baua:
Bundesanstalt für Arbeitsschutz
und Arbeitsmedizin
Federal Institute for Occupational
Safety and Health

HAZARD ASSESSMENT

OUTCOME DOCUMENT

for

4-tert-butylphenol

EC No 202-679-0

CAS No 98-54-4

Member State(s): Germany

Dated: 15 June 2016

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Version 1.3

1. HAZARD SUBJECT TO ASSESSMENT

4-tert-butylphenol (ptBP) was originally selected for hazard assessment in order to clarify suspected hazard properties:

Endocrine Disruption with regard to 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.	✓
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 and CLP data as well as other available relevant information.

3. BASIS FOR REASONING[1]

For ptBP several in vitro and in vivo studies are available which clearly show that ptBP acts as an estrogen agonist both in vitro and in vivo. In vivo data for several fish species show that this alteration of the function of the endocrine system results in adverse effects in intact organisms. They provide a clear link between the mode of action and the adverse effects observed. Data for other fish species substantiate the estrogen mode of action and adverse effects observed fit to this mode of action:

Available in vitro data show, that ptBP is able to bind to the estrogen receptor and activate it:

- all available competent binding assays using fish receptors showed that ptBP binds to the ER receptor. Some results indicate that its affinity may be in the same order of maginitude as observed for 4-tert-octylphenol. With regard to human and rat receptors

[1] 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.

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- The competitive ligand-binding studies clearly demonstrated that ptBP is able to displace specifically bound E2 from the ER ligand-binding pocket. The RBA of ptBP for ERs derived from human or rainbow trout ranged from 2.1E-6 to 7.7E-5. Thus, ptBP acts as a ligand of the ER. Binding of ptBP to the ER leads to activation of the ER-mediated pathway and consequently to transcriptional activation of typically estrogen-responsive genes.

Available in vivo data shows that the estrogen mode of action results in severe adverse effects in fish:

- ptBP causes effects in *P.promelas* which are clearly diagnostic for an estrogen mode of action. VTG induction and histological changes (gonadal duct feminisation) appeared. Effects observed on secondary sex characteristics are usually considered as indicators for endocrine activity and not adverse effects. In this case effects were very severe and should thus be considered as adverse. Adverse effects on growth observed at this concentration fit to this mode of action but is not diagnostic for an endocrine mode of action.

- A Change of the sex-ratio towards an increased number of females was observed for *Sander lucioperca*. This endpoint is considerd to be indicative for an estrogen agonist mode of action and is an apical adverse effect. Other effects observed for these species substantiate the estrogen mode of action.

- Indication of an estrogenic mode of action is available for one additional species (*C. carpio*) for which no apical endpoints were assessed. Effects observed in *O.latipes* fit to the mode of action.

A read-across to 4-tert-pentylphenol, 4-tert-octylphenol and 4-nonylphenol substantiates the endocrine disruption.

Compared to 4-nonylphenol, effects observed in *S. lucioperca* were in the similar concentration range. The in vitro potency is comparable.

4. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS IF NECESSARY

Indication of a tentative plan is not viewed as a commitment by the authority. Any commitment to prepare a REACH Annex XV dossier (SVHC, restrictions) and/or CLP Annex VI dossier should be made via the Registry of Intentions.

Follow-up action	Date for intention	Actor
SVHC Dossier due to endocrine disruption for the environment	August 2016	Germany