AGREEMENT OF THE MEMBER STATE COMMITTEE

ON THE IDENTIFICATION OF

4,4'-(1-methylpropylidene)bisphenol (Bisphenol B)

AS A SUBSTANCE OF VERY HIGH CONCERN

According to Articles 57 and 59 of
Regulation (EC) 1907/2006[1]

Adopted on 3 June 2021

This agreement concerns

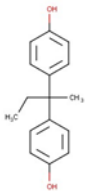
Substance name: 4,4'-(1-methylpropylidene)bisphenol (Bisphenol B)

EC number: 201-025-1

CAS number: 77-40-7

Molecular formula: $C_{16}H_{18}O_2$

Structural formula:



[1]Regulation (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 2021) on identification of *4,4'-(1-methylpropylidene)bisphenol (Bisphenol B) (EC No. 201-025-1)* as a substance of very high concern due to its endocrine disrupting properties for which there is scientific evidence of probable serious effects to the environment and 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 Regulation.

The Annex XV dossier was circulated to Member States on 10 March 2021 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 24 May 2021 and agreed in the written procedure of the Member State Committee with closing date of 3 June 2021.

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

4,4'-(1-methylpropylidene)bisphenol (Bisphenol B) **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 the environment and 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 Regulation.**

UNDERLYING ARGUMENTATION
FOR IDENTIFICATION OF A SUBSTANCE OF VERY HIGH CONCERN

4,4'-(1-methylpropylidene)bisphenol (**Bisphenol B**) is identified as a substance of very high concern in accordance with Article 57(f) of Regulation (EC) 1907/2006 (**REACH**) because of its endocrine disrupting properties for which there is scientific evidence of probable serious effects to the environment and human health which gives rise to an equivalent level of concern to those for other substances listed in points (a) to (e) of Article 57 REACH.

Endocrine disrupting properties - Article 57(f):

Adverse effects

Consistent adverse effects are observed in rodents and fish exposed to bisphenol B (**BPB**). The observed adverse effects in mammalian vertebrates are reduced sperm count and quality consistently observed in several reliable studies in two species (rats and mice). In fish, adverse effects include an altered hepato-somatic index and gonado-somatic index in male and female zebrafish. Qualitative observations of altered testis tubules and a decreased amount of mature spermatids in males also provide supportive evidence. BPB was demonstrated to significantly reduce fecundity of adult fish exposed for 21 days and to decrease embryo hatching and survival of F1 generation in a reliable study. Supportive evidence is provided by the induction of malformations (no detailed information) in zebrafish in one study. **BPB therefore induces adverse effects on the male reproductive system in rodents and fish.**

Estrogenic activity

BPB exposure leads to higher estrogen and lower androgen levels in both *in vitro* and *in vivo* studies in rodents and fish. Additionally, *in vitro* data unambiguously show the estrogenic activity of BPB: competitively binding to the oestrogen receptor (**ER**) of several vertebrate species (e.g. human, bovine, rat, mouse and medaka in the µM range), activation of ER signalling pathway (e.g. ER transactivation in reporter cell lines, increased promoter occupancy and induction of ER-regulated gene expression) and physiological cell response (e.g. proliferation) with similar or higher potency than 4,4'-isopropylidenediphenol (bisphenol A; **BPA**). This estrogeno-mimetic activity of BPB is also supported by the results of immature rat uterotrophic assays with increase in watery uterine content and blotted uterine weight. This effect was similar to BPA, but with a slightly higher magnitude for BPB. In fish, the increase in levels of vitellogenin (**VTG**) gene expression in the liver of male medaka and male zebrafish, and the increase in ER-regulated cyp19a1b expression in the brain of male zebrafish also strongly support the estrogenic activity of BPB.

BPB was therefore shown to have clear estrogenic effects in rats and fish.

Other potential modes of action

BPB was shown to bind the androgen receptor (**AR**) and to induce an anti-androgenic response in most vertebrate cell lines including in human cells but this effect was not confirmed in the Hershberger assay. **Therefore, BPB possibly has**

anti-androgenic effects.

The *in vivo* data also showed a decrease in luteinising hormone (**LH**) - and follicle stimulating hormone (**FSH**) -related gene expression in brain and gonads of male zebrafish and a decrease in plasma LH and FSH levels in rats, suggesting an action of BPB via the hypothalamic-pituitary axis. It is however not known whether it may be a cause, a consequence or a specific mode of action in addition to estrogenic and possible anti-androgenic effects.

Oxidative stress was reported in several rodent studies and may also have an impact on the testis. It is however not known whether it may be a consequence or a specific mode of action in addition to estrogenic and possible anti-androgenic effects.

Plausibility of the link between effects and endocrine activity

BPB may have multiple modes of action that interact or superimpose and are difficult to distinguish from each other. The estrogenic effects of BPB are established in fish and rats and anti-androgenic effects are suggested. Estrogenic and anti-androgenic modes of action are known to be involved in the regulation of spermatogenesis and are closely inter-related. Considering the concomitant decrease in plasma testosterone levels and the increase in plasma estradiol levels, the link between these endocrine activities and the adverse effects on the male reproductive system in rodents and fish is highly plausible.

Relevance of effects and endocrine modes of action

In the present assessment, the *in vivo* available evidence on rodents shows that BPB can affect the male reproductive system. These observed adverse effects in mammalian vertebrates are considered relevant for effects on human health and on mammalian wildlife species in the environment (such as mice, rats) and supportive for non-mammalian vertebrate species (fish, amphibians) with respect to the underlying mode of action and adverse effects.

Supportive evidence from BPA

The link between the observed effects and the specific endocrine activity is supported by the data on BPA, as BPB and BPA share very similar structures, adverse effects and modes of action. BPA has been identified already as SVHC due to its endocrine disrupting properties relevant for human health and the environment. It should be noted that considering the extremely large database available for BPA, it was decided to focus the SVHC identification for BPA due to its endocrine properties for human health on the endpoints having the strongest plausible link at the time of the identification. Male reproduction was not included. However, the effects of BPA on male reproduction are acknowledged, in addition to female reproduction, in the justification to classify BPA as Repro 1B for reproduction. In contrast, the endpoints included in the BPA SVHC identification for human health are largely not investigated for BPB. However, when data are available, they provide indications of a similar effect of BPB to BPA for female reproduction and metabolic effects. This support the consistency of effects between BPB and BPA.

Conclusion on endocrine disrupting properties

Overall, BPB has estrogen agonist properties and induces adverse effects on the male reproductive system in rodents and fish that are plausibly mediated by this endocrine activity.

Supportive evidence is provided by the consideration that BPB possibly has androgen-antagonist properties. This endocrine activity could also plausibly contribute to the adverse effects on the male reproductive system in rodents and fish.

The effects on rodents are relevant for human health and the effects in fish and rodents are relevant for the environment as an effect on the reproductive function can have consequences at a population level.

Therefore, there is scientific evidence that BPB fulfils the definition of an endocrine disruptor relevant for the environment and human health.

The effects of BPB due to its endocrine disrupting properties are considered to be of equivalent level of concern to substances listed in Article 57 points (a) to (e). The concern is substantiated by the severity and irreversibility of the effects on organisms and populations that may have long term consequences, the large variety of species that may be adversely affected and the difficulties to quantify a safe level of exposure with regard to the endocrine mediated effects. An equivalent level of concern is also supported by the potential for combined exposure with other bisphenols that share similar modes of action. The assessment shares similar lines of argumentation as for previous SVHC identifications of BPA for its ED properties, for which a considerable amount of data is available. Due to the very close structural similarity between BPB and BPA, commonalities of effects and of modes of action, the main arguments justifying the equivalent level of concern of BPA are also relevant to BPB.

Therefore, it is concluded that the substance *4,4'-(1-methylpropylidene)bisphenol (Bisphenol B)* 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 the environment and 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 Regulation.

Reference:

Support Document (Member State Committee, 3 June 2021)