AGREEMENT OF THE MEMBER STATE COMMITTEE
ON THE IDENTIFICATION OF
4-HEPTYLPHENOL, BRANCHED AND LINEAR
[substances with a linear and/or branched alkyl chain with a carbon number of 7 covalently bound predominantly in position 4 to phenol, covering also UVCB- and well-defined substances which include any of the individual isomers or a combination thereof] (4-HPbl)
AS SUBSTANCES OF VERY HIGH CONCERN

According to Articles 57 and 59 of
Regulation (EC) 1907/2006[1]
Adopted on 14 December 2016

This agreement concerns

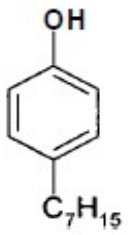
Substance name: 4-Heptylphenol, branched and linear (4-HPbl)[2]

EC number: -

CAS number: -

Molecular formula: $C_{13}H_{20}O$

Structural formula:



(branched and linear)

[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

[2] The full name of the entry as it is proposed for the Candidate List is: 4-Heptylphenol, branched and linear [substances with a linear and/or branched alkyl chain with a carbon number of 7 covalently bound predominantly in position 4 to phenol, covering also UVCB- and well-defined substances which include any of the individual isomers or a combination thereof]

Austria 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-Heptylphenol, branched and linear (4-HPbl)*[3] as substances of very high concern due to their 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.

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

4-heptylphenol, branched and linear [substances with a linear and/or branched alkyl chain with a carbon number of 7 covalently bound predominantly in position 4 to phenol, covering also UVCB- and well-defined substances which include any of the individual isomers or a combination thereof] (4-HPbl) **are identified as substances of very high concern meeting the criteria of Article 57 (f) of Regulation (EC) 1907/2006 (REACH) because they are substances 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.**

[3] The full name of the entry as it is proposed for the Candidate List is: 4-Heptylphenol, branched and linear [substances with a linear and/or branched alkyl chain with a carbon number of 7 covalently bound predominantly in position 4 to phenol, covering also UVCB- and well-defined substances which include any of the individual isomers or a combination thereof]

UNDERLYING ARGUMENTATION

FOR IDENTIFICATION OF SUBSTANCES OF VERY HIGH CONCERN

Endocrine disrupting properties – Article 57(f):

Based on the available mechanistic information from *in silico* and *in vitro* studies with 4-heptylphenol isomers, it can be concluded that 4-HPbl is able to bind to the estrogen receptors of fish, humans and rats and to activate these receptors.

In an *in vivo* study with *Sander lucioperca* (Demska-Zakęś, 2005)[4] the ratio of male fish (according to histological determination) was significantly decreased at the lowest used 4-n-heptylphenol (4nHP) concentration (1 µg/L) after 28 days of exposure. The shift in sex ratio was dose-dependent, leading to 98 and 100% female fish at 88 and 144 days post hatch, respectively, indicating that the observed effects on the sex characteristics were irreversible.

The appearance of intersex species comprising sex characteristics from both sexes, e.g. testis-ova / ovotestis and formation of an oviduct (with regressed spermatogenic lobules in the same fish), was significant at 4nHP concentrations of at least 1 µg/L.

4-HPbl belongs to a group of structurally similar alkylphenols monoalkylated predominantly in 4-position with different alkyl chain lengths. To substantiate the findings for 4-HPbl, a read across approach is applied using the following source alkylphenols:

- 4-Nonylphenol, branched and linear: substances with a linear and/or branched alkyl chain with a carbon number of 9 covalently bound in position 4 to phenol, covering also UVCB- and well-defined substances which include any of the individual isomers or a combination thereof
- 4-tert-octylphenol (4-(1,1,3,3-tetramethylbutyl)phenol, EC number: 205-426-2)
- 4-tert-pentylphenol (p-(1,1-dimethylpropyl)phenol, EC number: 201-280-9)
- 4-tert-butylphenol (4-(1,1-dimethylethyl) phenol, EC number: 202-679-0)

Regarding chain length, 4-HPbl is in the middle of 4-nonylphenol, branched and linear and 4-tert-octylphenol on the one side and 4-tert-pentylphenol and 4-tert-butylphenol on the other side. The findings for 4-HPbl were substantiated by the effects seen also in tests performed with the source substances.

- *In vitro* data confirm that all four source substances and the target substance do interact with the estrogen receptors.
- As for 4-HPbl it was demonstrated that exposure to 4-nonylphenol and 4-butylphenol (branched and linear forms) lead to a female biased sex ratio in *Sander lucioperca* at low concentration (effects seen at lowest dose of 1 µg/L).
- Substantial effects were also seen in other fish species (such as *Pimephales promelas, Danio rerio, Oryzias latipes, Cyprinus carpio, Oncorhynchus mykiss*) for the source chemicals. These include effect data like a female biased sex ratio and indicative effects like feminisation of gonadal ducts, testis-ova and effects on secondary sex characteristics.

4-Nonylphenol and 4-tert-octylphenol are already identified as substances of very high concern due to their endocrine disrupting properties for the environment, which are considered to give rise to an equivalent level of concern. The effects observed for 4-HPbl are similar to those for 4-tert-octylphenol and 4-nonylphenol and occur in similar concentration ranges.

In summary, it is demonstrated that endocrine disrupting properties for the environment occur for alkylphenols with alkyl chain lengths of 4,5,7,8 and 9 C-atoms.

Taking all the evidence into consideration 4-HPbl is identified as an endocrine disruptor for the environment according to the OECD guidance document (OECD, 2012) and the WHO/IPCS definition for endocrine disrupters.

[4] More information about different studies and references to them can be found in the Support document for 4-HPbl prepared in the context of the identification of these substances as SVHCs.

4-HPbl are assessed as substances giving rise to an equivalent level of concern due to their estrogenic mode of action and the type of effects caused by this mode of action (e.g. shift in sex ratio).

- At 1 µg/L the ratio of male fish was significantly decreased and intersex fish appeared. At 10 µg/L the ratio of female fish was significantly increased to approximately 75% while at 200 µg/L approximately 100% fish were female. These effects remained manifest even after the exposure had ceased underlining that exposure during sensitive life stages may change the endocrine feedback system for the entire life.

- On the basis of the available data for 4-HPbl itself and from read across, it appears difficult to derive a safe level although it may exist. A read-across from 4-tert-octylphenol and 4-nonylphenol indicates that

    - Effects on non-traditional endpoints may start at much lower concentrations than those considered in the 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 both invertebrates 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.

- Read across of the effects observed for the similar alkylphenols 4-nonylphenol and 4-tert-octylphenol shows that an exposure during sensitive life stages may result in effects that remain during the entire life and even in the following generations. Thus local exposure of migratory species might not only locally affect population stability but also in other areas.

Thus in summary, the endocrine mediated effects observed in fish after exposure to 4-HPbl 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-HPbl 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-HPbl, 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, 4-HPbl are considered to 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-HPbl and their adverse effects, it is concluded that 4-HPbl are substances 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 (Member State Committee, 14 December 2016)