Analysis of the most appropriate risk management option (RMOA)

Substance Name: Tributyl citrate (TBC)

EC Number: 201-071-2

CAS Number: 77-94-1

Authority: France

Date: March 2016

Cover Note

Tributyl citrate (TBC) has been identified in composition and migration tests performed on PVC-toys, as the substance is used as a substitute of DEHP (EC No 204-211-0).
In the framework on the French National Strategy on Endocrine Disruptors in 2015, the French Competent Authority requested ANSES to evaluate the toxicological profile of TBC and verify whether this substance is a valid substitute to DEHP, in particular regarding its endocrine disrupting properties or if risk management measures should be necessary for this substance.

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1 IDENTITY OF THE SUBSTANCE

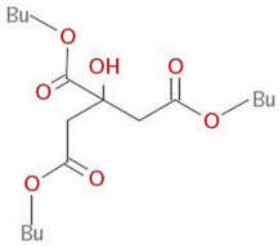
1.1 Other identifiers of the substance

Table 1.1-1: Constituent

EC number:	201-071-2
EC name (public):	tributyl citrate
CAS number:	77-94-1
IUPAC name (public):	1,2,3-tributyl 2-hydroxypropane-1,2,3-tricarboxylate
Index number in Annex VI of the CLP Regulation:	/
Molecular formula:	$C_{18}H_{32}O_7$
Molecular weight or molecular weight range:	360,45 $g.mol^{-1}$
Synonyms:	TBC 1,2,3-tributyl 2-hydroxypropane-1,2,3-tricarboxylate

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

Structural formula:



1.2 Similar substances/grouping possibilities

There are read-across (bridging) possibilities for ATEC, TEC, ATBC and ATEHC (Chemservice, 2012-11-23, provided in TBC registration dossier).

Table1.2-1: Constituent

EC number:	201-070-7
EC name (public):	Triethyl citrate
CAS number:	77-93-0
IUPAC name (public):	1,2,3-triethyl 2-hydroxypropane-1,2,3-tricarboxylate
Index number in Annex VI of the CLP Regulation:	none
Molecular formula:	$C_{12}H_{20}O_7$
Molecular weight or molecular weight range:	276.3
Synonyms:	TEC

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

Structural formula:

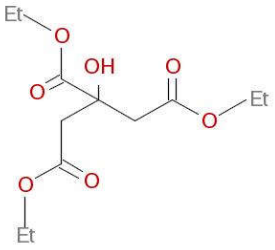


Table 1.2-2: Constituent

EC number:	205-617-0
EC name (public):	Acetatetriethylhexyl citrate
CAS number:	144-15-0
IUPAC name (public):	tris(2-ethylhexyl) 2-acetoxypropane-1,2,3-tricarboxylate
Index number in Annex VI of the CLP Regulation:	none
Molecular formula:	$C_{32}H_{58}O_8$
Molecular weight or molecular weight range:	570.4
Synonyms:	tris(2-ethylhexyl)-O-acetylcitrate ATEHC

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

Structural formula:

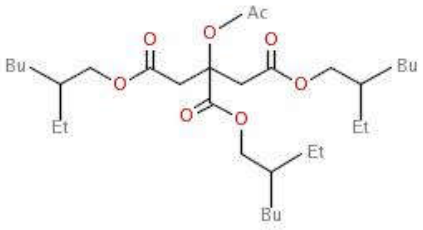


Table 1.2-3: Constituent

EC number:	201-067-0
EC name (public):	Tributyl O-acetylcitrate
CAS number:	77-90-7
IUPAC name (public):	Tributyl 2-acetoxypropane-1,2,3-tricarboxylate
Index number in Annex VI of the CLP Regulation:	none
Molecular formula:	$C_{20}H_{34}O_8$
Molecular weight or molecular weight range:	402.5 g/mol
Synonyms:	ATBC Tributyl O-acetylcitrate tributyl 2-acetoxypropane-1,2,3-tricarboxylate 1,2,3-propanetricarboxylic acid, 2-(acetyloxy)-, tributyl ester Acetyl tributyl citrate

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

Structural formula:

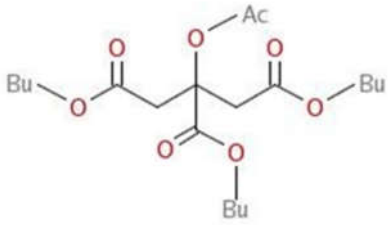
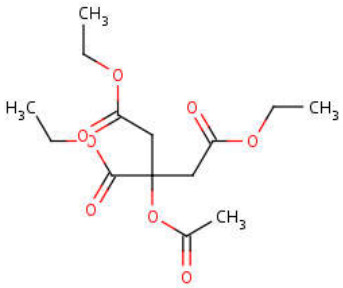


Table 1.2-4: Constituent

EC number:	201-066-5
EC name (public):	Triethyl O-acetylcitrate
CAS number:	77-89-4
IUPAC name (public):	1,2,3-propanetricarboxylic acid, 2-(acettyloxy)-, triethyl ester
Index number in Annex VI of the CLP Regulation:	none
Molecular formula:	$C_{14}H_{22}O_8$
Molecular weight or molecular weight range:	318.3
Synonyms:	ATEC

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

Structural formula:



2 OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Table 2-1: Completed or ongoing processes

RMOA	☐ Risk Management Option Analysis (RMOA) other than this RMOA	
REACH Processes	Evaluation	☐ Compliance check, Final decision
		☐ Testing proposal
		☐ CoRAP and Substance Evaluation
	Authorisation	☐ Candidate List

		☐ Annex XIV
	Restri -ction	☐ Annex XVII[1]
Harmonised C&L		☐ Annex VI (CLP) (see section 3.1)
Processes under other EU legislation		☐ Plant Protection Products Regulation Regulation (EC) No 1107/2009
		☐ Biocidal Product Regulation Regulation (EU) 528/2012 and amendments
Previous legislation		☐ Dangerous substances Directive Directive 67/548/EEC (NONS)
		☐ Existing Substances Regulation Regulation 793/93/EEC (RAR/RRS)
(UNEP) Stockholm convention (POPs Protocol)		☐ Assessment
		☐ In relevant Annex
Other processes/ EU legislation		☐ Other (provide further details below)

[1] Please specify the relevant entry.

3 HAZARD INFORMATION (INCLUDING CLASSIFICATION)

3.1 Classification

3.1.1 Harmonised Classification in Annex VI of the CLP

There is no existing Harmonised Classification for TBC.

3.1.2 Self classification

- In the registration: no existing harmonized classification for TBC;
- The following hazard classes are in addition notified among the aggregated self classifications in the C&L Inventory:

Index No	International Chemical Identification	EC No	CAS No	Classification		Spec. Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement code(s)		
-		201-071-2	77-94-1	Eye Dam.1 Aquatic Acute 1	H318 H400	-	-

3.1.3 CLP Notification Status

Table 3.1.3-1: CLP Notifications

	CLP Notifications[2]
Number of aggregated notifications	4
Total number of notifiers	232

[2] C&L Inventory database, http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database (accessed 22 September 2015)

3.2 Additional hazard information

Most of the hazard information available in the registration dossier are based on a read-across that is evaluated below.

3.2.1 Read-across justification

The read-across is based on the hypothesis that the 'source' substance TBC and the 'target' substance ATBC have similar toxicological properties because they hydrolyse to a common compound and non-common products predicted to have no toxicological effects. This prediction is supported by a published toxicological study on the substances themselves (Finkelstein and gold, 1959).

The registrant proposed a category approach with TEC, ATEC, ATBC and ATEHC that is available in the registration dossier (Chemservice, 2012). Read-across acceptance or rejection is detailed below.

Substance identity

The target and the source substances are both monoconstituents. The impurity profiles of TBC, ATBC, TEC, ATEHC are available. ATEC is only preregistered and therefore its impurity profile is not available.

As the identified impurity for ATBC is the 'target' substance TBC, the impurity is not considered to add new hazard for the chemical safety assessment of the 'target' and 'source' substances. No hazardous impurities has been identified for TBC. No hazardous impurities have been identified for ATEHC.

Table 3.2-1: Target substances identity

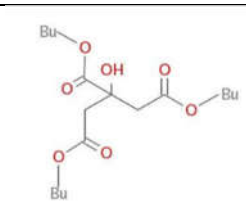
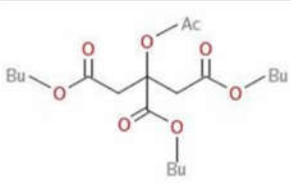
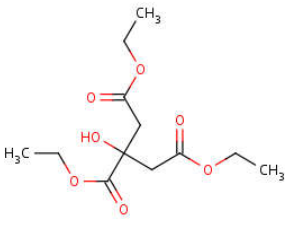
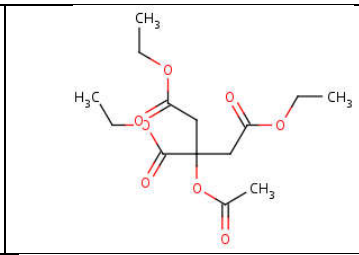
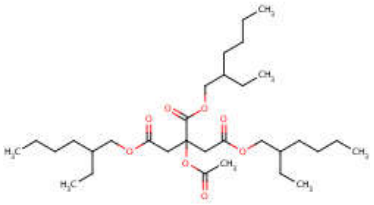
Name	CAS	Molecular structure	Purity	Identified impurities
TBC	77-94-1		Confidential	None specified

Table 3.2-2: Source substances identity

Name	CAS	Molecular structure	Purity	Identified impurities
ATBC	77-90-7		Confidential	TBC
TEC	77-93-0		Confidential	None specified

ATEC	77-89-4		No data	No data
ATEHC	144-15-0		Confidential	Confidential

Structural similarity

The 'source' TBC and the 'target' substance ATBC share structural similarities. The structures differ only in the presence of an acetyl instead of an hydroxyl moiety. Differences with other citrate esters were differences also in the side chains for TEC, ATEC or ATEHC.

Toxmatch modelling tool has been used and high similarity scores (Tanimoto (fingerprints) indices and Hellinger distance) were obtained for TBC/ATBC.

Physico-chemical properties

Table 3.2-3: Physico-chemical properties of category members

Substance	TEC	TBC	ATEC	ATBC	ATEHC
Molecular weight	276.3	360.5	318.3	402.5	570.8
Density	1.140	1.043	1.135	1.052	0.983
Vapour pressure	0.0025 hPa at 25°C	1.01E-04 hPa (EPIsuite)	0.0076 hPa;	0.04944 Pa (EPIsuite)	0.0318 Pa (EPIsuite)
Log Pow	1.17	3.5	1.34 (EPIsuite) 3.73 (ACD/labs)	4.86	> 5.7
Water solubility	58.1 g/L at pH 3.4	102.7 mg/L at 20°C	688.2 mg/L (EPIsuite)	4.49 mg/L at 20°C	< 0.05 mg/L at 20°C;

From these data, ATEHC shows different physico-chemical properties (molecular weigh > 500, log Pow > 5, low solubility in water).

Toxicokinetics

According to Patty's Bruns and Werners, 1962, TBC and ATBC will be both hydrolysed to citric acid and butanol whereas TEC and ATEC will be hydrolysed to citric acid and ethanol. No information was available for ATEHC.

Based on the physico-chemical properties of TEC, absorption is expected to be favoured and high. Absorption of tributylcitrate are expected to be absorbed to a

higher extent than Tributyl-O-acetylcitrate considering their molecular weights, water solubility and LogPow values but to a lesser extent than TEC.

In vivo investigations concerning the absorption, metabolism and excretion of tributyl-O-acetylcitrate (Dow chemical company, 1992, cited also in US EPA (2003)) show that ATBC was absorbed at > 70 % in urine. No experimental data are available on other category members.

In the study of Dow chemical company, 1992, the toxicokinetics and metabolism of ATBC were studied in rats. Groups of 4-5 male Sprague Dawley rats received a single oral dose of ^{14}C-ATBC (70 mg/kg bw, gavage). Absorption of dosed ^{14}C-ATBC from the gastrointestinal tract was rapid (half-time of 1 h) and extensive (at least 67% of ^{14}C dose absorbed). Absorbed ^{14}C-ATBC was rapidly and completely metabolized in the rat, primarily by hydrolyse to polar metabolites. Most of the absorbed radioactivity was rapidly eliminated from the blood with a half-life of 3.4 hours. Between 99% and 102% of the administrated radioactivity was recovered in the urines (59-70%), feces (25-36%), expired CO_2 (2%), tissues and carcass (0,36-1,26%) by study end (48 h). At least 9 radiolabeled metabolites were found in urines. Five were positively identified (acetyl citrate, monobutyl citrate, acetyl monobutyl citrate, dibutyl citrate and acetyl dibutyl citrate). The major labeled urinary metabolite was the monobutyl citrate, that is also expected to be the major metabolite of TBC. Only 7 % of tributyl-O-acetylcitrate were found unchanged in the faeces. At least 3 metabolites and unchanged ATBC were identified in feces. The data on metabolites were not quantified. It should be noted that in this study, the substance was dissolved in corn oil which could have enhanced the absorption from fairly to well.

In vitro studies is available with ATBC and TBC (Davis, 1991 ; Edlund et Sotelius, 1991 as cited in US EPA, 2003 ; CPSC, 2010 ; SCENIHR, 2008). Dose levels of test material were as follows: 100 µg ATBC/mL (248 nmoles/mL), 100 µg TBC/mL (252 nmoles/mL) 14.8 µg n-butanol/ml (200 nmoles/mL). The half-lives are: 32 hours for ATBC, 4 hours for TBC and only seconds for n-butanol. Both ATBC and the intermediate metabolite TBC undergo rapid metabolism in both human serum and rat liver homogenates which would be expected to yield the principal metabolites acetic acid, citric acid and butanol. The butanol would then be expected to further oxidize to butanoic acid and assimilated by ß-oxidation. In addition, only traces of TBC were detected from the deacetylation of ATBC to TBC in human serum. Although a direct stoichiometry of butanol formed from ATBC and TBC was not observed, these results are partially explained based on the fact that butanol also is metabolized in the rat liver homogenate at a rate of 37 nmoles/ml/hr. It also may be suggested that an initial single or double debutylation may yield products which are less readily hydrolysed in the system; products which would be, as fully ionisable carboxylic acids, readily excreted *in vivo* (Author of report).

There is no *in vivo* toxicokinetic study performed with TBC. In order to confirm that monobutyl citrate is also the major metabolite in urine of TBC and to determine the similarities in the toxicocinetic profile between ATBC and TBC, an *in vivo* toxicokinetic study with TBC would be necessary. This study would also permit to exclude potential non common compounds that might be formed with TBC. A comparative *in vivo* study with TBC/ATBC with quantified data on metabolite would add strength to the read-across.

To conclude, no toxicokinetic data are available on TEC, ATEHC and ATEC to support the read-across. Furthermore, available toxicokinetic data on TBC/ATBC are not sufficient to support the read-across. In particular, a reliable comparison on qualitative and quantitative metabolism is not available to ensure and define the limits of the read-across.

Comparison of data from human health endpoints

- Toxicity data of the target and source substance

Differences in the toxic hazard classification by Cramer has been found with the OECD QSAR toolbox. ATEC, ATBC and ATEHC are classified Cramer class III (high) whereas TEC and TBC are Cramer class I (low).

There is only one comparative experimental published study available in the dossier. Finkelstein and Gold, 1959, investigated the acute and short-term toxicological properties (growth, hematology, pathology) of ATBC, TBC, ATEC, TEC. There is no data with ATEHC that could support the read-across.

In the acute toxicity study performed with TBC and ATBC, one dose was administred by gavage to a group of five rats from 10 to 30 cm^3/kg (approximately 10000 to 30000 mg/kg per bw based on density). No deaths were observed among the rats. In the acute toxicity study performed with TEC and ATEC, doses ranging from 5 to 15 cm^3/kg (approximately 5000 to 15 000 mg/kg) were administred by gavage to rats. The LD50 was around 7 cm^3/kg.

Sub-chronic toxicity was also investigated in this study. Immature Wistar rats (n = 4/sex/dose), 21-day old, were exposed to a diet containing 0, 5% or 10% ATBC and 5 or 10% TBC (approximately 0; 7500; 15000 mg/kg bw/d) for 6 weeks and 8 weeks. The 5% ATBC or TBC diet had no deleterious effect on the growth. However, growth was reduced approximately 35% in rats fed the 10% ATBC or TBC diet. This effect may be due to frequent diarrhea. Treatment with ATBC or TBC had no effect on blood counts (measured prior to treatment and 4 and 8 weeks later) and gross or microscopic pathology (40 tissues examined at the end of the 8-week study period). No effects on growth was observed with TEC and ATEC in the 6-week study (admixture in 0.5, 1 and 2% in diet). Treatment with ATEC or TEC had no effect on blood counts and gross or microscopic pathology.

The same authors also performed a short-term feeding study on two cats. Each cat received 5 ml/kg/d ATBC or TBC (around 5000 mg/kg/d) *via* gavage for 2 months. The treated cats developed diarrhea and demonstrated a 30% reduction in body weight relative to controls (NOAEL < 5 mL/kg/d). No changes were observed in the appearance and behavior of the cats, or in urine, blood chemistry or blood count (Finkelstein et Gold, 1959). The small group sizes in this study limit interpretation of these results. Conversely, effects were observed with TEC and ATEC. The effects were studied in six cats for a period of 8 weeks. The doses were 0.25 cm^3/kg (approximately 284 mg/kg) for TEC and 0.5 cm^3/kg for ATEC (approximately 586 mg/kg). Weakness, ataxia and depression progressed to a fairly advanced degree but all animals survived throughout the entire period. There were no effects on weight, blood count, hemoglobin, blood sugar and blood nitrogen. Effects observed on heart were observed at doses which proved fatal and therefore impaired a proper assessment of the effects.

Althoughthe study did not follow the current standart requirements, similar systemic toxicity profiles for acute and sub-chronic toxicity was observed and support the proposed read-across for systemic toxicity (reproductive, mutagenicity and cancerogenicity endpoints) with ATBC.

Different irritation potentials were observed between the source substances TEC, TBC, ATEC, ATBC and ATEHC. Similarly, according to SCTEE opinion 28/9/99, different skin sensitisation potential has been observed in the category (positive for ATEC and TEC and negative for ATBC). Therefore, it is not possible to predict the sensitisation potential of TBC.

- Toxicity data of non-common compounds

There is no toxicological available data on non-common compounds such as acetylated metabolites of ATBC.

Conclusion

Category members TEC, TBC, ATEC, ATBC and ATEHC share structural similarities. Although it is considered a prerequisite for read-across it is not sufficient to enable the prediction of human health properties.

Well-found hypothesis of biotransformation to a common compound is available with the source substance ATBC and the target substance TBC. Furthermore, a toxicological study performed with ATBC and TBC supports the read-across. However, the study was very limited and no data on the toxicokinetic of TBC is available.

As no toxicokinetic data are available with other citrates of the category, and because the available data on physico-chemical or toxicological properties show differences, we conclude that there is no basis to support the read-across with TEC, ATEC and ATEHC.

In conclusion, read-across hypothesis with ATBC would be supported for systemic effects on sub-chronic toxicity, reproductive toxicity, genotoxicity and cancerogenicity if an *in vivo* toxicokinetic study on TBC and comparative quantitative metabolism data with TBC and ATBC were available.

Read-across is not supported for irritation and sensitisation as TBC may be more reactive than ATBC at the site of contact.

Moreover, it is not known how small structural differences may impact mechanistic studies such as binding affinities and therefore change the endocrine disrupting potential. With the available data, read-across is not appropriate so far. If ATBC and TBC are biotransformed to common compounds without any non common compounds, read-across may be justified.

Table 3.2-4: Data matrix for read-across assessment as provided by the registrant

	TBC	**ATBC**
Toxicokinetics	Hydrolysis to citric acid and butanol (Patty's)	Hydrolysis to citric acid and butanol (Patty's); Metabolites identified: acetyl citrate, mono(di)(tri)butyl citrate, acetyl(mono)(di)butyl citrate, acetic acid, butyric acid, buthanol (CIR, 1998; US EPA, 2003)
Acute toxicity; oral (LD50)	31.3 g/kg bw (=30 cm^3; based on density of 1.043) (Finkelstein and Gold, 1959)	31.6 g/kg bw (=30 cm^3; based on density of 1.0528) (Finkelstein and Gold, 1959)
Skin irritation/corrosion	No data	Not irritating (rabbit, study report, 1975)
Eye irritation	No data	Presumably not irritating (study report, 1975)
Skin sensitisation	No data	Sensitising (guinea-pig; Unilever Ltd., 1976); Not sensitizing (human, CSTEE, 1999)
Sub-chronic repeated dose toxicity study (90-	Non-toxic in rats, 6-week study (admixture in diet at 5% and 10%); Non-	NOAEL: 1000 mg/kg bw (comparable to OECD 408, study report, 2003);

day), oral	toxic in cats (oral gavage, 8- week study, 5.2 g/kg bw) (Finkelstein and Gold, 1959)	NOAEL: 300 mg/kg bw (OECD 408, Study report, 1991); Non-toxic in rats (admixture in diet at 0.5% and 10%, 6- week study); Non-toxic in cats (oral gavage, 8-week study, 5.3 g/kg bw) (Finkelstein and Gold, 1959)
Mutagenicity	No data Negative prediction in DERE k for Ames	Negative (Ames test, OECD 471, US EPA 2003); Negative (chromosome aberration, CSTEE, 1999); Negative (at HPRT –locus in CHO cells, CSTEE, 1999); Negative (Mouse Lymphoma Cells, study report, 1991); Negative (UDS Assay *in vivo*, OECD 486, study report, 1999); Negative (chromosome aberration in bone marrow cells *in vivo*, OECD 475, study report, 2002)
Toxicity to reproduction (development)	No data	NOAEL: 100 mg/kg bw (fertility, development) (comparable to OECD 416, Robbins, 1994, as cited in US EPA, 2003) NOAEL: 300 mg/kg bw (reproductive), 1000 mg/kg bw (developmental) (OECD 408, Chase and Willoughby, 2002) NOAEL: 250 mg/kg bw (developmental) (no guideline, Larionov and Cherkassova, 1977, as cited in US EPA, 2003)
Carcinogenicity	No data	No carcinogenic activity (guideline study, as cited in US EPA, 2003); No treatment related neoplastic lesions (as cited in US EPA, 2003)

Acute Toxicity

There is only one published study available in the dossier with TBC (Finkelstein and gold, 1959). LD_{50} oral was above 5000 mg/kg bw.

Irritation and sensitisation potential

No reliable data are available on the irritation or sensitisation potential of TBC. It is not possible to conclude on these endpoints.

Sub-chronic toxicity

Read-across with ATBC is proposed for this endpoint (pending read-across acceptance). See RMOA of ATBC for detailed assessment.

Reproductive toxicity and ED potential

As concluded in the RMOA of ATBC, ATBC is not considered as toxic for reproduction and no alert was found on estrogenic and androgenic activity, showing no potential

endocrine disruption properties for these specific pathways. Nevertheless, some uncertainties remain (activation of PXR pathway, no solid information on potential thyroid effects…).

A read-across with data on ATBC is proposed. Also a toxicokinetic study is missing in order to fully quantify and confirm the read-across plausibility, it appears probable that read-across is acceptable. In this case, TBC would not be considered as a reproductive toxicant and based on the current available data on ATBC. No alert was found on potential endocrine disruption properties.

TBC is not listed as a potential endocrine disruptor in the SIN list. DHI and BKH have not closed ATBC as endocrine disruptor[3]. TBC was not investigated in the US Tox21 program.

Based on the danish QSAR database, ATBC is predictive to be positive for PXR binding receptor whereas inconsistent results were obtained for TBC. Both ATBC and TBC were negative for Estrogen and androgen binding receptor according to QSAR analysis.

Table 3.2-5: QSAR prediction for endocrine and molecular endpoints (Danish QSAR database 12/11/2015)

		Battery	CASE Ultra	Leadscope	SciQSAR
ATBC/ TBC	Estrogen Receptor α Binding, Full training set (Human in vitro)	NEG_IN	NEG_IN	NEG_IN	NEG_IN
ATBC/ TBC	Estrogen Receptor α Binding, Balanced Training Set (Human in vitro)	NEG_IN	NEG_OUT	NEG_IN	NEG_IN
ATBC/ TBC	Estrogen Receptor α Activation (Human in vitro)	NEG_IN	NEG_IN	NEG_IN	NEG_IN
ATBC/ TBC	Androgen Receptor Antagonism (Human in vitro)	NEG_IN	NEG_IN	NEG_IN	NEG_IN
ATBC/ TBC	Thyroid Receptor α Binding (Human in vitro) (mg/L)	OUT			
ATBC/ TBC	Thyroid Receptor β Binding (Human in vitro) (mg/L)	OUT			
ATBC	Pregnane X Receptor (PXR) Binding (human in vitro)	POS_IN	OUT	POS_IN	POS_IN
TBC		INC_OUT	NEG_IN	OUT	POS_IN

AD: applicability domain; INC: inconclusive; NEG: negative; POS: positive; IN: inside applicability domain; OUT: outside applicability domain

Genetic toxicity

A read-across with data on ATBC is proposed (pending read-across acceptance). As concluded in the RMOA of ATBC, all available data suggest that ATBC is not genotoxic.

QSAR analysis of TBC (DEREK, Danish QSAR database, OECD toolbox) were performed and no alerts for mutagenicity were obtained.

[3] Commission européenne (CE) DG Environnement (2000) Towards the establishment of a priority list of substances for further evaluation of their role in endocrine disruption - preparation of a candidate list of substances as a basis for priority setting. Final report. RPS BKH Consulting Engineers, No. M0355008/1786Q/10/11/00 (RPS BKH Consulting Engineers, Delft)
Commission européenne (CE) DG Environnement (2002a) Endocrine Disrupters: study on gathering information on 435 Substances with insufficient data. Final report. RPS BKH Consulting Engineers, No. B4-3040/2001/325850/MAR/C2 (RPS BKH Consulting Engineers, Delft)
DHI Water & Environment (DHI) (2007) Study on enhancing the Endocrine Disrupter priority list with a focus on low production volume chemicals. DHI, No. ENV.D.4/ETU/2005/0028r (DHI, Horsholm)

Carcinogenicity

A read-across with data on ATBC is proposed (pending read-across acceptance). ATBC did not produce neoplastic lesions in any of the dose groups up to the highest dose (1000 mg/kg bw/d) tested and has therefore no carcinogenic potential in rats.

3.2.2 Environmental hazard

Abiotic degradation of TBC was calculated using EPIWin (Hydrowin, v2.00) and the half-lives predicted are 1.92 years at pH 8 and 19.18 years at pH 7, so the hydrolysis takes place very slowly.
Based on ready biodegradability test (OECD 301F), tributyl citrate is considered to be rapidly biodegradable (73-74% of biodegradation after 28 days).
No experimental data for soil biodegradation, nor simulation tests, nor metabolites identification are available for TBC. Only experimental results from the read-across with ATBC are available. ATBC can be considered to be readily biodegradable based on the results on mineralisation in soil and compost (study report, 2000). The reduced degradation in one test with compost can probably be attributed to deficiencies in the applied method (study report, 2000). It can be assumed that the the read across is plausible as tributyl citrate (CAS 77-94-1) is a near analogue to the test substance acetyl tributyl citrate.

No experimental data are available for bioaccumulation of TBC. The Bioconcentration Factor (BCF) value of TBC is 94.7 L/kg wet wt (program BCFBAF v3.01), based on the traditional method and taken into account the experimentally determined LogPow of 3.5 (study report, 2011). The Arnot-Gobas method resulted in a value of 6.54 L/kg wet wt. TBC is not considered as a substance bioaccumulable.

Ecotoxic tests revealed that TBC is not toxic on invertebrates (OECD 202) with an EC_{50} (48h) of 66.9 mg/L, nor on algae (OECD 201) with an EC_{50} (72h) of 100.4 mg/L (growth rate) and 23.86 mg/L (biomass) (study report, 2010ab). The short-term toxicity to fish was predicted by ECOSAR v1.00, which resulted in a LC_{50} (96h) of 6.80 mg/L, concerning SAR for ester and suggesting a low toxicity concern (US EPA 2000). No experimental results on long term ecotoxicity tests are available. No other papers dealing on aquatic nor terrestrial toxicity of TBC are published nor available on Scopus and Google scholar on the date of 14 december 2015.
Regarding endocrine disruptor concern, data available in CSR from Lead registrant, IUCLID and disseminate website from ECHA are not linked to a potential endocrine disruptor of TBC on environment. Several regulatory websites have been also consulted and no one report any endocrine disruptor concern. Regarding endocrine disruptor concern, there is not enough data to conclude on an alert for environment.

4 INFORMATION ON (AGGREGATED) TONNAGE AND USES[4]

4.1 Tonnage and registration status

Table: Tonnage and registration status

From ECHA dissemination site		
☒ Full registration(s) (Art. 10)	☐ Intermediate registration(s) (Art. 17 and/or 18)	
Tonnage band (as per dissemination site)		
☐ 1 – 10 tpa	☐ 10 – 100 tpa	☐ 100 – 1000 tpa
☒ 1000 – 10,000 tpa	☐ 10,000 – 100,000 tpa	☐ 100,000 – 1,000,000 tpa
☐ 1,000,000 – 10,000,000 tpa	☐ 10,000,000 – 100,000,000 tpa	☐ > 100,000,000 tpa
☐ <1 . . . . . >+ tpa (e.g. 10+ ; 100+ ; 10,000+ tpa)		☐ Confidential
Joint submission.		

4.2 Overview of uses

Table 4.2-1: Uses

	Use(s)
Uses as intermediate	
Formulation	Adhesives, sealants ; coatings and paints, thinners, paint removes,ink and toners, laboratory chemicals, lubricants, greases, release products, perfumes, fragrances, polymer preparations and compounds, cosmetics, personal care products.
Uses at industrial sites	Polymer preparations and compounds ,Perfumes, fragrances; Cosmetics, personal care products Lubricants, greases, release products Laboratory chemicals
Uses by professional workers	Adhesives, sealants Coatings and paints, thinners, paint removes Ink and toners Polymer preparations and compounds Lubricants, greases, release products Laboratory chemicals
Consumer	Adhesives, sealants

[4] *Please provide here the date when the dissemination site was accessed.*

Uses	Coatings and paints, thinners, paint removes Ink and toners Polymer preparations and compounds
Article service life	Vehicles Machinery, mechanical appliances, electrical/electronic articles Stone, plaster, cement, glass and ceramic articles Metal articles Plastic articles

4.3 Additional information

TBC is a plasticizer for PVC.

- Citric acid is the starting material for a number of citrate ester plasticisers (US: plasticizers), such as tributyl citrate, acetyl tributyl citrate (ATBC), triethyl citrate, acetyl triethyl citrate and tri-2-ethylhexyl citrate. These plasticisers are used primarily to plasticise vinyl resins in applications such as toys, pacifiers, medical devices and packaging films. Tributyl citrate is largely used in food-wrapping cling film. (Plasticisers.org)
- In their data base, the Danish EPA registered 2 type of products that contain TBC : Colored Textiles and Light sticks (Danish EPA database).
- TBC can be used in pharmaceuticals coatings.

5 JUSTIFICATION FOR THE RISK MANAGEMENT OPTION

TBC is an alternative to phthalates in various applications, including sensitive ones like toys. In the framework of the French National Strategy on Endocrine Disruptors in 2015, the French Competent Authority requested ANSES to evaluate its toxicological profile and check whether risk management measures should be necessary for this substance.

There is very limited data available on TBC for human health and environment risk assessment. In order to meet the requirements as described in annexes VII, VIII, IX and X, a read-across has been proposed by the registrant with other citrate esters (ATBC, ATEHC, TEC, ATEC).

Based on expected similar hydrolysis between ATBC and TBC, an analogue approach seems plausible for systemic effects on sub-chronic toxicity, reproductive toxicity, genotoxicity and cancerogenicity and on endrocrine disrupting effects. However, a detailed description of the *in vivo* toxicokinetic profile of TBC, its metabolites including their proportion in urine are judged necessary to confirm the read-across hypothesis. In particular, steric hindrance of substances plays a major role on nuclear receptor binding.

The read-across for effects at site of contact such as skin or eye irritations and skin sensitisation cannot be supported. Indeed, TBC may be more reactive than ATBC at the site of contact due to the absence of acetyl. This small change in the structure may impact properties such as permeability or protein binding.

As detailed in the RMOA of ATBC, ATBC is not considered as toxic for reproduction and no alert was found on potential endocrine disruption properties, in particular on estrogenic and androgenic activity. However, there is a concern for activation of the PXR pathway but it is currently unclear which adverse effects this may lead

to. So, it is not possible to conclude on the endocrine disruptor character of ATBC because there is no solid information on the other ED effects (thyroid, …).
Danish EPA, Swedish chemical agency (KEMI) and Ireland agree with France's conclusions based on the current available data (following ED Expert Group discussions the 2-3 September 2015). In particular, Ireland considers that PXR/ SXR interaction is not endocrine disruption.

With regard to the environment, TBC does not fulfill the criteria for a PBT nor vPvB-substance. Considering all available data of the acute toxicity tests on aquatic organisms, the substance does not have to be classified. Regarding endocrine disruptor concern, there is not enough data to conclude an alert for environment.

Analysis of the most appropriate risk management options:

As read-across is not supported for skin or eye irritation and skin sensitisation, there is a datagap for these endpoints.

ATBC is on the ECHA list of substances potentially subject to compliance checks (ECHA list December 2015). Therefore, a concomittent CCH on TBC dossier would be the most suitable option.

The toxicokinetic study cannot be requested in a compliance check (CCH) as this is not a requirement of REACH annexes. It could therefore be requested during substance evaluation (SeV). As conclude for ATBC on its potential endocrine disruption properties, TBC is judged of low priority for SeV.

Table 5-1: SVHC Roadmap 2020 criteria

	Yes	No
a) Art 57 criteria fulfilled?		x
b) Registrations in accordance with Article 10?	x	
c) Registrations include uses within scope of authorisation?	x	
d) Known uses not already regulated by specific EU legislation that provides a pressure for substitution?	x	

5.1 References

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- Boettcher M & Wydra V (2010b). Toxicity of CITROFOL®BI to Pseudokirchneriella subcapitata (formerly known as Selenastrum Capricornutum) in an Algal Growth Inhibition Test. Testing laboratory: IBACON GmbH, Rossdorf, Germany. Report no.: 57472210. Owner company: Jungbunzlauer Ladenburg GmbH, 68526 Ladenburg, Germany. Report date: 2010-12-16.

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- CSTEE (1999) Opinion on the toxicological characteristics and risks of certain citrates and adipates used as a substitute for phthalates as plasticisers in certain soft PVC products

- Finkelstein M, Gold H. (1959) Toxicology of the citric acid esters: tributyl citrate, acetyl tributyl citrate, triethyl citrate, and acetyl triethyl citrate. Toxicology. 1959 May;1(3):283-98.

- Johnson (2002) Final report on the safety assessment of acetyl triethyl citrate, acetyl tributyl citrate, acetyl trihexyl citrate, and acetyl trioctyl citrate. Int J Toxicol. 2002;21 Suppl 2:1-17.

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