



Ángel Nadal, PhD
Professor of Physiology
Institute of Bioengineering and CIBERDEM
Miguel Hernández University of Elche,
Alicante, Spain
nadal@umh.es

The Endocrine Society

ENDOCRINE
SOCIETY 

1916-2016
100 YEARS
OF HORMONE SCIENCE TO HEALTH

Over 18,000 members from over 120
countries

Committed to excellence in hormone science
and incorporation into patient care and
public health

ENDOCRINE
SOCIETY 

Tremendous concern about environmental

This guidance is a significant improvement over prior evaluations of BPA by EFSA

- Replacing “breastfed” in line 190 to include infants exposed through e.g., consumer products.
- Removing the classification scheme in Table 1.
- Cautiously interpret ‘toxicokinetic’ studies that are unable to know or control BPA levels.
- Cautiously interpret (or avoid interpreting) extrapolations from toxicokinetic studies to biomonitoring studies.
- Review important literature prior to 2013 for many endpoints.
- Assess the activity of BPA when co-exposure occurs with endogenous hormones.
- Include cross-sectional study designs in the inclusionary criteria.
- Identify sources of funding in studies, to reduce risk of bias.
- Ensure that expert judgment includes scientists with expertise in hormonal systems and endocrinology in all steps, but particularly the completion of table 10.
- Clarify the term “sufficient number of animals” and provide additional explanation throughout section 9.

Section 2.2 – Target population (Page 7)

“The target population of the hazard assessment is the EU general population, including specific vulnerable groups (unborn children and breast-fed infants).”

Replacing “breastfed” in line 190 to include infants exposed through e.g., consumer products.

Section 2.4 – Endpoints relevant to the hazard assessment (Page 7)

The classification scheme in table 1 using the phrases “likely”, “as likely as not”, and “unlikely” should be discarded.

Table 1: Likelihood² for BPA effects (as taken from outcome of WoE approach in EFSA CEF Panel, 2015)

Effects classified as “Likely”
<ul style="list-style-type: none">• General toxicity (liver and kidney weight increase)• Mammary gland proliferative changes
Effects classified “As likely as not”
<ul style="list-style-type: none">• Reproductive and developmental effects• Neurological, neurobehavioural and neuroendocrine effects• Immune effects• Cardiovascular effects• Metabolic effects• Carcinogenicity
Effects classified as “Unlikely”
<ul style="list-style-type: none">• Genotoxicity

The classification, as it stands, may create bias or predispose judgment in the evaluation of effects through the revised protocol.

Section 2.4 – Endpoints relevant to the hazard assessment (Page 7)

The revised BPA protocol should be implemented without extensive reference to previous evaluations, which had serious flaws.

The new transparent and systematic methodology approach by EFSA should help to incorporate opinion of scientists with expertise in Endocrinology.

This should help to avoid flaws by choosing:

Most appropriate and relevant end-points

Most appropriate, sensitive animal and cell models

Comparison of studies using the same dose range, age, timing of exposure.

Identify studies with appropriate controls.

Section 2.5 – Identification of the hazard assessment sub-questions (Page 8)

For the evaluation of toxicokinetic data in animals and humans, it is important to acknowledge the following issues:

- First, for a study to be considered a toxicokinetic study, actual administered doses must be known.

We recommend that EFSA note studies in the literature that self-identify as ‘toxicokinetic’ studies that do not meet these criteria.

- Second, it must be acknowledged that toxicokinetic studies examine individuals (animals or humans) administered BPA via a single route of exposure, yet EFSA’s own work has shown that humans encounter BPA via multiple routes of exposure.

Thus, extrapolations from toxicokinetic studies to biomonitoring studies (designed to evaluate exposures) must be done with caution – or perhaps not at all.

Section 3.1 Time span of evidence search (Pages 9 and 10)

The prior reviews of the literature conducted by EFSA did not use the same criteria to evaluate and weigh data. For some endpoints (mammary gland proliferation, neurodevelopment, metabolic effects), important data published prior to 2013 exist.

We recommend the entirety of the literature to be examined under this new protocol.

A partial list of important references pre-dating 2013 has been provided.

Section 4.2.4.3 – Mode of action studies (Page 12)

“Studies that investigate possible mode of action of BPA must be conducted using BPA alone....” (line 368-369).

We note that BPA will not be assessed as part of a mixture in the context of this protocol, limiting the ability to reflect real-world exposures. The activity of BPA should be assessed when co-exposure occurs with endogenous hormones. This should also be reflected in Table 5.

Include data prior 2013. Some studies are missing and interpretation of others contains flaws.

Section 4.2.5 – Inclusion/exclusion criteria for human, animal and MoA studies (Page 13)

“Only epidemiological studies with cohort and case-control designs will be systematically appraised for humans. Studies with a cross-sectional design bear some limitations in relation to the scope of the BPA review and therefore will only be considered in case of need for supporting information in a narrative manner. “ (lines 384-387)

We also recommend inclusion of cross-sectional study designs.

We understand the difficulty with human literature. Perhaps the weight of evidence approach used to evaluate BPA and childhood obesity in the EDC disease burden and cost work by Prof. Trasande, NYU, USA could be used. It might represent a way to incorporate cross sectional studies.

Include data published prior to 2013 by reasons already mentioned (EFSA new criteria)

Section 5.1 – Data extraction (Page 15)

The source of funding for a study is an important potential component of risk of bias where there may exist conflicts of interest.

We recommend that the source of funding be recorded for all studies.

Section 7.3 – Quality appraisal of animal studies (Pages 22 and 23)

The use of the SciRAP criteria is a great improvement.

However, Table 10 (page 23) cannot be completed without expert judgement about what should be considered a ‘sensitive’ model and a ‘sensitive’ endpoint. Scientists with expertise in endocrinology and detailed knowledge of hormonal systems will be essential for accurate completion of Table 10.

It is unclear what is meant by “a sufficient number of animals”.

Clarification should be provided so that academic studies are not disadvantaged in assessments.

Table 10: Quality appraisal tool (adapted from SciRAP)

#	Key Q	Quality aspect	Rating [Fulfilled (F), Partially Fulfilled (PF) Not fulfilled (NF)]
1		The test compound or mixture was unlikely to contain any impurities that may significantly have affected its toxicity.	
2	A	A concurrent negative control group was included.	
3	B	A reliable and sensitive animal model was used for investigating the test compound and selected endpoints.	
4		Animals were individually identified.	
5		Housing conditions (temperature, relative humidity, light-dark cycle) were appropriate for the study type and animal model.	
6		The number of animals per sex in each cage was appropriate for the study type and animal model.	
7		The test system is unlikely to contain contaminants that could affect study results, such as phytoestrogens and estrogenic contamination.	
8		An adequate number of doses was selected	
9	C	The timing and duration of administration do not seem to be inappropriate for investigating the included endpoints.	
10	D	Reliable and sensitive test methods were used for investigating the selected endpoints.	
11	E	Measurements do not seem to have been collected at unsuitable time point in order to generate sensitive, valid and reliable data.	
12	F	The statistical methods have been clearly described and do not seem inappropriate, unusual or unfamiliar and a sufficient number of animals per dose group was used	
Overall assessment of quality			<ul style="list-style-type: none"> • Reliable without restrictions (R) • Reliable with restrictions (RR) • Not reliable (NR)

Section 9 – Relevance and adversity of the effect for human health (Page 30)

This section is extremely vague and **relies exclusively on expert judgement**. Additional explanation is needed to ensure that a sufficient and transparent justification is provided.