National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

Knowledge brief

Policy summary of public consultation regarding EFSA draft opinion on TDI for bisphenol A

RIVM

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At the end of 2021, the European Food Safety Authority (EFSA) published a draft opinion on bisphenol A entitled *Re-evaluation of the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs*. EFSA proposed to lower the temporary tolerable daily intake (TDI) from 4 µg/kg body weight to 0.04 ng/kg body weight per day. This is a reduction by a factor of 100,000. The proposal to reduce the TDI was based on an assessment of studies on this subject that appeared in the scientific literature between 2013 and 2018. All the scientific literature prior to 2013 had already been incorporated into the previous EFSA opinion on BPA from 2015. EFSA invited interested parties to submit comments in a public consultation that ran from 15 December 2021 to 22 February 2022.
As part of this public consultation, EFSA organised two stakeholder meetings. On 24 January 2022, there was a public meeting attended by RIVM staff as well as NVWA-BuRO staff. On 25 January 2022, there was a meeting for risk assessment experts, which was open to a maximum of two experts per Member State. The Dutch delegation consisted of a representative of RIVM and a representative of NVWA-BuRO.

Together with NVWA-BuRO, RIVM submitted a written response as part of the public consultation. This knowledge brief gives an overview of the key issues covered by RIVM and NVWA-BuRO in their response. The brief contains the policy summary presented to the Ministry of Health, Welfare and Sport on 7 April 2022. See the appendix to this document for the full text of RIVM/NVWA-BuRO's response.

1. According to RIVM/NVWA-BuRO, scientific studies published prior to 2013 should be included in the overall assessment and derivation of the TDI. The draft opinion failed to do so, as it only considered studies published between 2013 and 2018.
2. One of the goals of the EFSA opinion was to determine the critical effect dose. This is the lowest dose at which adverse effects occur following exposure to BPA. The critical effect dose is then extrapolated to a health-based limit value for humans, allowing for uncertainties. In this case, the health-based limit value and the TDI were the same.
EFSA determined that the critical effect of BPA is immunotoxicity. More specifically, EFSA determined the critical effect on the basis of an animal study that showed an increase in helper T-cell counts. These are white blood cells that play a key role in cellular immune mechanisms, including the development of allergic pneumonitis. RIVM agreed with EFSA that BPA in low concentrations can have effects on the immune system. RIVM previously discussed these effects in a workshop with external experts. The findings of that workshop were published and shared with EFSA (Hessel et al., 2015). However, RIVM/NVWA-BuRO did not agree with EFSA's conclusion that the increase in helper T-cell counts as determined by EFSA is in itself an adverse effect. According to RIVM/NVWA-BuRO, this is a mechanistic change that can *potentially* lead to an adverse effect. The development of allergic pneumonitis, which is the adverse effect assumed by EFSA when helper T-cell

counts change, was not actually measured in the animal study that EFSA selected. Hence, the animal study yielded a mechanistic indication for *potential* effects of BPA on the immune system. Based on the available data, it cannot be stated with certainty that every exposure to BPA at the same dose leads to adverse effects.
3. As pointed out in the guidance for immunotoxicity risk assessment for chemicals (WHO/IPCS 2012), functional studies into adverse effects on the immune system are needed to understand and draw conclusions on the immunostimulatory and immunosuppressive effects of chemicals. However, the Extended One Generation Toxicity Study (OECD-TG-443) is the only OECD template currently available that offers the opportunity to test effects on the developing immune system. This study is currently only conducted in specific cases at high-tonnage production levels under REACH legislation, and has not been conducted for BPA. More and more studies in the scientific literature point to the need for a review of statutory requirements on studies into adverse effects on the immune system, not only with regard to BPA. RIVM/NVWA-BuRO expressed their concern about this in their response, and highlighted the need for further BPA testing.
4. Once the critical effect has been determined, the critical effect dose from the animal test is extrapolated to the health-based limit value (TDI) for humans. RIVM/NVWA-BuRO had several critical comments regarding the uncertainty factors that EFSA applied to these extrapolation steps and, overall, argued that several steps lacked appropriate scientific support. RIVM/NVWA-BuRO proposed a different study that might be used to derive the factor for extrapolating the critical effect dose from animals to humans. When that alternative factor is used, the TDI is higher. See Appendix 1 for details.
5. The risk characterisation of a substance requires an exposure assessment as well as a hazard assessment. The EFSA mandate specified a 're-evaluation of the risks to public health related to the presence of BPA in foodstuffs'. In other words, the current mandate covers a re-evaluation of the exposure, which should be carried out within the framework set out in the draft EFSA opinion. However, the exposure calculations were based on the exposure data from the 2015 opinion. Given the considerable commotion surrounding BPA in recent years, it seems likely that BPA substitution has already taken place and that more alternative substances have come into use. This is why RIVM/NVWA-BuRO expect that BPA exposure from dietary sources has changed since 2015 and that EFSA's data set is no longer appropriate. RIVM/NVWA-BuRO asked EFSA why that data set was not updated and why exposure (an important risk assessment criterion) was not extensively discussed in the opinion. RIVM/NVWA-BuRO confirmed that, based on the assessed exposure data from 2015, the TDI proposed by EFSA was exceeded. RIVM/NVWA-BuRO did not expect exposure from dietary sources to have decreased to the same degree. However, RIVM/NVWA-BuRO were of the opinion that EFSA should have collected new (and more recent) data on the presence of BPA in foodstuffs and should have assessed exposure levels on the basis of such recent data and the latest food surveys, in order to:

- inform Member States on any changes in BPA concentrations in foodstuffs, for example a decrease relative to EFSA's data set from 2015;
- enable Member States/the EU to monitor the effects of existing measures to limit BPA levels;
- inform Member States on the relevant current risk factors and provide them with the data they need to advise national authorities and the EU on migration limits for BPA in foodstuffs.

6. RIVM/NVWA-BuRO argued that the proposed lowering of the TDI could accelerate the phasing out/substitution of BPA in food contact materials. This could inadvertently lead to substitution by other bisphenols. Indeed, other bisphenols are already found in food (see for example Van Leeuwen et al. 2019; DOI: 10.1016/j.chemosphere.2018.12.189) and can have equal or even stronger oestrogenic and androgenic activity compared with BPA

(see for example Punt et al. 2019; DOI: 10.1007/s00204-019-02479-6). RIVM/NVWA-BuRO wondered whether EFSA acknowledged the need for an effective follow-up plan for the assessment of BPA analogues, in order to prevent the use of other, more harmful substitutes that might result from publication of the low TDI. Although risk management was not covered by the EFSA mandate, the acceleration of substitution (and the potential consequences for public health) could be directly linked to the proposed new TDI. A concluding remark on this important issue, which is directly linked to the EFSA opinion, was missing from the latest version of the draft. RIVM/BuRO pointed this out.

Follow-up
The public consultation has since closed. EFSA will publish the final version of its opinion, including the definitive TDI, after processing stakeholders' input. If EFSA decides to maintain the proposed TDI following the public consultation, this will in all likelihood have major consequences for, among other things, 1) the use of BPA; 2) the use of alternative substances and materials to substitute BPA; 3) the re-use of plastics that contain BPA; 4) the measures required to limit exposure to BPA in the environment.
RIVM and NVWA-BuRO will have to consult with the Ministry of Health, Welfare and Sport and/or the interdepartmental consultative committee on endocrine disruptors on the follow-up steps required in the event that EFSA maintains the proposed TDI. These steps can build on previous RIVM studies on BPA and alternatives to BPA (Appendix 2).

In its opinion, EFSA focuses solely on determining the TDI without including a risk analysis and risk management plan. Nevertheless, these are important follow-up steps. An exploration of risk-mitigating measures for the group of bisphenols is currently underway at the European Chemicals Agency (ECHA) (All news - ECHA).

Appendix 1: Public consultation regarding EFSA opinion on bisphenol A (BPA) – RIVM and NVWA-BuRO

The chapter titles and section numbers refer to the parts of the opinion to which the response relates.
Most recent revision: 21 February 2021 at 15:30
Comments to be entered per section

1.3.2 Previous EFSA assessments (502 CHARACTERS)
RIVM / NVWA-BuRO suggests to take up the previous assessment by the Committee for Risk Assessment (RAC) that identified bisphenol A as reproductive toxicant in category Repro. 1B (H360F), Skin Sens. 1 (H317), Eye Dam. 1 (H318), and STOT SE 3 (H335), as well as the previous assessments by REACH Member State Committee (MSC) that identified bisphenol A as SVHC under articles 57C and F of REACH based on its reproductive and endocrine disrupting properties for human health and the environment respectively.
2.3 Methodologies (392 CHARACTERS)
In the current evaluation of BPA new studies from 2013 –2018 were considered, which is logical as studies before 2013 were evaluated in the previous BPA opinion. However, it seems that only the studies from this period were taken into account in the weight of evidence assessment. We believe that in the WoE all available information should be considered, including studies dating before 2013.

3.1.1.4 Human equivalent dose (1956 CHARACTERS)

Since substance specific information on the kinetics of BPA is available a Human Equivalent Dose Factor (HEDF) of 0,0115 is applied, which means the PoD is divided by a factor 87 to extrapolate from mouse-to-human. The generic uncertainty factor for extrapolation from mice to human is 4, so the correction for interspecies differences based on the substance specific data is approximately a factor 20 more conservative compared to the standard approach for how HBGVs are derived.
RIVM / NVWA-BuRO disagrees with the HED factor that is used in the present deduction of the TDI. RIVM / NVWA-BuRO considers that the study of Doerge et al. (2011: DOI: 10.1016/j.toxlet.2011.09.020) is not suitable for the derivation of the HEDF. In the study of Doerge most of the levels of unconjugated BPA are below the LOD. This introduces a large uncertainty in the data and probably results in a significant underestimation of the AUC for free BPA. Comparison of this AUC with the estimated human AUC results in an unreliable HEDF.
Reliable data on the clearance of BPA may be more appropriate to derive the HEDF. Studies in various species (mice, rats, dogs, sheep, pigs, monkeys and horses, see Taylor et al, 2011; Collet et al, 2015) indicate that the clearance of BPA is similar across the species. In 2018 Poet & Hayes used allometric scaling to calculate clearance of BPA in mice, rats, monkeys and humans. They concluded that the clearance of BPA was virtually equal between species when allometric scaling was taken into account. Based on their calculations Poet and Hays concluded that a HEDF of 0.9 for extrapolation from mouse-to-human as well as for rat-to-human would be appropriate.
RIVM / NVWA-BuRO proposes to use that the HEDF 0.9 to derive the human equivalent doses for data from studies with mice and rats.
RIVM / NVWA-BuRO noted that the study by Poet and Hayes (2018) is not addressed in the current draft opinion on BPA. RIVM / NVWA-BuRO suggests that this study is to be included in the opinion.

3.1.3. Immunotoxicity (1742 Characters)

EFSA proposes a cellular mechanism by which allergic inflammation in the lungs can occur upon BPA exposure. The upregulation of the Th17 cells and corresponding cytokines have a key role in this process. As stated by EFSA, it is not clear how BPA interacts at molecular level and where in the cascade this interaction takes place. Can EFSA include more information/ discussion, or propose a plausible mechanism on the molecular initiating event, to further support the proposed mechanism? Since the opinion is a mechanism driven assessment, it is important to elucidate the mechanism as complete as possible. The present opinion lacks a discussion on whether the endocrine properties of BPA fit in the assumed model.
Lines 3224-3227: The Th17 cytokines IL-17, IL-21, and IL-23 were not taken forward for BMD analysis, because (amongst others) they are not considered very close to the apical endpoint. This reasoning is not a logical one, (1) since the relationship between Th17 cells and allergic responses has been clearly shown (as is reiterated in the text) and (2) Th17 cells themselves are in fact taken forward for BMD analysis, (3) in a Th17-driven allergy model, at least IL-17 and IL-23 can be judged as markers of the allergic response. A similar reasoning holds for IL-17 (lines 3402-3405).
lines 3381-3382: four studies in mice, of which two dealt with exposure during development, and one with exposure during adulthood. What happened to study number 4?
lines 3392-3394: PGD2 was not taken forward for BMD analysis, because (amongst others) it is not considered very close to the apical endpoint. It is fair to say that PDG2 production is one of the critical mediators.
line 3441: “Likely” should read “Very Likely”

line 3547: "G-CSF" should read "C-CSF"?

3.1.6. Reproductive and developmental toxicity (Characters 796)
Section 3.1.6.2 Animal studies; & table 20 (and 3.2.2)
RIVM / NVWA-BuRO considers that, without clarification of the following warnings regarding data quality, the BMDL (of 14.9 ng/kg bw per day) for effects on the ratio of primordial follicles versus total follicles is not suitable to serve as a PoD and should not be considered for establishing a HBGV. It is noted that the obtained AIC of the full model is 2 to 7 points lower than the AICs of the individual models. According to the EFSA decision tree (figure 1 in annex I) this triggers an alert, and indicates a problem in the data. In addition, the 363-fold difference between the BMDU and BMDL (i.e. ratio between BMDU and BMDL is 363) also indicates a quality issue of the data. RIVM / NVWA-BuRO suggests that the quality of these data is assessed thoroughly before using these data to derive a reference point. Guidance on which details could be assessed are mentioned in the EFSA BMD guidance (2017) section 2.5.7

3.2.4 Derivation of HBGV
Detailed response of RIVM/ NVWA-BuRO on 3.2.4 derivation of HBGV is in the attachment.
We agree with EFSA that BPA stimulates the immune system after antigen stimulation at low doses and that the (developing) immune system is a sensitive target to BPA exposure, as concluded earlier (Hessel et al., 2016). In previously published studies, credible evidence for adverse immune effects were provided after developmental exposure to BPA in the low dose range (see references in Hessel et al. 2016; DOI: 10.1016/j.reprotox.2016.06.020). Also the study of Luo et al. (2016) finds a consistent pattern of dose-dependent increase both in female and male offspring, indicative of immunostimulation, and thus these findings are in line with previous observations.
RIVM / NVWA-BuRO however does not agree that the key study of Luo et al. (2016) in section 3.2.4. provides sufficiently robust information to derive a critical effect dose. The study of Luo et al. (2016) measured only a narrow window of immune parameters (Th17 cells in the spleen and associated cytokines in serum) and there are several shortcomings in this study:

- Not all data on the immunophenotyping of the spleen are shared, e.g. CD4/CD8 ratio, B/T cell ratio;
- Effects on Th1, Th2, and Treg cells were not evaluated, providing an incomplete picture of immune effects;
- Immunophenotyping is only shown in relative values and not in absolute values;
- Background levels of BPA, for instance through exposure via food, drinking water or polycarbonate caging, are not measured.

This study shows that BPA stimulates some immunological parameters, but it does not provide any information if, and to what extent, this stimulation would lead to an adverse effect. Although indeed Th17 cells have been linked to autoimmunity and asthma, the animals were not challenged in this study.
RIVM / NVWA-BuRO notes the selection of this endpoint by EFSA is in line with a more general trend towards selection of upstream effects as critical endpoints for derivation of health-based guidance values (HBGVs) for which it is difficult to conclude if they are considered adverse or are causally linked to adversity at similar dose-levels. In the assessment of EFSA, the results from the Luo et al. (2016) study are linked to other studies that found effects of BPA on the immune system. From a mechanistic perspective this is a sound way of argumentation. It is however not possible to causally link the effect level from this study to effect levels of studies that investigated functional immune

effects. To prevent introduction of such uncertainty in derivation of HBGVs, we consider it important that a critical effect is selected of which its adversity is not debatable.
WHO-IPCS has published a risk assessment framework for immunotoxicity that provides clear guidelines on how to use different immunological parameters in risk assessment (WHO/IPCS Harmonization Project Document No. 10. Guidance for immunotoxicity risk assessment for chemicals, 2012). For immunostimulation, they state that general immune assays, such as lymphocyte phenotyping and cytokines may be used to support a mode-of-action (and thus support the biological plausibility of effects observed in other studies), but that such parameters are generally not considered to be reliable predictors of immunostimulation and therefore should not be used to derive an effect level for immunostimulation. Instead, functional tests should be performed to inform and conclude on the adversity of immunostimulatory effects.
It is remarkable and worrying that even after identification of the developmental immune system as sensitive target (e.g. by EFSA and RAC), functional parameters such as adjuvant effects were not included in the CLARITY study (i.e. Li et al. 2018a; 2018b). Hence, although the CLARITY study is of good quality, functional effects at lower dosages cannot be excluded based on this study.
In conclusion, even after this elaborate re-evaluation of EFSA that includes the recent CLARITY findings, RIVM / NVWA-BuRO concludes there is still no robust and credible stand-alone study that allows derivation of a TDI for BPA-induced developmental immunotoxicity, whereas the overall weight of evidence clearly points to developmental immunotoxicity as a sensitive target system for this substance. Thus, however we are aware this is not the mandate of the CEP Panel, we identify the need to perform a robust developmental immunotoxicity study with BPA to fill this data gap. Until then, we would suggest that any TDI derived should be treated as a 'tentative' TDI.
In this context, RIVM/ NVWA-BuRO would like to resonate a statement of Hessel et al. (2016), and conclude that "current regulatory hazard and risk assessment strategies may not give sufficient attention to possible developmental immunotoxicity of chemicals. The Extended One Generation Toxicity Study (OECD-TG-443) is the only OECD guideline based study that provides an opportunity for developmental immunotoxicity testing. However this study, and especially its immunotoxicity and neurotoxicity cohorts, is currently only carried out in exceptional cases at higher tonnage production levels under the REACH legislation. Evidence is accumulating that points to reconsideration of regulatory requirements for developmental immunotoxicity testing." As mentioned in WHO/IPCS (2012), functional immunotoxicity tests are needed to inform and conclude on the adversity of immunostimulatory and immunosuppressive effects of chemicals.

3.1.3.4 *In vitro* and mechanistic studies & 4.1.3 Hazard identification 4.1.3 Immunotoxicity (275 characters)

RIVM / NVWA-BuRO suggests to strengthen the conclusions that the cells that are affected by exposure to bisphenol A may lead to inflammatory reactions, and may play a role in immune related disorders (line 3640 and lines 12210-12211) by the evidence from epidemiological studies.

3.2.1 Dose–response modelling

Detailed response of RIVM/ NVWA-BuRO on 3.2.1 Dose–response modelling is in the attachment.
Lines 11841 - 11842
The current EFSA opinion on BMD modeling (https://doi.org/10.2903/j.efsa.2017.4658) provides several suggestions on how to (theoretically) deal with poor data and wide BMD confidence intervals (see below). It is suggested to change lines 11841-11842 accordingly.

In section 2.5.5 (Fitting models) of the BMD guidance, under topic '*Covariates*', EFSA suggests to "fit a given model to a combination of data sets which differ in a specific aspect, such as sex, species or exposure duration, but are similar otherwise" (i.e. the so-called Covariate Approach), to improve the precision of the estimated BMD(s). Applying the Covariate Approach is particularly of help when the individual data sets provide poor dose–response information.

In the situation where a wide confidence interval of BMD is derived (partly) due to substantial extrapolation outside the observed dose-range from the fitted model, EFSA suggests to consider to use a higher BMR plus an uncertainty factor to the BMDL (section 2.4.1 of the BMD guidance 'Establishing health-based guidance values').

Lines 11843 - 11848
Could EFSA explain why a cut-off value of 10 for the ratio of the lowest non-zero dose and the BMDL is a reasonable criterion to discard datasets for BMD analysis?

Based on this criterion, some relatively precise BMD estimates (i.e. with a small BMD CI) are discarded, e.g. Ogo et al. (2018) neutrophils in epididymis cauda confidence interval 0.5 – 4.62 ug/kg bw/d, and some BMD analyses with low precision of the estimated BMDs were however included, for instance Johnson et al.(2016) male rat 1.47 – 1520 ug/kg bw/d and Chen Z et al. (2018) platform duration (learning and memory) 1.07×10^4 - 2.4×10^7 ug/kg bw/d.

RIVM / NVWA-BuRO considers that comparing the lowest non-zero dose and the BMDL is not a sensible way to evaluate the BMD analysis. The level of protection of BMDL does not depend on the width of the confidence interval, because BMDL always remains what it is: a dose where the effect is smaller than the specified effect size (i.e. the BMR) with the confidence level used. However it might happen that sometime the data is very poor that the estimated BMD is highly imprecise and the use of a very low BMDL may be unwarranted. In that case a reasonable criterion to evaluate the analysis is the precision of the estimated BMD, i.e. the width of the BMD confidence interval determined by the ratio of BMDU and BMDL. This precision is determined by the quality of the data and reflects how informative the data is, which makes it an appropriate criterion for excluding or including the BMD analysis.

Table 19, Ma et al. (2018) [RefID 12637]
RIVM / NVWA-BuRO suggests EFSA to include the results from the combined analysis (with strain as covariate) as presented in section 3.2.3.1 of Annex I (instead of the separate analysis for each strain). The BMDs with improved precision (due to applying the covariate approach) are more preferable.

3.2.1.1 Immunotoxicity (603 characters)

Lines 11859 – 11861; 11900 - 11901
RIVM / NVWA-BuRO suggests EFSA to still perform the BMD analysis even with the lack of information on litter effects.

In this case without considering the litter effect, the uncertainty of the BMD tends to be underestimated (i.e. narrower confidence interval). But the analysis would still provide important information on the BMDs regarding these endpoints.

Line 11960: "lack of information" Did the authors actively contact the authors (O'Brien et al. 2014a) to try and obtain the missing information? This study seems a very important one the immunotoxicity of BPA.

3.3. Risk characterisation (1994 characters)

For risk characterization, besides the hazard assessment, an exposure assessment is required. The mandate states "re-evaluate the risks to public health related to the presence of BPA in foodstuffs". Thus a re-evaluation of exposure is within the mandate. However, for the exposure calculations the dataset of the 2015 opinion is re-used. Given the ongoing substitution of BPA, RIVM/ NVWA-BuRO expects that the exposure to BPA via food changed since 2015 and therefore expects the dataset is not accurate anymore. Why is this database not updated, and why is the exposure part (being an important aspect of the risk-assessment) not extensively discussed in the opinion?
RIVM / NVWA-BuRO agrees that, based on the proposed TDI, the 2015 assessed exposure exceeds the HBGV with several orders of magnitude. RIVM / NVWA-BuRO expects that the exposure from food stuff (change in occurrence data and changes in consumption patterns) did not decrease with a similar magnitude. Still, RIVM / NVWA-BuRO is of opinion that EFSA should have gathered new (recent) occurrence data of BPA in foodstuffs, and should have assessed the exposure with recent occurrence data and the latest food surveys, accordingly, in order to:

1) Provide the MSs with relevant information whether or not the BPA concentrations in food stuff changed, e.g. decreased compared to, at time of EFSA 2015 partially obsolete concentration data.
2) Allow the MSs/the EU to check the effects of already installed restriction measures to lower BPA concentrations.
3) Provide the MSs with information on the relevant (current) risk drivers, information needed to advice national authorities and the EU to set ML's for BPA in food stuff.

RIVM / NVWA-BuRO is of opinion that the current draft for public consultation did not meet a re-evaluation of the risks to public health related to the presence of BPA in foodstuffs as mandated. EFSA is advised to perform an up to date exposure assessment of BPA so it can be included in the BPA opinion.

4.3 Conclusion – Risk characterization (974 characters)

The proposed lowering of the TDI may lead to an acceleration of phase-out/ substitution of BPA in FCM. As a consequence this change may unintentionally result in regrettable substitution by other bisphenols. Other bisphenols are detected in food (see for example Van Leeuwen et al. 2019; DOI:) and may have equal or even stronger estrogenic- and androgenic activity compared to BPA (see for example Punt et al. 2019; DOI:). Does EFSA endorse the need for an adequate follow-up plan for the assessment of BPA analogues in order to avoid the use of other (more) harmful substitutes, which may be induced by publication of the low TDI? Risk management is not part of EFSA's tasks, however the acceleration of regrettable substitution (and the potential consequences for public health) are in direct relation with the new TDI. A concluding remark on this important issue, directly related to this opinion, is missing.

Appendix I - Benchmark dose analysis

Detailed response of RIVM/ NVWA-BuRO on Appendix I – Benchmark dose analysis is in the attachment.

RIVM / NVWA-BuRO very much appreciates the effort of the panel to perform and report the elaborate BMD analysis (incl. covariates).

Lines 151 – 152
The expressions of the exponential, Hill, inverse exponential, and log-normal models in this table are outdated. The correct formula are listed in the table below (Table 1). Also note that the four parameter Exponential and Hill models are termed Exponential model 5 and Hill model 5 (not 4) in PROAST, as can be observed in the list of fitted (continuous) models (e.g. line 226 in Annex I). Furthermore, 3-parameter versions of the inverse exponential and the lognormal models are also applied. RIVM / NVWA-BuRO suggests EFSA to modify the content of this table based on the following information (Table 1):

Table 1. Formula of the exponential, Hill, inverse exponential, and log-normal models

Model	Number of parameters	Formula
Null	1	$y = a$
Full	no. of groups	$y = \text{group mean}$
Exponential model 3	3	$y = a \cdot c^{1-e^{-(\frac{x}{b})^d}}$ with c = 'Inf'
Exponential model 5	4	$y = a \cdot c^{1-e^{-(\frac{x}{b})^d}}$
Hill model 3	3	$y = a \cdot c^{\frac{x^d}{b^d+x^d}}$ with c = 'Inf'
Hill model 5	4	$y = a \cdot c^{\frac{x^d}{b^d+x^d}}$
Inverse Exponential model 3	3	$y = a \cdot c^{e^{-(\frac{x}{b})^{-d}}}$, with c = 'Inf'
Inverse Exponential model 5	4	$y = a \cdot c^{e^{-(\frac{x}{b})^{-d}}}$
Log-Normal model 3	3	$y = a \cdot c^{\Phi(\ln b + d \cdot \ln x)}$, with c = 'Inf'
Log-Normal model 5	4	$y = a \cdot c^{\Phi(\ln b + d \cdot \ln x)}$

Lines 159 - 161
Could EFSA explain why a criterion of AIC of 5 was used to select between the three and four parameter models (of all four model families)? And how was this selection between the two types of models is realized by applying this criterion? According to our knowledge, within each model family the model resulting in the lowest AIC is selected. This is in line with statements made in section 2.5.7 of EFSA's BMD guidance and with Figure 1 of Annex I.

Lines 174- 175
RIVM / NVWA-BuRO suggests EFSA to rephrase this rationale.

When the total count of cells is large enough (e.g. million), then it is acceptable to consider this endpoint as continuous. By looking into the original article it may be possible to get an impression of the total number of cell count and therefore make the assumption based on that.

Sections 2.1.2 & 2.2.2 & 2.3.2, sections 3.1.2 & 3.2.2, section 4.1 & section 5.10.2
Could EFSA elaborate how exactly the BMRs were chosen/derived based on the information on the coefficient of variation of the dose-response data?

- RIVM / NVWA-BuRO would like to point out that, even though it is preferable to use a BMR which is based on biological or toxicological considerations, basing the choice of BMR on within group variability of a single study (or only several studies) is not justified. A recommended way is to analysis a large scale of dose-response data for certain endpoint and derive the 'typical' variance for that endpoint, which could then support the choice of an endpoint-specific BMR for the BMD analysis (Slob 2017 https://doi.org/10.1080/10408444.2016.1241756).

Sections 3.2.3.2 & 3.2.3.3
RIVM / NVWA-BuRO thinks that the analyses in these two sections are not necessary. In section 3.2.3.1, the BMD analysis with strain as a covariate (i.e. applying the covariate approach) was also carried out and BMDs with improved precision were derived. This result from section 3.2.3.1 should be used in the draft opinion.

Sections 4.9 & 4.10
RIVM / NVWA-BuRO suggests EFSA to perform the BMD analysis on the combined dose-response data from these two sections, in the same fashion of the analysis on the mean serum uric acid concentration (3.2.3.1.), but here use study as a covariate. This may improve the precision of the estimated BMDs.

Appendix 2: Overview of previous RIVM reports, scientific articles and activities relevant to BPA

NB: THE CONCLUSIONS IN THE SUMMARIES BELOW WERE FORMULATED IN THE YEAR IN WHICH THE RELEVANT REPORT OR SCIENTIFIC ARTICLE APPEARED. DUE TO THE POSSIBLE CHANGE OF THE TDI (2022), THOSE CONCLUSIONS MAY NO LONGER APPLY AS OF 2022.

2014
Bisphenol A: Part 1. Facts and figures on human and environmental health issues and regulatory perspectives
Bisphenol A : Part 1. Facts and figures on human and environmental health issues and regulatory perspectives | RIVM
Authors: J Bakker, JD te Biesebeek, PE Boon, P Bos, FA van Broekhuizen, R Geertsma, L Geraets, W de Jong, W Mennes, NGM Palmen, A Piersma, G Schuur, D Sijm, L van der Ven, K Verbist, M Wouters, M Zeilmaker
Follow-up steps and policy relevance: Part 2 of the study was commissioned in response to Part 1 (2015, see below): Bisphenol A: Part 2. Recommendations for risk management

2015
Bisphenol A: Part 2. Recommendations for risk management
Bisphenol A : Part 2. Recommendations for risk management | RIVM
Authors: J Bakker, BC Hakkert, EVS Hessel, RJ Luit, AH Piersma, DTHM Sijm, AG Rietveld, FA van Broekhuizen, H van Loveren, JK Verhoeven
The conclusions on the effects of BPA on the immune system were discussed during a workshop with experts. The findings were published in a scientific article:
Ellen V S Hessel, Janine Ezendam, Fleur A van Broekhuizen, Betty Hakkert, Jamie DeWitt, Berit Granum, Laurence Guzylack, B Paige Lawrence, Andre Penninks, Andrew A Rooney, Aldert H Piersma, Henk van Loveren. Assessment of recent developmental immunotoxicity studies with bisphenol A in the context of the 2015 EFSA t-TDI. Reprod Toxicol 2016 Oct;65:448-456. doi: 10.1016/j.reprotox.2016.06.020. *Epub 2016 Jun 25.*

Follow-up steps and policy relevance:
- The report entitled 'Dietary sources of exposure to bisphenol A in the Netherlands' (2016, see below) was commissioned in response to this report.
- This resulted in a request for a report on alternatives to BPA in 2018: 'Substitution of bisphenol A: a review of the carcinogenicity, reproductive toxicity, and endocrine disruption potential of alternative substances.'
- RIVM advised EFSA to reconsider the TDI. EFSA followed this advice, but did not make any changes. However, EFSA is currently engaged in a process to review the TDI (see RIVM's 2017 response as part of the public consultation on EFSA's Bisphenol A (BPA) hazard assessment protocol). See the following link for the EFSA outcomes: Bisphenol A: new immune system evidence useful but limited | EFSA
- RIVM's response to EFSA: EFSA agrees with RIVM that potential effect of BPA on the immune system requires further attention | RIVM

2016
Dietary sources of exposure to bisphenol A in the Netherlands
Dietary sources of exposure to bisphenol A in the Netherlands | RIVM
Authors: PE Boon, JD te Biesebeek, H Brants, MC Bouwmeester, EVS Hessel

2017
RIVM's response as part of the public consultation on EFSA's Bisphenol A (BPA) hazard assessment protocol
Parties involved: RIVM experts in the RIVM-wide group of experts on endocrine disruptors
RIVM pointed out that it did not agree with the exclusion from the hazard assessment of the Menard studies, which raised some matters of concern. See the following link for the protocol: DOI: 10.2903/sp.efsa.2017.EN-1354

2018
Substitution of bisphenol A: a review of the carcinogenicity, reproductive toxicity, and endocrine disruption potential of alternative substances.
DOI: 10.1080/10408444.2019.1701986
Authors: den Braver-Sewradj SP, van Spronsen R, Hessel EVS.
This study shows that many structural BPA analogues (other bisphenols) are used as alternatives to BPA. In animal studies, many of these structural analogues appear to cause effects similar to those of BPA. Note, however, that far fewer data from such studies are available for these structural analogues. For this and other reasons, it is not clear whether there is a difference in potency (the dose that produces the effects)

between BPA and structural analogues. We therefore recommend considering the entire group of bisphenols rather than just the effects of each individual analogue in cases where toxicity data for structural analogues of BPA are limited. Besides a list of structural analogues, other alternative substances and materials were studied. Some alternatives were clearly shown to have an endocrine-disrupting effect. For other alternatives, there were not enough data on carcinogenic, endocrine disrupting or reprotoxic effects to make statements regarding the extent to which those substances are safe. A few substances might be interesting candidates as alternatives to BPA, as the limited available data suggest they do not exhibit endocrine-disrupting, reprotoxic or carcinogenic activity. However, given the limited data on which this inference is based, a more extensive evaluation of their effects is required before any of these substances can be said to be a truly safe alternative to BPA. The overall conclusion of the study is that, for most alternative substances and materials to BPA, the available data are insufficient to conclude that they are safe, and that structural analogues should be used with caution as alternatives to BPA, as they appear to exhibit similar effects.

Follow-up steps and policy relevance:

- Manuscript published in the scientific literature. There is considerable demand for the publication and for responses to it.
- RIVM will offer the publication to relevant bodies.