

**AGREEMENT OF THE MEMBER STATE COMMITTEE
ON THE IDENTIFICATION OF
4,4'-ISOPROPYLIDENEDIPHENOL (BISPHENOL A)
AS A SUBSTANCE OF VERY HIGH CONCERN**

**According to Articles 57 and 59 of
Regulation (EC) 1907/2006¹**

Adopted on 14 June 2017

This agreement concerns

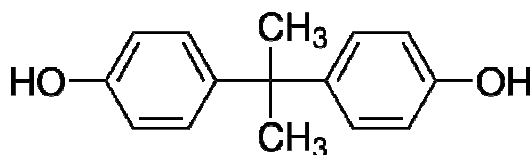
Substance name: 4,4'-isopropylidenediphenol (bisphenol A, BPA)

EC number: 201-245-8

CAS number: 80-05-7

Molecular formula: C₁₅H₁₆O₂

Structural formula:



¹Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC

France presented a proposal in accordance with Article 59(3) and Annex XV of the REACH Regulation (2 March 2017, submission number SPS-013185-17) on the identification of *4,4'-isopropylidenediphenol (bisphenol A)* as a substance of very high concern due to its endocrine disruptive properties for which there is scientific evidence of probable serious effects to **human health** which give rise to an equivalent level of concern to those of other substances listed in paragraphs (a) to (e) of Article 57 of REACH.

The Annex XV dossier was circulated to Member States on 9 March 2017 and the Annex XV report was made available to interested parties on the ECHA website on the same day according to Articles 59(3) and 59(4).

Comments were received from both Member States and interested parties on the proposal.

The dossier was referred to the Member State Committee on 22 May 2017 and discussed in the meeting on 12-16 June 2017 of the Member State Committee.

Agreement of the Member State Committee in accordance with Article 59(8):

***4,4'-isopropylidenediphenol (bisphenol A, BPA)* is identified as a substance meeting the criteria of Article 57 (f) of Regulation (EC) 1907/2006 (REACH) because it is a substance with endocrine disrupting properties for which there is scientific evidence of probable serious effects to human health which give rise to an equivalent level of concern to those for other substances listed in paragraphs (a) to (e) of Article 57 of REACH.**

UNDERLYING ARGUMENTATION FOR IDENTIFICATION OF A SUBSTANCE OF VERY HIGH CONCERN

Endocrine disrupting properties - Article 57(f):

Human Health:

Bisphenol A is identified as a substance of very high concern in accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH) because it is a substance with *endocrine disrupting properties* for which there is scientific evidence of probable serious effects to human health which gives rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 REACH.

Bisphenol A has a harmonised classification for the hazard class Reproductive toxicity category 1B (H360F 'May damage fertility') based on effects on reproductive function. BPA has been identified recently as SVHC according to Article 57(c) of REACH and included in the Candidate List by decision of ECHA ED/01/2017 of 4 January 2017.

BPA has been shown to affect the reproductive function, mammary gland development, cognitive function and metabolism through pathways that commonly involve disruption of estrogenic regulation. The effects on female reproductive function include the induction, after both developmental and adult exposures, of cystic ovaries, changes in the uterus morphology, alteration of fertility parameters as well as estrous cycle disturbance. The estrous cycle is a perfectly synchronised and sequenced event that relies on a permanent endocrine dialogue between the ovary and the hypothalamo-pituitary system. Those pathways differentiate during fetal life and are largely influenced by numerous factors and in particular the steroid environment of the foetus. BPA at the adult stage alters the endocrine steroidogenic function of the ovary and more specifically the production of estrogens by the follicle, leading to disturbance in the estrous cycle. At the neuroendocrine level, BPA can also act during the perinatal/postnatal organisation or adult activation of the hypothalamus-pituitary system through changes in kisspeptin, gonadotrophin-releasing hormone (GnRH) expression, activity or liberation and sex steroid receptor expression that impact estrous cyclicity.

The effects on the mammary gland, depending on the period of exposure, include: modifications in the mammary tissue such as an increased number of terminal end buds (TEBs) relative to the ductal area, fewer apoptotic TEB cells, increased lateral branching and ductal hyperplasia, increased cell proliferation and decreased apoptosis in the glandular epithelium, ductal (and occasionally lobuloalveolar) and intraductal hyperplasia - ultimately increasing its susceptibility to chemical carcinogens. These effects were observed in rodent or in non-human primate following prenatal and/or post-natal exposure to BPA. Available data also support the plausibility that BPA, through interaction with the nuclear estrogen receptors (ERs), or G protein-coupled estrogen receptor (GPER) and indirectly with the progesterone receptor (PR), modulates estrogen and progestin agonist activities. Emerging epigenetic studies have suggested changes related to estrogen-dependent genes (such as EZH2 and HOTAIR), as well as HOX genes (involved in embryogenesis and post-natal development) which could be associated with BPA induced abnormal development and increased cancer susceptibility of the mammary gland.

BPA has been reported to alter memory and learning after developmental, pubertal or adult exposure, based on multiple converging experimental studies reporting this functional effect as well as molecular and cellular changes in the brain (reduced expression of NMDAR, altered synaptogenesis). These effects involve disturbance of estrogenic pathways as evidenced by the reversal of the functional, cellular and molecular effects of BPA by an ER antagonist and interference of BPA with estradiol-induced effects on behavior and spine density/neurogenesis.

The effects of BPA on metabolism in rodent and non-rodent after prenatal and/or perinatal or adult exposures include alteration of insulin secretion and/or release by β -pancreatic cell, or of insulin signalisation (signaling mechanisms) within insulin-sensitive organs (i.e., liver, muscle, adipose tissues) leading to variations in the expression levels of hepatic or adipose tissue markers which are indicative of a state of insulin resistance. It is therefore considered that BPA may increase the incidence of type-2 diabetes. Additionally, *in vivo* and *in vitro* experimental studies indicate that these effects may involve ER α , ER β or GPR30 pathways. Other hormones such as leptin and adiponectin, which are involved in resistance to insulin and lipogenesis, are also modified following BPA exposure. This shows that BPA could interfere in the balanced interplay between insulin secretion and insulin action that controls glycaemia. Most of the *in vitro* studies showing adverse effects of BPA on adipocyte differentiation and function point to alteration of endocrine mechanisms (e.g., adiponectin release, insulin signaling cascade effectors). Overall, it is suggested that the pancreas is targeted by BPA, that the mechanisms could differ depending on the period of exposure (fetal life or adulthood) and that an ED MoA is involved. Lastly, mainly based on similarities in homeostatic regulation of insulin production and sensitivity between animals and humans, these effects are considered relevant for humans.

The steps of the respective mechanisms of action are specific for each effect. The complexity of the toxic response to BPA suggests multiple MoA that may interact but **most importantly, the available evidence shows that disruption of the estrogenic pathway is central and consistently involved in each of the four effects.**

In conclusion, on the basis of evidence available in relation to alteration of reproductive function, mammary gland development, cognitive function and metabolism, BPA can be considered an endocrine disruptor for human health.

It is not excluded that BPA may also alter other physiological functions, e.g. the immune function, through a similar ED MoA but the level of evidence is considered insufficient at the moment for this effect to be presented.

The range of experimental effects induced by BPA in relation to its ED MoA is predictive of serious health outcomes. All these ED-related effects are characteristically (but not only) observed after developmental exposure to BPA, with consequences that are observed later in life. As they appear a long time after the exposure, they are indeed considered permanent and irreversible. In addition, the effects of BPA are associated with conditions that may lead to a reduced quality of life. In particular breast cancers, neurobehavioural disorders and diabetes are observed with high prevalence and increasing trends during the last decades in Europe and raise indisputable societal concern, also in relation to their potential economic burden on the health systems. Finally, for each of the four effects, the database shows important uncertainties in establishing a quantitative dose-response as well as safe levels, with some studies identifying effects at doses below the point of departure used by RAC for DNEL derivation and on-going discussions on the shape of the dose-response relationship and the parameters impacting the dose-response (period of exposure and concomitant presence of estrogen in particular).

Overall, based on the WoE presented, BPA is identified as an SVHC according to article 57(f) for probable serious effects on human health, due to its endocrine disrupting properties, which are of ELoC.

Therefore, it is concluded that the substance *4,4'-isopropylidenediphenol (bisphenol A)* meets the criteria of Article 57(f) of REACH, due to its endocrine disrupting properties for which there is scientific evidence of probable serious effects to human health which give rise to an equivalent level of concern to those for other substances listed in paragraphs (a) to (e) of Article 57 of REACH.

Reference:

Support Document (Member State Committee, 14 June 2017)