their pups were directly gavaged daily from postnatal day (PND) 1 to 90 with BPA where after the testes were histologically evaluated for altered germ cell apoptosis, sperm production, and altered spermiation. DNA and RNA was isolated from isolated sperm to assess changes.	0, 2.5, 25, 250, 2,500 and 25,000 µg/kg bw/d	-	F1	No exposure related effects were observed.	Extensive dose range applied.

Reference	Analysed species and sex	Study design	Tested doses	Critical effect(s) observed	Studied generation	Lowest effect level	Comments/Main limitations for risk assessment
Ferguson et al. (2014)[61]	Rat, males and females	Pregnant rats were dosed orally on GD6–21. Body weight, pubertal age, oestrous cyclicity, and adult serum hormone levels were measured. Adolescent play, running wheel activity, flavoured solution intake, female sex behaviour, and manually elicited lordosis were assessed.	2.5 or 25.0 µg/kg bw/d	BPA treatment did not alter any measured endpoint.	F1	No significant/treatment related effects were observed.	Only two doses tested.
Fergusonet al. (2015)[60]	Rat, males and females	Pregnant rats were doses on GD6–21. Beginning on PND1 and continuing until PND21, the pups were orally treated with the same dose their dam had received. Body weight, pubertal age, oestrous cyclicity, and adult serum hormone levels were measured. Adolescent play, running wheel activity, flavoured solution intake, female sex behaviour, and manually elicited lordosis were assessed.	2.5 or 25.0 µg/kg bw/d	BPA treatment did not alter any measured endpoint.	F1	No significant/treatment related effects were observed.	Only two doses tested.
Galyon et al. (2016)[25]	Rat, male and female	Rat dams were fed BPA in drinking water from 2 weeks prior to mating and through pregnancy and lactation. Glucose tolerance was tested at 6 weeks and 6 months, liver and skeletal muscles tissue was collected from 3 w and 10 m old offspring.	0 and 239 µg/d during pregnancy; 466 µg/d during lactation	Male but not female offspring had impaired glucose tolerance at 6 weeks and 6 months. Sex and tissue-specific effects on insulin signalling proteins were reported.	F1	239 µg/d during pregnancy; 466 µg/d during lactation (around 2 mg/kg bw assuming bw 125-500 mg).	Not clear whether effects should be considered adverse; only one dose tested.
Gear et al. (2017)[54]	Rat, male and female	Part of CLARITY. Dams were dosed with BPA from GD6 – PND0. Pups were dosed from PND1 continuously or until PND21, to day of sacrifice at PND21, PND90 or 6 months. Subsequently, isolated hearts were analysed by quantitative morphometry and histopathology.	0, 2.5, 25, 250, 2,500 or 25,000 µg/d	Decreased collagen in hearts females at PND90 and PND180; cardiomyopathy incidence and severity increased in females at PND21 with myocardial degeneration in both males and females at PND21 and PND90.	F1	2.5 µg/d Females	High level cardiomyopathy in controls; No apparent dose-response; effects at PND21 but not statistically significant at later time points.

Reference	Analysed species and sex	Study design	Tested doses	Critical effect(s) observed	Studied generation	Lowest effect level	Comments/Main limitations for risk assessment
Gear and Belcher (2017)[55]	Mouse, male and female	Dams were treated via the diet from conception, offspring were separated from the mothers at PND21 and exposed via the diet until 12-14 weeks of age where after histological analysis was performed.	0, 0.03, 0.3, 3.0, 30, 300 ppm (doses from 4-40,000 µg/kg bw/d)	No effects on gestation period, pups per litter and sex ratio. Increase spleen weight; increase histological and microstructural changes in the spleen.	F1	4 µg/d	Not clear whether effects should be considered adverse; no clear dose-response.
Hass et al. (2016) [26]	Rat, male and female	Dams were gavaged BPA daily from GD7 to PND22, analysed during life (3 m-14 m). In the offspring, growth, sexual maturation, weights and histopathology of reproductive organs, oestrus cyclicity and sperm counts were assessed. Neuro-behavioural development was investigated using a behavioural testing battery including tests for motor activity, sweet preference, anxiety and spatial learning.	0, 25, and 250 µg/kg bw, 5 and 50 mg/kg bw	Males: Decreased sperm count only at lowest dose. Females: increased body weight late in life and altered spatial learning.	F1	-	Effects very limited in magnitude; no dose-responses observed.
Jardim et al. (2017)[56]	Mouse, male and female	Mice were gavaged BPA from PND21 to 60. The mice performed the behavioural memory tests and the [3H] glutamate uptake and NMDA receptor subunits (2A and 2B) analyses were carried out in the hippocampus and cerebral cortex of mice.	0 and 5 mg/kg bw/d	Impaired object recognition memory in both sexes; Impaired spatial memory in females and impaired passive avoidance memory in males. Also a decrease in the [^{3}H] glutamate uptake and NMDA receptor subunit levels in the cortical and hippocampal regions was observed depending on the sex.	No study on developmental effects.	5 mg/kg bw/d	Only one dose tested.
Jedeon et al. (2016)[29]	Rat, male and female	Female rats were exposed by gavage from GD1 until weaning; pups were subsequently exposed at the same dose in the drinking water during the next 44 days (the time necessary for the full growth of the rat incisor). At PND65 enamel defects were assessed.	0 and 5 µg/kg bw	A moderate phenotype enamel hypo-mineralisation was observed with 12.5% of enamel breakdown.	F1	5 µg/kg bw/d	not clear whether effects should be considered adverse; only one dose tested.

Reference	Analysed species and sex	Study design	Tested doses	Critical effect(s) observed	Studied generation	Lowest effect level	Comments/Main limitations for risk assessment
Jiang et al. (2016)[30]	Rat, male	Adult male rats were administered BPA for 8 weeks by gavage. Thereafter, the reproductive system was dissected.	0.5 or 5 mg/kg bw	Reduced sperm motility, deformity ratios and histological changes.	No study on developmental effects.	0.5 mg/kg bw/d	Only two doses tested; very limited dose-dependency.
Jinpeng et al. 2018	Rat, male and female	Part of CLARITY. Animals were dosed by oral gavage continuously and were euthanized on postnatal day (PND) 21, 90, 6 month and 1 year. At these time points, leukocyte compositions (including B cells, T cells, NK cells, granulocytes, monocytes, macrophages and dendritic cells) were determined in spleen and thymus.	0, 2.5, 25, 250, 2,500 and 25,000 µg/kg bw/d	Most, if not all, of these alterations were found to be transient with no persistent trend over the one-year period.	F1	No exposure related effects were observed.	Extensive dose range applied.
Johnson et al. (2015)[59]	Rat, males and females	Part of CLARITY. Animals were dosed from gestational day 6 to parturition, and offspring were directly orally dosed until weaning PND21. At adulthood, animals were tested for seven days in the Barnes maze. Also, serum testosterone concentrations were measured.	0, 2.5, 25, and 25,000 µg/kg bw/d	At-2500: more incorrect holes sniffed on day 7 -2500: females were less likely than control females to locate the escape box (latency) 2.5: prolonged latency in females, not significant 2.5: improved latency in males, significance uncertain. No differences in serum T in males and females.	F1	No significant/treatment related effects were observed.	No dose-response, not clear whether effects should be considered adverse.
Jones et al. (2016)[31]	Rat, male	(1) Juvenile rats were exposed by gavage pre- and post-natally (GD7-PND14) and the number and size of motor neurons were examined in adulthood; (2) adult rats were doses BPA for 28 days in drinking water after which the soma size of motor neurons was measured.	0, 5, 50, 500, and 5,000 µg/kg bw	No effect on neural survival or soma size in experiment (1); decrease in soma size in retrodorsolateral nucleus (RDLN) pool in experiment (2).	F0, F1	5 µg kg/bw d	not clear whether effects should be considered adverse.
Kazemi et al. (2016)[32]	Rat, male	Rats were exposed by gavage for 35 days; plasma hormone levels and testis were analysed at D36.	0, 5, 25, and 125 µg/kg bw	Reduced bw; seminiferous tuble diameter and thickness of seminiferous epithelial was decreased.	No study on developmental effects.	5 µg/kg bw/d	No dose-response relationships observed.

Reference	Analysed species and sex	Study design	Tested doses	Critical effect(s) observed	Studied generation	Lowest effect level	Comments/Main limitations for risk assessment
Kazemi et al. (2017)[66]	Rat, male	BPA was administered by gavage for 35 consecutive day. Thereafter, levels of aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase were determined, liver histology was performed and serum protein were visualised.	5, 25 and 125 µg/kg	Decreased bodyweight at 25 and 125 mg/kg. ALP and AST decreased significantly at all doses, decreased Beta-2 protein and increased Gama protein serum levels in rats.	F0	5 µg/kg bw	Not clear whether effects should be considered adverse, limited dose-response relationship observed.
Ke et al. (2016)[33]	Mouse, male	Female mice were exposed from the first day of childbirth and throughout lactation. After weaning, the male offspring from the mothers were daily administered BPA in water similar to the BPA water that their mothers drank. Part of male offspring was sacrificed at the age of 8 weeks, the rest mice were killed at the age of 10 months. Blood, liver and the perigonadal white adipose tissue were analysed.	0, 0.5 µg/kg bw/d	Hepatic accumulation of triglycerides and cholesterol; abnormalities in liver cells (gene expression, methylation).	F1	0.5 µg/kg bw/d	Not clear whether effects should be considered adverse; only one dose tested.
Komada et al. (2014)[34]	Mouse, newborn	Exposure by oral gavage from GD6 to GD18, 20 and 200 µg/kg bw/d, At 1 and 3 d after birth, tests for the presence of behavioural abnormalities and a detailed histologic analysis of the neocortex and were performed, respectively.	0, 20 and 200 µg/kg bw/d	abnormal neuronal development (at 20 and 200 µg/kg bw) and behaviour (at 200 µg/kg bw.)	F1	20 µg/kg bw/d	Not clear whether effects should be considered adverse; no dose-response relationship present.
Li et al. (2016)[36]	Mouse, adult, female	An experimentally induced delayed implantation model was used to study the implantation process. Mice were exposed orally from PND22, for 5 weeks, during mating period until D9 of pregnancy, when uterine tissues were examined.	0, 60 and 600 µg/kg bw/d	Improper endometrial epithelial and stromal functions, reduced number of implantation sites. Expression of progesterone receptor and its downstream target gene was markedly suppressed.	F0	60 µg/kg bw/d	Limited and inconsistent data on dose-response; unconventional study design (experimentally induced delayed implantation Model; 3x-d dosing; depletion oestrogen from other sources).

Reference	Analysed species and sex	Study design	Tested doses	Critical effect(s) observed	Studied generation	Lowest effect level	Comments/Main limitations for risk assessment
Li et al. (2016)[35]	Mouse, male	Mice were treated subcutaneously for 30 days, where after the insulin signalling and glucose transporters in the hippocampus and prefrontal cortex were detected by western blot.	0 and 100 µg/kg bw	Decrease of insulin sensitivity, GLUT1, 3 protein levels, hyper-activation of IR/IRS/AKT/GSK3 axis in mouse brain.	No study on developmental effects.	100 µg /kg/d	Exposure route not relevant; not clear whether effects should be considered adverse; only one dose tested.
Li et al. (2018)[67]	Rat, male and female	Part of CLARITY. Animals were dosed by oral gavage continuously and were euthanized on PND21, 90, 6 month and 1 year. Subsequently, measurements of lympho-proliferation in response to mitogenic stimuli, immunoglobulin production by B cells, and cellular activation of T cells, NK cells, monocytes, granulocytes, macrophages and dendritic cells.	0, 2.5, 25, 250, 2,500 and 25,000 µg/kg bw/d	No dose dependent, statistically significant effects observed.	F1	No exposure related effects were observed.	Extensive dose range applied.
Ling et al. (2016)[37]	Mouse, male and female	Pregnant mice were exposed by osmotic pump from E14.5-E18.5; neuronal migration in the foetus visualised at E18.5 after transfecting a plasmid by in utero electroporation.	0, 40 and 400 µg/kg bw	Neural migration in the cortical plate was significantly decreased in the 40 µg/kg group (not in the 400 µg/kg group).	F1 (embryo)	40 µg/kg bw/d	Adversity of endpoint unclear; exposure route not relevant; no dose-dependency observed.
Luo et al. (2016)[38]	Mouse, male and female	Pregnant mice were exposed via drinking water from GD0-PND 21. At PNDs 21 and 42, blood was collected from the offspring for cytokine measurement and spleens were collected for determination of Th17 cell frequency and expression of the transcription factor retinoic acid-related orphan receptor.	0, 10, 100 or 1,000 nM in drinking water (equivalent doses 0.5, 5 and 50 µg/kg bw, recalculated using TGD, assuming bw of 30 gr).	Dose-dependent Increase in Th17 cells in spleen (gender specific; most pronounced in females), effect on gene expression and cytokines.	F1	Around 5 µg/kg bw/d (increase 0.5 µg/kg bw/d not yet stat. significant).	Only intermediate parameters were included; functional consequences unclear.

Reference	Analysed species and sex	Study design	Tested doses	Critical effect(s) observed	Studied generation	Lowest effect level	Comments/Main limitations for risk assessment
Mahalingam et al. (2017)[65]	Mice, female	Daily oral dosing of the dams in the respective treatment groups was started on GD 11 and continued until the birth of pups. Some of the adult F1 females were used to generate the F2 progeny, and at least one F2 female from each litter was euthanized at three months and 12 months of age. Ovaries were collected or assessment of histological analysis of follicle numbers and health as well as mRNA levels of steroidogenic enzymes.	0.5, 20, and 50 µg/ kg/day	Decreased preantral follicle numbers in F1. Estradiol levels were decreased at three months in F1 at 20 and 50, µg /kg/day. In F2, at 12 m, BPA at 20 µg/kg/day significantly reduced testosterone levels during diestrus. In both F1 and F2, various ovarian mRNA levels of steroidogenic enzymes were decreased.	F1 and F2	No significant/treatment related effects were observed.	Not clear whether effects should be considered adverse, effect size limited, functional reproductive parameters not reported, limited dose-response relationship observed.
Mandrup et al. (2016)[39]	Rat, male and female	Dams were gavaged BPA daily from GD7 to the day before expected birth. Effects on the mammary gland in the offspring were measured at 22, 100, and 400 days of age.	0, 0.025, 0.25, 5, and 50 mg/kg bw	Male offspring showed increased mammary outgrowth on pup day PND22; increased prevalence of intraductal hyperplasia was observed in females at PD 400,	F1	No consistent effect. Increased mammary outgrowth was observed only in males, only at a dose of 0.025 µg/kg bw/d). Intraductal hyperplasia was observed in females, only at a dose of 0.25 µg/kg bw/d).	No dose-response relationship, inconsistent results.
Medwid et al. (2016)[40]	Mouse, adult, male	Pregnant mice fed 25 mg/kg diet from GD7 until delivery. At 8 weeks of age, offsprings were sacrificed, blood samples and adrenalglands were collected for hormone assays and western blot analysis, respectively.	0 and 25 mg kg food pellet	Increased adrenal gland weight (males and females); elevated plasma corticos-terone levels (males and females), increase expression of StAR and cyp11A1 (female).	F1	4.8 mg/kg bw/d (recalculated using TGD, assuming bw of 30 gr).	Not clear whether effects should be considered adverse; critical effect size unclear; only one dose tested.

Reference	Analysed species and sex	Study design	Tested doses	Critical effect(s) observed	Studied generation	Lowest effect level	Comments/Main limitations for risk assessment
Menard et al. (2014)[80]	Rat, female	Pregnant and lactating rats were treated by gavage from GD15 to weaning (D21). At D45, Immune parameters of offspring were tested after oral tolerance or immunisation to OVA.	0, 0.5, 5, 50 µg/kg bw/d	Increase of anti-OVA IgG titers at all BPA dosages in OVA-tolerized rats, and at 5 µg/kg/d in OVA-immunized rats compared to control rats treated with vehicle. In BPA-treated and OVA tolerized rats, increased anti-OVA IgG titers were associated with higher IFN secretion by the spleen, and an increase of activated T-cells. Also, when BPA-treated OVA-tolerized rats were orally challenged with OVA, colonic inflammation occurred, with neutrophil infiltration, increased IFN and decreased TGF.	F1	0.5 µg/kg bw/d (for IgG titers)	Oral allergy/tolerance model limited relevance for workers; only for one parameter all doses were tested; limited dose response information.
Menard et al. (2014)[81]	Rat, female	Rats were fed with BPA for GD15 to weaning. Immune parameters of offspring were tested after oral tolerance or immunisation to OVA; or infection by intestinal nematodes.	0 and 5 µg/kg bw/d	Decrease in OVA-induced IFN secretion and T-cells/ dendritic cells in spleen and mesenteric lymph nodes; 1.5-fold increase in *N. brasiliensis* living larvae in the intestine of BPA-exposed rats compared to controls.	F1	5 µg/kg bw/d	Oral allergy/tolerance model limited relevant for workers; only one dose tested.
Moore-Ambriz (2015)[41]	Mouse, young adult, female	Mice were exposed to 50 µg/kg bw/d by gavage for a period of 3 reproductive cycles.	0 and 50 µg/kg bw	No effect on parameters related to ovulation, but it reduced the fraction of fertilized oocytes after in vitro fertilisation or mating.	No study on developmental effects.	50 µg/kg bw/d	No effects reported that were considered adverse; only one dose tested; limited number of animals.

Reference	Analysed species and sex	Study design	Tested doses	Critical effect(s) observed	Studied generation	Lowest effect level	Comments/Main limitations for risk assessment
NTP (2018)(draft)[72]	Rat, male and female	CLARITY regulatory perinatal and chronic study. BPA was administered by oral gavage from GD 6 through the start of labor and then directly to pups from PND 1, until 1 year or 2 years. In addition, a stop-dose study arm was included with animals dosed only until PND 21. Data collected included body weights, litter parameters, age at vaginal opening, vaginal cytology, clinical chemistry, sperm parameters, organs weights and histopathology.	0, 2.5, 25, 250, 2,500 and 25,000 µg/kg bw/d Positive control: (0.05 and 0.5 µg/kg bw/d)	Few significant effects, not clear whether these were treatment related. In the stop-dose group, at 2 years there was a statist significant increase in incidence of female mammary gland adenocarcinoma (22% vs 6%) and adenoma and adenocarcinoma combined (24% vs 8%) at 2.5 µg/kg bw/d. In the continuous dose arm, there was an increase in female mammary gland atypical foci at 2.5 µg/kg bw/d (14% vs 0% (interim) and 15% vs 4% (termination)). There was a significant trend (p=0.037) for uterine stromal polyps in the interim sacrifice group of the continuous dose arm.	F1	No clear exposure-related effects reported.	Study with extended dose range and various parameters, conducted following FDA GLP regulations.
Nygaard et al. (2015)[82]	Mouse, males and females	Dams were exposed to BPA in drinking water from time of mating and until the end of the lactation period. Offspring were administered 10 mg OVA intraperitoneally without adjuvant at PND4 and 18. At PND25 they were challenged OVA intranasally. Analysis at PND30.	0, 10 or 100 mg/mL (equivalent to 0, 2 or 20 mg/kg)	At 100 mg/mL: increased eosinophil numbers in bronchoalveolar lavage fluid (BALF) and a trend of increased OVA-specific IgE levels.	F1	20 mg/kg bw	Relevance airway allergy and model unclear; food tolerance not relevant for workers.

Reference	Analysed species and sex	Study design	Tested doses	Critical effect(s) observed	Studied generation	Lowest effect level	Comments/Main limitations for risk assessment
Patel et al. (2017)[57]	Rat, female	Part of CLARITY. Rats were dosed with BPA from GD6 until up to 1 year. Ovarian morphology and serum estradiol and progesteronea were analysed at PND1, 21, 90, and at 6 months and 1 year.	0, 2.5, 25, 250, 2,500 and 25,000 µg/kg	Reduction of ovarian follicle numbers and reduction of sex steroid levels at some doses and time points.	F1	-	Effects only borderline significant; decrease follicle count only observed at PND21; no dose-response relationship.
Quan et al. (2016)[42]	Rat, male	Rats were exposed by gavage from GD14-21 and analysed at PND21 and levels of sex hormones and reactive oxygen species, expressions of proteins and genes in the Akt/mTOR, and mitochondrial apoptosis pathways were measured. Sperm quality was assessed at PND50.	0, 1, 10 and 100 mg/kg bw	Effects on hormones, oxidative stress, inhibition spermatogenesis, apoptosis.	F1	1 mg/kg bw/d Sperm density and abnormalities	Limited or lack of dose-response; relevance of parameters; relatively high doses applied.
Rahman et al. (2016)[44]	Mouse, analysed at PND 120, male	Mice were gavaged BPA from GD7-14. At PND120, function, fertility, related processes and protein profiles of F1 spermatozoa were assessed.	0, 50 µg/kg, bw, 5 and 50 mg/kg bw	Inhibition sperm count, motility parameters and intracellular ATP, reduced litter size	F1	50 µg/kg bw/d Only for intracellular ATP reduction and SOD2; other effects only at higher doses (reduced litter size only observed at highest tested dose.	Adversity of most critical parameter unclear; no dose response for intracellular ATP reduction; functional effects only observed at high doses.
Rebuli et al. (2015)[73]	Rat, males and females	Part of CLARITY. Animals were dosed by oral gavage from GD 6 and continued until parturition, pups after birth until postnatal day (PND) 21. Behavioural assessments were performed either on PND25-27 or PND97-125, and included open field, elevated plus maze, and zero maze.	0, 2.5, 25, and 25,000 µg/kg bw/d	No consistent effects of BPA were observed for any endpoint, in either sex, at either age compared to vehicle controls.	F1	No significant/treatment related effects were observed.	National Research Council guidelines followed; limited study power was noted.

Reference	Analysed species and sex	Study design	Tested doses	Critical effect(s) observed	Studied generation	Lowest effect level	Comments/Main limitations for risk assessment
Santamaria et al. (2016)[45]	Rat, adult, female	Low dose exposure to pregnant rats via drinking water from GD9 to weaning on PND21. Oestrous cycle was assessed in offspring treated with BPA from PND45-90. At PND90, blood and ovaries from F1 dams were obtained.	0, 0.5 and 50 µg/kg bw	Abnormalities in ovaries and follicles.	F1	0.5 µg/kg bw/d (calculated by authors based on mean body weight dams).	Not clear whether effects should be considered adverse; only one dose tested; effects difficult to interpret.
Suglia et al. (2016)[46]	Mouse, male,	Pregnant mice were exposed during a foetal-perinatal period (10d post coitum to PND31), body weight, food intake, fat mass, and hypothalamic signals related to anorexigenic control of food intake were analysed at day 78.	0 and 10 µg/mL in drinking water	Reduced body weight and food intake; decreased epididymal fat mass; effects on gene expression in hypothalamus.	F1	1.8 mg/kg bw/d (specified by authors)	Not clear whether effects should be considered adverse; only one dose tested.
Tarapore et al. (2016; 2017)[47,48]	Rat, male	Female rats were fed a diet with BPA before and during pregnancy. Different stages of spermatogenesis was analysed in, offspring at PND210.	0, 2.5, 25, 250 and 2,500 µg/kg bw/d	Impaired spermatogenesis, measured as an increased fraction of seminiferous tubules with impaired spermatogenesis at the round spermatid step 1.	F1	25 µg/kg bw/d	Only one dose tested with standard diet; limited number of animals; no pattern in the results.
Tiwari and Vanage (2017)[58]	Rat, male	Rats received BPA by gavage for 6d, where after lipid peroxidation and various antioxidant enzymes were measured in bone marrow cells and blood lymphocytes, and in testis and epididymis.	0, 0.01 and 5 mg/kg bw/d	Increased lipid peroxidation and decreased activity various antioxidants in various cells/tissues.	No study on developmental effects.	0.01 mg/kg bw/d	Not clear whether effects should be considered adverse.
Van Esterik (2014; 2015)[49,50]	Mouse, male and female	Mice were exposed during gestation and lactation via pellet; Offspring were followed for 20 weeks. Glucose tolerance test, spontaneous locomotor activity, histopathology, clinical chemistry, gene expression analysis and DNA methylation was performed.	8 doses (0-3,000 µg/kg bw	Reduction in tissue and body weights; physical activity; biochemical parameters.	F1	Lowest BMDL05: 233 µg/kg bw/d (interscapular weight in females). (dose was calculated by authors based on food consumption).	Not clear whether effects should be considered adverse (noted as non-toxic doses by the authors).

Reference	Analysed species and sex	Study design	Tested doses	Critical effect(s) observed	Studied generation	Lowest effect level	Comments/Main limitations for risk assessment
Whitehead et al. (2016)[52]	Mouse, foetus, sex not reported	Pregnant mice fed 25 mg/kg diet from GD7.5-18.5. Thereafter foetal pancreata were collected and analysed for morphological changes.	0 and 25 mg/kg diet	Increased number of islet-cell clusters, increased glucagon expression in islets and numbers of glucagon-expressing islet-cell clusters.	F1	4.8 mg/kg bw/d (recalculated using TGD, assuming bw of 30 gr).	Not clear whether effects should be considered adverse; only one dose tested.
Xie et al. (2016)[53]	Mouse, male	Newborn male mice were subcutaneously injected with BPA on PND1-21. At PND22, histological analysis was performed on the testes.	0 and 0.01, 0.1 and 5 mg/kg body weight	Testis: signs of meiotic arrest (spermatogonia and spermatocytes with markedly less round spermatids), increased apoptosis, abnormal proliferation.	No study on developmental effects.	100 µg kg bw/d	Model not relevant for workers. Exposure route not relevant for workers; limited dose-response.

Abbreviations: AST - aspartate aminotransferase; ALT - alanine aminotransferase; BPA - bisphenol A; FDA - Food and Drug Administration; GD - gestation day; GLP - Good Laboratory Practice; GLUT 1,3 - transporter 1, 3; GPx - glutathione peroxidase; MDA - malondialdehyde; NO - nitric oxide; PND - post natal day; OVA - ovalbumine; StAR - steroidogenic acute regulatory protein; SOD2 - superoxide dismutase.

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