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GUIDANCE

Guidance on the data requirements for the safety assessment of bisphenols other than Bisphenol A (BPA) and their derivatives

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The declarations of interest of all scientific experts active in EFSA's work are available at https://open.efsa.europa.eu/experts.

Abstract

Concerns regarding the safety of bisphenol A (BPA) and the resulting restrictions on its use in food contact materials (FCM) have been broadened to other 'bisphenols and bisphenol derivatives' (BPs). Several of these substances are considered hazardous due to their classification as carcinogenic, mutagenic, toxic to reproduction (CMR) or endocrine disrupting for human health under Regulation (EC) 1272/2008. In accordance with Regulation (EU) 2024/3190, the European Food Safety Authority (EFSA) was mandated to publish a scientific output detailing the information necessary for the safety assessment of hazardous BPs other than BPA and their derivatives when used in FCM. The FCM Panel developed a guidance defining the data requirements needed to assess the safety of such substances, including BPs not classified as hazardous to avoid regrettable substitutions. This guidance complements the EFSA FCM Note for Guidance. The proposed requirements address different migration scenarios and focus on key toxicological endpoints of concern, including immunotoxicity, developmental and reproductive toxicity and metabolic effects, as well as toxicokinetic properties. Already at the migration level below 0.05 mg/kg food, additional data beyond standard genotoxicity testing are requested, reflecting the potential for low-dose adverse effects observed for BPA and structurally related compounds. The guidance specifies the use of in vivo, in vitro and in silico approaches, including extended one-generation reproductive toxicity studies, targeted immunotoxicity testing and studies supporting physiologically based kinetic modelling.

KEYWORDS

bisphenol A, bisphenols, food contact materials, guidance, safety assessment, toxicokinetics, toxicological data requirements

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1 | INTRODUCTION

1.1 | Background and Terms of Reference

Concerns regarding the safety of bisphenol A (BPA) and the resulting restrictions on its use have been broadened to other 'bisphenols and bisphenol derivatives'[1] referred to as bisphenols (BPs) in this guidance. The available data (retrieved from EFSA and ECHA opinions as well as other documents, such as national assessments) showed that there are several differences in the nature and magnitude of the adverse effects they induce and in their toxicokinetic properties (Ao et al., 2022; Mhaouty-Kodja et al., 2024; Siracusa et al., 2018).

Commission Regulation (EU) 2024/3190 of 19 December 2024 concerns the use of bisphenol A (BPA) and other BPs with harmonised classification for specific hazardous properties in certain materials and articles intended to come into contact with food. It entered into force on 19 January 2025, amending Regulation (EU) No 10/2011 and repealing Regulation (EU) 2018/213. This Regulation prohibits the use of BPA in food contact materials (FCM) and establishes that hazardous BPs[2] may be used in the manufacture of FCM and articles for a specific application provided that their use has been authorised.

According to Article 6.4 of Regulation (EU) 2024/3190, EFSA '…*shall publish scientific output detailing the information necessary for the assessment of the use of hazardous bisphenols or hazardous bisphenol derivatives, in the manufacture of a food contact materials and articles for a specific application, supplementing or updating where necessary the detailed guidelines referred to in Article 9(2) of Regulation (EC) No 1935/2004. The Authority and the European Chemicals Agency shall collaborate with each other for this purpose*'.

In July 2025, EFSA issued a self-task mandate requesting the FCM Panel to produce a scientific output specifying the information needed to assess the safety of hazardous BPs when used in the manufacture of FCM. The task should be completed by 19 January 2027.

1.2 | Interpretation of the Terms of Reference

The mandate request was addressed by the preparation and publication of a guidance in which the data required for the safety assessment of the use of hazardous BPs in FCM are detailed.

Considering the definition reported in Regulation (EU) 2024/3190, *'hazardous bisphenol or hazardous bisphenol derivative' means a bisphenol or a bisphenol derivative listed in Part 3 of Annex VI to Regulation (EC) No 1272/2008, due to its harmonised classification as category 1A or 1B 'mutagenic', 'carcinogenic', 'toxic to reproduction' or category 1 'endocrine disrupting' for human health*. This guidance relates to all BPs classified accordingly.

Also, in the case of applications for the assessment of BPs not classified as hazardous within the meaning of Regulation 2024/3190 ('non-classified BPs') and intended to be used to manufacture FCM, data outlined in this guidance should be provided to avoid regrettable substitution.

2 | RELATIONSHIP OF THIS GUIDANCE TO THE EFSA NOTE FOR GUIDANCE

This guidance complements the current EFSA 'Note for Guidance for the Preparation of an Application for the Safety Assessment of a Substance to be used in Plastic Food Contact Materials' (EFSA AFC Panel, 2008, referred to in the following text as 'EFSA NfG') and the requirements contained therein. For both plastic and non-plastic[3] applications, Section 3 of this guidance on the toxicological data requirements complements Section 7 on 'Toxicological data' of the EFSA NfG. Furthermore, for non-plastic applications, Appendix A on 'FCM migration testing strategies' of this guidance complements Section 4 on 'Data on migration of substance' of the EFSA NfG. The other sections of the EFSA NfG should be followed when assessing the use of hazardous BPs in both plastic and non-plastic applications, as well as non-classified BPs.

3 | TOXICOLOGICAL DATA REQUIREMENTS AT THE LOWEST MIGRATION LEVEL (BELOW 0.05 MG/KG FOOD)

The EFSA BPA re-evaluation (EFSA CEP Panel, 2023) identified BPA as an immunotoxicant and reproductive toxicant at low dose levels (below 0.83 µg/kg bw per day, i.e. the exposure corresponding to the lowest migration level), at which adverse metabolic effects like hyperuricaemia may also occur. Most of the BPs currently considered as hazardous are classified as Repro 1B, and available data indicate that they may exert effects at the same level or lower than BPA (Mhaouty-Kodja et al., 2024). Consequently, additional data to the genotoxicity tests requested in Section 7 of the EFSA NfG for substances

[1]According to Regulation 2024/3190, 'bisphenol' means *'a substance consisting of two hydroxyphenyl functional groups linked by one bridging atom, in accordance with structure A laid down in Annex I and includes the salt form of the bisphenol. Additional groups may be attached to the bridging atom'*; and 'bisphenol derivative' means *'a substance indicated by the general structure B laid down in Annex I, not including the salt form of a bisphenol'*.

[2]https://chem.echa.europa.eu/obligation-lists/clhList?pageIndex=1&pageSize=100.

[3]According to Article 2(1) of Regulation 2024/3190.

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with migration below 0.05 mg/kg food/food simulant (EFSA AFC Panel, 2008) should be provided to assess whether these hazardous BPs can be used safely in FCM.

The requested data shall be obtained in compliance with the principles of good laboratory practice (GLP) provided in Directive 2004/10/EC and of OECD test guidelines (TGs) when available.[4]

The data requirements outlined in this guidance are considered the most appropriate scientific support to the risk assessment of BPs. However, there may be circumstances where additional data or tests to those indicated in this document are required for the evaluation. Conversely, if the applicant considers some data requested in the guidance as irrelevant to a particular case, these may be omitted, provided the omission is scientifically justified.

3.1 | Toxicological data

To obtain information on immunotoxicity, developmental and reproductive toxicity (DART) and metabolic effects of BPs, an Extended One-Generation Reproductive Toxicity (EOGRT) study, including cohorts 1 and 3, should be conducted according to the most recent version of the OECD TG 443 (OECD, 2018a), supplemented with additional parameters/investigations as specified below. The applicant may expand the EOGRT study by including the extension of cohorts 2A and 2B, if relevant information related to neurotoxicity becomes available from other studies (including in vitro or in silico), or during the conduct of the study. The study design, including any further expansions, should be scientifically justified and documented.

The EOGRT study should be conducted by extending the pre-mating exposure period for the parental animals (P0) from minimally 2 weeks to minimally 10 weeks in order to cover the full spermatogenesis and folliculogenesis cycles.[5] Such an EOGRT study, with extended pre-mating exposure and the parameters/investigations specified below, will capture effects in both adult and in utero/early life stages.

For assessing potential immunotoxicity and metabolic effects, in addition to what is already listed in cohorts 1 and 3 of the EOGRT study (OECD TG 443, 2018a), the following parameters/investigations should be included:

- Serum total immunoglobulin isotypes (i.e. IgM, IgG, IgA and IgE). It is suggested to start with total IgG, IgM, IgA and IgE. If changes in total IgG are observed, it is recommended to evaluate IgG isotypes (IgG1, IgG2a, IgG2b and IgG3 in mice or IgG1, IgG2a, IgG2b and IgG2c in rats).
- Markers of inflammation (e.g. complement components C3, C4 and C5, α2-macroglobulin or haptoglobin, fibrinogen, IL-1β, IL-6, IL-17).
- Blood lymphocyte subpopulations (in addition to CD3+, CD4+ and CD8+ T lymphocytes, B lymphocytes and NK cells, naïve CD45RA+/CD62Lhi/CD44low vs. memory T cells CD45RO+/CD62low/CD44hi, Th1/Th2/Th17/Treg), intracellular Forkhead box P3 (T-cell differentiation marker) (FoxP3) and intracellular RORγt should be measured.
- Functional tests that do not require in vivo antigen stimulation should be conducted, e.g. natural killer (NK) cell functional analysis, macrophage quantification and functional assays, such as phagocytic activity, as well as assessment of $CD4^+$ T-cell differentiation and activation. In addition, cytokine production by B and T lymphocytes, following in vitro stimulation, can be evaluated, e.g. using anti-CD3 and anti-CD28 antibodies for T-cell activation and B-cell activating factor (BAFF), or anti-CD40 antibodies for B-cell stimulation. This is to comprehensively assess the major cell populations involved in the immune response. Splenocytes are recommended as preferred cell source, as they provide a representative mix of immune cell types, including T cells, B cells, macrophages and NK cells.
- In cohort 3 of the EOGRT study, the applicant may consider using ovalbumin as an antigen in an additional group of animals to cover inadvertent immunostimulation.
- Hepatic and serum uric acid.

3.1.1 | Data to be provided in case in vivo toxicity studies are already available

Since hazardous BPs have been classified as such and classification is based on data, it is likely that, for these BPs, toxicity studies will already be available. However, these studies might not have been performed with the inclusion of the parameters/investigations suggested in Section 3.1. In such a case, additional data may need to be submitted so that, in total, the information provided covers the data requirements related to immunotoxicity, DART and metabolic effects, allowing the derivation of a reference point.

(a) Immunotoxicity

Applicants should provide a scientifically sound weight-of-evidence (WoE) approach, integrating data from animal and non-animal tests, as well as other complementary sources (including read-across (EFSA Scientific Committee, 2025)) to ensure robust, transparent and biologically meaningful conclusions on the immunotoxic potential of hazardous BPs.

[4]Regardless of the source (industry, public sector, academia or other scientific organisations), EFSA critically and rigorously evaluates all the data submitted as well as the design of the studies that produced them to ensure that they meet the standards required to ensure consumer protection.

[5]This is also recommended in the ECHA Guidance on Information Requirements and Chemical Safety Assessment, Chapter 7.a, Section R.7.6 (Guidance on IR&CSA – Chapter R.7a).

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In vitro or in silico methods are recommended when animal studies have already been conducted but did not specifically assess immunotoxicity. In this case, applicants should assess the potential immunotoxicity using new approach methodologies (NAMs) to exclude potential BP-induced inadvertent immunostimulation (e.g. skin and respiratory sensitisation) and/or immunosuppression.

The published key characteristics of immunotoxicants (Germolec et al., 2022) offer a way to organise and evaluate immunotoxic hazard findings for a knowledge-based objective approach to evaluating mechanistic data that should complement other approaches, such as mode of action or adverse outcome pathways.

For both adverse effects (immunostimulation and immunosuppression), several non-animal-based approaches, including in vitro and in silico methods, are available (see the OECD Detailed Review Paper (DRP), 2022; OECD TG 497, 2021 on Defined Approaches for Skin Sensitisation; Johnson et al., 2025) especially covering contact hypersensitivity, formally validated and included in OECD TGs. The OECD DRP (OECD, 2022) provides guidance on in vitro immunotoxicity testing, with a focus on immunosuppression, including validated methods such as the IL-2 Luc assay and the IL-2 Luc LTT assay (OECD TG 444A, 2025a; Pahović et al., 2023). In addition, T helper 17 (Th17) cells, which represent the critical endpoint identified in the EFSA BPA opinion (EFSA CEP Panel, 2023), can also be studied in vitro (Malaisé et al., 2020; Pahović et al., 2023).

As no complete set of formally validated in vitro or in silico methods is available to address all potential adverse immune effects, applicants should justify the selected approach. The justification should show that the approach is fit for purpose and reliable in terms of reproducibility, accuracy, precision, specificity and robustness, in line with international standards (OECD TG 211 (2017), OECD TG 286 (2018b); Cöllen et al., 2024). Appropriate positive controls should also be used. For advice on determining biologically relevant effect sizes and adversity, the applicant should consult the EFSA guidance on biological relevance (EFSA, 2017, currently under revision).

Further requirements specifically concerning the in vitro studies are reported in Section 3.3.

(b) Developmental and reproductive toxicity

In case in vivo DART studies (e.g. OECD TGs 422 (2016), 415 (1983), 416 (2001)) are already available for a hazardous BP, these may be sufficient, provided that the resulting information matches the requirements of cohort 1 of an EOGRT study.

(c) Metabolic effects

Studies following OECD test guidelines routinely investigate predictive parameters for metabolic effects, such as body weight (gain), cholesterol, glucose, triglyceride and thyroid hormone levels. Uric acid (the only indicator of a possible metabolic effect found for BPA) is not a standard parameter. So, in case the available in vivo toxicity studies for a hazardous BP did not assess hepatic and serum uric acid, at least an in vitro measurement of xanthine oxidase activation (e.g. Kostić et al., 2015; Ma et al., 2018) is required. BPA, for which activation of xanthine oxidase was the mode of action underlying its increasing effect on hepatic uric acid synthesis, should be included as reference substance. Further requirements for in vitro studies are detailed in Section 3.3.

3.2 | Toxicokinetic data

Three studies are requested to address the toxicokinetic properties of hazardous BPs, i.e. an in vivo absorption, distribution, metabolism and excretion (ADME) study; an in vitro comparative metabolism (IVCM) study; and an in vitro intrinsic clearance (Clint) study. For the in vitro studies, further requirements are detailed in Section 3.3.

In vivo ADME study:

Key kinetic parameters from the regulatory ADME study, like peak plasma concentration (C_{max}), the area under the concentration–time curve (AUC), time to reach C_{max} (T_{max}) and half-life ($t_{1/2}$) provide insights into how efficiently a chemical is absorbed and how long it remains in the body. However, the regulatory in vivo ADME studies, performed according to OECD TG 417 (OECD, 2010), often provide data on internal exposure (concentrations in blood, plasma and tissues) only for total radioactivity and not separately for the parent chemical and/or its metabolite(s). The individual quantification of the parent chemical and its (main) metabolites in blood or plasma and in tissues would significantly increase their usefulness and value for physiologically based kinetic (PBK) model development. Therefore, when a new in vivo ADME study has to be performed, it is recommended to include these additional parameters.

IVCM study:

This study should compare at least rats and humans (and any other species if used in the toxicological data set), as described in the 2021 EFSA opinion (EFSA PPR Panel, 2021) that provides the necessary experimental design of both preliminary and main test. Briefly, for hepatic biotransformation, pooled primary hepatocytes from animals and humans are the recommended test system as it is the best surrogate for predicting in vivo metabolism. Test item concentrations are selected primarily by

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considering physicochemical properties, such as the partition coefficient (LogP), distribution coefficient (LogD) and solubility, together with cytotoxicity and assay-specific requirements. Testing should be conducted as follows:

- three concentrations: high, medium and low, with the high concentration being not cytotoxic (i.e. viability ≥ 80% compared to solvent control),
- at three time points, selected depending on the use of hepatocytes in suspension (4 h being the longest) or plated,
- in three biological replicates, to address the variability of the assay protocol.

These data allow to compare the biotransformation pathway in humans and animals and are used for the parameterisation of PBK models.

In vitro Clint study:

Clint is determined by the activity of enzymes metabolising the substance and is calculated based on either disappearance of the parent compound or the formation of metabolite(s) over time. The selection of the approach mainly depends on the a priori knowledge on which metabolite(s) are formed and on the availability of the corresponding analytical standards. Also, the characteristics of the chemical being tested can guide the choice (EFSA PPR Panel, 2021, 2025; Gouliarmou et al., 2018). Once the in vitro Clint is derived, it can be converted into an in vivo hepatic metabolic clearance by using various clearance models, considering liver weight, liver blood flow and the unbound fraction of the substance in plasma and some scaling factors. Clint is primarily requested to enable PBK/quantitative in vitro to in vivo extrapolation (QIVIVE). A simple generic model, making use of the EFSA TK plate (Dorne et al., 2023), is suggested as first tier, estimating to what extent the parent compound (which, for BPs, is generally considered the toxicological relevant molecule) actually reaches receptors in tissues other than liver. Having these data would help in selecting the dose to be tested and allow a better interpretation of the dynamic effects aimed to a robust risk assessment.

Where specific ADME parameters are unavailable, in silico approaches, such as quantitative structure–activity relationship (QSAR) models, may be used to estimate them. However, QSAR predictions that are insufficiently developed for certain parameters, such as biotransformation and CLint, should be considered as supporting evidence only.

3.3 | Requirements for in vitro studies

In order to increase the quality and predictivity of in vitro study results, especially regarding the quantitative aspects, it is requested that each in vitro toxicological study is complemented by an in vitro distribution study that should be conducted following the approach described in the OECD Guidance Document on Good In Vitro Method Practices (GIVIMP) (OECD TG 286, 2018b). Special emphasis should be given to the transporter activity and metabolic capacity of the in vitro test system used in toxicological studies. Differences in uptake and metabolism between in vitro systems and humans can cause major differences in the actual intracellular exposure to the parent compound and/or the metabolites and, therefore, between in vitro and in vivo toxicity.

In accordance with the recent EFSA opinion on QIVIVE in the developmental neurotoxicity in vitro battery (EFSA PPR Panel, 2025), the metabolic competence of the test system used in toxicological studies should be characterised and the minimal requirement for ADME parameters integrated in PBK models for QIVIVE indicated. Since the in vitro distribution parameters are rarely characterised, the nominal concentration typically used for in vitro dose–response curves is not the correct metric and leads to misinterpretation of results (Kramer et al., 2015). This is particularly relevant for BPA alternatives, since in most cases only the parent substances, but not their conjugates, are able to activate nuclear receptors (NRs), triggering many of the adverse outcomes.

4 | TOXICOLOGICAL DATA REQUIREMENTS AT THE INTERMEDIATE (BETWEEN 0.05 AND 5 MG/KG FOOD) AND HIGHEST MIGRATION LEVEL (ABOVE 5 MG/KG FOOD)

The data requested for the lowest migration level apply also to the higher levels. When the pre-mating exposure period for the parental animals in the EOGRT study is extended to minimally 10 weeks, the total exposure duration of these animals is comparable to that in a 90-day repeated dose toxicity study (OECD TG 408, 2025b). This means that such an EOGRT study covers the requirement of a 90-day study also for the safety assessment of hazardous BPs migrating between 0.05 and 5 mg/kg food, i.e. no additional toxicological data are required for a migration between 0.05 and 5 mg/kg food.

For the highest migration level (above 5 mg/kg food), the toxicological data set required for hazardous BPs should be complemented with the long-term toxicity/carcinogenicity data required for this migration level indicated in Section 7 of the EFSA NfG (EFSA AFC Panel, 2008).

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ABBREVIATIONS

ADME	absorption, distribution, metabolism and excretion
AUC	area under the curve
BAFF	B-cell activating factor
BP/BPs	bisphenol/bisphenols
BPA	bisphenol A
Clint	intrinsic clearance
C_{max}	maximum concentration
CMR	carcinogenic, mutagenic or toxic to reproduction
DART	developmental and reproductive toxicity
DNT	developmental neurotoxicity
DRP	detailed review paper
ECHA	European Chemicals Agency
EOGRT	extended one-generation reproductive toxicity
FCM	food contact materials
FoxP3	Forkhead box P3 (T-cell differentiation marker)
Fu	fraction unbound
GIVIMP	good in vitro method practices
GLP	good laboratory practice
Ig	immunoglobulin
IL	interleukin
IL-2 Luc LTT	interleukin-2 luciferase lymphocyte transformation test
IVB	in vitro battery
IVCM	in vitro comparative metabolism
JRC	Joint Research Centre
LogD	distribution coefficient
LogP	partition coefficient
NfG	note for guidance
NK	natural killer
NRs	nuclear receptors
OECD	Organisation for Economic Co-operation and Development
PBK	physiologically based kinetic
QIVIVE	quantitative in vitro to in vivo extrapolation
QSAR	quantitative structure–activity relationship
RORγt	retinoic-acid-receptor-related orphan receptor gamma t
$t_{1/2}$	half-life
TG	test guideline
Th17	T-helper 17 cells
T_{max}	time to maximum concentration
WoE	weight of evidence

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AUTHOR CONTRIBUTIONS

Under Regulation 178/2002, the Scientific Panel is the author of the scientific output. Contributions include Working Groups who provide the draft assessment which is reviewed and adopted by the Panel; EFSA staff members who provide scientific support including *inter alia* data collection and analysis and literature searching; and other contributors such as staff of national food safety agencies, EFSA trainees and interim staff members who have contributed meaningfully to the work.

REQUESTOR

European Commission

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A

FCM migration testing strategies for non-plastics

To estimate the likely maximum daily intake of the substance, its impurities, breakdown and reaction products, migration data should be provided as requested in Section 4 of the EFSA NfG (EFSA AFC Panel, 2008), independently of the material and article types. Ideally, these data should give a realistic account of migration into foodstuffs.

There are three main approaches generally applicable for any FCM types: (i) direct measurement in foods, (ii) simulation of migration and (iii) migration modelling. For more details, see Section 5 on 'Data on migration' from the EFSA CEF Panel Opinion on 'Recent developments in the risk assessment of chemicals in food and their potential impact on the safety assessment of substances used in food contact materials' (EFSA CEF Panel, 2016).

Currently, only plastic materials and articles have an EU harmonised Regulation[6] that provides official standard testing conditions, including food simulants, and is complemented by technical guidelines for compliance testing (see Joint Research Center (JRC) EURL website[7]). For other materials and articles, e.g. printing inks and coatings, there is no EU-specific Regulation. It is recommended to follow JRC technical guidelines on migration testing, such as the 'testing conditions for kitchenware articles in contact with foodstuffs' addressing plastics, inorganic materials, coatings, organic materials other than plastic, paper and boards (Beldi et al., 2025). If there are no JRC technical guidelines, the guidance documents of Member States could be followed. In all cases, the results of specific migration testing obtained in food shall prevail over the results obtained in food simulants, meaning that, for risk assessment, the applicability of simulation must be checked (EFSA CEF Panel, 2016).

[6]Regulation (EU) No 10/2011, as amended.

[7]Joint Research Centre – European Commission, https://commission.europa.eu/about/departments-and-executive-agencies/joint-research-centre_en.

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ANNEXES

The annex listed below is available under the Supporting Information section of the online version of this guidance.

ANNEX A

Public Consultation on draft statement on data requirements for the safety assessment of hazardous bisphenols other than bisphenol A (BPA) and their derivatives

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