

**OPINION OF THE MEMBER STATE COMMITTEE  
ON THE IDENTIFICATION OF  
4-TERT-BUTYLPHENOL  
AS A SUBSTANCE OF VERY HIGH CONCERN**

**According to Articles 57 and 59 of  
Regulation (EC) 1907/2006<sup>1</sup>  
Adopted on 15 December 2016**

**This opinion concerns**

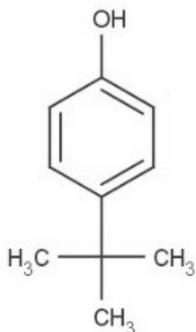
**Substance name:** 4-tert-butylphenol (ptBP, PTBP)

**EC number:** 202-679-0

**CAS number:** 98-54-4

**Molecular formula:** C<sub>10</sub>H<sub>14</sub>O

**Structural formula:**



---

<sup>1</sup> 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 (30 August 2016, submission number SPS-012446-16) on identification of *4-tert-butylphenol (PTBP)* 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.

The Annex XV dossier was circulated to Member States on 6 September 2016 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 November 2016 and was discussed in the meeting on 12-16 December 2016 of the Member State Committee.

MSC **did not reach** unanimous agreement on whether the information provided in the SVHC proposal is sufficient to constitute an equivalent level of concern to CMRs in accordance with Article 57 (f) of the REACH Regulation.

Pursuant to Articles 59 (9) and 85(8) of REACH in order for the Commission to draft a proposal on the identification of the substance in accordance with the procedure outlined in Article 133 (3) of the REACH Regulation, the Member State Committee provides this opinion, consisting of the view of the majority of its members, including its grounds.

Two MSC members expressed a minority view, including their grounds that is made available in a separate document.

In accordance with Article 59 (9), a final decision on the identification of PTBP shall be taken in accordance with the procedure referred to in Article 133(3).

### **Opinion of the Member State Committee in accordance with Article 59(8):**

***4-tert-butylphenol (PTBP)* should be identified as a substance of very high concern 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 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**

### **Endocrine disrupting properties – Article 57(f):**

For 4-tert-butylphenol there is scientific evidence from good quality studies that the substance causes endocrine mediated adverse effects in several fish species:

- *In vitro* data unambiguously show that 4-tert-butylphenol acts as a ligand of estrogen receptor in fish and mammalian cells. Modulation of 4-tert-butylphenol-dependent and ER-mediated gene expression was observed on transcriptional, protein and cell physiological levels showing that 4-tert-butylphenol activates fish and mammal estrogen receptors.
- *In vivo* data substantiate the endocrine mode of action. Endpoints indicative for an estrogenic mode of action were affected in all fish species tested (3 species). Effects observed included Vitellogenin (VTG) induction, feminization of gonadal ducts and other histological alterations and reduced male secondary sex characteristics.
- A sex ratio biased towards females was observed in one fish species. This endpoint is both diagnostic for an endocrine mode of action and an adverse effect.

Other observed adverse effects (reduced reproduction, reduced growth) in fish are plausibly due to an estrogenic mode of action. But other modes of action cannot be entirely ruled out.

Effects observed are similar to those observed for 4-tert-octylphenol and 4-nonylphenol and occur at similar test concentrations. Effects observed are regarded as endpoints of particular relevance because they are likely to manifest themselves at the population level.

An analysis of results based on the OECD Guidance Document for endocrine disruptors reveals that 4-tert-butylphenol needs to be considered as endocrine disruptor. It fulfills the WHO/IPCS definition of an endocrine disruptor and the recommendations from the European Commission's Endocrine Disruptors Expert Advisory Group for a substance to be identified as an endocrine disruptor.

In conclusion, 4-tert-butylphenol can be considered to be an endocrine disruptor in the environment. This conclusion is supported by read-across from other alkylphenols (4-nonylphenol and 4-tert-octylphenol) with regard to the environment.

4-tert-butylphenol is considered as a substance giving rise to an equivalent level of concern with regard to the environment due to its estrogen agonist mode of action in fish and the type of effects caused by this mode of action in fish. Based on data for 4-tert-butylphenol as well as other estrogen agonists, evidence that the substance is of an equivalent level of concern includes:

- Exposure to 4-tert-butylphenol resulted in effects in fish on reproduction parameters (fecundity) as well as on sexual development (changes in sex ratio) and growth. Results for one fish species show that exposure to 4-tert-butylphenol may result in a complete sex reversal resulting in all female populations. This effect is considered a serious effect to the environment.
- Read-across of the effects observed for the structurally similar 4-nonylphenol and 4-tert-octylphenol in fish show that exposure during sensitive life stages may result in effects that remain during the entire life and even in following generations and even after exposure ceased. Thus local exposure of migratory species might not only affect population stability locally but also in other areas.
- On the basis of the available data for 4-tert-butylphenol itself and from read-across it appears difficult to derive a safe level although it may exist. Read-across from 4-tert-octylphenol and 4-nonylphenol with regard to organisms in the environment indicates that
  - Effects on non-traditional endpoints may start at much lower concentrations than those considered in OECD test guidelines.

- It is not possible to clearly conclude that effects on other organisms such as invertebrates and amphibians are endocrine mediated, although steroids are known to play an important role in invertebrates (Kendall et al., 1998) and amphibians. Owing to the lack of in-depth knowledge of their endocrine system and the lack of test systems, it is currently difficult to estimate which species may be more sensitive than fish and which concentration can be regarded as safe for the environment.

Thus in summary, the endocrine mediated effects observed in fish after exposure to 4-tert-butylphenol and anticipated on the basis of read-across from other alkylphenols are considered to have the potential to adversely affect population stability and recruitment. These adverse effects not only persist after cease of exposure but also occur after exposure at sensitive live stages. They thus may adversely affect populations in the longer-term and migratory species not only locally but also in regions where no exposure occurred. No reliable information is available for 4-tert-butylphenol about whether it can cause ED-related adverse effects on taxa other than fish. 4-tert-octylphenol and 4-nonylphenol cause effects in amphibians and invertebrates that might be endocrine mediated, i.e. caused by an estrogen-like mode of action, although it is not possible to clearly conclude that they are endocrine mediated. Similar effects may be caused by 4-tert-butylphenol, but there are no confirmatory data. Based on current data and knowledge, a safe level of exposure is difficult to derive although it may exist.

*In summary*, there is scientific evidence that *4-tert-butylphenol* 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.

**Conclusion:** Taking into account all available information on the intrinsic endocrine disrupting properties of *4-tert-butylphenol* and its adverse effects, it is concluded that PTBP should be identified as a substance with endocrine disrupting properties for which there is scientific evidence of probable serious effects to the environment which gives rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 of REACH.

## **Reference:**

Support Document to the MSC opinion on *4-tert-butylphenol (PTBP)* (Member State Committee, 15 December 2016)