



**RÉPUBLIQUE
FRANÇAISE**

*Liberté
Égalité
Fraternité*



anses

A quelles substances s'intéresse-t-on?

CLAIRE BEAUSOLEIL

**RISK ASSESSMENT DEPARTMENT (DER)
REACH-CLP-ENDOCRINE DISRUPTORS UNIT (URCP)**

ADEREST

**Association pour le Développement des Etudes et Recherches
Epidémiologiques en Santé et Travail
*9 juin 2023***

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Structuration des règlements sur les substances chimiques en Europe

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Guidance sur les PEs et identification des composés PEs

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Quelques exemples de substances identifiées SVHC PE sous REACH

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Nouvelles classes de danger pour les PEs

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ED List.

Structuration des règlements sur les substances chimiques en Europe



Les substances et produits chimiques règlementés selon leurs usages



Polluants atmosphériques



Médicaments



Produits
industriels



Additifs
alimentaires



Produits phyto-sanitaires



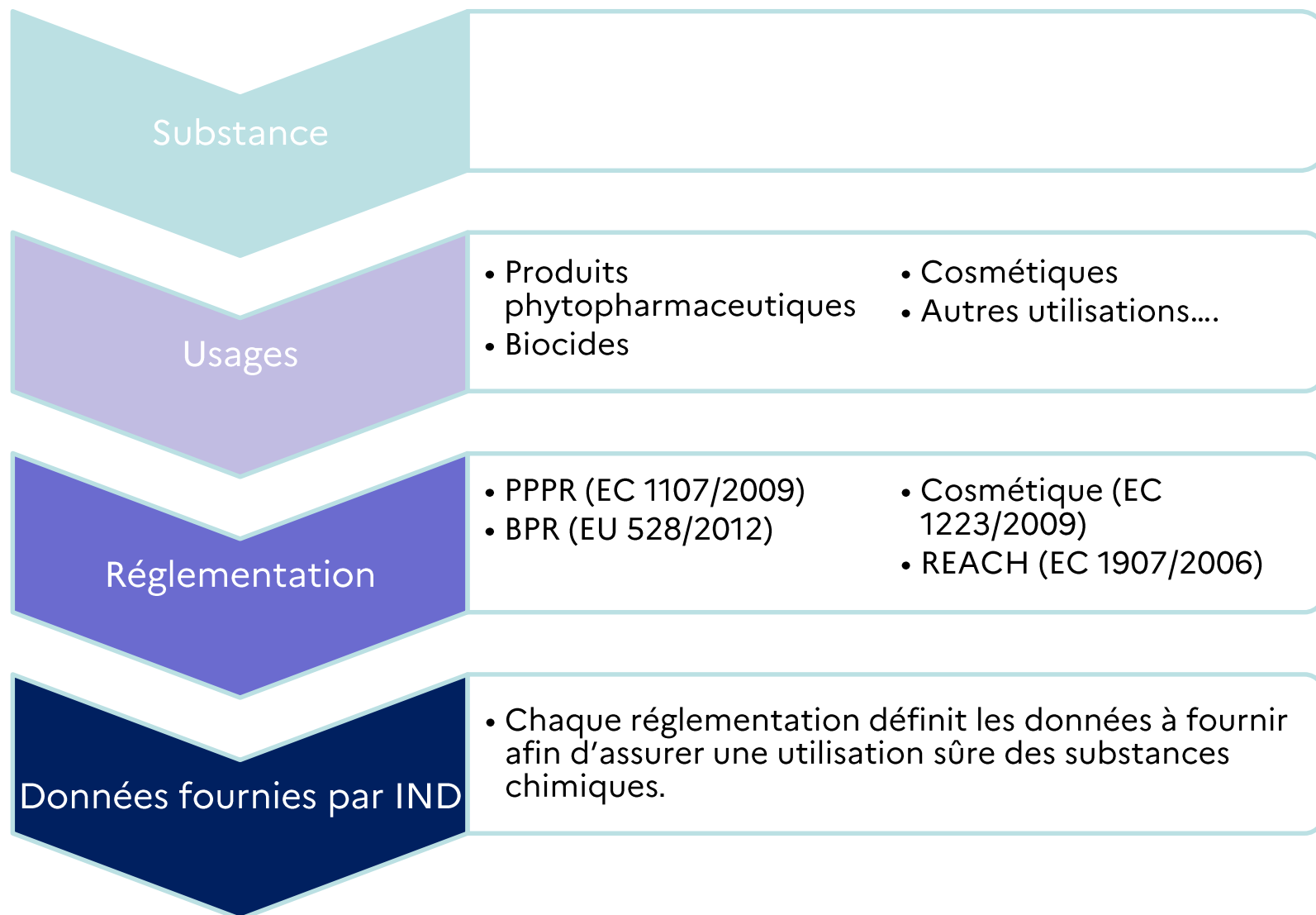
Produits cosmétiques et d'hygiène



Nettoyants, désinfectants,
détergents



Une réglementation



- **Substances chimiques : REACH**

- Enregistrement
- Evaluation
- Autorisation
- Restriction

- Santé humaine
- Environnement

SVHC PE

CLP PE



Produits sans AMM:

- Dispositifs médicaux
- Produits cosmétiques

- Listes positives et/ou
- Listes négatives

- **Produits nécessitant une AMM:**

- Médicaments
- Produits biocides
- Produits
phytopharmaceutiques

CLP PE



AMM: Autorisation de mise sur le marché

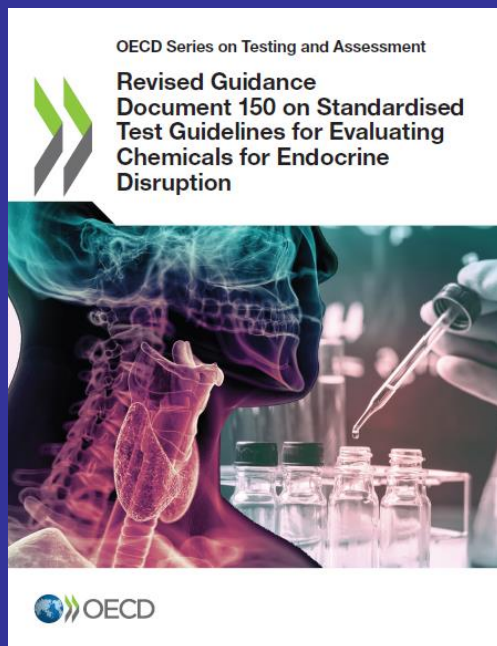
Substance extrêmement préoccupante (SVHC)



SVHCs which may be included in Annex XIV to REACH, and for which thereby the authorisation requirement will be established, are substances with the following properties:

Legal reference	Hazard class	Identification criteria
Article 57 (a) REACH	Carcinogenicity category 1 A/B	Section 3.6 of Annex I to the Regulation (EC) No 1272/2008 (CLP Regulation)
Article 57 (b) REACH	Germ cell mutagenicity category 1 A/B	Section 3.5 of Annex I to the CLP Regulation
Article 57 (c) REACH	Reproductive toxicity category 1 A/B, adverse effects on sexual function and fertility or on development	Section 3.7 of Annex I to the CLP Regulation
Article 57 (d) REACH	Persistent, bioaccumulative and toxic (PBT)	Annex XIII to the REACH Regulation (as amended3)
Article 57 (e) REACH	Very persistent and very bioaccumulative (vPvB)	Annex XIII to the REACH Regulation (as amended3)
Article 57 (f) REACH	<p>Equivalent level of concern to those of other substances listed in point (a) to (e) of Article 57 of REACH. It is clear from ECHA's decisions identifying SVHCs that, on a case-by case basis, at least substances with the following hazard properties may give rise to an equivalent level of concern:</p> <ul style="list-style-type: none"> -Respiratory sensitising properties (Article 57(f) - human health) -Specific target organ toxicity after repeated exposure (Article 57(f) - human health) -Endocrine disrupting properties (Article 57(f) - human health) - Endocrine disrupting properties (Article 57(f) - environment) 	<p>Substances - such as those having endocrine disrupting properties or those having persistent, bioaccumulative and toxic properties or very persistent and very bioaccumulative properties, which do not fulfil the criteria of Article 57 points (d) or (e) - for which there is scientific evidence of probable serious effects to human health or the environment which give rise to an equivalent level of concern to those of other substances listed in Article 57 points (a) to (e) and which are identified on a case-by-case basis in accordance with the procedure set out in Article 59 of REACH.</p>

Quels guides d'évaluation?



Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009

European Chemical Agency (ECHA) and European Food Safety Authority (EFSA) with the technical support of the Joint Research Centre (JRC)

Niklas Andersson, Maria Arena, Domenica Auteri, Stefania Barmaz, Elise Gignard, Aude Kienzler, Peter Lepper, Alfonso Maria Lostia, Sharon Munn, Juan Manuel Parra Morte, Francesca Pellizzato, Jose Tarazona, Andrea Terron and Sander Van der Linden

Abstract

This Guidance describes how to perform hazard identification for endocrine-disrupting properties by following the scientific criteria which are outlined in Commission Delegated Regulation (EU) 2017/2100 and Commission Regulation (EU) 2018/605 for biocidal products and plant protection products, respectively.

© 2018 European Chemicals Agency and © European Food Safety Authority.

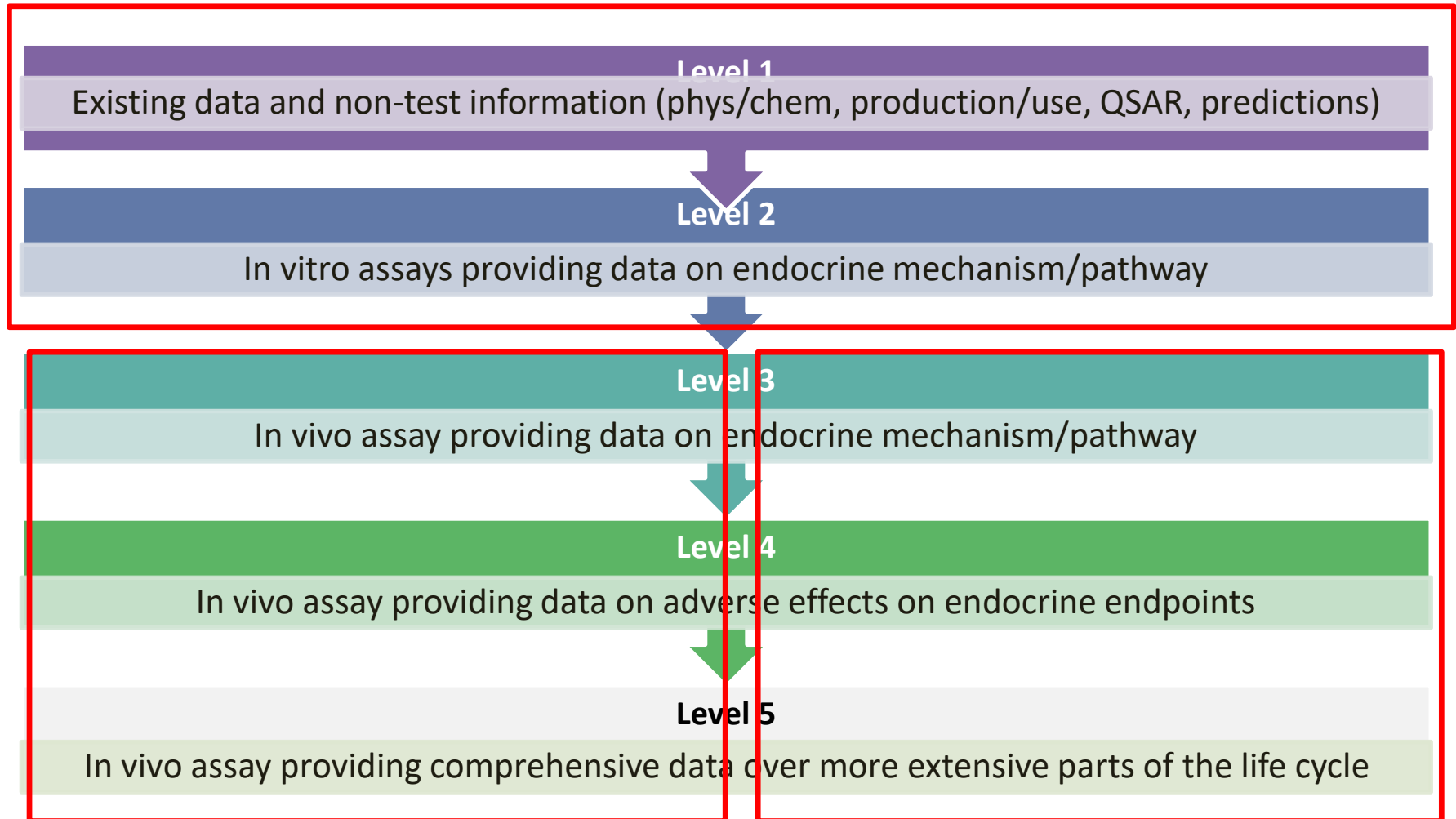
Keywords: biocidal product, plant protection product, endocrine disruptor, guidance, hazard identification

Requestor: European Commission

Question numbers: EFSA-Q-2016-00825, ECHA-18-G-01-EN

Correspondence: For biological products: biocides@echa.europa.eu
For plant protection products: pesticides.peerreview@efsa.europa.eu

OECD Endocrine Testing and Assessment Conceptual Framework



mammalian



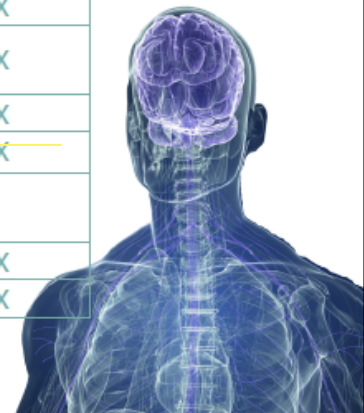
non-mammalian
(may be mutually informative)



Updated CF & OECD Test Guidelines for ED detection

Test Guidelines number and Name*	Level of Conceptual Framework	Mode of action covered/ presumably detected		
		Oestrogen	Androgen	Thyroid
TG 455: In Vitro Oestrogen Receptor Transactivation Assay	2	X		
TG 458: In Vitro Androgen Receptor Transactivation Assay	2		X	
TG 456: H295R Steroidogenesis Assay	2	X	X	
TG 493: In Vitro Oestrogen Receptor Binding Assay	2	X		
TG 229: Fish Short-Term Reproduction Test	3	X	X	
TG 230: Fish Screening Assay	3	X	X	
TG 231: Amphibian Metamorphosis Assay	3			X
TG 440: Uterotrophic Bioassay	3	X		
TG 441: Hershberger Bioassay	3		X	X
TG 234: Fish Sexual Development Test	4	X	X	
TG 241: Larval Amphibian Growth and Development Assay	4	X	X	X
TG 407: 28-day Repeated Dose Toxicity Study in Rodents	4	X	X	X
TG 408: 90-day Repeated Dose Toxicity Study in Rodents	4	X	X	X
TG 414: Prenatal Developmental Toxicity Study	4	X	X	X
TG 421: Reproduction/Developmental Toxicity Screening Test	4	X	X	X
TG 422: Combined Repeated Dose Reproduction/Developmental Toxicity Screening Test	4	X	X	X
TG 426: Developmental Neurotoxicity Study	4	X	X	X
TG 451-3: Combined Chronic Toxicity/Carcinogenicity Study	4	X	X	X
TG 240: Medaka Extended One-Generation Reproductive Toxicity Study	5	X	X	
TG 416: Two Generation Reproduction Toxicity Study	5	X	X	X
TG 443: Extended One-Generation Reproductive Toxicity Study	5	X	X	X

*Test guidelines may evolve following best practices and emerging science.



Courtesy OECD

Substances actives (SA) biocides ou phyto-pharmaceutiques

Pour identifier les SA phytopharmaceutiques et Biocides présentant des propriétés de perturbations endocriniennes pour l'Homme et les organismes non-cibles, l'EFSA et l'ECHA ont développé un document guide (GD) applicable au 07/06/2018:

Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009

European Chemical Agency (ECHA) and European Food Safety Authority (EFSA) with the technical support of the Joint Research Centre (JRC)

Niklas Andersson, Maria Arena, Domenica Auteri, Stefania Barmaz, Elise Grignard, Aude Kienzler, Peter Lepper, Alfonso Maria Lostia, Sharon Munn, Juan Manuel Parra Morte, Francesca Pellizzato, Jose Tarazona, Andrea Terron and Sander Van der Linden

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For plant protection products: pesticides.peerreview@efsa.europa.eu

Quelques exemples de substances identifiées SVHC PE sous REACH

Comité des États membres

Le comité des États membres (MSC) participe à différentes procédures REACH telles que les procédures d'évaluation et d'autorisation. Il est chargé de résoudre les divergences d'opinions entre les États membres et sur les propositions d'identification de substances extrêmement préoccupantes (SVHC). Le comité rend des avis sur les projets de recommandations de l'ECHA concernant la liste d'autorisation (annexe XIV) et sur le projet de plan d'action continu communautaire (CoRAP) pour la procédure d'évaluation des substances. Si le MSC ne peut parvenir à un accord, l'affaire est transmise à la Commission européenne pour qu'une décision soit prise.

Évaluation des dossiers

Lorsque les États membres proposent des modifications, le MSC cherche à parvenir à un accord unanime sur les projets de décisions de l'ECHA concernant:

- les propositions d'essai;
- les contrôles de conformité.



Chair of the MSC is
Katinka van der Jagt

- CV
- Declaration of interests

Bisphenol S (BPS)

Substance Name: 4,4'-sulphonyldiphenol

EC Number: 201-250-5

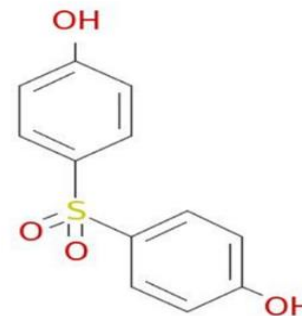
CAS Number: 80-09-1

**MEMBER STATE COMMITTEE SUPPORT DOCUMENT
FOR IDENTIFICATION OF**

4,4'-SULPHONYLDIPHENOL

**AS A SUBSTANCE OF VERY HIGH CONCERN BECAUSE
OF ITS TOXIC FOR REPRODUCTION (ARTICLE 57C),
ENDOCRINE DISRUPTING PROPERTIES (ARTICLE
57(F) - ENVIRONMENT), ENDOCRINE DISRUPTING
PROPERTIES (ARTICLE 57(F) - HUMAN HEALTH)
PROPERTIES**

Adopted on 28 November 2022



Harmonised classification and labelling

BPS is covered by Index number 604-098-00-1 in part 3 of Annex VI to the CLP Regulation as follows:

Table 6: Classification according to Annex VI, Table 3 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008

Index No	Chemical name	EC No	CAS No	Classification		Labelling			Spec. Conc. Limits, M-factors and ATEs ⁶	Notes
				Hazard Class and Category Code(s)	Hazard statement code(s)	Pictogram, Signal Word Code(s)	Hazard statement code(s)	Suppl. Hazard statement code(s)		
604-098-00-1	Bisphenol S; 4,4'-sulphonyldiphenol	201-250-5	80-09-1	Repr. 1B	H360FD	GHS08 Dgr	H360FD			

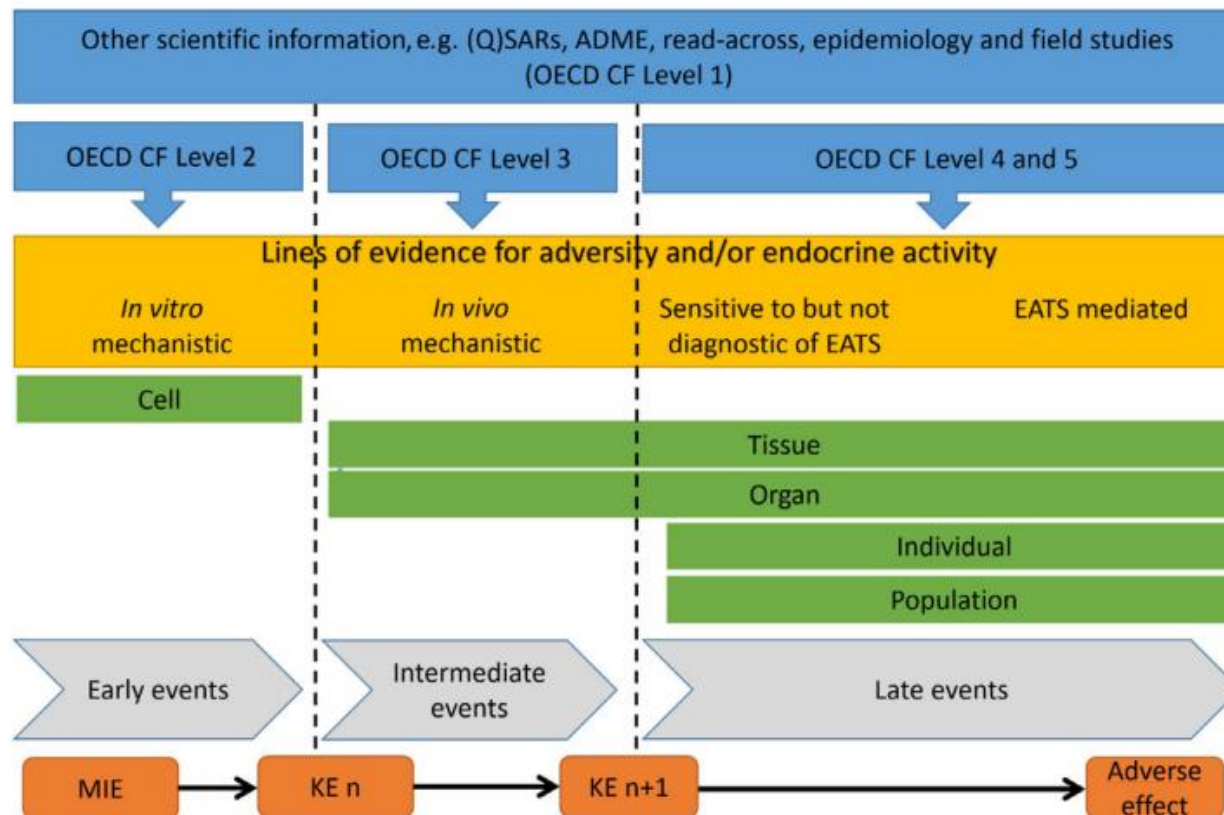
SVHC SUPPORT DOCUMENT - 4,4'-SULPHONYLDIPHENOL

Bisphenol S has a harmonised classification⁹ as Repr. 1B – H360FD, on the basis of treatment-related adverse effects on fertility, reproduction and pregnancy outcome (i.e. decreased number of implantation sites and prolonged estrous cycle) and treatment-related adverse effects on development (i.e. post-implantation loss) in several independent studies in animals. The RAC opinion (RAC, 2020) can be found on: <https://echa.europa.eu/documents/10162/03fac9dc-94e7-a81c-fed5-1c5008a1c1bc>.

How the lines of evidence can be organised to support the postulated mode of action



Guidance for the identification of endocrine disruptors in biocides and pesticides



KE: key event; MIE: molecular initiating event.

Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009

European Chemical Agency (ECHA) and European Food Safety Authority (EFSA) with the technical support of the Joint Research Centre (JRC).

Abstract
This Guidance describes how to perform hazard identification for endocrine-disrupting properties by following the scientific criteria which are outlined in Commission Delegated Regulation (EU) 2017/2100 and Commission Regulation (EU) 2018/605 for biocidal products and plant protection products, respectively.

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Keywords: biocidal product, plant protection product, endocrine disruptor, guidance, hazard identification

Requester: European Commission

Question numbers: EFSA-Q-2016-08025, ECHA-18-G-01-EN

Correspondence: for biological products: biocides@echa.europa.eu
for plant protection products: pesticides-peerreview@efsa.europa.eu

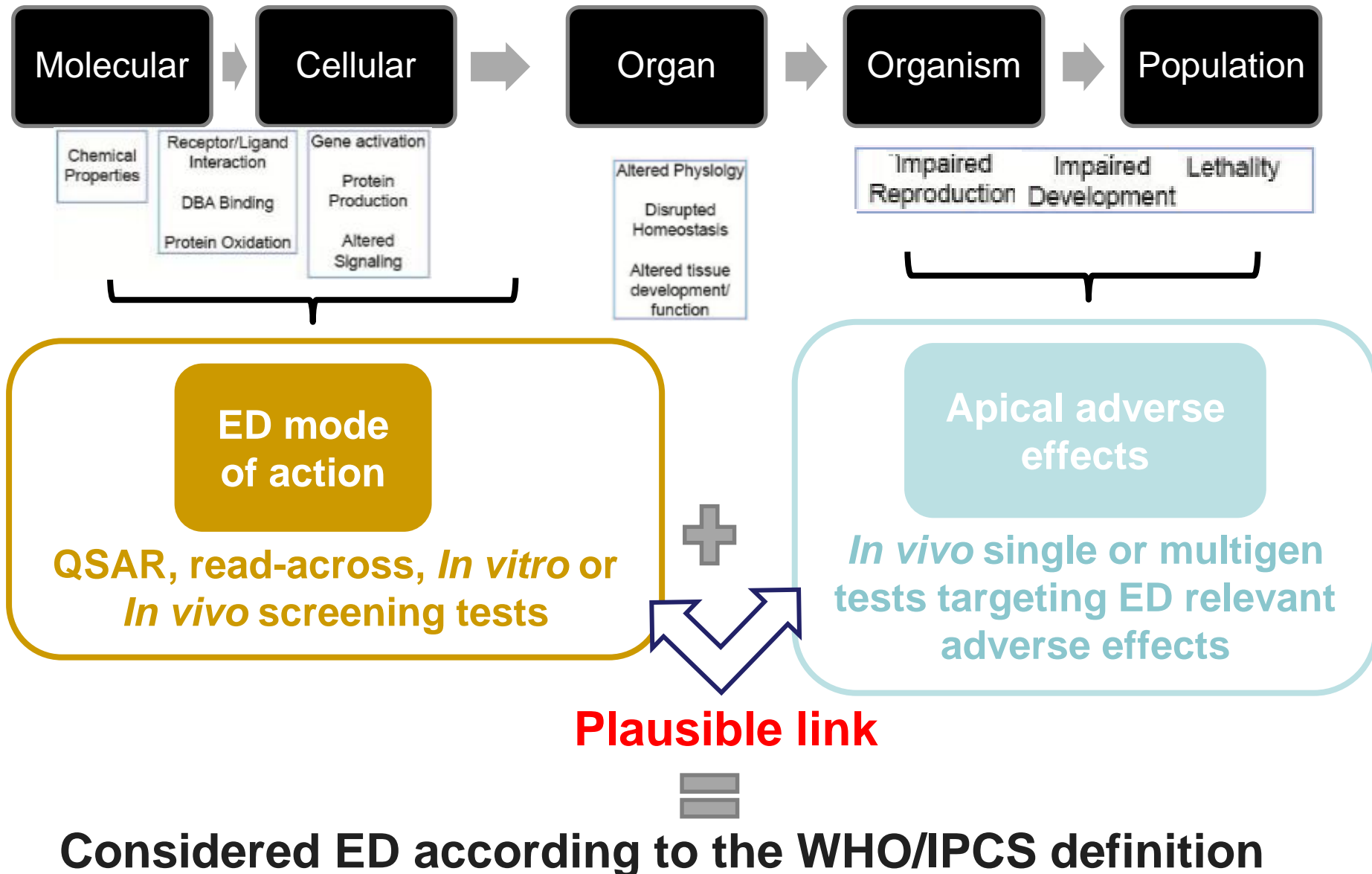
OECD Series on Testing and Assessment

Revised Guidance Document 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption

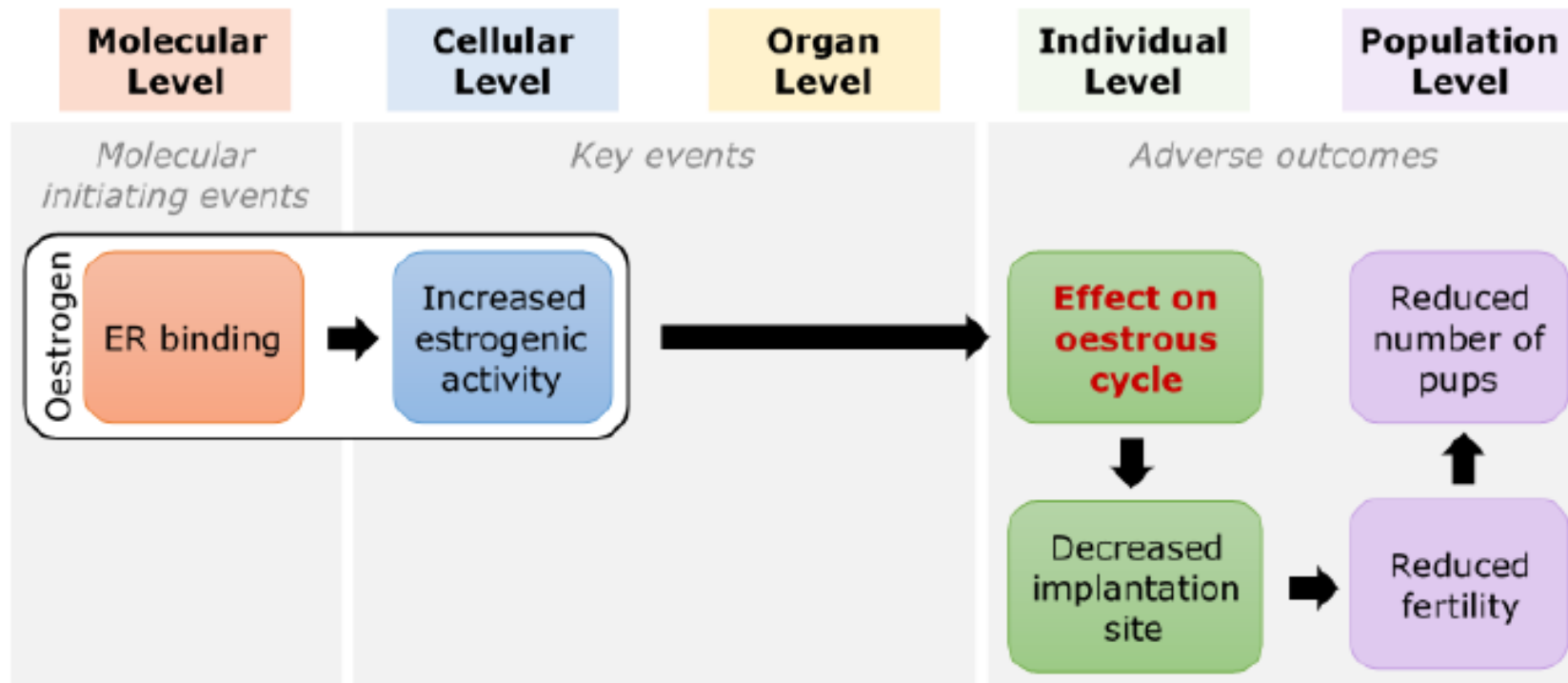


OECD

Identification of endocrine disruptors under REACH



Postulated estrogenic MoA affecting female reproduction in mammals :



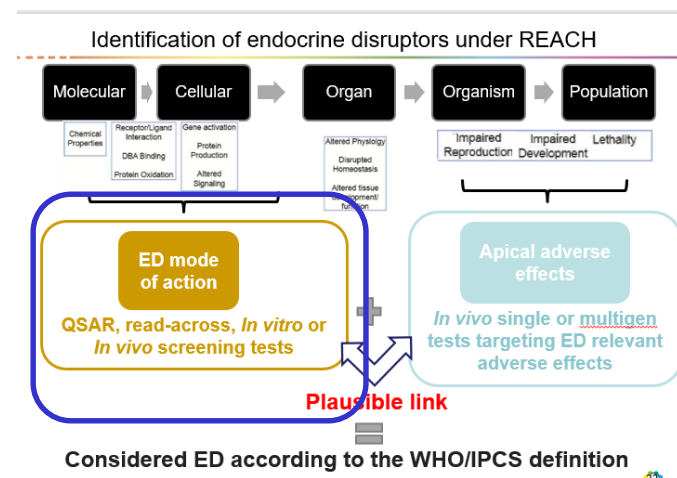
Legend: EATS-mediated adverse effect / Sensitive but not diagnostic of EATS

Fig : Estrogenic MoA affecting female reproduction in mammals quoted from Bisphenol S SVHC dossier, ECHA 2022

Note: "The MoA presented here does not describe every detail of the biology but instead focuses on describing critical steps, acknowledging that other activities could also influence each of the key events described."

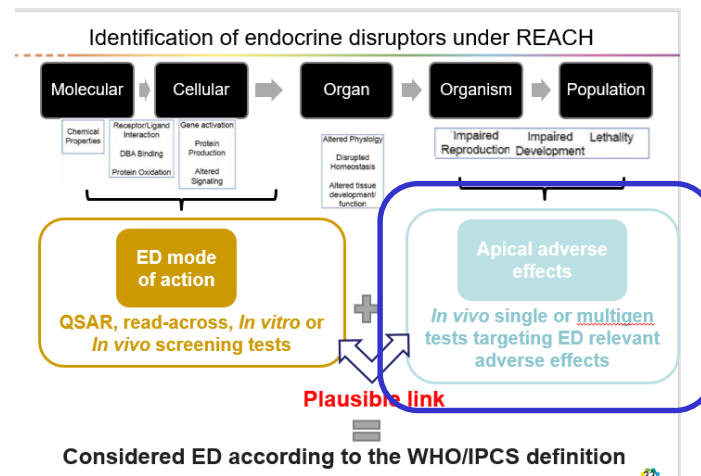
Table 15 : Analysis of mode of action

	Event	Supporting evidence
MIE	ER activation	<p>Strong evidence:</p> <ul style="list-style-type: none"> Studies show binding of BPS to ER (Blair <i>et al.</i>, 2000; Yamasaki <i>et al.</i>, 2004; Laws <i>et al.</i>, 2006; Akahori <i>et al.</i>, 2008; Zhang <i>et al.</i>, 2018; Liu <i>et al.</i>, 2019b). Several studies show an agonist activation of ER (among others Grignard <i>et al.</i>, 2012; Kang <i>et al.</i>, 2014; Dvorakova <i>et al.</i>, 2016; Le Fol <i>et al.</i>, 2017; Rosenmai <i>et al.</i>, 2014; Mesnage <i>et al.</i>, 2017; Kojima <i>et al.</i>, 2018; Pelch <i>et al.</i>, 2019).
KE1	Increased estrogenic activity	<p>Strong evidence:</p> <ul style="list-style-type: none"> Uterotrophic assays show increase in uterus weight (Yamasaki <i>et al.</i>, 2004; Conley <i>et al.</i>, 2016). Supported also by Akahori <i>et al.</i> (2008).
KE2	Disturbed estrous cycle	<p>Strong evidence:</p> <ul style="list-style-type: none"> 3/3 TG studies show disturbed estrous cycle (OECD TG 443, P0 and F1B, no effect on F1A; OECD TGs 421 and 422). Among them 2 studies show a prolongation of diestrus. 3 additional studies report a disturbed cycle (Shi <i>et al.</i>, 2019a and 2019b; Ahsan <i>et al.</i>, 2018). The Shi studies describe a prolongation of diestrus and estrus phases.
KE3	Decreased implantation sites	<p>Strong evidence:</p> <ul style="list-style-type: none"> Decreased number of implantation sites observed in 3/3 TG studies (significant in OECD TG 422; trend in OECD TG 443 P0 and F1B; and OECD TG 421)
AO1	Reduced fertility	<p>Strong evidence:</p> <ul style="list-style-type: none"> Fertility rate reduced in 2/3 TG studies (OECD TGs 421 and 422; no effect in OECD TG 443) Fertility affected in another 2 studies (Ahsan <i>et al.</i>, 2018, Nevoral <i>et al.</i>, 2018)
AO2	Decreased number of pups	<p>Strong evidence:</p> <ul style="list-style-type: none"> Reduced number of pups in 3/4 TG studies (OECD TGs 443, 421 and 422, no effect in OECD TG 414) Also observed in other studies (Shi <i>et al.</i>, 2019a; Ahsan <i>et al.</i>, 2018)



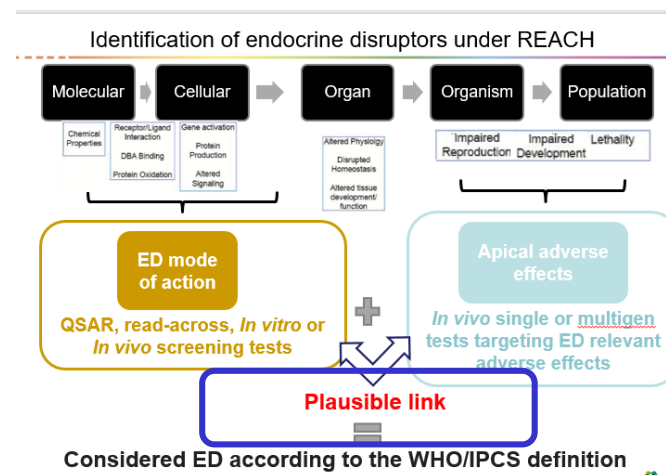
SVHC SUPPORT DOCUMENT - 4,4'-SULPHONYLDIPHENOL

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Evaluation du lien de plausibilité entre les effets néfastes observés et l'activité endocrinienne

“In conclusion, the effects on the female reproductive organs and functional parameters are consistent with an estrogenic mode of action of BPS. The adverse effects on the estrous cycle are EATS-mediated, therefore, in the absence of information proving the contrary, **the biologically plausible link is already pre-established based on existing scientific knowledge.** There is strong evidence that the adverse effects on fertility and sexual function are plausibly linked to the estrogenic activity of the substance. BPS is therefore an endocrine disruptor according to the WHO/IPCS definition with regard to human health.”



Equivalent level of concern (ELOC)



Bisphenols widely used and found in the environment.



Effects on organisms and populations are considered to be severe and irreversible

eg. :

- effects on estrous cycle,
- sex ratio, etc.,



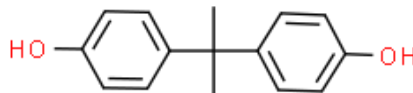
- observed following developmental exposure.



Bisphenols sharing the same mode of action, effects at low concentration



Overall, there is scientific evidence of probable serious effects of BPS to the environment and human health due to its endocrine disrupting properties, which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 of the REACH Regulation.



**Substance Name: 4,4'-isopropylidenediphenol
(BPA, Bisphenol A)**

EC Number: 201-245-8

CAS Number: 80-05-7

MEMBER STATE COMMITTEE

SUPPORT DOCUMENT FOR IDENTIFICATION OF

**4,4'-ISOPROPYLIDENEDIPHENOL (BPA,
BISPHENOL A) AS A SUBSTANCE OF VERY HIGH
CONCERN BECAUSE OF ITS ENDOCRINE
DISRUPTING PROPERTIES WHICH CAUSE
PROBABLE SERIOUS EFFECTS TO HUMAN HEALTH
WHICH GIVE RISE TO AN EQUIVALENT LEVEL OF
CONCERN TO THOSE OF CMR¹ AND PBT/vPvB²
SUBSTANCES**

Adopted on 14 June 2017

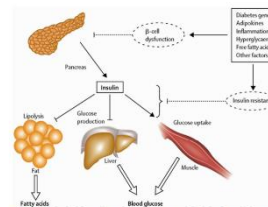


Figure 17: Pathophysiology of hyperglycemia and increased circulating fatty acids in type 2 diabetes from Shumet et al., 2005.

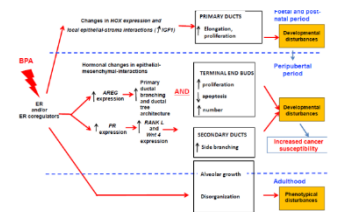


Figure 13: Some cascades of events from BPA action on ER or on its coregulators to the developmental and phenotypic disturbances of the mammary gland.

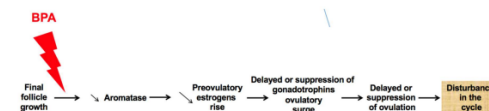


Figure 5: Sequential cascade from the endocrine effect of BPA to its adverse effects.
A clearly demonstrated target of BPA is **aromatase**, in the preovulatory follicle. The BPA-induced reduction in the expression of this steroidogenic enzyme induces a reduction in the synthesis of estrogens. Thus, the preovulatory rise of estrogens is attenuated. Consequently, the estrogen-induced gonadotrophins ovulatory surge, is delayed or suppressed, and this induces disturbances in the cycle.

Bisphenol A (BPA)

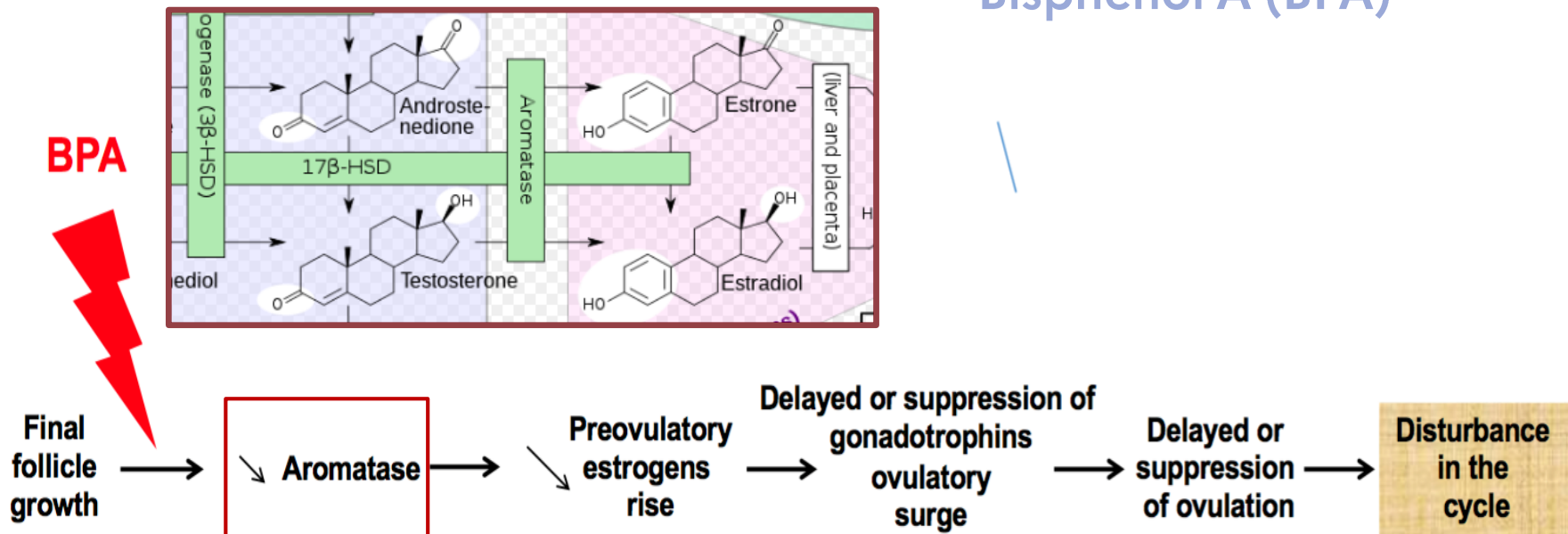


Fig.1 : Sequential cascade from the endocrine effect of BPA to its adverse effects (BPA SVHC HH dossier, 14 June 2017).

"A clearly demonstrated target of BPA is aromatase, in the preovulatory follicle. The BPA-induced reduction in the expression of this steroidogenic enzyme induces a reduction in the synthesis of estrogens. Thus, the preovulatory rise of estrogens is attenuated. Consequently, the estrogen-induced gonadotrophins ovulatory surge, is delayed or suppressed, and this induces disturbances in the cycle."



Substance Name: Resorcinol

EC Number: 203-585-2

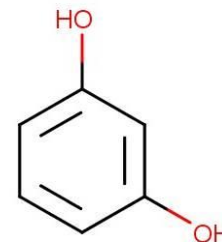
CAS Number: 108-46-3

**SUPPORT DOCUMENT TO THE OPINION OF THE
MEMBER STATE COMMITTEE ON IDENTIFICATION
OF**

RESORCINOL

**AS A SUBSTANCE OF VERY HIGH CONCERN
BECAUSE OF ITS ENDOCRINE DISRUPTING
PROPERTIES (ARTICLE 57(F) - HUMAN HEALTH)**

Adopted on 12 June 2020



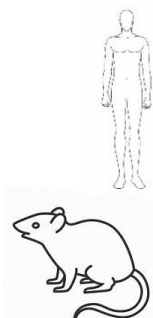
Uses:

- As a medicinal ingredient in **human dermatology** since late in the 19th century.
- Approved for use in humans in Europe and the United States by the European Medical Agency (**EMA**) and the Food and Drugs Administration (**FDA**).
- Has been commonly used in **chemical peels** for lightening called Jessner's solution,
- Recent clinical studies have investigated the efficacy of topical resorcinol in **hidradenitis suppurativa (HS) lesions** as an alternative to other medication (Cordero-Ramos et al., 2022; Molinelli et al., 2020; Pascual et al., 2017).



Apical effects:

- Symptoms of severe **hypothyroidism**,
- Indications of effects on **locomotor activity** and **sensorimotor function**



Mode of action: inhibition of **TPO (thyroperoxidase)** in *in vitro* studies



Even if an ED MoA, an apical effect and a plausible biological have been identified, the identification of the substance as an ED has not been endorsed. The elaboration of a CLP dossier for its ED properties is planned.



Nouvelles classes de danger pour les PEs

New ED Hazard classes – text human health - definition

*« **Endocrine activity** » means an interaction with the endocrine system that may result in a response of that system, of target organs and/or target tissues, and that confers on a substance or the mixture the potential to alter one or more functions of the endocrine system.*

• *« **Adverse effect** » means a change in morphology, physiology, growth, development, reproduction or lifespan of an organism, system, population or subpopulation that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences.*

• *« **Biologically plausible link** » means the correlation between one or a series of biological processes leading to an adverse effect and an endocrine activity, where the correlation is consistent with existing knowledge.*

New ED Hazard classes – text human health - definition

ED hazard classes:

- Based on the definition of the WHO,
- To be applied across all legislation,
- Separated classes: human health and environment (*Distinction of ED for human health or environment already exists today across the legislative framework*).

Quoted from FOURTH ANNUAL FORUM ON ENDOCRINE DISRUPTORS September, 2022 Brussels FOURTH ANNUAL FORUM ON ENDOCRINE DISRUPTORS - Streaming Service of the European Commission ([europea.eu](https://ec.europa.eu/europea/europea_en))

Categories

Criteria

CATEGORY 1

Known or presumed endocrine disruptors for human health

The classification in Category 1 shall be largely based on evidence from at least one of the following:

- a) human data;
- b) animal data;
- c) non-animal data providing an equivalent predictive capacity as data in points a or b.

Such data shall provide evidence that the substance meets all the following criteria:

- (a) endocrine activity;
- (b) an adverse effect in an intact organism or its offspring or future generations;
- (c) a biologically plausible link between the endocrine activity and the adverse effect.

However, where there is information that raises serious doubt about the relevance of the adverse effects to humans, classification in Category 2 may be more appropriate.

Cf. Acte délégué modifiant le règlement CLP; acte délégué devant entrer en vigueur en début d'année après examen par le Parlement européen et le Conseil : <https://environment.ec.europa.eu/system/files/2022-12/Delegated%20Regulation%20amending%20Regulation%2012722008.pdf>
<https://environment.ec.europa.eu/system/files/2022-12/Annexes%20to%20the%20Delegated%20Regulation.pdf>

Categories

Criteria

CATEGORY 2

Suspected endocrine disruptors for human health

A substance shall be classified in Category 2 where all the following criteria are fulfilled:

(a) there is evidence of:

- i. an endocrine activity; and
- ii. an adverse effect in an intact organism or its offspring or future generations;

(b) the evidence referred to in point (a) is not sufficiently convincing to classify the substance in Category 1;

(c) there is evidence of a biologically plausible link between the endocrine activity and the adverse effect.

Where there is evidence conclusively demonstrating that the adverse effects are not relevant to humans, the substance shall not be considered an endocrine disruptor for human health.

Guidance on the Application of the Criteria

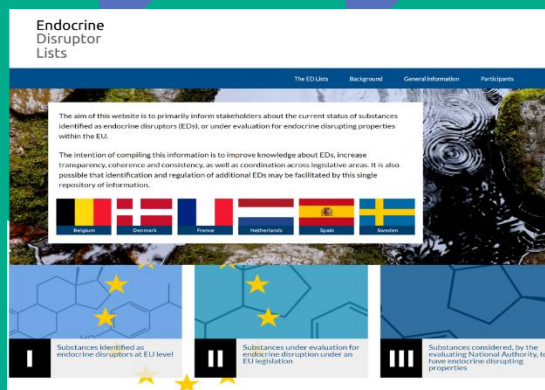
Endocrine disruption for human health
Endocrine disruption for environment

Under discussion

EU commenting
phase from May
2023 to April 2024.



ED List










Endocrine Disruptor Lists

The ED Lists
Background
General information
Participants


The aim of this website is to primarily inform stakeholders about the current status of substances identified as endocrine disruptors (EDs), or under evaluation for endocrine disrupting properties within the EU.

The intention of compiling this information is to improve knowledge about EDs, increase transparency, coherence and consistency, as well as coordination across legislative areas. It is also possible that identification and regulation of additional EDs may be facilitated by this single repository of information.


 Belgium
 Denmark
 France
 Netherlands
 Spain
 Sweden



I
Substances identified as endocrine disruptors at EU level



II
Substances under evaluation for endocrine disruption under an EU legislation



III
Substances considered, by the evaluating National Authority, to have endocrine disrupting properties

<https://edlists.org>

Les ED listes informent les parties prenantes sur l'état actuel des substances identifiées PE en Europe:

- **List I:** identifiées PEs au niveau de l'UE
 - PPPR
 - BPR
 - REACH
- **List II:** substances en cours d'évaluation dans l'UE pour des propriétés de perturbation endocrinienne possibles.
- **List III :** Substances considérées comme ayant des propriétés de perturbation endocrinienne par une des autorités nationales participantes.

List I: Substances identified as endocrine disruptors at EU level

This list contains substances that have undergone an evaluation of endocrine disrupting properties, as regulated in the EU in PPPR, BPR or REACH, and which are identified and legally adopted as endocrine disruptors.

Currently (April 2022) no compounds are identified/regulated for endocrine disrupting properties under the [Cosmetic Products Regulation](#) although the Commission is performing a targeted literature screening of [selected compounds](#).

Latest update 2022/4						
4-Nonylphenol, branched, ethoxylated	127087-87-0	932-098-4	☛	Environmental candidate list year:	2013	REACH
				Environmental authorisation list year:	2019	
4-Nonylphenol, branched, ethoxylated 1 - 2.5 moles ethoxylated	127087-87-0	500-315-8	☛	Environmental candidate list year:	2013	REACH
				Environmental authorisation list year:	2019	
4-Nonylphenol, ethoxylated 1 - 2.5 moles ethoxylated	26027-38-3	500-045-0	☛	Environmental candidate list year:	2013	REACH
				Environmental authorisation list year:	2019	
4-t-Nonylphenol-diethoxylate	156609-10-8		☛	Environmental candidate list year:	2013	REACH
				Environmental authorisation list year:	2019	
4-tert-butylphenol	98-54-4	202-679-0	☛	Environmental candidate list year:	2019	REACH
				CoRAP list year:	2014	
4,4'-(1-methylpropylidene)bisphenol Bisphenol B	77-40-7	201-025-1	♥ ☛	Health candidate list year:	2021	REACH
				Environmental candidate list year:	2021	
4,4'-isopropylidenediphenol; Bisphenol A	80-05-7	201-245-8	♥ ☛	Health candidate list year:	2017	REACH
				Environmental candidate list year:	2018	



Merci pour votre attention

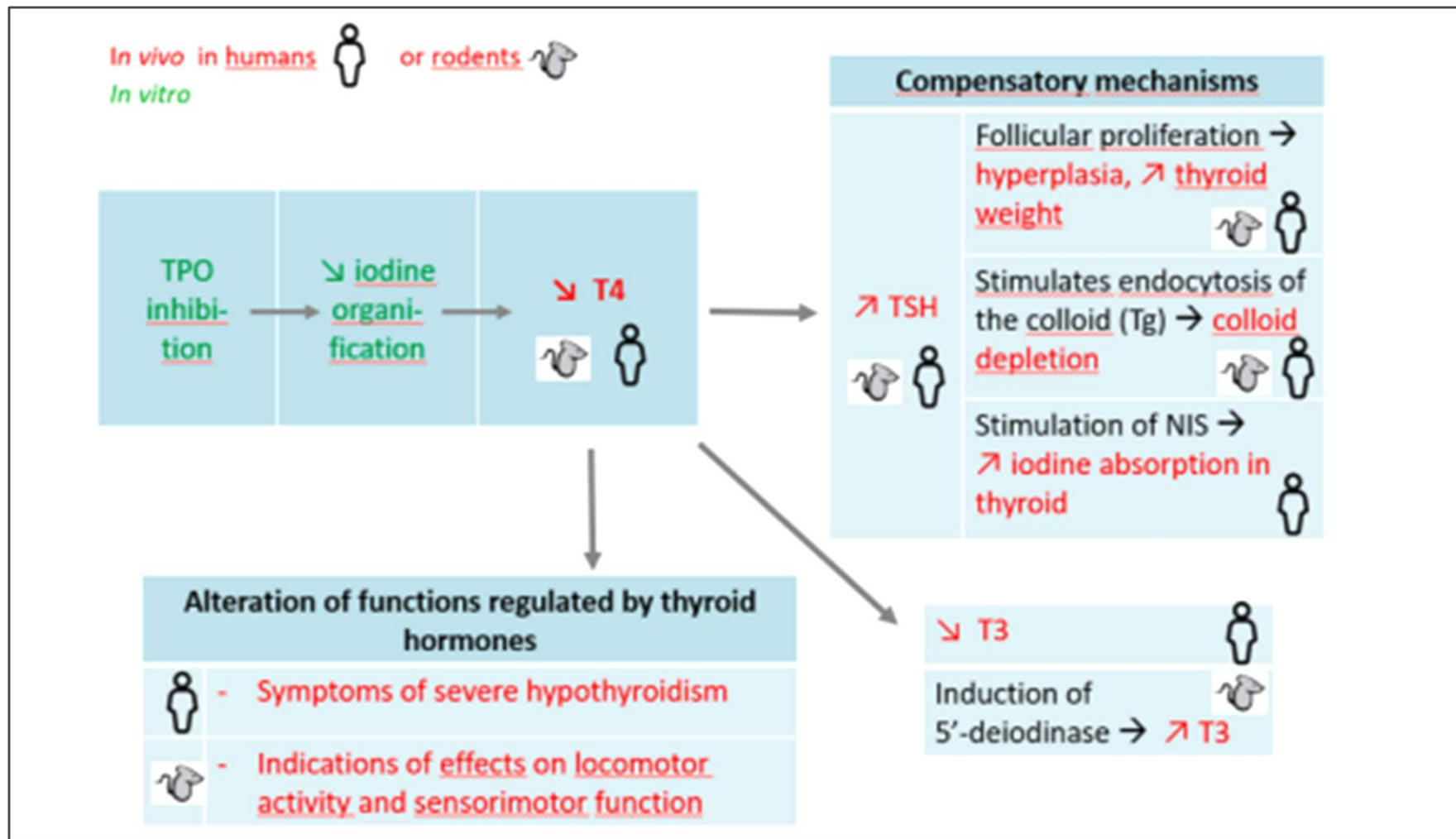


Fig 2: Biological plausible link between findings observed after exposure to resorcinol from Pasquier et al., 2023

List III:

Substances considered, by the evaluating National Authority, to have endocrine disrupting properties

This list contains substances that are considered as endocrine disruptors at the national level in one of the participating Member States, due to e.g. ED properties or structural similarities with known EDs.

It should be noted that these compounds are not necessarily considered as suspected EDs at the EU level. The European Commission or Member States may decide at a later stage on the need for further evaluation of these substances.

Latest update 2022/4

Substances no longer on list

Name and abbreviation ^a	CAS no.	EC / List no.	Health Effects	Environmental Effects	Also appears on lists
2-tert-butyl-4-methoxyphenol	25013-16-5	246-563-8	♥		List II
Bisphenol AF	1478-61-1	216-036-7	♥		
Dipentyl phthalate	131-18-0	205-017-9	♥	♦	
Octamethylcyclotetrasiloxane (D4)	556-87-2	209-136-7	♥		
Prochloraz	67747-09-5	266-994-5	♥	♦	
Propyl 4-hydroxybenzoate; Propylparaben	94-13-3	202-307-7	♥		List II
Salicylic acid	69-72-7	200-712-3	♥		List II
Triclocarban	101-20-2	202-924-1	♥		List II
Tris(methylphenyl)phosphate	1330-78-5	215-548-8	♥		

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Bisphenol AF (BPAF), CAS no.1478-61-1

Synonyms: 4,4'-(Hexafluoroisopropylidene)diphenol

BPAF is a fluorinated organic diphenol and a structural analog to Bisphenol A in which the two methyl groups are replaced with trifluoromethyl groups (Figure 1). BPAF has broad applications and is for example used as cross-linking reagent in the production of fluoropolymers and fluoroelastomers and as a monomer in production of many polymers. Since no registration dossiers on BPAF are available, it is assumed that it is produced and/or imported to EU in tonnages less than 100 tpa. BPAF has been detected in different environmental samples and in samples from humans. At present there is a lack of toxicological information on BPAF and is therefore currently undergoing extensive evaluations for *in vivo* toxicity by the National Toxicology Program, USA.

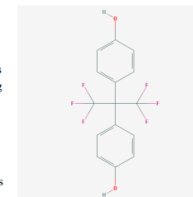


Figure 1. 2D structure from PubChem

4. Human health hazard assessment

4.10.3 Endocrine disruption

4.10.3.1 General approach – human health

4.10.3.2 *In vitro* information indicative of endocrine activity

Lei et al. (2017)

Summary: In this study, the effects of BPAF (>98% purity, CAS no. 1478-61-1) (and other

Tris(methylphenyl)phosphate (TMPP), CAS no. 1330-78-5

Synonyms: Tricresyl phosphate (TCP)

TMPP is a mixture of the 3 isomers *ortho*-, *meta*-, and *para*-cresols (Figure 1) and is used in the manufacturing of e.g. plastics, organophosphate flame retardants and solvents. TMPP is registered under REACH with a tonnage band of 1 000 - 10 000 tonnes per annum and is classified as Rep. 2 or self-classification as Rep. 1B; H360: May damage fertility or the unborn child. It is used in a variety of products such as furniture, electronics, textiles etc., and has been detected in the environment and in humans. The *ortho* isomer of TMPP, known as tri-*ortho*-cresyl phosphate (TOCP), is the most toxic of the 3 isomers and have been identified to cause neurotoxicity in humans and susceptible animals.

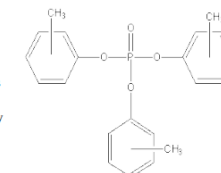


Figure 1. 2D structure from <https://www.huidziekten.nl/allergie/stoffen/tricresyl-phosphate.htm>

4. Human health hazard assessment