Analysis of the most appropriate risk management option (RMOA)

Substance Name: 4, 4'-methylenedi-2,6-xylenol (TMBPF)

EC Number: 226-378-9

CAS Number: 5384-21-4

Authority: FR

Date: 12/09/2017

Cover Note

Brief description of the main reasons that lead to the preparation of the RMOA, such as particular screening activities, review of previous assessment, or national programme.

In the framework of the French National Strategy on Endocrine Disruptors in 2016, the French Competent Authority requested ANSES to evaluate the toxicological profile of 4, 4'-methylenedi-2,6-xylenol and verify whether risk management measures should be necessary for this substance. Previously, an ANSES opinion in 2015 has been emitted to the use of 4, 4'-methylenedi-2,6-xylenol as in food contact material.

Comments and additional relevant information are invited on this RMOA by DD Month YYYY.

DISCLAIMER

The author does not accept any liability with regard to the use that may be made of the information contained in this document. Usage of the information remains under the sole responsibility of the user. Statements made or information contained in the document are without prejudice to any further regulatory work that ECHA or the Member States may initiate at a later stage. Risk Management Option Analyses and their conclusions are compiled on the basis of available information and may change in light of newly available information or further assessment.

1 IDENTITY OF THE SUBSTANCE

1.1 Other identifiers of the substance

Table: Other Substance identifiers

EC name (public):	**4, 4'-methylenedi-2,6-xylenol**
IUPAC name (public):	4,4'-methylenebis(2,6-dimethylphenol)
Index number in Annex VI of the CLP Regulation:	
Molecular formula:	C17H20O2
Molecular weight or molecular weight range:	256.3395
Synonyms:	*4*,4'-methylen-bis-(2,6-xylenol) 4,4'-Methylenedi-2,6-xylenol Tetramethyl Bisphenol F TMBPF

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

Structural formula:

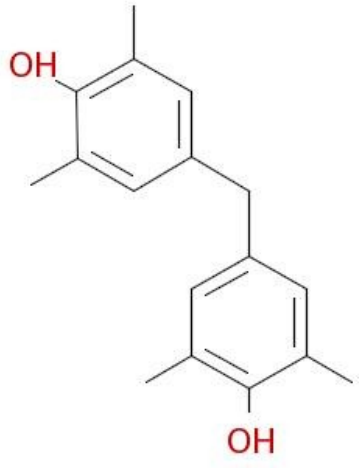


Table: Constituent

EC number:	226-378-9
EC name (public):	4,4’-methylnedi-2,6-xylenol
CAS number:	5384-21-4
CAS name (public):	
IUPAC name (public):	4,4’-methylnebis(2,6-dimethylphenol)
Index number in Annex VI of the CLP Regulation:	
Molecular formula:	C17H20O2
Molecular weight or molecular weight range:	256.3395
Synonyms:	*4,4'-methylen-bis-(2,6-xylenol)* *4,4'-Methylenedi-2,6-xylenol* *Tetramethyl Bisphenol F* *TMBPF*

1.2 Similar substances/grouping possibilities

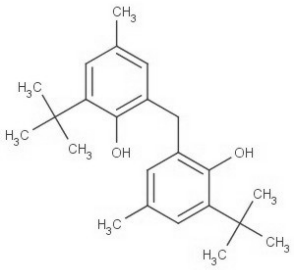
The registrant propose in its dossier a read across of TMBPF with the substance 6,6'-di-tert-butyl-2,2'-methylenedi-p-cresol (EC No 204-327-1) and tert-dodecanethiol (EC No 246-619-1) as support information for ecotoxicity endpoints such as aquatic short term tests with *Pimephales promelas and Ceriodaphnia dubia* respectively *and human health toxicity endpoints*. No justification of read across is presented in the registred dossier.

The following tables present general information of the substances proposed for the read across by the registrant:

Table 1: General information of 6,6'-di-tert-butyl-2,2'-methylenedi-p-cresol.

EC number:	204-327-1
EC name (public):	6,6'-di-tert-butyl-2,2'-methylenedi-p-cresol
CAS number:	119-47-1
CAS name (public):	
IUPAC name (public):	2,2'-methylenebis(6-tert-butyl-4-methylphenol)
Index number in Annex VI of the CLP Regulation:	
Molecular formula:	C23H32O2
Molecular weight or molecular weight range:	340.5
Synonyms:	2,2'-Methylen-bis(4-methyl-6-tert-butylphenol) 2,2'-methylene-bis-(4-methyl-6-tert-butylphenol) 2,2'-Methylenebis(4-methyl-6-tert-butylphenol) 2,2'-methylenebis(6-tert-butyl-4-methylphenol) 6,6'-di-tert-butyl-2,2'-methylenedi-p-cresol DBMC Ionol 46

Molecular formula:



According to disseminated web site of ECHA, 6,6'-di-tert-butyl-2,2'-methylenedi-p-cresol has been added to CORAP 2016 by Denmark for the following concerns: suspected reprotoxic and potential endocrine disruptor. Regarding environmental issues, the substance has been evaluated by UK under the previous EU chemicals legislation for a PBT/vPvB concern[1]. They concluded that the substance does not have PBT/vPvB properties.

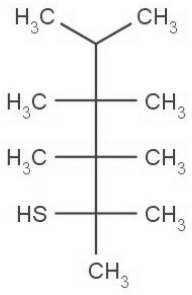
1 PBT fact sheet available in ECHA's web site.

Table 2: General information of tert-dodecanethiol

EC number:	246-619-1
EC name (public):	tert-dodecanethiol
CAS number:	25103-58-6
CAS name (public):	
IUPAC name (public):	2,3,3,4,4,5-hexamethylhexane-2-thiol
Index number in Annex VI of the CLP Regulation:	
Molecular formula:	C11H24S to C13H28S
Molecular weight or molecular weight range:	202.39984 g/mol
Synonyms:	TDM (tert-Dodecyl Mercaptan) tert-Dodecanethiol tert-Dodecyl Thiol

According to disseminated web site of ECHA, the substance has been evaluated by UK under the previous EU chemicals legislation for a PBT/vPvB concern and added to PACT list in 2015 for the same concern. According to the UK-authority's assessment the substance does not have PBT/vPvB properties.

Molecular formula:



However, in the framework of this RMOA, read-across results are not considered in this evalution as their validity is questionable. The substances above are therefore not used for TMBPF evaluation. The QSAR predicted value for TMBPF are described using only two analogous substances such as 6, 6'-di-tert-butyl-2, 2'-methylenedi-p-cresol and methyl-3-(3,5–di-tert-butyl-4-hydroxyphenyl)propionate.

No justifications are given for quality of the QSAR. Moreover, the comparison between 6, 6'-di-tert-butyl-2',-methylenedi-p-cresol and the target substance

(4,4'-methylenedi-2,6-xylenol) is questionnable as the phycico-chemical parameters are different between these analogous. The water solubility for the target chemical is observed at 100 mg/L compared to 7µg/L for the 6, 6'-di-tert-butyl-2',-methylenedi-p-cresol, the Log Kow is observed at 1.215 for the target chemical compared to 6.25 for the the 6, 6'-di-tert-butyl-2',-methylenedi-p-cresol. These remarks confirmed that the QSAR prediction is not relevant and is unjustified.

2 OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Table: Completed or ongoing processes

There is no completed nor ongoing processes on the substance or to the relevant constituent, impurity, additive or degradation (transformation) product/metabolite.

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[2]
Harmonised C&L		☐ Annex VI (CLP) (see section 3.1)
Processes under other EU legislation		☐ Plant Protection Products Regulation
		☐ Biocidal Product Regulation
Previous legislation		☐ Dangerous substances Directive
		☐ Existing Substances Regulation

2 Please specify the relevant entry.

(UNEP) Stockholm convention	☐ Assessment
	☐ In relevant Annex
Other processes/ EU legislation	☐ Other (provide further details below)

3 HAZARD INFORMATION (INCLUDING CLASSIFICATION)

3.1 Classification

3.1.1 Harmonised Classification in Annex VI of the CLP

There is no harmonized classification.

3.1.2 Self classification

Classification & Labelling notified by industry to ECHA:

- Hazardous to the aquatic environment (acute / short-term)

Hazard category: Aquatic Acute 1

Hazard statement: H400: Very toxic to aquatic life.

- Hazardous to the aquatic environment (long-term)

Hazard category: Aquatic Chronic 1

Hazard statement: H411: Toxic to aquatic life with long lasting effects.

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

Hazard Class and Category Code(s)	Hazard Statement Code(s)	Number of Notifiers
Aquatic Acute 1	H400	26
Aquatic Chronic 1	H411	2
Skin Irrit. 2	H315	24
Eye Irrit. 2	H319	24

STOT SE 3	H335	23

3.1.3 Proposal for Harmonised Classification in Annex VI of the CLP

There is no current proposal for classification nor any intention indicated in the register of intentions

3.1.4 CLP Notification Status

Table: CLP Notifications

	CLP Notifications[3]
Number of aggregated notifications	5
Total number of notifiers	28

3.2 Additional hazard information

Human hazards properties presented are based on available data from the chemical safety report (CSR) and Anses report (Opinion, 2016 (in French)) of 4,4'-methylenedi-2,6-xylenol.

Human Health:

- Toxicokinetics and ADME

There is no relevant study and result to conclude on the toxicokinetic behaviour of the compound.

- Acute toxicity

Oral route:

The LD 50 value is reported to be 2000 mg/kg body weight. Based on the results obtained from the CSR, it can be concluded that the test compound 4,4'-methylenedi-2, 6-xylenol is non toxic to Wistar albino rats at the tested dose level of 2000 mg/kg body weight.

Dermal route:

In OECD 402 study, five male and five female healthy young adult rats were randomly selected and used for conducting acute dermal toxicity study. A limit dose of 2000 mg/ kg body weight of test item moistened with 0.2 ml distilled water was applied by single dermal application and observed for 14 days after treatment. No animal died at the maximum dose. The acute dermal median lethal dose of 4,4'-methylenedi-2,6-xylenol was >2000 mg/kg body weight.

3 C&L Inventory database, http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database (accessed 05 February 2016)

- Repeated doses study

Oral route:

A subacute study was conducted to evaluate the toxic effects of repeated administration of 4,4'-methylenedi-2,6-xylenol in male and female Sprague-Dawley rats by gavage. 4,4'-methylenedi-2, 6-xylenol was administered to 6 animals/sex/species in Polyethylene Glycol-400 at doses of 0,250,500 and 1000 mg/kg/bw/day for 28 days. No effects were reported and therefore the NOAEL was considered to be 1000 mg/kg bw/day when Sprague-Dawley rats exposed to 4,4'- methylenedi-2, 6-xylenol orally.

Dermal route:

In a QSAR approach (Prediction is done using QSAR Toolbox version 3.1), the repeated dose toxicity NOAEL (no observed adverse effect level) of 4,4'-methylenedi-2,6-xylenol to rabbit by the dermal route was estimated at a dose concentration of 950 mg/kg bw/day. On the basis of this NOAEL value it is concluded that the test substance is not toxic to rabbit by the dermal route upto the above mentioned dose.

- Skin irritation and corrosion

Three healthy young adult female rabbits were used for conducting acute dermal irritation study. Under the experimental test conditions,it was concluded that 4, 4'-methylenedi-2, 6-xylenol was non-irritating to the skin of female New Zealand White rabbits under the experimental conditions tested.
Based on 404 guideline OCDE study, it can be concluded that the dermal irritation index score is zero. Therefore the test compound 4, 4'- Methylenedi-2, 6-xylenol is "Non Iirritant" to skin of the New Zealand white rabbits.

- Eye irritation and corrosion

Based on 405 guideline OCDE study, it can be concluded that under the experimental test conditions,4, 4'- methylenedi-2, 6-xylenol is "Non Irritant" to New Zealand White female rabbit eyes.

- Sensitization

According to the quantitative structure activity relationship model prediction, 4,4'-methylenedi-2,6-xylenol was predicted as not being sensitising to guinea pig skin by Guinea pig maximisation test.

- *In vitro* and *in vivo* genotoxicity

There is no reported data neither *in vitro* nor *in vivo*. Based on the QSAR prediction for *in vitro* bacterial reverse mutation assay test on Salmonella typhimurium strain TA 100 without S9 metabolic activation, it was estimated that 4,4'-methylenedi-2,6-xylenol does not exhibit positive gene mutation.
Based on the prediction for *in vitro* mammalian chromosome aberration test on Chinese hamster Lung (CHL) without S9 metabolic activation, it was estimated that 4,4'-methylenedi-2,6-xylenol does not exhibit positive chromosomal effect.
At the tonnage level of TMBPF (100-1000 tpa), the lack of some genotoxicity data should be considered as a data gap.

- Carcinogenicity

No information

- Reproductive and developmental toxicity

No animal studies are available for the substance 4,4'-methylenedi-2,6-xylenol.

In a QSAR approach (OECD QSAR 3.1 Prediction (Read Across using 2 nearest analogs, 6, 6'-di-tert-butyl-2, 2'-methylenedi-p-cresol and methyl-3-(3,5 –di-tert-butyl-4-hydroxyphenyl)propionate)) ,a LOAEL for reproduction/developmental (Low observed adverse effect level) value of 4,4'-methylenedi-2,6-xylenol in rat for toxicity to reproduction was predicted to be 200 mg/kg bw/day. Hence it was concluded that the test substance 4,4'-methylenedi-2,6-xylenol shall not exhibit toxic effect to rat below the above mention dose.

- Neurotoxicity

No information

- Immunotoxicity

No information

- Endocrine disruption

- ER (estrogen receptor alpha) and AR (androgen receptor) CALUX (Chemically Activated LUciferase eXpression) assays

The ER CALUX reporter gene assay is designed to test oestrogenic and antioestrogenic activity of compounds in vitro. The AR CALUX reporter gene assay is designed to test androgenic and antiandrogenic activity of compounds in vitro.

ER and AR CALUX assays were realized for TMBPF. TMBPF tested in the range concentrations of 3.81×10^{-6} M to 3.81×10^{-8}M (5 different concentrations) does not show oestrogenic or androgenic activity. At 1.14×10^{-5} M and 3.81×10^{-5} M, no androgenic activity is observed but an E2 activity close to 30 % is observed.
It should be noted that the anti-estrogenic or anti-androgenic activities were not measured and that the pathway *via* the receptor ER ß was not investigate nor the genomic mediations.

- DR CALUX assay (Dioxin Responsive Chemical-Activated LUciferase gene eXpression (DR-CALUX®) cell-based assay)

The DR CALUX bioassay is a suitable screening method for dioxins and dioxin-like-PCBs.
TMBPF tested in the range concentrations of 9.14×10^{-5} M to 3.05×10^{-8} M (8 different concentrations) shows no dioxin-like activity.
In conclusion, in the conditions of the test DR-CALUX, TMBPF does not show dioxin-like potential.

- Uterotrophic *in vivo* assay

The study was realized on 5 groups of 6 immature Sprague Dawley female rats treated during 3 consecutive days with TMBPF at 0, 100, 300, 1000 mg / kg / d and 17 αlpha -ethinylestradiol at 0.2 mg / kg / d (positive control).
No effect of the treatment with TMBPF, whatever is the dose, was observed on the weight of the uterus while the administration of 17 αlpha -ethinylestradiol induced a significant increase of the weight of the uterus. No histological changes (hyperplasie or pathology) were observed at the groups treated with TMBPF compared to the control.
In the conditions of the study, TMBPF did not produce in vivo estrogenic effect. This study was conducted following OCDE guidelines (440) and in conformity with GLP.

- In vitro œstrogenic/androgenic assay on recombined β-galactosidase yeast

TMBPF was tested at 50 µg/L and 100 mg/L using an *in vitro* assay based on recombined yeasts Saccharomyces cerevisiae. 17β-estradiol (5 ng/L to 10 µg/L) and dihydrotestosterone (10 ng/L to 20 µg/L) were tested as positive control on recombined yeasts that expressed ER and AR, respectively.
In the described experimental conditions, no oestrogeno-mimetic or androgeno-mimetic activities were observed with TMBPF.

- In vitro assays on USO2 Erα et USO2 AR cells.

U2OS recombined cells expressing stable ER α and AR receptors binding to GFP were incubated with TMBPF at concentrations of 0.39 to 200 µM during 22hr (USO2 Erα assay) and 4hr (USO2 AR). In the described experimental conditions, TMBPF does not induced ER α or AR agonist activity.

- LUMICELL assay : agonist oestrogenic activity

The LUMICELL assay estimates the potential of transactivation mediated by the human α or β estrogen receptors. The test was performed according to the guideline 455 of the OECD and the good laboratory practices. In the described experimental conditions, the TMBF showed toxic effect in a range of concentrations of 10 to 100 µg / mL. TMBPF at 10^{-4} µg / mL to 1 µg / mL revealed no estrogenic activity in the LUMICELL assay.

- LUMICELL assay : antagonist oestrogenic activity

The estrogenic antagonist activity of TMBPF was performed *in vitro* using the LUMICELL assay according to the guidelines 457 of the OECD and the good laboratory practices. In the described experimental conditions, TMBPF showed toxic effect in a range concentration of 10 to 100 µg / mL and without estrogenic antagonist activity at 10^{-4} to 1 µg / mL.

Enzymatic activity assay

A study was performed to estimate the capacity of TMBPF to inhibit the human recombined aromatase. The measure of the activity aromatase was realized according to the guideline of the US-EPA. A very weak inhibition, insufficient to be considered as positive was observed in the strongest tested concentrations. In these conditions, it can be concluded that TMBPF does not show the capacity to inhibit the human aromatase.

In conclusion, regarding the activation of the receptors ER, AR, AhR, the evaluation does not highlight an endocrine disruptor effect of TMBPF. Moreover, on the basis of the uterotrophic test on rodents (Guideline OECD 440), TMBPF did not show estrogenic effect in vivo.

Regarding the test of aromatase enzymatic inhibition, TMBPF does not show inhibiting activity of the enzyme aromatase. Nevertheless, a ED can also act by activation / inhibition implying other types of enzymes and receptors that those evaluated in the report and according to different modes of action. Moreover, as describes recently by Danish member state, TMBPF (apart from being tested and predicted to bind to the ER, but not to activate it) is predicted to act as an AR antagonist (based on positive predictions in models in Leadscope and SciQSAR in the Danish QSAR database).

Environment:

Environmental hazards properties presented are based on available data from the chemical safety report (CSR) of 4,4'-methylenedi-2,6-xylenol. No other papers dealing on e-fate and ecotoxicity of TMBPF are published nor available on Scopus and Google scholar on the date 05 february 2016.

- E-fate and Ecotoxicity of TMBPF

TMBPF is a solid with a melting point of 182°C at an atmospheric pressure of 990 hPa. According to data TMBPF exhibits solubility in water of 100 mg/L (25 °C), and has a low volatility vapour pressure of $2.56.10^{-6}$ Pa (25 °C). TMBPF is unlikely to partition from aqueous systems to the atmosphere (Henry's Law Constant = $7.81.10^{-7}$Pa m^3/mol, HENRYWIN v3.20). Concerning the dissociation constant (pKa) a very low value of 1.6×10^{-12} is reported in the CSR of Lead registrant, this very low value seems not to be correct and it does not reflect the real character of dissociation of the substance. A review of this parameter needs to be conducted in order to have more reliable information.

According to PBT profiler[4], if the substance is released to air, TMBPF is expected to undergo atmospheric oxidation in air with an estimated half-life of about 0.34 days

If release into water, TMBPF is not expected to volatilize from water surfaces. According to modelling data base (Epi Suite v4.1) the substance exhibits a half-life value of 2.78 hours (25°C) indicating a rapid hydrolysis. No information about products from hydrolysis is available.

- PBT assessment

Concerning degradation, all information was generated by different modelling tools. According to modelling data base (Epi Suite v4.1), TMPBF shows a rapid hydrolysis (half-life value of 2.8 hours (25°C)). Results from *QSAR toolbox* show that TMBPF exhibits a biodegradation rate of 59.1% after 28 days. In contrast, results from *BIOWIN* indicate that TMBPF is not readily biodegradable. No

4 Screening tool developed by U.S. Environmental Protection Agency that use a combination of database queries and background estimations to estimate the persistence, bioaccumulation, and toxicity of organic chemicals.

information concerning degradation products from hydrolysis and biodegradation is available.

Modelisation half-lives for environmental compartments show controversy results especially for the sediment compartment. According to data from *PBT profiler*, TMBPF exhibits a half-life of 38 days in water and 340 days in sediments, but results from *Danish QSAR data base* show a half-life of 15 days in water and 135 days in sediments. Results in soil indicate a half-life of 75 days (PBT profiler) and 61.17 days (*QSAR toolbox*).

According to registration dossier TMBPF presents an estimate adsorption coefficient (log Koc) of 5.03 (*KOCWIN Program v2.00*) but taking into account the log Kow of 1.21 reported in their dossier, this parameter is estimated to 1.92. Considering the value of 5.03, it is expected a tendency of adsorption of TMBPF onto suspended solids and sediments. Clarifications of this parameter are needed in order to have a reliable interpretation.

Taking all these data into consideration suggest an alert regarding P/vP criteria of TMBPF especially in the sediment compartment and further information from standardized tests would be necessary for clarifications of aquatic biodegradation.

Bioaccumulation modelisation are controversy, BCF values of 1340 g/L (*PBT profiler) and* 1300 g/L (EPI Suite[5]) were estimated considering a log kow of 5.21 for both methods. However, the log Kow value used in these estimations do not correspond to the value presented in the registration dossier (Log Kow=1.21). Taking into account screening criteria, a log Kow of 1.21 of TMBPF indicates a low potential of bioaccumulation. However, new estimations of BCF values based on a robust log Kow would be necessary to obtain more reliable information.

Ecotoxicity data is fully based in modelling estimations (QSAR Toolbox, Danish EPA model, ECOSAR). Parameters as Log Kow and water solubility considered for estimation and selection of categories members in QSARs are different to those reported in the registration dossier. Thus, the validity of ecotoxicity information is questionable and their interpretation must be taken with caution. Additionally, the registrant present data from a read across with the substances tert-dodecanethiol (CAS no. 25103-58-6) and 6,6'-di-tert-butyl-2,2'-methylenedi-p-cresol (CAS no. 119-47-1). These information is not considered in the evaluation due to differences in structure and physical-chemical properties of both substances compared with TMBPF. No long-term data for aquatic species is available. The following data is presented for short-term results:

- Fish: 96h-LC_{50} ranged from 0.30 to 0.72 mg/L;

- Invertebrates *(Ceriodaphnia dubia*):48h- LC_{50} was estimated to 0.16 mg/L;

- Algae (S. subspicatus): EC_{50} (duration not reported) was estimated to 0.023 mg/L.

The toxicity estimated to the aquatic micro-organisms *Tetrahymena pyriformis*, considering:

- Effect population (24h-EC_{50}) is 2.41 mg/L

- Growth inhibition (72h-IGC_{50}) is 2.19 mg/L

Considering the sentivity of algae given in short-term results as screening criteria, TMBPF could be considered as potential T. Likewise, according to CLP criteria and

5 Estimation Programs Interface

as proposed by registrant, TMBPF warrant a classification as Aquatic Acute 1 and Aquatic Chronic 1 considering its persistent behavior. However, normalized short-term and long term tests would be necessary to obtain more reliable information. No information about monitoring data of this substance was found in the literature.

- Endocrine disruptor characteristic of TMBPF for the environment

Regarding endocrine disruptor concern, no information was identified specifically for environment. No information related on the toxicity of TMBPF on aquatic or terrestrial organisms are published and available in EPA Actor, TedXlist, Estrogenic Activity database (FDA), SPIN, Scopus, google scholar, on the date of 05 february 2016. However, based on positive predictions in models in Leadscope and SciQSAR in the Danish QSAR database, TMBPF is predicted to act as an AR antagonist. Moreover, as no information from degradation products are available, it is not possible to exclude ED mode of actions.

4 INFORMATION ON (AGGREGATED) TONNAGE AND USES[6]

Provide confidential information in Annex I, if considered necessary.

4.1 Tonnage and registration status

Table: Tonnage and registration status

From ECHA dissemination site	
Registrations	☒ Full registration(s) (Art. 10) ☐ Intermediate registration(s) (Art. 17 and/or 18)
Total tonnage band for substance (excluding volume registered under Art 17 or Art 18, or directly exported)	100-1,000 tpa

6 *Please provide here the date when the dissemination site was accessed.*

4.2 Overview of uses

Tetramethyl bisphenol F (TMBPF) is used primary to manufacture specialized epoxy resins with higher chemical & temperature resistance. Therefore, the substance is used as precursor to manufacture the co-monomere tetramethyl bisphenol F diglycidyl ether (TMBPF - DGE - CAS number: 113693-69-9)[7] and bisphenol F cyano ester (CAS number: 101657-77-6)[8].

TMBPF is also used as raw material for flame retardant polycarbonate and as antioxidant in rubber compounds[9].

In France, substitution of Bisphenol A diglycidyl ether (BADGE) by TMBPF- DGE to produce epoxide resins in industrial foodstuffs is under evaluation. Epoxy resin could be used as coatings in light metallic in food contact material (aqueous, acidic, alcoholic and fatty foods).

The following information is extracted from ECHA dissemination web site:

Table: Uses

	Use(s)
Uses as intermediate	Industrial use resulting in manufacture of another substance
Formulation	Laboratory chemical in formulation of preparations.
Uses at industrial sites	Industrial use resulting in manufacture of another substance (use of intermediates)

The table above could include available non-confidential information on tonnages for the listed uses.

7 Information obtained from notice of ANSES- French Agency for Food, Environmental and Occupational Health & Safety , published 15 Juin 2016

8 According to web site of DEEPAK NOVOCHEM: http://www.dntl.co.in/flame_retardant-category-6/tetra_methyl_bis_phenol_f_%28tmbpf%29-product-8.htm

9 According to web site of DEEPAK NOVOCHEM: http://www.dntl.co.in/flame_retardant-category-6/tetra_methyl_bis_phenol_f_%28tmbpf%29-product-8.htm

5 JUSTIFICATION FOR THE RISK MANAGEMENT OPTION

5.1 Need for (further) risk management

TMBPF is a monoconstituant substance used to manufacture specialized epoxy resins. Nowadays, substitution of diglycidyl ether of bisphenol A (BADGE) by the co-monomere TMBPF-DGE to produce epoxide resins in industrial foodstuffs is under evaluation. In the framework on the French National Strategy on Endocrine Disruptors in 2016, the French Competent Authority requested ANSES to evaluate its toxicological and ecotoxicological profile and verify whether risk management measures should be necessary for this substance.

Concerning TMBPF, toxicological data are incomplete because mainly based in unrelevant QSAR prediction model. No justifications are given for quality of the QSAR. In these conditions, it can be considered that the toxicological data available in the dossier are not fulfilling REACH annexes requirement (annex IX). The QSAR predicted value for TMBPF are described using only two analogous substances such as 6, 6'-di-tert-butyl-2, 2'-methylenedi-p-cresol and methyl-3-(3,5–di-tert-butyl-4-hydroxyphenyl)propionate.

Moreover, the comparison between 6, 6'-di-tert-butyl-2',-methylenedi-p-cresol and the target substance (4,4'-methylenedi-2,6-xylenol) is largely questionnable as the physico-chemical parameters are strongly different between these analogous. The water solubility for the target chemical is given at 100 mg/L compared to 7µg/L for the 6, 6'-di-tert-butyl-2',-methylenedi-p-cresol, the Log Kow is given at 1.215 for the target chemical compared to 6.25 for the 6, 6'-di-tert-butyl-2',-methylenedi-p-cresol. These remarks confirmed that all toxicological values provided by the QSAR prediction are not relevant for interpretation of the toxicity of TMBPF.

No additional data concerning the genotoxicity of TMBPF was found during the bibliographical review. Thus, it is not possible to conclude *in vitro* and *in vivo* on the mutagenicity and genotoxicity of TMBPF. So, it seems essential that TMBPF is tested through 2 *in vitro* studies of genotoxicity at least: a test of gene mutation on bacteria, and a test of the *in vitro* micronucleus (EFSA on 2011). Repeated dose toxicity study is missing via oral route, as well as the EOGRTS (or any other multi-generation study).

Regarding the activation of the receptors ER, AR, AhR, the evaluation does not highlight an endocrine disruptor effect of TMBPF. On the basis of the uterotrophic test on rodents (Guideline OECD 440), TMBPF did not show estrogenic effect in vivo.

Regarding the test of aromatase enzymatic inhibition, TMBPF does not show inhibiting activity of the enzyme aromatase. Nevertheless, a ED can also act by activation / inhibition implying other types of enzymes and receptors that those evaluated in the report and according to different modes of action.

In the current state of the knowledge and with regard to the guidelines of the OECD (OECD, 2012) for the evaluation of PE, it is considered that on the basis of the supplied data, there is no enough data to identify potential ED effects although the *in vitro* data are altogether reassuring.

Regarding environmental issues, evaluation was based in information from the registration dossier of Lead registrant. No additional information from external

sources (scientific papers, reports, etc) were found. Physico-chemical parameters as pka, log Kow and log Koc, need to be reviewed, in order to have reliable information that allows an appropriate interpretation. Information about biodegradation, bioaccumulation and ecotoxicity tests (aquatic and terrestrial) presented in the registration dossier are based in modelling estimations (QSAR Tool box, Danish EPA model, EPI suite). The validity of these data is questionable due to contradictions related to parameters used in their estimations as log Kow and water solubility compared with those presented in the registration dossier. Then, no final conclusion can be attributed concerning PBT/vPvB properties and the derivations of PNECs need to be reviewed. Reliable data from standardized tests are needed in order to clarify PBT/vPvB alerts described in the section 3.2 (Hazard information) and to improve the environmental risk assessment.

Regarding endocrine disruptor concern, no information was identified specifically for environment. No information related on the toxicity of TMBPF on aquatic or terrestrial organisms are published and available in EPA Actor, TedXlist, Estrogenic Activity database (FDA), SPIN, Scopus, google scholar, on the date of 05 february 2016. However, based on positive predictions in models in Leadscope and SciQSAR in the Danish QSAR database, TMBPF is predicted to act as an AR antagonist. Moreover, as no information from degradation products are available, it is not possible to exclude ED mode of actions.

Table: SVHC Roadmap 2020 criteria

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

* The registration dossier refers uses as intermediate but a commercial web site mention that TMBPF is also used as raw material for flame retardant polycarbonate and as antioxidant in rubber compounds (*see section 4.2 Overview of uses)*

5.2 Conclusions of the analysis of the most appropriate risk management options:

In order to have information about the genotoxicity and reprotoxicity of TMBPF together with a consistent dossier that allow clarifying uncertainties about PBT/vPvB properties and environmental risk assessment, a **full Compliance Check** on TMBPF dossier would be the most suitable option.

5.3 References

Chemical Safety report (CSR) of 4, 4'-methylenedi-2,6-xylenol, last update