HAZARD ASSESSMENT

OUTCOME DOCUMENT

for

4-Heptylphenol, branched and linear (4-HPbl) [1]

EC No._ -
CAS No: -

Member State(s): Austria

Dated: September 2016

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[1] Please note that 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]

1. HAZARD SUBJECT TO ASSESSMENT

4-HPbl belongs to the class of alkylphenols, which comprises already confirmed endocrine disrupting chemicals. It was selected for hazard assessment in order to clarify suspected endocrine disruptive properties for the environment.

2. OUTCOME OF HAZARD ASSESSMENT

The available information on the substance and the hazard assessment conducted has led the assessing Authority to the following considerations, as summarised in the table below.

Hazard Assessment Outcome	**Tick box**
According to the authority's assessment the substance is not an ED in accordance with the WHO (2002) definition based on the currently available information.	
According to the authority's assessment the substance is an ED in accordance with the WHO/IPCS (2002) definition.	x
According to the authority's assessment further information would be needed to confirm the ED properties but follow-up work is not relevant or carried out at present.	

This outcome is based on the REACH data as well as other available relevant information.

3. BASIS FOR REASONING[2]

Based on the available mechanistic information from QSAR data (moderate estrogen binding activity for all 117 possible monosubstituted heptylphenols according to OECD Toolbox) and *in vitro* studies on 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 a reliable long term study using *Sander lucioperca* the ratio of male fish (according to histological determination) was significantly decreased at the lowest 4-n-heptylphenol concentration (1 µg/L) after 28 days of exposure. The shift in sex ratio was dose-dependent, leading to 98 and 100% fish with female sex characteristics at 88 dph and 144 dph, 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, formation of an oviduct (with regressed spermatogenic lobules in the same fish) significantly appeared also at concentrations of at least 1 µg/L.

To substantiate the findings for 4-HPbl a read across approach was applied using the following source alkylphenols:

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[2] Assessments of ED properties are based on the WHO/IPCS definition of an endocrine disruptor.

"An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations."

WHO/IPCS Report 2002: Global Assessment of the state-of-the-science of Endocrine disruptors, Executive Summary (Chapter 1) page 1 section 1.1

Under the REACH Regulation endocrine disruptors may be identified in accordance with Article 57(f) on a case-by-case basis as substances of very high concern (SVHCs), where there is scientific evidence of probable serious effects to human health or the environment, which give rise to an equivalent level of concern to CMR or PBT/vPvB substances.

- 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)

- 4-*tert*-pentylphenol (*p*-(1,1-dimethylpropyl)phenol)

- 4-*tert*-butylphenol (4-(1,1-dimethylethyl) phenol)

Regarding chain length, 4-HPbl is between 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 for the source substances.

- *In vitro* data confirm that all four source substances and the target substance do interact with estrogen receptors

- As for 4-n-heptylphenol it was demonstrated that exposure to 4-n-nonylphenol and 4- -butylphenol (branched and linear forms) lead to a female biased sex ratio in *Sander lucioperca* at a low concentration (effects seen at lowest dose of 1 µg/L).

Substantial effects were also seen in other fish species (*Pimephales promelas*, *Danio rerio*, *Oryzias latipes*, *Cyprinus carpio*, *Oncorhynchus mykiss*) for the source chemicals. These include female biased sex ratio and indicative effects such as feminisation of gonadal ducts, testis-ova and changes in secondary sex characteristics. Some of the effects occurred at the same concentration.In summary, it is demonstrated that endocrine disrupting properties for the environment occur for alkylphenyls with alkyl chain lengths of 4,5,7,8 and 9 C-atoms.

In an oral 28-day repeated dose study with rats effects on male reproductive organ weights were observed. These were most pronounced by a decrease in absolute and relative weights of the seminal vesicles by 51 and 41%, respectively. In the same study increase in relative thyroid/parathyroid and adrenal glands weights and decrease in absolute thymus weight in males were reported in the highest dose group (450 mg/kg bw/day). Other increases in absolute and relative organ weights were also observed at 450 mg/kg/day dose group including liver (both sexes by 22 to 60%, females also in the 150 mg/kg/day dose group) and kidney (females only, 102 to 122%). In males reduced body weights (-19%) and body weight gains were reported. In the highest dosage group both sexes suffered from systemical toxic side effects (clinical signs and deaths). Histopathological changes included vacuolation of the liver and renal lesions compatible with tubular nephropathy that corresponds well to changes in clinical chemistry parameters. In males depletion of secretion of the seminal vesicles and of lymphoid of the thymus occurred in the highest dose group.

The observed significant relative and absolute weight decrease in male mammals, together with the observed depletion of secretion of the seminal vesicles at the highest dose, might indicate an estrogen mode of action for phenol, heptyl derivs.. However, at this concentration systemic effects including one death and reduced mean body weights >10% were observed.

In a reproductive/developmental screening assay with phenol, heptyl derivs. effects on male and female reproduction cannot be excluded due to the reduced live litter size at the two highest dose levels.

In summary, taking all the evidence into consideration it is concluded that 4-HPbl fulfils the WHO/IPCS definition for endocrine disrupters for the environment.

It is further noted that 4-HPbl fulfils also the European Commission's draft scientific criteria for endocrine disruptors, which were recently published in the context of the Biocidal Products

Regulation and the Plant Protection Products Regulation (European Commission, 2016[3]).

The available data raise a concern for endocrine disruptive effects in humans, but are deemed to be insufficient for the identification of an endocrine disruptor for human health.

AT presented the case in the Endocrine Disruptor Expert Group with the following substance identity:

Substance Name(s): Phenol, heptyl derivs

EC Number(s): 276-743-1

CAS Number(s): 72624-02-3

After close exchange with ECHA on substance identity a group entry is now proposed in the submitted SVHC dossier. This group entry is in analogy to 4-Nonylphenol, branched and linear, and covers also phenol, heptyl derivs.

In summary, there was support from six member states experts, who agreed that phenol, heptyl derivs. is an endocrine disurpor for the environment. An expert of another member state answered the question with “possibly”. Most of the suggestions from these member state experts as well as ECHA experts were taken up in order to improve the dossier.

After close exchange with ECHA on substance identity a group entry is proposed:

Substance Name(s)[4]: 4-Heptylphenol, branched and linear (4-HPbl)

EC Number(s): -

CAS Number(s): -

This group entry is in analogy to 4-Nonylphenol, branched and linear, and covers also phenol, heptyl derivs.

[3] European Commission (2016): Draft Commission Delegated Regulation (EU) …/… of XXX setting out scientific criteria for the determination of endocrine-disrupting properties pursuant to Regulation (EU) No 528/2012 (Text with EEA relevance); see http://ec.europa.eu/health/endocrine_disruptors/docs/2016_bpcriteria_en.pdf

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4. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS IF NECESSARY

An RMO analysis has been carried out by AT in parallel to the ED EG group consultation. Based on the outcome and discussion of the performed analysis and the outcome of the written procedure in the ED EG as well as taking into account discussions regarding substance identity an SVHC dossier for a group entry 4-heptylphenol, branched and linear including phenol, heptyl derivs. was submitted to ECHA (according to REACH Regulation, article 57 (f)).

Follow-up action	**Date for intention**	**Actor**
RMOA for phenol, heptyl derivs.	Already submitted (RMOA conclusion document published in July 2016)	Austria, in cooperation with DE
SVHC for 4-heptylphenol, branched and linear (4-HPbl)	Already submitted in August 2016	Austria