SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

2,4,6-tribromophenol

EC No 204-278-6

CAS No 118-79-6

Evaluating Member State: Norway

Dated: 09.05.2016

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2012

The evaluating Member State (eMSCA) concludes that more data is indeed required to clarify both the initial concern for including this substance on the CoRAP and additional concern that was identified during the evaluation. However, as this substance no longer have any active registrations according to the ECHA dissemination website, the evaluation is terminated with several open concerns.

If in future the inactive registrations are activated, or there are new registrants, authorities shall consider including the substance again in the CoRAP for obtaining the information which is considered important to clarify the concern related to this substance. In such a situation the potential registrants are recommended to take note of these conclusions and make appropriate testing proposals to ECHA.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Content

Part A. Conclusion

1. CONCERNS SUBJECT TO EVALUATION

2,4,6-tribromophenol (2,4,6-TBP) was originally selected for substance evaluation in order to clarify concerns about: CMR. Suspected PBT/vPvB. Wide dispersive use. High (aggregated) tonnage. High RCR.

- Human health:
Several studies indicated concern for effects on developmental reprotoxicity following exposure to 2,4,6-TBP. The effects were observed in the absence of marked maternal toxicity. The available information is however inadequate to support a robust human reproductive risk assessment, as the studies are either screening or range-finding studies or studies of low reliability.

- Environment:
Information on the biodegradation and bioaccumulation of 2,4,6-TBP was considered insufficient, including information on formation of transformation or degradation products which is necessary to assess whether the P and B criterion may be fulfilled. 2,4,6-TBP is very toxic to aquatic organisms. Due to uncertainties about degradation rates and high aggregated tonnage a risk for the aquatic environment could not be excluded. For the environment risk characterization ratios close to 1 were identified at the highest tonnage level.

During the evaluation also other concerns were identified. The additional concerns were:

- Several *in vitro* studies in open literature addressed potential endocrine disrupting properties of 2,4,6-TBP, both in the environment and in humans. 2,4,6-TBP appears to interfere with thyroid function and has a high affinity for the transthyretin (TTR). In addition, 2,4,6-TBP is found to interfere with estrogen and androgen signalling.
- Sub-acute studies indicated adverse effects, both by oral and inhalation exposure at doses suggesting some concern for organ toxicity, but no long-term studies are available.
- Data from open literature showed widespread presence of 2,4,6-TBP in indoor air and in house dust, suggesting the potential for long-term human exposure and that inhalation may be regarded as a relevant human exposure route.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

- 2005 CICAD (Concise International Chemical Assessment Document 66): 2,4,6-TRIBROMOPHENOL AND OTHER SIMPLE BROMINATED PHENOLS
- 2012 EFSA Panel on Contaminants in the Food Chain: Scientific Opinion on Brominated Flame Retardants (BFRs) in Food: Brominated Phenols and their Derivatives1
- 2013 OECD SIDS Initial assessment report

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluating Member State (eMSCA) concludes that more data is indeed required to clarify both the initial concern for including this substance on the CoRAP and additional concern that was identified during the evaluation. However, as this substance no longer has any active registrations according to the ECHA's register/dissemination website, the evaluation is terminated with several open concerns.

If in future the inactive registrations are activated, or there are new registrants, authorities shall consider including the substance again in the CoRAP for

obtaining the information which is considered important to clarify the concern related to this substance. In such a situation the potential registrants are recommended to take note of these conclusions and make appropriate testing proposals to ECHA.

In this report the evaluation performed is based on information on the ECHA dissemination website as well as other publically available information on 2,4,6-TBP. The report includes specifications on what data would clarify the identified concern. The report includes also some additional data that was published after the initial evaluation was performed (2012). The possible environment risk characterization ratios close to 1, as mentioned in the initial concern, were not further evaluated due to the inactivation of the registrations.

2,4,6-TBP is very toxic to aquatic life and there are several self-classifications for chronic effects of 2,4,6-TBP notified in the C&L Inventory (see section 7.6.2). The eMSCA considers that available data are sufficient for a classification as Aquatic Acute 1 and Aquatic Chronic 1, according to the CLP regulation (EC No. 1272/2008). Further, the substance is irritating to the eye (see section 7.9.2) and sensitizing to the skin (see section 7.9.3). For the time being the eMSCA has not taken any decision on whether to proceed with a proposal for harmonised classification.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION **Conclusions**	**Tick box**
Need for follow-up regulatory action at EU level *[if a specific regulatory action is already identified then, please, select one or more of the specific follow-up actions mentioned below]*	
Harmonised Classification and Labelling	(x)
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	x

4. FOLLOW-UP AT EU LEVEL

See section 5 below.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

The substance evaluation of 2,4,6-TBP was terminated as this substance no longer have any active registrations. The eMSCA concluded that further information would have been necessary to clarify the concerns regarding suspected PBT/vPvB, reproduction toxicity and endocrine disruption properties.
The eMSCA is of the opinion that as the above mentioned hazards remain unverified, a further assessment should be undertaken in the event of possible new future registrations , or if inactivated registrations are activated.

However, harmonised classification at least for aquatic toxicity (Aquatic Acute 1 and Aquatic Chronic 1) would be warranted based on the available data. Further, the substance is irritating to the eye and sensitizing to the skin. For the time being the

eMSCA has not taken any decision on whether to proceed with a proposal for harmonised classification.

Table 2

REASON FOR REMOVED CONCERN The concern could be removed because	Tick box
Clarification of hazard properties/exposure	
Actions by the registrants to ensure safety, as reflected in the registration dossiers i.e.the registrations were revoked/inactivated.	x

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

See section 3 and 5.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

See section 1 for the concerns subject to evaluation. An overview of the outcome of the evaluation is summarized in Table 1.

Table 1 Evaluated endpoints

EVALUATED ENDPOINTS Endpoint evaluated	Outcome/conclusion
Persistency	**No conclusion reached.** 2,4,6-TBP or a possible transformation product (2,4,6-tribromoanisole) meets the *screening P criteria*. A study on aerobic and anaerobic transformation in aquatic sediment systems (OECD 308) with identification of transformation or degradation products in individual amounts above 0.1% would clarify whether the P criterion is fulfilled.
Bioaccumulation	**No conclusion reached**. Based on additional studies found in open literature during the evaluation it is concluded that the potential for bioaccumulation of 2,4,6-TBP or a possible transformation product (2,4,6-tribromoanisole) in aquatic organisms is low. However, more information would be needed to conclude whether the B criterion may be fulfilled based on the potential for bioaccumulation in terrestrial organisms.
Repeated dose toxicity	**No conclusion reached.** No sub-chronic or chronic repeated dose toxicity studies are available. A 28-days repeated dose study indicates that 2,4,6-TBP exposure induces liver and kidney toxicities at high dose exposure and squamous hyperplasia of the forestomach and adjacent area. Several *in vitro* studies suggest that 2,4,6-TBP may have endocrine disrupting potential. Data from a sub-chronic toxicity study (90-days repeated dose) including measurements examining potential thyroid hormone disrupting effects, would clarify the concern for health hazard during long term exposure.
Reprotoxicity (development)	**No conclusion reached.** The available information suggests a concern for developmental toxicity, but is not considered adequate to support a robust risk assessment nor a CLH proposal. The main

	concern is related to peri-natal development and developmental neurotoxicity. An EOGRTS study in rats by oral route, including the basic Cohorts 1A/1B, and Cohorts 2A/2B for developmental neurotoxicity, is considered the most suitable study to clarify the concern for reproductive toxicity.
Endocrine disrupting properties (environment and human health)	**No conclusion reached.** Environment: Results from *in silico*, *in vitro* and *in vivo* studies suggest that 2,4,6-TBP may interact with the endocrine system through multiple MoA. An extended and modified Fish Sexual Developmental test (FSDT, OECD 234) would clarify the concern for possible endocrine disruptive properties (estogenic/androgenic) of 2,4,6-TBP in the aquatic environment. For clarifying the possible thyroid-mediated endocrine disruptive properties the Larval Amphibian Growth and Development Assay (LAGDA, OECD 241) would be the optimal test in amphibians. Human health: *In vitro* studies indicate a potential for endocrine disruption that is relevant for humans. An appropriately designed EOGRTS study will not only address the data gaps for reproductive and developmental toxicity, but is also likely to give valuable information on potential endocrine MoAs in mammals.

7.2. Procedure

The evaluation of 2,4,6-TBP was intended to be targeted on possible reprotoxic effects and PBT properties. However, in the end more endpoints were evaluated, as additional concerns with this substance were revealed.

A summary of substance evaluation procedural history:
- 28 February 2012-26 February 2013: The initial evaluation was performed. During this period there were informal interactions with the Lead Registrant. The eMSCA identified that more data was required to confirm both the initial concern for including this substance on the CoRAP and additional concern that was identified during the evaluation.
- 27 February 2013: A draft decision to require more information from the Registrants was submitted to ECHA. This draft decision reflected the registration status at that point and that registered tonnage was above 1000 tonns per year.
- 6 April 2013: The Registrants were notified by ECHA of the draft decision.
- May 2013: ECHA received the registrants´comments
- June 2013-March 2014: Communication/discussions between ECHA, Registrants and the eMSCA on the further evaluation procedure.
- 17 March 2014 The Lead Registrant inactivated his registration of 2,4,6-tribromphenol.
- 27 June 2014: The eMSCA decided to proceed with the evaluation since several concerns were identified. However due to the consequent reduction of the aggregated tonnage (which now was below 10 tons) it was considered disproportionate to require the information to clarify the concerns identified.
- 27 December 2015: All registrations were inactivated according to information on the ECHA dissemination website.

- 9 May 2016: The evaluation performed was reported as required by REACH Article 48, based on information on the ECHA dissemination website as well as other publically available information on 2,4,6-TBP.

The source of information was

- ECHA dissemination website: http://echa.europa.eu/registration-dossier/-/registered-dossier/5191/1#sRegistrationData
- 2005 CICAD (Concise International Chemical Assessment Document 66): 2,4,6-TRIBROMOPHENOL AND OTHER SIMPLE BROMINATED PHENOLS
- SFT (2009): Current state of knowledge and monitoring requirements - Emerging "new" brominated flame retardants in flame retarded products and the environment (TA-2462/2009)
- 2012 EFSA Panel on Contaminants in the Food Chain: Scientific Opinion on Brominated Flame Retardants (BFRs) in Food: Brominated Phenols and their Derivatives1
- 2013 OECD SIDS Initial assessment report
- Other publically available information

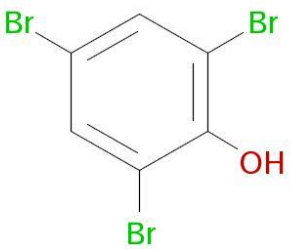
7.3. Identity of the substance

Table 2 Substance identity

SUBSTANCE IDENTITY	
Public name:	2,4,6-tribromophenol
EC number:	204-278-6
CAS number:	118-79-6
Index number in Annex VI of the CLP Regulation:	Not applicable
Molecular formula:	C6H3Br3O
Molecular weight range:	330.8
Synonyms:	-

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



Multiconstituent/UVCB substance/others

The substance is a monoconstituent. There is no information on impurities on the ECHA dissemination website.

7.4. Physico-chemical properties

Table 3 Overview of physiochemical properties

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	White to off-white solid. Observations made during the performance of a GLP activated sludge respiration inhibition test. Study Report 2010.
Vapour pressure	0.063 Pa at 25 °C. Test: A GLP compliant test designed to be compatible with Test Method A.4 specified in Commission Regulation (EC) 440/2008 of 30 May 2008. Study Report 2010.
Water solubility	50 mg/L at 19 ± 1 °C. The test was performed in line with OECD Guidelines 105 and EEC Directive 92/69 EEC A.6. The flask method was used for the determination of the water solubility. Study Report 1999.
Partition coefficient n-octanol/water (Log Kow)	4.6 x 10E+3 (log Kow = 3.7) at 23.5 +/- 0.5 °C. Test method: OECD Guideline 117 (Partition Coefficient (n-octanol / water), HPLC Method).
Flammability	Not highly flammable. Two preliminary parallel flammability tests were performed. The tests were negative. The test item is not flammable in the conditions of this test. Based on the results of the preliminary test no further testing was required. Test Method A.10 in Test Method Regulation. Study Report 2010.
Explosive properties	No data available. Not evaluated by the eMSCA.
Oxidising properties	No data available. Not evaluated by the eMSCA.
Granulometry	No data available. Not evaluated by the eMSCA.
Stability in organic solvents and identity of relevant degradation products	No data available. Not evaluated by the eMSCA.
Dissociation constant	No key studies, but WoE information. pKa 6.08 in two of these studies and 5.97 in the third comparison.
Viscosity	No data available. Not evaluated by the eMSCA.The substance is solid at room temperature.

These endpoints were not targeted and no further evaluation has been performed by the eMSCA.

7.5. Manufacture and uses

Under the heading 'Guidance on safe use' on the ECHA dissemination website it is stated that "Guidance on safe use is not required because the polymerization is taken place outside the EU/EEA".

7.5.1. Quantities

At the start of the evaluation in 2012 the aggregated tonnage was 1000-10 000 t/year. After notification of the draft decision to require more information from the registrants, the former Lead Registrant deactivated his registration. The remaining registered tonnage was 1-10 t/year due to this change. By December 2015 all remaining registrations were deactivated. Per 6 May 2016 there are according to the ECHA dissemination website no active registrations of 2,4,6-TBP. For more details on the procedure see Section 7.2.

7.5.2. Overview of uses

Table 4 Uses according to ECHA dissemination website 06 May 2016

USES (source: ECHA dissemination website)	Use(s)
Uses as intermediate	No data
Formulation	No data
Uses at industrial sites	– **Identified use name:** Manufacture of plastic products – **Environmental release category:** ERC 4: Industrial use of processing aids in processes and products, not becoming part of articles – **Process category:** PROC 14: Production of preparations or articles by tabletting, compression, extrusion, pelletisation – **Chemical product category:** PC 32: Polymer preparations and compounds – **Sector of end use** SU 12: Manufacture of plastics products, including compounding and conversion – **Substance supplied to that use in form of** As such – **Subsequent service life relevant for that use?** No
Uses by professional workers	No data
Consumer Uses	No data
Article service life	No data

Information on use from other sources:

Known use for 2,4,6-TBP is as a flame retardant in thermoplastic polyester and epoxy resins, in acrylonitrile-butadiene-styrene resins, in phenolic resins and polystyrene (SFT, 2009).

According to WHO (2005) 2,4,6-TBP was by far the most widely produced brominated phenol with a production volume of approximately 2500 t / year in Japan and 9500 t / year worldwide in 2001. 2,4,6-TBP is not used directly as a flame retardant but rather as

an intermediate for such products as an end stop for brominated epoxy resin made from tetrabromobisphenol A (probably the largest application), tribromophenylallyl ether, and 1,2-bis(2,4,6-tribromophenoxyethane). It is the second most prevalent flame retardant used in acrylonitrile-butadiene-styrene resins. 2,4,6-TBP has also been used as a fungicide for wood preservation but is not notified as biocide in the EU any longer. Brominated phenol production and use as a reactive flame retardant intermediate or as a wood preservative may result in release to the environment.

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

2,4,6-TBP has no harmonised classification in Annex VI of CLP.

7.6.2. Self-classification

- According to the ECHA dissemination website:

Eye Irrit. 2 H319: Causes serious eye irritation.
Skin Sens. 1 H317: May cause an allergic skin reaction.
Aquatic Acute 1 H400: Very toxic to aquatic life.

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory:

Acute Tox. 3 H301: Toxic if swallowed.
Acute Tox. 4 H312: Harmful in contact with skin.
Skin Irrit. 2 H315: Causes skin irritation.
Acute Tox. 4 H332: Harmful if inhaled.
Repr. 2 H361: Suspected of damaging fertility or the unborn child.
STOT SE 2 H371 (Nervous System): May cause damage to the nervous system.
STOT RE 2 H373 (Liver, kidney): May cause damage to liver and kidneys through prolonged or repeated exposure.
STOT SE 3 H335 (Respiratory system) (Inhalation): May cause respiratory irritation.
Aquatic Chronic 2 H411: Toxic to aquatic life with long lasting effects.

7.7. Environmental fate properties

7.7.1. Degradation

7.7.1.1. Hydrolysis

A study from 2010 referred on the ECHA dissemination website showed 2,4,6-TBP to be hydrolytically stable in water with less than 10% hydrolysis after 10 days at pH 4, 7 and 9 at 50ºC. The study (OECD 111) was reported to be GLP compliant with a reliability factor of 1. According to Lyman et al. (1990) 2,4,6-TBP is not likely to undergo hydrolysis in the environment due to the lack of hydrolysable functional groups.

7.7.1.2. Phototransformation

7.7.1.2.1. Phototransformation in air

According to a study from 1978 referred on the ECHA dissemination website direct photolysis by UV light of 2,4,6-TBP on silica gel plates indicated a half-life of 4.6 hours (VCC (1978) as referred in WHO (2005)). The method used was not a recognised guideline, but the study is acceptable for the substance evaluation as regards phototransformation in air.

7.7.1.2.2. Phototransformation in water

A study from 1979 referred on the ECHA dissemination website reported photodegradation of tribromophenol according to a biphasic curve with a half life of 1 hour in the first phase and a half life of 11.5 hours in the second phase. The study did not contain any replicates or controls and therefore is of limited reliability, especially since the first-order half-life is calculated from only two measurements. Eight phototransformation products were observed but only 3,5-dibromo-1,2-dihydroxybenzene was tentatively identified as a major product. This study did not follow an accepted guideline and was not performed to GLP.

More recent and better quality studies are summarized below:

A study on the photolysis of brominated phenols supports the rapid first-order degradation of 2,4,6-TBP with a first-order rate constant (k_1) of 167 min^{-1} (Mas et al. 2011). This translates as a first order half-life of 15 min. Photolysis was performed at room temperature in quartz tubes using low-pressure mercury vapor lamp predominantly emitting light at 254 nm. Mas et al. (2011) propose that 2,4,6-TBP (and other bromophenols) photodegrade by reductive debromination by successive losses of bromine atoms. 2-bromophenol, 4-bromophenol and 2,4-dibromophenol were positively identified as phototransformation products whilst interestingly 3,5-dibromo-1,2-dihydroxybenzene was not reported as a product of 2,4,6-transformation. The first-order degradation rate constants for these transformation products are 118, 220 and 156 min^{-1}.

The major primary photoproduct of 4-bromophenol in an aqueous oxygenated solution has been reported as 1,4-benzoquinone (Rayne et al., 2009). Work by Lipczynska-Kochany (1992) using a flash photolysis system followed by high performance liquid chromatography (HPLC) indicated that 1,4-benzoquinone was the major primary photoproduct of 4-bromophenol, while resorcinol was the only primary photoproduct of 2-bromophenol. UV irradiation experiments (250-400 and 285-325nm) in a glass container provided a photolytic half-life for 2-bromophenol of 115 mins (Eriksson et al., 2004). It should be noted that although this system differed from that used by Mas et al. (2011) it also estimated the photolytic half-life of 2,4,6-TBP to be 15 mins. It has also been demonstrated that 2,4-dibromophenol in aqueous solution under simulated light (350 W Xenon lamp fitted with 290nm cut-off filter) can phototransform to 2-hydroxy-2,3',4,5'-tetrabromodiphenyl ether, however the main photoproducts were identified as 4-bromo-1,2-dihydroxybenzene, 2-bromo-1,4-dihydroxybenzene and 4,6-dibromo-1,2-dihydroxybenzene (Liu et al., 2011).

7.7.1.2.3. Phototransformation in soil

ECHA dissemination website has no information on this endpoint. No information found in open literature.

7.7.1.3. Biodegradation

7.7.1.3.1. Biodegradation in water

Estimated data

ECHA dissemination website does not contain any estimations on biodegradation in water.

QSAR estimates is performed in order to preliminary identify 2,4,6-TBP potential for persistency, see Table 5. BIOWIN within the US EPA's EPIWIN (version 4.1) suite predicts that 2,4,6-TBP is not readily biodegradable. This is based on the seven predictive models found within the BIOWIN suite. A summary is as follows:

Table 5 QSAR estimates on 2,4,6-TBP

Model	**Probability cut off point**	**Results**
Biowin 1 (Linear Model Prediction):	<0.5	0.3748- Does not biodegrade fast
Biowin 2 (Non-linear Model Prediction):	<0.5	0.003- Does not biodegrade fast
Biowin 3 (Ultimate biodegradation timeframe):	<2.2	2.1165= months
Biowin 4 (Primary biodegradation timeframe):		2.9496 =weeks
Biowin 5 (MITI linear model prediction):	<0.5	0.3090- Not readily degradable
Biowin 6 (MITI non-linear model prediction):	<0.5	0.1432- Not readily degradable
Biowin 7 (Anaerobic model prediction):	<0.5	0.7259- Biodegrades fast

According to Chapter R11 PBT Assessment Guidance the results from the BIOWIN model can be used in a screening assessment for persistence in the following way:

BIOWIN 2 and BIOWIN 3: Does not biodegrade fast (probability <0.5) and ultimate biodegradation timeframe prediction ≥ months (value <2.2)

According to estimated data with BIOWIN 2 and BIOWIN3 2,4,6-TBP meets the screening criteria for P. Under anaerobic conditions the substance is estimated to biodegrade fast.

Screening tests

ECHA dissemination website report data from several studies performed on the biodegradation of 2,4,6-TBP in water. Theese include: 1) a research study focussing on the isolation of an anaerobic debrominating bacterium from marine sediment (1995, non-guideline); 2) a biodegradation study in anoxic marine sediments (1991, non-, guideline); 3) an aerobic biodegradation study (non–guideline, 1975); 4) an aerobic biodegradation study (non –guideline, 1976).

Two anaerobic research studies on biodegradation are described. The first study focuses on isolating a reductively debrominating bacterium capable of debrominating 2,4,6-TBP (Steward, 1995). Rapid degradation (2-3 days) of 2,4,6-TBP was observed in enriched cultures of bacteria isolated from marine sediment from the burrow of a bromometabolite-producing marine hemichordate. In the second research study anoxic marine sediment samples from three fjords, one of which received effluent water from a paper and pulp mill, were collected (Abrahammson and Klick, 1991). In two of the sediments (including the one from the fjord which received effluent water from a paper and pulp mill) debromination of 2,4,6-TBP and 2,6 DBP was a fast process, described to occur within a few days, even at a temperature of 6 ºC. In the third sediment a slow debromination of 2,4,6-TBP and formation of 2,4-DBP and to a minor extent 2,6-DBP was observed at 30 ºC. The difference in dehalogenation ability was attributed to differences in microbial composition due to adaptation to a polluted environment.

Two aerobic biodegradation tests are reported on the ECHA dissemination website. One study (1975), with inoculum from a domestic sewage treatment plant, showed no significant biodegradation when 2,4,6-TBP was exposed to sewage enriched cultures. In another study (1976), water from treatment ponds at a sewage treatment plant was seeded with bacteria from either primary effluent or a commercially available source. No biodegradation of 2,4,6-TBP was observed in this study.

In addition the following information was obtained from open literature:

According to WHO (2005) brominated phenols are generally not readily biodegradable and will persist in the environment. However, adapted communities of microorganisms and specialist communities (such as anaerobic or sulfidogenic) may degrade the compounds.

2,4,6-TBP, present at 100 mg/litre, reached 49% of its theoretical biochemical oxygen demand in 28 days using an activated sludge inoculum at 30 mg/litre in the Japanese MITI test, a result that fails the criterion for ready biodegradability (CITI, 1992) In addition microorganisms in water collected from two ponds were not able to degrade 2,4,6-TBP over 32 days (VCC 1990), seemingly same data as referenced "1976" on ECHA web page). Kondo et al. (1988) report that 2,4,6-TBP (10 mg/L) was degraded by 82% in seawater and by 9% in freshwater over 3 days.

Further open literature describes 2,4,6-TBP to rapidly debrominate with a half life of 4 days under anaerobic conditions in a methanogenic sediment-water system (Peijnenburg, 1992). In this study 2,4,6-TBP was only assessed in one sediment water system (Loosdrechtse plassen) and the characterisation of the sediment showed it had a very high organic carbon content and a low pH, therefore the results should be interpreted with care. 2,4,6-TBP dehalogenated quite rapidly over 14 days in an anoxic marine sediment slurry (equal amounts water:sediment) at room temperature with dibromophenol identified as a transient intermediate (King, 1988). More than 90% of the added 2,4,6-TBP (10-1,000 µM) was lost within 48h. The Author notes that in this study bacterial dehalogenation was probably related to the production of DBP by the hemichordate *S. kowalewskii* at the sediment sampling site, although other sources or pollution could not be ruled out. The experiments were not performed according to GLP or following a recognised OECD standard.

Simulation tests (water and sediments)

No data available.

7.7.1.3.2. Biodegradation in soil

ECHA dissemination website report a GLP, guideline study (OECD 307) on degradation in soil from 2008. The rate of degradation of [14C]- 2,4,6-TBP was studied in three Brazilian soils under aerobic conditions at 20 °C. For this purpose, agricultural soil samples were treated with the [14C] labelled test substance at 10 mg/Kg[3] and incubated in the laboratory for 120 days. An abiotic control was performed in parallel to estimate the degradation rate under sterile conditions when incubated at the same conditions. The air was sterilized by filtration through a 0.22 µm membrane. The mean half-life (biodegradation) of the test substance 2,4,6-TBP was 7 days (ranging from 5 to 10 days), indicating non-persistence in the tested soils. The end result of the metabolic pathway under aerobic conditions was the mineralisation of the test substance to carbon dioxide and the formation of bound residues.

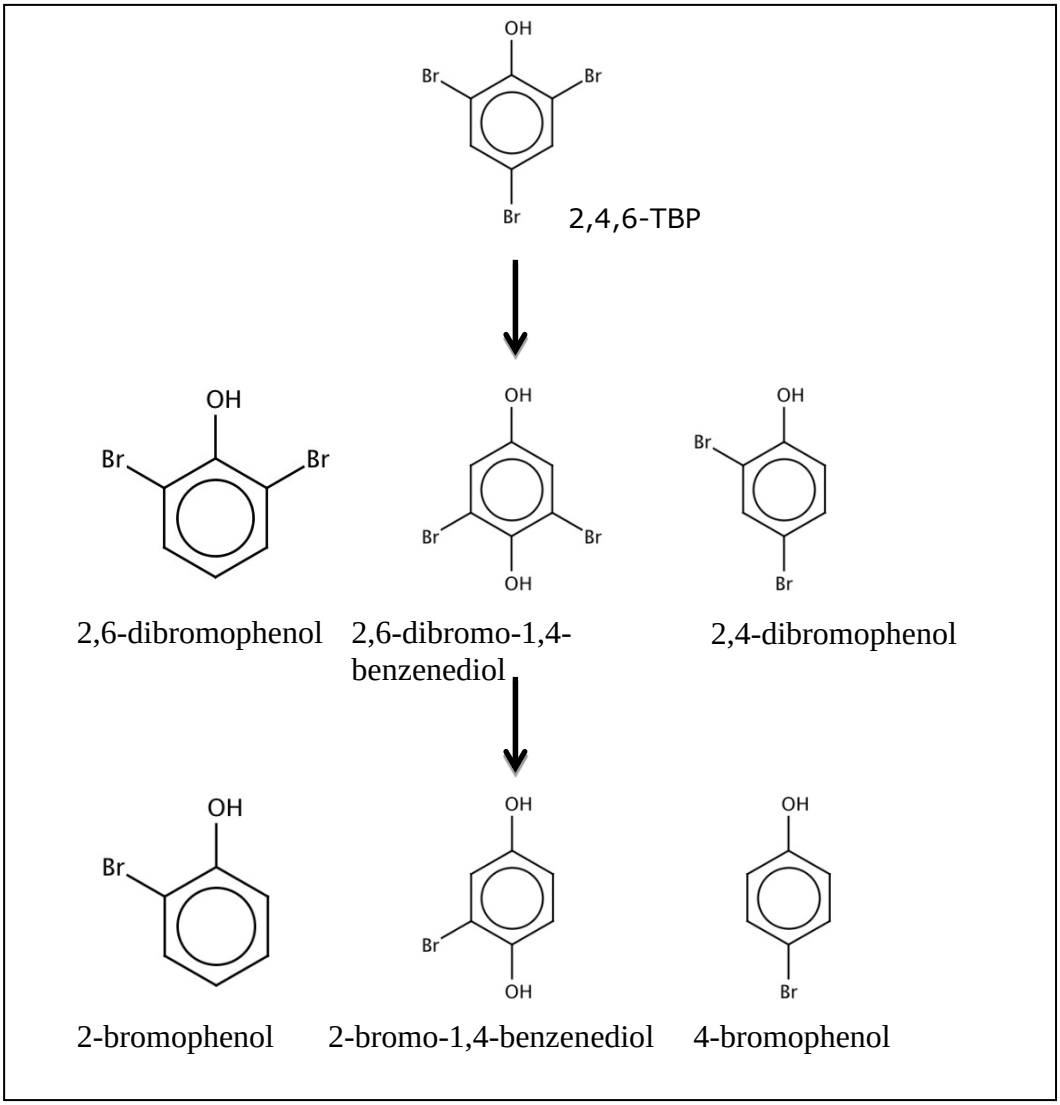
These half-lives have been confirmed by further studies found in open literature performed on aerobic soils amended with 0.5% sewage sludge (Nyholm et al. 2010). Half-lives in aerobic soils amended with activated and digested sludge (0.5%) were reported to be between 8 and 10 days and 7 days for anaerobic sewage amended soils. No transformation products were identified. This study was not performed to GLP or an accepted OECD standard.

7.7.1.3.3. Identity and composition of degradation products/metabolites for the PBT assessment

Predicted biodegradation pathway for 2,4,6-TBP

In the absence of information on the transformation products of 2,4,6-TBP the University of Minnesota Biocatalyst/Biodegradation database pathway prediction system was used to predict plausible pathways for the microbial degradation of chemical compounds (http:// http://umbbd.ethz.ch/predict/). 2,6-Dibromo-1,4-benzenediol was identified as a possible transformation product under aerobic conditions based upon the oxidative degradation of halogenated phenols (Tomasi et al., 1995). 2,4-dibromophenol, 2,6-dibromophenol, 2,6-dibromo-1,4-benzenediol were proposed as transformation products under both aerobic and anaerobic conditions followed by subsequent debromination to bromophenol, see Figure 1.

Figure 1 Predicted biodegradation of 2,4,6-TBP



The P and B properties of the predicted biotransformation products were evaluated and are summarised in Table 6 where test data were unavailable BIOWIN was used. These data suggest that it is unlikely that the predicted biotransformation products are likely to persist in the environment.

Table 6 P and B properties of predicted biotransformation products

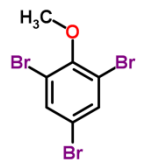
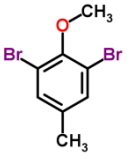
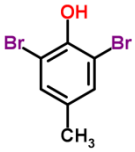
Transformation product	Log K_{OW}	Persistence[2]	Bioaccumualtion[2]
2,4-dibromophenol	3.48[1], 3.29[2]	Not P	Not B (BCF 62-75)
2,6-dibromophenol	2.37[1], 3.29[2]	Not P	Not B (BCF 77-91)
2,6-dibromo-1,4-benzenediol	2.81[2]	Not P	Not B (BCF 12)
2-bromophenol	2.35[1], 2.4[2]	Not P	Not B (BCF 17-22)
4-bromophenol	2.62[1], 2.4[2]	Not P	Not B (BCF 24-28)
2-bromo-1,4-benzenediol	1.92[2]	Not P	Not B (BCF 6)

[1] WHO, 2005; [2] BIOWIN vers 4.1 estimation.

In addition, methylated debromination of 2,4,6-TBP has been found to be a minor degradation pathway. This has been shown to occur in the presence of specific bacterial strains (e.g. *Bacillus sp.* GZT) resulting in the formation of 1,3-dibromo-2-methoxy-5-methylbenzene and 2,6-dibromo-4-methylphenol (Zu et al., 2012). Bacterial strains capable of *O*-methylation are found in both freshwater and marine systems and can also form 2,4,6-tribromoanisole [CAS no: 607-99-8] (Allard et al., 1987). In a study with zebrafish fed a diet with 2,4,6-tribromophenol (in a mixture of several brominated flame retardants) for up to 42 d, 2,4,6-tribromoanisole was detected as a probable metabolite of tribromophenol in the fish (Nyholm et al., 2009).

2,4,6-tribromoanisole has been shown to occur in food and drink as a fungal metabolite and affects taste and odour (Whitfield et al., 1997). 2,4,6-tribromoanisole has a very low odour threshold and has been reported to occur in cases of mustiness in packaged foods. Tribromoanisole has been reported by Agus et al., 2011, to occur in wastewater effluent (up to 6.6 ng/L), in river and marine sediments (0.7 ng/kg in 2 out of 12 sites) (Watanabe et al., 1985) and in fish tissue and shellfish samples (Watanabe et al. 1983).

Table 7 Predicted P and B properties of potential methylated transformation products

Structure			
Name:	2,4,6-tribromoanisole	1,3-dibromo-2-methoxy-5-methylbenzene	2,6-dibromo-4-methylphenol
SMILES:	COc1c(Br)cc(Br)cc1Br	Brc1cc(cc(Br)c1OC)C	Brc1cc(cc(Br)c1O)C
CAS:	607-99-8	51699-89-9	2432-14-8
Log K_{OW}	4.48	4.40¤	3.84¤
Predicted P	Not readily biodegradable	Not readily biodegradable	Not readily biodegradable
Predicted B	BCF# 420 BCF* 2047	BCF# 372 BCF* 1622	BCF# 159 BCF* 109
PB	**# No *Borderline**	**# No *No**	**# No *No**

#Regression based BCF, *Arnot-Gobas method, ¤KOWWIN v.167 estimate, ¤¤KOWWIN v.168 estimate

There are no data available on the ECHA dissemination website on the potential transformation products of 2,4,6-TBP by *O*-methylation and hence no information on potential P or B properties for possible methylated transformation products.

2,4,6-tribromoanisole has been identified as a probable metabolite in a fish study and has been detected in the environment. Persistency data have been predicted by BIOWIN v 4.1, see Table 7. The Biowin data suggest that all three metabolites are not ready biodegradable.

The predicted P properties of 2,4,6-tribromoanisole using BIOWIN v 4.1 suggest that it does not biodegrade fast and therefore meets the screening criterion for P.

7.7.1.4. Summary and discussion on degradation

2,4,6-TBP was shown to be hydrolytically stable. The photolytic half-life in air is 4.6 hours. The first-order kinetic photolytic half-life in water was <1 hour. This is not expected to be a significant route of degradation, since the brominated phenols partition predominantly to soil/sediment, where UV levels are likely to be low (WHO, 2005).

Overall, there is a lack of data generated from reliable biodegradation studies in the aquatic compartment. None of the studies are performed according to recognised guidelines or to GLP. In the aerobic biodegradation studies no significant biodegradation have been reported and results from the Japanese MITI test suggest that 2,4,6-TBP is

not readily biodegradable. These studies therefore support a weight of evidence conclusion that 2,4,6-TBP is not readily biodegradable. Estimated data generated by BIOWIN (version 4.1) predicts that 2,4,6-TBP does not biodegrade rapidly. A thorough review of all available information suggests that the substance is not readily biodegradable in water and meets the screening criterion for P.

However, rapid de-halogenation has been shown to occur in anaerobic sediments in polluted environments or in anaerobic sediments where a background concentration was related to halophenol-producing marine hemichordates. Further 2,4,6-TBP was rapidly biodegraded in soils under aerobic conditions with a arithmetic mean half-life of 7 days at 20ºC (3 soils).

Modelling suggests the products of degradation to be 2,6-dibromo-1,4-benzenediol, 2,4-dibromophenol, 2,6-dibromophenol and bromophenol, with 2,4-dibromophenol confirmed in laboratory studies. None of these biotransformation products are likely to persist based on BIOWIN estimations.

However, it has been shown that certain commonly found anaerobic bacteria in both marine and freshwater systems can transform 2,4,6-TBP to 2,4,6-tribromoanisole via *O*-methylation. 2,4,6-tribromoanisole has also been identified as a probable metabolite of 2,4,6-TBP in fish and has been detected in the environment in a number of monitoring studies. The predicted P properties of the transformation product 2,4,6-tribromoanisole using BIOWIN v 4.1 suggest that it does not biodegrade fast and therefore meets the screening criterion for P.

In conclusion, 2,4,6-TBP or a transformation product meet the screening P criteria. A study on aerobic and anaerobic transformation in aquatic sediment systems (OECD 308) with identification of transformation or degradation products in individual amounts above 0.1% would clarify the concern.

7.7.2. Environmental distribution

7.7.2.1. Adsorption/desorption

ECHA dissemination website report an Adsorption - Desorption value using a Batch Equilibrium Method study (OECD 106) performed to GLP. The results showed that 2,4,6-TBP strongly bind to soils with a pH range of 4.6-5.8 at 20ºC. Using Freundlich isotherms a geometric mean of three soils gave an adsorption coefficient of 2253 ml/g (1020 to 3022 ml/g) and a desorption coefficient of 4119 ml/g (3334-5686 ml/g). The mean Koc and Kom were determined to be 2253 ml/g and 1307 ml/g respectively. A Koc of 2253 and log Kow of 3.7 indicates that once 2,4,6-TBP is released into the water / sediment system it will preferentially partition to sediment and that the substance is only slightly mobile in soil and sediment.

7.7.2.2. Volatilisation

No information on the ECHA dissemination website.

Data from open literature:

Volatilisation of non-dissociated 2,4,6-TBP from water surfaces is not expected to be an important fate process based on an estimated Henry's law constants of between 3.6×10^{-3} and 8.4×10^{-4} Pa m^3/mol (Lyman et al. 1990; Meyland and Howard 1991). The vapour pressure of 2,4,6-TBP is 0.063 Pa indicating low volatilisation.

7.7.2.3. Distribution modelling

No information on the ECHA dissemination website.

7.7.2.4. Summary and discussion of environmental distribution

2,4,6-TBP is strongly absorbed to soil particles with an arithmetic mean absorption coefficient normalised to organic carbon of K_{OC} 2253 g/ml. The mean absorption coefficient normalised to organic matter K_{OM} was determined to be 1307 ml/g. A Koc of 2253 and log Kow of 3.7 indicates that once 2,4,6-TBP is released into the water / sediment system it will preferentially partition to sediment and that the substance is only slightly mobile in soil and sediment. Volatilisation of non-dissociated 2,4,6-TBP from water surfaces is not expected to be an important fate process based on an estimated Henry's law constants of between 3.6×10^{-3} and 8.4×10^{-4} Pa m^3/mol.

7.7.3. Bioaccumulation

7.7.3.1. Estimated data

According to EPISuite, the bioconcentration factor (BCF) was calculated using BCFBAF v3.01 to be 122. This indicates that 2,4,6-TBP has a low potential for bioaccumulation in aquatic organisms.

7.7.3.2. Screening data

An octanol water partition coefficient test is available which resulted in a log K_{ow} of 3.7 which indicates that 2,4,6-TBP may have a low potential to bioconcentrate in the lipids of aquatic organisms e.g. fish. However, assumptions from octanol water partition coefficient tests should be viewed with caution as they are often not representative of other processes that occur associated with bioconcentration. These include adsorption, distribution, metabolism and excretion (ADME).

ECHA dissemination website contain the following bioaccumulation studies on 2,4,6-TBP: 1) a BCF of 20 (edible fraction) and 140 (visceral fraction) in a study in blue gill sunfish (non-guideline, 1978); 2) a BCF of 83 in fathead minnow described as not assignable (non-guideline, 1980); 3) a BCF of 513 in a study in zebra fish described as not assignable (non-guideline, 1996); 4) a research study focussing on determination of 2,4,6-TBP in different ocean fish (non –guideline, 1995).

The fish bioconcentration test in blue gill sunfish (*Lepomis macrochirus*) indicate that 2,4,6-TBP does not bioconcentrate significantly (study referred as Stoner Laboratories, 1978 in WHO, 2005.) . The edible and visceral fractions were analysed using radiolabelled 2,4,6-TBP. No data were given regarding weights of the fish or the methods used for calculation of bioaccumulation other than concentration in water compared with concentration in fish. The BCF was reported as 20 (edible) and 140 (visceral). Steady state was achieved within 3 days and elimination (>90%) within 7 days. A BCF of 83 was reported in a study in fathead minnow (Spehar, 1980). The most conservative BCF reported is 513 measured in zebra fish (Butte et al., 1987, considered and re-evaluated by Devillers et al., 1996). These data are also reported in the review of the WHO report (2005) .

In addition, in a study with zebrafish fed a diet with 2,4,6-tribromophenol (in a mixture of several brominated flame retardants) for up to 42 d a half life of less than 2 days was measured for 2,4,6-tribromophenol. 2,4,6-TBP appeared to be both biotransformed and rapidly eliminated (Nyholm et al. 2009)

Considering all available data the weight of evidence indicate that 2,4,6-TBP has a low potential for bioconcentration in aquatic organisms.

7.7.3.3. Evaluation of metabolites

The P and B properties of the biotransformation products predicted with BIOWIN were evaluated and summarised in Table 6. These data suggest that the predicted biotransformation products are not likely to bioaccumulate.

As described in section 7.7.1.3.3 it has also been shown that certain commonly found anaerobic bacteria (e.g. *Bacillus* sp*.* GZT) in both marine and freshwater systems can transform 2,4,6-TBP to 2,4,6-tribromoanisole via *O*-methylation (Allard, 1987). 2,4,6-tribromoanisole has also been identified as a probable metabolite of 2,4,6-tribromophenol in a fish study (Nyholm et al. 2009) and has been detected in the environment.

Prediction of the B properties for 2,4,6-tribromoanisole, Table 7, based on the estimated log Kow of 4.48 and estimated BCF of 2047 using BCFBAF v3.01 (Arnot and Gobas method) suggests that the compound may meet the B criteria. Data generated from EPI Suite (BCFBAF v3.01) include B predictions based on regression based method and Arnot-Gobas method. The two potential metabolites via *O*-methylation; 2,4,6-tribromoanisole and 1,3-dibromo-2-methoxy-5-methylbenzene have a higher BCF predicted with the Arnot-Gobas method than the regression based BCF due to the methylation which according to the model will predict that they are not biotransformed (Jon Arnot, pers. comm.). In addition, both substances have a slightly higher log K_{ow} than 2,4,6-TBP and this will also cause an elevated BCF with the Arnot-Gobas method.

In a study by Veith et al. (1979) 2,4,6-tribromoanisole (and 29 other chemicals) were tested for bioconcentration with the fathead minnow in 32 d exposure. 30 fish were transferred to a test tank and samples of five fish were removed after 2, 4, 8, 16, 24 and 32 d of exposure, frozen, and analysed for for residues. The first five samples were analysed as a composite, but the 32 d samples were generally analysed individually to determine mean and standard deviation. The concentration of the test chemical in the tank was measured each weekday, the mean measured exposure (C_w) was 4.8 µg/L. A BCF of 865 was obtained for 2,4,6-tribromoanisole in this study.

In the study by Nyholm et al. (2009) with zebrafish fed a diet with 2,4,6-tribromophenol, 2,4,6-tribromoanisole was detected as a probable metabolite in the fish. The levels of 2,4,6-tribromoanisole increased during the exposure period but appeared to be rapidly eliminated by the zebrafish after the exposure period. The cumulative exposure of 2,4,6-tribromoanisole from the feed accounted for only 2.5% of the measured amount in the fish exposed for 42 d.

The measured BCF of 865 and the evidence that 2,4,6-tribromoanisole is rapidly eliminated from the organism do not suggest that 2,4,6-tribromoanisole meets the B criteria.

7.7.3.4. Terrestrial bioaccumulation

No data are available from the ECHA dissemination website. The results of the fish tests indicate that 2,4,6-TBP will not bioaccumulate in the aquatic compartment. The mean Koc is determined to be 2253 ml/g. A Koc of 2253 and log Kow of 3.7 indicates that once 2,4,6-TBP is released into the water / sediment system it will preferably partition to sediment and that the substance is only slightly mobile in soil and sediment.

The QSAR estimated log Koa (octanol-air partition coefficient) is 9.97 indicating that biomagnification in terrestrial food chain might occur. Due to the strong binding potential of 2,4,6-tribromophenol to soil and sediment particles (K_{OC} 2253), more information

would be needed to assess whether the B criterion may be fulfilled based on the potential for bioaccumulation in terrestrial organisms.

7.7.3.5. Summary and discussion of bioaccumulation

The weight of evidence considering all data indicate that 2,4,6-TBP has a low potential for bioconcentration in aquatic organisms.

Considering the metabolites modelling predicts that the biotransformation products are not likely to bioaccumulate, except for metabolites predicted to occur via *O*-methylation. Of the potential metabolites 2,4,6-tribromoanisole has also been identified as a probable metabolite in a fish study and has been detected in the environment in a number of monitoring studies. The measured BCF of 865 for 2,4,6-tribromoanisole and the evidence that the substance is rapidly eliminated from the organism do not suggest that 2,4,6-tribromoanisole meets the B criteria.

A Koc of 2253 and log Kow of 3.7 indicates that once 2,4,6-TBP is released into the water / sediment system it will preferably partition to sediment and that the substance is only slightly mobile in soil and sediment. Moreover, an estimated log Koa of 9.97 indicate that biomagnification in terrestrial food chain might occur. More information would be needed to conclude whether the B criterion may be fulfilled based on the potential for bioaccumulation in terrestrial organisms. A test on bioaccumulation in Terrestrial Oligochaetes OECD (317) would clarify the concern.

7.8. Environmental hazard assessment

7.8.1. Aquatic compartment (including sediment)

The majority of the data presented is extracted from the ECHA dissemination website. In addition, the WHO report (2005) which includes toxicity data for other brominated phenols plus 2,4,6-TBP has been used.

7.8.1.1. Fish

7.8.1.1.1. Short-term toxicity to fish

The key study reported on is a fish acute toxicity test using carp (*Cyprinus carpio*) performed according to GLP and OECD 203, assigned with a reliability factor of 1. Two tests were performed with carp exposed to concentrations ranging from 0.1 to 3.2 mg/l in a static system at 20.4-20.8 ^{O}C and a pH of 7.2- 8.2. Stock solutions were prepared in acetone and a solvent control was included. Seven carp were exposed per concentration and a control. During the first EC50, test aeration was introduced after 24 hours of exposure, while the second study was performed without aeration. Samples for analysis were taken at the start and at the end of the test. In the second test additional samples were taken after 48 hours of exposure. Analytical chemistry performed on the test solutions which indicate that the concentrations were not within ±20 % of the nominal concentration and therefore, the lethal effect concentration should be reported on measured concentrations. The LC50 is at a nominal concentration of 1.1 mg/L but if the measured concentrations are applied this would equate to approx. 0.8 mg/L.

A supporting study (reliability factor of 2) was performed using fathead minnow (*Pimephales promelas*) exposed to flow through conditions. The 96 hour LC50 was calculated to be 6.25 mg/L however there was no chemical analysis performed on the test substance and therefore the concentrations are only reported as nominal. Therefore, the actual concentration may have been significantly less than the nominal values, based on the results in the study using carp above, and because no solubilising agent was used.

An additional study performed which assessed behavioural reactions and mortality in rainbow trout (*Oncorhynychus mykiss*). No chemical analysis was performed and no international guidelines or GLP were recorded. However the tests appear to have been performed well and may also be considered. An appropriate solvent control was used to aid solubilisation. There were mortalities recorded after 96 hours at the second lowest concentration (0.21 mg/L) and above and an approximate LC50 at a nominal concentration of 0.24 mg/L. In a similar study, 2,4,6-TBP was exposed to blue gill sunfish for 96 hours and mortalities were recorded at 0.24 mg/L (10%) and above (LC90 at 0.32 mg/L), approximate 96 hour LC50 between 0.24 mg/L and 0.32 mg/L.

In a further study fathead minnow *(Pimephales promelas)* was used as the test species. Limited detail is available on this study and the 96 hour LC50 was reported as >6.5 and <6.8 mg/L, however, the 2,4,6-TBP was "solubilized with sodium hydroxide to make the stock chemical solution" which may have affected the toxicity of the 2,4,6-TBP as the toxicity of some phenolics may be decreased as pH increases.

According to WHO (2005), 96 hour LC50s for 2,4,6-TBP in fish range from 0.2 to 6.8 mg/L.

The key study is acceptable for the substance evaluation as regards short term toxicity to fish.

7.8.1.1.2. Long-term toxicity to fish

No data are presented on the ECHA dissemination website regarding long-term toxicity to fish.

Long-term toxicity data for three trophic levels is important in order to perform a sound risk assessment. Publicly available literature suggest that 2,4,6-TBP has a potential for causing endocrine disruption, transgenerational effects and early life-stage toxicity in fish at low concentrations. More data on long-term toxicity to fish would be needed to clarify the concern, see section 7.10.

7.8.1.2. Aquatic invertebrates

7.8.1.2.1. Short-term toxicity to aquatic invertebrates

The key study referred on the ECHA dissemination website is performed according to OECD 202 (acute *Daphnia magna* toxicity test) and according to GLP. After a range-finding test, a final test was performed with Daphnia exposed for a maximum of 48 hours to concentrations ranging from 0.10 to 10 mg/l in a static system. Stock solutions were prepared in acetone and a solvent control was included. The test was performed in duplicate with 10 daphnia per vessel. Samples for analysis were taken at 0.10, 1.0 and 10 mg/l at the start and at the end of the test. Analysis of the samples taken during the final test showed that the average measured concentrations were in agreement with nominal (115, 113 and 96 %, respectively). The study has a reliability factor of 1 and analytical chemistry performed during the study indicate that measured concentrations were within nominal concentrations. Acute toxicity (EC50), calculated after 48 hours exposure, was recorded as 0.26 mg/L and the NOEC was 0.1 mg/L.

In addition supporting studies using *D. magna* were performed but not according to international guidelines or GLP. Based on the quality of the data a reliability factor of 3 should be considered. The toxicity tests were performed over a 4 -day exposure period with daphnids ca. 12 hours old. The reported LC50 for 2,4,6-TBP was determined to be 1.31 mg/L. Further supporting study was performed using *D. magna* under flow through conditions. The study was not performed according to GLP or international test guidelines, no analytical chemistry done and the results are based on median tolerance limits. Test results indicate that the 48 hour LC1, LC50 and LC99 were 1.2, 5.5 and 24.6 mg/L, respectively.

In the WHO report. (2005) 48 hour LC/EC50s of 2,4,6-TBP in daphnids ranged from 0.3 to 5.5 mg/L for 2,4,6-TBP, however, there is limited details regarding some of these studies in the literature.

The key study is acceptable for the substance evaluation as regards short-term toxicity to aquatic invertebrates.

7.8.1.2.2. Long-term toxicity to aquatic invertebrates

The key study reported on the ECHA dissemination website was performed according to OECD 211 (*D. magna* reproduction test) and GLP .The experimental set-up included 10 vessels per test concentration and 20 vessels for the control groups (blank-control and treatment-control), each containing one neonate (<24h old) Daphnia magna in 50 ml test medium. The nominal concentrations of tribromophenol tested were 0.012, 0.025, 0.050, 0.1 and 0.15 mg/l. The study duration was 21 days and the test solutions were renewed three times a week. The daphnids were fed on a daily basis. At the start of the test and every workday, the condition of the parental daphids was recorded and during the reproductive phase the number of living offspring, immobile young and appearance of unhatched (aborted) eggs were recorded. At the end of the test, the lengths of the surviving parental daphnids were measured. Mortality of the parental daphnids in the controls did not exceed 20% at the end of the test. The mean number of living offspring per control parent at the end of the test was >/= 60. No significant mortality of parents was observed at 0,012 and 0,025 mg/L, while parents died increasingly with increasing concentrations at concentrations of 0,050 mg/l and higher, resulting in 80% mortality at 0,15 mg/l. Hence, the mortality of parental daphnids was clearly treatment related. No statistically significant effects on reproductive capacity or body lengths of the parental daphnids were observed (Tukey test p=0.05). The lowest derived 21 -day NOEC value was 0.025 mg/L (survival), and the lowest 21 -day LOEC value was 0.05 mg/L (survival).

In the WHO report (2005) 21-day chronic NOECs for daphnid reproduction were reported at 0.1 mg/L for 2,4,6-TBP, however these data are from unpublished literature.

The key study is acceptable for the substance evaluation as regards long-term toxicity to aquatic invertebrates.

7.8.1.3. Algae and aquatic plants

The key study reported on the ECHA dissemination website has been performed according to OECD 201 (algal toxicity test) and GLP, it is assigned a reliability factor of 1. Analytical chemistry was also performed and indicated that the measured concentrations were within nominal concentrations. The test concentrations ranged from 0.10 to 2.2 mg/L. The EC50 and EC10 (72h) for cell growth inhibition was 0.40 mg/L and 0.14 mg/L, respectively. The EC50 and EC10 (72h) for growth rate reduction was 0.87 and 0.26 mg/L, respectively. The NOEC for algal growth was 0.10 mg/L and based on the most sensitive endpoint the EC50 for 2,4,6-TBP exposed to the freshwater alga was 0.40 mg/L.

In the WHO report (2005) several algal studies are indicated with 72 hour EC50s for 2,4,6-TBP ranging from 0.4 to 1.6 mg/L, however the data are limited or from unpublished literature.

The key study is acceptable for the substance evaluation as regards toxicity to algae and aquatic plants.

7.8.1.4. Sediment organisms

No data available on the ECHA dissemination website for toxicity to sediment organisms.

The environmental distribution modelling indicates that when 2,4,6-TBP is released into the water / sediment system it will preferentially partition to sediment. Toxicity testing to sediment organisms would clarify any concern.

7.8.1.5. Other aquatic organisms

No data available.

7.8.2. Terrestrial compartment

7.8.2.1. Toxicity to soil macro organisms

The acute toxicity of 2,4,6-TBP to the annelid worm *Eisenia foetida* was determined after 14 days of exposure in artificial soil. The test was performed according to OECD test guideline 207 (earthworm acute toxicity test) and according to GLP. The concentrations tested ranged from 100 -1000 mg/kg dry mass of artifical soil, dry soil d.s. (nominal concentrations). Acutely toxic effects were recorded at concentrations of 180 mg/kg d.s. 2,4,6-TBP, a 14 day EC50 was calculated as 201 mg/kg d.s. and a NOEC of 100 mg/kg d.s. was reported.

The study is acceptable for the substance evaluation as regards toxicity to soil macro-organisms.

7.8.2.2. Toxicity to terrestrial plants

No data available.

7.8.2.3. Toxicity to soil micro-organisms

A toxicity study has been reported on the ECHA dissemination website where microorganisms seeded from sewage and soil supernatant were exposed to different concentrations of 2,4,6-TBP for a period of 96 hours with the endpoint of oxygen consumption as an indicator of microbial respiratory inhibition. The study was not performed according to any technical guidance however it was performed according to good scientific principles and resulted in toxicity being observed in concentrations above 100 mg/L.

An additional study performed with *Tetrahymena pyriformis* indicated a 60-h inhibition of growth affecting 50% of the population (IGC50) at a concentration of 2.95 mg/L 2,4,6-TBP in cultures under static conditions . The test does not appear to have been conducted in soil or to any recognised test guidelines and hence the relevance may be questionable.

The information is acceptable for the substance evaluation as regards toxicity to soil micro-organisms.

7.8.2.4. Toxicity to other terrestrial organisms

Acute toxicity of 2,4,6-TBP has been assessed using a contact and oral exposure test to the honey bee (Apis mellifera) reported on the ECHA dissemination website. The tests were performed according to OECD TG 213 and 214 (Honeybees: acute oral toxicity test and Honeybees acute contact toxicity test) and according to GLP. The results indicated that there were no differences in mortalities in both endpoints when compared with the controls and the LD50s for 2,4,6-TBP were >100 µg/bee. The NOEC for both endpoints were reported at the highest tested dosage (100 µg/bee).

7.8.3. Microbiological activity in sewage treatment systems

7.8.3.1. Toxicity to aquatic micro-organisms

A test is reported on the ECHA dissemination website that was performed according to OECD Guideline 209 (Activated Sludge, Respiration Inhibition Test). Activated sludge was exposed to a range of concentrations of 2,4,6-TBP (10, 31, 100, 313 and 1000 mg/L). The test duration was 3 hours and the tests were performed according to GLP. The results of the test indicated a 3 hour EC50 of 173.15 mg/L and a NOEC value of 10 mg/L.

The study is acceptable for the substance evaluation as regards toxicity to aquatic micro-organisms.

7.8.4. Non compartment specific effects relevant for the food chain (secondary poisoning)

7.8.4.1. Toxicity to birds

A study is reported on the ECHA dissemination website where bobwhite quail (*Colinus virginianus*) was exposed to 2,4,6-TBP according to EPA OPP 71-1 (Avian Acute Oral Toxicity Test) and GLP. The oral LD50 values in the sexes combined or separate were established as exceeding 2000 mg/kg body weight (nominal). The no observed effect level (NOEL) in this study was 19 mg/kg body weight for both sexes, based on clinical signs (hunched and abnormal posture, abnormal gait and quick breathing) observed at 61 mg/kg body weight. However, these effects were reversed after 3 days in all concentrations up to 2000 mg/kg except the females in the 61 mg/kg and therefore was not considered as causing an adverse effect.

The relevance of these findings could be reassessed if more information on neurotoxicity becomes available.

7.8.4.2. Toxicity to mammals

Available data on repeated dose and reproductive toxicity to mammals are insufficient in order to establish a robust NOAEL, see section 7.9.10.

2,4,6-tribromophenol has been self-classified by one notifier with reproductive toxicity Cat. 2 and Specific Target Organ Toxicity Repeated Exposure (STOT RE 2).

7.8.5. PNEC derivation and other hazard conclusions

Table 8 PNEC derivation and other hazard conclusions

Hazard assessment conclusion for the environment compartment	Hazard conclusion	Remarks/Justification
Freshwater	NOEC value 25µg/l PNEC: 0.25 µg/L	Assessment factor: 100* The lowest long-term NOEC value available 25µg/l (*D. magna*), 2 available long-term studies for different trophic levels, an assessment factor (50) taken from Table R.10-4 of the ECHA guidance documents, and applying an additional assessment factor to account for

		the lack of data from a long term fish test in particular due to the potential endocrine disruptive properties.
Marine water	NOEC value 25µg/l PNEC: 0.025 µg/L	Assessment factor: 1000
Intermittent releases to water	Not evaluated	
Sediments (freshwater)	Data lacking	
Sediments (marine water)	Data lacking	
Sewage treatment plant	NOEC 10mg/L PNEC: 1 mg/L	Assessment factor: 10 PNECstp based upon the NOEC for respiratory inhibition of sewage microorganisms (10mg/l) and the appropriate assessment factor (10) taken from Table R.10.6 of the ECHA guidance document.
Soil	NOEC 100 mg/kg soil dw PNEC: 100 µg/kg soil dw	Assessment factor: 1000 PNECsoil based upon earthworms (*Eisenia foetida*) acute toxicity test: 14 day NOEC 100 mg/kg dry soil and the appropriate assessment factor (1000) for short-term toxicity tests taken from Table R.10-10 of the ECHA Guidance document.
Air	Not evaluated	
Secondary poisoning	Data lacking	See section 7.8.4

*Publicly available literature suggests that 2,4,6-TBP has a potential for causing endocrine disruption, transgenerational effects and early life-stage toxicity in fish at low concentrations, detailed in section 7.8.1.1.2. Taking these data into consideration the application of an assessment factor of 100 for freshwater and 1000 for marine water seems more appropriate to account for the additional uncertainties and seriousness of the potential effects. Consequently the PNEC for freshwater is 0.25 µg/L, with an assessment factor of 100 being applied. The choice of assessment factor is according to table R.10-4 of the ECHA guidance documents with an additional assessment factor applied to account for the lack of data from a long term fish test in particular due to the potential endocrine disruptive properties.

7.8.6. Conclusions for classification and labelling

According to the data available for the environmental hazard assessment (ECHA dissemination website and other sources of literature), i.e. the substance fails the criterion for ready biodegradability and the lowest aquatic chronic NOEC is 0.025 mg/L, the eMSCA concludes that 2,4,6-tribromophenol is to be classified as Aquatic Acute 1 H 400 "Very toxic to Aquatic Life" and Aquatic Chronic 1, H 410; "Very toxic to aquatic life with long lasting effects", according to the CLP regulation (EC No. 1272/2008).

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

Based on the rat studies reported in the ECHA dissemination website 2,4,6-TBP was rapidly absorbed from the gastro-intestinal tract and was rapidly excreted via urine and faeces. About 0.01% of the administered dose was retained in tissues after 48 h; in the kidneys (27 µg/kg), liver (6 µg/kg), and lungs (14 µg/kg). The half-life of 2,4,6-TBP in body tissues, including fat and brain, was calculated to range between 1.5 and 2.3 h. The rate constant for elimination was 0.3, and the half-life in blood was 2.03 h, indicating effective urine excretion (50-91% within 48 h).

There are no studies directly addressing metabolic products of 2,4,6-TBP, and there are no non-human toxicokinetic data available by dermal or inhalation exposure route. The pharmacokinetics appeared to follow a one-compartment model, and altogether the data indicate lack of bioaccumulation.

This endpoint is not targeted and no further evaluation has been performed by the eMSCA.

7.9.2. Acute toxicity and Corrosion/Irritation

Based on the studies reported on the ECHA dissemination website, acute toxicity by each exposure route was concluded as follows: The lowest reported acute oral LD50 value in rats for this substance is 1486 mg/kg bw, the acute inhalation LC50 in rats for this substance is considered to be greater than 50 000 mg/m^3, the dermal LD50 in rats is considered to be greater than 2000 mg/kg bw, and the acute dermal LD50 in rabbits is considered to be greater than 8000 mg/kg bw. In the view of the eMSCA, 2,4,6-TBP appears to have a low acute toxicity by all exposure routes. This endpoint is not targeted and no further evaluation has been performed by the eMSCA.

2,4,6-TBP was tested for irritation and corrosion in several studies in rabbits. The conclusion of the eMSCA is that 2,4,6-TBP is irritating to the eye, and not irritating to the skin.

This endpoint is not targeted and no further evaluation has been performed by the eMSCA.

7.9.3. Sensitisation

Based on a study reported on the ECHA dissemination website 2,4,6-TBP is considered to be a strong sensitizer to guinea pig skin (OECD 406, 1996). 2,4,6-TBP is self-classified as a skin sensitiser according to the ECHA C&L inventory: Skin Sens. 1H317: May cause an allergic skin reaction.

This endpoint is not targeted and no further evaluation has been performed by the eMSCA.

7.9.4. Repeated dose toxicity

The following studies are reported on the ECHA dissemination website:

- *A 28-day oral toxicity study (OECD 407, 2002).* Rats (5 per sex per dose) received doses of 50, 150 or 1000 mg/kg bw 2,4,6-TBP by oral gavage. Local toxicity in the form of squamous hyperplasia of the limiting ridge of the forestomach was observed at a dose

of 50 mg/kg bw/day and above. Thus, a local LOAEL of 50 mg/kg bw/day is indicated. The NOAEL for systemic toxicity for 2,4,6-TBP was considered to be 150 mg/kg bw/day as the liver effects observed at 150 mg/kg bw/day (increased serum albumin in females and centrilobular hepatocellular hypertrophy) were considered adaptive and not adverse. Adverse effects in liver and kidney were observed at the high dose.

- *A combined repeated dose toxicity study (OECD 422, 1999) with the reproduction/developmental toxicity screening test.* Rats were administrated doses of 100, 300, and 1000 mg/kg bw/day (12 animal/dose/sex) by oral gavage. At the high dose, reduced body weight gain and signs of liver and kidney damage was reported. Salivation was observed in both sexes and significant increase in creatinine in blood was observed in males at 300 mg/kg bw per day. The NOAEL in this study is considered to be 100 mg/kg bw/day for both sexes.

- *A sub-acute inhalation toxicity study of dust of 2,4,6-TBP (1977).* The study was conducted on three groups of 10 rats exposed to 0, 0.1 and 0.92 mg 2,4,6-TBP/L (0, 100 and 920 mg/m3) for 6 h per day, 5 days per week, for 3 weeks. This is an old study and it does not meet current standards for testing protocols. The actual experimental conditions in this inhalation study are poorly described and therefore, the study has a low reliability; i.e. there is no information on the size of the particles generated, and only nominal concentrations of the particles are provided. Therefore, a definitive NOAEC can not be set. Hypoactivity, salivation, lacrimation and red nasal discharge during testing was observed in the exposed groups. The females in the low dose group and both the males and females in high dose group exhibited reduced body weight gains. Gross and histopathological changes in the liver and kidneys were reported in the 0.92 mg/L groups.

- *A dermal sub-acute toxicity study (1977)*. Four groups of 4 rabbits (5 per sex per dose) at doses of 0, 100, 300 or 1000 mg/kg bw/day were dermally exposed for 28 days, 5 days/week. The systemic NOAEL was considered to be 1000 mg/kg bw/day based on the slight degree of irritation with no serious indicatives of toxic effects. The study is an old study and it does not meet the detail requirements for current guidelines, however, its experimental design and findings are reasonable and acceptable.

Conclusion:
No sub-chronic or chronic repeated dose toxicity studies are reported on the ECHA dissemination website. A sub-acute inhalation toxicity study is of low quality and reliability. Reduced body weight gain, liver and kidney damage were reported in the available inhalation and oral exposure studies at the high doses. Furtheremore, hyperplasia of forestomach was reported in the sub-acute study.

The widespread presence of 2,4,6-TBP especially in indoor air and in house dust indicates that exposure via the inhalation route is relevant for the general population, see section 7.12.1. Additionally, several *in vitro* studies suggest that 2,4,6-TBP may have endocrine disrupting potential, see section 7.10.

Data from a sub-chronic toxicity (90-days repeated dose) study via the inhalation route, including measurements examining potential thyroid hormone disrupting effects, would clarify the concern for health hazard during long term exposure.

7.9.5. Mutagenicity

The following studies are reported on the ECHA dissemination website:
Three independent *in vitro* gene mutation studies in bacteria (OECD 471) were negative. Two *in vitro* chromosomal aberration tests (OECD 473) were positive with and without metabolic activation. Two *in vivo* micronucleus assays (OECD 474) up to maximum tolerance dose by i.p. injection were negative, and these *in vivo* studies are more

relevant to predicting potential hazard to humans. Under the conditions of these assays, no evidence of genotoxicity was observed.

This endpoint is not targeted and no further evaluation has been performed by the eMSCA.

7.9.6. Carcinogenicity

There is no data on carcinogenicity. There are no epidemiological data which suggests there may be a concern for carcinogenicity of 2,4,6-TBP, and the available genotoxicity data are negative. However, the 28-days repeated dose oral gavage study indicates that 2,4,6-TBP exposure induces squamous hyperplasia of the forestomach and adjacent area, and incidence and severity of the effects increase with treatment doses. This observation, together with the widespread presence of 2,4,6-TBP in indoor air and in house dust further stress the need for more data on long-term exposure to clarify the concern.

To clarify concern related to long-term repeated exposures data from a sub-chronic toxicity study, as described in section 7.9.4 would be useful.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

Reproductive toxicity was identified as an endpoint of concern in the initial CoRAP justification. The information available on reproductive toxicity on the ECHA dissemination website further strengthens the initial concern; however, the available information on reproductive toxicity is not adequate to support a robust risk assessment.

One combined repeated dose and reproductive toxicity screening test (OECD 422, 1999) and two developmental toxicity studies are available to inform on reproductive toxicity. The developmental studies are of low reliability for the purpose of risk assessment. One of the developmental studies is a range-finding study (Pilot teratology study, 1978) whereas the second developmental study is a non-guideline, inhalation study from 1998 (Lyubimov 1998) that is inadequately reported. Neither a study on prenatal developmental toxicity nor a two generation reprotoxicity study is available on the ECHA dissemination website.

In the combined repeated dose and reproduction/developmental toxicity screening test (OECD 422, 1999), gestational or early post-partum parameters (decreased neonatal viability and body weights on day 0 and 4 after birth in both sexes) were observed at 1000 mg/kg bw/day. No adverse effects were seen on reproductive parameters including estrous cycle, fertility, implantation index, or delivery index. The reproductive/developmental NOAEL was set at 300 mg/kg bw/day, while the parental systemic toxicity NOAEL was defined at 100 mg/kg bw/day.

In the rat developmental range-finding study from 1978 (Pilot teratology study, 1978), 2,4,6-TBP was administered by gavage at 0, 10, 30, 100, 300, 1,000 and 3,000 mg/kg/day from GD 6-15. Increased post-implantation losses and decreased number of viable foetuses were observed at 1000 mg/kg bw/day in the absence of observed behavioural effects in the dams and only a transient reduction in maternal body weight gain between GD6 and GD12. All dams in the 3000 mg/kg bw/day group died after one day of treatment. The indicative NOAELs for maternal and developmental toxicity were reported to be 1000 and 300 mg/kg bw/day, respectively.

In the second developmental study (Lyubimov 1998), which included behavioural examinations, no maternal deaths and no effects on maternal mean body weights were observed. A dose-dependent increase in embryo lethality (pre-implantation and post-

implantation losses) and decrease in foetal body weight at gestation day 21 was reported. Embryotoxicity and foetotoxicity were seen at dose levels that were reported not to be maternally toxic. In addition, behavioural effects were reported in the dams at the two highest exposures whereas a reduced grooming behaviour and reduced emotionality was reported in the pups (both males and females) in all treatment groups.

According to the ECHA dissemination website a maternal LOAEC of 1 mg/m^3 air and a NOEC of 0.03 mg/m^3 air is reported, based on decreased orientation reaction and a LOAEC of 0.3 mg/m^3 air (NOEC of < 0.03) based on delayed ear unfolding and lower incisor eruption and a reduced grooming behaviour. The study is fairly large (25 pregnant females per exposure group), but it is inadequately reported and only parts of the findings are represented in figures or tables, thus the study was been assigned a reliability score of 3. A major caveat of this study is that the actual doses and the form of the substance must be regarded as uncertain and that reported levels of early pup mortality in controls was high.

Despite the clear shortcomings of the study by Lyubimov (1998), the study gives rise to concern that 2,4,6-TBP has neurotoxic and developmental neurotoxic properties in dams and in offspring, respectively. In support of possible neurodevelopmental toxicity are data suggesting effects of 2,4,6-TBP on hormone signalling (as described in section 7.10) and a study reporting toxicity and stimulation of cell differentiation in cultured SH-SY5Y human neuroblastoma cells at concentrations of 0.1 µM and above (Rios et al., 2003 as reported by WHO 2005).

Conclusion:
A OECD 422 screening study and two developmental studies of low reliability raise the concern that 2,4,6-TBP may be a reproductive toxicant. The OECD 422 study reports an increased neonatal mortality of pups exposed to a high dose of 2,4,6-TBP (1000 mg/kg bw/day) and this observation is supported by the developmental inhalation study (Lyubimov, 1998). Neither a definitive developmental toxicity study according to current guidelines nor a 2-generation study (or an extended one-generation reproductive toxicity study (EOGRTS, OECD 433)) has been performed.

The available information suggests a concern for developmental toxicity, but is not considered adequate to support a robust risk assessment nor a CHL proposal. In addition, several *in vitro* studies suggest that 2,4,6-TBP may have endocrine disrupting potential, see section 7.10. These observations, together with the widespread presence of 2,4,6-TBP in indoor air and in house dust further stress the need for more data on reprotoxicity to clarify this suspected concern. The main concern is related to peri-natal development and developmental neurotoxicity. An EOGRTS study in rats by oral route, including the basic Cohorts 1A/1B, and Cohorts 2A/2B for developmental neurotoxicity, is considered the most suitable study to clarify the concern for reproductive toxicity.

7.9.8. Hazard assessment of physico-chemical properties

Not applicable.

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

Indicative DNELs may be based on the sub-acute repeated oral and dermal dose studies and the combined repeated dose toxicity and reproductive toxicity screening (OECD 422, 1999). However, no definitive DNELs for long-term toxicity or reproductive toxicity can be derived based on the available data.

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

2,4,6-TBP is shown to cause serious eye irritation (hazard statement proposed by the former registrants: H319, hazard category Eye irritant 2) and is a skin sensitizer (hazard category Skin sensitizer 1, hazard statement H317; may cause an allergic skin reaction). The former registrants have classified it as Eye Irrit. 2 H319: Causes serious eye irritation and Skin Sens. 1 H317: May cause an allergic skin reaction. Other self classifications have been notified to C&L Inventory, cf. section 7.6.2.

The information on reproductive toxicity is insufficient. The available studies on developmental toxicity are of insufficient quality to support a robust human reproductive hazard assessment. However, the available data do suggest that there is a concern that 2,4,6-TBP may induce reproductive toxicity, in particular perinatal and neurodevelopmental toxicity.

In addition, other studies suggest that 2,4,6-TBP may have endocrine disrupting potential and possible neurotoxic effects, further stressing the need for more data on reproductive toxicity including developmental neurotoxicity. An extended one-generation reproductive toxicity study (EOGRTS, OECD 443) including at least the cohorts 2A and 2B for developmental neurotoxicity endpoints would provide data to clarify whether 2,4,6-TBP has adverse effects on fertility, development, the endocrine system and/or neurodevelopment.

The widespread presence of 2,4,6-TBP in indoor air and in house dust may indicate frequent and long-term human exposure. Data from a well-conducted sub-chronic toxicity (90-Day Repeated dose) study would be useful to clarify this concern.

The information on sub-chronic toxicity study (90 day) and on long-term repeated dose toxicity study (≥ 12 months) is insufficient. The 28-days repeated dose (oral) study on the ECHA dissemination website indicates that 2,4,6-TBP exposure induces liver and kidney damage at higher exposure doses as well as squamous hyperplasia of the forestomach and adjacent area, and incidence and severity of the effects increased with treatment doses. Whether the forestomach toxicity is related to local irritation or to another mode of action should be clarified due to its relevance for human risk assessment. Data from a well-conducted sub-chronic toxicity (90-Day Repeated dose study, preferably by the inhalation route) should adress both local and systemic toxicities. The inclusion of measurements examining potential thyroid hormone disrupting effects could clarify the concern for endocrine disrupting properties of 2,4,6-TBP.

7.10. Assessment of endocrine disrupting (ED) properties

There are no studies specifically addressing potential endocrine disruptive properties of 2,4,6-TBP on the ECHA dissemination website. The studies cited below are all from the open literature.

7.10.1. *In silico* and *in vitro* data

Prediction modelling (e.g. *in silico* or computational approaches) and/or *in vitro* studies suggest that 2,4,6-TBP may interact with various nuclear receptors and enzymes related to the function of the endocrine system.

Olsen et al. (2002) characterized the estrogen-like activity of brominated phenols, including 2,4,6-TBP using the estrogen-dependent human breast cancer cell line MCF-7. 2,4,6-TBP exhibited a relative binding affinity for the estrogen receptor (ER) of approximately 0.0004 compared with 17β-estradiol. 2,4,6-TBP was able to displace only 43% of radiolabelled estrogen when tested at concentrations up to 1 µM. Although 2,4,6-TBP displayed binding to the ER at high concentrations, this weak binding potency was

not of sufficient magnitude to elicit cellular responses associated with either ER agonistic or ER antagonistic responses in the MCF-7 cells.

Larsson et al. (2006) demonstrated that 2,4,6-TBP can interact with an active site of the human androgen receptor (AR) by a combination of computational ligand docking studies, insect cell-expressed AR binding assays and activation of the AR in transiently transfected human hepatocellular liver carcinoma (HEPG2) cells. The computational docking studies showed that 2,4,6-TBP could potentially dock to the active site, albeit were considered too small to fully interact with the whole active site of the AR to cause either AR agonistic or antagonistic activity. Ligand binding studies (<100 uM) and *in vitro* activation assays (1 uM) confirmed that 2,4,6-TBP were not binding, inhibiting or activating the human AR in these studies.

A suite of yeast reporter-gene assays was used to assess 2,4,6-TBP and other brominated phenols ability to interact with the human ER and AR (Ezechiaš et al., 2012). In this study, 2,4,6-TBP exhibited moderate anti-estrogenic (IC50=9-14µM) and anti-androgenic activities (IC50~4 µM) by binding to and inhibiting normal activity of these receptors.

Several *in vitro* studies have demonstrated that 2,4,6-TBP may affect enzymes in the steroid synthesis and/or metabolism pathways and potentially disrupt the normal activity of endogenous steroids. 2,4,6-TBP was shown to affect steroid metabolism (IC50=0.3µM) by inhibiting estradiol sulfotransferase that potentially may be involved in the increase in circulating levels of estradiol and prolongation of estrogenic stimulation (Hamers et al., 2006). 2,4,6-TBP also induced Cytochrome P450 (CYP19A) aromatase activity in the human adrenocortical carcinoma cell line H295 in the concentration range 0.5-7.5 µM (Canton et al., 2005). Induction of CYP19A aromatase is expected to stimulate the transformation of testosterone to estradiol and thus elevate circulating levels of estradiol and suppress production of testosterone. Increased activity of CYP19A aromatase may potentially lead to estrogenicity and anti-androgenicity in organisms reliant upon the two sex steroids for proper sexual development and reproduction.

2,4,6-Tribromophenol inhibited (IC50=4.8nM) binding of thyroxine (T4) to the human plasma transport protein transthyretin (TTR) at low nanomolar concentrations (Hamers et al., 2006). Meerts et al. 2000 confirm that 2,4,6-TBP binds to the human TTR with an high affinity (relative affinity of 1.2 compared to T4). Such chemical interactions with the TTR may be indicative of potential interference with natural transport of the main thyroid hormone (TH) to the thyroid gland. 2,4,6-Tribromophenol also inhibited (IC50=40uM) the production of the biologically active TH triiodothyronine (T3) from T4 in human liver microsomes (Butt et al., 2011). No agonistic or antagonistic activity of 2,4,6-TBP were detected at concentrations of 1 uM in the thyroid hormone (TH) receptor-mediated cellular activity of the T-screen to indicate direct interaction with the TH receptor (Hamers et al., 2006), however. In a recent study (Butt and Stapleton, 2013) using human liver cytosol, 2,4,6-TBP was reported to inhibit thyroid hormone sulfotransferase activity at nanomolar concentrations (IC_{50}=8.3 nM).

Although these studies suggest that 2,4,6-TBP may be endocrine active through multiple modes of action (MoA), assessment of the endocrine disrupting potential *in vivo* is dependent on whether adverse effects relevant to an endocrine disrupting MoA can be documented.

7.10.2. *In vivo* studies - Environment

A 2-generation study (Klimisch code 3) with zebrafish (Danio rerio), exposed from 2-120 days post fertilization (dpf, F0-generation) to 0.3 and 3.0 µg/L of 2,4,6-TBP (Deng et al., 2010), suggests that chronic 2,4,6-TBP exposure decreased the fecundity in females (LOEC=0.3 µg/L, NOEC<0.3 µg/L) and altered the male frequency in the F0-generation (LOEC=0.3 µg/L, NOEC<0.3 µg/L), and increased embryonic malformations (LOEC=0.3

µg/L, NOEC<0.3 µg/L), mortality (LOEC=0.3 µg/L, NOEC<0.3 µg/L) and reduced growth in the F1-generation (LOEC=0.3 µg/L, NOEC<0.3 µg/L). Several treatment-related effects of 2,4,6-TBP on indicators of endocrine modulation such as decrease in female plasma testosterone (T) and decrease in plasma estradiol (E2) concentrations (LOEC=3 µg/L, NOEC<0.3µg/L), potentially due to a reduction of ovarian testosterone synthesis by 3β-hydroxysteroid dehydrogenase (3β-HSD), 17β-hydroxysteroid dehydrogenase (17β-HSD) and cytochrome P450 17α-hydroxysteroid dehydrogenase (CYP17), as well as decrease in the conversion of T to E2 by CYP19A aromatase in the ovaries. A simultaneous reduction in the ER-mediated production of vitellogenin (Vtg) in the female liver suggest that changes in systemic estradiol concentrations may have also affected successful reproduction (e.g. effects on fecundity in females) through interference with vitellogenesis.

The study by Deng et al. (2010) suggest that the MoA of 2,4,6-TBP was gender-specific, as 2,4,6-TBP caused an increase in male plasma E2 and T (LOEC=3 µg/L, NOEC <0.3µg/L), potentially by stimulation of steroid synthesis (e.g. increase in 3β-HSD, 17β-HSD and CYP17) in combination with induction of CYP19A leading to an increase in T to E2 conversion in the testes. The increase in plasma T can potentially explain the masculinization observed as an increase in male frequency at 0.3 and 3.0 µg/L, whereas the rise in E2 may be associated with the observed stimulation of male Vtg synthesis at 3.0 µg/L in the F0 generation. An increase in male gonado-somatic index (GSI) at 0.3 µg/L and brain somatic index (3.0 µg/L) in males and females were also observed, although the value of these endpoints as indicators of endocrine disruption is doubtful. Increase in malformations, reduction of survival and retardation of growth in the F1 generation were observed after exposure to 0.3 and 3.0 µg/L 2,4,6-TBP, but although clearly affecting the fish adversely, may not be clearly linked to an endocrine MoA based on the current study results. However, as the effects were seen at relatively low concentrations, this may indicate specific interactions with developmental processes rather than an unspecific MoA. Lack of performance of the study according to validated (regulatory valid) protocols and use of a limited concentration range, two exposure concentrations and lack of effort to verify the exposure concentrations, limits the reliability and usefulness for regulatory purposes, however.

An oral exposure study of 2,4,6-TBP in adult zebrafish (Klimisch code 3), exposed for 6 weeks to 33, 330 and 3300 ug 2,4,6-TBP/g dry weight (dw) feed (Halden et al., 2010), provide additional support for suggestions of adverse effects in fish after exposure to 2,4,6-TBP. An increase in number of atretic follicles and number of oocytes with decreased vitellogenesis were suggested associated with an observed reduction in fertilization success of oocytes. Although these adverse effects were not clearly associated with an endocrine MoA, increase in female plasma concentrations of Vtg may indicate interference with ER-mediated endocrine processes either directly (i.e. ER agonistic action) or indirectly through modulation of circulating estrogen levels. No changes in male Vtg production were observed, but a treatment-related disturbance of gonad development was observed as reduction of number of spermatid cysts. Although a reduction of egg fertilization at the highest concentration (nominal feed concentration of 2,4,6-TBP: 3300 µg/g dw) were reported, no changes to fecundity or spawning success were observed to suggest that the F0-generation was clearly affected. No mechanistic studies were presented to positively identify an endocrine MoA for effects observed at the F0-generation.

7.10.3. *In vivo* studies - Human health

Studies in mammals: No studies specifically addressing endocrine disrupting effects were located.

7.10.4. Summary of ED environment

Results from *in silico*, *in vitro* and *in vivo* studies suggest that 2,4,6-TBP may interact with the endocrine system through multiple MoA. 2,4,6-TBP seems to produce adverse effects such as reduction of oocyte development, reduction of fertilization success and fecundity, and shift in male ratios of zebrafish being suggestive of an ED MoA. Uncertainty in the complete MoA of 2,4,6-TBP limit the ability to clearly state that 2,4,6-TBP can be confirmed as an ED, and with the current level of knowledge may be appropriately classified as a potential ED. To provide causal link between a putative ED MoA and adverse effects as well as adopting to regulatory valid approaches, additional testing would be necessary. An extended and modified Fish Sexual Developmental test (FSDT, OECD 234) would clarify possible endocrine disruptive properties of 2,4,6-TBP in fish.

2,4,6-TBP has also been reported to interact /interfere with the transport of TH thyroid hormones and interfere with TH regulation at low concentrations *in vitro*, albeit adverse effect *in vivo* are largely unknown. Due to the concern of a potential of 2,4,6-TBP to interfere with the TH system and the crucial role of TH in the amphibian development, provision of data from an amphibian metamorphosis (OECD test 231) test would be necessary. This is motivated by findings that 2,4,6-TBP interfere with TH transport functions and regulation *in vitro* (Butt et al., 2011; Hamers et al., 2006) and that interference with TH-mediated processes in amphibians by 2,4,6-TBP are presently not known. However, performing the OECD 241 Larval Amphibian Growth and Development Assay (LAGDA) would be the optimal test for clarifying thyroid-mediated ED properties of 2,4,6-TBP in amphibians.

7.10.5. Summary of ED human health

No studies regarding endocrine disruption in mammals due to 2,4,6-TBP exposure were found, but the *in vitro* studies described above indicate a potential for endocrine disruption that is relevant for humans. Positive results from the FSDT and/or the LAGDA test would strengthen the concern from a human health perspective. A concern for reproductive and neurodevelopmental toxicity, is described in section 7.9.7. An appropriately designed EOGRTS study will not only address the data gaps for reproductive and developmental toxicity, but is also likely to give valuable information on potential endocrine MoAs in mammals.

7.11. PBT and VPVB assessment

7.11.1. Persistence

A substance is considered to be persistent (P) if it has a degradation half-life >60 days in marine water or >40 days in fresh or estuarine water, or >180 days in marine sediment or >120 days in freshwater or estuarine sediment or soil. A substance is considered to be very persistent (vP) if it has a half-life >60 days in marine, fresh or estuarine water, or >180 days in marine, freshwater or estuarine sediment, or soil.

TBP is hydrolytically stable. The photolytic half-life in air is 4.6 hours and the first-order kinetic photolytic half-life in water is <1 hour. However, this is not expected to be a significant route of degradation, since the substance partition predominantly to soil/sediment, where UV levels are likely to be low.

For the anaerobic biodegradation studies the results regarding rapid degradation may only be applicable to the specific conditions in the described experiments that are not representative for environmental systems in general. Modelling (BIOWIN) suggests that 2,4,6-TBP is not ready biodegradable. In an aerobic biodegradation study (non-guideline)

no significant biodegradation was reported. In the Japanese MITI test 49% of the theoretical biochemical oxygen demand were reached in 28 days and consequently the condition for ready biodegradability was not met.

2,4,6-TBP thereby fulfils the screening criteria for being potentially P or vP according to Table R 11-4 in Guidance on Information Requirements and Chemical Safety Assessment, Section R.11. PBT/vPvB assessment.

It has been shown that certain commonly found anaerobic bacteria (e.g. *Bacillus* sp. GZT) in both marine and freshwater systems can transform 2,4,6-TBP to 2,4,6-tribromoanisole. The predicted P properties of 2,4,6-tribromoanisole using BIOWIN suggest that it does not biodegrade fast and therefore meets the screening criteria for P or vP.

Based on the available data 2,4,6-TBP and the possible metabolite 2,4,6-tribromoanisole fulfil the screening criteria for being potentially P or vP.

7.11.2. Bioaccumulation

A substance is considered to be bioaccumulative (B) if it has a bioconcentration factor (BCF) >2,000 L/kg or very bioaccumulative (vB) if it has a BCF >5,000 L/kg. REACH Annex XIII also allows a weight of evidence approach.

From a fish bioconcentration test a BCF (edible) of 20 and a BCF (visceral) of 140 was reported for 2,4,6-TBP. Estimated BCF of 122 with EPIWIN supports the experimental BCF values. Several other studies reported a BCF of 80-513. Based on the available data 2,4,6-TBP does not fulfil the B or vB criteria.

2,4,6-tribromoanisole has been shown to be a possible degradation product of 2,4,6-TBP and has been identified as a probable metabolite in fish and has also been detected in the environment in a number of monitoring studies. Prediction of the B properties for 2,4,6-tribromoanisole based on the estimated log Kow of 4.48 and estimated BCF of 2047 using BCFBAF v3.01 (Arnot and Gobas method) suggests that the compound may meet the B criteria. However, the measured fish BCF of 865 for 2,4,6-tribromoanisole and the evidence that the substance is rapidly eliminated from the organism do not suggest that 2,4,6-tribromoanisole meets the B or vB criteria.

The weight of evidence suggests that neither 2,4,6-TBP nor the possible degradation product/metabolite 2,4,6-tribromoanisole fulfils the B or vB criteria for aquatic organisms.

However, due to the strong binding potential of 2,4,6-tribromophenol to soil and sediment particles and the estimated high log Koa more information would be needed to conclude whether the B criterion may be fulfilled based on the potential for bioaccumulation in terrestrial organisms.

7.11.3. Toxicity

A substance fulfils the toxicity criterion (T) when:
- the long term no observed effect concentration (NOEC) for marine or freshwater organisms is less than 0.01 mg/L (10 µg/L); or
- the substance is classified as carcinogenic (category 1A or 1B), mutagenic (category 1A or 1B) or toxic for reproduction (category 1A, 1B or 2); or

- there is other evidence of chronic toxicity, as defined by the classifications STOT (repeated exposure), category 1 or category 2, according to Regulation (EC) No 1272/2008.

Information on long-term toxicity to algae and invertebrates and information on short-term toxicity to fish are available on the ECHA dissemination website. The lowest NOEC reported there is 0.025 mg/L for a *Daphnia magna* reproduction study, which would not fulfil the T criterion. However, publicly available literature suggest that 2,4,6-TBP has a potential for causing endocrine disruption, transgenerational effects and early life-stage toxicity in fish at low concentrations. In a fish study effects have been observed as low as 0.003 mg/L and NOEC values of 0.0003 mg/L was reported. Taking this information into account 2,4,6-TBP would fulfil the T criterion. However, as explained in the endocrine disruptive effects assessment in section 7.10 the study has shortcomings and the results would need to be verified by further studies.

The majority of notifiers to the Classification and Labelling Inventory have provided a classification for 2,4,6-TBP which would not fulfil the T criterion based on the human health hazard classification. However 2,4,6-TBP has been self-classified by one notifier with Reproductive Toxicity cat. 2 and Specific Target Organ Toxicity, Repeated Exposure (STOT RE 2), which would lead to the substance fulfilling the T-criterion.

Based on the available data 2,4,6-TBP may potentially fulfil the T criterion.

7.11.4. Overall conclusion

Based on the available data 2,4,6-TBP and the possible metabolite 2,4,6-tribromoanisole fulfil the screening criteria for being potentially P or vP. 2,4,6-TBP may potentially also fulfil the T criterion. However, the weight of evidence suggests that neither 2,4,6-TBP nor the possible metabolite 2,4,6-tribromoanisole fulfil the B or vB criteria for aquatic organisms. No data are available to conclude whether the B criterion may be fulfilled based on the potential for bioaccumulation in terrestrial organisms.

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Modelling data

No data modelling for worker, consumer or indirect exposure via the environment has been performed due to lack of data on current manufacture, production, import and use volumes in the EU (registrations inactive).

7.12.1.2. Monitoring data

7.12.1.2.1. Worker

One study from the open literature was identified that includes measurements of 2,4,6-TBP in plasma from three occupational groups (Thomsen et al., 2001). They analysed 2,4,6-TBP in plasma from three occupational groups in Norway. The authors measured levels ranging from 0.17 to 81 ng/g fat (as reported in EFSA 2012).

7.12.1.2.2. Consumer

Consumer exposure includes exposure from house dust, indoor air as well as dermal or oral contact with consumer products.

There are no available data concerning the possible leaching of 2,4,6-TBP or un-reacted brominated phenols from plastics containing fire retardants derived from 2,4,6-TBP.

The substance is present in indoor air and dust. The concentrations of 2,4,6-TBP in indoor air are significantly higher than in outdoor air and this suggests that anthropogenic sources in the indoor environment contribute to human exposure.

Table 9 Measured exposure levels of 2,4,6-TBP in indoor air and dust

Matrix	Concentration	Location	Reference
Indoor air	<2.0-6.8 ng/m^3	Japan	Saito et al., 2007
Indoor air	220 and 430 pg/m^3	Japan	Takigami et al., 2009
House dust	15 and 30 ng/g	Japan	Takigami et al., 2009
House dust	16-620 ng/g	Japan	Suzuki et al., 2008

Suzuki et al. (2008) combined chemical fractionation with *in vitro* competitive human TTR-binding assay and GC-MS to analyze TTR-binding compounds dust extract. House dust samples were collected from 19 households and three institutions in Japan. The median concentration of 2,4,6-TBP in crude extracts of indoor dust samples was reported to be 34 ng/g and 90 ng/g in house dust and institution dust, respectively (Suzuki et al., 2008).

In a study by Takigami et al.,(2009) the levels of polyhalogenated compounds including 2,4,6-TBP was analysed in indoor air and dust samples from two modern residential homes in Japan. Concentration of 2,4,6-TBP was found at 220-690 and 280-430 pg/m^3 air in house A and B, respectively. The concentrations were higher in the living rooms than in the bedrooms. The indoor concentrations were well above those in outdoor air (73 and 49 pg/m^3 air). The levels in dust were determined to be 30 and 15 ng/g (Takigami et al., 2009).

These studies indicate frequent and long-term exposure of 2,4,6-TBP of the general population in the indoor environment.

7.12.1.2.3. Indirect exposure of humans via the environment

Indirect exposure via the environment includes exposure from food and beverages, drinking water and inhalation of outdoor air.

2,4,6-TBP has been detected in outdoor air and in food items. Much of the 2,4,6-TBP present in marine foods probably stems from natural sources. There are some studies relating to concentrations of 2,4,6-TBP in drinking water and in food stuff. In an EFSA report (EFSA 2012) these data are reviewed.

The following values have been measured in outdoor air, background and urban areas, in Scandinavia: <0.3-27 pg/m^3(Schlabach et al., 2011).

7.12.2. Environment

7.12.2.1. Modelling data

EUSES exposure modelling for environmental compartments has not been performed due to lack of data on current manufacture, production, import and use volumes in the EU (registrations inactive).

7.12.2.2. Monitoring data

Data on environmental concentrations have been reviewed by WHO (2005), Covaci et al. (2011) and ESFA (2012).

For illustrative purposes a selection of environmental monitoring data are presented in Table 10.

7.12.2.2.1. Aquatic compartment (incl. sediment)

Marine environment

2,4,6-TBP is known to be formed naturally through biosynthesis, particularly in the marine environment where the necessary precursors are available. As stated by WHO (2005): " Several species of marine algae are known to contain simple brominated phenols. It is known that brominated phenols occur naturally through production by marine benthic animals. Acorn worms (Enteropneusta) produce and excrete large amounts of bromophenols without any obvious dietary source of these compounds. Natural bromophenols, such as 4-BP, 2,4-DBP, 2,6-DBP, and 2,4,6-TBP, are a consistent feature of pristine marine soft-bottom habitats, and their spatial and temporal abundance correlates with the abundance of infauna these matabolites." However, the natural production of brominated phenols does not appear to occur in fresh waters (Gribble, 2000).

The reported range in concentrations for seawater were from non-detectable to 16.2 ng/L.

For marine sediments the reported range spaned over several orders of magnitude: from <0.02 ng/g dw to 3690 ng/g dw. The highest concentrations were found in the Rhone estuary, France.

Marine invertebrates (polychaetes and crustaceans) could obtain rather high concentrations. Measured values from 0.9 ng/g dw to 2360 ng/g dw and from 40 ng/g ww to 7000 ng/g ww have been reported for different species.

The reported concentrations in marine fish were in general lower than in invertebrates and varied between 2.2 and 155 ng/g dw and between 0.1 and 68.8 ng/g ww (mean value).

The reported concentrations in liver samples from arctic seabirds were in the range <12.1–332 ng/g ww. In seabird eggs (herring gull) a mean concentration of 62.5 ng/g ww has been measured in one study. Reported liver concentrations in ringed seals and harbour seals were in the range <12.1–164 ng/g ww (mean value), whereas they were <12.1 – 66 ng/g ww in blood plasma in polar bears.

Freshwater environment

The reported range in concentration for freshwater were from non-detectable to 3.84 ng/l. For freshwater sediment the reported concentrations (Japan) ranged from 0.9 ng/g dw to 36 ng/g dw. In liver samples from freshwater fish mean concentrations of 42.4 ng/g ww (perch) and 66.3 ng/g ww (brown trout) has been reported, however uncertainties due to possible matrix effects in the analytical methods could not be

excluded in that study (Norwegian Environment Agency, 2013).

Table 10 2,4,6-TBP concentrations in the environment

Marine environment	**Concentration**	**Location**	**Remarks**	**Reference**
Seawater	0.58–16.2 ng/L	Korea, South-East coast	Higher concentration near a nuclear power plant	Sim et al., 2011
Seawater	ND – 6 ng/L	German Bight		Reineke et al., 2006
Marine sediments	26–3690 ng/g dw	Rhone estuary, France	Estuarine samples.	Tolosa et al., 1991
Marine sediments	0.8–1.3 ng/g dw	Osaka Prefecture, Japan	Estuarine. Detected in 5 of 6 samples.	Watanabe et al., 1985
Marine sediments	<0.02–7.8 ng/g dw	Nordic waters	Including brackish waters	Schlabach et al., 2011
Marine invertebrates. Polychaete annilids	40–3220 ng/g ww	German Bight, English Channel	Range of means	Goerke and Weber, 1.991
Marine invertebrates. Polychaete annilids	500-7000 ng/g ww	Norwegian Sea	Range	Jensen et al., 1992
Marine invertebrates. Crustacea	0.9–2.1 ng/g dw	-	Detected in 5 of 5 samples	Boyle et al., 1992
Marine invertebrates. Crustacea	6.4–2360 ng/g dw	Hong Kong	Range of means, detected in all 63 samples	Chung et al., 2003
Marine fish. Salmonid species	5.1-33.2 ng/g dw	Anchor Point, AK, USA	Detected in 4 samples; 4 species of salmon	Boyle et al., 1992
Marine fish	2.2-155 ng/g dw	Hong Kong	Range of means; detected in 30 of 42 samples	Chung et al. 2003
Marine fish	<0.03–86 ng/g lw	Nordic waters	Including brackish waters	Schlabach et al., 2011
Marine fish	0.1–1.2 ng/g ww	New South Wales, Australia	Range of means; detected in 19 of 32 samples	Whitfield et al., 1998
Marine fish, Atlantic cod	Mean 68.8 ng/g ww	Northern Norway	Liver, detected in 60% of samples	Norwegian Environment Agency, 2013
Seabirds, herring gull	Mean 62.5 ng/g ww	Northern Norway	Eggs, detected in 80% of samples	Norwegian Environment Agency, 2013

Seabirds, common eider	<12.1–332 ng/g ww	Spitsbergen, Norwegian Arctic	Liver samples; 3.7% lipid	Sagerup et al., 2010
Marine mammals, ringed seals	<12.1–90.8 ng/g ww	Spitsbergen, Norwegian Arctic	Liver samples; 3.5% lipid	Sagerup et al., 2010
Marine mammals, Harbor seal	Mean 164 ng/g ww	Northern Norway	Liver, detected in 100% of samples	Norwegian Environment Agency, 2013
Marine mammals, polar bear	<12.1 ng/g ww	Spitsbergen, Norwegian Arctic	Blood plasma samples; 0.9% lipid	Sagerup et al., 2010
Marine mammals, polar bear	9-66 ng/g ww (1044-7311 ng/g lw).	Spitsbergen, Norwegian Arctic	Blood plasma samples	Norwegian Environment Agency, 2013
Freshwater environment	**Concentration**	**Location**	**Remarks**	**Reference**
Surface water	ND – 3.84 ng/L, mean: 1.27	Korea, South-East	River samples	Sim et al., 2011
Freshwater sediments	0.9–36 ng/g dw	Osaka Prefecture, Japan	Upper river. Detected in 5 of 6 samples.	Watanabe et al., 1985
Freshwater sediments	1.5–4 ng/g dw	Non-industrial site, Japan	Detected in 1 of 11 sediments	EAJ, 1998
Freshwater fish, perch	Mean 42.4 ng/g ww	Norway mainland	Liver, detected in 67% of samples	Norwegian Environment Agency, 2013
Freshwater fish, brown trout	Mean 66.3 ng/g ww	Norway mainland	Liver, detected in 40% of samples	Norwegian Environment Agency, 2013

7.12.2.2.2. Terrestrial compartment

2,4,6-TBP was detected with average concentrations of 81, 54 and 27 ng/g ww in the Norwegian terrestrial environment in liver samples from moose, field mice and shrew, respectively (Norwegian Environment Agency, 2013). However, the authors state that there are uncertainties in these values due to the potential natural sources as well as possible matrix effects in the analytical method.

7.12.2.2.3. Atmospheric compartment

In outdoor air, background and urban areas in Scandinavia, concentrations in the range <0.3-27 pg/m^3 have been measured (Schlabach et al., 2011).

7.12.3. Combined exposure assessment

7.12.3.1. Modelling data

No data modelling for the combined exposure has been performed due to lack of data on current manufacture, production, import and use volumes in the EU (registrations inactive).

7.12.3.2. Monitoring data

The combined human exposure assessment considers exposure from all sources (both sources of consumer exposure and indirect exposure of humans via the environment). Due to lack of data it is not possible to evaluate the relative contribution of consumer exposure and indirect exposure via the environment to the human body burden of 2,4,6-TBP. The internal dose, e.g. assessed using biomonitoring data, reflects an integrated exposure over time comprising various sources and pathways.

Few studies measuring 2,4,6-TBP levels in human biological material have been located. Biomonitoring studies show a general low level exposure of the general population.

Blood analyses

In a study, the levels of selected BFRs in archived human serum samples were measured (Thomsen et al., 2002a). 2,4,6-TBP concentrations ranged from 0.077 to 1.3 ng/g lipids in serum samples collected from males ages 40 to 50 during 1977 to 1999. In serum samples collected in 1998 from varying aged males and females, concentrations of 2,4,6-TBP ranged from 0.20 to 26 ng/g lipids (Thomsen et al. 2002a; EFSA 2012).

Smeds and Saukko analysed BFRs including brominated phenols in human adipose tissue samples obtained from routine medico-legal autopsies in Finland. 2,4,6-TBP was not detected in any of the 29 samples analysed (LOD approximately 0.5 ng/g fat) (Smeds and Saukko, 2003; EFSA 2012).

Several BFRs including 2,4,6-TBP was measured in maternal blood as well as in cord blood and in umbilical cords from 6 Japanese mother-infant pairs (Kawashiro, 2008; EFSA 2012). 2,4,6-TBP was detected in all umbilical cord samples (mean value: 33 pg/g wet weight, range 23-44 pg/g wet weight), but only in some of the blood samples probably due to higher limit of quantification in the blood samples. Mean concentrations were 22 pg/g wet weight (range: LOQ-130 pg/g wet weight) in maternal blood and 37 pg/g wet weight (range: LOQ-110 pg/g wet weight) in cord blood samples.

Dallaire at al. (2009) determined the concentrations of brominated organic compounds including 2,4,6-TBP in plasma from Nunavik Inuit adults from the Canadian Arctic collected in 2004. For 2,4,6-TBP the percentage of detection was 87 % and the mean concentration was 58 ng/L (range: LOD-280 ng/L) (Dallaire at al., 2009; EFSA 2012).

Two recent studies from the group of HM Stapleton reports measurements of a range of BFRs including 2,4,6-TBP in serum and placenta in a cohort of pregnant women recruited from an US observational prospective cohort study (the Healthy Pregnancy, Healthy Baby study). The study populations were predominantly women with a lower socioeconomic standing. The serum measurements reported were part of a methodological study concerning a new method for analysis of a range of BFRs (Butt et al. (2016). 2,4,6-TBP was detected in all samples with a mean concentration of 19.2 ng/g lipid weight in serum and a mean concentration of 15.4 ng/g lipid in placenta (Leonetti et al., 2016).

Breast milk analysis

Thomsen et al. (2002b) developed a method for the determination of several halogenated flame retardants including 2,4,6-TBP in human milk. The analysis of a pooled human milk sample from about 20 Norwegian mothers sampled in 2001 revealed a concentration of 627 pg/g fat for 2,4,6-TBP (Thomsen et al., 2002b; EFSA 2012).

In Japan, Ohta et al. (2004) reported the concentrations of brominated compounds, including tribromophenols in human milk from primiparae and multiparae women. Individual samples were pooled to analyze 4 pools for primipare women, and 5 pools for

multiparae women. The concentrations of 2,4,6-TBP were in the range of approximately 800-8000 pg/g fat (Ohta et al., 2004; EFSA 2012).

The above mentioned studies points to a widespread exposure of the general population to 2,4,6-TBP. The substance is also found in breast milk.

7.13. Risk characterisation

7.13.1. Human Health

There are no data on current manufacture, production, import and use volumes in the EU (registrations inactive). Consequently emissions from current sources and their contribution to human exposure of 2,4,6-TBP cannot be assessed.
2,4,6-TBP has been detected in indoor air, in house dust, however it is not possible to link these data to current production and subsequent life cycle of consumer articles. Furthermore, 2,4,6-TBP has been detected in human biological material, in certain food items and in surface water. Due to lack of data it is not possible to evaluate the relative contribution of consumer exposure and indirect exposure via the environment to the human body burden of 2,4,6-TBP.

Definitive NOAELs for long-term toxicity or reproductive toxicity could not be established based on the available data. Consequently no DNELs could be derived and no risk characterisation for human health could be performed.

7.13.2. Environment

There are no current registrations of 2,4,6-TBP (registrations inactive). Consequently information on emissions from current manufacture, production, import and use volumes in the EU is lacking and the contribution to environmental concentrations cannot be assessed. Therefore EUSES exposure modelling for the environment cannot be performed and PECs cannot be calculated, consequently no risk characterisation for the environment could be performed.

Monitoring data show that 2,4,6-TBP has been detected in a broad range of environment samples, including in different biota samples. As 2,4,6-TBP can also be formed naturally in the marine environment, it is not possible to evaluate the contribution from natural versus (previous) anthropogenic sources.

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7.15. Abbreviations

AR	Androgen receptor
PBT	Persistent, Bioaccumulative and Toxic
BFRs	Brominated flame retardants
PNEC	Predicted No Effect Concentration
bw	Body weight
CAS No	Chemical Abstracts Service registry number
CLP	Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006
CMR	Carcinogenic, mutagenic and/or toxic to reproduction
2,4/2,6-DBP	2,4/2,6-dibromophenol
dw	Dry weight
DNEL	Derived No Effect level
EC No	European Inventory of Existing Commercial Chemical Substances (EINECS) number
ECHA	European Chemicals Agency
EC_{50}	Effective concentration, 50%
ED	Endocrine disruptor
EEA	European Economic Area
EFSA	European Food Safety Authority
EPA	Environmental Protection Agency
eMSCA	Evaluating Member State Competent Authority
EOGRTS	Extended One-Generation Reproductive Toxicity Study
ER	Estrogen receptor
E2	Estradiol
FSDT	Fish Sexual Developmental test
GD	Gestational day
GSI	Gonado-somatic index
i.p. injection	Intraperitoneal injection
3β-HSD	3β-hydroxysteroid dehydrogenase
17β-HSD	17β-hydroxysteroid dehydrogenase
LAGDA	Larval Amphibian Growth and Development Assay

LC_{50}	Lethal Concentration, 50%
LD_{50}	Lethal Dose, 50%
LOAEL	Lowest Observed Adverse Effect Level
LOD	Limit of detection
LOQ	Limit of quantitation
MoA	Mode of action
MSCA	Member State Competent Authority
OECD	Organisation for Economic Co-operation and Development
PBT	Persistent Bioaccummulative Toxic
RCR	Risk Characterisation Ratio
REACH	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
T	Testosterone
TBP	Tribromophenol
2,4,6-TBP	2,4,6-tribromophenol
TH	Thyroid hormone
T3	Triiodothyronine
T4	Thyroxine
TTR	Transthyretin
vPVB	Very Persistent and Very Bioaccumulative
VTG	Vitellogenin
WHO	World Health Organisation
ww	Weight per weight