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) 1907/2006[1]

Adopted on 14 December 2017

This agreement concerns

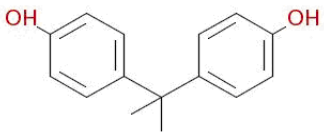
Substance name: 4,4'-isopropylidenediphenol (bisphenol A, BPA)

EC number: 201-245-8

CAS number: 80-05-7

Molecular formula: $C_{15}H_{16}O_2$

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

Germany presented a proposal in accordance with Article 59(3) and Annex XV of the REACH Regulation (28 August 2017, submission number SPS-013574-17) on identification of *4,4'-isopropylidenediphenol (bisphenol A)* 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 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 5 September 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 20 November 2017 and discussed in the meeting on 11-15 December 2017 of the Member State Committee.

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

4,4'-isopropylidenediphenol (bisphenol A) **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 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.**

UNDERLYING ARGUMENTATION
FOR IDENTIFICATION OF A SUBSTANCE OF VERY HIGH CONCERN

Endocrine disrupting properties - Article 57(f):

Environment:

Bisphenol A (BPA) 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 the environment for which there is scientific evidence of probable serious effects to the environment which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 of REACH Regulation.

The analysis of results for fish and amphibians according to the OECD Guidance Document for Endocrine Disrupters reveals that BPA needs to be considered as an endocrine disruptor. It fulfils the WHO/IPCS definition of an endocrine disruptor as interpreted by the European Commission's Endocrine Disruptor Expert Advisory Group in their recommendations for a substance to be identified as an endocrine disruptor.

For BPA there is scientific evidence from good quality studies that the substance causes endocrine mediated adverse effects in several fish and amphibian species.

BPA clearly acts as an oestrogen agonist in fish.

In several **fish** species clear evidence that BPA acts as oestrogen agonist is provided:

- *In vitro* data unambiguously show that BPA binds to vertebrate (human and fish) oestrogen receptors in the µM range and modulates gene expression. BPA also competitively inhibits androgenic activity of a known AR agonist.
- The oestrogen agonist mode of action is unambiguously substantiated by *in vivo* data in several species. Diagnostic for the oestrogenic mode of action are the observed Vitellogenin (VTG) induction, changes in gonadal staging, testis ova, altered sex ratio, and reduced male secondary sex characteristics.

The effects observed are clearly adverse, such as the skewed sex ratio towards females. A direct link between the oestrogenic mode of action *in vivo* (e.g. VTG induction, testis, ova) and the adverse effects (sex ratio, reduced egg production) is provided for *O. latipes*, *D. rerio* and is very likely for *P. promelas*. Additionally, for six other fish species adverse effects which are known to be sensitive towards an oestrogenic mode of action were demonstrated, such as affected growth, behaviour and fertilisation success.

In addition, there is evidence that BPA potentially acts as oestrogen agonist in **amphibians**:

- An agonistic VTG induction was demonstrated in hepatocytes of *X. laevis* at

22.8 µg/L *in vitro*. Further evidence is provided by the *in vitro* studies demonstrating binding to the oestrogen receptor in other vertebrates.

- The oestrogenic mode of action is substantiated in *X. laevis* by a skewed sex ratio (23 µg/L), a delay of development, altered testicular structure (2.28 µg/) and the ability to induce Vitellogenin *in vivo* (22.8 µg/L) as well as similar results for E2.
- A direct link is provided between VTG induction *in vitro* and *in vivo* through a plausible binding to the oestrogen receptor and changes of the sex ratio and reproduction observed *in vivo* for *X. laevis* as well as three other species. These effects are considered adverse.

BPA clearly acts as a thyroid antagonist in <u>amphibians</u>:

- *In vitro* studies with amphibian, fish and mammal cells demonstrate that BPA is interfering with the HPT (Hypothalamic-Pituitary-Thyroid) axis (e.g. thyroid receptor, transport proteins).
- The endocrine mode of action is substantiated by *in vivo* data. Diagnostic for a thyroid mode of action in amphibians is the accelerated/asynchronous development or an abnormal histopathology, which could be demonstrated in 3 species. BPA inhibited the (TH induced and spontaneous) metamorphosis *in vivo*, leading to a delayed development and disturbed life-cycle in *R. rugosa, X. laevis* and *X. tropicalis*.
- Hence, a direct link between the *in vitro* and *in vivo* evidence can be shown. The observed in vivo effects (delayed development and disturbed life-cycle) are considered adverse.

In addition, there is some evidence that BPA also may act via a thyroidal mode of action in **<u>fish</u>**, although data is scarce. This is substantiated by *in vitro* studies, demonstrating an interference with the HPT axis and thyroid-related hormones in fish cells together with accelerated embryonic development in *O. latipes* which was blocked by the thyroid-antagonist amiadorone *in vivo*. The thyroid-mediated effects (accelerated development, earlier hatching and smaller individuals) are considered adverse.

Further support for endocrine-related effects of BPA

The analysis of **<u>invertebrate taxa</u>** revealed indications that adverse effects of BPA are possibly endocrine-mediated. It has to be kept in mind that there is still lack of an agreed guidance document which is clearly defining biological plausible links between endocrine modes of action and adverse effects for invertebrate taxa and that knowledge is still scarce in light of the large number and variety of invertebrates and their endocrine systems.

- In <u>molluscs</u>, characteristic adverse effects on reproduction and development were an increased egg production, mitigated by anti-oestrogens in two species *in vivo*, as well as the induction of superfemales, malformations of genital tissues (known for E2 and OP) in four species as well as embryo malformations in two species. BPA acts similar to known vertebrate-type (xeno-)oestrogens. A possible oestrogen receptor binding (*in vitro*, *in vivo*), mRNA expression and increased VTG or VTG-like protein levels were shown in three species.
- For arthropods such as insects and crustaceans ecdysteroids are known to regulate reproduction- and development-related processes. For <u>insects</u>, adverse effects of BPA were similar as for (xeno-)oestrogens (OP, NP, EE2),

comprising a delayed development, reduced fecundity and emergence rates as well as increased weight/growth. *In vitro* evidence for antagonistic ecdysteroid receptor binding and changes in mRNA expression is provided for *Drosophila* and *Chironomus*. For crustaceans, adverse *in vivo* effects are associated with embryo malformations, developmental delay, molting disturbances and altered reproductive outcome (enhanced or reduced). Effects were similar to (xeno-)oestrogens and could be mitigated by ecdysteroids. Due to the close relationship to insects, a binding or interference with the ecdysteroid receptor and ecdysteroid related processes is possible.

For further invertebrate species, such as echinoderms, poriferans or cnidarians, data for BPA and knowledge of the endocrine systems is very fragmentary. However, developmental disturbances including embryo malformations are typical after BPA exposure and similar to the effects observed for other (xeno-)oestrogens in these groups.

Overall, Bisphenol A is clearly shown to disrupt steroid- (oestrogen) and thyroid mediated processes in fish and amphibians respectively, leading to adverse effects on the organisms which can affect population stability and recruitment. Endocrine-mediated effects occurred and at lower concentrations than acute, systemic or narcotic toxicity.

BPA is also identified as an SVHC according to article 57(f) for probable serious effects on human health due to its endocrine disrupting properties on the basis of data on mammals. There is a large degree of conservation of the primary amino acid sequences in proteins, which implies large commonalities between non-mammalian and mammalian vertebrate species in regard to hormones, enzymes and receptors involved in the EATS (Estrogen/Androgen/Thyroidal/Steroidogenesis) modalities (OECD 2017: Draft revised OECD Guidance No. 150). Evidence of endocrine disruptive properties of BPA on mammalian vertebrate species therefore provides further support for similar properties in non-mammalian vertebrates, in particular with regard to disruption of oestrogenic pathways.

Bisphenol A is considered as a substance giving rise to an equivalent level of concern due to its endocrine modes of action and the type of effects caused by these modes of action in wildlife species (fish, amphibians).

The assessment followed the same line of arguments as for previous SVHC-identifications according to 57(f) ED for the environment. Due to the amount of data available for BPA a large number of arguments for an equivalent level of concern can be provided. All arguments are used in a weight of evidence and as such, none of the arguments alone are decisive for the decision and not all of them are needed to conclude on the equivalent level of concern. We decided to present the available evidence to get a view on the overall picture on the data analysed.

- BPA causes severe effects on reproduction- and development-related processes (including sexual development) in fish and amphibians, clearly linked to the endocrine mode of action. Results for fish demonstrate that BPA may cause a complete sex reversal resulting in all-female phenotype populations. In amphibians, thyroidal pathways, metamorphosis and development are disturbed, and additionally sex ratio skewed via a suspected additional oestrogen mode of action. Supporting evidence is provided by effects observed in invertebrates.
- BPA in particular causes severe effects on organisms when exposure took place during sensitive time windows or early life stages, also after short-term exposures when exposure later ceases. Many of these effects have to be regarded as irreversible, such as sex reversal or embryo or adult malformations which may have long-term consequences for the population. Moreover, some effects may only occur after exposure during particular seasons as shown for amphibians.
- BPA elicits long-term effects across generations and affects populations and communities. Transgenerational effects were observed for several fish species, where the following generations became much more sensitive to BPA exposure (after continuous as well as short-term exposures of the parental generation). Long-term effects were shown in one mesocosm study, where low BPA concentrations affected the fish population and changes in gonad morphology are likely endocrine-mediated.
- BPA affects a large variety of ecologically important species in different ecosystems, covering lentic, lotic, marine and terrestrial environments. BPA exposure is not restricted to certain environments but shown to be ubiquitously present. Certain fish (and also mollusc) species were shown to be particularly sensitive, but as data is only available for a small proportion of existing species, it is not possible to exclude that further species are equally or even more sensitive. Also endangered species such as amphibians may be affected. It has to be kept in mind, that effects first become prominent in later life stages or in the next generation, even when organisms have migrated to uncontaminated regions.
- BPA has already, based on available data including a large number of results from studies on mammalian mainly rodent species, been concluded to be an endocrine disrupter of concern for human health according to Article 57 (f) of REACH. Whereas the available mammalian studies are relevant for human health, it is plausible, that they are also of relevance for other mammalian species including mammalian wildlife species. In relation to the environment, adverse effects concerning development and reproduction are generally regarded as endpoints of particular relevance because such effects are likely to manifest themselves at the population level. The effects observed in rats are of particular concern for mammalian wildlife species with a natural low reproductive output (including endangered species) as negative effects on reproduction have an even higher potential for causing long term negative effect at the population level for such taxa. However, it is unclear whether the effects observed for mammals in the human health assessment will lead to population level effects in mammalian wildlife species.
- Based on the current data and knowledge it appears difficult to derive and quantify a safe level of exposure for BPA, although it might exist. Effects on non-traditional endpoints and in specific species occurred at lower concentrations than those considered by standard OECD test guidelines. Moreover, as effects often occur in certain species, or after exposure during specific time windows and early life stages, some effects might be overlooked. Effects of BPA are presumably provoked via different modes of action and a greater variety of species could be affected.

In conclusion, there is scientific evidence that Bisphenol A causes probable serious effects in the environment which give rise to an equivalent level of concern to those

of other substances listed in points (a) to (e) of Article 57 of REACH Regulation.

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 the environment 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, 14 December 2017)